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REVIEW ARTICLE

Purinergic signalling in the gastrointestinal tract and related organs in health and disease

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Abstract Purinergic signalling plays major roles in the physiology and pathophysiology of digestive organs. Adenosine 5′-triphosphate (ATP), together with nitric oxide and vasoactive intestinal peptide, is a cotransmitter in non-adrenergic, non-cholinergic inhibitory neuromuscular transmission. P2X and P2Y receptors are widely expressed in myenteric and submucous enteric plexuses and participate in sympathetic transmission and neuromodulation involved in enteric reflex activities, as well as influencing gastric and intestinal epithelial secretion and vascular activities. Involvement of purinergic signalling has been identified in a variety of diseases, including inflammatory bowel disease, ischaemia, diabetes and cancer. Purinergic mechanosensory transduction forms the basis of enteric nociception, where ATP released from mucosal epithelial cells by distension activates nociceptive subepithelial primary afferent sensory fibres expressing P2X3 receptors to send messages to the pain centres in the central nervous system via interneurons in the spinal cord. Purinergic signalling is also involved in salivary gland and bile duct secretion.

Keywords Gastrointestinal muscle · Enteric plexuses · Epithelial secretion · Irritable bowel syndrome · Pain · Cancer · Salivary gland

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Salivary glands

Parotid gland
Submandibular gland

Gall bladder and bile ducts

Gall bladder
Bile ducts

Summary and future directions

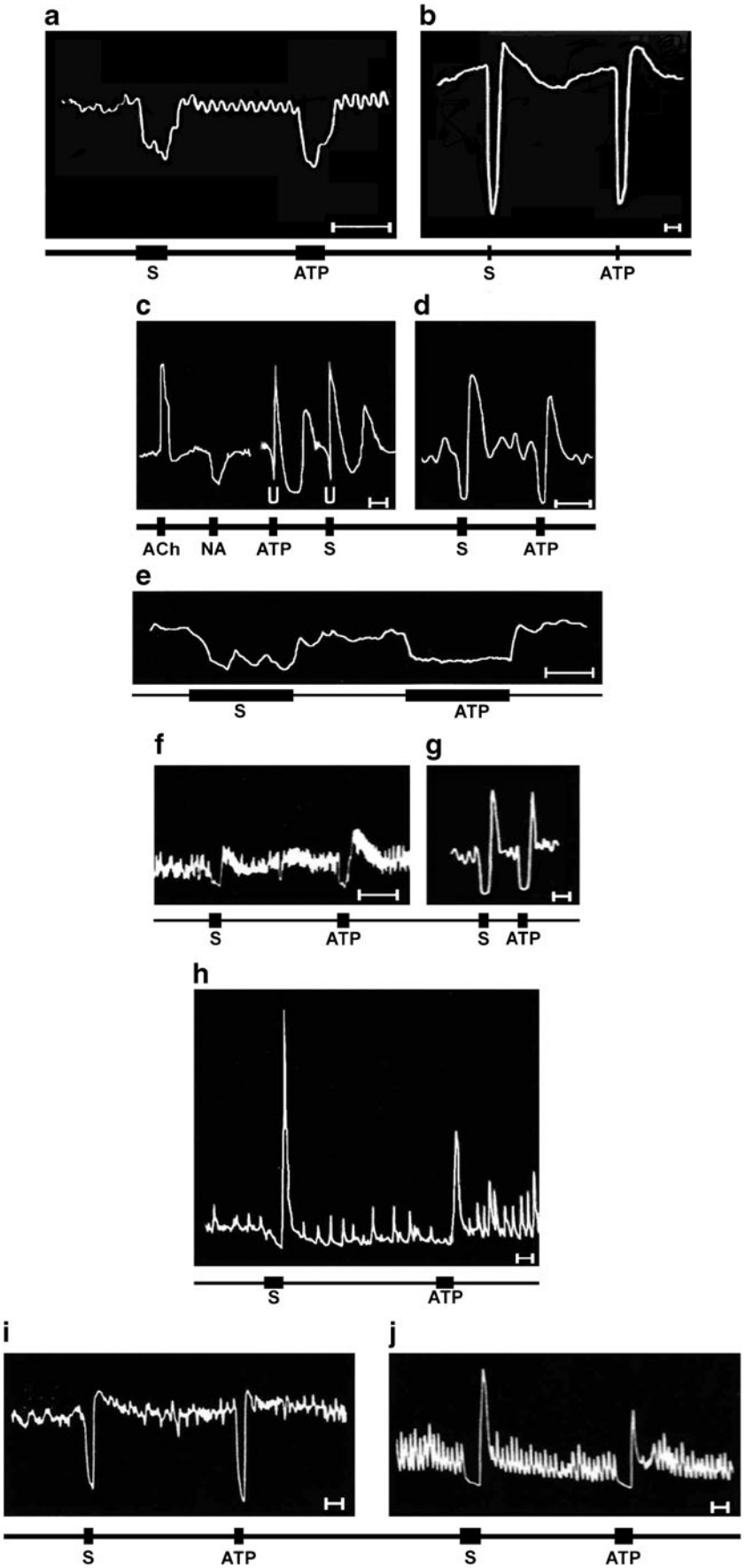
Introduction

Atropine-resistant responses of gastrointestinal smooth muscle to parasympathetic nerve stimulation were recognised early [419, 472, 544]. It was not until the early 1960s, however, that autonomic transmission other than adrenergic and cholinergic was identified. Electrical activity was recorded in the guinea pig taenia coli using the sucrose gap technique, and after stimulation of the intramural nerves in the presence of adrenergic and cholinergic blocking agents, inhibitory hyperpolarisations and relaxations were reported ([106, 107]; see [95]). These hyperpolarisations were blocked by tetrodotoxin (TTX), a neurotoxin that prevents the action potential in nerves without affecting the excitability of smooth muscle cells [77], establishing that they were inhibitory junction potentials (IJPs) in response to stimulation of non-adrenergic, non-cholinergic (NANC) nerves. Later NANC transmitters were shown to be present in intrinsic enteric neurons controlled by vagal or sacral parasympathetic nerves [108]. NANC mechanical responses were identified at about the same time in the stomach upon stimulation of the vagus nerve [459, 460].

Identification of the transmitter released during NANC inhibitory transmission in the gut was the next step. Several criteria were postulated by Eccles and also by Paton to be needed to be satisfied to establish a neurotransmitter: synthesis and storage in nerve terminals; release by a Ca^{2+}-dependent mechanism; mimicry by the exogenously applied transmitter of the nerve-mediated responses; inactivation by neuronal uptake and/or ectoenzymes; and parallel block by drugs of responses to stimulation by nerves and exogenously applied transmitter [198]. Different substances were considered in the late 1960s, including amino acids, monoamines and neuropeptides, but none satisfied the criteria. However, hints in a paper by Drury and Szent-Györgyi [191] showing extracellular actions of purines on heart and blood vessels, papers showing extracellular actions of adenosine 5′-triphosphate (ATP) on autonomic ganglia [216] and a paper showing release of ATP during antidromic stimulation of sensory nerves supplying the rabbit ear artery [326] led Burnstock and his colleagues to look at ATP and this satisfied all the criteria needed to establish it as a transmitter involved in NANC inhibitory neurotransmission (Fig. 1; [109]). A review article was published formulating the purinergic neurotransmission hypothesis [82]. Few believed in this hypothesis over the next 20 years and it was often ridiculed at meetings and symposia. Resistance to this concept was understandable because ATP was well known as an intracellular energy source involved in the Krebs cycle, and it seemed unlikely that such a ubiquitous molecule would also act as an extracellular signaller. It is now recognised that ATP, an ancient biological molecule, appears to have evolved both as an intracellular energy source and an extracellular signalling molecule. Much evidence is now available in support of the purinergic hypothesis (see [1, 83, 84, 86, 88, 97, 103, 194, 289, 336, 511, 527, 646, 700, 760]).

Purines can influence motility, secretion and absorption in a variety of direct and indirect ways. Purines can be released from intrinsic enteric nerves, sympathetic nerves or sensory motor nerves during axon reflexes, to act directly on smooth muscle purinoceptors mediating relaxation or contraction or on epithelial cell receptors. They act on prejunctional nerve terminals to modify transmitter release from motor and inhibitory neural control pathways. They participate in synaptic transmission in myenteric and submucosal ganglia that are involved in the control of gastrointestinal motility, mucosal secretion and absorption. They act on blood vessels or interstitial cells of Cajal (ICC) thereby indirectly modulating motility patterns. Purines also can act on sensory nerve endings in the gut wall after release from epithelial cells to initiate local and/or central reflex activity that alters gastrointestinal motility and secretory patterns and initiate nociception. Other signalling roles for ATP in the gut have emerged through the

Fig. 1 Mimicry of *inhibitory* responses of various gastrointestinal smooth muscle preparations to transmural stimulation and ATP, often followed by rebound contractions. Hyoscine (1.3 μmol/l) and guanethidine (3.5 μmol/l) were present except where stated. **a** Guinea pig stomach preparations consisting of strips (4×40 mm) cut as a spiral around the mid portion of the stomach; transmural stimulation (*S*, 5 Hz for 30 s), ATP (5 μmol/l for 30 s). **b** Guinea pig taenia coli, transmural stimulation (*S*, 5 Hz for 15 s), ATP (1 μmol/l for 15 s). **c** Guinea pig ileum, acetylcholine (*ACh*, 0.006 μmol/l for 30 s, hyoscine omitted), noradrenaline (*NA*, 0.17 μmol/l for 30 s, hyoscine omitted), ATP (5 μmol/l for 30 s), transmural stimulation (*S*, 5 Hz for 30 s); **d** guinea pig colon, transmural stimulation (*S*, 5 Hz for 15 s), ATP (5 μmol/l for 15 s). **e** Biopsy specimen of human colon cut as 10×5×4 mm strips; transmural stimulation (*S*, 5 Hz for 2 min), ATP (400 μmol/l for 2 min). **f** Rat duodenum, transmural stimulation (*S*, 5 Hz for 20 s), ATP (10 μmol/l for 20 s). **g** Rat ileum, transmural stimulation (*S*, 5 Hz for 30 s), ATP (50 μmol/l for 30 s). **h** Rat rectum, transmural stimulation (*S*, 3 Hz for l min), ATP (200 μmol/l for l min). **i** Mouse colon, transmural stimulation (*S*, 5 Hz for 30 s), ATP (40 μmol/l for 30 s). **j** Mouse rectum, transmural stimulation (*S*, 5 Hz for 1 min), ATP (40 μmol/l for 1 min). Time markers, 1 min (Reproduced from [110], with permission from Wiley)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years, including synaptic transmission between neurons in myenteric and submucosal plexuses, control of epithelial cell secretion and absorption, as a sympathetic nerve cotransmitter in controlling intestinal vascular tone and initiating colic pain. The roles of purines in gut pain and inflammation and the possible roles of purinergic signalling in various gut diseases will be considered (see [99]).

There was early evidence for cotransmission in sympathetic nerves supplying the guinea pig taenia coli [647]. Stimulation of periarterial sympathetic nerves led to release of tritium from guinea pig taenia coli preincubated in [^{3}H]adenosine (which is taken up and converted largely to [^{3}H]ATP), and the release of both tritium and noradrenaline (NA) was blocked by guanethidine. It has been claimed that ATP is the sole transmitter in sympathetic nerves supplying arterioles in the submucosal plexus of the intestine, while NA release from these nerves acts as a modulator of ATP release [209]. 'Axon reflex' activity is widespread in autonomic effector systems and forms an important physiological component of autonomic control of blood vessels and visceral organs, including the gut [88, 328]. The early work of Holton [326] showing ATP release during antidromic stimulation of sensory collaterals, taken together with the evidence for glutamate in primary afferent sensory neurons, suggests that ATP and glutamate may be cotransmitters in these nerves. Most enteric neurons are derived from neural crest tissue that differs from that which forms the sympathetic and parasympathetic systems and form a local control system that is capable of acting independently [234]. Cotransmission occurs in enteric neurons and the concept of 'chemical coding' was proposed as a consequence of the patterns of co-localisation defining specific neuron types [235]. A subpopulation of intramural enteric nerves provides NANC inhibitory innervation of gastrointestinal smooth muscle. Three major cotransmitters are released from these nerves: (1) ATP producing fast IJPs; (2) nitric oxide (NO) also producing IJPs, but with a slower time course; and (3) vasoactive intestinal peptide (VIP) producing slow tonic relaxations [91]. The proportions of the effects mediated by these three transmitters vary considerably in different regions of the gut and in different species. For example, in some sphincters, the NANC inhibitory nerves primarily utilise VIP, in others they utilise NO, and in non-sphincteric regions of the intestine, ATP is more prominent. ATP and NO have been shown to co-mediate NANC relaxation of the circular muscle of the human sigmoid colon [49].

Gastrointestinal tract

A detailed account of purinergic neuromuscular transmission in different regions of the gut is available [103].

Smooth muscle

Non-adrenergic, non-cholinergic (NANC) neuromuscular transmission

NANC inhibitory nerves are prominent in many regions of the gut (see [87, 91, 337]), but NANC excitatory nerves have also been described, notably in the guinea pig ileum, and in the gastrointestinal tract of lower vertebrates (Fig. 2) [81, 89, 110, 628]. They are also found in neonatal development (see [89, 91]). While ATP, NO and VIP appear to be cotransmitters in many of the inhibitory NANC nerves, there is much variability in their proportional effects in different regions of the gut and between species. In general, it seems that in most species, NO is the dominant cotransmitter in anterior regions of the gut, while ATP is more prominent in the posterior regions. The $P2Y_1$ receptor is the main receptor subtype mediating NANC inhibitory responses in the mouse gut, partly by direct action on smooth muscle and partly by activating enteric neurons that release ATP and NO [271]. There is evidence that prostaglandin is responsible for the rebound contraction following stimulation of NANC inhibitory nerves [111].

Two pathways of similar magnitude were involved in nerve-mediated relaxation of pig lower oesophageal sphincter: one via NO and one via an apamin-sensitive pathway, mediated by ATP and adenosine 5′-diphosphate (ADP), acting on $P2Y_1$ receptors [214]. A selective $P2Y_1$ receptor antagonist, MRS2179, reduced the non-nitrergic component in both pigs [214] and humans [206]. ATP and adenosine are reported to augment the contractions of the guinea pig oesophagus both to cholinergic nerve stimulation and applied acetylcholine (ACh) [375]. Immunoreactivity for P2X2 and P2X3 receptors was colocalised with vesicular glutamate transport 2, a specific marker for sensory intraganglionic laminar endings (IGLEs), in the mouse oesophagus [387, 693]. ATP may be a neuromodulator in IGLEs via a P2X2, P2X3 and/or P2X2/3 receptor-mediated pathway in the oesophagus.

Although many early papers did not favour purinergic involvement in NANC inhibitory transmission in the stomach (e.g. [11, 23, 229, 316, 344, 429, 430, 521]), there is good evidence that ATP is involved in most species in concert with NO and, to a lesser extent, VIP [45, 91, 161, 162, 211, 283, 480, 491, 523, 526, 532, 728, 751]. Vagally induced NANC gastric relaxation of cat stomach is inhibited by P2 receptor desensitisation with α,β-methylene ATP (α,β-meATP), but it is likely that this is due to interference with ganglionic transmission in the vagal pathway, rather than neuromuscular blockade [176, 177]. Responses to stimulation of enteric inhibitory neurons were reported to be substantially reduced by apamin, which blocks small conductance Ca^{2+}-activated K^+ channels [30], in the circular muscle coat of the antrum, but not fundus [154]. Studies of gastric volume from anaesthetised rabbits showed that the relaxations produced by vagal nerve

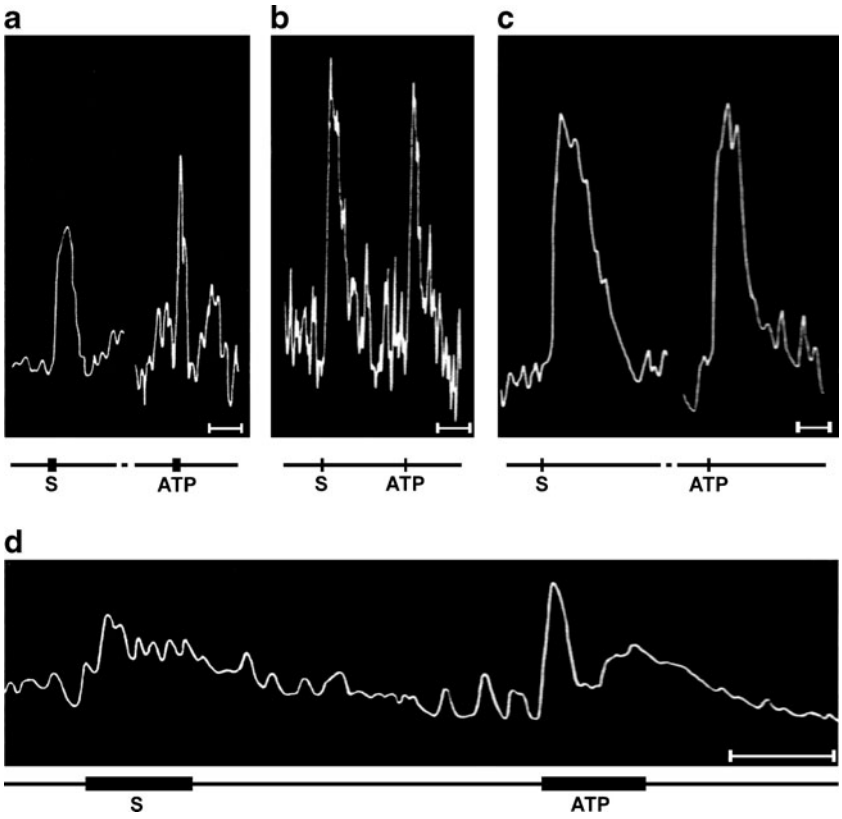


Fig. 2 Mimicry of *excitatory* responses of gut segments from lower vertebrates to transmural stimulation and ATP. Hyoscine (1.3 μmol/l) and guanethidine (3.5 μmol/l) were present throughout. **a** Lizard ileum; transmural stimulation (*S*, 10 Hz for 1 min), ATP (10 μmol/l for l min). **b** Toad duodenum, transmural stimulation (5 Hz for 15 s), ATP (10 μmol/l for 15 s). **c** Toad ileum, transmural stimulation (5 Hz for 15 s), ATP (25 μmol/l for 15 s). **d** Goldfish large intestine, transmural stimulation (10 Hz for 1 min), ATP (12 μmol/l for 1 min). Time markers: **a**–**c**, 5 min; **d**, 1 min (reproduced from [110], with permission from Wiley)

stimulation were mimicked by ATP, but not VIP. Purinergic inhibitory neuromuscular transmission is lacking in the antrum of $P2Y_1$ receptor knockout mice [278].

There is evidence that ATP mediates the non-cholinergic component of the excitatory junction potential (EJP) and contraction of intestinal smooth muscle [747]. ATP also caused a fast contraction of rat ileum by stimulation of cholinergic interneurons in the myenteric plexus [595]. Evidence was presented for two types of P2 receptor in guinea pig ileum, one where α,β-meATP and 2-methylthio ATP (2-MeSATP) were equipotent in eliciting direct contraction of smooth muscle and another where α,β-meATP, but not 2-MeSATP, produced contractions by activating cholinergic nerves [384].

There is purinergic inhibitory neuromuscular transmission in the duodenum and jejunum of most species of laboratory animals [41, 91, 457, 522, 620, 705, 729, 730]. Purinergic NANC transmission has been reported in the ileum of pig [158, 217] and humans [729, 748]. ATP and NO are NANC cotransmitters in rat ileum [48, 627]. P1 (A_1) receptors mediate prejunctional inhibition of release of ACh, ATP and other transmitters including tachykinins from enteric nerve terminals [46, 91, 427, 605, 687], while presynaptic A_{2A} receptors mediate facilitation of cholinergic transmission [684].

ATP and NO are cotransmitters in NANC inhibitory nerves in the colon [65, 67, 200, 324, 382, 554, 586, 673, 746]. β-Nicotinamide adenine dinucleotide (β-NAD) may be the purinergic inhibitory neurotransmitter in the colon, but not in the caecum [291]. The results using $P2Y_1$ knockout mice support this view [245, 246, 278]. It has been claimed that β-NAD is the inhibitory neurotransmitter, rather than ATP, in human and non-human primate colons [196, 348]. However, evidence supporting this claim has been questioned [290]. Both purinergic and nitrergic components of NANC inhibitory transmission are inhibited by apamin, but it is more effective on the purinergic component [277]. Schisandrin, a Chinese herbal medicine, has been claimed to induce NANC relaxation of the rat colon, mediated by ATP and NO, but not VIP or adenosine [733].

Development of NANC transmission

In developmental studies, NANC nerve-mediated effects were observed before birth in mouse and rabbit small intestine [263]. Quinacrine fluorescence, which indicates the presence of high levels of vesicle-bound ATP, appears before birth in enteric neurons of rabbit ileum and stomach, 3 days before catecholamine fluorescence [159]. At 17 days of gestation, NANC inhibitory and cholinergic excitatory innervation appeared simultaneously in rabbit and in mouse. The appearance of adrenergic innervation, however, lagged far behind the other two components. In an electrophysiological study of developmental changes in the innervation of the guinea pig taenia coli, the purinergic inhibitory system appeared before

and matured faster than the cholinergic excitatory system [750]. P2X3 receptor-immunoreactive nerves in the embryonic (E) rat stomach are of both intrinsic and extrinsic origin [721]. Extrinsic sensory nerve fibres express P2X3 receptors as early as E12 and extend rapidly over the whole stomach by E14. The intrinsic enteric neuron cell bodies positive for P2X immunoreactivity did not appear until birth (P1). They peaked by P14 and then decreased in maturing animals. IGLEs and intramuscular arrays were first observed at P1 and P7, respectively. P2X3-positive neurons also expressed NO synthase (NOS) throughout perinatal development. Postnatal developmental changes in purinergic signalling in the small intestine have been described (see [92, 333]). In rat duodenal segments, ATP and ADP produced contractile responses at P1; the responses increased with age, but gradually decreased after P7 and were gone by day 21. In contrast, the relaxant responses to ATP and ADP appeared at day 21 and continued to increase thereafter. Responses to adenosine or adenosine monophosphate (AMP) were not elicited before day 14, which were small relaxations that increased with age. A_{2B} receptors were present at day 15 in the eat duodenum, but A_1 receptors did not appear until after day 20, both receptor subtypes mediating relaxation, while A_{2B} receptors mediated contraction of the muscularis mucosa from day 10. The longitudinal muscle of the colon relaxed via A_{2B} and P2Y receptors, while the muscularis mucosa contracted via A_1 and $P2Y_2$ or $P2Y_4$ receptors. From P3 to P8, $P2Y_1$ receptors mediated contraction of the mouse gastrointestinal tract, but there was relaxation of longitudinal muscle throughout the gastrointestinal tract from day 12 onwards [272]. The shift from contraction to relaxation occurred 1 week before weaning, associated with changes that take place in the gut when the food compositions change from maternal milk to solid food.

Receptor identification

ATP and ADP produce contractions of rabbit oesophageal muscularis mucosae [548] and purinoceptors were identified [704]. Adenosine, acting via A_1 receptors, contracted cat oesophageal smooth muscle [615].

The P2 receptor subtypes involved in gastric motility are still not entirely clear (see [532]). Most reports suggest that a P2Y receptor is involved in relaxation. It seems likely that a P2X receptor is involved in contraction [494]. There is immunostaining for P2X receptors in the muscularis externa and muscularis mucosa [91]. The muscularis mucosae of the rabbit stomach contracted in response to ATP and ADP, but not to AMP or adenosine [549]. Muscular P2Y receptors mediate relaxation in the mouse stomach [492]. A novel function of the $P2Y_{14}$ receptor, associated with the contractility of the rodent stomach, has been reported [43]. Cytidine-5′-diphosphocholine, an endogenous nucleotide, used for the treatment of neurodegenerative disorders, produced contractions of mouse gastric fundus through, at least in part, purinoceptors and Rho/Rho kinase signalling [303]. Uridine adenosine tetraphosphate produces contraction of gastric smooth muscle via P2Y receptors [744].

Analysis of the P2 receptor subtypes involved in motility in the small intestine revealed that:

1. $P2Y_1$ receptors mediate NANC inhibitory transmission to intestinal smooth muscle of laboratory animals and humans [243, 246, 690]. α,β-MeATP has a potent relaxant action in some preparations [366, 367, 535]. It seems likely that α,β-meATP is acting on P2X3 receptors [172, 644] on nerve varicosities to release ATP, which then acts on $P2Y_1$ receptors on smooth muscle eliciting relaxation (see [396]). Occupation of $P2Y_1$ receptors on the taenia coli activated phospholipase (PL) C, increased production of inositol 1,4,5-trisphosphate ($InsP_3$) and released intracellular Ca^{2+} ($[Ca^{2+}]_i$) [406]. This led to enhanced production of spontaneous transient outward currents, which caused hyperpolarisation. It has been proposed that β-nicotinamide, an adenine dinucleotide, which acts on $P2Y_1$ receptors, is released together with ATP from NANC inhibitory nerves supplying the gut [496, 497]. The responses of rat ileal myocytes to ADP were not competitively blocked by pyridoxalphosphate-6-azophenyl-2′,5′-disulfonic acid (PPADS) [685]. High levels of $P2Y_6$ receptor mRNA were found in the human small intestinal muscle [147]. Uridine diphosphate (UDP) activation of $P2Y_6$ receptors produced contraction of mouse ileum [763].
2. $P2Y_2$ and/or $P2Y_4$ receptors mediate smooth muscle contractions in the small intestine of most lower vertebrates [81, 628], since they are activated by uridine 5′-triphosphate (UTP) as well as by ATP [366, 367, 384, 705].
3. Contraction of rat duodenal muscularis mucosae smooth muscle is mediated by P2X receptors [367].
4. Contraction is mediated by P2X receptors in guinea pig ileum [358, 376, 380, 488, 602, 702, 703]. α,β-meATP-induced ileal contractions were inhibited in P2X1 receptor knockout mice [683]. ATP and α,β-meATP produced contractions that were antagonised by atropine and it was concluded that P2 receptors mediated release of ACh from cholinergic enteric nerves [39, 40, 47, 384, 488, 512, 639, 640, 759].

Patch-clamped enzymatically dispersed smooth muscle cells from mouse ileum were activated by P2 purinergic agonists whose effects were attenuated by apamin [688]. Myocytes isolated from the longitudinal muscle of jejunum and ileum showed a slow transient increase in $[Ca^{2+}]_i$ in response to ATP and 2-MeSATP, suggesting P2Y receptor mediation [63]. The NANC relaxation of the human ileal longitudinal and circular muscle is inhibited by MRS2179, a

selective $P2Y_1$ receptor antagonist [669]. Duodenal brush border intestinal alkaline phosphatase degrades ATP released from the epithelium and stimulates HCO_3^- secretion via P2Y receptor activation [483]. The ecto-purinergic system may regulate cell surface pH, maintaining a protective alkaline microclimate during acid stress.

Fast relaxations of the guinea pig taenia coli in response to ultraviolet light (UV) (340–380 nm) closely resembled the relaxations produced by NANC inhibitory nerve stimulation and ATP [105]. The responses to UV light were unaffected by TTX and were not due to ATP release, so it was proposed that UV light was probably acting on some components of the purinergic receptor complex. The first structure–activity studies of analogues of adenine nucleotides in taenia coli showed that di- or triphosphate groupings were of prime importance in binding adenine nucleotides to the putative smooth muscle receptor and that hydrolysis of the terminal phosphates was not a requirement for inhibitory activity. Later studies extended these findings [455, 599, 600] and the actions of enantiomers of 2-azido analogues on taenia were also examined [163]. Separate receptors for adenosine (P1) and ATP/ADP (P2) were proposed [85], and this was supported by later studies of the guinea pig taenia coli [75, 219, 600]. Theophylline blocked relaxations produced by adenosine, but not by ATP. The stereoselectivity of P2 and P1 receptors was studied in the taenia coli. It was shown that while P2 receptors mediating inhibitory responses in taenia coli showed marked stereoselectivity, those mediating excitatory responses in guinea pig bladder showed little stereoselectivity [112]. The A_2 receptor subtype was identified in the guinea pig taenia coli [112] and later adenosine analogues were shown to relax guinea pig taenia coli via P1 (A_{2B}) receptors [558]. β-NAD acts via Pl receptors, while β-nicotinamide adenine dinucleotide phosphate (NADP) acts as a P2 receptor agonist [100, 643]. The potent agonist N^6-methylATP and the less potent agonist 2′-deoxyATP were shown to be selective for P2Y receptors in the taenia coli, but were inactive at P2X receptors [113]. Structure–activity relationships of pyridoxal-6-arylazo-5′-phosphate and phosphonate derivatives as P2 receptor antagonists showed that the phenylazo phosphate derivative and the ethyl phosphonate analogue of isoPPADS had antagonist actions on the guinea pig taenia coli P2Y receptor [391]. Diadenosine polyphosphates were claimed to act as P2Y agonists in the taenia coli with a potency order $AP_3A = AP_4A > ATP > AP_4 = AP_5A$, relaxations that were antagonised by suramin [335]. Comparison of the structure–activity relationships of ectonucleotidases with those of the P2 receptor was described on the guinea pig taenia coli [696]. Methylene isosteres of ATP and ADP resisted dephosphylation. Isopolar phosphonate analogues of ATP were inactive on P2Y receptors in taenia coli [164].

In murine colonic myocytes, there was a high potency of pyrimidines and it was suggested that ATP activated the low-threshold voltage-activated non-selective cation currents and depressed the relatively high-threshold voltage-activated (L-type) Ca^{2+} current via $P2Y_4$ receptors and stimulation of the PLC/protein kinase C (PKC) pathways [485]. Relaxation of the rat colon longitudinal muscle was elicited via P2Y and P1 (A_2) receptors [25]. ATP release of Ca^{2+} from intracellular stores was mediated by P2Y receptors, shown by employing single channel recording from cell patches of mouse colonic and ileal smooth muscle cells [44, 399, 688]. $P2Y_1$ receptors mediate inhibitory motor control of colonic excitability and transit in the mouse [349, 756], human [243, 244] and rat [294] colon. ATP and β-NAD and their metabolites, ADP and ADP-ribose, produced relaxation of murine colonic smooth muscle, and it was suggested that they might be involved in motility disorders [195]. It was concluded in a recent review that the $P2Y_1$ receptor-mediated inhibition may be a general phenomenon in the gut.

At least three subtypes of P2 receptors were claimed to be present in the circular muscle of the guinea pig colon [747], namely: P2 receptors, producing apamin-sensitive hyperpolarisation and relaxation, activated by ATP and sensitive to suramin and PPADS; P2 receptors, producing an apamin-sensitive hyperpolarisation and relaxation, which are activated by adenosine-5′-(β-thio)-diphosphate (ADPβS), but resistant to suramin and PPADS; and P2 receptors produce contractions, which are activated by ADPβS and are sensitive to suramin and PPADS. Canine colon circular myocytes expressed mRNAs for P2X2, P2X3 and P2X4 receptors, while longitudinal myocytes expressed mRNAs for P2X3 and P2X5 receptors, but no mRNA for P2X1, P2X6 or P2X7 receptors [425]. Activation of these receptors produced non-selective cation currents that depolarised and excited muscles in both layers. ATP also elicited contractions of the longitudinal muscle of the mouse distal colon acting directly on smooth muscle and indirectly via activation of cholinergic neurons [761]. Immunohistochemistry showed that $P2Y_1$ receptor proteins are dominant in smooth muscle cells of rat distal colon that mediate the potent effects of ADPβS, while neuronal P2X3 receptors might be involved in the relaxant response to α,β-meATP [674], probably via ATP release and activation of $P2Y_1$ receptors. It was also suggested that neuronal $P2Y_2$ receptors mediate relaxation, partially via NO release. RT-PCR and pharmacological characterisation of P1 receptors in the guinea pig distal colon led to the suggestion that adenosine mediates relaxation through two different receptor subtypes: A_1 receptors on enteric neurons and A_{2B} receptors on smooth muscle [371].

Adenosine, ATP and related compounds produced contraction of the muscularis mucosae of the rat colon [24, 26, 334]. It was concluded that P1 (A_1) and P2Y receptors mediated these responses. However, immunohistochemical expression of P2X1 receptors in the smooth muscle of the muscularis mucosae, but not the muscularis externa, suggested that P2X1 rather than P2Y receptors were involved. The presence of P1 (A_1) receptors in rat colon muscularis mucosae, mediating contraction, was confirmed in a later study [566], although part of the response was

claimed to be due to products of the cyclooxygenase pathway [567]. ATP inhibited swelling-activated Cl^- currents in canine colonic smooth muscle, and it was suggested that this may be related to the regulation of myogenic activation in response to distension [181]. Intestinal myofibroblasts form a monolayer network beneath the mucosal epithelium. mRNA for $P2Y_2$ receptors was expressed and ATP induced increases in $[Ca^{2+}]_i$ and contraction of these cells [502]. The human cathelicidin, LL-37, is involved in innate immune responses, angiogenesis and wound healing. It was suggested that LL-37 stimulated migration of the human colon cell line, Caco-2, via P2X7 receptors [499] affecting intestinal epithelial barrier integrity [533].

ATP released as a cotransmitter from nerves or by paracrine/autocrine release from non-neural cells and its breakdown product, adenosine, acted on guinea pig distal colon mucosal epithelial cells to increase short circuit currents corresponding to electrogenic Cl^- secretion and also activated electrogenic K^+ secretion via P1 (A_{2B}) receptors on both apical and basolateral surfaces [753]. Intestinal epithelial cells form a permeable, but selective, barrier that functions as defence against pathogens as well as performing digestive functions. They secrete and respond to cytokines that recruit neutrophils and macrophages. ATP and UTP, via $P2Y_2$ receptors, serve as chemotactic agents by stimulating the migration of neutrophils and macrophages through the intestinal epithelial cell barrier [420]. It was suggested that this mechanism may contribute to the inflammatory mechanisms that contribute to inflammatory bowel disease. $P2Y_4$ receptors have also been identified immunohistochemically in the human bowel [145].

Postjunctional P1 (A_1 and A_2) receptors mediate relaxation of rat and mouse duodenum longitudinal muscle [308, 495, 762]. Adenosine-induced relaxation of possum duodenum is mediated by A_3, as well as A_{2A} receptors [711]. P1 (A_1 and/or A_{2B}) receptors mediate contraction of rat ileal muscularis mucosae [508, 509]. P1 receptor-mediated contraction of the ileum of *Suncus murinus*, a primitive insectivore, has been reported [500].

Sphincter control

There is evidence for the involvement of ATP in the control of pyloric and internal anal sphincters [562, 629] and in the NANC inhibitory responses of the lower oesophageal sphincter [351, 743]. Studies of NANC inhibitory responses of the rat pyloric sphincter provided evidence for components mediated by both NO and ATP [354, 629] via $P2Y_1$ receptors, but P2X4 receptors were also expressed in this sphincter [596]. An ATP component was involved in relaxation of the rabbit sphincter of Oddi [352], and ATP and ADP were shown to have inhibitory actions on the cat sphincter of Oddi [551]. An excitatory response to ATP in the possum sphincter of Oddi involved P2X receptors, whereas the later inhibitory response was mediated by P2Y receptors [713]. ATP was considered early as a possible NANC inhibitory transmitter in the human internal anal sphincter [80]. Both ATP and adenosine were shown to produce concentration-dependent relaxations of the guinea pig [156], rabbit [59], rat [510, 529] and sheep [3] internal anal sphincter. Relaxation and hyperpolarisation during electrical field stimulation of the mouse internal anal sphincter was mediated by the cotransmitters ATP and NO [383]. ATP hyperpolarised and relaxed the internal anal sphincter of guinea pig [440, 562] and rat [171]. $P2Y_1$ receptors mediated the effects and both apamin-sensitive K^+ channels and apamin-insensitive conductances were involved in hyperpolarisation and relaxation of the mouse internal anal sphincter [466].

Enteric plexuses

Enteric ganglia

Elegant electrophysiological studies, carried out during the past 20 years, demonstrated purinergic synaptic transmission between enteric neurons in both myenteric and submucous plexuses in both in situ and tissue culture preparations (see [68, 97, 98, 248, 250, 252, 341, 569, 570, 572, 671]). In a recent study of the development of the mouse enteric nervous system [313], almost all enteric neurons responded to ATP early at E11.5, E12.5, E15.5 and E18.5, and receptors for ATP were expressed early in E11.5 cultures, followed by the appearance of receptors to 5-hydroxytryptamine (5-HT). ATP is released together with ACh from the majority of presynaptic terminals [436].

Myenteric ganglia. P2X receptors The effects of ATP in single myenteric neurons from guinea pig small intestine were first shown by Katayama and Morita [378], using intracellular electrodes. ATP produced hyperpolarisation in 80 % of AH neurons and depolarisation in 90 % of S neurons.

The studies of purinergic signalling in guinea pig myenteric neurons have been extended by several groups. Whole cell and outside-out patch-clamp recordings have been used to characterise the physiological and pharmacological features of P2X receptors on myenteric neurons of the guinea pig ileum [34]. Agonist rank order of potencies were as follows: adenosine-5′-(γ-thio)-triphosphate (ATPγS)=ATP=2-MeSATP >>α,β-meATP=β,γ-methylene ATP, while adenosine and UTP were inactive. Fast excitatory postsynaptic currents (fEPSCs) were recorded in primary cultures of myenteric neurons from guinea pig intestine [435, 757]. Hexamethonium-resistant fEPSCs were abolished by PPADS. The slowly desensitising receptors that were α,β-meATP insensitive were likely to be P2X1 receptors [34], whereas the minority of rapidly desensitising receptors were probably P2X2 receptors. The fast excitatory postsynaptic potentials (EPSPs) mediated in part by P2X receptors were prominent in myenteric neurons along the small and large intestine, but were rare in the gastric corpus [435]. P2X and nicotinic

receptors were shown to be linked in a mutually inhibitory manner in guinea pig myenteric neurons [758]. P2X2 receptors are expressed by subtypes of guinea pig enteric neurons, namely inhibitory motor neurons, vasomotor neurons, cholinergic secretomotor neurons, intrinsic sensory neurons and the endings of vagal afferent fibres in the stomach [120, 482]. Studies using P2X2 receptor knockout mice showed that P2X2 receptors contribute to fast synaptic excitation of myenteric neurons in small intestine [572]. P2X2 homomeric receptors appear to be the predominant receptors mediating fast synaptic excitation in the gut [248, 250, 524]. Intrinsic sensory neurons in the gut, identified as Dogiel type II neurons, express P2X2 receptors [237].

P2X3 receptors are expressed by excitatory and inhibitory motor neurons, ascending interneurons and cholinergic secretomotor neurons [557], but were claimed not to be expressed by intrinsic sensory neurons in guinea pig ileum [675]. Peristalsis was impaired in the small intestine of mice lacking P2X3 receptors [57]. The distribution of the mRNA and protein of P2X2 and P2X3 receptors has been described in the rat enteric nervous system [722]. It was shown that the P2X2 receptor was the dominant P2X receptor subtype in the myenteric plexus. Most myenteric S neurons in guinea pig small intestine expressed P2X3 receptors with about half of these being inhibitory motoneurons [571]. P2X5 receptors were present on nerve fibres that envelop ganglion cell bodies in the myenteric and submucous plexuses in mouse intestine, probably as heteromultimers with P2X2 receptors on enteric sensory neurons [587].

