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REVIEW ARTICLE

Purinergic signalling in endocrine organs

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Abstract There is widespread involvement of purinergic signalling in endocrine biology. Pituitary cells express P1, P2X and P2Y receptor subtypes to mediate hormone release. Adenosine 5′-triphosphate (ATP) regulates insulin release in the pancreas and is involved in the secretion of thyroid hormones. ATP plays a major role in the synthesis, storage and release of catecholamines from the adrenal gland. In the ovary purinoceptors mediate gonadotrophin-induced progesterone secretion, while in the testes, both Sertoli and Leydig cells express purinoceptors that mediate secretion of oestradiol and testosterone, respectively. ATP released as a cotransmitter with noradrenaline is involved in activities of the pineal gland and in the neuroendocrine control of the thymus. In the hypothalamus, ATP and adenosine stimulate or modulate the release of luteinising hormone-releasing hormone, as well as arginine-vasopressin and oxytocin. Functionally active P2X and P2Y receptors have been identified on human placental syncytiotrophoblast cells and on neuroendocrine cells in the lung, skin, prostate and intestine. Adipocytes have been recognised recently to have endocrine function involving purinoceptors.

Keywords Pituitary · Thyroid · Pancreas · Ovary · Testes · Hypothalamus

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Introduction

Physiological events in the periphery are locally as well as centrally regulated. The local regulation is concerned with precise functional adjustments according to local needs and is executed predominantly by exocrine/paracrine cells and local neurons. Endocrine/paracrine cells, which secrete bioactive peptides, are found in epithelial structures almost everywhere in the body, including the thyroid (parafollicular cells), epithelium of the airways, the gastro-entero-pancreatic region and the genito-urinary tract. The peptide hormone-producing endocrine cells have an endodermal origin. There is a growing number of reports that purinoceptors on endocrine cells mediate release of hormones (see [65,338,382,411,487,511,513,514]).

Pituitary gland (hypophysis)

The pituitary gland is the master endocrine gland lying beneath the hypothalamus. It has an anterior lobe that secretes: thyroid-stimulating hormone (TSH), which stimulates growth of the thyroid gland and releases its hormone; adrenocorticotropic hormone (ACTH), which regulates the endocrine activities of the adrenal cortex which produces cortisol; follicle stimulating hormone (FSH), which promotes secretion of oestrogen and the development of eggs and sperm cells; gonadotrophins; growth hormone; prolactin; luteinising hormone (LH) that releases oestrogen, progesterone and testosterone; lipotropin and melanocyte-stimulating hormone (MSH). The posterior lobe (neurohypophysis) secretes vasopressin (VP) and oxytocin (OT), which are synthesised in the hypothalamus and transported to the pituitary, where they are stored before release. The anterior pituitary hormones do not act on endocrine glands, but directly affect specific tissues; prolactin causes breast development and milk production and MSH stimulates pigment cells. There are five cell types in the anterior pituitary, namely lactotrophs, somatotrophs, corticotrophs, gonadotrophs and thyrotrophs, as well as pituitary stem cells [161].

Adenosine triphosphatase activity was identified in the neural lobe of the bovine pituitary gland, giving an early indication for the presence of purinergic signalling [574]. Adenosine 5′-triphosphate (ATP) was reported early to induce release of VP from neurohypophysial neurosecretory granules [403,424]. In another early paper, intraperitoneal injection of caffeine was shown to cause a rise in plasma corticosterone and stimulated ACTH release, suggesting that events in the pituitary-adrenal axis were modulated (at least in part) by an effect on adenosine receptors [373,474]. Later, adenosine was shown to regulate the release of ACTH from cultured anterior pituitary cells [10]. In electron microscopic studies, Ca^{2+}-ATPase was shown to be present on the plasma membranes on the granular, but not the non-granular, folliculo-stellate cells (FSC) of the rat anterior pituitary [490] and nerve endings [539]. A more recent study has shown that ATP is released from pituitary cells and then broken down by ecto-NTPDase1-3 [218]. Inhibiting the activity of ecto-NTPDases with ARL 67151 led to an increase in ATP release from perfused pituitary cells and apyrase enhanced the degradation of released ATP. Pannexins mediate ATP release in the pituitary gland; pannexin 1 was dominantly expressed in the anterior lobe, while pannexin 2 expression was dominant in the intermediate and posterior pituitary [308]. Pannexin 1 isoforms have been shown to be present in rat pituitary cells and appear to be associated with P2X2, P2X3 and P2X4, as well as P2X7 receptor channels and ATP release [309].