Studies of purinergic signalling in dispersed primary cultures of guinea pig myenteric plexus were carried out by the group of Mulholland. Extracellular ATP was shown to mediate Ca^{2+} signalling in primary cultures of neurons from guinea pig myenteric plexus via a PLC-dependent mechanism [393]. Different enteric neurons responded to combinations of ATP with ACh, ATP with substance P (SP), ATP with ACh, ATP with ACh and SP, ATP with bombesin or ATP with ACh and bombesin [392].

Two distinct types of P2 receptors are linked to a rise in $[Ca^{2+}]_i$ in guinea pig intestinal myenteric neurons. Both intestinal AH and S neuronal phenotypes responded to ATP by increases in $[Ca^{2+}]_i$ [139, 140]. ATP regulates synaptic transmission by both pre- and post-synaptic mechanisms in guinea pig myenteric neurons. Where ACh and ATP act as cotransmitters, there is an interaction between nicotinic and P2X receptors [173]. In the C-terminal tail of P2X2 receptors, there is cross-inhibition between $\alpha 3\beta 4$ nicotinic and P2X2 receptors [173]. ATP augments nicotinic fast depolarisations, but inhibits muscarinic and SP-mediated depolarisations in both AH and S neurons [374].

Exogenous and endogenous ATP released during increases in intraluminal pressure inhibit intestinal peristalsis in guinea pig [318]. A major role is played by ATP in excitatory neuroneuronal transmission in both ascending and descending reflex pathways to the longitudinal and circular muscles of the guinea pig ileum triggered by mucosal stimulation [143, 638]. Descending inhibitory reflexes involve P2X receptor-mediated transmission from interneurons to motor neurons in guinea pig ileum [58, 70]. Distension-evoked descending contractile responses of the circular and longitudinal muscle layers are regulated by separate sympathetic pathways, one mediated by P2 receptors, the other by 5-HT3 receptors [486]. Inhibitory interactions occur between P2X and γ-aminobutyric acid (GABA)-A receptors on myenteric neurons from the guinea pig small intestine [377].

IGLEs have been identified as specialised mechanosensitive endings of vagal afferent neurons arising from the nodose ganglion. P2X2 receptors are present on IGLEs in the mouse gastrointestinal tract, mainly in the stomach, some in the intestine [121]. IGLEs were first demonstrated at birth showing strong immunostaining for P2X3 receptors, and P2X3 receptors expressed on extrinsic nerves appeared as early as E12 in developing rat stomach in the trunk and branches of the vagus nerve [721].

Neuron cell bodies in the myenteric ganglia appear in the first trimester. Neurons expressing P2X3 receptors peaked at 45 % during development, but at P60 only 11 % were P2X3 receptor immunoreactive. Several enteric neurotransmitters have been claimed to modulate ATP release by acting on NANC neuronal cell bodies in the myenteric plexus. For example, morphine or enkephalin inhibition of NANC-evoked relaxations was reversed by nalaxone [356, 616]. Enkephalin is very effective in inhibiting NANC IJPs evoked in human colon [339]. ATP transiently facilitates ACh release from myenteric motoneurons via prejunctional P2X2 receptors, and following breakdown to ADP and adenosine, there is inhibition of ACh release via $P2Y_1$ and P1 receptors [192]. Evidence has been presented that 5-HT released ATP from nerve varicosities isolated from the myenteric plexus of the guinea pig ileum [8, 247]. GABA receptors mediate relaxation of rat duodenum by activating intramural NANC neurons in guinea pig intestine [410], rat duodenum [454], dog ileocolonic junction [64] and guinea pig distal colon [481].

Myenteric ganglia. P2Y receptors Evidence for the expression of P2Y receptors on enteric neurons in addition to P2X receptors has been presented [255, 676, 710, 723, 724]. In the mouse gastrointestinal tract, $P2Y_1$ receptors on NANC myenteric neurons mediate relaxation [271]. In the guinea pig enteric nervous system, slow excitatory synaptic transmission on S-type neurons is mediated by $P2Y_1$ receptors [341]. $P2Y_1$ receptors mediate slow excitatory synaptic potentials on interneurons during descending inhibition in guinea pig ileum [661]. $P2Y_2$ receptors are expressed by S-type (Dogiel type I) neurons in both the myenteric and submucosal plexuses throughout the guinea pig gut. In the myenteric plexus, 40–

60 % of P2X3 receptor-immunoreactive neurons were immunoreactive for $P2Y_2$ receptors and all P2X3 receptor-immunoreactive neurons expressed $P2Y_2$ receptors in the submucosal plexus [723]. Thirty to 36 % of neurons in ganglia in the myenteric, but not submucosal plexus of the guinea pig gut, expressed $P2Y_6$ receptors [724]. Forty to 46 % of the neurons in both myenteric and submucosal plexuses were immunoreactive for $P2Y_{12}$ receptors. Twenty-eight to 35 % of $P2Y_6$ receptor-immunoreactive neurons coexist with NOS, while all $P2Y_{12}$ receptor-immunoreactive neurons were immunopositive for calbindin, probably AH intrinsic sensory neurons. In the rat distal colon, $P2Y_1$ and $P2Y_6$ immunoreactivity was located on smooth muscles, $P2Y_4$ and $P2Y_6$ receptor immunoreactivity on glial cells in both plexuses, $P2Y_4$ receptors on ICCs, while $P2Y_2$ and $P2Y_{12}$ receptors were identified on enteric neurons [676]. There is a shift from contraction to relaxation via $P2Y_1$ receptors during postnatal development of mouse intestinal smooth muscle 1 week before weaning, perhaps associated with the change from maternal milk to solid food [272]. The role of both P2X and P2Y receptors in sympathetic transmission at functionally identified synapses in the enteric nervous system has been reviewed [310].

Myenteric ganglia. Adenosine (P1) receptors P1 (adenosine) receptors on myenteric neurons were claimed following the demonstration that in the guinea pig ileum, methylxanthines (P1 receptor blockers) antagonised the dipyridamole (adenosine uptake inhibitor)-induced inhibition of peristaltic activity [618, 678]. Adenosine inhibited forskolin-induced excitation of myenteric nerves suggesting that adenosine acts to prevent activation of adenylate cyclase by substances mediating slow EPSPs [745]. Adenosine applied to AH (type II) neurons, but not to S (type I) neurons, resulted in membrane hyperpolarisation and decreases in input resistance following opening of K^+ channels [537]. Adenosine suppressed nicotinic synaptic transmission in myenteric ganglia of the guinea pig gastric antrum and small intestine, by interacting with presynaptic P1 receptors on AH type II neurons [134–137]. A minority subset of AH neurons also express A_2 subtype receptors coupled to adenylate cyclase mediating excitation of these neurons [138]. Adenosine acting at A_1 presynaptic receptors suppressed slow EPSPs and amplified slow inhibitory postsynaptic potentials in myenteric neurons [134, 374].

Adenosine suppressed cyclic AMP (cAMP) formation in myenteric ganglia in vitro [720]. Reduction of cholinergic synaptic transmission via prejunctional A_1 receptors involves the activation of pertussis toxin-insensitive G proteins [35]. Differential gene expression of A_1, A_{2A}, A_{2B} and A_3 receptors in human enteric neurons has been reported [141]. Fine-tuning modulation of myenteric and submucosal motoneuron activity by adenosine has been claimed acting via presynaptic A_1 receptors [153, 256]. Synaptosomal preparations from the guinea pig ileum myenteric plexus have been described [74, 189]. Adenosine inhibited the nicotinically induced release of [^{3}H]ACh from synaptosomes [565, 617]. Both A_1 and A_2 subtypes appear to be involved [131, 132].

A neuroprotective role for adenosine in ischaemia has been postulated [178]. The P1 agonist, 5′-*N*-ethylcarboxamidoadenosine (NECA), is a potent inhibitor of morphine withdrawal-induced diarrhoea in rats [664]. A_{2B} receptors mediate inhibition of secretion and it was suggested that A_{2B} adenosine agonists may be of clinical value in the management of some types of diarrhoea [312].

Submucosal ganglia Adenosine depolarised submucosal neurons by acting at P1 (A_2-like) receptors and to act presynaptically via P1 (A_1) receptors to inhibit the release of ACh from intramural nerves and of NA from sympathetic nerves in the submucosal plexus [31, 32].

Slow postsynaptic inhibitory and excitatory potentials in S neurons of the submucous plexus of the guinea pig caecum were mimicked by various transmitters, the non-reversing type of slow excitatory postsynaptic potential was mimicked only by ATP [478]. ATP-induced fast transient depolarisation of most AH-type neurons and fast transient depolarisation followed by slower onset, longer lasting depolarisation of S-type neurons was reported [33], mediated by P2X and P2Y receptors, respectively [37]. Many neurons in the submucous plexus were immunopositive for P2X3 receptors and were colocalised with calretinin and calbindin, indicating labelling of intrinsic sensory neurons [722]. Using whole-cell patch recording, superfusion of ATP and analogues was shown to evoke rapidly desensitising inward current, and ATP-induced single channel currents were also recorded [33, 285], perhaps involving P2X4 or P2X6 receptors (see [90]). Functional interactions between nicotinic and P2X receptors have been demonstrated in freshly dissociated guinea pig submucosal neurons in primary culture [36, 285, 758]. Later, two subtypes of P2X receptors were identified in neurons of guinea pig ileal submucosal plexuses [286]. Fast inhibitory interactions between P2X and 5-HT_3 receptors in guinea pig submucosal neurons were described [38]. Fast, slow and intermediate EPSPs were recorded in neurons of the submucous plexus of the guinea pig ileum [487]. P2X receptors mediated a subpopulation of fast EPSPs. The slow EPSPs and intermediate EPSPs were blocked by MRS2179, a $P2Y_1$ selective antagonist. A $P2Y_1$ receptor has been cloned and characterised from guinea pig submucosa. $P2Y_1$ receptor signalling involved in synaptic transmission in the human submucous nerve plexus is a predominant pathway, and the A_3 receptor inhibits purinergic and cholinergic transmission in the human enteric nervous system [717].

Intrinsic sensory neurons Both intrinsic and extrinsic sensory nerves are present in the enteric nervous system (see [62,

412]). Intrinsic sensory neurons are located in both the submucosal and myenteric ganglia [236]. Their terminals are largely in a subepithelial plexus. They mediate enteric reflex activities, including peristalsis. Extrinsic sensory nerves also have terminals in the subepithelial plexus. Their cell bodies are in dorsal root and nodose ganglia. They, too, can evoke enteric reflex activities via the spinal cord and brainstem and they mediate visceral pain. Most of the data about intrinsic enteric sensory nerve activities has been reported for the guinea pig ileum. However, this may or may not represent comparable activities in other species and regions of the gastrointestinal tract.

The intrinsic sensory neurons have been identified electrophysiologically as AH-type and morphologically as Dogiel type II cells, while S-type (that include Dogiel type I neurons) are motoneurons or interneurons. Depending on the species, most AH cells express calbindin and/or calretinin. Adenosine acts presynaptically via A_1 receptors and postsynaptically via A_1, A_{2A} and A_3 receptors on intrinsic sensory neurons [129]. Synaptic transmission to intrinsic sensory neurons is mediated by P2X receptors [54], perhaps of the P2X2 subtype in guinea pig intestine [120]. Postsynaptic inhibition via P2Y receptors has also been claimed to be present on intrinsic sensory nerves [52, 53]. P2X3 receptors are expressed by intrinsic sensory nerves in rat ileum and distal colon [722] and on sensory neurons in human myenteric plexus. $P2Y_{12}$ receptors are expressed by sensory neurons in guinea pig myenteric plexus [724].

Mucosal terminals of intrinsic sensory neurons in the guinea pig intestine are activated by ATP and α,β-meATP [54], which supports the hypothesis of Burnstock [91, 93] that ATP released from mucosal epithelial cells has a dual action on P2X3 and/or P2X2/3 receptors on subepithelial sensory nerve terminals. It was proposed that ATP acts on the terminals of low-threshold intrinsic enteric sensory neurons to initiate or modulate intestinal reflexes, while it acts on the terminals of high-threshold extrinsic sensory fibres to initiate pain. Support for this hypothesis was gained from a rat pelvic sensory nerve–colorectal preparation [718]. Distension of the colorectum led to an increase in the release of ATP from mucosal epithelial cells and also evoked pelvic nerve excitation, which was mimicked by application of ATP and α,β-meATP and attenuated by the selective P2X3 and P2X2/3 antagonist, 2′(3′)-*O*-(2,4,6-trinitrophenyl) ATP (TNP-ATP), and by PPADS. Purinergic mechanosensory transduction has also been implicated in reflex control of intestinal secretion [149, 726]. Extrinsic and possibly intrinsic sensory nerves associated with mucosal epithelial cells appear to be sensitive to pH, involving P2X2 and P2X2/3 receptors [329].

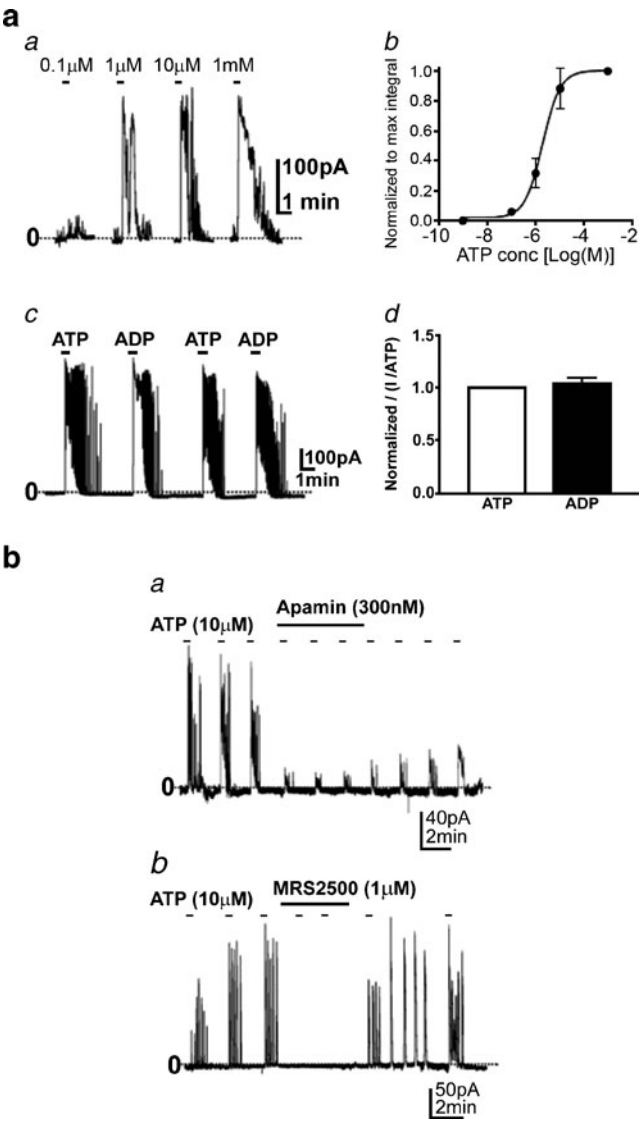
Enteric glial cells

Enteric glia, in about a 2:1 ratio with enteric neurons (depending on species) [240], display morphological and molecular similarities to astrocytes in the central nervous system (CNS) and they stain for glial fibrillary acidic protein [362, 505, 588]. They respond to ATP and UTP via P2 receptors by increasing intracellular calcium, probably via $P2Y_2$ or $P2Y_4$ receptors [393]. Later evidence showed release of Ca^{2+} from intracellular stores supporting the involvement of P2Y receptors [598]. Cultured enteric glia responded to ATP [288, 755]. Immunohistochemical studies showed expression of P2X7 receptors on enteric glial cells [679] as well as $P2Y_4$ receptors [677]. Ectonucleotide NTPDase2 is exclusively localised on the surface of enteric glial cells, suggesting that enteric glia regulate the responses to ATP and UTP [72]. Evidence was presented to suggest that enteric glia release ATP, to participate in intercellular propagation of Ca^{2+} waves between enteric glial cells and Ca^{2+} wave-induced ATP release was shown to elicit neuronal responses [755]. ATP release from enteric glia was also proposed to produce a feedback system for ICCs to modulate slow wave activity [101]. It has been suggested that ATP released from sympathetic nerves activates enteric glia [301]. Purinergic neuron–glia interactions in the enteric nervous system have been described, reflecting similar mechanisms in the CNS [300]. It was shown that stimulation of enteric neurons elicited increased $[Ca^{2+}]_i$ in enteric glial cells, mimicked by exogenously applied ATP, probably by $P2Y_4$ receptors. Parasympathetic and sympathetic varicosities in the myenteric plexus co-release ATP with ACh and NA, respectively ([8, 515]; see [98]). It was concluded from an electrophysiological study of a mouse enteric neuron–glial culture preparation that neuronal cells primarily express P2X receptors, while glial cells primarily express P2Y receptors [241].

Interstitial cells of Cajal and fibroblast-like cells

ICCs are a specialised cell type that act as pacemakers to regulate the activities of smooth muscle cells in the gut. P2X2 and P2X5 receptors were shown to be expressed on ICC's in guinea pig intestine [101] and more recently $P2Y_4$ receptors were also identified on ICCs in guinea pig gastrointestinal tract mediating modulation of intracellular Ca^{2+} oscillations [677]. This is consistent with ATP being released as a cotransmitter from enteric nerves and glial cells to regulate the activities of these cells [101]. Purinergic modulation of pacemaker $[Ca^{2+}]_i$ activity in ICC's was mediated by P2X receptors [239]. ICCs in human and murine small intestine express $P2Y_1$ and $P2Y_4$ receptors [126].

$P2Y_1$ receptors have been identified on 'fibroblast-like cells' that form a network of cells distinct from ICCs located between intestinal circular and longitudinal smooth muscle, near terminals of enteric motor neurons and with gap junction connectivity with muscle cells [414]. Apamin and MRS2500,



◀ **Fig. 3** **a** Effects of ATP on fibroblast-like cells were concentration-dependent and repeatable. *a* Brief exposures (20 s) to ATP (0.1, 1 and 10 μm and 1 mm) at a holding potential of −50 mV (approximate resting potential of murine colonic muscles) caused large outward currents, resolved at 0.1 μm and nearly maximal at 10 μm. *b* ATP concentration vs. current response in six cells. The *X*-axis is the log of ATP concentration (metre), and the *Y*-axis is the integral of ATP response current (area under the curve; AUC) normalised to the maximum response integral. Data were fitted with a Boltzmann function and EC_{50} was calculated to be 1.96 μm (Hill slope=1.19). Averaged AUC at maximal ATP concentration (1 mm) was 55.19±33.1 pA min (n=6). *c*, *d* Outward currents elicited in a platelet-derived growth factor receptor α-positive (PDGFRα$^+$) cell by alternating exposures to ATP (10 μm) and ADP (10 μm). ATP and ADP had similar effects and repetitive application yielded reproducible responses. Note responses were often spontaneous transient outward current-like and often extended past the period of exposure. *d* Averaged current responses to ATP and ADP in seven cells. There were no significant difference in maximum current elicited by either ATP or ADP (ATP=47.8±20.0 pA pF^{-1} and ADP=47.8±20.3 pA pF^{-1}; P=0.4337) or in integrated current responses (ATP=165.9±82.7 pA min and ADP=133.5±60.1 pA min; P=0.6416; n=7). **b** Blockade of ATP responses by small conductance Ca^{2+}-activated K^+ channel blocker and $P2Y_1$ antagonist. *a* Brief exposures (20 s) to ATP (10 μm) elicited reproducible large outward currents in PDGFRα$^+$ cells (average 26.0±5.8 pA pF^{-1}, n=6) that were reduced by apamin (300 nm) (7.8±6.1 pA pF^{-1}, n=6; P=0.0008). *b* MRS2500 (1 μm) blocked outward currents elicited by ATP (control ATP response 37.5±19.2 pA pF^{-1}; after MRS2500 1.0±1.0 pA pF^{-1}, n=8; P<0.0001) (reproduced from [414], with permission from The Physiological Society)

a selective $P2Y_1$ antagonist, blocked the activation of currents and increase in $[Ca^{2+}]_i$ by purine nucleotides (see Fig. 3). The majority of subserosal interstitial cells, probably fibroblast-like cells, in the guinea pig proximal colon respond to ATP via $P2Y_1$ receptors and may thereby contribute to smooth muscle relaxation [652]. Three cell types form a syncytium in mouse colon, namely smooth muscle cells, ICCs and platelet-derived growth factor receptor α-positive cells, and these cells are claimed to show differential expression of genes related to purinergic signalling [553].

Mucosal epithelium

There are a wide variety of signalling roles for purines and pyrimidines in mucosal and glandular epithelial cells in most regions of the gastrointestinal tract [69, 130, 133, 583]. ATP modulates gastric acid and intestinal secretion and both P2Y and P2X receptors are expressed by mucosal epithelial cells and gastric glands ([280, 298, 672]; see [91]). ATP and adenosine are potent stimulants of fluid and electrolyte secretion in the colon following release from both local cells and nerves (see [91, 233, 583]).

Epithelium of oesophagus

Extracellular ATP has long been recognised as a stimulant of ciliary activity in frog oesophagus and in water and mucous-transporting epithelia (see [437]). Other studies have been carried out on monolayer tissue cultures of epithelial cells grown from frog oesophagus [534, 695]. ATP enhances ciliary beat frequency two- to threefold and induces pronounced changes in the metachronal wave parameters [269]. In addition, membrane fluidisation was induced, and increases in cytosolic Ca^{2+}, principally from internal stores, coupled to membrane hyperpolarisation were necessary to activate all these cellular effects [9, 655]. Studies from this group have also established the existence of two P2 receptors, one of which is probably a P2Y receptor [270] and that the actions of ATP depends on PKC producing sustained enhancement of ciliary beat frequency via activation of calcium influx through non-voltage-operated Ca^{2+} channels [437]. HCl-induced activation of transient receptor potential vanilloid (TRPV) 1 causes ATP release from oesophageal epithelial cells [450].

Gastric acid secretion

Purinergic modulation of gastric acid secretion was first reported by Kidder [388], who showed that ATP or the ATP analogue 5′-adenylyl methylene diphosphonate added to the serosal bathing solution of the bullfrog gastric mucosa inhibited gastric acid secretion, although they were unaware at that time of purinergic receptors and did not explain their findings in these terms. Another study at this time of the effect of vagal nerve stimulation on gastric acid secretion in anaesthetised dogs led to the conclusion that, in addition to cholinergic nerves, an unsuspected second neural pathway existed which was capable of influencing gastric acid secretion [654]. Gastric hypersecretion of pylorus-ligated rats was inhibited dose-dependently by ADP and AMP [489]. ATPases are involved in the regulation of the gastric acid secretory process [227, 490, 504, 591]. NTPDase has been localised in the gastric mucosa and probably plays a role in the control of acid and pepsin secretion and mucous production, as well as contractility of the stomach [603].

There were also early suggestions that extracellular receptors to adenosine were responsible for modulation of acid secretions to the secretagogues, histamine and methacholine [261, 262, 624] using a dog gastric fundus preparation; theophylline was shown to block the adenosine actions. In a study of basal acid secretion in whole rat stomach, it was shown that, while adenosine caused a significant reduction in basal acid secretion, ATP and ADP significantly increased basal acid secretion [253]. Vagally mediated stimulation of gastric acid secretion by intravenously administered adenosine derivations was demonstrated in anaesthetised rats [561]. The authors took this to indicate that adenosine can stimulate gastric acid secretion by activating the vagus nerves via adenosine receptors in afferent pathways. The potent effects of the adenosine analogue N^6-phenylisopropyladenosine (R-PIA) on inhibitory gastric acid secretion in the rat was taken to indicate that the P1 receptor involved was of the A_1 subtype [606]. Gastric acid secretion was measured in conscious rats with an indwelling gastric cannula [284]. The potent P1 receptor antagonist 8-phenyltheophylline augmented gastric acid output, supporting a role for adenosine as a regulator of gastric acid secretion. Data was presented to suggest that endogenous adenosine generated by gastric cells interacts with parietal cell adenosine receptors to mediate acid secretion to histamine [260, 262].

Following up their earlier study of the effect of intravenous adenosine in anaesthetised rats, Puurunen and Huttunen [560] presented evidence to indicate that adenosine inhibits gastric acid secretion by a decrease in stimulation of vagal impulses to the stomach and that it acts in the brain via P1 receptors insensitive to xanthine. Another study, using unanaesthetised rats with indwelling gastric cannulas, showed a rank order for P1 receptor agonists in decreasing gastric acid output of NECA=R-PIA>2-chloroadenosine>S-PIA [699]. NECA decreased the volume of gastric secretion, whereas R-PIA had no effects on volume, but significantly increased the pH of the secretions. In an attempt to characterise the effects of adenosine, ATP and ADP on acid secretion in isolated rabbit gastric cells, it was claimed that there were stimulating receptors to adenosine that were inhibited by methylxanthines, perhaps mediated via P1 receptors, and inhibitory receptors to ATP, α,β-meATP and ADP, which were reduced by indomethacin, perhaps mediated via P2 receptors [6, 7, 279]. It was claimed that there were P1 (A_2 subtype) receptors on rabbit parietal cells which mediate the stimulatory effects of adenosine and analogues on gastric acid production [7, 530]. Data was also presented to suggest that ATP selectively inhibits histamine-stimulated gastric acid secretion by acting directly on parietal cells, perhaps mediated by P2Y receptors with some part due to prostaglandin production [281].

Adenosine has been shown to decrease or increase production of gastrin, a known stimulant of gastric secretions,

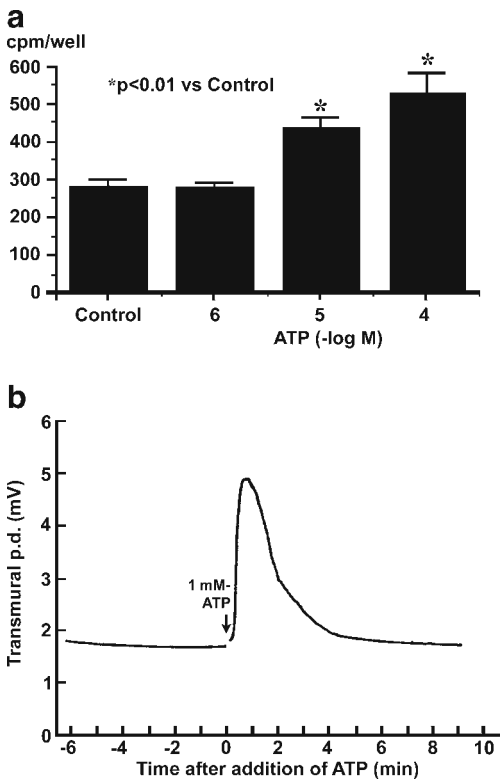


Fig. 4 **a** Dose-dependent effect of ATP on mucous secretion from rabbit gastric mucous cells in primary culture. Cells pre-labelled with [^{3}H]glucosamine were incubated with ATP for 30 min. Secreted proteins (solubilised in with NaOH and neutralised with 1 N HCl) were measured using a scintillation counter and expressed as counts per minute per well. Values are means±SEM for four determinations (reproduced from [531], with permission from Elsevier). **b** Time course of the change in potential difference across the wall of the rat jejunum following the addition of 1 mmol/l ATP to the mucosal bathing medium. Positive values for potential indicate that the serosal side is positive with respect to the mucosal side (reproduced from [400], with permission from Wiley)

perhaps via A_1 or A_2 subtypes, thereby indirectly modulating gastric acid secretion [608, 698]. It was later shown that adenosine may suppress immunoreactive gastrin release by activating A_1 receptors on G cells, leading to inhibition of gastric acid secretion [739]. Adenosine may also act via A_{2A} receptors to augment somatostatin release and consequently influence gastric acid secretion [732, 738].

It has been suggested that muscularis mucosae may augment gastric acid secretion, and in a study designed to test this hypothesis, it was shown that there are contractions of the muscularis mucosae to ATP and ADP, but it was concluded that muscularis mucosae relaxation, rather than contraction, might be allied to acid secretion [549].

Gastric mucous secretion

ATP stimulated mucous glycoprotein secretion by rabbit gastric mucous cells in primary culture (Fig. 4a) [531]. The order of potency of ATP analogues was α,β-meATP>ATP>2-MeSATP; the efficacy of ATP analogues to increase $[Ca^{2+}]_i$ was similar. A study of mucin secretion in the goblet cell line, HT29-C1.16E, suggested that both ATP and carbachol produce exocytotic release of mucin by acting on the same granular pool [51]. P1 receptor agonists had no effect. P2 receptor-mediated stimulation of mucous secretion appeared to be mediated by intracellular calcium, not by endogenous prostaglandin E_2. An autoradiographic study of sections of rabbit fundus with [^{35}S]2′-deoxy adenosine-5′-*O*-(1-thiotriphosphate), regarded as a radioligand for P2Y receptors, shows a selective distribution over the mucosa, but not muscle layer, and was paralleled by high-density binding on gastric gland plasma membranes [672].

Intestinal secretion

The first hint that extracellular ATP might be involved in electrolyte secretion in the intestine was the observation that ATP, either in the mucosal or the serosal fluid, caused a transient increase in the potential difference and short circuit current across the wall of rat small intestine or colon (Fig. 4b) [400]. Later, ATP, ADP and AMP, but not adenosine, were shown to increase cAMP-mediated stimulation of active ion transport in dispersed enterocytes prepared from the guinea pig small intestine [407], and later, ATP was shown to stimulate Ca^{2+} uptake in isolated rat intestinal epithelial cells [577].

Rabbit ileal mucosa, when mounted in a flux chamber and subjected to electrical field stimulation, secreted Cl^-, a change reflected in an increase in short circuit current, and it was suggested that the mediator was likely to be a combination of ACh and NANC neurotransmitters released from nerves lying close to the secretory epithelium [342], the major NANC transmitter involved being VIP [233]. Differential effects of apical and basolateral UTP on intestinal epithelial Cl^- secretion have been described [626]. There is a loss of regulation of Cl^- transport by ATP and UTP in the jejunum of $P2Y_4$-null mice [580]. Mechanical stimulation releases nucleotides to activate neural $P2Y_1$ and P2X1 or P2X3 receptors to trigger neural reflex Cl^- secretion in guinea pig distal colon [150]. In another study from this group, mechanically evoked reflex Cl^- secretion in rat distal colon was claimed to be triggered by endogenous nucleotides acting via $P2Y_1$, $P2Y_2$ and $P2Y_4$ receptors [142]. In a later study, using $P2Y_4$ knock-out mice, it was shown that the $P2Y_4$ receptor fully mediates the chloride-secreting response to UTP in both small and large intestines, except on the basolateral side of the jejunum, where both $P2Y_2$ and $P2Y_4$ receptors are involved [268]. Apical targeting of the $P2Y_4$ receptor is controlled by hydrophobic and basic residues in the cytoplasmic tail [193]. Further, K^+ secretion was activated via luminal $P2Y_2$ and $P2Y_4$ receptors in mouse colon [462]. Activation of $P2Y_2$ receptors on mouse duodenocytes enhances bicarbonate secretion via elevation of $[Ca^{2+}]_i$ [185].

Experiments carried out by Cuthbert and Hickman [165] confirmed the earlier reports about the effects of ATP on transepithelial ion transport but, since they found that TTX virtually abolished the effects of ATP on electrogenic chloride secretion, they suggested that the effects of ATP were indirect, via neural elements in the intramural plexus.

Under resting conditions, the mammalian distal colon has a $NaCl^-$ absorptive epithelium, the absorption occurring at surface cells in colonic crypts, and intracellular Ca^{2+} or cAMP are important second messengers that activate $NaCl^-$ secretion [60]. ATP released from the luminal side of epithelial cells in guinea pig colon by hypotonic stimulation appears to exert an

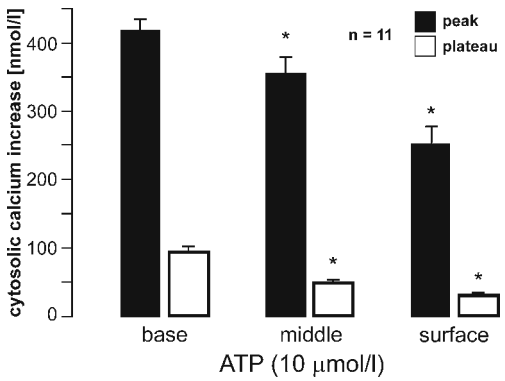


Fig. 5 ATP-induced (10 μmol/l) $[Ca^{2+}]_i$ increase in the rat isolated, intact colonic crypt was measured with the Ca^{2+}-sensitive dye fura-2 and a video imaging set-up along the axis of the crypt. The cells were classified as basal, middle and surface cells according to their location. Base refers to the very base, middle refers to 50 % of total length in the middle of the crypt and surface refers to only cells at the very surface. Both the ATP-induced $[Ca^{2+}]_i$ peak and plateau decrease along the crypt axis. *Asterisks* indicate significant differences of peak and plateau $[Ca^{2+}]_i$ increases compared between basal and middle and middle and surface cells (reproduced from [431], with permission from Springer)

inhibitory effect on electrogenic Na^+ absorption, probably via $P2Y_2$ receptors on the apical membranes [731]. $P2Y_6$ receptors mediate colonic NaCl secretion in rat colon, as evidenced by RT-PCR localisation of $P2Y_6$ receptor mRNA and activation by UDP [409]. Activation of P2Y receptors may improve the absorption of water-soluble and high molecular weight compounds from the rat ileum [397]. Distal colonic Na^+ absorption is inhibited by $P2Y_2$, but not $P2Y_4$, receptors [463]. A study of ATP actions in isolated crypts of rat distal colon, using the fura-2 technique to measure $[Ca^{2+}]_i$ (Fig. 5) [431] led to the following conclusions that basolateral ATP induces $[Ca^{2+}]_i$ in isolated crypts and acts as a secretagogue in the distal rat colon; basolateral P2Y receptors are responsible for this ATP-induced NaCl secretion; ATP action is not mediated by adenosine; and ATP-induced $[Ca^{2+}]_i$ signals are mostly located at the crypt base, which is the secretory part of the colonic crypt. The rank order of potencies for these actions was 2-MeSATP>ADP>ATP >>UTP, suggesting that a $P2Y_1$ receptor might be involved. In a later abstract, this group reported that luminal ATP induces K^+ secretion via a $P2Y_2$ receptor in rat distal colonic mucosa [385]. It is interesting that TNP-ATP, which has since been identified as a potent antagonist at P2X1 and P2X3 receptors [686], was shown to block colonic Cl^- channels [682], although there do not appear to be reports of the effects of TNP-ATP on P2Y receptors. In situ hybridisation studies have shown that the mRNA for P2X4 receptors is localised in rat intestinal crypts [653].

ATP regulation of Cl^- secretion has also been demonstrated in a human intestinal epithelial cell line, Caco-2, grown on permeable membrane supports and assayed for Cl^- secretion by measuring short circuit current [353]. The potency order on the apical side was UTP>ATP>UDP>2-MeSATP=ADP and on the basolateral side UTP=2-MeSATP=ATP>ADP >> UDP, suggesting that two different P2Y receptor subtypes are involved. UDP increases $[Ca^{2+}]_i$, leading to increase in Cl^- secretion from mouse intestinal epithelium [76], suggesting that $P2Y_6$ receptors might be involved.

The strong presence of ecto-diphosphohydrolase (apyrase) in rat small intestinal brush-border membranes has been demonstrated [611], consistent with the view that nucleotides have potent actions in mucosal epithelial cells. A study of goblet cell-like clone derived from colonic HT-29 cells led to the conclusion that ATP-stimulated increase in Cl^- current does not require an increase in $[Ca^{2+}]_i$ suggesting the involvement of either another signalling pathway or direct activation of Cl^- channels via purinergic receptors [305]. ATP-stimulated electrolyte and mucin secretion by this human intestinal goblet cell line has been reported [474]. Exogenous ATP added to the medium bathing the mucosal surface of the intestine inhibits calcium transport to reduce the unidirectional flux of Ca^{2+} from the mucosal to serosal side [715]. Inhibition of uptake of amino acids (including leucine, lysine, alanine, valine and isoleucine) from isolated intestinal epithelial cells by extracellular ATP has been demonstrated [568] as well as regulation of Na^+-dependent sugar transport [394]. ATP synthase generates extracellular ATP to regulate bicarbonate secretion in rat duodenum [694], via $P2Y_1$ receptors in guinea pig duodenum [215]. ATP-induced muscularis mucosae contraction evokes epithelial secretion in rabbit distal colon via NANC secretomotor nerve stimulation and prostaglandin synthesis [550]. ATP is released as a neurotransmitter to stimulate mucosal secretion of electrolytes and H_2O via $P2Y_1$ receptors expressed by VIPergic secretomotor nerves [213, 712]. ATP is released by mechanical deformation from enterochromaffin cells to act as an autocrine or paracrine messenger to stimulate release of 5-HT from enterochromaffin cells via $P2Y_1$ receptors or on P2X3 receptors on sensory nerve subepithelial nerve terminals [726].

Adenosine was claimed to stimulate electrolytic secretion in isolated epithelia of rabbit colon [295] and the P1 receptor antagonist, theophylline, caused an increase in short circuit current and reversed the direction of net Cl^- movement in rabbit ileum [5]. An examination of the effects of various analogues of adenosine led to the conclusion that the A_1 receptor subtype is present in rat jejunal mucosal epithelial cells [575]. Earlier studies showed that increases in short circuit current, in both small and large intestine, were preferential to ATP, with adenosine having significantly less effect [165, 400]. Adenosine has been shown to inhibit intestinal fluid secretion and a study of the relative actions of various adenosine agonists and antagonists led to the conclusion that the P1 (A_{2B}) receptor subtype is involved [312]. Neutrophil–epithelial cross-talk at the intestinal lumen surface is mediated by secretion of adenosine and interleukin (IL)-6 from inflamed epithelial cells [622]. A_{2B} receptors mediate signalling through the adenylate cyclase 6 isoform in intestinal epithelial cells and the authors suggest that this may have therapeutic implications for intestinal inflammation and diarrhoea, where the A_{2B} receptor is upregulated [402]. Luminal adenosine stimulates chloride secretion through A_1 receptors in mouse jejunum [267] and rapidly increases glucose transport [395]. Adenosine is a negative regulator of mitogen-activated protein kinase (MAPK) and pro-inflammatory signalling in human epithelial cells [364]. *Clostridium difficile* causes widespread infection by releasing toxins that break down epithelial tight junctions and compromising the intestinal epithelial barrier. CD73-mediated liberation of adenosine has been shown to protect intestinal epithelial cells from *C. difficile* toxin-induced damage [607]. Neurotensin stimulates Cl^- secretion in human colonic mucosae, involving mucosal nerves, adenosine and prostaglandins [579]. Mechanical stimulation of human enterochromaffin cells releases ATP which breaks down to adenosine to act via A_3 receptors to modulate 5-HT release [716]. In addition to roles in secretion, UDP has been shown to promote intestinal epithelial cell migration via the $P2Y_6$ receptor [503].

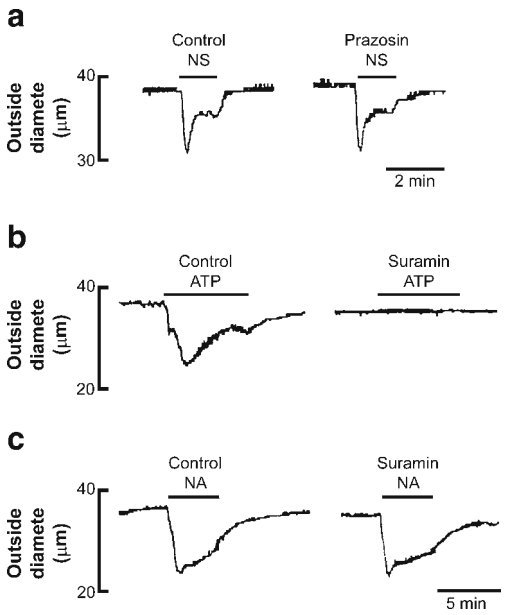


Fig. 6 Constrictions of submucosal arteries of guinea pig in response to nerve stimulation are not mediated by noradrenaline but through the activation of P2 receptors. **a** Nerve-evoked constrictions (NS, 100 pulses at 10 Hz) were unaffected by the α_1-adrenoceptor antagonist, prazosin (0.1 μmol/l). **b** Constrictions to exogenously applied ATP (3 μmol/l) were abolished by the P2 receptor antagonist, suramin (100 μmol/l). **c** Suramin (100 μmol/l) had no effect on the contraction evoked by the exogenous application of noradrenaline (*NA*, 3 μmol/l). Vessel diameter of isolated superfused submucosal arteries was measured using an on-line computer analysis of TV images with an Imaging Technology system, sampling data at 10–20Hz with a resolution of less than 1 μm (reproduced from [209], with permission from John Wiley and Sons)

Purinergic vascular control in gut

The possibility that nucleotides were responsible for the initial rapid response, particularly at low frequency stimulation of sympathetic nerves, of the perfused intestinal microcirculation of anaesthetised cats was first raised by Taylor and Parsons [656], a secondary, slower phase being mediated by adrenoceptors. The initial rapid phase was completely abolished by selective desensitisation of the ATP receptor with α,β-meATP. In a follow-up study, these authors demonstrated that functional P2X receptors were present in both arterial and venous blood vessels of the cat intestinal circulation [657].

An important paper was published in 1992 in which it was shown that the postjunctional responses (EJPs as well as constrictions) of guinea pig submucosal arterioles to sympathetic nerve stimulation were mediated solely through the activation of P2X receptors by ATP or a related purine nucleotide (Fig. 6); the function of neurally released NA was to act through prejunctional α_2-adrenoceptors to depress transmitter release [209]. The finding was confirmed and extended by another laboratory, which examined the relative potencies of a number of purinergic agonists on guinea pig submucosal arterioles and showed that the constrictions were antagonised by suramin and PPADS [251]. Surprenant and her colleagues speculated in review articles [648, 681] that sympathetic purinergic control of arterioles is involved in extrinsically mediated mucosal reflex activity, particularly during inflammatory conditions. In another paper, it was considered that ACh inhibits neurogenic constriction of guinea pig interstitial submucosal arterioles by prejunctional modulation of ATP release from the perivascular sympathetic nerves with no major role for endothelial paracrine factors [408].

It has been known for some time that ATP, when injected inter-arterially, elicited pronounced vasodilatation in the denervated cat small intestine [225]. In terms of current knowledge, this could be due to several possible mechanisms, such as action of ATP on endothelial P2Y receptors leading to release of NO, a direct action on P2Y receptors located on vascular smooth muscle or breakdown of ATP by ectoenzymes to adenosine to act on P1 receptors (see [102]). ATP applied to equine colonic arterial and venous rings induced a biphasic response, contraction followed by sustained relaxation [660]. The relaxant response was reduced, but not eliminated in endothelium-free preparations, suggesting that a mechanism other than NO was involved.

Adenosine acting through P1 receptors can increase blood flow in interstitial vessels in two ways: by direct action on A_2-like receptors on vascular smooth muscle to produce vasodilatation; and by indirect action on A_1 prejunctional receptors on sympathetic vasoconstrictor nerves to inhibit release of the cotransmitters NA and ATP [293, 547, 559, 604]. A_1 and to a lesser extent A_{2A} and A_{2B} receptors contribute to adenosine-mediated vasodilatation of vessels in the rat jejunum [438].

Sensory nerves mediate protective vasodilatation in rat gastric mucosa [330], and there was an earlier report that ATP causes an increase in gastric blood flow [734]. This is of interest since ATP is a cotransmitter in sensory motor nerves and, upon release, acts on P2Y receptors present in the vascular smooth muscle [104].

Mesenteric arteries supplying the gastrointestinal tract of rat, guinea pig, rabbit and dog have been shown to be innervated by sympathetic nerves in which ATP is a major cotransmitter with NA [78, 79, 187, 357, 411, 453, 493, 528, 623, 689]. For the sympathetic nerves in the jejunal branches of the rabbit mesenteric artery, like those supplying submucosal arterioles, ATP appears to be the sole transmitter, while NA acts prejunctionally [564]. In a later paper [208], it was concluded that, while contraction of the rabbit jejunal artery to short trains of stimuli is predominantly purinergic, a noradrenergic component can be revealed at higher frequencies of stimulation or during longer trains of stimuli.

Pathophysiology

A limited number of studies have been conducted to date on changes in purinergic signalling in the diseased gut. ATP and

adenosine have been implicated in the development of gastric ulcers, Hirschsprung's and Chagas diseases, ischaemia and colonic tumours [91]. Extracellular nucleotides and their receptors have been implicated in the pathogenesis of inflammatory bowel disease (IBD) [634]. P2Y receptors on smooth muscle and ATP production in myenteric neurons increase in postoperative ileus, probably contributing to delayed colonic transit [691]. Several reviews have highlighted the potential of purinergic drugs for the treatment of functional bowel disorders [99, 249, 327, 398]. Malnutrition affects millions of people. In an undernourished rat model, the density of P2X2 and P2X7-immunoreactive neurons in the enteric plexuses was increased, and these changes were reversible in re-fed rats [282]. The P2X2 and P2X7 receptors were expressed on NOS-positive inhibitory neurons, intrinsic sensory neurons and cholinergic secretomotor neurons. There are reviews of the purinergic literature about gut disorders [13, 17, 91, 96, 99, 103, 299, 327].

Inflammatory bowel disease

Acid sensing is of critical importance for the survival of the epithelial cells throughout the gastrointestinal tract, and its importance for mucosal defence, lipid uptake and cystic fibrosis has been discussed [379]. Nearly all the acid sensors occur on intrinsic sensory neurons and P2X3 receptors are upregulated in inflammation and hypersensitivity [719]. This has been taken to suggest that the aberrant function of molecular acid sensors may contribute to abnormal hyperalgesia and pain [329]. Intestinal inflammation increases the expression of $P2Y_6$ receptors on epithelial cells and the release by UDP of CXCL8 (a chemokine known for its chemoattraction ability to recruit neutrophils during the acute phase of colitis) [296, 297]. Intraduodenal administration of ATP concomitantly with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) attenuated the NSAID-induced increase in intestinal permeability in healthy humans, and it was suggested that ATP may also be beneficial in the treatment of intestinal disorders where intestinal permeability changes were involved [71]. $P2Y_2$ receptor expression is upregulated in intestinal epithelial cells by the transcription factor C/EBPβ during inflammation [174].

Nucleotides and their receptors have been explored in the pathogenesis of IBD. P2X3 receptor expression was increased in enteric plexuses of human IBD, suggesting a role in dysmotility and pain [737]. The possibility that P2X receptor antagonists could be used for the treatment of IBS was raised [249]. P2X receptors on intrinsic enteric neurons may elicit enhanced gastrointestinal propulsion and secretion, and it has been suggested that they might be used for treating constipation-predominant IBS, while P2X antagonists might be useful for treating diarrhoea-predominant IBS. Peripheral sensitisation of P2X3 receptors on vagal and spinal afferents in the stomach may contribute to the development of visceral hyperalgesia [168]. During chronic interstitial inflammation induced by infection of mice with the parasite *Schistosoma mansoni*, purinergic modulation of cholinergic nerve-mediated effects was impaired [172]. In inflamed gastrointestinal tract, glial cells proliferate and produce cytokines, suggesting that P2X7 receptors may play a role in the response of enteric glia to inflammation [679].

In trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice, the purinergic component of sympathetic cotransmission to colonic submucosal arterioles was reduced, perhaps due to increased degradation of extracellular ATP and P2X1 receptor expression was increased [447]. Propulsive motility is attenuated in the ulcerated region of the TNBS-inflamed colon, and this is associated with a decrease in the purinergic component of the descending inhibitory limb of the peristaltic reflex circuit [645]. P2X3 receptor mRNA expression in dorsal root ganglia (DRG) was significantly decreased in the ovariectomised rat model of colitis, an effect that was reversed by oestrogen [212]. It has been suggested that ATP is a critical autocrine regulator of mechanosensitive 5-HT release, which is involved in the pathogenesis of IBD and that P2X3 receptors on enterochromaffin cells are downregulated in ulcerative colitis [442]. CD39 (NPTDase1) was upregulated in the submucosa during colitis that contributed to impaired sympathetic regulation of gastrointestinal blood flow, compromising epithelial barrier function [506]. Increase in sympathetic innervation of the mesenteric arteries supplying the colon was reported in inflamed human bowel [61]. Dysregulation occurs in 59 % of purinoceptor genes in IBD, including $P2Y_6$, $P2Y_{13}$, $P2Y_{14}$, P2X5, A_{2A} and A_{2B} receptors [589].

P2X7 receptors play a pivotal role in intestinal inflammation and are involved in the development of visceral hypersensitivity [381]. P2X7 receptors on epithelial and immune cells are implicated in the pathogenesis of diseases based on the dysregulation of immune responses in inflammatory bowel disease [170]. Activation of neuronal P2X7 receptor/pannexin 1 mediates death of enteric neurons during colitis [302]. This supported an earlier study of TNBS-induced colitis, using high-density oligonucleotide microassay analysis, and oral N^6-(3-iodobenzyl)-5′-*N*-methylcarboxamidoadenosine blocked the colitis-induced upregulation of P2X1, P2X4, P2X7, $P2Y_2$ and $P2Y_6$ receptors [309]. Extracellular ATP evokes cell death in human intestinal epithelial cells, largely via P2X7 receptors, and the implications of this in inflammatory conditions and immune responses were considered [635]. It has also been reported that ATP mediates mast cell-dependent intestinal inflammation via P2X7 receptors [415]. An adenosine A_3 agonist has been claimed to be protective in two murine models of colitis [452].

Tumour necrosis factor-α upregulates A_{2B} receptor expression and signalling in intestinal epithelium in colitis [401]. Blockade of A_{2B} receptors ameliorates mouse colitis [403] as does A_{2B} gene deletion [404]. The inhibitory effects of

adenosine on enteric neuromuscular activities are reduced in inflamed colon [12]. It has been reported that oxidative stress disrupts purinergic neuromuscular transmission in the inflamed colon [581]. It was claimed that this can be prevented by treatment with a free radical scavenger, resulting in improved motility. It has been suggested that A_{2B} receptors play a role in the control of T cell-mediated colitis by suppressing the expression of pro-inflammatory cytokines, while sparing anti-inflammatory activity mediated by IL-10 and transforming growth factor-β [498]. A_{2A} receptors also mediate the inhibitory effects of adenosine on colonic motility in the TNBS model of experimental colitis [13, 563]. Inhibition of adenosine deaminase attenuates inflammation in experimental colitis [14]. Adenosine, acting via A_3 receptors, has been implicated in intestinal anti-inflammation activities [265, 309]. A_{2A} receptors have also been implicated in the anti-inflammatory actions of adenosine [519], and A_{2A} receptor agonists have been developed for the treatment of inflammatory bowel disease [201]. A_{2B} receptors mediate regulation of 5-HT synthesis and release from hypoxic enterochromaffin cells in IBD [167]. A_{2B} receptor antagonists appear to be effective against murine colitis [405]. The involvement of adenosine A_1 and A_{2A} receptors [16] and A_3 receptors [573] in colitis has been described. Reviews of the roles of adenosine signalling in gastrointestinal inflammation are available [146, 207]. Blockade of adenosine deaminase reduces chronic experimental colitis through the recruitment of A_{2A} and A_3 receptors [15]. There has been an investigation of adenosine deaminase in patients with Crohn's disease [458]. The inhibition of adenosine kinase by GP515 has been explored as a potential target for the treatment of colitis [621]. In a review about purinergic receptors in gastrointestinal inflammation [403], it was concluded that P1 (A_{2A} and A_{2B}) and P2Y receptor-based therapy is highly promising for the treatment of inflammatory conditions of the gut, as well as for fibrotic liver diseases (see [477]). Serum adenosine deaminase activity has been claimed to be a predictor of disease severity in ulcerative colitis [55]. It has been reported that ENTPase 7 is preferentially expressed in epithelial cells of mouse small intestine [417]. ATP released from colonic mucosal epithelial cells of IBS patients excites enteric cholinergic motor neurons via P2X receptors [29]. The role of adenosine as an immune modulator of IBD has been reviewed [736]. Genetic polymorphisms of CD39 have been linked to Crohn's disease [413]. A large migration of neutrophils into the intestinal mucosa is a feature of IBD. It has been shown that release of ATP by activated neutrophils and necrotic intestinal epithelial cells stimulates epithelial cell P2X7 receptors leading to activation of caspase 1 and secretion of pro-inflammatory cytokines, such as IL-1β [123]. P2X7 receptor expression was shown to be weak in intestinal biopsies obtained during the active phase of IBD.

Chagas disease

Chagas disease is caused by the protozoan parasite, *Trypanosoma cruzi*. Transmission to humans occurs through blood-sucking reduviid bugs, but it may also occur through blood infusion or organ transplant. Little is known about the neurotransmitters most affected in Chagas disease, but there are hints that purinergic signalling might be impaired and there is evidence for a preferential destruction of intrinsic inhibitory neurons [166]. Both low affinity Mg^{2+}-activated ATPase and high affinity (Ca^{2+}-Mg^{2+}) ATPase [122, 228] as well as adenosine kinase [389] are present in *T. cruzi*, which rapidly break down extracellular nucleotides. E-NTPDase (CD39) and ecto-adenosine deaminase activity are decreased in lymphocytes of patients with the indeterminate form of Chagas disease [637]. Regulation of these extracellular nucleotides through ectonucleotidase activities on the platelets of patients with the indeterminate form of Chagas disease represents control of purine-mediated thrombogenic function in the cardiovascular system [636]. Enhancement of P2X7 receptor-associated cell permeabilisation occurs during the acute phase of Chagas disease [155]. Purinergic signalling through other P2X receptor subtypes and P2Y receptors may also be impaired, perhaps because the parasite protozoan that causes the disease contains high levels of ATPases. Thymus atrophy induced by *T. cruzi* infection may involve ATP-induced cell death via P2X7 receptors [456]. However, experiments using P2X7 knockout mice suggested that P2X4 and P2Y receptors may also be involved [119].

Hirschsprung's disease

Hirschsprung's disease is a congenital abnormality of the enteric nervous system and is characterised by the absence of ganglion cells in the submucosal and myenteric plexuses of the hind gut and by chronic constriction of the aganglionic region. There is hyperinnervation of the Hirschsprung's human gut by extrinsic sympathetic nerves and preganglionic parasympathetic nerves (see [254, 350]). Enteric nerves arising from intrinsic neurons containing various neurotransmitters including ATP show substantial reductions in density in aganglionic segments [421, 422, 582]. IJPs were not recorded in aganglionic segments of human colon [230, 525], and ATP caused contraction of the muscle [749]. IJPs were also not evoked in aganglionic segments of piebald-lethal mouse colon [116, 525, 578]. In the aganglionic intestine, there was only weak P2X3 receptor immunostaining in the myenteric and submucous plexuses compared to normal intestine [210]. The absence of expression of $P2Y_1$ and $P2Y_2$ receptors in the aganglionic intestine in Hirschsprung's disease has been

described [518], which suggests that purinergic inhibitory neurotransmission is absent and may account for the contracted state of the aganglionic gut in Hirschsprung's disease.

Motility disorders

Bile evokes ATP depletion and contributes to the early mucosal permeability alteration and barrier lesions that occur during experimental oesophageal reflux [649]. It has been suggested that purinergic signalling might be involved in achalasia or symptomatic diffuse oesophageal spasm [182, 222]. ATP production in myenteric neurons and P2Y receptor expression on smooth muscle in postoperative ileus increase, contributing to delayed colonic transit [691]. Agonists acting on P2X receptors on intrinsic enteric neurons may enhance gastrointestinal propulsion and might be useful for treating constipation, while P2X antagonists might be useful for treating diarrhoea. P2Y receptor stimulation has been proposed to be beneficial for the treatment of constipation [249]. Increased apoptotic cell death in enteric neurons and ICCs from the colon of patients with slow transit constipation has been reported [275], probably as the result of activation of P2X7 receptors. Prejunctional $P2Y_1$ receptors modulate the activity of excitatory enteric motoneurons and might be therapeutic targets for patients with functional disorders affecting colonic motility [21]. Disturbed motility occurs with intestinal anaphylaxis. Allergic diarrhoea, in a model of food allergy, was accompanied by chronic inflammation and mast cell hyperplasia in the colon [434], and it was suggested that sustained alteration in purinergic neurotransmission contributed to the disturbed motility characterised by this condition. Herpes simplex virus type-1 infects the enteric nervous system and affects gut motor function; contractions mediated by adenosine acting via A_1 or A_{2A} receptors on smooth muscle and A_{2A} and A_3 receptors in the myenteric plexus were impaired in virus-infected rats [764].

Gastric ulcers

Helicobacter pylori infection and gastric hyperacidity results in the development of gastric ulceration [287, 465]. ATP was shown to be involved in the development of gastric hypersecretion and ulceration in pylorus-ligated rats [489]. It was shown that in pylorus-ligated rats, gastric acid secretion was an ATP-dependent process and that adenosine acting via P1 receptors inhibited the development of ulceration. Methylxanthines, which blocked the action of adenosine, stimulated the acid content of gastric secretions [365] and promoted gastric ulceration [204, 319]. Dipyridamole, which leads to an increase in extracellular adenosine, significantly reduced the extent of gastric bleeding and ulcer formation [538]. Intracerebral or subcutaneous administration of adenosine increased stress-induced gastric lesions [670]. However, in contrast, it was reported that adenosine receptor activation in the brain reduced stress-induced ulcer formation [259, 697].

Diabetes

Relaxations in response to NANC nerve stimulation were reduced in longitudinal strips of gastric fundus from 8-week streptozotocin-induced diabetic rats [360], but NANC contractions were enhanced [361]. IJPs of reduced amplitude were observed in gastric smooth muscle from streptozotocin-induced diabetic rats [727]. The rate of hyperpolarisation of single IJPs was slower in the circular muscle of the caecum of streptozotocin diabetic (8-week) rats [338]. Maximum relaxant responses and sensitivity of the colon to ATP were unchanged in 8-week streptozotocin diabetic rats, but the responses to adenosine were reduced [307]. Diabetic enteric neuropathy was associated with apoptosis in the myenteric plexus of the rat colon [304].

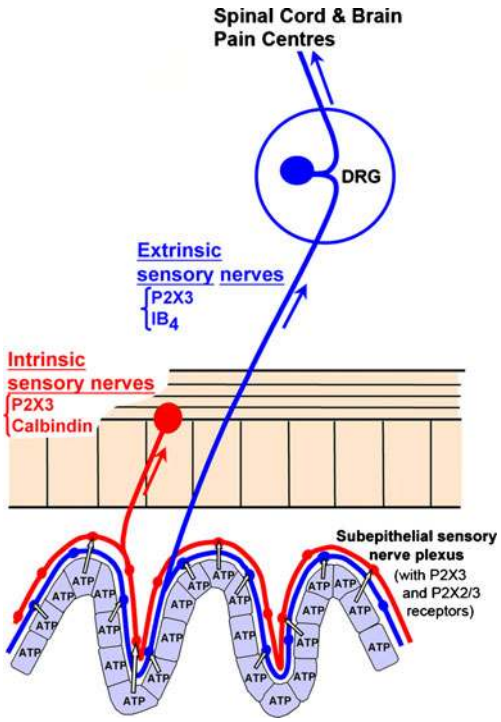


Fig. 7 Schematic of a novel hypothesis about purinergic mechanosensory transduction in the gut. It is proposed that ATP released from mucosal epithelial cells during moderate distension acts preferentially on P2X3 and/or P2X2/3 receptors on low-threshold subepithelial intrinsic sensory nerve fibres (labelled with calbindin) to modulate enteric reflexes. ATP released during extreme (colic) distension also acts on P2X3 and/or P2X2/3 receptors on high-threshold extrinsic sensory nerve fibres (labelled with isolectin B4 (IB_4)) that send messages via the dorsal root ganglia (DRG) to pain centres in the central nervous system (reproduced from [94], with permission from Wiley-Liss, Inc.)

Nociception

Submucosal intrinsic sensory neurons and extrinsic sensory nerves both show positive immunoreactivity for P2X3 receptors [722]. It has been proposed that during excessive intestinal distension, high-threshold extrinsic enteric sensory fibres are activated via P2X3 and P2X2/3 receptors by ATP released from mucosal epithelial cells, leading to initiation of nociceptive impulses that pass messages through the DRG to pain centres in the CNS [93]. This hypothesis was supported by experiments on a rat pelvic sensory nerve–colorectal preparation ([718]; Fig. 7). Colorectum distension led to pressure-dependent increase in the release of ATP from mucosal epithelial cells and evoked pelvic sensory nerve excitation. This excitation was mimicked by application of ATP and attenuated by the selective P2X3 and P2X2/3 antagonist, TNP-ATP, and by PPADS. The sensory activity in the nerves was potentiated by ARL-67156, an ATPase inhibitor. It has been claimed recently that subepithelial fibroblasts in rat ductal villi also release ATP by mechanical stimuli, which has actions on $P2Y_1$ receptors expressed by the fibroblasts, as well as activating P2X3 receptors on subepithelial sensory neurons [238]. ATP release and P2X3 and P2X2/3 receptor-mediated nociceptive sensory nerve responses were enhanced in the rat TNBS model of colitis [719]. Different mechanosensory information from the colon to the spinal cord is conveyed by lumbar splanchnic (LSN) and sacral pelvic (PN) nerves. Forty percent of LSN afferents responded to α,β-meATP compared to 7 % of PN afferents [73]. Enhancement of P2X3 receptor-mediated signalling in an animal model of colonic inflammation has been reported. This was due, at least in part, by the appearance of P2X3 receptor expression in a greater number of calcitonin gene-related peptide-labelled small nociceptive neurons in the DRG [719]. Purinergic mechanosensory transduction has also been shown to contribute to post-infectious mechano-hypersensitivity [585]. P2X3 receptor expression was increased in human IBD enteric plexuses suggesting a potential role in dysmotility and pain [737]. Substances are released from various sources under these conditions that often act synergistically to cause sensitisation of afferent nerves to mechanical or chemical stimuli. Receptors to a variety of substances (including ATP released during gut distension) represent potential targets for drug treatment for abnormal bowel function and visceral pain (see [327, 398]). The sensitising effects of P2X3 receptor agonists on mechanosensory function were demonstrated in oesophagitis [536]. Visceral hyperalgesia is associated with an increase in ATP activity and enhanced expression of P2X3 receptors in colonic sensory neurons [725]. Selective P2X3 and P2X2/3 receptor antagonists that are orally bioavailable and do not degrade in vivo are in clinical trials for the treatment of pain (see [186, 266]).

Ischaemia

Purinergic signalling has been identified in the development of intestinal ischaemia–reperfusion injury. For example, adenosine acts via both A_{2A} and A_{2B} receptors, and A_{2A} receptors provide potential protection and is a novel therapeutic target for intestinal ischaemia–reperfusion injury [180, 203, 314]. ATP attenuated intestinal dysfunction produced by ischaemia, but not that caused by reperfusion in rabbits [650]. In ischaemia–reperfusion of the intestine, there was a decrease in P2X2 receptor expression in the myenteric and submucosal plexus [545].

Injury

$P2Y_1$ receptor signalling has been shown to mediate wound-induced cyclooxygenase (COX)-2 expression through both p38 MAPK and PKC pathways in intestinal subepithelial myofibroblasts [359]. It was suggested that this might indicate a novel treatment for intestinal barrier dysfunction during inflammation.

Cancer

Colorectal cancer is a major disease. $[Ca^{2+}]_i$ was increased in the HT-29 human colonic adenoma cell line by ATP and ADP [325]. HT-29 cells were depolarised by UTP>ATP>ADP> adenosine [446]. Cultured human colonic tumour cells (LoVo) were resistant to ATP cytotoxicity, but verapamil increased sensitivity to ATP [152]. P2U (i.e. $P2Y_2$ and/or $P2Y_4$) receptors are expressed by HT-29 cells [160, 516, 542].

ATP transiently increased Cl^- conductance in the highly differentiated sub-clone of the HT-29 colonic cancer cell line, HT-29-C116E [305, 306]. ATP activation of Cl^- conductance was also reported in the T84 human colonic adenocarcinoma cell line [179]. A decrease of intracellular Cl^- and Na^+ and an increase in Ca^{2+} in HT-29 cells response to both ATP and UTP via P2U ($P2Y_2$ and/or $P2Y_4$) receptors was shown [754]. P2U receptor mRNA in both primary cultures of human colorectal carcinoma cells and HT-29 cells was reported, where they play a role in the regulation of cell proliferation and apoptosis [331]. Resistance to ursolic acid-induced apoptosis in HT-29 cells was mediated by $P2Y_2$ receptors [441]. ATP induced apoptosis and inhibited growth of primary cultures of colorectal carcinomas [331], probably via $P2Y_2$ receptors [332]. $P2Y_2$, $P2Y_4$ and $P2Y_6$ receptor mRNAs were located on the apical membranes of human colonic Caco-2 adenocarcinoma cells [114, 464]. The hypotonicity-induced release of ATP from basolateral, but not apical, membranes of Caco-2 cells was facilitated by caveolin-1 [668]. $P2Y_2$ and $P2Y_4$ receptors were upregulated in human colon cancer [517]. Gβγ-Subunits mediate regulation of increase in $[Ca^{2+}]_i$ during $P2Y_2$ receptor activation [340]. $P2Y_2$ receptors have

oncogenic potential mediating transformation of colorectal RKO cancer cells [315]. Proliferation of Caco-2 cells is evoked by ATP acting via P2Y receptors [115]. Tissue from patients with colorectal cancers showed increased expression of an ATP-binding cassette super-family transporter, multi-drug resistance protein-2 [323]. CD39 (NTPDase1) modulated colorectal tumour growth and liver metastasis and the expression of both $P2Y_2$ and P2X7 receptors [413]. The activities of CD73 and adenosine deaminase were higher in primary human colorectal tumours [205] and in human colorectal adenocarcinomas [658]. Gene expression of adenosine kinase is significantly increased in human colorectal cancer [276]. There is heterogeneity of chemosensitivity of colorectal adenocarcinoma, and this may be used to identify patients who would benefit from specific chemotherapeutic agents alone or in combination [128, 343, 701]. Surgeons often wash the abdominal cavity with distilled water to lyse colorectal cancer cells remaining after surgery, and it has been shown that water induces release of ATP from epithelial cells, which then causes cell death of tumour cells via P2X7 receptors [613].

Adenosine facilitates tumour survival [443, 641]. Proliferation in poorly differentiated HT-29 cells is promoted by adenosine via A_1 receptors and there is inhibition of tumour growth by adenosine deaminase or A_1 receptor antagonists [432]. However, adenosine had less effect on more differentiated cells [433]. It has been claimed that adenosine suppresses growth of CW2 human colonic cancer cells by inducing apoptosis via A_1 receptors [594]. A_{2B} receptor expression is enhanced in proliferating colorectal cancer cells and A_{2B} receptor antagonists are being explored for the treatment of colorectal cancer therapy [449]. There is significant inhibition of the growth of xenografted subcutaneous human colon adenocarcinoma cell line, HCT116, in nude mice by a single low-level intravenous dose of [^{32}P]ATP [127]. Growth of colorectal cancer cell lines HCT116 and 80514 were inhibited in vitro and in vivo by 8-chloro-adenosine [117]. Primary colon carcinoma growth was inhibited by A_3 receptor agonists [223, 520], although a later paper claimed that A_3 receptors mediated proliferation of Caco-2, DLD1 and HT-29 colorectal tumour cell lines [264]. The A_3 receptor agonist CF101 stabilised the tumour in 35 % of the patients with refractory metastatic colorectal cancer in a phase II, multi-centre study [642]. Adenosine has been claimed to induce apoptosis in Caco-2 colonic cancer cell [735]. Adenosine upregulates CXCR4, which is a chemokine receptor that plays a crucial role in determining the ability of cancer cells to metastasize from the primary tumour. CXCR4 enhances the proliferative and migratory responses of HT-29 cells [576]. Adenosine can stimulate migration of colon cancer cells and caffeine significantly inhibits this action [473].

ATP produces hyperpolarisation of the human gastric signet ring cell carcinoma cell line (JR-1), probably mediated by P2Y receptors [311]. Proliferation was reduced and apoptosis induced in the human gastric carcinoma cell line (HGC-27) by ATP and adenosine [593, 692]. The benefits of chemotherapeutic drugs in patients with gastric cancer have been examined using an ATP-based chemotherapy response assay [426, 540]. Infection of the gastric body by *Heliobacter pylori* contributes to the progression of gastric carcinoma [592]. Gastric cancer cells show a loss of A_3 receptors [151]. Kyse-140, a human oesophageal squamous carcinoma cell line, and cancer cell primary cultures both expressed $P2Y_2$ receptors, which mediated inhibition of growth [451]. Using the ATP-tumour chemosensitivity assay, heterogeneity of chemosensitivity in oesophageal cancer has been reported [444]. Neuroendocrine tumours are a heterogeneous group of neoplasms originating from enteric chromaffin cells and these tumours express A_{2A} and A_{2B} receptors, the activation of which leads to increased proliferation [372], a potential target for therapy [373]. Gastrointestinal stromal tumours that originate from pacemaker cells of the gastrointestinal tract release ATP, which may be important for tumour homeostasis and immune surveillance escape [50].

Salivary glands

Salivary acinar and ductal epithelial cells are responsible for the controlled secretion of fluid and electrolytes and of specific proteins and growth factors [148]. There are several Ca^{2+}-mobilising receptors involved in these activities, including muscarinic receptors, α-adrenoceptors and SP receptors, but it is now well recognised that there are also Ca^{2+}-mobilising receptors for extracellular ATP in rat and mouse parotid acini [232, 242, 470, 631] and in rat, mouse and human submandibular acinar and duct cells [273, 347, 416, 665, 666, 740]. Stimulation of the NANC component of parasympathetic nerves produced increased production of saliva from parotid, submandibular glands [199]. Potassium-evoked release of purines from rat submaxillary gland has been demonstrated, although it was not possible in the experiments described to discriminate between neuronal and non-neuronal elements as the source of purines released by depolarisation [220]. Zinc ions are present in high concentrations in acinar secretory vesicles. They are co-released during salivation and play a physiological role in salivary secretions. The zinc sensing receptor enhances secretion of ATP from ductal cells [614]. Intra-arterial administration of various nucleotides, including ATP and ADP, to the cat submandibular salivary gland led to an increase in blood flow, possibly mimicking neurally released ATP as a cotransmitter in parasympathetic and/or sympathetic nerves [368]. NTPDase3 was co-expressed with NTPDase2 and 5′-nucleotidase in subpopulations of epithelial cells in the salivary glands of mice and guinea pigs [423]. Reviews of the distribution and function of

P2 nucleotide receptors in salivary glands are available [513, 667].

Parotid gland

In a seminal paper, Gallacher [242] showed that in acinar cells of the parotid gland, ATP evoked a marked increase in membrane conductance, K^+ efflux and amylase secretion; a P2 receptor was implicated, since adenosine had no effect and the responses could be blocked by quinidine, but not by theophylline. Extracellular ATP was later shown to elevate intracellular free calcium in rat parotid acinar cells and the possibility that ATP plays a neurotransmitter role in the parotid gland raised [470]. In fact, ATP was found to be more effective than muscarinic and α-adrenergic agonists and SP as a stimulus for elevating $[Ca^{2+}]_i$ levels [471]. ATP induces oscillatory changes in $[Ca^{2+}]_i$ in HSY cells, a salivary ductal cell line from human parotid [663]. Purinoceptors mediate spontaneous Ca^{2+} oscillations and associated cell swelling in rat parotid ductal cells and regulation of electrolyte reabsorption from the primary saliva in the resting state [619]. Coomassie brilliant blue G was a more potent antagonist of P2 receptor-mediated responses of rat parotid acinar cells than Reactive blue 2 (Cibacron blue 3GA) [630]. Further studies by this group led them to suggest that ATP may function as a neurotransmitter to modulate salivary fluid secretion by stimulating Ca^{2+}-sensitive Cl^- and K^+ channels and multiple Na^+ uptake pathways in the rat parotid acinar cell [631]. They showed that some of these pathways were similar to those activated by carbachol while others were unique to ATP. Extracellular ATP increases the conductance to both Na^+ and Cl^- in parotid acinar cells through independent mechanisms [19]. A later paper showed that P2X7 receptors were essential from anion activation and that Na^+ regulates anion conductivity and permeation through this receptor [574]. It was suggested that the source of the ATP could be as a cotransmitter from nerves or directly from acinar vesicles or secretory granules into the lumen following muscarinic stimulation [513].

Two distinct $[Ca^{2+}]_i$ responses to ATP were distinguished in rat parotid acinar cells raising the possibility that both P2X7 and P2Y receptors were implicated [469, 632]. To learn more about the ATP-binding site of the P2X7 receptor in these acinar cells, the isothiocyanate compound, 4,4′-diisothiocyanato-stilbene-2,2′-disulfonic acid, was examined and found to be an effective antagonist at the parotid P2X7 receptor [633]. A study by another group showed an inhibitory effect of ATP^{4-} on the ACh-mediated response of rat parotid acini and presented evidence to suggest that this was due to interactions of the activated P2X7 receptor with the PLC-coupled processes underlying the muscarinic cholinergic response [369]. 2′(3′)-*O*-(4-benzoylbenzoyl) adenosine 5′-triphosphate (BzATP), acting via P2X7 receptors on rat parotid acinar cells, leads to the formation of large pores [274]. ATP, acting through P2X7 receptors, causes Na^+ entry by opening cation-permeable channels, and thereafter, the increase in $[Na^+]_i$ triggers Ca^{2+} release from intracellular ryanodine-sensitive stores, while UTP acting through P2U (= $P2Y_2$ and/or $P2Y_4$)-type receptors caused Ca^{2+} release independent of external Na^+ [232]. In a somewhat conflicting paper, activation of P2X7 receptors on rat parotid acinar cells was claimed to cause a large entry of Ca^{2+} into the cells [662]. In an abstract, a P2X7 receptor was identified in rat parotid salivary glands which was modulated by Mn^{2+} and Ni^{2+}, but not by Cd^{2+} [18]. Activation of P2X7 receptors by ATP in mouse parotid acinar cells occurs in two steps: slow assembly (which requires an intact cytoskeleton) and rapid gating (which does not) [439]. Duct cell P2X7 receptors are pre-assembled and therefore continuously subject to rapid gating by ATP. A study of P2X7 receptor knockout mice led to the conclusion that cholinergic stimulation leads to the release of ATP that can, via P2X7 receptors, upregulate parotid salivary secretion [514].

The results of a study using RT-PCR showed strong expression of P2X4 and P2X7 receptor mRNA in parotid glands, which correlated well with the responses of the parotid acinar cells to extracellular ATP [659]. It was further shown that parasympathetic denervation of the parotid gland increased the number of cells with P2X4 responses and the levels of P2X4 mRNA, opening up important general issues about trans-synaptic regulation of P2X receptor expression. Another study describes how ATP, acting through P2X7 receptor-mediated PLD, may produce a Ca^{2+}-independent PKC to account for the finding that ATP shortened the duration and decreased the magnitude of ACh-induced Ca^{2+} release from rat parotid acinar cells [231]. Functional interactions between P2X4 and P2X7 receptors in mouse parotid acinar cells have been described [118, 556]. Ectonucleotidase and 5′-nucleotidase levels in parotid acini have been reported [188]. A recent study claims that P2X4 receptors are largely localised on the basal and basolateral surfaces of mouse parotid acinar cells, activated by ATP released as a cotransmitter from autonomic unmyelinated nerve fibre varicosities that surround acini, while P2X7 receptors are located largely on the apical surface of acini cells, activated by autocrine/paracrine ATP release from acinar cells ([56]; Fig. 8).

Using a rat parotid secretory granule preparation, ATP was shown to activate Ca^{2+}-independent membrane-associated PLA_2 [484]. ATPγS was active to a lesser extent, while UTP, cytosine triphosphate and cytosine 5′-*O*-(thiotriphosphate) showed little activation. It was suggested that the PLA_2 located in the granular membranes may participate in the liberation of arachidonic acid in parietal cells that is regulated through a mechanism mediated by ATP. Nucleotides are important modulators of Ca^{2+} release from parotid salivary glands under physiological conditions and a decrease in ATP levels may impact Ca^{2+} signalling in pathological situations [539].