In the cloned pituitary cell line GH3 and rat anterior pituitary cells, adenosine activity via A_1 receptors inhibits prolactin release [121,353,416]. A regulatory role for adenosine in modulating adenylate cyclase activity and reducing prolactin release from primary cultures of rat anterior pituitary cells in both basal and vasoactive intestinal peptide (VIP)-stimulated conditions has been suggested [284]. Adenosine, acting through A_1 receptors, however, was claimed to stimulate the release of prolactin from the anterior pituitary in vitro [609]. More recently studies show that hormone-containing endocrine cells express mostly A_1 receptors, while non-endocrine follicle stimulating cells express mostly A_{2B} receptors [438]. Adenosine regulates thrombomodulin and endothelial protein C receptor expression in FSC [437]. Adenosine stimulated cells of the hypothalamus-pituitary-adrenal cortical axis [519]. The involvement of A_1 receptors has been described in the inhibition of gonadotrophin secretion of LH and FSH induced by adenosine acting via A_2 in rat hemipituitaries in vitro [414]. A_2 receptors have also been implicated in the stimulatory effects of adenosine on prolactin secretion [415]. ATP, acting after breakdown to adenosine via A_1 receptors, induces stellation of 37 % of pituicytes and it was suggested that there is purinergic regulation of pituicyte morphological plasticity and subsequent modulation of hormone release [461]. Further VP and OT reverse adenosine-induced pituicyte stellation [462]. A_{2B} receptors mediate adenosine inhibition of taurine efflux from pituicytes [417]. It has been claimed that adenosine increases interleukin (IL) 6 and decreases release of tumour necrosis factor from anterior pituitary cells [445]. Adenosine signalling pathways in the pituitary gland have been reviewed, highlighting the effects of adenosine on pituitary cell proliferation and the evidence for opposing actions on endocrine and FSC [438–440]. Briefly, A_1 receptors are expressed in rodent pituitary endocrine cell lines mediating hormone release, whereas A_{2B} receptors appear to

be predominant in primary anterior pituitary cell cultures consisting mainly of FSC mediating stimulation of IL-6 secretion.

Growth hormone releasing hormone (GHRH) is secreted by arcuate neurons into the hypothalamic portal vessels and stimulates growth hormone (GH) release by activating GHRH receptors on somatotrophs. Pulsatile release of GH involves P1 receptors expressed on somatotroph cells [489]. A_{2A} receptor gene expression has been reported to occur transiently during the embryological development of the anterior and intermediate lobes of the pituitary gland [581]. There are no reports of A_3 receptors in the pituitary gland. Adenosine, acting via A_1 receptors, specifically blocks the terminal N-type Ca^{2+} channel in isolated rat neurohypophysial terminals, leading to inhibition of the release of both VP and OT [580]. The functions of the pituitary gland are tightly controlled by neuronal and hormonal afferents of the brain. The roles of melatonin and adenosine in rodent pituitary function have been discussed [258]. Adenosine stimulates connexin 43 expression and gap-junctional communication in FSC [305].

Adenosine is an important regulator of the functions of pituitary tumour GH4 cells, which secrete prolactin and growth hormone, by modulating, in an autocrine manner, the activity of L-type voltage-dependent calcium channels [439,612].

Adenosine increased release of IL-6 from primary anterior pituitary cell cultures [445] and the implications of this finding for inflammation and tumorigenesis were discussed [439]. Adenosine-induced IL-6 expression in FSC is mediated via A_{2B} receptors coupled to protein kinase (PK) C and p38 mitogen-activated protein kinase (MAPK) [440].

Extracellular ATP was shown to activate phospholipase (PL) C and mobilise intracellular calcium in primary cultures of sheep anterior pituitary cells [566]. Later it was shown that uridine 5′-triphosphate (UTP), as well as ATP, were potent agonists on these cells [117], suggestive of $P2Y_2$ (and/or $P2Y_4$) receptors on lactotrophs in the rat adenohypophysis [71]. ATP, adenosine 5′-diphosphate (ADP) and UTP stimulate cultured gonadotrophs from rat pituitary gland and gonadotroph-derived αT3-1 cells, probably mediated by $P2Y_2$ and/or $P2Y_4$ receptors [91,92]. It was proposed that ATP represents a paracrine/autocrine factor in the regulation of Ca^{2+} signalling and secretion of gonadotrophs consistent with mediation by P2X2 and/or P2X5 receptor channels [542].

Molecular cloning and functional characterisation of rat pituitary $P2Y_2$ receptors were carried out and shown to be located on rat primary gonadotrophs, GH3 cells, and mixed sheep pituitary cells [93,94]. An autocrine/paracrine role of ATP in the regulation of release of prolactin from most (if not all) mammotrophs was proposed [383].

Evidence was presented for the presence of at least two types of purinoceptor on all five types of cells in the anterior pituitary, namely $P2Y_2$ and P2X1, although the existence of a subpopulation of cells expressing P2X2/3 and $P2Y_1$ was not excluded [575]. P2X2 receptors have been shown to be localised at the electron microscope level on pituicytes and a subpopulation of neurosecretory axons in the rat neurohypophysis [321]. The primary P2X2 receptor transcript in rat pituitary cells undergoes extensive alternative splicing, with generation of six isoforms [276]. A heteropolymeric P2X2 receptor has been claimed to mediate hormone release from lactotrophs, somatotrophs and gonadotrophs [512]. The mRNAs for wild-type and spliced channels were identified in enriched somatotrophs, where they were shown to be functional, but not gonadotroph or lactotroph fractions.