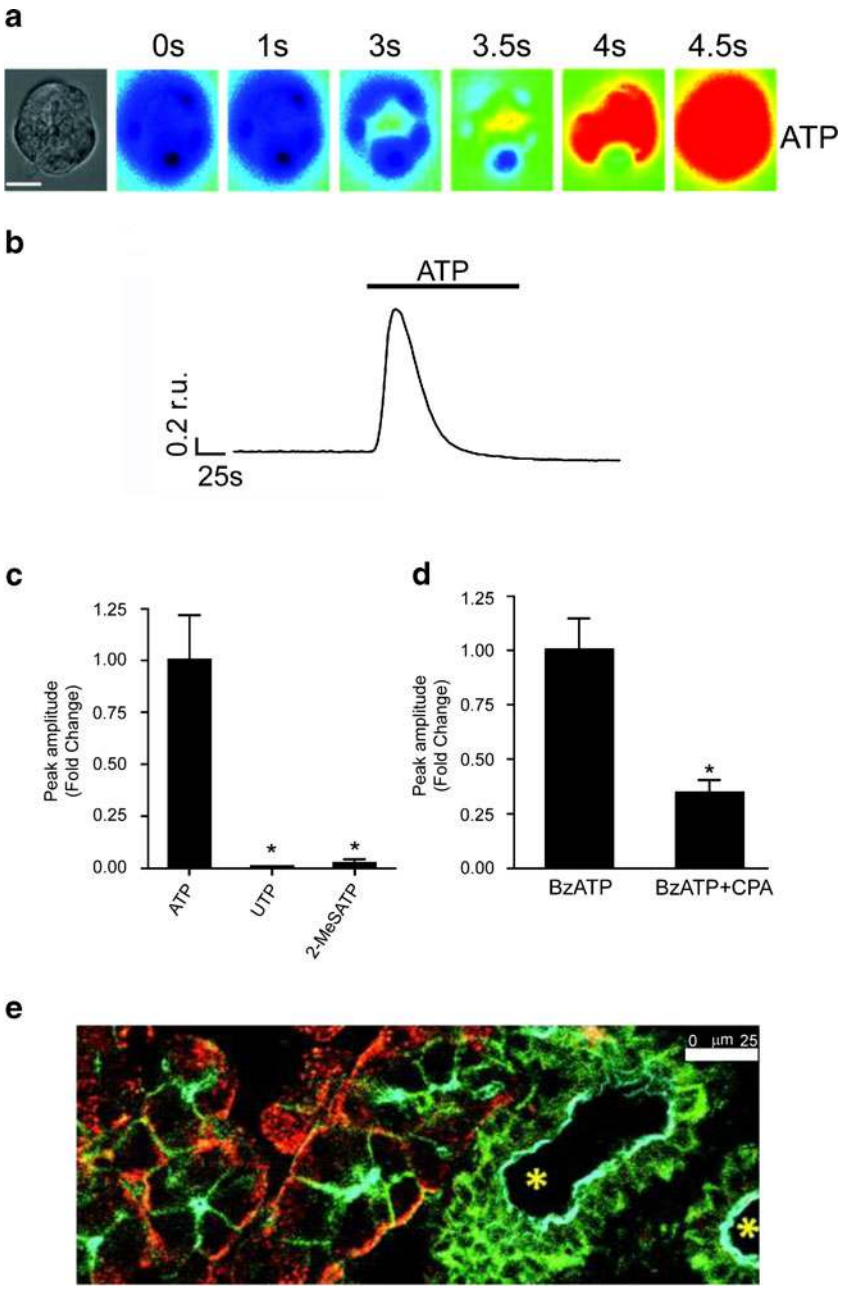


Fig. 8 **a**–**d** P2X receptor $[Ca^{2+}]_i$-evoked changes exhibit similar kinetics in mouse parotid acinar cells. **a** Acinar cells were loaded with fura-2 AM and ratio images were obtained at 2 Hz. The ratio images depict $[Ca^{2+}]_i$ rise following a sequential application of ATP (1 mm) stimulation in the same acinar cell cluster. *Scale bar* for the acinar unit, 17 μm. **b** Representative line trace depicting $[Ca^{2+}]_i$ responses in parotid acinar clumps evoked by ATP (1 mm). *Scale bar* indicates fluorescence ratio units (r.u.) and time in seconds. **c** Peak $[Ca^{2+}]_i$ amplitudes evoked by 1 mm ATP compared with that evoked by treatment with 300 μm UTP ($n=3$), 100 μm α-methylthio-ATP (2-MeSATP; $n=7$). The results are represented as a fold change in peak $[Ca^{2+}]_i$ amplitudes. *Asterisks* denote significant difference from control values. **d** Peak $[Ca^{2+}]_i$ amplitudes evoked following selective P2X7 receptor activation using 500 μm 2′(3′)-*O*-(4-benzoylbenzoyl) adenosine 5′-triphosphate (BzATP) with ($n=5$) or without ($n=5$) prior Ca^{2+} store depletion using 30 μm cyclopiazonic acid. **e** Confocal images from mouse parotid gland slice preparations (10 μm thickness) labelled with P2X4 (*red*) and P2X7 (*green*) receptor antisera and F-actin (*cyan*) using Alexa Fluor 647-conjugated phalloidin. *Asterisks* mark ducts in the parotid lobules. *Scale bar* is 25 μm (reproduced from [56], with permission from The Physiological Society)

Submandibular gland

The effect of ATP on various types of preparations from submandibular salivary glands has been reported, including the human submandibular duct cell line, HSG-PA [390, 416, 740], rat submandibular gland acini [345–347], crude cell suspensions of whole rat submandibular glands [175, 418, 475, 665, 752] or ductal cells [10], a mouse submandibular

epithelial salivary cell line, ST_{885} [273], and an immortalized cell line SMG C10 cells, originally obtained from the rat submandibular salivary gland [22].

The presence of a P_{2U}-like receptor, where the agonist profile was UTP=ATP>ATPγS>ADP>ADPβS with both α,β-meATP and 2-MeSATP having little or no effect, was identified in a human submandibular duct cell line HSG-PA [740]. The cells challenged by UTP hyperpolarised which provided the driving force for net Cl^- efflux [390]. In the most recent paper on HSG cells, in addition to a P2U receptor mediating $InsP_3$ formation to nucleotides, the authors suggested that Ca^{2+} influx might be mediated by a second, perhaps P2X receptor [416].

Studies of rat submandibular gland acini identified, as for parotid acini, a P2X7 receptor activated by ATP^{4-} which promoted Ca^{2+} and Na^+ influx, but not release, from intracellular stores [345–347]. A later paper showed activation of PLD by P2X7 agonists in rat submandibular gland acini [552] and ductal cells [555]. Activation of P2X7 receptors in mouse submandibular glands triggers an intracellular signalling cascade involving PKC and MAPK leading to stimulation of NADPH oxidase and the subsequent generation of reactive oxygen species [612]. ATP also acts via P2X7 receptors to inhibit muscarinic-induced fluid secretion in murine submandibular glands [501]. The presence of two populations of P2X7 receptors in the plasma membrane of rat submandibular gland has been claimed, in raft and non-raft compartments [258]. There is also an unusual report that P2X7 receptors mediate depolarisation of mitochondrial as well as plasma membranes [257], which is interesting in view of earlier reports of intracellular immunolocalisation of P2X7 receptors [20]. ATP via P2X7 receptors increased the production of reactive oxygen species in rat submandibular glands, and the authors speculate that purinergic receptors could be regulators of the bactericidal properties of saliva by promoting the secretion of peroxidase from acinar cells and by activating Duox2 [226]. It was reported that P2X7 receptor activation induces inflammatory responses in mouse submandibular gland cells [714].

For mixed duct and acinar cell suspensions, again a P2X7 receptor coupled to a non-selective cation channel was described, occupation of which by ATP potentiates the responses to both carbachol and SP [418, 475]. In a subsequent paper from this group, using suspensions of submandibular ductal cells only, two purinergic receptors were identified, a metabotropic, probably $P2Y_1$ receptors and a P2X ionotropic receptor coupled to a manganese-permeant calcium channel and to kallikrein secretion [10]. In the most recent study by another group, coordinated actions of P2X7 (luminal) and P_{2U}-like (basolateral) receptors were proposed that mediate part of the transcellular cystic fibrosis transmembrane regulator (CFTR)-like Cl^- transport by acinar and duct cells to determine the final electrolyte composition of salivary fluid [752]. $P2Y_2$ receptors (= old P2U receptor, including $P2Y_4$ receptors) identified in both acinar and ductal cells of rat submandibular gland increased with time in culture, and it was speculated that changes in expression of the $P2Y_2$ receptor on salivary gland cells may be related to pathological challenges to the gland in vivo [665]. This group included a review of the field in an experimental paper, their main observations being:

1. $P2Y_1$ receptor activity is present in submandibular glands, although it tends to decline with age.
2. $P2Y_2$ receptors are present in cell lines and are upregulated during short-term culture of normal glands and following ligation of the main secretory duct of submandibular gland.
3. The P2X subtypes, P2X4 and P2X7, and the P2Y subtypes, $P2Y_1$ and $P2Y_2$, are co-expressed in salivary glands and salivary cell lines, and exhibit distinct basolateral, as opposed to apical, localisation in polarised cell monolayers as well as having discrete patterns of intracellular signalling [666].

In mouse submandibular ductal cells, P2X7 receptors are present, but P2X4 receptors are also involved in some ATP effects [555].

The conclusion from a study of nucleotide actions of the mouse submandibular salivary cell line, ST_{588}, was that two P2 receptor subtypes were probably present, one where ATP and UTP were equipotent (probably $P2Y_2$) and another where 2-MeSATP was active (possibly a $P2Y_1$ receptor) [273]. $P2Y_2$ receptors are upregulated in duct-ligated rat submandibular gland, and it was suggested that this may be an important component of the response to injury and that during recovery there is a return to $P2Y_2$ receptor levels [4]. $P2Y_2$ receptor activation upregulates vascular cell adhesion molecule-1 expression and enhances lymphocyte adherence from a human submandibular gland cell line [27]. Mechanical stimulation in submandibular gland cells results in the release of ATP, which then acts via $P2Y_2$ receptors to produce Ca^{2+} waves resulting in synchronised salivary gland cell function [590]. It was suggested that $P2Y_2$ receptors may be a novel target for dry mouth symptoms.

There is convincing evidence for the expression of Na^+–H^+ exchanger (NHE) isoforms in the basolateral membrane of rat submandibular gland duct and acinar cells (NHE1) and NHE2 and NHE3 in the luminal membrane of these cells which shows that the activities of the basolateral and luminal NHEs are regulated by P2 receptors (P2U receptors in the isolated membrane and P2X7 receptors in the luminal membrane) in a membrane-specific manner, which may play an important role in co-ordinating the overall process of Na^+ absorption [428]. Another study [370] has shown that extracellular ATP and BzATP, a potent agonist for P2X7 receptors, substantially increased the release of arachidonic acid from rat

submandibular gland ductal cells; these effects involved activation of PLA_2 by the purinergic agonists. It has been suggested that propofol, a widely used intravenous anaesthetic agent, potentiates the response, probably mediated by P2X4 receptors, of submandibular acinar cells [218].

An RT-PCR and pharmacological study of postnatal development of purinergic signalling in salivary glands, using dispersed cell aggregate preparations from the submandibular–sublingual gland complex of 1-day-old and 1-, 2-, 3- and 4-week old rats, showed that functional $P2Y_1$ receptors were expressed in immature (1 day postnatal) salivary glands and that receptor activity decreased as the glands matured, suggesting that $P2Y_1$ receptors may have an important role during salivary gland development [541]. $P2Y_1$ receptors have been shown to play important roles in embryonic chick development [476].

Ecto-ATP diphosphohydrolase and ecto-5′-nucleotidase have been identified in cultured rat submandibular glands, which hydrolyse ATP released as a cotransmitter from nerve terminals at the basal border of cells [320]. Ecto-nucleotide pyrophosphatase/phosphodiesterase (E-NPP) is colocalised with NTPDase and ecto-5′-nucleotidase in cells cultured from submandibular salivary glands [321]. Dry mouth is a common side effect caused by antidepressant therapy, and antidepressant drugs have been shown to modulate E-NPPs from submandibular gland cells [322].

Neurons in the parasympathetic submandibular ganglion innervate the submandibular gland to control secretion of saliva. ATP, probably released as a cotransmitter with ACh in preganglionic nerves, acts on both postsynaptic P2X [445, 625] and P1 and P2Y (probably $P2Y_2$) [2] receptors. Occupation of P1 and P2Y receptors led to inhibition of N- and P/Q-type voltage-dependent Ca^{2+} channel currents via $G_{i/o}$ proteins [2].

Both P2X and P2Y subtypes are expressed by cells of the salivary glands, and opportunities for utilisation of these receptors as pharmaceutical targets for diseases involving salivary gland dysfunction appear promising (see [19, 667]). Primary Sjögren's syndrome is a common inflammatory autoimmune disorder characterised by decreased secretion of saliva leading to symptoms of dry mouth. ATP, probably released as a cotransmitter in sympathetic and/or parasympathetic nerves, increased $[Ca^{2+}]_i$ in the acini of labial salivary glands via P2Y receptors to activate saliva production in both saliva glands from healthy and Sjögren's patients [546]. It was

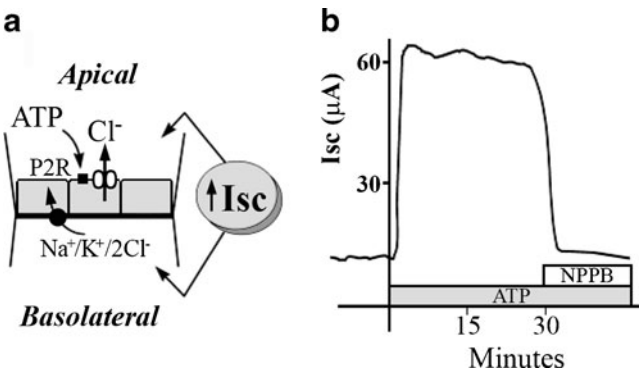


Fig. 9 ATP stimulates transepithelial secretion across cholangiocyte monolayers. In this example, polarised cell monolayers are mounted in an Ussing chamber, and the transepithelial movement of Cl^- ions from the basolateral to apical space is measured as short circuit current (Isc, *A*). Under basal conditions, Isc is low (**b**). However, addition of ATP (*bar*) activates $P2Y_2$ receptors (P2R) in the apical membrane and elicits a brisk Cl^- secretory response as demonstrated by a marked increase in Isc. Apical Cl^- secretion occurs via opening of apical membrane Cl^- channels and is inhibited by application of the selective anion channel blocker 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB, *bar*) (reproduced from [583], with permission from Elsevier)

Table 1 RT-PCR to detect human adenosine receptor mRNA in human intestine

	A_1	A_{2a}	A_{2b}	A_3
Jejunum				
Whole thickness	− (−)	− (+)?	++	++
Mucosa/submucosa	− (−)	++	++	+
Mucosa	− (−)	+	++	+
Mucosa	− (+)?	++	++	++
Submucous plexus	− (+)	− (+)	+	+
Longitudinal/circular	+ (++)	++	++	+
Ileum				
Whole thickness	+ (+)	++	+	+
Mucosa/submucosa	ND	ND	ND	ND
Mucosa	− (+)	++	+	+
Submucous plexus	ND	ND	ND	ND
Caecum				
Whole thickness	− (−)	+	++	+
Mucosa/submucosa	− (+)	++	+	+
Mucosa	− (−)	+	++	+
Submucous plexus	− (+)	− (−)	+	− (+)
Colon				
Whole thickness	− (−)	− (−)	+	− (+)?
Mucosa/submucosa	− (−)	− (−)	++	+
Mucosa	ND	ND	ND	ND
Submucous plexus	− (+)	− (+)?	++	+
Human cell lines				
HT-29 (colonic epithelium)	+ (+)	+++	+++	− (−)?
T-84 (colonic epithelium)	− (+)	+	+++	− (−)?
T98G (glioblastoma)	++	+++	+++	− (+)

ND not done, + or − indicates receptor mRNA detected or not detected, respectively. Failure to detect adenosine receptor mRNA after the first round of PCR reflects either absence or low expression. If the results of RT-PCR were negative, an aliquot of the first PCR reaction was amplified a second time, and the result is indicated in parentheses. Failure to detect adenosine receptor mRNA after the second round of PCR is likely to be due to its absence. A question mark indicates a possible faint expression of receptor mRNA (reproduced from [130], with permission from Springer)

Table 2 Cellular localisation of adenosine A_1, A_{2A}, A_{2B} and A_3 receptor immunoreactivities in human small and large intestine

Human intestinal region/cell type	A_1	A_{2a}	A_{2b}	A_3
Jejunum				+
Longitudinal muscle	±	±	−	
Myenteric plexus neurons	+	+	+	
Glia	−	−	+++	
Circular muscle	+	−	−	
Submucous plexus neurons	−	+++	+++	
Nerve fibres/neurites	−	+	+	+
Epithelia	−	+	+	+
Colon				+
Longitudinal muscle	±	−	−	
Myenteric plexus neurons	−	+	+	
Glia	−	−	+	
Circular muscle	+	+	+	
Submucous plexus neurons	+++	+	+	
Epithelia	+			
T98G				+
U373				+
BON cells				+

− absent, + present (or present ≤2 neurons), ± marginally detectable, ++ three to six neurons, +++ >6 neurons (reproduced from [130], with permission from Springer)

speculated that there may be some abnormality in the innervation of salivary glands in Sjögren's syndrome. Another study suggested that the $P2Y_2$ receptor is upregulated in the submandibular gland of the NOD B10 mouse model of Sjögren's syndrome [610].

Gall bladder and bile duct

Gall bladder

Stimulation in vivo of the cervical vagus nerve produces contraction of the guinea pig gall bladder. Following block of this response by atropine, a relaxation is revealed which is not affected by the adrenergic neuron blocker, guanethidine. This relaxation is, however, blocked by hexamethonium, indicating that the NANC inhibitory neurons are located in the wall of the gall bladder. There was early evidence to suggest that the intrinsic NANC inhibitory neurons, like those in the gut, were purinergic [169]. The NANC relaxation was mimicked by ATP and intrinsic nerve cell bodies exhibit fluorescence for quinacrine which binds to high levels of granule-bound ATP. Release of ATP from strips of guinea pig gall bladder during transmural stimulation of intrinsic nerves was demonstrated [651]. ATP release was stimulation frequency-dependent and both ATP release and contractions were completely abolished in Ca^{2+}-free medium; this suggests mediation by P2X receptors. It is likely that prostaglandins participate in the contractile response, since responses of the guinea pig gall bladder to ATP were antagonised by indomethacin [184]. Activation of an apical Cl^- conductance by extracellular ATP in *Necturus* gall bladder is mediated by

Table 3 Functional distribution of luminal P2 receptors in gastrointestinal epithelial cells

Tissue	Species	P2 receptor	Endogenous agonist	Function	Signalling	Reference
Jejunum	Mouse	$P2Y_4$	ATP=UTP	Cl^- secretion ↑		[157]
Duodenal villus	Rat	P2X7		Apoptosis ??		[298]
Pancreatic duct	Guinea pig	$P2Y_2$	ATP=UTP	HCO_3^- secretion ↑	Ca^{2+} ↑	[355]
	Rat	P2X7	Bz-ATP		Ca^{2+} ↑	[317]
	Rat	$P2Y_2$, $P2Y_4$, P2X7	UTP/ATP	Cl^- secretion ↑	Ca^{2+} ↑	[448]
	Dog		ATP	Mucin secretion ↑	Ca^{2+} ↑	[507]
PDEC	Human	$P2Y_2$/$P2Y_4$	UTP/ATP	Cl^- secretion ↑	Ca^{2+} ↑	[124]
CFPAC-1	Mouse	$P2Y_2$/$P2Y_6$	ATP=UTP/UDP	Cl^- secretion ↑		[157]
Gall bladder	Mouse	$P2Y_2$	ATP/UTP	HCO_3^- secretion ↑	Ca^{2+} ↑	[144]
	Necturus	P2	ATP	Cl^- secretion ↑	cAMP ↑	[680]
Bile duct	Rat	$P2Y_1$, $P2Y_2$	ATP, UTP	HCO_3^- secretion ↑		
		$P2Y_4$, $P2Y_6$	ADP, UDP			
			2MeSATP			
	Rat	$P2Y_2$/$P2Y_4$	UTP/ATP	Cl^- secretion ↑		[609]
Colon	Rat, mouse	$P2Y_2$/$P2Y_4$	UTP/ATP	K^+ secretion ↑ Na^+ absorption ↓	Ca^{2+} ↑ ?	[386]
Caco-2	Human	$P2Y_2$, $P2Y_4$, $P2Y_6$	UTP/ATP	Cl^- secretion ↑	Ca^{2+} ↑	[464]

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cAMP, not by $[Ca^{2+}]_i$ [680]. A recent paper has shown that ATP stimulates $P2Y_4$ receptors within the gall bladder musculature and, in turn, stimulates prostanoid production via COX-1 leading to increased excitability of gall bladder smooth muscle [42].

$P2Y_6$ receptor mRNA was identified on mature gall bladder epithelial cells and UDP shown to promote current changes in cystic fibrosis gall bladder epithelia, suggesting that the $P2Y_6$ receptors may be a target for the treatment of cystic fibrosis gall bladder disease [424].

Biliary duct

The extra-hepatic biliary tract is innervated by dense networks of extrinsic and intrinsic nerves that regulate both smooth muscle tone and epithelial cell function [28]. ATP activates ion permeabilities in rat biliary epithelial cells (cholangiocytes that form the intrahepatic bile ducts) via two pathways, extracellular Ca^{2+}-dependent and Ca^{2+}-independent [467], implicating P2X and P2Y receptors. Cl^- secretion, measured by both electrophysiological and radio-nucleotide methods, is stimulated though the activation of $P2Y_2$ receptors in rat bile duct epithelial cells [224]. Ca^{2+}-dependent activation of chloride currents in rat biliary epithelial cells is regulated by calmodulin-dependent protein kinase II [468]. Extracellular nucleotides modulate secretory and absorptive functions of cholangiocytes by activating Na^+/H^+ exchange mechanisms [202]. Apical $P2Y_2$ and basolateral $P1(A_1)$ receptors regulate Na^+/H^+ exchange activity (acid/base transport) in rat cholangiocytes [765]. Basolateral ADP was more potent in stimulating transepithelial currents [597], consistent with mediation by $P2Y_1$, $P2Y_{12}$ or $P2Y_{13}$ receptors. ATP, ADP and AMP are present in rat, pig and human bile, perhaps released by paracrine and/or autocrine activities, in sufficient concentrations to regulate biliary secretion [125]. Evidence has been presented to suggest that tachykinins and ATP may be excitatory cotransmitters in NANC nerves supplying the guinea pig common bile duct [543]. ATP is released into the bile by both hepatocytes and cholangiocytes, where it functions as a potent paracrine/autocrine stimulator for cholangiocyte secretion (Fig. 9) [583, 584]. Both small and large cholangiocytes show mechanosensitive vesicular ATP release, but this is greater in small cholangiocytes [709].

A key role in modifying the volume and composition of bile is played by fluid absorption and secretion across intrahepatic bile duct units (IBDUs). $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$ and P2X4 receptor mRNAs were expressed in isolated, microperfused IBDUs using RT-PCR [190]. In human intrahepatic biliary epithelial cell lines [706], ATP and UTP increase $[Ca^{2+}]_i$, probably via $P2Y_2$ or $P2Y_4$ receptors. Purinoceptors mediate activation of cholangiocytes to secrete Cl^- and HCO_3^- in the intrahepatic bile ducts [597]. Vesicles containing ATP within the biliary epithelial cells are in part responsible for the initiation of purinergic signalling in the biliary system [601].

RT-PCR from cultured rat cholangiocytes detected transcripts for P2X2, P2X3, P2X4 and P2X6 receptors, and immunohistochemistry showed that the P2X4 receptor protein was dominant, particularly in intrahepatic bile ducts, and functional studies implicated the P2X4 receptor in modulation of biliary secretion [183]. Fluid flow (shear stress) induces cholangiocyte mechanosensitive ATP release through calcium signalling and chloride transport via PKC-dependent pathways [707]. Portal fibroblasts inhibit the proliferation of bile duct epithelia via blockade of P2Y activation and expression of NTPDase2 [363]. TRPV4 is expressed on cholangiocyte cilia in intrahepatic bile duct units and its activation induces increases in bile flow, ATP release and bicarbonate secretion [292]. It has been suggested that cholangiocyte primary cilia are chemosensory organelles that detect biliary nucleotides via $P2Y_{12}$ receptors [461]. The existence of a P2 receptor signalling axis was proposed, present along the intrahepatic biliary tree, with upstream small cholangiocytes releasing ATP, which then serves as a signalling molecule for downstream large cholangiocytes [708].

It was suggested that ATP release may be a key regulator of biliary secretion and a target to modulate bile flow in the treatment of cholestatic liver disease. It has been claimed that extracellular ATP induces IL-6 transcription in bile duct epithelial cells via the $P2Y_{11}$ receptor [742]. $P2Y_{13}$-deficient mice exhibit a decrease in hepatic high-density lipoprotein cholesterol uptake, hepatic cholesterol content and biliary cholesterol output [66]. Pharmacological activation of $P2Y_{13}$ receptors with ADP increases reverse cholesterol transport and it was suggested that $P2Y_{13}$ agonists may have a potential role as a novel target for the treatment of dyslipidemia. Cholangiopathies are characterised by impaired cholangiocyte secretion. Ursodeoxycholic acid (UDCA) is widely used for cholangiopathy treatment. Data has been presented that indicates that UDCA stimulates a CFTR-dependent apical ATP release from cholangiocytes to act on P2Y receptors, which, through $[Ca^{2+}]_i$ increase and PKC activation, stimulates Cl^- efflux and fluid secretion [221]. Bile ductular proliferation is markedly upregulated in biliary fibrosis and cirrhosis. The ectonucleotidase NTPDase2 has been shown to be a critical regulator of bile ductular proliferation and IL-6 to downregulate NTPDase2 mRNA expression [741]. The apical P2Y–$InsP_3$ receptor signalling pathway mediating Cl^- transport may be a potential target for increasing secretion for the treatment of cholestatic liver disease [197]. Bicarbonate secretion is a function of cholangiocytes and it has been reported that cAMP regulates bicarbonate secretion from cholangiocytes via release of ATP into the bile [479].

Summary and future directions

Purinoceptors are widely expressed by non-neuronal cells as well as neurons in the gut and associated organs (see Tables 1, 2 and 3). Exploration of the therapeutic potential of purinergic-related drugs for inflammatory and motility disorders is in its infancy and should be encouraged in future investigations.

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References

1. Abbracchio MP, Burnstock G, Verkhratsky A, Zimmermann H (2009) Purinergic signalling in the nervous system: an overview. Trends Neurosci 32:19–29
2. Abe M, Endoh T, Suzuki T (2003) Extracellular ATP-induced calcium channel inhibition mediated by P1/P2Y purinoceptors in hamster submandibular ganglion neurons. Br J Pharmacol 138: 1535–1543
3. Acheson A, Rayment S, Eames T, Mundey M, Nisar P, Scholefield J, Wilson VG (2009) Investigation of the role of adrenergic and non-nitrergic, non-adrenergic neurotransmission in the sheep isolated internal anal sphincter. Neurogastroenterol Motil 21:335–345
4. Ahn JS, Camden JM, Schrader AM, Redman RS, Turner JT (2000) Reversible regulation of $P2Y_2$ nucleotide receptor expression in the duct-ligated rat submandibular gland. Am J Physiol Cell Physiol 279:C286–C294
5. Ahsan MA, Ilundain A, Naftalin RJ, Sandhu BK, Smith PM (1987) Effects of theophylline, choleragen and loperamide on rabbit ileal fluid and electrolyte transport in vitro. Br J Pharmacol 92:743–754
6. Ainz LF, Gil-Rodrigo CE, Gómez R, Malillos M, Requejo D, Gandarias JM (1989) Effects of various physiologic adenine derivatives on the secretion of acid in isolated gastric glands in rabbits. Rev Esp Fisiol 45:281–286
7. Ainz LF, Salgado C, Gandarias JM, Gómez R, Vallejo A, Gil-Rodrigo CE (1993) P1(A_2/R_a)-purinoceptors may mediate the stimulatory effect of adenosine and adenosine analogs on acid formation in isolated rabbit parietal cells. Pharmacol Res 27:319–334
8. Al Humayyd M, White TD (1985) 5-Hydroxytryptamine releases adenosine 5′-triphosphate from nerve varicosities isolated from the myenteric plexus of guinea-pig ileum. Br J Pharmacol 84:27–34
9. Alfahel E, Korngreen A, Parola AH, Priel Z (1996) Purinergically induced membrane fluidization in ciliary cells: characterization and control by calcium and membrane potential. Biophys J 70:1045–1053
10. Amsallem H, Metioui M, VandenAbeele A, Elyamani A, Moran A, Dehaye JP (1996) Presence of a metabotropic and an ionotropic purinergic receptor on rat submandibular ductal cells. Am J Physiol 271:C1546–C1555
11. Andrews PLR, Lawes INC (1985) Characteristics of the vagally driven non-adrenergic, non-cholinergic inhibitory innervation of ferret gastric corpus. J Physiol 363:1–20
12. Antonioli L, Fornai M, Blandizzi C, Salvadorini C, Colucci R, Breschi MC, Del Taca M (2005) The inhibitory effects of adenosine on enteric neuromuscular activity are decreased in inflamed colonic tissues. Gastroenterology 128:A273
13. Antonioli L, Fornai M, Colucci R, Ghisu N, Blandizzi C, Del Tacca M (2006) A2a receptors mediate inhibitory effects of adenosine on colonic motility in the presence of experimental colitis. Inflamm Bowel Dis 12:117–122
14. Antonioli L, Fornai M, Colucci R, Ghisu N, Da SF, Natale G, Kastsiuchenka O, Duranti E, Virdis A, Vassalle C, La MC, Mugnaini L, Breschi MC, Blandizzi C, Del Taca M (2007) Inhibition of adenosine deaminase attenuates inflammation in experimental colitis. J Pharmacol Exp Ther 322:435–442
15. Antonioli L, Fornai M, Colucci R, Awwad O, Ghisu N, Tuccori M, Da SF, La Motta C, Natale G, Duranti E, Virdis A, Blandizzi C (2010) The blockade of adenosine deaminase ameliorates chronic experimental colitis through the recruitment of adenosine A_{2A} and A_3 receptors. J Pharmacol Exp Ther 335:434–442
16. Antonioli L, Fornai M, Colucci R, Awwad O, Ghisu N, Tuccori M, Del Tacca M, Blandizzi C (2011) Differential recruitment of high affinity A1 and A2A adenosine receptors in the control of colonic neuromuscular function in experimental colitis. Eur J Pharmacol 650:639–649
17. Antonioli L, Colucci R, Pellegrini C, Giustarini G, Tuccori M, Blandizzi C, Fornai M (2013) The role of purinergic pathways in the pathophysiology of gut diseases: pharmacological modulation and potential therapeutic applications. Pharmacol Ther 139:157–188
18. Arkle S, Hanahoe A, Shum CMC (1998) Effects of KN-62, RO-31-8220, Mn^{2+}, Ni^{2+} and Co^{2+} on ATP^{4-}-stimulated responses in rat parotid salivary glands in vitro. Br J Pharmacol 125:83P
19. Arreola J, Melvin JE (2003) A novel chloride conductance activated by extracellular ATP in mouse parotid acinar cells. J Physiol 547: 197–208
20. Atkinson L, Milligan CJ, Buckley NJ, Deuchars J (2002) An ATP-gated ion channel at the cell nucleus. Nature 420:42
21. Aulí M, Martínez E, Gallego D, Opazo A, Espín F, Martí-Gallostra M, Jiménez M, Clavé P (2008) Effects of excitatory and inhibitory neurotransmission on motor patterns of human sigmoid colon in vitro. Br J Pharmacol 155:1043–1055
22. Aure MH, Roed A, Galtung HK (2010) Intracellular Ca^{2+} responses and cell volume regulation upon cholinergic and purinergic stimulation in an immortalized salivary cell line. Eur J Oral Sci 118:237–244
23. Baer HP, Frew R (1979) Relaxation of guinea-pig fundic strip by adenosine, adenosine triphosphate and electrical stimulation: lack of antagonism by theophylline or ATP treatment. Br J Pharmacol 67: 293–299
24. Bailey SJ, Hourani SMO (1990) A study of the purinoceptors mediating contraction in the rat colon. Br J Pharmacol 100:753–756
25. Bailey SJ, Hourani SMO (1992) Effects of purines on the longitudinal muscle of the rat colon. Br J Pharmacol 105:885–892
26. Bailey SJ, Hickman D, Hourani SMO (1992) Characterization of the P1-purinoceptors mediating contraction of the rat colon muscularis mucosae. Br J Pharmacol 105:400–404
27. Baker OJ, Camden JM, Rome DE, Seye CI, Weisman GA (2008) $P2Y_2$ nucleotide receptor activation up-regulates vascular cell adhesion molecule-1 expression and enhances lymphocyte adherence to a human submandibular gland cell line. Mol Immunol 45:65–75
28. Balemba OB, Salter MJ, Mawe GM (2004) Innervation of the extrahepatic biliary tract. Anat Rec A: Discov Mol Cell Evol Biol 280:836–847
29. Balestra B, Vicini R, Cremon C, Zecchi L, Dothel G, Vasina V, De GR, Paccapelo A, Pastoris O, Stanghellini V, Corinaldesi R, De Ponti F, Tonini M, Barbara G (2012) Colonic mucosal mediators from patients with irritable bowel syndrome excite enteric cholinergic motor neurons. Neurogastroenterol Motil 24:1118-e570
30. Banks BEC, Brown C, Burgess GM, Burnstock G, Claret M, Cocks TM, Jenkinson DH (1979) Apamin blocks certain neurotransmitter-induced increases in potassium permeability. Nature 282:415–417

31. Barajas-López C (1993) Adenosine reduces the potassium conductance of guinea pig submucosal plexus neurons by activating protein kinase A. Pflugers Arch 424:410–415
32. Barajas-López C, Surprenant A, North RA (1991) Adenosine A_1 and A_2 receptors mediate presynaptic inhibition and postsynaptic excitation in guinea pig submucosal neurons. J Pharmacol Exp Ther 258:490–495
33. Barajas-López C, Espinosa-Luna R, Gerzanich V (1994) ATP closes a potassium and opens a cationic conductance through different receptors in neurons of guinea pig submucous plexus. J Pharmacol Exp Ther 268:1397–1402
34. Barajas-López C, Huizinga JD, Collins SM, Gerzanich V, Espinosa-Luna R, Peres AL (1996) P_{2x}-purinoceptors of myenteric neurons from the guinea-pig ileum and their unusual pharmacological properties. Br J Pharmacol 119:1541–1548
35. Barajas-López C, Peres AL, Espinosa-Luna R (1996) Cellular mechanisms underlying adenosine actions on cholinergic transmission in enteric neurons. Am J Physiol 271:C264–C275
36. Barajas-López C, Espinosa-Luna R, Zhu Y (1998) Functional interactions between nicotinic and P2X channels in short-term cultures of guinea-pig submucosal neurons. J Physiol 513:671–683
37. Barajas-López C, Espinosa-Luna R, Christofi FL (2000) Changes in intracellular Ca^{2+} by activation of P2 receptors in submucosal neurons in short-term cultures. Eur J Pharmacol 409:243–257
38. Barajas-López C, Montaño LM, Espinosa-Luna R (2002) Inhibitory interactions between 5-HT_3 and P2X channels in submucosal neurons. Am J Physiol Gastrointest Liver Physiol 283:G1238–G1248
39. Barthó L, Lénárd LJ, Maggi CA (1997) Evidence for the involvement of P2-purinoceptors in the cholinergic contraction of the guinea-pig ileum. Br J Pharmacol 121:1507–1508
40. Barthó L, Undi S, Benkó R, Wolf M, Lázár Z, Lénárd L Jr, Maggi CA (2006) Multiple motor effects of ATP and their inhibition by P purinoceptor antagonist, pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid in the small intestine of the guinea-pig. Basic Clin Pharmacol Toxicol 98:488–495
41. Bartlett V, Stewart RR, Nakatsu K (1979) Evidence for two adenine derivative receptors in rat ileum which are not involved in the nonadrenergic, noncholinergic response. Can J Physiol Pharmacol 57:1130–1137
42. Bartoo AC, Nelson MT, Mawe GM (2008) ATP induces guinea pig gallbladder smooth muscle excitability via the $P2Y_4$ receptor and COX-1 activity. Am J Physiol Gastrointest Liver Physiol 294: G1362–G1368
43. Bassil AK, Bourdu S, Townson KA, Wheeldon A, Jarvie EM, Zebda N, Abuin A, Grau E, Livi GP, Punter L, Latcham J, Grimes AM, Hurp DP, Downham KM, Sanger GJ, Winchester WJ, Morrison AD, Moore GB (2009) UDP-glucose modulates gastric function through $P2Y_{14}$ receptor-dependent and -independent mechanisms. Am J Physiol Gastrointest Liver Physiol 296:G923–G930
44. Bayguinov O, Hagen B, Bonev AD, Nelson MT, Sanders KM (2000) Intracellular calcium events activated by ATP in murine colonic myocytes. Am J Physiol Cell Physiol 279:C126–C135
45. Beck K, Calamai F, Staderini G, Susini T (1988) Gastric motor responses elicited by vagal stimulation and purine compounds in the atropine-treated rabbit. Br J Pharmacol 94:1157–1166
46. Begg M, Dale N, Llaudet E, Molleman A, Parsons ME (2002) Modulation of the release of endogenous adenosine by cannabinoids in the myenteric plexus-longitudinal muscle preparation of the guinea-pig ileum. Br J Pharmacol 137:1298–1304
47. Benkó R, Undi S, Wolf M, Barthó L (2005) Effects of acute administration of and tachyphylaxis to α, β-methylene ATP in the guinea-pig small intestine. Basic Clin Pharmacol Toxicol 97:369–373
48. Benkó R, Undi S, Wolf M, Magyar K, Tóvölgyi Z, Rumbus Z, Barthó L (2006) P_2 purinoceptors account for the non-nitrergic NANC relaxation in the rat ileum. Naunyn Schmiedebergs Arch Pharmacol 373:319–324
49. Benkó R, Undi S, Wolf M, Vereczkei A, Illènyi L, Kassai M, Cseke L, Kelemen D, Horváth ÖP, Antal A, Magyar K, Barthó L (2007) P_2 purinoceptor antagonists inhibit the non-adrenergic, non-cholinergic relaxation of the human colon in vitro. Neuroscience 147:146–152
50. Berglund E, Berglund D, Akcakaya P, Ghaderi M, Daré E, Berggren PO, Köhler M, Aspinwall CA, Lui WO, Zedenius J, Larsson C, Bränström R (2013) Evidence for Ca^{2+}-regulated ATP release in gastrointestinal stromal tumors. Exp Cell Res 319:1229–1238
51. Bertrand CA, Laboisse CL, Hopfer U (1999) Purinergic and cholinergic agonists induce exocytosis from the same granule pool in HT29-Cl.16E monolayers. Am J Physiol 276:C907–C914
52. Bertrand PP (2003) ATP and sensory transduction in the enteric nervous system. Neuroscientist 9:243–260
53. Bertrand PP (2004) Bursts of recurrent excitation in the activation of intrinsic sensory neurons of the intestine. Neuroscience 128:51–63
54. Bertrand PP, Bornstein JC (2002) ATP as a putative sensory mediator: activation of intrinsic sensory neurons of the myenteric plexus via P2X receptors. J Neurosci 22:4767–4775
55. Beyazit Y, Koklu S, Tas A, Purnak T, Sayilir A, Kurt M, Turhan T, Celik T, Suvak B, Torun S, Akbal E (2012) Serum adenosine deaminase activity as a predictor of disease severity in ulcerative colitis. J Crohn's Colitis 6:102–107
56. Bhattacharya S, Verrill DS, Carbone KM, Brown S, Yule DI, Giovannucci DR (2012) Distinct contributions by ionotropic purinoceptor subtypes to ATP-evoked calcium signals in mouse parotid acinar cells. J Physiol 590:2721–2737
57. Bian X, Ren J, DeVries M, Schnegelsberg B, Cockayne DA, Ford AP, Galligan JJ (2003) Peristalsis is impaired in the small intestine of mice lacking the $P2X_3$ subunit. J Physiol 551:309–322
58. Bian XC, Bertrand PP, Bornstein JC (2000) Descending inhibitory reflexes involve P2X receptor-mediated transmission from interneurons to motor neurons in guinea-pig ileum. J Physiol Lond 528:551–560
59. Biancani P, Walsh J, Behar J (1985) Vasoactive intestinal peptide: a neurotransmitter for relaxation of the rabbit internal anal sphincter. Gastroenterology 89:867–874
60. Binder HJ, Sandle GI (1994) Electrolyte transport in the mammalian colon. In: Johnson LR (ed) Physiology of the gastrointestinal tract. Raven, New York, pp 2133–2171
61. Birch DJ, Knight GE, Boulos PB, Burnstock G (2008) Analysis of the innervation of human mesenteric vessels in non-inflamed and inflamed bowel—a confocal and functional study. Neurogastroenterol Motil 20:660–670
62. Blackshaw LA, Brookes SJ, Grundy D, Schemann M (2007) Sensory transmission in the gastrointestinal tract. Neurogastroenterol Motil 19:1–19
63. Blottiére HM, Loirand G, Pacaud P (1996) Rise in cytosolic Ca2+ concentration induced by P2-purinoceptor activation in isolated myocytes from the rat gastrointestinal tract. Br J Pharmacol 117: 775–780
64. Boeckxstaens GE, Pelckmans PA, Rampart M, Ruytjens IF, Verbeuren TJ, Herman AG, Van Maercke YM (1990) $GABA_A$ receptor-mediated stimulation of non-adrenergic non-cholinergic neurones in the dog ileocolonic junction. Br J Pharmacol 101:460–464
65. Boeckxstaens GE, Pelckmans PA, Herman AG, Van Maercke YM (1993) Involvement of nitric oxide in the inhibitory innervation of the human isolated colon. Gastroenterology 104:690–697
66. Boeynaems JM, Sirtori CR (2010) The unexpected roles of extracellular ADP and $P2Y_{13}$ receptor in reverse cholesterol transport. Purinergic Signal 6:361–363
67. Börjesson L, Nordgren S, Delbro DS (1997) DMPP causes relaxation of rat distal colon by a purinergic and a nitrergic mechanism. Eur J Pharmacol 334:223–231

68. Bornstein JC (2008) Purinergic mechanisms in the control of gastrointestinal motility. Purinergic Signal 4:197–212
69. Bornstein JC (2012) Enteric neural regulation of mucosal secretion. In: Johnson LR, Ghishan FK, Kaunitz JD, Merchant JL, Said HM, Wood JD (eds) Physiology of the gastrointestinal tract. Elsevier Academic, San Diego, pp 769–790
70. Bornstein JC, Costa M, Grider JR (2004) Enteric motor and interneuronal circuits controlling motility. Neurogastroenterol Motil 16(Suppl 1):34–38
71. Bours MJ, Troost FJ, Brummer RJ, Bast A, Dagnelie PC (2007) Local effect of adenosine 5′-triphosphate on indomethacin-induced permeability changes in the human small intestine. Eur J Gastroenterol Hepatol 19:245–250
72. Braun N, Sevigny J, Robson SC, Hammer K, Hanani M, Zimmermann H (2004) Association of the ecto-ATPase NTPDase2 with glial cells of the peripheral nervous system. Glia 45:124–132
73. Brierley SM, Carter R, Jones W III, Xu L, Robinson DR, Hicks GA, Gebhart GF, Blackshaw LA (2005) Differential chemosensory function and receptor expression of splanchnic and pelvic colonic afferents in mice. J Physiol 567:267–281
74. Briggs CA, Cooper JR (1981) A synaptosomal preparation from the guinea pig ileum myenteric plexus. J Neurochem 36:1097–1108
75. Brown CM, Burnstock G (1981) Evidence in support of the P_1/P_2 purinoceptor hypothesis in the guinea-pig taenia coli. Br J Pharmacol 73:617–624
76. Brown GP, Harvey BJ (2000) The role of intracellular calcium and UDP-stimulated chloride secretion across murine intestinal epithelium. J Physiol 526:5P
77. Bülbring E, Tomita T (1967) Properties of the inhibitory potential of smooth muscle as observed in the response to field stimulation of the guinea-pig taenia coli. J Physiol 189:299–315
78. Bulloch JM, Starke K (1989) Presynaptic α_2-autoinhibition in a vascular neuroeffector junction where ATP and noradrenaline act as co-transmitters. Br J Pharmacol 99:279–284
79. Bültmann R, von Kügelgen I, Starke K (1991) Adrenergic and purinergic cotransmission in nicotine-evoked vasoconstriction in rabbit ileocolic arteries. Naunyn Schmiedebergs Arch Pharmacol 344:174–182
80. Burleigh DE, D'Mello A, Parks AG (1979) Responses of isolated human internal anal sphincter to drugs and electrical field stimulation. Gastroenterology 77:484–490
81. Burnstock G (1969) Evolution of the autonomic innervation of visceral and cardiovascular systems in vertebrates. Pharmacol Rev 21:247–324
82. Burnstock G (1972) Purinergic nerves. Pharmacol Rev 24:509–581
83. Burnstock G (1975) Purinergic transmission. In: Iversen LI, Iversen SD, Snyder SH (eds) Handbook of psychopharmacology, vol 5. Plenum, New York, pp 131–194
84. Burnstock G (1975) Comparative studies of purinergic nerves. J Exp Zool 194:103–133
85. Burnstock G (1978) A basis for distinguishing two types of purinergic receptor. In: Straub RW, Bolis L (eds) Cell membrane receptors for drugs and hormones: a multidisciplinary approach. Raven, New York, pp 107–118
86. Burnstock G (1979) Past and current evidence for the purinergic nerve hypothesis. In: Baer HP, Drummond GI (eds) Physiological and regulatory functions of adenosine and adenine nucleotides. Raven, New York, pp 3–32
87. Burnstock G (1992) Neuromuscular transmission and neuromodulation in the gastrointestinal tract. In: Heading RC, Wood JD (eds) Gastrointestinal dysmotility: focus on cisapride. Proc. 2nd Int. Cisapride Investigators Meeting, Nice, December 3–4 1990. Raven, New York, pp 41–60
88. Burnstock G (1993) Physiological and pathological roles of purines: an update. Drug Dev Res 28:195–206
89. Burnstock G (1996) Purinoceptors: ontogeny and phylogeny. Drug Dev Res 39:204–242
90. Burnstock G (1997) Commentary on paper by G. Burnstock, G. Campbell, D. Satchell & A. Smythe (1970) entitled "Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut" In: Birmingham AT, Brown DA (eds) Landmarks in pharmacology. Br. J. Pharmacol. (Golden Jubilee 1946–1996), pp 334–357
91. Burnstock G (2001a) Purinergic signalling in gut. In: Abbracchio MP, Williams M (eds) Handbook of experimental pharmacology, volume 151/II. Purinergic and pyrimidinergic signalling II—cardiovascular, respiratory, immune, metabolic and gastrointestinal tract function. Springer, Berlin, pp 141–238
92. Burnstock G (2001b) Purinergic signalling in development. In: Abbracchio MP, Williams M (eds) Handbook of experimental pharmacology, volume 151/I. Purinergic and pyrimidinergic signalling I—molecular, nervous and urinogenitary system function. Springer, Berlin, pp 89–127
93. Burnstock G (2001) Purine-mediated signalling in pain and visceral perception. Trends Pharmacol Sci 22:182–188
94. Burnstock G (2001) Expanding field of purinergic signaling. Drug Dev Res 52:1–10
95. Burnstock G (2004) A moment of excitement. Living history series. The discovery of non-adrenergic, non-cholinergic neurotransmission. Physiol News 56:7–9
96. Burnstock G (2006) Pathophysiology and therapeutic potential of purinergic signalling. Pharmacol Rev 58:58–86
97. Burnstock G (2007) Physiology and pathophysiology of purinergic neurotransmission. Physiol Rev 87:659–797
98. Burnstock G (2008) The journey to establish purinergic signalling in the gut. Neurogastroenterol Motil 20:8–19
99. Burnstock G (2008) Commentary.Purinergic receptors as future targets for treatment of functional GI disorders. Gut 57:1193–1194
100. Burnstock G, Hoyle CHV (1985) Actions of adenine dinucleotides in the guinea-pig taenia coli: NAD acts indirectly on P_1-purinoceptors; NADP acts like a P_2-purinoceptor agonist. Br J Pharmacol 84:825–831
101. Burnstock G, Lavin S (2002) Interstitial cells of Cajal and purinergic signalling. Auton Neurosci 97:68–72
102. Burnstock G, Ralevic V (1994) New insights into the local regulation of blood flow by perivascular nerves and endothelium. Br J Plast Surg 47:527–543
103. Burnstock G, Verkhratsky A (2012) Purinergic signalling and the nervous system. Springer, Heidelberg, pp 1–715
104. Burnstock G, Warland JJI (1987) P_2-purinoceptors of two subtypes in the rabbit mesenteric artery: reactive blue 2 selectively inhibits responses mediated via the P_{2y}- but not the P_{2x}-purinoceptor. Br J Pharmacol 90:383–391
105. Burnstock G, Wong H (1978) Comparison of the effects of ultraviolet light and purinergic nerve stimulation on the guinea-pig taenia coli. Br J Pharmacol 62:293–302
106. Burnstock G, Campbell G, Bennett M, Holman ME (1963) The effects of drugs on the transmission of inhibition from autonomic nerves to the smooth muscle of the guinea pig taenia coli. Biochem Pharmacol 12(Suppl):134–135
107. Burnstock G, Campbell G, Bennett M, Holman ME (1964) Innervation of the guinea-pig taenia coli: are there intrinsic inhibitory nerves which are distinct from sympathetic nerves? Int J Neuropharmacol 3:163–166
108. Burnstock G, Campbell G, Rand MJ (1966) The inhibitory innervation of the taenia of the guinea-pig caecum. J Physiol 182:504–526
109. Burnstock G, Campbell G, Satchell D, Smythe A (1970) Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. Br J Pharmacol 40:668–688

110. Burnstock G, Satchell DG, Smythe A (1972) A comparison of the excitatory and inhibitory effects of non-adrenergic, non-cholinergic nerve stimulation and exogenously applied ATP on a variety of smooth muscle preparations from different vertebrate species. Br J Pharmacol 46:234–242
111. Burnstock G, Cocks T, Paddle B, Staszewska-Barczak J (1975) Evidence that prostaglandin is responsible for the 'rebound contraction' following stimulation of non-adrenergic, non-cholinergic ('purinergic') inhibitory nerves. Eur J Pharmacol 31:360–362
112. Burnstock G, Hills JM, Hoyle CHV (1984) Evidence that the P_1-purinoceptor in the guinea-pig taenia coli is an A_2-subtype. Br J Pharmacol 81:533–541
113. Burnstock G, Fischer B, Hoyle CHV, Maillard M, Ziganshin AU, Brizzolara AL, von Isakovics A, Boyer JL, Harden TK, Jacobson KA (1994) Structure activity relationships for derivatives of adenosine 5′-triphosphate as agonists at P_2 purinoceptors: heterogeneity within P_{2X} and P_{2Y} subtypes. Drug Dev Res 31:206–219
114. Buzzi N, Bilbao PS, Boland R, de Boland AR (2009) Extracellular ATP activates MAP kinase cascades through a P2Y purinergic receptor in the human intestinal Caco-2 cell line. Biochim Biophys Acta 1790:1651–1659
115. Buzzi N, Boland R, Russo de Boland A (2010) Signal transduction pathways associated with ATP-induced proliferation of colon adenocarcinoma cells. Biochim Biophys Acta 1800:946–955
116. Bywater RAR, Taylor GS (1982) Electrophysiological studies on the colon of the piebald-lethal mouse. Proc Aust Physiol Pharmacol Soc 13:250P
117. Carlson CC, Chinery R, Burnham LL, Dransfield DT (2000) 8-Cl-adenosine-induced inhibition of colorectal cancer growth in vitro and in vivo. Neoplasia 2:441–448
118. Casas-Pruneda G, Reyes JP, Pérez-Flores G, Pérez-Cornejo P, Arreola J (2009) Functional interactions between $P2X_4$ and $P2X_7$ receptors from mouse salivary epithelia. J Physiol 587:2887–2901
119. Cascabulho CM, Menna-Barreto RF, Coutinho-Silva R, Persechini PM, Henriques-Pons A (2008) $P2X_7$ modulatory web in *Trypanosoma cruzi* infection. Parasitol Res 103:829–838
120. Castelucci P, Robbins HL, Poole DP, Furness JB (2002) The distribution of purine $P2X_2$ receptors in the guinea-pig enteric nervous system. Histochem Cell Biol 117:415–422
121. Castelucci P, Robbins HL, Furness JB (2003) $P2X_2$ purine receptor immunoreactivity of intraganglionic laminar endings in the mouse gastrointestinal tract. Cell Tissue Res 312:167–174
122. Cataldi de Flombaum MA, Stoppani AO (1992) High-affinity calcium-stimulated, magnesium-dependent adenosine triphosphatase in *Trypanosoma cruzi*. Comp Biochem Physiol B 103:933–937
123. Cesaro A, Brest P, Hofman V, Hébuterne X, Wildman S, Ferrua B, Marchetti S, Doglio A, Vouret-Craviari V, Galland F, Naquet P, Mograbi B, Unwin R, Hofman P (2010) Amplification loop of the inflammatory process is induced by $P2X_7R$ activation in intestinal epithelial cells in response to neutrophil transepithelial migration. Am J Physiol Gastrointest Liver Physiol 299:G32–G42
124. Chan HC, Cheung WT, Leung PY, Wu LJ, Chew SB, Ko WH, Wong PY (1996) Purinergic regulation of anion secretion by cystic fibrosis pancreatic duct cells. Am J Physiol 271:C469–C477
125. Chari RS, Schutz SM, Haebig JE, Shimokura GH, Cotton PB, Fitz JG, Meyers WC (1996) Adenosine nucleotides in bile. Am J Physiol 270:G246–G252
126. Chen H, Redelman D, Ro S, Ward SM, Ördög T, Sanders KM (2007) Selective labeling and isolation of functional classes of interstitial cells of Cajal of human and murine small intestine. Am J Physiol Cell Physiol 292:C497–C507
127. Cheng Y, Yang J, Agarwal R, Green GM, Mease RC, Pomper MG, Meltzer SJ, Abraham JM (2011) Strong inhibition of xenografted tumor growth by low-level doses of [^{32}P]ATP. Oncotarget 2:461–466
128. Cho YB, Lee WY, Song SY, Choi SH, Shin HJ, Ahn KD, Lee JM, Kim HC, Yun SH, Chun HK (2009) In vitro chemosensitivity based on depth of invasion in advanced colorectal cancer using ATP-based chemotherapy response assay (ATP-CRA). Eur J Surg Oncol 35:951–956
129. Christofi FL (2001) Unlocking mysteries of gut sensory transmission: is adenosine the key? News Physiol Sci 16:201–207
130. Christofi FL (2008) Purinergic receptors and gastrointestinal secretomotor function. Purinergic Signal 4:213–236
131. Christofi FL, Cook MA (1986) Affinity of various purine nucleosides for adenosine receptors on purified myenteric varicosities compared to their efficacy as presynaptic inhibitors of acetylcholine release. J Pharmacol Exp Ther 237:305–311
132. Christofi FL, Cook MA (1987) Possible heterogeneity of adenosine receptors present on myenteric nerve endings. J Pharmacol Exp Ther 243:302–309
133. Christofi FL, Cook MA (1997) Purinergic modulation of gastrointestinal function. In: Jacobson KA, Jarvis MF (eds) Purinergic approaches in experimental therapeutics. Wiley-Liss, New York, pp 261–282
134. Christofi FL, Wood JD (1993) Endogenously released adenosine acts at A_1 receptors to suppress slow excitatory transmission (slow EPSP) and enhance slow inhibitory transmission (slow IPSP) in the myenteric plexus of guinea-pig small intestine. Gastroenterology 104:A490
135. Christofi FL, Wood JD (1993) Presynaptic inhibition by adenosine A_1 receptors on guinea pig small intestinal myenteric neurons. Gastroenterology 104:1420–1429
136. Christofi FL, Wood JD (1994) Electrophysiological subtypes of inhibitory P1 purinoceptors on myenteric neurones of guinea-pig small bowel. Br J Pharmacol 113:703–710
137. Christofi FL, Tack J, Wood JD (1992) Suppression of nicotinic synaptic transmission by adenosine in myenteric ganglia of the guinea-pig gastric antrum. Eur J Pharmacol 216:17–22
138. Christofi FL, Baidan LV, Fertel RH, Wood JD (1994) Adenosine A_2 receptor-mediated excitation of a subset of AH/type 2 neurons and elevation of cAMP levels in myenteric ganglia of guinea-pig ileum. Neurogastroenterol Motil 6:67–78
139. Christofi FL, Guan Z, Lucas JH, Rosenberg Schaffer LJ, Stokes BT (1996) Responsiveness to ATP with an increase in intracellular free Ca^{2+} is not a distinctive feature of calbindin-D28 immunoreactive neurons in myenteric ganglia. Brain Res 725:241–246
140. Christofi FL, Guan Z, Wood JD, Baidan LV, Stokes BT (1997) Purinergic Ca^{2+} signaling in myenteric neurons via P_2 purinoceptors. Am J Physiol 272:G463–G473
141. Christofi FL, Zhang H, Yu JG, Guzman J, Xue J, Kim M, Wang YZ, Cooke HJ (2001) Differential gene expression of adenosine A1, A2a, A2b, and A3 receptors in the human enteric nervous system. J Comp Neurol 439:46–64
142. Christofi FL, Wunderlich J, Yu JG, Wang YZ, Xue J, Guzman J, Javed N, Cooke H (2004) Mechanically evoked reflex electrogenic chloride secretion in rat distal colon is triggered by endogenous nucleotides acting at P2Y1, P2Y2, and P2Y4 receptors. J Comp Neurol 469:16–36
143. Clark SR, Costa M, Tonini M, Brookes SJ (1996) Purinergic transmission is involved in a descending excitatory reflex in the guinea-pig small intestine. Proc Aust Neurosci Soc 7:176
144. Clarke LL, Harline MC, Gawenis LR, Walker NM, Turner JT, Weisman GA (2000) Extracellular UTP stimulates electrogenic bicarbonate secretion across CFTR knockout gallbladder epithelium. Am J Physiol Gastrointest Liver Physiol 279:G132–G138
145. Clunes MT, Davidson RA, Bellingham M, Corbett AD, Bovell DL, Burnstock G (2002) Immunohistochemical localization of the $P2Y_4$ receptor in human bowel. J Physiol 543:48P
146. Colgan SP, Fennimore B, Ehrentraut SF (2013) Adenosine and gastrointestinal inflammation. J Mol Med (Berlin) 91:157–164

147. Communi D, Parmentier M, Boeynaems JM (1996) Cloning, functional expression and tissue distribution of the human $P2Y_6$ receptor. Biochem Biophys Res Commun 222:303–308
148. Cook DI, Young JA (1989) Fluid and electrolyte secretion by salivary glands. In: Forte JG (ed) Handbook of physiology, the gastrointestinal system. Salivary, pancreatic, gastric and hepatobiliary secretion, section 6, volume III. American Physiological Society, Bethesda, pp 1–23
149. Cooke HJ, Wunderlich J, Christofi FL (2003) "The force be with you": ATP in gut mechanosensory transduction. News Physiol Sci 18:43–49
150. Cooke HJ, Xue J, Yu JG, Wunderlich J, Wang YZ, Guzman J, Javed N, Christofi FL (2004) Mechanical stimulation releases nucleotides that activate P2Y1 receptors to trigger neural reflex chloride secretion in guinea pig distal colon. J Comp Neurol 469:1–15
151. Cornberg M, Schoefl C, Jandl O, Potthoff A, Mix H, Goeke M, Beil W, Manns MP, Wagner S (2000) Differential expression of the adenosine receptor subtypes in human gastric mucosa and cancer cells. Gastroenterology 118:A304
152. Correale P, Caraglia M, Procopio A, Marinetti MR, Guarrasi R, Fabbrocini A, Bianco AR, Tagliaferri P (1993) Transmembrane ion flux modifiers verapamil and ouabain modulate cytotoxic effects of extracellular ATP on human tumor cells in vitro. Int J Oncol 3:847–851
153. Correia-de-Sá P, Adães S, Timóteo MA, Vieira C, Magalhães-Cardoso T, Nascimento C, Duarte-Araújo M (2006) Fine-tuning modulation of myenteric motoneurons by endogenous adenosine: on the role of secreted adenosine deaminase. Auton Neurosci 126–127:211–224
154. Costa M, Furness JB, Humphreys CM (1986) Apamin distinguishes two types of relaxation mediated by enteric nerves in the guinea-pig gastrointestinal tract. Naunyn Schmiedebergs Arch Pharmacol 332:79–88
155. Coutinho CMLM, Pons AH, Araujo-Jorge TC, Persechini PM, Coutinho-Silva R (1998) Enhancement of P2Z-associated cell permeabilization during acute phase of Chagas' disease. Drug Dev Res 43:38
156. Crema A, Frigo GM, Lecchini S, Manzo L, Onori L, Tonini M (1983) Purine receptors in the guinea-pig internal anal sphincter. Br J Pharmacol 78:599–603
157. Cressman VL, Lazarowski E, Homolya L, Boucher RC, Koller BH, Grubb BR (1999) Effect of loss of $P2Y_2$ receptor gene expression on nucleotide regulation of murine epithelial Cl^- transport. J Biol Chem 274:26461–26468
158. Crist JR, He XD, Goyal RK (1992) Both ATP and the peptide VIP are inhibitory neurotransmitters in guinea-pig ileum circular muscle. J Physiol 447:119–131
159. Crowe R, Burnstock G (1981) Perinatal development of quinacrine-positive neurons in the rabbit gastrointestinal tract. J Auton Nerv Syst 4:217–230
160. Cummins MM, O'Mullane LM, Barden JA, Cook DI, Poronnik P (2000) Purinergic responses in HT29 colonic epithelial cells are mediated by G protein α-subunits. Cell Calcium 27:247–255
161. Currò D, Preziosi P (1998) Non-cholinergic non-adrenergic relaxation of the rat stomach. Gen Pharmacol 31:697–703
162. Currò D, Ipavec V, Preziosi P (2008) Neurotransmitters of the non-adrenergic non-cholinergic relaxation of proximal stomach. Eur Rev Med Pharmacol Sci 12(Suppl 1):53–62
163. Cusack NJ, Planker M (1979) Relaxation of isolated taenia coli of guinea-pig by enantiomers of 2-azido analogues of adenosine and adenine nucleotides. Br J Pharmacol 67:153–158
164. Cusack NJ, Hourani SMO, Loizou GD, Welford LA (1987) Pharmacological effects of isopolar phosphonate analogues of ATP on P_2-purinoceptors in guinea-pig taenia coli and urinary bladder. Br J Pharmacol 90:791–795
165. Cuthbert AW, Hickman ME (1985) Indirect effects of adenosine triphosphate on chloride secretion in mammalian colon. J Membr Biol 86:157–166
166. da Silveira AB, D'Avila Reis D, de Oliveira EC, Neto SG, Luquetti AO, Poole D, Correa-Oliveira R, Furness JB (2007) Neurochemical coding of the enteric nervous system in chagasic patients with megacolon. Dig Dis Sci 52:2877–2883
167. Damen R, Haugen M, Svejda B, Alaimo D, Brenna O, Pfragner R, Gustafsson BI, Kidd M (2013) The stimulatory adenosine receptor ADORA2B regulates serotonin (5-HT) synthesis and release in oxygen-depleted EC cells in inflammatory bowel disease. PLoS One 8:e62607
168. Dang K, Bielfeldt K, Lamb K, Gebhart GF (2005) Gastric ulcers evoke hyperexcitability and enhance P2X receptor function in rat gastric sensory neurons. J Neurophysiol 93:3112–3119
169. Davison JS, Al-Hassani M, Crowe R, Burnstock G (1978) The non-adrenergic, inhibitory innervation of the guinea-pig gallbladder. Pflugers Arch 377:43–49
170. de Campos NE, Marques-da-Silva C, Corrêa G, Castelo-Branco MT, de Souza HS, Coutinho-Silva R (2012) Characterizing the presence and sensitivity of the P2X7 receptor in different compartments of the gut. J Innate Immun 4:529–541
171. De Luca A, Li CG, Rand MJ (1999) Nitrergic and purinergic mechanisms and their interactions for relaxation of the rat internal anal sphincter. J Auton Pharmacol 19:29–37
172. De Man JG, De Winter BY, Seerden TC, De Schepper HU, Herman AG, Pelckmans PA (2003) Functional evidence that ATP or a related purine is an inhibitory NANC neurotransmitter in the mouse jejunum: study on the identity of P2X and P2Y purinoceptors involved. Br J Pharmacol 140:1108–1116
173. Decker DA, Galligan JJ (2010) Molecular mechanisms of cross-inhibition between nicotinic acetylcholine receptors and P2X receptors in myenteric neurons and HEK-293 cells. Neurogastroenterol Motil 22(901–8):e235
174. Degagné É, Turgeon N, Moore-Gagné J, Asselin C, Gendron FP (2012) $P2Y_2$ receptor expression is regulated by C/EBPβ during inflammation in intestinal epithelial cells. FEBS J 279:2957–2965
175. Dehaye JP (1993) ATP^{4-} increases the intracellular calcium concentration in rat submandibular glands. Gen Pharmacol 24:1097–1100
176. Delbro D, Fändriks L (1982) ATP induces non-cholinergic, non-adrenergic gastric relaxation in vivo. Acta Physiol Scand Suppl 508:67
177. Delbro D, Fändriks L (1984) Inhibition of vagally induced non-adrenergic, non-cholinergic gastric relaxation by P2-purinoceptor desensitization. Acta Physiol Scand 120:12A
178. Deshpande NA, McDonald TJ, Cook MA (1999) Endogenous interstitial adenosine in isolated myenteric neural networks varies inversely with prevailing PO_2. Am J Physiol 276:G875–G885
179. Dho S, Stewart K, Foskett JK (1992) Purinergic receptor activation of Cl^- secretion in T84 cells. Am J Physiol 262:C67–C74
180. Di Paola R, Melani A, Esposito E, Mazzon E, Paterniti I, Bramanti P, Pedata F, Cuzzocrea S (2010) Adenosine A_{2A} receptor-selective stimulation reduces signaling pathways involved in the development of intestine ischemia and reperfusion injury. Shock 33:541–551
181. Dick GM, Bradley KK, Horowitz B, Hume JR, Sanders KM (1998) Functional and molecular identification of a novel chloride conductance in canine colonic smooth muscle. Am J Physiol 275:C940–C950
182. DiMarino AJ Jr (1974) Characteristics of lower esophageal sphincter function in symptomatic diffuse esophageal spasm. Gastroenterology 66:1–6
183. Doctor RB, Matzakos T, McWilliams R, Johnson S, Feranchak AP, Fitz JG (2005) Purinergic regulation of cholangiocyte secretion: identification of a novel role for P2X receptors. Am J Physiol Gastrointest Liver Physiol 288:G779–G786

184. Doggrell SA, Scott GW (1980) The effects of time and indomethacin on contractile responses of the guinea-pig gall bladder in vitro. Br J Pharmacol 71:429–434
185. Dong X, Smoll EJ, Ko KH, Lee J, Chow JY, Kim HD, Insel PA, Dong H (2009) P2Y receptors mediate Ca^{2+} signaling in duodenocytes and contribute to duodenal mucosal bicarbonate secretion. Am J Physiol Gastrointest Liver Physiol 296: G424–G432
186. Donnelly-Roberts D, McGaraughty S, Shieh CC, Honore P, Jarvis MF (2008) Painful purinergic receptors. J Pharmacol Exp Ther 324: 409–415
187. Donoso MV, Steiner M, Huidobro Toro JP (1997) BIBP 3226, suramin and prazosin identify neuropeptide Y, adenosine 5′-triphosphate and noradrenaline as sympathetic cotransmitters in the rat arterial mesenteric bed. J Pharmacol Exp Ther 282:691–698
188. Dowd FJ, Murphy HC, Li L (1996) Metabolism of extracellular ATP by rat parotid cells. Arch Oral Biol 41:855–862
189. Dowe GH, Kilbinger H, Whittaker VP (1980) Isolation of cholinergic synaptic vesicles from the myenteric plexus of guinea-pig small intestine. J Neurochem 35:993–1003
190. Dranoff JA, Masyuk AI, Kruglov EA, LaRusso NF, Nathanson MH (2001) Polarized expression and function of P2Y ATP receptors in rat bile duct epithelia. Am J Physiol Gastrointest Liver Physiol 281: G1059–G1067
191. Drury AN, Szent-Györgyi A (1929) The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. J Physiol 68:213–237
192. Duarte-Araújo M, Nascimento C, Timóteo MA, Magalhães-Cardoso MT, Correia-de-Sá P (2009) Relative contribution of ecto-ATPase and ecto-ATPDase pathways to the biphasic effect of ATP on acetylcholine release from myenteric motoneurons. Br J Pharmacol 156:519–533
193. DuBose DR, Wolff SC, Qi AD, Naruszewicz I, Nicholas RA (2013) Apical targeting of the $P2Y_4$ receptor is directed by hydrophobic and basic residues in the cytoplasmic tail. Am J Physiol Cell Physiol 304:C228–C239
194. Dubyak GR, El Moatassim C (1993) Signal transduction via P2-purinergic receptors for extracellular ATP and other nucleotides. Am J Physiol 265:C577–C606
195. Durnin L, Hwang SJ, Ward SM, Sanders KM, Mutafova-Yambolieva VN (2012) Adenosine 5-diphosphate-ribose is a neural regulator in primate and murine large intestine along with β-NAD^+. J Physiol 590:1921–1941
196. Durnin L, Sanders KM, Mutafova-Yambolieva VN (2013) Differential release of β-NAD^+ and ATP upon activation of enteric motor neurons in primate and murine colons. Neurogastroenterol Motil 25:e194–e204
197. Dutta AK, Woo K, Doctor RB, Fitz JG, Feranchak AP (2008) Extracellular nucleotides stimulate Cl^- currents in biliary epithelia through receptor-mediated IP3 and Ca^{2+} release. Am J Physiol Gastrointest Liver Physiol 295:G1004–G1015
198. Eccles JC (1964) The physiology of synapses. Springer, Berlin, pp 1–316
199. Ekström J, Asztely A, Tobin G (1998) Parasympathetic non-adrenergic, non-cholinergic mechanisms in salivary glands and their role in reflex secretion. Eur J Morphol 36(Suppl):208–212
200. El-Mahmoudy A, Khalifa M, Draid M, Shiina T, Shimizu Y, El-Sayed M, Takewaki T (2006) NANC inhibitory neuromuscular transmission in the hamster distal colon. Pharmacol Res 54:452–460
201. El-Tayeb A, Michael S, Abdelrahman A, Behrenswerth A, Gollos S, Nieber K, Müller CE (2011) Development of polar adenosine A_{2A} receptor agonists for inflammatory bowel disease: synergism with A_{2B} antagonists. ACS Med Chem Lett 2:890–895
202. Elsing C, Kassner A, Stremmel W (1996) Sodium, hydrogen antiporter activation by extracellular adenosine triphosphate in biliary epithelial cells. Gastroenterology 111:1321–1332
203. Eltzschig HK, Rivera-Nieves J, Colgan SP (2009) Targeting the A2B adenosine receptor during gastrointestinal ischemia and inflammation. Expert Opin Ther Targets 13:1267–1277
204. Ernster VL (1984) Epidemiologic studies of caffeine and human health. Prog Clin Biol Res 158:377–400
205. Eroglu A, Canbolat O, Demirci S, Kocaoglu H, Eryavuz Y, Akgül H (2000) Activities of adenosine deaminase and 5′-nucleotidase in cancerous and noncancerous human colorectal tissues. Med Oncol 17:319–324
206. Estrada O, Lecea B, Aulí M, Farré R, Suñol X, Clave P (2006) Inhibitory purinergic neurotransmission in human lower esophageal sphincter. Neurogastroenterol Motil 18:780
207. Estrela AB, Abraham WR (2011) Adenosine in the inflamed gut: a Janus faced compound. Curr Med Chem 18:2791–2815
208. Evans RJ, Cunnane TC (1992) Relative contributions of ATP and noradrenaline to the nerve evoked contraction of the rabbit jejunal artery. Dependence on stimulation parameters. Naunyn Schmiedeberg's Arch Pharmacol 345:424–430
209. Evans RJ, Surprenant A (1992) Vasoconstriction of guinea-pig submucosal arterioles following sympathetic nerve stimulation is mediated by the release of ATP. Br J Pharmacol 106:242–249
210. Facer P, Knowles CH, Tam PK, Ford AP, Dyer N, Baecker PA, Anand P (2001) Novel capsaicin (VR1) and purinergic ($P2X_3$) receptors in Hirschsprung's intestine. J Pediatr Surg 36:1679–1684
211. Fahrenkrug J, Haglund U, Jodal M, Lundgren O, Olbe L, de Muckadell OB (1978) Nervous release of vasoactive intestinal polypeptide in the gastrointestinal tract of cats: possible physiological implications. J Physiol 284:291–305
212. Fan J, Yu L, Zhang W, Zhao T, Yu Y, Gao J, Zou D, Ni X, Ma B, Burnstock G (2009) Estrogen altered visceromotor reflex and $P2X_3$ mRNA expression in a rat model of colitis. Steroids 74:956–963
213. Fang X, Hu HZ, Gao N, Liu S, Wang GD, Wang XY, Xia Y, Wood JD (2006) Neurogenic secretion mediated by the purinergic $P2Y_1$ receptor in guinea-pig small intestine. Eur J Pharmacol 536:113–122
214. Farré R, Auli M, Lecea B, Martinez E, Clave P (2006) Pharmacologic characterization of intrinsic mechanisms controlling tone and relaxation of porcine lower esophageal sphincter. J Pharmacol Exp Ther 316:1238–1248
215. Fei G, Fang X, Wang GD, Liu S, Wang XY, Xia Y, Wood JD (2013) Neurogenic mucosal bicarbonate secretion in guinea pig duodenum. Br J Pharmacol 168:880–890
216. Feldberg W, Hebb C (1948) The stimulating action of phosphate compounds on the perfused superior cervical ganglion of the cat. J Physiol 107:210–221
217. Fernández E, Guo X, Vergara P, Jimenez M (1998) Evidence supporting a role for ATP as non-adrenergic non-cholinergic inhibitory transmitter in the porcine ileum. Life Sci 62:1303–1315
218. Fernandez M, Pochet S, Chaïb N, Métioui M, Gómez-Muñoz A, Marino A, Dehaye JP (2001) Potentiation by propofol of the response of rat submandibular acinar cells to purinergic agonists. Cell Calcium 30:167–180
219. Ferrero JD, Frischknecht R (1983) Different effector mechanisms for ATP and adenosine hyperpolarization in the guinea-pig taenia coli. Eur J Pharmacol 87:151–154
220. Filinger EJ, Perec CJ, Stefano FJ (1989) Potassium-evoked efflux of [^{3}H]purines from the rat submaxillary gland. Gen Pharmacol 20: 285–288
221. Fiorotto R, Spirli C, Fabris L, Cadamuro M, Okolicsanyi L, Strazzabosco M (2007) Ursodeoxycholic acid stimulates cholangiocyte fluid secretion in mice via CFTR-dependent ATP secretion. Gastroenterology 133:1603–1613
222. Fisher RS, Cohen S (1975) Disorders of the lower esophageal sphincter. Annu Rev Med 26:373–390
223. Fishman P, Bar-Yehuda S, Ohana G, Barer F, Ochaion A, Erlanger A, Madi L (2004) An agonist to the A_3 adenosine receptor inhibits

colon carcinoma growth in mice via modulation of GSK-3β and NF-κB. Oncogene 23:2465–2471
224. Fitz JG, Basavappa S, McGill J, Melhus O, Cohn JA (1993) Regulation of membrane chloride currents in rat bile duct epithelial cells. J Clin Invest 91:319–328
225. Folkow B (1949) The vasodilator action of adenosine of adenosine triphosphate. Acta Physiol Scand 17:311–317
226. Fontanils U, Seil M, Pochet S, El OM, Garcia-Marcos M, Dehaye JP, Marino A (2010) Stimulation by $P2X_7$ receptors of calcium-dependent production of reactive oxygen species (ROS) in rat submandibular glands. Biochim Biophys Acta 1800:1183–1191
227. Forte JG, Lee HC (1977) Gastric adenosine triphosphatases: a review of their possible role in HCl secretion. Gastroenterology 73:921–926
228. Frasch AC, Cazzulo JJ, Stoppani AO (1978) Solubilization and some properties of the Mg^{2+}-activated adenosine triphosphatase from *Trypanosoma cruzi*. Comp Biochem Physiol B 61:207–212
229. Frew R, Lundy PM (1982) Evidence against ATP being the nonadrenergic, noncholinergic inhibitory transmitter in guinea pig stomach. Eur J Pharmacol 81:333–336
230. Frigo GM, Del Tacca M, Lecchini S, Crema A (1973) Some observations on the intrinsic nervous mechanism in Hirschsprung's disease. Gut 14:35–40
231. Fukushi Y (1999) Heterologous desensitization of muscarinic receptors by P_{2Z} purinoceptors in rat parotid acinar cells. Eur J Pharmacol 364:55–64
232. Fukushi Y, Ozawa T, Kanno T, Wakui M (1997) Na^+-dependent release of intracellular Ca^{2+} induced by purinoceptors in parotid acinar cells of the rat. Eur J Pharmacol 336:89–97
233. Furness JB (2006) The enteric nervous system. Blackwell, Massachusetts, pp 137–147
234. Furness JB (2012) The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol 9:286–294
235. Furness JB, Morris JL, Gibbins IL, Costa M (1989) Chemical coding of neurons and plurichemical transmission. Annu Rev Pharmacol Toxicol 29:289–306
236. Furness JB, Jones C, Nurgali K, Clerc N (2004) Intrinsic primary afferent neurons and nerve circuits within the intestine. Prog Neurobiol 72:143–164
237. Furness JB, Robbins HL, Xiao J, Stebbing MJ, Nurgali K (2004) Projections and chemistry of Dogiel type II neurons in the mouse colon. Cell Tissue Res 317:1–12
238. Furuya S, Furuya K (2013) Roles of substance P and ATP in the subepithelial fibroblasts of rat intestinal villi. Int Rev Cell Mol Biol 304:133–189
239. Furuzono S, Nakayama S, Imaizumi Y (2005) Purinergic modulation of pacemaker Ca^{2+} activity in interstitial cells of Cajal. Neuropharmacology 48:264–273
240. Gabella G, Trigg P (1984) Size of neurons and glial cells in the enteric ganglia of mice, guinea-pigs, rabbits and sheep. J Neurocytol 13:49–71
241. Gade AR, Akbarali HI (2013) Electrophysiological characterization of purinergic receptors in mouse enteric neuron–glia culture. FASEB J 27:1093.24
242. Gallacher DV (1982) Are there purinergic receptors on parotid acinar cells? Nature 296:83–86
243. Gallego D, Hernández P, Clavé P, Jiménez M (2006) $P2Y_1$ receptors mediate inhibitory purinergic neuromuscular transmission in the human colon. Am J Physiol Gastrointest Liver Physiol 291:G584–G594
244. Gallego D, Gil V, Aleu J, Martínez-Cutillas M, Clavé P, Jiménez M (2011) Pharmacological characterization of purinergic inhibitory neuromuscular transmission in the human colon. Neurogastroenterol Motil 23:792-e338
245. Gallego D, Gil V, Martínez-Cutillas M, Mañe N, Martín MT, Jiménez M (2012) Purinergic neuromuscular transmission is absent in the colon of $P2Y_1$ knocked out mice. J Physiol 590:1943–1956
246. Gallego D, Malagelada C, Accarino A, De Giorgio R, Malagelada JR, Azp-Iroz F, Jimenez M (2012) Purinergic (P2Y1) and nitrergic neuromuscular transmission in the human small intestine. Neurogastroenterol Motil 24:81
247. Galligan JJ (1996) Electrophysiological studies of 5-hydroxytryptamine receptors on enteric neurons. Behav Brain Res 73:199–201
248. Galligan JJ (2002) Pharmacology of synaptic transmission in the enteric nervous system. Curr Opin Pharmacol 2:623–629
249. Galligan JJ (2004) Enteric P2X receptors as potential targets for drug treatment of the irritable bowel syndrome. Br J Pharmacol 141: 1294–1302
250. Galligan JJ, North RA (2004) Pharmacology and function of nicotinic acetylcholine and P2X receptors in the enteric nervous system. Neurogastroenterol Motil 16(Suppl 1):64–70
251. Galligan JJ, Herring A, Harpstead T (1995) Pharmacological characterization of purinoceptor-mediated constriction of submucosal arterioles in guinea pig ileum. J Pharmacol Exp Ther 274:1425–1430
252. Galligan JJ, LePard KJ, Schneider DA, Zhou X (2000) Multiple mechanisms of fast excitatory synaptic transmission in the enteric nervous system. J Auton Nerv Syst 81:97–103
253. Gandarias JM, Ainz LF, Gil-Rodrigo CE, Goiriena JJ, Gómez R, Martinez I (1985) Effect of various adenine derivatives on gastric acid secretion in the isolated rat stomach. Rev Esp Fisiol 41:83–87
254. Gannon BJ, Burnstock G, Noblett HR, Campbell PE (1969) Histochemical diagnosis of Hirschsprung's disease. Lancet 293: 894–895
255. Gao N, Hu HZ, Zhu MX, Fang X, Liu S, Gao C, Wood JD (2006) The $P2Y_1$ purinergic receptor expressed by enteric neurones in guinea-pig intestine. Neurogastroenterol Motil 18:316–323
256. Gao N, Hu HZ, Liu S, Gao C, Xia Y, Wood JD (2007) Stimulation of adenosine A_1 and A_{2A} receptors by AMP in the submucosal plexus of guinea pig small intestine. Am J Physiol Gastrointest Liver Physiol 292:G492–G500
257. Garcia-Marcos M, Fontanils U, Aguirre A, Pochet S, Dehaye JP, Marino A (2005) Role of sodium in mitochondrial membrane depolarization induced by $P2X_7$ receptor activation in submandibular glands. FEBS Lett 579:5407–5413
258. Garcia-Marcos M, Pérez-Andrés E, Tandel S, Fontanils U, Kumps A, Kabré E, Gómez-Muñoz A, Marino A, Dehaye JP, Pochet S (2006) Coupling of two pools of $P2X_7$ receptors to distinct intracellular signaling pathways in rat submandibular gland. J Lipid Res 47: 705–714
259. Geiger JD, Glavin GB (1985) Adenosine receptor activation in brain reduces stress-induced ulcer formation. Eur J Pharmacol 115:185–190
260. Gerber JG, Payne NA (1988) Endogenous adenosine modulates gastric acid secretion to histamine in canine parietal cells. J Pharmacol Exp Ther 244:190–194
261. Gerber JG, Fadul S, Payne NA, Nies AS (1984) Adenosine: a modulator of gastric acid secretion in vivo. J Pharmacol Exp Ther 231:109–113
262. Gerber JG, Nies AS, Payne NA (1985) Adenosine receptors on canine parietal cells modulate gastric acid secretion to histamine. J Pharmacol Exp Ther 233:623–627
263. Gershon MD, Thompson EB (1973) The maturation of neuromuscular function in a multiply innervated structure: development of the longitudinal smooth muscle of the foetal mammalian gut and its cholinergic excitatory, adrenergic inhibitory, and non-adrenergic inhibitory innervation. J Physiol 234:257–277
264. Gessi S, Merighi S, Varani K, Cattabriga E, Benini A, Mirandola P, Leung E, Mac Lennan S, Feo C, Baraldi S, Borea PA (2007) Adenosine receptors in colon carcinoma tissues and colon tumoral

cell lines: focus on the A_3 adenosine subtype. J Cell Physiol 211: 826–836
265. Gessi S, Merighi S, Varani K, Leung E, Mac Lennan S, Borea PA (2008) The A_3 adenosine receptor: an enigmatic player in cell biology. Pharmacol Ther 117:123–140
266. Gever J, Cockayne DA, Dillon MP, Burnstock G, Ford APDW (2006) Pharmacology of P2X channels. Pflugers Arch 452:513–537
267. Ghanem E, Lövdahl C, Daré E, Ledent C, Fredholm BB, Boeynaems JM, Van Driessche W, Beauwens R (2005) Luminal adenosine stimulates chloride secretion through A_1 receptor in mouse jejunum. Am J Physiol Gastrointest Liver Physiol 288: G972–G977
268. Ghanem E, Robaye B, Leal T, Leipziger J, Van DW, Beauwens R, Boeynaems JM (2005) The role of epithelial $P2Y_2$ and $P2Y_4$ receptors in the regulation of intestinal chloride secretion. Br J Pharmacol 146:364–369
269. Gheber L, Priel Z (1994) Metachronal activity of cultured mucociliary epithelium under normal and stimulated conditions. Cell Motil Cytoskeleton 28:333–345
270. Gheber L, Priel Z, Aflalo C, Shoshan Barmatz V (1995) Extracellular ATP binding proteins as potential receptors in mucociliary epithelium: characterization using [^{32}P]-3′-O-(4-benzoyl)benzoyl ATP, a photoaffinity label. J Membr Biol 147:83–93
271. Giaroni C, Knight GE, Ruan H-Z, Glass R, Bardini M, Lecchini S, Frigo G, Burnstock G (2002) P2 receptors in the murine gastrointestinal tract. Neuropharmacology 43:1313–1323
272. Giaroni C, Knight GE, Zanetti E, Chiarelli RA, Lecchini S, Frigo G, Burnstock G (2006) Postnatal development of P2 receptors in the murine gastrointestinal tract. Neuropharmacology 50:690–704
273. Gibb CA, Singh S, Cook DI, Poronnik P, Conigrave AD (1994) A nucleotide receptor that mobilizes Ca^{2+} in the mouse submandibular salivary cell line ST885. Br J Pharmacol 111:1135–1139
274. Gibbons SJ, Washburn KB, Talamo BR (2001) $P2X_7$ receptors in rat parotid acinar cells: formation of large pores. J Auton Pharmacol 21: 181–190
275. Gibbons SJ, De Giorgio R, Miller SM, Schmalz PF, Young-Fadok TM, Szurszewski JH, Stanghellini V, Farrugia G (2004) Elevated apoptotic cell death in enteric neurons and intramuscular interstitial cells of Cajal from colon of patients with slow-transit constipation. Gastroenterology 126:A219
276. Giglioni S, Leoncini R, Aceto E, Chessa A, Civitelli S, Bernini A, Tanzini G, Carraro F, Pucci A, Vannoni D (2008) Adenosine kinase gene expression in human colorectal cancer. Nucleosides Nucleotides Nucleic Acids 27:750–754
277. Gil V, Gallego D, Moha Ou Maati H, Peyronnet R, Martínez-Cutillas M, Heurteaux C, Borsotto M, Jiménez M (2012) Relative contribution of SK_{Ca} and TREK1 channels in purinergic and nitrergic neuromuscular transmission in the rat colon. Am J Physiol Gastrointest Liver Physiol 303:G412–G423
278. Gil V, Martínez-Cutillas M, Mañé N, Martín MT, Jiménez M, Gallego D (2013) $P2Y_1$ knockout mice lack purinergic neuromuscular transmission in the antrum and cecum. Neurogastroenterol Motil 25:e170–e182
279. Gil-Rodrigo CE, Galdiz B, Gandarias JM, Gomez R, Ainz LF (1990) Characterization of the effects of adenosine, adenosine 5′-triphosphate and related purines on acid secretion in isolated rabbit gastric glands. Pharmacol Res 22:103–113
280. Gil-Rodrigo CE, Gomez R, Gandarias JM, Galdiz B, Carou M, Bergaretxe I, Vallejo A, Ainz LF (1993) Effect of adenosine 5′-triphosphate on secretagogue-stimulated (^{14}C)-aminopyrine accumulation by rabbit isolated gastric glands. Gen Physiol Biophys 12:27–36
281. Gil-Rodrigo CE, Bergaretxe I, Carou M, Galdiz B, Salgado C, Ainz LF (1996) Inhibitory action of extracellular adenosine 5′-triphosphate on parietal cells isolated from rabbit gastric mucosa. Gen Physiol Biophys 15:251–264
282. Girotti PA, Misawa R, Palombit K, Mendes CE, Bittencourt JC, Castelucci P (2013) Differential effects of undernourishment on the differentiation and maturation of rat enteric neurons. Cell Tissue Res
283. Glasgow I, Mattar K, Krantis A (1998) Rat gastroduodenal motility in vivo: involvement of NO and ATP in spontaneous motor activity. Am J Physiol 275:G889–G896
284. Glavin GB, Westerberg VS, Geiger JD (1987) Modulation of gastric acid secretion by adenosine in conscious rats. Can J Physiol Pharmacol 65:1182–1185
285. Glushakov AV, Melishchuk AI, Skok VI (1996) ATP-induced currents in submucous plexus neurons of the guinea-pig small intestine. Neurophysiology (Moscow) 28:77–85
286. Glushakov AV, Glushakova HY, Skok VI (1998) Two types of P_{2X}-purinoceptors in neurons of the guinea pig ileum submucous plexus. Neurophysiology (Moscow) 30:242–245
287. Goldman H, Rosoff CB (1968) Pathogenesis of acute gastric stress ulcers. Am J Pathol 52:227–244
288. Gomes P, Boesmans W, Janssens J, Neunlist M, Tack J, Vanden Berghe P (2007) Enteric neurons signal to glia via an ATP-dependent paracrine pathway. Neurogastroenterol Motil 19:43–44
289. Gordon JL (1986) Extracellular ATP: effects, sources and fate. Biochem J 233:309–319
290. Goyal RK (2011) Evidence for β-nicotinamide adenine dinucleotide as a purinergic, inhibitory neurotransmitter in doubt. Gastroenterology 141:e27–e28
291. Goyal RK, Sullivan MP, Chaudhury A (2013) Progress in understanding of inhibitory purinergic neuromuscular transmission in the gut. Neurogastroenterol Motil 25:203–207
292. Gradilone SA, Masyuk AI, Splinter PL, Banales JM, Huang BQ, Tietz PS, Masyuk TV, LaRusso NF (2007) Cholangiocyte cilia express TRPV4 and detect changes in luminal tonicity inducing bicarbonate secretion. Proc Natl Acad Sci U S A 104:19138–19143
293. Granger DN, Richardson PD, Kvietys PR, Mortillaro NA (1980) Intestinal blood flow. Gastroenterology 78:837–863
294. Grasa L, Gil V, Gallego D, Martín MT, Jiménez M (2009) $P2Y_1$ receptors mediate inhibitory neuromuscular transmission in the rat colon. Br J Pharmacol 158:1641–1652
295. Grasl M, Turnheim K (1984) Stimulation of electrolyte secretion in rabbit colon by adenosine. J Physiol 346:93–110
296. Grbic DM, Degagné E, Langlois C, Dupuis AA, Gendron FP (2008) Intestinal inflammation increases the expression of the $P2Y_6$ receptor on epithelial cells and the release of CXC chemokine ligand 8 by UDP. J Immunol 180:2659–2668
297. Grbic DM, Degagné É, Larriveé JF, Bilodeau MS, Vinette V, Arguin G, Stankova J, Gendron FP (2012) $P2Y_6$ receptor contributes to neutrophil recruitment to inflamed intestinal mucosa by increasing CXC chemokine ligand 8 expression in an AP-1-dependent manner in epithelial cells. Inflamm Bowel Dis 18:1456–1469
298. Gröschel-Stewart U, Bardini M, Robson T, Burnstock G (1999) Localisation of $P2X_5$ and $P2X_7$ receptors by immunohistochemistry in rat stratified squamous epithelia. Cell Tissue Res 296:599–605
299. Grundy D, Al-Chaer ED, Aziz Q, Collins SM, Ke M, Taché Y, Wood JD (2006) Fundamentals of neurogastroenterology: basic science. Gastroenterology 130:1391–1411
300. Gulbransen BD, Sharkey KA (2009) Purinergic neuron-to-glia signaling in the enteric nervous system. Gastroenterology 136:1349–1358
301. Gulbransen BD, Bains JS, Sharkey KA (2010) Enteric glia are targets of the sympathetic innervation of the myenteric plexus in the guinea pig distal colon. J Neurosci 30:6801–6809
302. Gulbransen BD, Bashashati M, Hirota SA, Gui X, Roberts JA, MacDonald JA, Muruve DA, McKay DM, Beck PL, Mawe GM, Thompson RJ, Sharkey KA (2012) Activation of neuronal P2X7

receptor-pannexin-1 mediates death of enteric neurons during colitis. Nat Med 18:600–604
303. Guldali O, Savci V, Buyukafsar K (2011) CDP-choline-induced contractions in the mouse gastric fundus through purinoceptors and Rho/Rho-kinase signalling. Life Sci 88:473–479
304. Guo C, Quobatari A, Shangguan Y, Hong S, Wiley JW (2004) Diabetic autonomic neuropathy: evidence for apoptosis in situ in the rat. Neurogastroenterol Motil 16:335–345
305. Guo X, Merlin D, Harvey RD, Laboisse C, Hopfer U (1995) Stimulation of Cl^- secretion by extracellular ATP does not depend on increased cytosolic Ca^{2+} in HT-29.cl16E. Am J Physiol 269: C1457–C1463
306. Guo XW, Merlin D, Laboisse C, Hopfer U (1997) Purinergic agonists, but not cAMP, stimulate coupled granule fusion and Cl^- conductance in HT29-Cl.16E. Am J Physiol 273:C804–C809
307. Gür S, Karahan ST (1997) Effects of adenosine 5′-triphosphate, adenosine and acetylcholine in urinary bladder and colon muscles from streptozotocin diabetic rats. Arzneimittelforschung 47:1226–1229
308. Gustafsson LE, Wiklund NP, Lundin J, Hedqvist P (1985) Characterization of pre- and post-junctional adenosine receptors in guinea-pig ileum. Acta Physiol Scand 123:195–203
309. Guzman J, Yu JG, Suntres Z, Bozarov A, Cooke H, Javed N, Auer H, Palatini J, Hassanain HH, Cardounel AJ, Javed A, Grants I, Wunderlich JE, Christofi FL (2006) ADOA3R as a therapeutic target in experimental colitis: proof by validated high-density oligonucleotide microarray analysis. Inflamm Bowel Dis 12:766–789
310. Gwynne RM, Bornstein JC (2007) Synaptic transmission at functionally identified synapses in the enteric nervous system: roles for both ionotropic and metabotropic receptors. Curr Neuropharmacol 5:1–17
311. Hamada E, Imai Y, Hazama H, Takahashi M, Nakajima T, Ota S, Terano A, Omata M, Kurachi Y (1993) P_2-purinergic receptor in human gastric signet ring cell carcinoma cell line: a patch clamp study. Gastroenterology 104:A829
312. Hancock DL, Coupar IM (1995) Functional characterization of the adenosine receptor mediating inhibition of peristalsis in the rat jejunum. Br J Pharmacol 115:739–744
313. Hao MM, Boesmans W, Van den Abbeel V, Jennings EA, Bornstein JC, Young HM, Vanden Berghe P (2011) Early emergence of neural activity in the developing mouse enteric nervous system. J Neurosci 31:15352–15361
314. Hart ML, Jacobi B, Schittenhelm J, Henn M, Eltzschig HK (2009) Cutting edge: A2B adenosine receptor signaling provides potent protection during intestinal ischemia/reperfusion injury. J Immunol 182:3965–3968
315. Hatanaka H, Takada S, Choi YL, Fujiwara S, Soda M, Enomoto M, Kurashina K, Watanabe H, Yamashita Y, Sugano K, Mano H (2007) Transforming activity of purinergic receptor P2Y, G-protein coupled, 2 revealed by retroviral expression screening. Biochem Biophys Res Commun 356:723–726
316. Heazell MA (1975) Is ATP an inhibitory neurotransmitter in the rat stomach? Br J Pharmacol 55:285P–286P
317. Hede SE, Amstrup J, Christoffersen BC, Novak I (1999) Purinoceptors evoke different electrophysiological responses in pancreatic ducts. P2Y inhibits K^+ conductance, and P2X stimulates cation conductance. J Biol Chem 274:31784–31791
318. Heinemann A, Shahbazian A, Barthó L, Holzer P (1999) Different receptors mediating the inhibitory action of exogenous ATP and endogenously released purines on guinea-pig intestinal peristalsis. Br J Pharmacol 128:313–320
319. Henry JP, Stephens PM (1980) Caffeine as an intensifier of stress-induced hormonal and pathophysiologic changes in mice. Pharmacol Biochem Behav 13:719–727
320. Henz SL, Ribeiro CG, Rosa A, Chiarelli RA, Casali EA, Sarkis JJ (2006) Kinetic characterization of ATP diphosphohydrolase and 5′-nucleotidase activities in cells cultured from submandibular salivary glands of rats. Cell Biol Int 30:214–220
321. Henz SL, Fürstenau CR, Chiarelli RA, Sarkis JJ (2007) Kinetic and biochemical characterization of an ecto-nucleotide pyrophosphatase/phosphodiesterase (EC 3.1.4.1) in cells cultured from submandibular salivary glands of rats. Arch Oral Biol 52:916–923
322. Henz SL, Cognato GP, Vuaden FC, Bogo MR, Bonan CD, Sarkis JJ (2009) Influence of antidepressant drugs on Ecto-nucleotide pyrophosphatase/phosphodiesterases (E-NPPs) from salivary glands of rats. Arch Oral Biol 54:730–736
323. Hinoshita E, Uchiumi T, Taguchi K, Kinukawa N, Tsuneyoshi M, Maehara Y, Sugimachi K, Kuwano M (2000) Increased expression of an ATP-binding cassette superfamily transporter, multidrug resistance protein 2, in human colorectal carcinomas. Clin Cancer Res 6:2401–2407
324. Hirst GD, Bywater RA, Teramoto N, Edwards FR (2004) An analysis of inhibitory junction potentials in the guinea-pig proximal colon. J Physiol 558:841–855
325. Hitchin BW, Dobson PR, Ruprai A, Hardcastle J, Hardcastle PT, Taylor CJ, Brown BL (1991) Purinoceptors and second messenger signalling in the human colonic adenoma cell line. J Physiol 438: 80P
326. Holton P (1959) The liberation of adenosine triphosphate on antidromic stimulation of sensory nerves. J Physiol Lond 145:494–504
327. Holzer P (2004) Gastrointestinal pain in functional bowel disorders: sensory neurons as novel drug targets. Expert Opin Ther Targets 8: 107–123
328. Holzer P (2006) Efferent-like roles of afferent neurons in the gut: blood flow regulation and tissue protection. Auton Neurosci 125: 70–75
329. Holzer P (2007) Taste receptors in the gastrointestinal tract. V. Acid sensing in the gastrointestinal tract. Am J Physiol Gastrointest Liver Physiol 292:G699–G705
330. Holzer P, Livingston EH, Saria A, Guth PH (1991) Sensory neurons mediate protective vasodilatation in rat gastric mucosa. Am J Physiol 260:G363–G370
331. Höpfner M, Lemmer K, Jansen A, Hanski C, Riecken EO, Gavish M, Mann B, Buhr H, Glassmeier G, Scherübl H (1998) Expression of functional P_2-purinergic receptors in primary cultures of human colorectal carcinoma cells. Biochem Biophys Res Commun 251: 811–817
332. Höpfner M, Maaser K, Barthel B, von Lampe B, Hanski C, Riecken EO, Zeitz M, Scherubl H (2001) Growth inhibition and apoptosis induced by P2Y2 receptors in human colorectal carcinoma cells: involvement of intracellular calcium and cyclic adenosine monophosphate. Int J Color Dis 16:154–166
333. Hourani SMO (1999) Postnatal development of purinoceptors in rat visceral smooth muscle preparations. Gen Pharmacol 32:3–7
334. Hourani SMO, Bailey SJ, Nicholls J, Kitchen I (1991) Direct effects of adenylyl 5′-(β, γ-methylene)diphosphonate, a stable ATP analogue, on relaxant P1-purinoceptors in smooth muscle. Br J Pharmacol 104:685–690
335. Hourani SMO, Bailey SJ, Johnson CR, Tennant JP (1998) Effects of adenosine 5′-triphosphate, uridine 5′-triphosphate, adenosine 5′-tetraphosphate and diadenosine polyphosphates in guinea-pig taenia caeci and rat colon muscularis mucosae. Naunyn Schmiedebergs Arch Pharmacol 358:464–473
336. Hoyle CHV (1992) Transmission: purines. In: Burnstock G, Hoyle CHV (eds) The autonomic nervous system. Autonomic neuroeffector mechanisms. Harwood Academic, Chur, pp 367–407
337. Hoyle CHV, Burnstock G (1989) Neuromuscular transmission in the gastrointestinal tract. In: Wood JD (ed) Handbook of physiology, section 6: the gastrointestinal system, vol. I: motility and circulation. American Physiological Society, Bethesda, pp 435–464

338. Hoyle CHV, Reilly WM, Lincoln J, Burnstock G (1988) Adrenergic, but not cholinergic or purinergic, responses are potentiated in the cecum of diabetic rats. Gastroenterology 94:1357–1367
339. Hoyle CHV, Kamm MA, Burnstock G, Lennard-Jones JE (1990) Enkephalins modulate inhibitory neuromuscular transmission in circular muscle of human colon via δ-opioid receptors. J Physiol 431:465–478
340. Hu H, O'Mullane LM, Cummins MM, Campbell CR, Hosoda Y, Poronnik P, Dinudom A, Cook DI (2010) Negative regulation of Ca^{2+} influx during $P2Y_2$ purinergic receptor activation is mediated by Gβγ-subunits. Cell Calcium 47:55–64
341. Hu HZ, Gao N, Zhu MX, Liu S, Ren J, Gao C, Xia Y, Wood JD (2003) Slow excitatory synaptic transmission mediated by $P2Y_1$ receptors in the guinea-pig enteric nervous system. J Physiol 550:493–504
342. Hubel KA (1984) Electrical stimulus-secretion coupling in rabbit ileal mucosa. J Pharmacol Exp Ther 231:577–582
343. Huh JW, Park YA, Lee KY, Sohn SK (2009) Heterogeneity of adenosine triphosphate-based chemotherapy response assay in colorectal cancer—secondary publication. Yonsei Med J 50:697–703
344. Hunt WB, Parsons DG, Wahid A, Wilkinson J (1978) Influence of 2-2′-pyridylisatogen tosylate on responses produced by ATP and by neural stimulation on the rat gastric copus. Br J Pharmacol 63:378P–379P
345. Hurley TW, Shoemaker DD, Ryan MP (1993) Extracellular ATP prevents the release of stored Ca^{2+} by autonomic agonists in rat submandibular gland acini. Am J Physiol 265:C1472–C1478
346. Hurley TW, Ryan MP, Shoemaker DD (1994) Mobilization of Ca^{2+} influx, but not of stored Ca^{2+}, by extracellular ATP in rat submandibular gland acini. Arch Oral Biol 39:205–212
347. Hurley TW, Ryan MP, Moore WC (1996) Regulation of changes in cytosolic Ca^{2+} and Na^{+} concentrations in rat submandibular gland acini exposed to carbachol and ATP. J Cell Physiol 168:229–238
348. Hwang SJ, Durnin L, Dwyer L, Rhee PL, Ward SM, Koh SD, Sanders KM, Mutafova-Yambolieva VN (2011) β-Nicotinamide adenine dinucleotide is an enteric inhibitory neurotransmitter in human and nonhuman primate colons. Gastroenterology 140:608–617
349. Hwang SJ, Blair PJ, Durnin L, Mutafova-Yambolieva V, Sanders KM, Ward SM (2012) P2Y1 purinoreceptors are fundamental to inhibitory motor control of murine colonic excitability and transit. J Physiol 590:1957–1972
350. Ikawa H (1981) Study of acetylcholine and muscarinic receptors in Hirschsprung's disease. Jpn J Pediatr Surg 17:237–247
351. Imaeda K, Suzuki H (1997) Properties of inhibitory transmission in smooth muscle of the guinea pig lower esophageal sphincter. J Auton Nerv Syst 65:132
352. Imoto A, Inoue R, Tanaka M, Ito Y (1998) Inhibitory NANC neurotransmission in choledocho-duodenal junction of rabbits—a possible role of PACAP. J Auton Nerv Syst 70:189–199
353. Inoue CN, Woo JS, Schwiebert EM, Morita T, Hanaoka K, Guggino SE, Guggino WB (1997) Role of purinergic receptors in chloride secretion in Caco-2 cells. Am J Physiol 272:C1862–C1870
354. Ishiguchi T, Takahashi T, Itoh H, Owyang C (2000) Nitrergic and purinergic regulation of the rat pylorus. Am J Physiol 279:G740–G747
355. Ishiguro H, Naruse S, Kitagawa M, Hayakawa T, Case RM, Steward MC (1999) Luminal ATP stimulates fluid and HCO_3^- secretion in guinea-pig pancreatic duct. J Physiol 519(Pt 2):551–558
356. Ishii T, Shimo Y (1983) Nerve-mediated non-adrenergic inhibitory responses of guinea-pig taenia caeci: further evidence of depression by morphine. J Pharm Pharmacol 35:828–830
357. Ishikawa S (1985) Actions of ATP and α, β-methylene ATP on neuromuscular transmission and smooth muscle membrane of the rabbit and guinea-pig mesenteric arteries. Br J Pharmacol 86:777–787
358. Ivancheva C, Rahamimoff R, Radomirov R (2001) Apamin-sensitive nitric oxide- and ATP-mediated motor effects on the guinea pig small intestine. Gen Physiol Biophys 20:97–108
359. Iwanaga K, Murata T, Hori M, Ozaki H (2013) Purinergic P2Y1 receptor signaling mediates wound stimuli-induced cyclooxygenase-2 expression in intestinal subepithelial myofibroblasts. Eur J Pharmacol 702:158–164
360. Jenkinson KM, Reid JJ (1995) Effect of diabetes on relaxations to non-adrenergic, non-cholinergic nerve stimulation in longitudinal muscle of the rat gastric fundus. Br J Pharmacol 116:1551–1556
361. Jenkinson KM, Reid JJ (2000) Altered non-adrenergic non-cholinergic neurotransmission in gastric fundus from streptozotocin-diabetic rats. Eur J Pharmacol 401:251–258
362. Jessen KR, Burnstock G (1982) The enteric nervous system in tissue culture: a new mammalian model for the study of complex nervous networks. In: Kalsner S (ed) Trends in autonomic pharmacology, vol II. Urban & Schwartzenberg, Baltimore, pp 95–115
363. Jhandier MN, Kruglov EA, Lavoie EG, Sevigny J, Dranoff JA (2005) Portal fibroblasts regulate the proliferation of bile duct epithelia via expression of NTPDase2. J Biol Chem 280:22986–22992
364. Jijon HB, Walker J, Hoentjen F, Diaz H, Ewaschuk J, Jobin C, Madsen KL (2005) Adenosine is a negative regulator of NF-κB and MAPK signaling in human intestinal epithelial cells. Cell Immunol 237:86–95
365. Johannesson N, Andersson K-E, Joelsson B, Persson CG (1985) Relaxation of lower esophageal sphincter and stimulation of gastric secretion and diuresis by antiasthmatic xanthines. Role of adenosine antagonism. Am Rev Respir Dis 131:26–30
366. Johnson CR, Hourani SMO (1994) Contractile effects of uridine 5′-triphosphate in the rat duodenum. Br J Pharmacol 113:1191–1196
367. Johnson CR, Charlton SJ, Hourani SMO (1996) Responses of the longitudinal muscle and the muscularis mucosae of the rat duodenum to adenine and uracil nucleotides. Br J Pharmacol 117:823–830
368. Jones CJ, Mann GE, Smaje LH (1980) The role of cyclic nucleotides and related compounds in nerve-mediated vasodilatation in the cat submandibular gland. Br J Pharmacol 68:485–497
369. Jorgensen TD, Gromada J, Tritsaris K, Nauntofte B, Dissing S (1995) Activation of P_{2z} purinoceptors diminishes the muscarinic cholinergic-induced release of inositol 1,4,5-trisphosphate and stored calcium in rat parotid acini. ATP as a co-transmitter in the stimulus-secretion coupling. Biochem J 312:457–464
370. Kabré E, Chaïb N, Boussard P, Merino G, Devleeschouwer M, Dehaye JP (1999) Study on the activation of phospholipases A_2 by purinergic agonists in rat submandibular ductal cells. Biochim Biophys Acta 1436:616–627
371. Kadowaki M, Takeda M, Tokita K, Hanaoka K, Tomoi M (2000) Molecular identification and pharmacological characterization of adenosine receptors in the guinea-pig colon. Br J Pharmacol 129:871–876
372. Kalhan A, Kidd M, Modlin I, Pfragner R, Rees DA, Ham J (2009) Adenosine A2 receptor signalling mediates chromogranin A secretion from neuroendocrine tumours. Neuroendocrinology 90:119
373. Kalhan A, Gharibi B, Vazquez M, Jasani B, Neal J, Kidd M, Modlin IM, Pfragner R, Rees DA, Ham J (2012) Adenosine A_{2A} and A_{2B} receptor expression in neuroendocrine tumours: potential targets for therapy. Purinergic Signal 8:265–274
374. Kamiji T, Morita K, Katayama Y (1994) ATP regulates synaptic transmission by pre- and postsynaptic mechanisms in guinea-pig myenteric neurons. Neuroscience 59:165–174
375. Kamikawa Y, Shimo Y (1982) Modulating effects of opioids, purine compounds, 5-hydroxytryptamine and prostaglandin E_2 on

cholinergic neurotransmission in a guinea-pig oesophagus preparation. J Pharm Pharmacol 34:794–797
376. Kamikawa Y, Serizawa K, Shimo Y (1977) Some possibilities for prostaglandin mediation in the contractile response to ATP of the guinea-pig digestive tract. Eur J Pharmacol 45:199–203
377. Karanjia R, García-Hernandez LM, Miranda-Morales M, Somani N, Espinosa-Luna R, Montaño LM, Barajas-López C (2006) Cross-inhibitory interactions between $GABA_A$ and P2X channels in myenteric neurones. Eur J Neurosci 23:3259–3268
378. Katayama Y, Morita K (1989) Adenosine 5′-triphosphate modulates membrane potassium conductance in guinea-pig myenteric neurones. J Physiol 408:373–390
379. Kaunitz JD, Akiba Y (2011) Purinergic regulation of duodenal surface pH and ATP concentration: implications for mucosal defence, lipid uptake and cystic fibrosis. Acta Physiol (Oxf) 201:109–116
380. Kazic T, Milosavljevic D (1977) Influence of pyridylisatogen tosylate on contractions produced by ATP and by purinergic stimulation in the terminal ileum of the guinea-pig. J Pharm Pharmacol 29: 542–545
381. Keating C, Pelegrin P, Martinez CM, Grundy D (2011) $P2X_7$ receptor-dependent intestinal afferent hypersensitivity in a mouse model of postinfectious irritable bowel syndrome. J Immunol 187: 1467–1474
382. Keef KD, Du C, Ward SM, McGregor B, Sanders KM (1993) Enteric inhibitory neural regulation of human colonic circular muscle: role of nitric oxide. Gastroenterology 105:1009–1016
383. Keef KD, Saxton SN, McDowall RA, Kaminski RE, Duffy AM, Cobine CA (2013) Functional role of vasoactive intestinal polypeptide in inhibitory motor innervation in the mouse internal anal sphincter. J Physiol 591:1489–1506
384. Kennedy I, Humphrey PP (1994) Evidence for the presence of two types of P2 purinoceptor in the guinea-pig ileal longitudinal smooth muscle preparation. Eur J Pharmacol 261:273–280
385. Kerstan D, Leipziger J, Gordjani N, Nitschke R, Greger R (1997) Luminal addition of ATP induces K^+ secretion via a $P2Y_2$ receptor in rat distal colonic mucosa. Pflugers Arch 433:R128
386. Kerstan D, Gordjani N, Nitschke R, Greger R, Leipziger J (1998) Luminal ATP induces K^+ secretion via a $P2Y_2$ receptor in rat distal colonic mucosa. Pflugers Arch 436:712–716
387. Kestler C, Neuhuber WL, Raab M (2009) Distribution of $P2X_3$ receptor immunoreactivity in myenteric ganglia of the mouse esophagus. Histochem Cell Biol 131:13–27
388. Kidder GW (1973) Effects of the ATP analog 5′-adenylyl methylenediphosphonate on acid secretion in frog gastric mucosa. Biochim Biophys Acta 298:732–742
389. Kidder GW (1982) Adenosine kinase from *Trypanosoma cruzi*. Biochem Biophys Res Commun 107:381–388
390. Kim HD, Bowen JW, James-Kracke MR, Landon LA, Camden JM, Burnett JE, Turner JT (1996) Potentiation of regulatory volume decrease by P_{2U} purinoceptors in HSG-PA cells. Am J Physiol 270:C86–C97
391. Kim YC, Camaioni E, Ziganshin AU, Ji XD, King BF, Wildman SS, Rychkov A, Yoburn J, Kim H, Mohanram A, Harden TK, Boyer JL, Burnstock G, Jacobson KA (1998) Synthesis and structure–activity relationships of pyridoxal-6-azoaryl-5′-phosphate and phosphonate derivatives as P2 receptor antagonists. Drug Dev Res 45:52–66
392. Kimball BC, Mulholland MW (1995) Neuroligands evoke calcium signaling in cultured myenteric neurons. Surgery 118:162–169
393. Kimball BC, Mulholland MW (1996) Enteric glia exhibit P_{2U} receptors that increase cytosolic calcium by a phospholipase C-dependent mechanism. J Neurochem 66:604–612
394. Kimmich G, Randles J (1980) Regulation of Na^+-dependent sugar transport in intestinal epithelial cells by exogenous ATP. Am J Physiol 238:C177–C183
395. Kimura Y, Turner JR, Braasch DA, Buddington RK (2005) Lumenal adenosine and AMP rapidly increase glucose transport by intact small intestine. Am J Physiol Gastrointest Liver Physiol 289:G1007–G1014
396. King BF, Townsend-Nicholson A (2008) Involvement of $P2Y_1$ and $P2Y_{11}$ purinoceptors in parasympathetic inhibition of colonic smooth muscle. J Pharmacol Exp Ther 324:1055–1063
397. Kinoshita N, Takahashi T, Tada S, Shinozuka K, Mizuno N, Takahashi K (2006) Activation of P2Y receptor enhances high-molecular compound absorption from rat ileum. J Pharm Pharmacol 58:195–200
398. Kirkup AJ, Brunsden AM, Grundy D (2001) Receptors and transmission in the brain–gut axis: potential for novel therapies. I. Receptors on visceral afferents. Am J Physiol Gastrointest Liver Physiol 280:G787–G794
399. Koh SD, Dick GM, Sanders KM (1997) Small-conductance Ca^{2+}-dependent K^+ channels activated by ATP in murine colonic smooth muscle. Am J Physiol 273:C2010–C2021
400. Kohn PG, Newey H, Smyth DH (1970) The effect of adenosine triphosphate on the transmural potential in rat small intestine. J Physiol 208:203–220
401. Kolachala V, Asamoah V, Wang L, Obertone TS, Ziegler TR, Merlin D, Sitaraman SV (2005) TNF-α upregulates adenosine 2b (A2b) receptor expression and signaling in intestinal epithelial cells: a basis for A2bR overexpression in colitis. Cell Mol Life Sci 62: 2647–2657
402. Kolachala VL, Obertone TS, Wang L, Merlin D, Sitaraman SV (2006) Adenosine 2b receptor (A2bR) signals through adenylate cyclase (AC) 6 isoform in the intestinal epithelial cells. Biochim Biophys Acta 1760:1102–1108
403. Kolachala VL, Bajaj R, Chalasani M, Sitaraman SV (2008) Purinergic receptors in gastrointestinal inflammation. Am J Physiol Gastrointest Liver Physiol 294:G401–G410
404. Kolachala VL, Ruble BK, Vijay-Kumar M, Wang L, Mwangi S, Figler HE, Figler RA, Srinivasan S, Gewirtz AT, Linden J, Merlin D, Sitaraman SV (2008) Blockade of adenosine A2B receptors ameliorates murine colitis. Br J Pharmacol 155:127–137
405. Kolachala VL, Vijay-Kumar M, Dalmasso G, Yang D, Linden J, Wang L, Gewirtz A, Ravid K, Merlin D, Sitaraman SV (2008) A2B adenosine receptor gene deletion attenuates murine colitis. Gastroenterology 135:861–870
406. Kong ID, Koh SD, Sanders KM (2000) Purinergic activation of spontaneous transient outward currents in guinea pig taenia colonic myocytes. Am J Physiol Cell Physiol 278:C352–C362
407. Korman LY, Lemp GF, Jackson MJ, Gardner JD (1982) Mechanism of action of ATP on intestinal epithelial cells. Cyclic AMP-mediated stimulation of active ion transport. Biochim Biophys Acta 721:47–54
408. Kotecha N (1999) Mechanisms underlying ACh induced modulation of neurogenic and applied ATP constrictions in the submucosal arterioles of the guinea-pig small intestine. Br J Pharmacol 126: 1625–1633
409. Köttgen M, Löffler T, Jacobi C, Nitschke R, Pavenstädt H, Schreiber R, Frische S, Nielsen S, Leipziger J (2003) P2Y6 receptor mediates colonic NaCl secretion via differential activation of cAMP-mediated transport. J Clin Invest 111:371–379
410. Krantis A, Costa M, Furness JB, Orbach J (1980) γ-Aminobutyric acid stimulates intrinsic inhibitory and excitatory nerves in the guinea-pig intestine. Eur J Pharmacol 67:461–468
411. Krishnamurty VS, Kadowitz PJ (1983) Influence of adenosine triphosphate on the isolated perfused mesenteric artery of the rabbit. Can J Physiol Pharmacol 61:1409–1417
412. Kunze WA, Bornstein JC, Furness JB (1995) Identification of sensory nerve cells in a peripheral organ (the intestine) of a mammal. Neuroscience 66:1–4
413. Künzli BM, Berberat PO, Dwyer K, Deaglio S, Csizmadia E, Cowan P, d'Apice A, Moore G, Enjyoji K, Friess H, Robson SC

(2011) Variable impact of CD39 in experimental murine colitis. Dig Dis Sci 56:1393–1403
414. Kurahashi M, Zheng H, Dwyer L, Ward SM, Don KS, Sanders KM (2011) A functional role for the 'fibroblast-like cells' in gastrointestinal smooth muscles. J Physiol 589:697–710
415. Kurashima Y, Amiya T, Nochi T, Fujisawa K, Haraguchi T, Iba H, Tsutsui H, Sato S, Nakajima S, Iijima H, Kubo M, Kunisawa J, Kiyono H (2012) Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. Nat Commun 3:1034
416. Kurihara K, Nakanishi N, Ueha T (1997) A calcium channel in human submandibular duct cell line, HSG cells, not regulated by P_{2U} purinergic receptor-mediated intracellular calcium mobilization. Arch Oral Biol 42:547–557
417. Kusu T, Kayama H, Kinoshita M, Jeon SG, Ueda Y, Goto Y, Okumura R, Saiga H, Kurakawa T, Ikeda K, Maeda Y, Nishimura J, Arima Y, Atarashi K, Honda K, Murakami M, Kunisawa J, Kiyono H, Okumura M, Yamamoto M, Takeda K (2013) Ectonucleoside triphosphate diphosphohydrolase 7 controls Th17 cell responses through regulation of luminal ATP in the small intestine. J Immunol 190:774–783
418. Lachish M, Alzola E, Chaib N, Métioui M, Grosfils K, Kabré E, Moran A, Marino A, Dehaye JP (1996) Study of nonspecific cation channel coupled to P_{2z} purinergic receptors using an acid load technique. Am J Physiol 271:C1920–C1926
419. Langley JN (1898) On inhibitory fibres in the vagus to the end of the oesophagus and stomach. J Physiol 23:407–414
420. Langlois C, Gendron FP (2009) Promoting Mϕ transepithelial migration by stimulating the epithelial cell $P2Y_2$ receptor. Eur J Immunol 39:2895–2905
421. Larsson LT (1994) Hirschsprung's disease—immunohistochemical findings. Histol Histopathol 9:615–629
422. Larsson LT, Shen Z, Ekblad E, Sundler F, Alm P, Andersson KE (1995) Lack of neuronal nitric oxide synthase in nerve fibers of aganglionic intestine: a clue to Hirschsprung's disease. J Pediatr Gastroenterol Nutr 20:49–53
423. Lavoie EG, Gulbransen BD, Martín-Satué M, Aliagas E, Sharkey KA, Sévigny J (2011) Ectonucleotidases in the digestive system: focus on NTPDase3 localization. Am J Physiol Gastrointest Liver Physiol 300:G608–G620
424. Lazarowski ER, Rochelle LG, O'Neal WK, Ribeiro CM, Grubb BR, Zhang V, Harden TK, Boucher RC (2001) Cloning and functional characterization of two murine uridine nucleotide receptors reveal a potential target for correcting ion transport deficiency in cystic fibrosis gallbladder. J Pharmacol Exp Ther 297:43–49
425. Lee HK, Ro S, Keef KD, Kim YH, Kim HW, Horowitz B, Sanders KM (2005) Differential expression of P2X-purinoceptor subtypes in circular and longitudinal muscle of canine colon. Neurogastroenterol Motil 17:575–584
426. Lee JH, Kim MC, Oh SY, Kwon HC, Kim SH, Kwon KA, Lee S, Jeong JS, Choi SR, Kim HJ (2011) Predictive value of in vitro adenosine triphosphate-based chemotherapy response assay in advanced gastric cancer patients who received oral 5-fluorouracil after curative resection. Cancer Res Treat 43:117–123
427. Lee JJ, Talubmook C, Parsons ME (2001) Activation of presynaptic A1-receptors by endogenous adenosine inhibits acetylcholine release in the guinea-pig ileum. J Auton Pharmacol 21:29–38
428. Lee MG, Schultheis PJ, Yan M, Shull GE, Bookstein C, Chang E, Tse M, Donowitz M, Park K, Muallem S (1998) Membrane-limited expression and regulation of Na^+–H^+ exchanger isoforms by P_2 receptors in the rat submandibular gland duct. J Physiol 513:341–357
429. Lefebvre RA (1986) Study on the possible neurotransmitter of the non-adrenergic non-cholinergic innervation of the rat gastric fundus. Arch Int Pharmacodyn Ther 280:110–136
430. Lefebvre RA, Willems JL (1979) Gastric relaxation by apomorphine and ATP in the conscious dog. J Pharm Pharmacol 31:561–563
431. Leipziger J, Kerstan D, Nitschke R, Greger R (1997) ATP increases $[Ca^{2+}]_i$ and ion secretion via a basolateral P2Y-receptor in rat distal colonic mucosa. Pflugers Arch 434:77–83
432. Lelièvre V, Muller JM, Falcòn J (1998) Adenosine modulates cell proliferation in human colonic adenocarcinoma. I. Possible involvement of adenosine A1 receptor subtypes in HT29 cells. Eur J Pharmacol 341:289–297
433. Lelièvre V, Muller JM, Falcòn J (1998) Adenosine modulates cell proliferation in human colonic carcinoma. II. Differential behavior of HT29, DLD-1, Caco-2 and SW403 cell lines. Eur J Pharmacol 341:299–308
434. Leng Y, Yamamoto T, Kadowaki M (2008) Alteration of cholinergic, purinergic and sensory neurotransmission in the mouse colon of food allergy model. Neurosci Lett 445:195–198
435. LePard KJ, Messori E, Galligan JJ (1997) Purinergic fast excitatory postsynaptic potentials in myenteric neurons of guinea pig: distribution and pharmacology. Gastroenterology 113:1522–1534
436. LePard KJ, Ren J, Galligan JJ (2004) Presynaptic modulation of cholinergic and non-cholinergic fast synaptic transmission in the myenteric plexus of guinea pig ileum. Neurogastroenterol Motil 16: 355–364
437. Levin R, Braiman A, Priel Z (1997) Protein kinase C induced calcium influx and sustained enhancement of ciliary beating by extracellular ATP. Cell Calcium 21:103–113
438. Li N, Harris PD, Zakaria ER, Matheson PJ, Garrison RN (2007) Role of adenosine receptor subtypes in rat jejunum in unfed state versus glucose-induced hyperemia. J Surg Res 139:51–60
439. Li Q, Luo X, Zeng W, Muallem S (2003) Cell-specific behavior of $P2X_7$ receptors in mouse parotid acinar and duct cells. J Biol Chem 278:47554–47561
440. Lim SP, Muir TC (1986) Neuroeffector transmission in the guinea-pig internal anal sphincter: an electrical and mechanical study. Eur J Pharmacol 128:17–24
441. Limami Y, Pinon A, Leger DY, Pinault E, Delage C, Beneytout JL, Simon A, Liagre B (2012) The $P2Y_2$/Src/p38/COX-2 pathway is involved in the resistance to ursolic acid-induced apoptosis in colorectal and prostate cancer cells. Biochimie 94:1754–1763
442. Liñán-Rico A, Wunderlich JE, Grants IS, Frankel WL, Xue J, Williams KC, Harzman AE, Enneking JT, Cooke HJ, Christofi FL (2013) Purinergic autocrine regulation of mechanosensitivity and serotonin release in a human EC model: ATP-gated $P2X_3$ channels in EC are downregulated in ulcerative colitis. Inflamm Bowel Dis 19:2366–2379
443. Linden J (2006) Adenosine metabolism and cancer. Focus on "Adenosine downregulates DPPIV on HT-29 colon cancer cells by stimulating protein tyrosine phosphatases and reducing ERK1/2 activity via a novel pathway". Am J Physiol Cell Physiol 291:C405–C406
444. Ling ZQ, Qi CJ, Lu XX, Qian LJ, Gu LH, Zheng ZG, Zhao Q, Wang S, Fang XH, Yang ZX, Yin J, Mao WM (2012) Heterogeneity of chemosensitivity in esophageal cancer using ATP-tumor chemosensitivity assay. Acta Pharmacol Sin 33:401–406
445. Liu DM, Adams DJ (2001) Ionic selectivity of native ATP-activated (P2X) receptor channels in dissociated neurones from rat parasympathetic ganglia. J Physiol 534:423–435
446. Lohrmann E, Cabantchik ZI, Greger R (1992) Transmitter-induced changes of the membrane voltage of HT29 cells. Pflugers Arch 421: 224–229
447. Lomax AE, O'Reilly M, Neshat S, Vanner SJ (2007) Sympathetic vasoconstrictor regulation of mouse colonic submucosal arterioles is altered in experimental colitis. J Physiol 583:719–730
448. Luo X, Zheng W, Yan M, Lee MG, Muallem S (1999) Multiple functional P2X and P2Y receptors in the luminal and basolateral membranes of pancreatic duct cells. Am J Physiol 277:C205–C215

449. Ma DF, Kondo T, Nakazawa T, Niu DF, Mochizuki K, Kawasaki T, Yamane T, Katoh R (2010) Hypoxia-inducible adenosine A2B receptor modulates proliferation of colon carcinoma cells. Hum Pathol 41:1550–1557
450. Ma J, Altomare A, Rieder F, Behar J, Biancani P, Harnett KM (2011) ATP: a mediator for HCl-induced TRPV1 activation in esophageal mucosa. Am J Physiol Gastrointest Liver Physiol 301: G1075–G1082
451. Maaser K, Höpfner M, Kap H, Sutter AP, Barthel B, von Lampe B, Zeitz M, Scherübl H (2002) Extracellular nucleotides inhibit growth of human oesophageal cancer cells via $P2Y_2$-receptors. Br J Cancer 86:636–644
452. Mabley J, Soriano F, Pacher P, Hasko G, Marton A, Wallace R, Salzman A, Szabo C (2003) The adenosine A_3 receptor agonist, N^6-(3-iodobenzyl)-adenosine-5′-N-methyluronamide, is protective in two murine models of colitis. Eur J Pharmacol 466:323–329
453. Machaly M, Dalziel HH, Sneddon P (1988) Evidence for ATP as a cotransmitter in dog mesenteric artery. Eur J Pharmacol 147:83–91
454. Maggi CA, Manzini S, Meli A (1984) Evidence that GABAA receptors mediate relaxation of rat duodenum by activating intramural nonadrenergic–noncholinergic neurones. J Auton Pharmacol 4:77–85
455. Maguire MH, Satchell DG (1979) The contribution of adenosine to the inhibitory actions of adenine nucleotides on the guinea-pig taenia coli: studies with phosphate-modified adenine nucleotide analogs and dipyridamole. J Pharmacol Exp Ther 211:626–631
456. Mantuano-Barradas M, Henriques-Pons A, Araujo-Jorge TC, Di Virgilio F, Coutinho-Silva R, Persechini PM (2003) Extracellular ATP induces cell death in $CD4^+/CD8^+$ double-positive thymocytes in mice infected with *Trypanosoma cruzi*. Microbes Infect 5:1363–1371
457. Manzini S, Maggi CA, Meli A (1985) Further evidence for involvement of adenosine-5′-triphosphate in non-adrenergic non-cholinergic relaxation of the isolated rat duodenum. Eur J Pharmacol 113:399–408
458. Maor I, Rainis T, Lanir A, Lavy A (2011) Adenosine deaminase activity in patients with Crohn's disease: distinction between active and nonactive disease. Eur J Gastroenterol Hepatol 23:598–602
459. Martinson J (1965) Studies on the efferent vagal control of the stomach. Acta Physiol Scand Suppl 255:1–24
460. Martinson J, Muren A (1963) Excitatory and inhibitory effects of vagus stimulation on gastric motility in the cat. Acta Physiol Scand 57:309–316
461. Masyuk AI, Gradilone SA, Banales JM, Huang BQ, Masyuk TV, Lee SO, Splinter PL, Stroope AJ, LaRusso NF (2008) Cholangiocyte primary cilia are chemosensory organelles that detect biliary nucleotides via $P2Y_{12}$ purinergic receptors. Am J Physiol Gastrointest Liver Physiol 295:G725–G734
462. Matos JE, Robaye B, Boeynaems JM, Beauwens R, Leipziger J (2005) K^+ secretion activated by luminal $P2Y_2$ and $P2Y_4$ receptors in mouse colon. J Physiol 564:269–279
463. Matos JE, Sorensen MV, Geyti CS, Robaye B, Boeynaems JM, Leipziger J (2007) Distal colonic Na^+ absorption inhibited by luminal $P2Y_2$ receptors. Pflugers Arch 454:977–987
464. McAlroy HL, Ahmed S, Day SM, Baines DL, Wong HY, Yip CY, Ko WH, Wilson SM, Collett A (2000) Multiple P2Y receptor subtypes in the apical membranes of polarized epithelial cells. Br J Pharmacol 131:1651–1658
465. McColl KE (1997) Pathophysiology of duodenal ulcer disease. Eur J Gastroenterol Hepatol 9(Suppl 1):S9–S12
466. McDonnell B, Hamilton R, Fong M, Ward SM, Keef KD (2008) Functional evidence for purinergic inhibitory neuromuscular transmission in the mouse internal anal sphincter. Am J Physiol Gastrointest Liver Physiol 294:G1041–G1051
467. McGill JM, Basavappa S, Mangel AW, Shimokura GH, Middleton JP, Fitz JG (1994) Adenosine triphosphate activates ion permeabilities in biliary epithelial cells. Gastroenterology 107:236–243
468. McGill JM, Yen MS, Basavappa S, Mangel AW, Kwiatkowski AP (1995) ATP-activated chloride permeability in biliary epithelial cells is regulated by calmodulin-dependent protein kinase II. Biochem Biophys Res Commun 208:457–462
469. McMillian MK, Soltoff SP, Cantley LC, Rudel R, Talamo BR (1993) Two distinct cytosolic calcium responses to extracellular ATP in rat parotid acinar cells. Br J Pharmacol 108:453–461
470. McMillian MK, Soltoff SP, Cantley LC, Talamo BR (1987) Extracellular ATP elevates intracellular free calcium in rat parotid acinar cells. Biochem Biophys Res Commun 149: 523–530
471. McMillian MK, Soltoff SP, Lechleiter JD, Cantley LC, Talamo BR (1988) Extracellular ATP increases free cytosolic calcium in rat parotid acinar cells. Differences from phospholipase C-linked receptor agonists. Biochem J 255:291–300
472. McSwiney BA, Robson JH (1929) The response of smooth muscle to stimulation of the vagus nerve. J Physiol 68:124–131
473. Merighi S, Benini A, Mirandola P, Gessi S, Varani K, Simioni C, Leung E, Maclennan S, Baraldi PG, Borea PA (2007) Caffeine inhibits adenosine-induced accumulation of hypoxia-inducible factor-1α, vascular endothelial growth factor, and interleukin-8 expression in hypoxic human colon cancer cells. Mol Pharmacol 72:395–406
474. Merlin D, Augeron C, Tien XY, Guo X, Laboisse CL, Hopfer U (1994) ATP-stimulated electrolyte and mucin secretion in the human intestinal goblet cell line HT29-C1.16E. J Membr Biol 137:137–149
475. Métioui M, Amsallem H, Alzola E, Chaib N, Elyamani A, Moran A, Marino A, Dehaye JP (1996) Low affinity purinergic receptor modulates the response of rat submandibular glands to carbachol and substance P. J Cell Physiol 168:462–475
476. Meyer MP, Clarke JDW, Patel K, Townsend-Nicholson A, Burnstock G (1999) Selective expression of purinoceptor $cP2Y_1$ suggests a role for nucleotide signalling in development of the chick embryo. Dev Dyn 214:152–158
477. Michael S, Warstat C, Michel F, Yan L, Müller CE, Nieber K (2010) Adenosine A_{2A} agonist and A_{2B} antagonist mediate an inhibition of inflammation-induced contractile disturbance of a rat gastrointestinal preparation. Purinergic Signal 6:117–124
478. Mihara S, Katayama Y, Nishi S (1985) Slow postsynaptic potentials in neurones of the submucous plexus of guinea pig caecum and their mimickry by noradrenaline and various peptides. Neuroscience 16: 1057–1066
479. Minagawa N, Nagata J, Shibao K, Masyuk AI, Gomes DA, Rodrigues MA, Lesage G, Akiba Y, Kaunitz JD, Ehrlich BE, LaRusso NF, Nathanson MH (2007) Cyclic AMP regulates bicarbonate secretion in cholangiocytes through release of ATP into bile. Gastroenterology 133:1592–1602
480. Minker E, Matejka Z (1981) Purinergic reflex activated by cathartics in the rat. Acta Physiol Acad Sci Hung 57:99–107
481. Minocha A, Galligan JJ (1993) Excitatory and inhibitory responses mediated by $GABA_A$ and $GABA_B$ receptors in guinea pig distal colon. Eur J Pharmacol 230:187–193
482. Misawa R, Girotti PA, Mizuno MS, Liberti EA, Furness JB, Castelucci P (2010) Effects of protein deprivation and re-feeding on $P2X_2$ receptors in enteric neurons. World J Gastroenterol 16: 3651–3663
483. Mizumori M, Ham M, Guth PH, Engel E, Kaunitz JD, Akiba Y (2009) Intestinal alkaline phosphatase regulates protective surface microclimate pH in rat duodenum. J Physiol 587:3651–3663
484. Mizuno-Kamiya M, Kameyama Y, Yashiro K, Fujita A (1998) ATP-mediated activation of Ca^{2+}-independent phospholipase A_2 in

secretory granular membranes from rat parotid gland. J Biochem (Tokyo) 123:205–212
485. Monaghan KP, Koh SD, Ro S, Yeom J, Horowitz B, Sanders KM (2006) Nucleotide regulation of the voltage-dependent nonselective cation conductance in murine colonic myocytes. Am J Physiol Cell Physiol 291:C985–C994
486. Monro RL, Bertrand PP, Bornstein JC (2002) ATP and 5-HT are the principal neurotransmitters in the descending excitatory reflex pathway of the guinea-pig ileum. Neurogastroenterol Motil 14:255–264
487. Monro RL, Bertrand PP, Bornstein JC (2004) ATP participates in three excitatory postsynaptic potentials in the submucous plexus of the guinea pig ileum. J Physiol 556:571–584
488. Moody CJ, Burnstock G (1982) Evidence for the presence of P_1-purinoceptors on cholinergic nerve terminals in the guinea-pig ileum. Eur J Pharmacol 77:1–9
489. Mózsik G, Beck Z, Füzesi Z, Kiss J, Nagy L, Palotai Z, Szilágyi A, Tárnok F, Tóth E, Vizi F (1978a) Cellular mechanisms of gastric hypersecretion in pylorus-ligated rats. Acta Physiol Scand Special Suppl.:187–198
490. Mózsik G, Kutas J, Nagy L, Tárnok F, Vizi F (1978b) Interrelationships between the cholinergic influences, gastric mucosa Na^+–K^+-dependent ATPase, ATP, ADP, ions of gastric juice and basal secretion in patients. Acta Physiol Scand Special Suppl.: 199–208
491. Mulè F, Serio R (2003) NANC inhibitory neurotransmission in mouse isolated stomach: involvement of nitric oxide, ATP and vasoactive intestinal polypeptide. Br J Pharmacol 140: 431–437
492. Mulè F, Naccari D, Serio R (2005) Evidence for the presence of P2y and P2x receptors with different functions in mouse stomach. Eur J Pharmacol 513:135–140
493. Muramatsu I (1986) Evidence for sympathetic, purinergic transmission in the mesenteric artery of the dog. Br J Pharmacol 87:478–480
494. Murthy KS, Makhlouf GM (1998) Coexpression of purinergic ligand-gated P2X and G protein-coupled P2Y receptors in smooth muscle. Preferential activation of P2Y receptors coupled to phospholipase C(PLC)-β1 via $G\alpha_{q/11}$ and to PLC-β3 via $G\beta g_i3$. J Biol Chem 273:4695–4704
495. Murthy KS, McHenry L, Grider JR, Makhlouf GM (1995) Adenosine A_1 and A_{2b} receptors coupled to distinct interactive signaling pathways in intestinal muscle cells. J Pharmacol Exp Ther 274:300–306
496. Mutafova-Yambolieva VN (2012) Neuronal and extraneuronal release of ATP and NAD^+ in smooth muscle. IUBMB Life 64:817–824
497. Mutafova-Yambolieva VN, Hwang SJ, Hao X, Chen H, Zhu MX, Wood JD, Ward SM, Sanders KM (2007) β-Nicotinamide adenine dinucleotide is an inhibitory neurotransmitter in visceral smooth muscle. Proc Natl Acad Sci U S A 104:16359–16364
498. Naganuma M, Wiznerowicz EB, Lappas CM, Linden J, Worthington MT, Ernst PB (2006) Cutting edge: critical role for A2A adenosine receptors in the T cell-mediated regulation of colitis. J Immunol 177:2765–2769
499. Nagaoka I, Tamura H, Hirata M (2006) An antimicrobial cathelicidin peptide, human CAP18/LL-37, suppresses neutrophil apoptosis via the activation of formyl-peptide receptor-like 1 and P2X7. J Immunol 176:3044–3052
500. Nagata K, Saito H, Matsuki N (1993) Adenosine induces contractions in suncus ileum. Jpn J Pharmacol 63:415–421
501. Nakamoto T, Brown DA, Catalán MA, Gonzalez-Begne M, Romanenko VG, Melvin JE (2009) Purinergic $P2X_7$ receptors mediate ATP-induced saliva secretion by the mouse submandibular gland. J Biol Chem 284:4815–4822
502. Nakamura T, Iwanaga K, Murata T, Hori M, Ozaki H (2011) ATP induces contraction mediated by the $P2Y_2$ receptor in rat intestinal subepithelial myofibroblasts. Eur J Pharmacol 657:152–158
503. Nakamura T, Murata T, Hori M, Ozaki H (2013) UDP promotes intestinal epithelial migration via the $P2Y_6$ receptor. Br J Pharmacol 170(4):884–892
504. Nandi J, Ray TK, Sen PC (1981) Studies of gastric Ca^{2+}-stimulated adenosine triphosphatase. I. Characterization and general properties. Biochim Biophys Acta 646:457–464
505. Neary JT (1996) Trophic actions of extracellular ATP on astrocytes, synergistic interactions with fibroblast growth factors and underlying signal transduction mechanisms. In: Chadwick DJ, Goode JA (eds) P2 purinoceptors: localization, function and transduction mechanisms. Wiley, Chichester, pp 130–141
506. Neshat S, DeVries M, Barajas-Espinosa AR, Skeith L, Chisholm SP, Lomax AE (2009) Loss of purinergic vascular regulation in the colon during colitis is associated with upregulation of CD39. Am J Physiol Gastrointest Liver Physiol 296:G399–G405
507. Nguyen TD, Moody MW, Savard CE, Lee SP (1998) Secretory effects of ATP on nontransformed dog pancreatic duct epithelial cells. Am J Physiol 275:G104–G113
508. Nicholls J, Hourani SMO (1997) Characterization of adenosine receptors on rat ileum, ileal longitudinal muscle and muscularis mucosae. Eur J Pharmacol 338:143–150
509. Nicholls J, Brownhill VR, Hourani SMO (1996) Characterization of P1-purinoceptors on rat isolated duodenum longitudinal muscle and muscularis mucosae. Br J Pharmacol 117:170–174
510. Nissan S, Vinograd Y, Hadari A, Merguerian P, Zamir O, Lernau O, Hanani M (1984) Physiological and pharmacological studies of the internal anal sphincter in the rat. J Pediatr Surg 19:12–14
511. North RA (2002) Molecular physiology of P2X receptors. Physiol Rev 82:1013–1067
512. Northway MG, Burks TF (1980) Stimulation of cholinergic nerves in dog intestine by adenine nucleotides. Eur J Pharmacol 65:11–19
513. Novak I (2003) ATP as a signaling molecule: the exocrine focus. News Physiol Sci 18:12–17
514. Novak I, Jans IM, Wohlfahrt L (2010) Effect of $P2X_7$ receptor knockout on exocrine secretion of pancreas, salivary glands and lacrimal glands. J Physiol 588:3615–3627
515. Nurgali K, Furness JB, Stebbing MJ (2003) Analysis of purinergic and cholinergic fast synaptic transmission to identified myenteric neurons. Neuroscience 116:335–347
516. Nylund G, Nordgren S, Delbro DS (2004) Expression of $P2Y_2$ purinoceptors in MCG 101 murine sarcoma cells, and HT-29 human colon carcinoma cells. Auton Neurosci 112:69–79
517. Nylund G, Hultman L, Nordgren S, Delbro DS (2007) $P2Y_2$- and $P2Y_4$ purinergic receptors are over-expressed in human colon cancer. Auton Autacoid Pharmacol 27:79–84
518. O'Donnell AM, Puri P (2008) Deficiency of purinergic P2Y receptors in aganglionic intestine in Hirschsprung's disease. Pediatr Surg Int 24:77–80
519. Odashima M, Bamias G, Rivera-Nieves J, Linden J, Nast CC, Moskaluk CA, Marini M, Sugawara K, Kozaiwa K, Otaka M, Watanabe S, Cominelli F (2005) Activation of A2A adenosine receptor attenuates intestinal inflammation in animal models of inflammatory bowel disease. Gastroenterology 129:26–33
520. Ohana G, Bar-Yehuda S, Arich A, Madi L, Dreznick Z, Rath-Wolfson L, Silberman D, Slosman G, Fishman P (2003) Inhibition of primary colon carcinoma growth and liver metastasis by the A3 adenosine receptor agonist CF101. Br J Cancer 89:1552–1558
521. Ohga A, Taneike T (1977) Dissimilarity between the responses to adenosine triphosphate or its related compounds and non-adrenergic inhibitory nerve stimulation in the longitudinal smooth muscle of pig stomach. Br J Pharmacol 60:221–231
522. Ohkawa H (1974) An analysis of the mechanical responses of the isolated ileum to single transmural stimulation and to drugs. Bull Yamaguchi Med School 21:31–45
523. Ohno N, Ito KM, Yamamoto Y, Suzuki H (1993) Suramin selectively

inhibits the non-adrenergic non-cholinergic inhibitory junction potential in the guinea-pig stomach. Eur J Pharmacol 249:121–123
524. Ohta T, Kubota A, Murakami M, Otsuguro K, Ito S (2005) $P2X_2$ receptors are essential for $[Ca^{2+}]_i$ increases in response to ATP in cultured rat myenteric neurons. Am J Physiol Gastrointest Liver Physiol 289:G935–G948
525. Okasora T, Okamoto E (1986) Electrophysiological and pharmacological study on innervation of the aganglionic colon in Hirschsprung's disease of human and murine model. Z Kinderchir 41:93–96
526. Okwuasaba FK, Hamilton JT, Cook MA (1977) Relaxations of guinea-pig fundic strip by adenosine, adenine nucleotides and electrical stimulation: antagonism by theophylline and desensitization to adenosine and its derivatives. Eur J Pharmacol 46:181–198
527. Olsson RA, Pearson JD (1990) Cardiovascular purinoceptors. Physiol Rev 70:761–845
528. Onaka U, Fujii K, Abe I, Fujishima M (1997) Enhancement by exogenous and locally generated angiotensin II of purinergic neurotransmission via angiotensin type 1 receptor in the guinea-pig isolated mesenteric artery. Br J Pharmacol 122:942–948
529. Opazo A, Lecea B, Gil V, Jimenez M, Clave P, Gallego D (2011) Specific and complementary roles for nitric oxide and ATP in the inhibitory motor pathways to rat internal anal sphincter. Neurogastroenterol Motil 23:e11–e25
530. Ota S, Hiraishi H, Terano A, Mutoh H, Kurachi Y, Shimada T, Ivey KJ, Sugimoto T (1989) Effect of adenosine and adenosine analogs on [^{14}C]aminopyrine accumulation by rabbit parietal cells. Dig Dis Sci 34:1882–1889
531. Ota S, Yoshiura K, Takahashi M, Hata Y, Kohmoto O, Kawabe T, Shimada T, Hiraishi H, Mutoh H, Terano A, Sugimoto T, Omata M (1994) P2 purinergic receptor regulation of mucus glycoprotein secretion by rabbit gastric mucous cells in a primary culture. Gastroenterology 106:1485–1492
532. Otsuguro KI, Ohta T, Ito S, Nakazato Y (1998) Two types of relaxation-mediating P_2 receptors in rat gastric circular muscle. Jpn J Pharmacol 78:209–215
533. Otte JM, Zdebik AE, Brand S, Chromik AM, Strauss S, Schmitz F, Steinstraesser L, Schmidt WE (2009) Effects of the cathelicidin LL-37 on intestinal epithelial barrier integrity. Regul Pept 156:104–117
534. Ovadyahu D, Eshel D, Priel Z (1988) Intensification of ciliary motility by extracellular ATP. Biorheology 25:489–501
535. Pacaud P, Feolde E, Frelin C, Loirand G (1996) Characterization of the P_{2Y}-purinoceptor involved in the ATP-induced rise in cytosolic Ca^{2+} concentration in rat ileal myocytes. Br J Pharmacol 118:2213–2219
536. Page AJ, O'Donnell TA, Blackshaw LA (2000) P2X purinoceptor-induced sensitization of ferret vagal mechanoreceptors in oesophageal inflammation. J Physiol Lond 523:403–411
537. Palmer JM, Wood JD, Zafirov DH (1987) Purinergic inhibition in the small intestinal myenteric plexus of the guinea-pig. J Physiol 387:357–369
538. Paret RS, Kumashiro R, Kodama Y, Matsumoto T (1982) The effect of dipyridamole on experimentally induced stress ulcers. Am Surg 48:594–598
539. Park HS, Betzenhauser MJ, Zhang Y, Yule DI (2012) Regulation of Ca^{2+} release through inositol 1,4,5-trisphosphate receptors by adenine nucleotides in parotid acinar cells. Am J Physiol Gastrointest Liver Physiol 302:G97–G104
540. Park JY, Kim YS, Bang S, Hyung WJ, Noh SH, Choi SH, Song SY (2007) ATP-based chemotherapy response assay in patients with unresectable gastric cancer. Oncology 73:439–440
541. Park MK, Garrad RC, Weisman GA, Turner JT (1997) Changes in $P2Y_1$ nucleotide receptor activity during the development of rat salivary glands. Am J Physiol 272:C1388–C1393
542. Parr CE, Sullivan DM, Paradiso AM, Lazarowski ER, Burch LH, Olsen JC, Erb L, Weisman GA, Boucher RC, Turner JT (1994) Cloning and expression of a human P2U nucleotide receptor, a target for cystic fibrosis pharmacotherapy. Proc Natl Acad Sci U S A 91:13067
543. Patacchini R, De Giorgio R, Barthó L, Barbara G, Corinaldesi R, Maggi CA (1998) Evidence that tachykinins are the main NANC excitatory neurotransmitters in the guinea-pig common bile duct. Br J Pharmacol 124:1703–1711
544. Paton WD, Vane JR (1963) Analysis of the responses of the isolated stomach to electrical stimulation and to drugs. J Physiol 165:10–46
545. Paulino AS, Palombit K, Cavriani G, Tavares-de-Lima W, Mizuno MS, Marosti AR, da Silva MV, Girotti PA, Liberti EA, Castelucci P (2011) Effects of ischemia and reperfusion on $P2X_2$ receptor expressing neurons of the rat ileum enteric nervous system. Dig Dis Sci 56:2262–2275
546. Pedersen AM, Dissing S, Fahrenkrug J, Hannibal J, Reibel J, Nauntofte B (2000) Innervation pattern and Ca^{2+} signalling in labial salivary glands of healthy individuals and patients with primary Sjogren's syndrome (pSS). J Oral Pathol Med 29:97–109
547. Pennanen MF, Bass BL, Dziki AJ, Harmon JW (1994) Adenosine: differential effect on blood flow to subregions of the upper gastrointestinal tract. J Surg Res 56:461–465
548. Percy WH, Miller AJ, Brunz JT (1997) Pharmacologic characteristics of rabbit esophageal muscularis mucosae in vitro. Dig Dis Sci 42:2537–2546
549. Percy WH, Warren JM, Brunz JT (1999) Characteristics of the muscularis mucosae in the acid-secreting region of the rabbit stomach. Am J Physiol 276:G1213–G1220
550. Percy WH, Fromm TH, Wangsness CE (2003) Muscularis mucosae contraction evokes colonic secretion via prostaglandin synthesis and nerve stimulation. Am J Physiol Gastrointest Liver Physiol 284: G213–G220
551. Persson CG (1976) Inhibitory innervation of cat sphincter of Oddi. Br J Pharmacol 58:479–482
552. Pérez-Andrés E, Fernández-Rodriguez M, González M, Zubiaga A, Vallejo A, García I, Matute C, Pochet S, Dehaye JP, Trueba M, Marino A, Gómez-Muñoz A (2002) Activation of phospholipase D-2 by $P2X_7$ agonists in rat submandibular gland acini. J Lipid Res 43: 1244–1255
553. Peri LE, Sanders KM, Mutafova-Yambolieva VN (2013) Differential expression of genes related to purinergic signaling in smooth muscle cells, PDGFRα-positive cells, and interstitial cells of Cajal in the murine colon. Neurogastroenterol Motil 25:e609–e620
554. Pluja L, Fernández E, Jimenez M (1999) Neural modulation of the cyclic electrical and mechanical activity in the rat colonic circular muscle: putative role of ATP and NO. Br J Pharmacol 126:883–892
555. Pochet S, Gómez-Muñoz A, Marino A, Dehaye JP (2003) Regulation of phospholipase D by $P2X_7$ receptors in submandibular ductal cells. Cell Signal 15:927–935
556. Pochet S, Seil M, El OM, Dehaye JP (2013) $P2X_4$ or $P2X_7$: which of these two receptors is the best target to promote salivation? Med Sci (Paris) 29:509–514
557. Poole DP, Castelucci P, Robbins HL, Chiocchetti R, Furness JB (2002) The distribution of $P2X_3$ purine receptor subunits in the guinea pig enteric nervous system. Auton Neurosci 101:39–47
558. Prentice DJ, Hourani SMO (1997) Adenosine analogues relax guinea-pig taenia caeci via an adenosine A_{2B} receptor and a xanthine-resistant site. Eur J Pharmacol 323:103–106
559. Proctor KG (1986) Possible role for adenosine in local regulation of absorptive hyperemia in rat intestine. Circ Res 59:474–481
560. Puurunen J, Huttunen P (1988) Central gastric antisecretory action of adenosine in the rat. Eur J Pharmacol 147:59–66
561. Puurunen J, Aittakumpu R, Tanskanen T (1986) Vagally mediated stimulation of gastric acid secretion by intravenously administered adenosine derivatives in anaesthetized rats. Acta Pharmacol Toxicol 58:265–271
562. Rae MG, Muir TC (1996) Neuronal mediators of inhibitory junction

potentials and relaxation in the guinea-pig internal anal sphincter. J Physiol 493:517–527
563. Rahimian R, Fakhfouri G, Daneshmand A, Mohammadi H, Bahremand A, Rasouli MR, Mousavizadeh K, Dehpour AR (2010) Adenosine A2A receptors and uric acid mediate protective effects of inosine against TNBS-induced colitis in rats. Eur J Pharmacol 649:376–381
564. Ramme D, Regenold JT, Starke K, Busse R, Illes P (1987) Identification of the neuroeffector transmitter in jejunal branches of the rabbit mesenteric artery. Naunyn Schmiedebergs Arch Pharmacol 336:267–273
565. Reese JH, Cooper JR (1982) Modulation of the release of acetylcholine from ileal synaptosomes by adenosine and adenosine 5′-triphosphate. J Pharmacol Exp Ther 223:612–616
566. Reeves JJ, Coates J, Jarvis JE, Sheehan MJ, Strong P (1993) Characterization of the adenosine receptor mediating contraction in rat colonic muscularis mucosae. Br J Pharmacol 110:1255–1259
567. Reeves JJ, Jarvis JE, Sheehan MJ, Strong P (1995) Further investigations into adenosine A_1 receptor-mediated contraction in rat colonic muscularis mucosae and its augmentation by certain alkylxanthine antagonists. Br J Pharmacol 114:999–1004
568. Reiser S, Christiansen PA (1971) Inhibition of amino acid uptake by ATP in isolated intestinal epithelial cells. Biochim Biophys Acta 233:480–484
569. Ren J, Bertrand PP (2008) Purinergic receptors and synaptic transmission in enteric neurons. Purinergic Signal 4:255–266
570. Ren J, Galligan JJ (2005) Dynamics of fast synaptic excitation during trains of stimulation in myenteric neurons of guinea-pig ileum. Auton Neurosci 117:67–78
571. Ren J, Galligan JJ (2007) A novel calcium-sensitive potassium conductance is coupled to $P2X_3$ subunit containing receptors in myenteric neurons of guinea pig ileum. Neurogastroenterol Motil 19:912–922
572. Ren J, Bian X, DeVries M, Schnegelsberg B, Cockayne DA, Ford AP, Galligan JJ (2003) $P2X_2$ subunits contribute to fast synaptic excitation in myenteric neurons of the mouse small intestine. J Physiol 552:809–821
573. Ren T, Grants I, Alhaj M, McKiernan M, Jacobson M, Hassanain HH, Frankel W, Wunderlich J, Christofi FL (2011) Impact of disrupting adenosine A_3 receptors ($A_3^{-/-}$ AR) on colonic motility or progression of colitis in the mouse. Inflamm Bowel Dis 17:1698–1713
574. Reyes JP, Pérez-Cornejo P, Hernández-Carballo CY, Srivastava A, Romanenko VG, Gonzalez-Begne M, Melvin JE, Arreola J (2008) Na^+ modulates anion permeation and block of $P2X_7$ receptors from mouse parotid glands. J Membr Biol 223:73–85
575. Reymann A, Gniess A (1988) Evidence for adenosine A_1 receptor action in rat jejunal mucosa. Eur J Pharmacol 149:155–158
576. Richard CL, Tan EY, Blay J (2006) Adenosine upregulates CXCR4 and enhances the proliferative and migratory responses of human carcinoma cells to CXCL12/SDF-1α. Int J Cancer 119:2044–2053
577. Richards NW, Allbee WE, Gaginella TS, Wallace LJ (1987) Exogenous ATP-stimulated calcium uptake in isolated rat intestinal epithelial cells. Life Sci 40:1665–1672
578. Richardson J (1975) Pharmacologic studies of Hirschsprung's disease on a murine model. J Pediatr Surg 10:875–884
579. Riegler M, Castagliuolo I, Wang C, Wlk M, Sogukoglu T, Wenzl E, Matthews JB, Pothoulakis C (2000) Neurotensin stimulates Cl^- secretion in human colonic mucosa in vitro: role of adenosine. Gastroenterology 119:348–357
580. Robaye B, Ghanem E, Wilkin F, Fokan D, Van DW, Schurmans S, Boeynaems JM, Beauwens R (2003) Loss of nucleotide regulation of epithelial chloride transport in the jejunum of $P2Y_4$-null mice. Mol Pharmacol 63:777–783
581. Roberts JA, Durnin L, Sharkey KA, Mutafova-Yambolieva VN, Mawe GM (2013) Oxidative stress disrupts purinergic neuromuscular transmission in the inflamed colon. J Physiol 591:3725–3737
582. Rogawski MA, Goodrich JT, Gershon MD, Touloukian RJ (1978) Hirschsprung's disease: absence of serotonergic neurons in the aganglionic colon. J Pediatr Surg 13:608–615
583. Roman RM, Fitz JG (1999) Emerging roles of purinergic signaling in gastrointestinal epithelial secretion and hepatobiliary function. Gastroenterology 116:964–979
584. Roman RM, Feranchak AP, Salter KD, Wang Y, Fitz JG (1999) Endogenous ATP release regulates Cl^- secretion in cultured human and rat biliary epithelial cells. Am J Physiol 276:G1391–G1400
585. Rong W, Keating C, Sun B, Dong L, Grundy D (2009) Purinergic contribution to small intestinal afferent hypersensitivity in a murine model of postinfectious bowel disease. Neurogastroenterol Motil 21(665–71):e32
586. Rózsai B, Lázár Z, Benkó R, Barthó L (2001) Inhibition of the NANC relaxation of the guinea-pig proximal colon longitudinal muscle by the purinoceptor antagonist PPADS, inhibition of nitric oxide synthase, but not by a PACAP/VIP antagonist. Pharmacol Res 43:83–87
587. Ruan H-Z, Burnstock G (2005) The distribution of $P2X_5$ purinergic receptors in the enteric nervous system. Cell Tissue Res 319:191–200
588. Rühl A (2005) Glial cells in the gut. Neurogastroenterol Motil 17:777–790
589. Rybaczyk L, Rozmiarek A, Circle K, Grants I, Needleman B, Wunderlich JE, Huang K, Christofi FL (2009) New bioinformatics approach to analyze gene expressions and signaling pathways reveals unique purine gene dysregulation profiles that distinguish between CD and UC. Inflamm Bowel Dis 15:971–984
590. Ryu SY, Peixoto PM, Won JH, Yule DI, Kinnally KW (2010) Extracellular ATP and P2Y2 receptors mediate intercellular Ca^{2+} waves induced by mechanical stimulation in submandibular gland cells: role of mitochondrial regulation of store operated Ca^{2+} entry. Cell Calcium 47:65–76
591. Sachs G, Wallmark B, Saccomani G, Rabon E, Stewart HB, DiBona DR, Berglindh T (1982) The ATP-dependent component of gastric acid secretion. Current topics in membrane and transport. Academic, San Diego, pp 135–159
592. Saha A, Hammond CE, Gooz M, Smolka AJ (2008) The role of Sp1 in IL-1β and H. pylori-mediated regulation of H, K-ATPase gene transcription. Am J Physiol Gastrointest Liver Physiol 295:G977–G986
593. Saitoh M, Nagai K, Nakagawa K, Yamamura T, Yamamoto S, Nishizaki T (2004) Adenosine induces apoptosis in the human gastric cancer cells via an intrinsic pathway relevant to activation of AMP-activated protein kinase. Biochem Pharmacol 67:2005–2011
594. Saito M, Yaguchi T, Yasuda Y, Nakano T, Nishizaki T (2010) Adenosine suppresses CW2 human colonic cancer growth by inducing apoptosis via A_1 adenosine receptors. Cancer Lett 290:211–215
595. Sakai K, Akima M, Matsushita H (1979) Analysis of the contractile responses of the ileal segment of the isolated blood-perfused small intestine of rats to adenosine triphosphate and related compounds. Eur J Pharmacol 58:157–162
596. Sakai Y, Ishida Y, Nobe H (2009) Regulation of gastric emptying related to nucleotides and purinoceptors in rat pyloric sphincter. IUPS 2009 July 27–Auguat 1, 2009, Kyoto:472
597. Salter KD, Fitz JG, Roman RM (2000) Domain-specific purinergic signaling in polarized rat cholangiocytes. Am J Physiol Gastrointest Liver Physiol 278:G492–G500
598. Sarosi GA, Barnhart DC, Turner DJ, Mulholland MW (1998) Capacitative Ca^{2+} entry in enteric glia induced by thapsigargin and extracellular ATP. Am J Physiol 275:G550–G555

599. Satchell DG, Maguire MH (1975) Inhibitory effects of adenine nucleotide analogs on the isolated guinea-pig taenia coli. J Pharmacol Exp Ther 195:540–548
600. Satchell DG, Maguire MH (1982) Evidence for separate receptors for ATP and adenosine in the guinea-pig taenia coli. Eur J Pharmacol 81:669–672
601. Sathe MN, Woo K, Kresge C, Bugde A, Luby-Phelps K, Lewis MA, Feranchak AP (2011) Regulation of purinergic signaling in biliary epithelial cells by exocytosis of SLC17A9-dependent ATP-enriched vesicles. J Biol Chem 286:25363–25376
602. Sato C, Tsujioka Y, Katsuragi T (1999) Cross desensitizations on contractions by P2-agonists of guinea pig ileum. Jpn J Pharmacol 80:311–317
603. Savegnago L, Nogueira CW, Fachinetto R, Rocha JBT (2005) Characterization of ATP and ADP hydrolysis activity in rat gastric mucosa. Cell Biol Int 29:559–566
604. Sawmiller DR, Chou CC (1991) Adenosine is a vasodilator in the intestinal mucosa. Am J Physiol 261:G9–G15
605. Sawynok J, Jhamandas KH (1976) Inhibition of acetylcholine release from cholinergic nerves by adenosine, adenine nucleotides and morphine: antagonism by theophylline. J Pharmacol Exp Ther 197: 379–390
606. Scarpignato C, Tramacere R, Zappia L, Del Soldato P (1987) Inhibition of gastric acid secretion by adenosine receptor stimulation in the rat. Pharmacology 34:264–268
607. Schenck LP, Hirata SA, Potentier MS, Li Y, Armstrong GD, MacDonald JA (2011) CD73-Mediated liberation of adenosine protects intestinal epithelial cells from *C. difficile* toxin-induced damage. Gastroenterology 140:S498
608. Schepp W, Soll AH, Walsh JH (1990) Dual modulation by adenosine of gastrin release from canine G-cells in primary culture. Am J Physiol 259:G556–G563
609. Schlenker T, Romac JM, Sharara AI, Roman RM, Kim SJ, LaRusso N, Liddle RA, Fitz JG (1997) Regulation of biliary secretion through apical purinergic receptors in cultured rat cholangiocytes. Am J Physiol 273:G1108–G1117
610. Schrader AM, Camden JM, Weisman GA (2005) $P2Y_2$ nucleotide receptor up-regulation in submandibular gland cells from the NOD.B10 mouse model of Sjögren's syndrome. Arch Oral Biol 50:533–540
611. Schweickhardt C, Sabolic I, Brown D, Burckhardt G (1995) Ecto-adenosinetriphosphatase in rat small intestinal brush-border membranes. Am J Physiol 268:G663–G672
612. Seil M, Fontanils U, Etxebarria IG, Pochet S, Garcia-Marcos M, Marino A, Dehaye JP (2008) Pharmacological evidence for the stimulation of NADPH oxidase by $P2X_7$ receptors in mouse submandibular glands. Purinergic Signal 4:347–355
613. Selzner N, Selzner M, Graf R, Ungethuem U, Fitz JG, Clavien PA (2004) Water induces autocrine stimulation of tumor cell killing through ATP release and P2 receptor binding. Cell Death Differ 11(Suppl 2):S172–S180
614. Sharir H, Hershfinkel M (2005) The extracellular zinc-sensing receptor mediates intercellular communication by inducing ATP release. Biochem Biophys Res Commun 332:845–852
615. Shim JO, Shin CY, Lee TS, Yang SJ, An JY, Song HJ, Kim TH, Huh IH, Sohn UD (2002) Signal transduction mechanism via adenosine A1 receptor in the cat esophageal smooth muscle cells. Cell Signal 14:365–372
616. Shimo Y, Ishii T (1978) Effects of morphine on non-adrenergic inhibitory responses of the guinea-pig taenia coli. J Pharm Pharmacol 30:596–597
617. Shinozuka K, Maeda T, Hayashi E (1985) Effects of adenosine on ^{45}Ca uptake and [^{3}H]acetylcholine release in synaptosomal preparation from guinea-pig ileum myenteric plexus. Eur J Pharmacol 113:417–424
618. Shinozuka K, Maeda T, Hayashi E (1985) Possibilities for adenosine modulation of peristaltic reflex in guinea pig isolated ileum. J Pharmacobiodyn 8:877–884
619. Shitara A, Tanimura A, Sato A, Tojyo Y (2009) Spontaneous oscillations in intracellular Ca^{2+} concentration via purinergic receptors elicit transient cell swelling in rat parotid ducts. Am J Physiol Gastrointest Liver Physiol 297:G1198–G1205
620. Shuba MF, Vladimirova IA (1980) Effect of apamin on the electrical responses of smooth muscle to adenosine 5′-triphosphate and to non-adrenergic, non-cholinergic nerve stimulation. Neuroscience 5:853–859
621. Siegmund B, Rieder F, Albrich S, Wolf K, Bidlingmaier C, Firestein GS, Boyle D, Lehr HA, Loher F, Hartmann G, Endres S, Eigler A (2001) Adenosine kinase inhibitor GP515 improves experimental colitis in mice. J Pharmacol Exp Ther 296:99–105
622. Sitaraman SV, Merlin D, Wang L, Wong M, Gewirtz AT, Si-Tahar M, Madara JL (2001) Neutrophil-epithelial crosstalk at the intestinal lumenal surface mediated by reciprocal secretion of adenosine and IL-6. J Clin Invest 107:861–869
623. Sjöblom-Widfeldt N, Gustafsson H, Nilsson H (1990) Transmitter characteristics of small mesenteric arteries from the rat. Acta Physiol Scand 138:203–212
624. Skoglund ML, Nies AS, Gerber JG (1982) Inhibition of acid secretion in isolated canine parietal cells by prostaglandins. J Pharmacol Exp Ther 220:371–374
625. Smith AB, Hansen MA, Liu DM, Adams DJ (2001) Pre- and postsynaptic actions of ATP on neurotransmission in rat submandibular ganglia. Neuroscience 107:283–291
626. Smitham JE, Barrett KE (2001) Differential effects of apical and basolateral uridine triphosphate on intestinal epithelial chloride secretion. Am J Physiol Cell Physiol 280:C1431–C1439
627. Smits GJ, Lefebvre RA (1996) ATP and nitric oxide: inhibitory NANC neurotransmitters in the longitudinal muscle-myenteric plexus preparation of the rat ileum. Br J Pharmacol 118:695–703
628. Sneddon JD, Smythe A, Satchell D, Burnstock G (1973) An investigation of the identity of the transmitter substance released by non-adrenergic, non-cholinergic excitatory nerves supplying the small intestine of some lower vertebrates. Comp Gen Pharmacol 4:53–60
629. Soediono P, Burnstock G (1994) Contribution of ATP and nitric oxide to NANC inhibitory transmission in rat pyloric sphincter. Br J Pharmacol 113:681–686
630. Soltoff SP, McMillian MK, Talamo BR (1989) Coomassie Brilliant Blue G is a more potent antagonist of P_2 purinergic responses than Reactive Blue 2 (Cibacron Blue 3GA) in rat parotid acinar cells. Biochem Biophys Res Commun 165:1279–1285
631. Soltoff SP, McMillian MK, Lechleiter JD, Cantley LC, Talamo BR (1990) Elevation of $[Ca^{2+}]_i$ and the activation of ion channels and fluxes by extracellular ATP and phospholipase C-linked agonists in rat parotid acinar cells. Ann N Y Acad Sci 603:76–90
632. Soltoff SP, McMillian MK, Talamo B (1992) ATP activates a cation-permeable pathway in rat parotid acinar cells. Am J Physiol 262: C934–C940
633. Soltoff SP, McMillian MK, Talamo BR, Cantley LC (1993) Blockade of ATP binding site of P2 purinoceptors in rat parotid acinar cells by isothiocyanate compounds. Biochem Pharmacol 45: 1936–1940
634. Somers GR, Hammet FM, Trute L, Southey MC, Venter DJ (1998) Expression of the $P2Y_6$ purinergic receptor in human T cells infiltrating inflammatory bowel disease. Lab Invest 78:1375–1383
635. Souza CO, Santoro GF, Figliuolo VR, Nanini HF, de Souza HS, Castelo-Branco MT, Abalo AA, Paiva MM, Coutinho CM, Coutinho-Silva R (2012) Extracellular ATP induces cell death in human intestinal epithelial cells. Biochim Biophys Acta 1820: 1867–1878
636. Souza VC, Schlemmer KB, Noal CB, Jaques JA, Bagatini MD, Pimentel VC, Carli LF, Leal CA, Fleck J, Moretto MB, Schetinger MR, Leal DB (2012) Purinergic system ecto-enzymes participate in

the thromboregulation of patients with indeterminate form of Chagas disease. Purinergic Signal 8:753–762
637. Souza VC, Schlemmer KB, Noal CB, Jaques JA, Zimmermann CE, Leal CA, Fleck J, Casali EA, Morsch VM, Schetinger MR, Leal DB (2012) E-NTPDase and E-ADA activities are altered in lymphocytes of patients with indeterminate form of Chagas' disease. Parasitol Int 61:690–696
638. Spencer NJ, Walsh M, Smith TK (2000) Purinergic and cholinergic neuro-neuronal transmission underlying reflexes activated by mucosal stimulation in the isolated guinea-pig ileum. J Physiol 522: 321–331
639. Sperlágh B, Vizi ES (1990) Stimulation of presynaptic P1 and P2 receptors at ATP in Auerbach's plexus. Eur J Pharmacol 183:1680
640. Sperlágh B, Vizi ES (1991) Effect of presynaptic P_2 receptor stimulation on transmitter release. J Neurochem 56:1466–1470
641. Spychala J (2000) Tumor-promoting functions of adenosine. Pharmacol Ther 87:161–173
642. Stemmer SM, Shani A, Klein B, Silverman MH, Lorber I, Farbstein M, Shmueli E, Figer A (2004) A phase II, multi-center study of a new non-cytotoxic A3 adenosine receptor agonist CF101, dose-finding (randomized blinded) in patients (pts) with refractory metastatic colorectal cancer. J Clin Oncol 22:232S
643. Stone TW (1981) Actions of adenine dinucleotides on the vas deferens, guinea-pig taenia caeci and bladder. Eur J Pharmacol 75:93–102
644. Storr M, Franck H, Saur D, Schusdziarra V, Allescher HD (2000) Mechanisms of α, β-methylene ATPS-induced inhibition in rat ileal smooth muscle: involvement of intracellular Ca2+ stores in purinergic inhibition. Clin Exp Pharmacol Physiol 27:771–779
645. Strong DS, Cornbrooks CF, Roberts JA, Hoffman JM, Sharkey KA, Mawe GM (2010) Purinergic neuromuscular transmission is selectively attenuated in ulcerated regions of inflamed guinea pig distal colon. J Physiol 588:847–859
646. Su C (1983) Purinergic neurotransmission and neuromodulation. Annu Rev Pharmacol Toxicol 23:397–411
647. Su C, Bevan JA, Burnstock G (1971) [^{3}H]adenosine triphosphate: release during stimulation of enteric nerves. Science 173:337–339
648. Surprenant A (1994) Control of the gastrointestinal tract by enteric neurons. Annu Rev Physiol 56:117–140
649. Szentpáli K, Kaszaki J, Tiszlavicz L, Lázár G, Balogh Á, Boros M (2001) Bile-induced adenosine triphosphate depletion and mucosal damage during reflux esophagitis. Scand J Gastroenterol 36:459–466
650. Taha MO, Miranda-Ferreira R, Fagundes DJ, Simões RS, Monteiro HP, Oliveira-Júnior IS, Soares KR, Martins MC, Monteiro HP, Balbino AT, Rodrigues FF, Arruda TB, Abrão MS, Jurkiewicz A, Caricati-Neto A (2010) Effects of 5′-adenosine triphosphate on intestinal ischemia–reperfusion in rabbits. Transplant Proc 42: 461–464
651. Takahashi T, Kusunoki M, Ishikawa Y, Kantoh M, Yamamura T, Utsunomiya J (1987) Adenosine 5′-triphosphate release evoked by electrical nerve stimulation from the guinea-pig gallbladder. Eur J Pharmacol 134:77–82
652. Tamada H, Hashitani H (2013) Calcium responses in subserosal interstitial cells of the guinea-pig proximal colon. Neurogastroenterology & Motility. doi:10.1111/nmo.12240
653. Tanaka J, Murate M, Wang CZ, Seino S, Iwanaga T (1996) Cellular distribution of the $P2X_4$ ATP receptor mRNA in the brain and non-neuronal organs of rats. Arch Histol Cytol 59:485–490
654. Tansey MF, Probst SJ, Martin JS (1975) Evidence of nonvagal neural stimulation of canine gastric acid secretion. Surg Gynecol Obstet 140:861–867
655. Tarasiuk A, Bar Shimon M, Gheber L, Korngreen A, Grossman Y, Priel Z (1995) Extracellular ATP induces hyperpolarization and motility stimulation of ciliary cells. Biophys J 68:1163–1169
656. Taylor EM, Parsons ME (1989) Adrenergic and purinergic neurotransmission in arterial resistance vessels of the cat intestinal circulation. Eur J Pharmacol 164:23–33
657. Taylor EM, Parsons ME (1991) Effects of α, β-methylene ATP on resistance and capacitance blood vessels of the cat intestinal circulation; a comparison with other vasoconstrictor agents and sympathetic nerve stimulation. Eur J Pharmacol 205:35–41
658. ten Kate J, Wijnen JT, van der Goes RG, Quadt R, Griffioen G, Bosman FT, Khan PM (1984) Quantitative changes in adenosine deaminase isoenzymes in human colorectal adenocarcinomas. Cancer Res 44:4688–4692
659. Tenneti L, Gibbons SJ, Talamo BR (1998) Expression and transsynaptic regulation of P_{2x4} and P_{2z} receptors for extracellular ATP in parotid acinar cells. Effects of parasympathetic denervation. J Biol Chem 273:26799–26808
660. Tetens J, Venugopal CS, Holmes EP, Koch CE, Hosgood G, Moore RM (2001) In vitro responses of equine colonic arterial and venous rings to adenosine triphosphate. Am J Vet Res 62:1928–1933
661. Thornton PD, Gwynne RM, McMillan DJ, Bornstein JC (2013) Transmission to interneurons is via slow excitatory synaptic potentials mediated by $P2Y_1$ receptors during descending inhibition in guinea-pig ileum. PLoS One 8:e40840
662. Tojyo Y, Tanimura A, Matsui S, Matsumoto Y (1997) Effects of extracellular ATP on cytosolic Ca2+ concentration and secretory responses in rat parotid acinar cells. Arch Oral Biol 42:393–399
663. Tojyo Y, Tanimura A, Nezu A, Morita T (2001) Possible mechanisms regulating ATP- and thimerosal-induced Ca^{2+} oscillations in the HSY salivary duct cell line. Biochim Biophys Acta 1539:114–121
664. Tomaru A, Ishii A, Kishibayashi N, Shimada J, Suzuki F, Karasawa A (1994) Possible physiological role of endogenous adenosine in defecation in rats. Eur J Pharmacol 264:91–94
665. Turner JT, Weisman GA, Camden JM (1997) Upregulation of $P2Y_2$ nucleotide receptors in rat salivary gland cells during short-term culture. Am J Physiol 273:C1100–C1107
666. Turner JT, Weisman GA, Landon LA, Park M, Camden JM (1998) Salivary gland nucleotide receptors: evidence for functional expression of both P2X and P2Y subtypes. Eur J Morphol 36:170–175
667. Turner JT, Landon LA, Gibbons SJ, Talamo BR (1999) Salivary gland P2 nucleotide receptors. Crit Rev Oral Biol Med 10:210–224
668. Ullrich N, Caplanusi A, Brône B, Hermans D, Larivière E, Nilius B, Van Driessche W, Eggermont J (2006) Stimulation by caveolin-1 of the hypotonicity-induced release of taurine and ATP at basolateral, but not apical, membrane of Caco-2 cells. Am J Physiol Cell Physiol 290:C1287–C1296
669. Undi S, Benko R, Wolf M, Illenyi L, Vereczkei A, Kelemen D, Cseke L, Csontos Z, Horvath ÖP, Bartho L (2009) The NANC relaxation of the human ileal longitudinal and circular muscles is inhibited by MRS 2179, a P_2 purinoceptor antagonist. Life Sci 84: 871–875
670. Ushijima I, Mizuki Y, Yamada M (1985) Development of stress-induced gastric lesions involves central adenosine A_1-receptor stimulation. Brain Res 339:351–355
671. Valdez-Morales E, Guerrero-Alba R, Liñan-Rico A, Espinosa-Luna R, Zarazua-Guzman S, Miranda-Morales M, Montaño LM, Barajas-López C (2011) P2X7 receptors contribute to the currents induced by ATP in guinea pig intestinal myenteric neurons. Eur J Pharmacol 668:366–372
672. Vallejo AI, Bo X, Burnstock G (1996) P2Y-purinoceptors in gastric gland plasma membranes. Eur J Pharmacol 312:209–214
673. Van Crombruggen K, Lefebvre RA (2004) Nitrergic-purinergic interactions in rat distal colon motility. Neurogastroenterol Motil 16:81–98
674. Van Crombruggen K, Van Nassauw L, Timmermans JP, Lefebvre RA (2007) Inhibitory purinergic P2 receptor characterisation in rat distal colon. Neuropharmacology 53:257–271

675. Van Nassauw L, Brouns I, Adriaensen D, Burnstock G, Timmermans J-P (2002) Neurochemical identification of enteric neurons expressing $P2X_3$ receptors in the guinea-pig ileum. Histochem Cell Biol 118:193–203
676. Van Nassauw L, Van Crombruggen K, De Jonge F, Burnstock G, Lefebvre RA, Timmermans J-P (2005) Distribution of P2Y receptor subtypes in the rat distal colon. Neurogastroenterol Motil 17:1
677. Van Nassauw L, Costagliola A, Van Op den bosch J, Cecio A, Vanderwinden J-M, Burnstock G, Timmermans J-P (2006) Region-specific distribution of the $P2Y_4$ receptor in enteric glial cells and interstitial cells of Cajal within the guinea-pig gastrointestinal tract. Autonomic Neuroscience: Basic and Clinical 126–127: 299–306
678. Van Nueten JM, Fontaine J, Helsen L, Janssen PA (1977) Inhibition by purines of peristaltic activity in the guinea-pig ileum. Arch Int Pharmacodyn Ther 227:168–170
679. Vanderwinden JM, Timmermans JP, Schiffmann SN (2003) Glial cells, but not interstitial cells, express P2X7, an ionotropic purinergic receptor, in rat gastrointestinal musculature. Cell Tissue Res 312:149–154
680. Vank C, Frömter E, Kottra G (1999) Activation of an apical Cl^- conductance by extracellular ATP in *Necturus* gallbladder is mediated by cAMP and not by $[Ca^{2+}]_i$. Pflugers Arch 438:486–496
681. Vanner S, Surprenant A (1996) Neural reflexes controlling intestinal microcirculation. Am J Physiol 271:G223–G230
682. Venglarik CJ, Singh AK, Wang R, Bridges RJ (1993) Trinitrophenyl-ATP blocks colonic Cl^- channels in planar phospholipid bilayers. Evidence for two nucleotide binding sites. J Gen Physiol 101:545–569
683. Vial C, Evans RJ (2001) Smooth muscles does not have a common P2x receptor phenotype: expression, ontogeny and function of P2x1 receptors in mouse ileum, bladder and reproductive systems. Auton Neurosci 92:56–64
684. Vieira C, Ferreirinha F, Silva I, Duarte-Araújo M, Correia-de-Sá P (2011) Localization and function of adenosine receptor subtypes at the longitudinal muscle—myenteric plexus of the rat ileum. Neurochem Int 59:1043–1055
685. Vigne P, Pacaud P, Loirand G, Breittmayer JP (1998) PPADS inhibits $P2Y_1$ purinoceptors in rat brain capillary endothelial cells and in rat ileal myocytes by an indirect mechanism. Biochem Biophys Res Commun 244:332–335
686. Virginio C, Robertson G, Surprenant A, North RA (1998) Trinitrophenyl-substituted nucleotides are potent antagonists selective for $P2X_1$, $P2X_3$, and heteromeric $P2X_{2/3}$ receptors. Mol Pharmacol 53:969–973
687. Vizi ES, Knoll J (1976) The inhibitory effect of adenosine and related nucleotides on the release of acetylcholine. Neuroscience 1:391–398
688. Vogalis F, Goyal RK (1997) Activation of small conductance Ca^{2+}-dependent K^+ channels by purinergic agonists in smooth muscle cells of the mouse ileum. J Physiol 502:497–508
689. von Kügelgen I, Starke K (1985) Noradrenaline and adenosine triphosphate as co-transmitters of neurogenic vasoconstriction in rabbit mesenteric artery. J Physiol 367:435–455
690. Wang GD, Wang XY, Hu HZ, Liu S, Gao N, Fang X, Xia Y, Wood JD (2007) Inhibitory neuromuscular transmission mediated by the $P2Y_1$ purinergic receptor in guinea pig small intestine. Am J Physiol Gastrointest Liver Physiol 292:G1483–G1489
691. Wang L, Yao H, Yang Y-E, Song I, Owyang C (2004) Enhanced purinergic pathway occurs in postoperative ileus: reversal by orphanin FQ. Gastroenterology 126:75
692. Wang MX, Ren LM (2006) Growth inhibitory effect and apoptosis induced by extracellular ATP and adenosine on human gastric carcinoma cells: involvement of intracellular uptake of adenosine. Acta Pharmacol Sin 27:1085–1092
693. Wang ZJ, Neuhuber WL (2003) Intraganglionic laminar endings in the rat esophagus contain purinergic $P2X_2$ and $P2X_3$ receptor immunoreactivity. Anat Embryol (Berl) 207:363–371
694. Watanabe C, Akiba Y, Nakano T, Guth PH, Engel E, Khurana S, Kaunitz JD (2009) Extracellular ATP synthase generates extracellular ATP, regulating bicarbonate secretion in rat duodenum. Gastroenterology 136:A-690
695. Weiss T, Gheber L, Shoshan Barmatz V, Priel Z (1992) Possible mechanism of ciliary stimulation by extracellular ATP: involvement of calcium-dependent potassium channels and exogenous Ca^{2+}. J Membr Biol 127:185–193
696. Welford LA, Cusack NJ, Hourani SMO (1986) ATP analogues and the guinea-pig taenia coli: a comparison of the structure-activity relationships of ectonucleotidases with those of the P_2-purinoceptor. Eur J Pharmacol 129:217–224
697. Westerberg VS, Geiger JD (1987) Central effects of adenosine analogs on stress-induced gastric ulcer formation. Life Sci 41: 2201–2205
698. Westerberg VS, Geiger JD (1988) Adenosine and gastric function. Trends Pharmacol Sci 9:345–347
699. Westerberg VS, Geiger JD (1989) Adenosine analogs inhibit gastric acid secretion. Eur J Pharmacol 160:275–281
700. White TD (1988) Role of adenine compounds in autonomic neurotransmission. Pharmacol Ther 38:129–168
701. Whitehouse PA, Knight LA, Di NF, Mercer SJ, Sharma S, Cree IA (2003) Heterogeneity of chemosensitivity of colorectal adenocarcinoma determined by a modified ex vivo ATP-tumor chemosensitivity assay (ATP-TCA). Anticancer Drugs 14:369–375
702. Wiklund NP, Gustafsson LE (1988) Agonist and antagonist characterization of the P_2-purinoceptors in the guinea pig ileum. Acta Physiol Scand 132:15–22
703. Wiklund NP, Gustafsson LE (1988) Indications for P_2-purinoceptor subtypes in guinea pig smooth muscle. Eur J Pharmacol 148:361–370
704. Will S, Triggle CR, Bieger D (1990) Mastocyte and smooth muscle purinoceptors of the rat oesophagus. Abstracts of IUPHAR Satellite Symposium, Noordwijk, July 6–8, 1990. p 33
705. Windscheif U, Pfaff O, Ziganshin AU, Hoyle CHV, Bäumert HG, Mutschler E, Burnstock G, Lambrecht G (1995) Inhibitory action of PPADS on relaxant responses to adenine nucleotides or electrical field stimulation in guinea-pig taenia coli and rat duodenum. Br J Pharmacol 115:1509–1517
706. Wolkoff LI, Perrone RD, Grubman SA, Lee DW, Soltoff SP, Rogers LC, Beinborn M, Fang SL, Cheng SH, Jefferson DM (1995) Purinoceptor P_{2U} identification and function in human intrahepatic biliary epithelial cell lines. Cell Calcium 17:375–383
707. Woo K, Dutta AK, Patel V, Kresge C, Feranchak AP (2008) Fluid flow induces mechanosensitive ATP release, calcium signalling and Cl^- transport in biliary epithelial cells through a PKCzeta-dependent pathway. J Physiol 586:2779–2798
708. Woo K, Sathe MN, Kresge C, Parameswara V, Esser V, Ueno Y, Venter J, Alpini G, Feranchak AP (2008) Functional differences in ATP release and P2 receptor-mediated secretion between small and large mouse cholangiocytes: potential existence of purinergic signaling axis along the intrahepatic biliary tract. Hepatology 48:795
709. Woo K, Sathe M, Kresge C, Esser V, Ueno Y, Venter J, Glaser SS, Alpini G, Feranchak AP (2010) Adenosine triphosphate release and purinergic (P2) receptor-mediated secretion in small and large mouse cholangiocytes. Hepatology 52:1819–1828
710. Wood JD (2006) The enteric purinergic $P2Y_1$ receptor. Curr Opin Pharmacol 6:564–570
711. Woods CM, Toouli J, Saccone GT (2003) A_{2A} and A_3 receptors mediate the adenosine-induced relaxation in spontaneously active possum duodenum in vitro. Br J Pharmacol 138:1333–1339
712. Woods CM, Toouli J, Saccone GT (2006) Exogenous adenosine

triphosphate and adenosine stimulate proximal sphincter of Oddi motility via neural mechanisms in the anesthetized Australian possum. Dig Dis Sci 51:1347–1356
713. Woods CM, Toouli J, Saccone GT (2007) Exogenous purines induce differential responses in the proximal and distal regions of the possum sphincter of Oddi. Auton Autacoid Pharmacol 27:27–38
714. Woods LT, Camden JM, Batek JM, Petris MJ, Erb L, Weisman GA (2012) P2X7 receptor activation induces inflammatory responses in salivary gland epithelium. Am J Physiol Cell Physiol 303:C790–C801
715. Wróbel J, Michalska L (1977) The effect of exogenous ATP on intestinal calcium transport. Comp Biochem Physiol 58A: 421–425
716. Wunderlich JE, Xue J, Kim M, Javed NH, Christofi F, Suntres Z, Yu JG, Grants I, Cooke HJ (2004) Mechanical stimulation of human enterochromaffin-BON cells release adenosine to act at A3 receptors to modulate 5-HT release. Gastroenterology 126:A-160
717. Wunderlich JE, Needleman BJ, Chen Z, Yu JG, Wang Y, Grants I, Mikami DJ, Melvin WS, Cooke HJ, Christofi FL (2008) Dual purinergic synaptic transmission in the human enteric nervous system. Am J Physiol Gastrointest Liver Physiol 294:G554–G566
718. Wynn G, Rong W, Xiang Z, Burnstock G (2003) Purinergic mechanisms contribute to mechanosensory transduction in the rat colorectum. Gastroenterology 125:1398–1409
719. Wynn G, Bei M, Ruan H-Z, Burnstock G (2004) Purinergic component of mechanosensory transduction is increased in a rat model of colitis. Am J Physiol Gastrointest Liver Physiol 287:G647–G657
720. Xia Y, Fertel RH, Wood JD (1997) Suppression of cAMP formation by adenosine in myenteric ganglia from guinea-pig small intestine. Eur J Pharmacol 320:95–101
721. Xiang Z, Burnstock G (2004) Development of nerves expressing $P2X_3$ receptors in the myenteric plexus of rat stomach. Histochem Cell Biol 122:111–119
722. Xiang Z, Burnstock G (2004) $P2X_2$ and $P2X_3$ purinoceptors in the rat enteric nervous system. Histochem Cell Biol 121:169–179
723. Xiang Z, Burnstock G (2005) Distribution of $P2Y_2$ receptors in the guinea pig enteric nervous system and its coexistence with $P2X_2$ and $P2X_3$ receptors, neuropeptide Y, nitric oxide synthase and calretinin. Histochem Cell Biol 124:379–390
724. Xiang Z, Burnstock G (2006) Distribution of $P2Y_6$ and $P2Y_{12}$ receptor: their colocalization with calbindin, calretinin and nitric oxide synthase in the guinea pig enteric nervous system. Histochem Cell Biol 125:327–336
725. Xu GY, Shenoy M, Winston JH, Mittal S, Pasricha PJ (2008) P2X receptor-mediated visceral hyperalgesia in a rat model of chronic visceral hypersensitivity. Gut 57:1230–1237
726. Xue J, Askwith C, Javed NH, Cooke HJ (2007) Autonomic nervous system and secretion across the intestinal mucosal surface. Auton Neurosci 133:55–63
727. Xue L, Suzuki H (1997) Electrical responses of gastric smooth muscles in streptozotocin-induced diabetic rats. Am J Physiol 272: G77–G83
728. Xue L, Imaeda Y, Suzuki H (1998) Effects of suramin on electrical and mechanical activities in antrum smooth muscle of guinea-pig stomach. J Auton Pharmacol 18:325–331
729. Xue L, Farrugia G, Sarr MG, Szurszewski JH (1999) ATP is a mediator of the fast inhibitory junction in human jejunal circular smooth muscle. Am J Physiol 276:G1373–G1379
730. Yagasaki O, Nabata H, Yanagiya I (1983) Effects of desensitization to adenosine 5′-triphosphate and vasoactive intestinal polypeptide on non-adrenergic inhibitory responses of longitudinal and circular muscles in the rat ileum. J Pharm Pharmacol 35:818–820
731. Yamamoto T, Suzuki Y (2002) Role of luminal ATP in regulating electrogenic Na^+ absorption in guinea pig distal colon. Am J Physiol Gastrointest Liver Physiol 283:G300–G308
732. Yang GK, Ming G, Kieffer T, Kwok YN (2007) Purinergic control of gastric somatostatin release. FASEB J 21:A809
733. Yang J, Ip PS, Yeung JH, Che CT (2011) Inhibitory effect of schisandrin on spontaneous contraction of isolated rat colon. Phytomedicine 18:998–1005
734. Yano S, Fujiwara A, Ozaki Y, Harada M (1983) Gastric blood flow responses to autonomic nerve stimulation and related pharmacological studies in rats. J Pharm Pharmacol 35:641–646
735. Yasuda Y, Saito M, Yamamura T, Yaguchi T, Nishizaki T (2009) Extracellular adenosine induces apoptosis in Caco-2 human colonic cancer cells by activating caspase-9/-3 via A_{2a} adenosine receptors. J Gastroenterol 44:56–65
736. Ye JH, Rajendran VM (2009) Adenosine: an immune modulator of inflammatory bowel diseases. World J Gastroenterol 15:4491–4498
737. Yiangou Y, Facer P, Baecker PA, Ford AP, Knowles CH, Chan CL, Williams NS, Anand P (2001) ATP-gated ion channel $P2X_3$ is increased in human inflammatory bowel disease. Neurogastroenterol Motil 13:365–369
738. Yip L, Kwok YN (2004) Role of adenosine A_{2A} receptor in the regulation of gastric somatostatin release. J Pharmacol Exp Ther 309:804–815
739. Yip L, Leung HC, Kwok YN (2004) Role of adenosine A_1 receptor in the regulation of gastrin release. J Pharmacol Exp Ther 310:477–487
740. Yu HX, Turner JT (1991) Functional studies in the human submandibular duct cell line, HSG-PA, suggest a second salivary gland receptor subtype for nucleotides. J Pharmacol Exp Ther 259:1344–1350
741. Yu J, Lavoie ÉG, Sheung N, Tremblay JJ, Sévigny J, Dranoff JA (2008) IL-6 downregulates transcription of NTPDase2 via specific promoter elements. Am J Physiol Gastrointest Liver Physiol 294: G748–G756
742. Yu J, Sheung N, Soliman EM, Spirli C, Dranoff JA (2009) Transcriptional regulation of IL-6 in bile duct epithelia by extracellular ATP. Am J Physiol Gastrointest Liver Physiol 296:G563–G571
743. Yuan S, Costa M, Brookes SJ (1998) Neuronal pathways and transmission to the lower esophageal sphincter of the guinea pig. Gastroenterology 115:661–671
744. Yuan W, Wang Z, Li J, Li D, Liu D, Bai G, Walsh MP, Gui Y, Zheng XL (2013) Uridine adenosine tetraphosphate induces contraction of circular and longitudinal gastric smooth muscle by distinct signaling pathways. IUBMB Life 65:623–632
745. Zafirov DH, Palmer JM, Wood JD (1985) Adenosine inhibits forskolin-induced excitation in myenteric neurons. Eur J Pharmacol 113:143–144
746. Zagorodnyuk V, Maggi CA (1994) Electrophysiological evidence for different release mechanism of ATP and NO as inhibitory NANC transmitters in guinea-pig colon. Br J Pharmacol 112: 1077–1082
747. Zagorodnyuk V, Maggi CA (1998) Pharmacological evidence for the existence of multiple P2 receptors in the circular muscle of guinea-pig colon. Br J Pharmacol 123:122–128
748. Zagorodnyuk VP, Shuba MF (1986) Nature of non-adrenergic inhibition in the smooth muscles of the human intestine. Neirofiziologiia 18:373–381
749. Zagorodnyuk VP, Vladimirova IA, Vovk EV, Shuba MF (1989) Studies of the inhibitory non-adrenergic neuromuscular transmission in the smooth muscle of the normal human intestine and from a case of Hirschsprung's disease. J Auton Nerv Syst 26:51–60
750. Zagorodnyuk V, Hoyle CHV, Burnstock G (1993) An electrophysiological study of developmental changes in the innervation of the guinea-pig taenia coli. Pflugers Arch 423:427–433
751. Zagorodnyuk V, Santicioli P, Maggi CA, Giachetti A (1996) The possible role of ATP and PACAP as mediators of apaminsensitive NANC inhibitory junction potentials in circular muscle of guinea-pig colon. Br J Pharmacol 119:779–786

752. Zeng W, Lee MG, Muallem S (1997) Membrane-specific regulation of Cl^- channels by purinergic receptors in rat submandibular gland acinar and duct cells. J Biol Chem 272:32956–32965
753. Zhang J, Halm ST, Halm DR (2009) Adrenergic activation of electrogenic K^+ secretion in guinea pig distal colonic epithelium: desensitization via the Y2-neuropeptide receptor. Am J Physiol Gastrointest Liver Physiol 297:G278–G291
754. Zhang W, Roomans GM (1997) Regulation of ion transport by P_{2U} purinoceptors and α_{2A} adrenoceptors in HT29 cells. Cell Biol Int 4: 195–200
755. Zhang W, Segura BJ, Lin TR, Hu Y, Mulholland MW (2003) Intercellular calcium waves in cultured enteric glia from neonatal guinea pig. Glia 42:252–262
756. Zhang Y, Lomax AE, Paterson WG (2010) $P2Y_1$ receptors mediate apamin-sensitive and -insensitive inhibitory junction potentials in murine colonic circular smooth muscle. J Pharmacol Exp Ther 333: 602–611
757. Zhou X, Galligan JJ (1996) P2X purinoceptors in cultured myenteric neurons of guinea-pig small intestine. J Physiol 496: 719–729
758. Zhou X, Galligan JJ (1998) Non-additive interaction between nicotinic cholinergic and P2X purine receptors in guinea-pig enteric neurons in culture. J Physiol 513:685–697
759. Ziganshin AU, Berdnikov EA, Ziganshina LE, Tantasheva FR, Hoyle CH, Burnstock G (1995) Effects of α, β-unsaturated sulphones and phosphonium salts on ecto-ATPase activity and contractile responses mediated via P2 chi- purinoceptors. Gen Pharmacol 26:527–532
760. Zimmermann H (1994) Signalling via ATP in the nervous system. Trends Neurosci 17:420–426
761. Zizzo MG, Mulè F, Serio R (2007) Evidence that ATP or a related purine is an excitatory neurotransmitter in the longitudinal muscle of mouse distal colon. Br J Pharmacol 151:73–81
762. Zizzo MG, Mastropaolo M, Lentini L, Mulè F, Serio R (2011) Adenosine negatively regulates duodenal motility in mice: role of A_1 and A_{2A} receptors. Br J Pharmacol 164: 1580–1589
763. Zizzo MG, Mastropaolo M, Grahlert J, Mule F, Serio R (2012) Pharmacological characterization of uracil nucleotide-preferring P2Y receptors modulating intestinal motility: a study on mouse ileum. Purinergic Signal 8:275–285
764. Zoppellaro C, Bin A, Brun P, Banzato S, Macchi V, Castagliuolo I, Giron MC (2013) Adenosine-mediated enteric neuromuscular function is affected during herpes simplex virus type 1 infection of rat enteric nervous system. PLoS One 8:e72648
765. Zsembery A, Spirlì C, Granato A, LaRusso NF, Okolicsanyi L, Crepaldi G, Strazzabosco M (1998) Purinergic regulation of acid/base transport in human and rat biliary epithelial cell lines. Hepatology 28:914–920