It has been proposed that ATP, coreleased with neuropeptides from neurohypophysial nerve terminals, acts as a paracrine/autocrine messenger, stimulating Ca^{2+} entry via a P2X2 receptor and secretion of VP, but not OT [550]. ATP was shown to be released stimulation-dependently from the rat isolated posterior lobe of the hypophysis to act via P2 receptors for local control of hormone secretion [502]. In addition, ATP, cosecreted with VP and OT from cells in the hypothalamus, has been claimed to play a role in the regulation of stimulus-secretion coupling in the neurohypophysis [299]. A recent study has shown that endogenous ATP potentiates VP, but not OT, secretion from neurohypophysial terminals [268]. The output of the neurohypophysial hormones VP and OT depends on the frequency and pattern of firing of their synthesising neurons in the hypothalamus. ATP released from pituicytes and/or nerve terminals in the hypophysis, when broken down by ecto-nucleotidases to adenosine, acts on A_1 receptors to modulate release of VP [460]. ATP, acting via P2Y receptors, triggers calcium mobilization in primary cultures of rat neurohypophysial astrocytes (pituicytes) ([551]; see [549], for a review of the multifaceted purinergic regulation of stimulus-secretion coupling in the neurohypophysis).

Mixed populations of rat anterior pituitary cells express mRNA transcripts for $P2Y_2$, P2X2, P2X3, P2X4 and P2X7 receptors ([277]; Table 1). The transcripts and functional $P2Y_2$ receptors were identified in lactotrophs and GH3 cells, but not in somatotrophs or gonadotrophs. Lactotrophs and GH3 cells also express transcripts of P2X3, P2X4 and P2X7 receptors. Functional P2X2 receptors were found in somatotrophs and gonadotrophs, but not in lactotrophs. A recent study reported that mRNA transcripts for all P2X receptor subunits (except for P2X5) were expressed in rat anterior pituitary, and of these the P2X4 mRNA transcripts were the most abundant [614,615]. They showed that thyrotropin-releasing hormone-

Table 1 Purinoceptor subtypes expressed by different endocrine cell types

Cell type	Purinergic receptor subtypes										
	P2X1	P2X2	P2X3	P2X4	P2X6	P2X7	$P2Y_1$	$P2Y_2$	$P2Y_4$	A_1	A_{2A}
Lactotrophs		X	✓	✓		✓	✓	✓		✓	
GH3 cells		-	✓	✓		✓		✓		✓	
Somatotrophs		✓	X	X		X		X			
Gonadotrophs		✓	X	X		X		X		✓	✓
Melanotrophs										✓	
Thyrotrophs			(P2X✓)								
Corticotrophs	✓			✓	✓	✓	✓	✓	✓	✓	✓
Folliculo-stellate cells (FSC)		–	–	–		–		✓			✓
Hypophyseal pituicytes (astrocytes)								✓		✓	
GH4Cl cell line						✓					

✓receptors present, *X* receptors absent

responsive cells, including lactotrophs, express homomeric and/or heteromeric P2X4 receptors, which facilitate Ca^{2+} influx and hormone secretion. Another study also described P2X7 receptors on GH3 cells and showed that they mediated increase in $[Ca^{2+}]_i$ and depolarisation [101]. ATP, operating via P2X2 receptors controls the pacemaker activity, voltage-gated Ca^{2+} influx and basal LH release in gonadotrophs [613]. A valuable review discusses the complexity of purinergic signalling in lactotrophs, which express multiple purinoceptors and also reports the presence of P2X receptors in thyrotrophs and corticotrophs, although the subtypes were not identified ([510]; Fig. 1a). Transcripts for $P2Y_1$, $P2Y_4$, $P2Y_6$ and $P2Y_{12}$, as well as $P2Y_2$ receptors, were identified in mixed anterior pituitary cells [217]. It was shown further that $P2Y_1$ receptors mediated the stimulatory actions of ADP (and ATP) for prolactin secretion and that of the P2X receptor subtypes previously recognised, the P2X4 receptors provided the major pathway for Ca^{2+} influx-dependent signalling and prolactin secretion. In the neurohypophysis, extracellular ATP released from nerve terminals may act directly on pituicytes to induce K^+ efflux via a P2Y receptor [552]. Thus, ATP can act as a neuron-glial signalling molecule within the neurohypophysis.

The Tpit/F1 cell line derived from pituitary FSC (glia-like cells in the anterior pituitary) exhibits responses to ATP consistent with those of normal FSC [89]. It was shown that ATP, acting via $P2Y_2$ receptors increased both nitric oxide (NO) secretion and NO synthase (NOS) mRNA in these cells. ATP actions on FSC in primary culture have also been shown to act via P2Y receptors in response to ATP coreleased with pituitary hormones ([558]; Fig. 1b). In a recent study, $P2Y_1$ and $P2Y_4$ receptors were shown to be expressed in the majority of gonadotrophs and thyrotrophs; $P2Y_2$ receptors were expressed in a small subpopulation of lactotrophs and almost all of the FSC; $P2Y_6$ receptors were expressed on macrophages; and $P2Y_{12}$ receptors were expressed on a small subpopulation of unidentified cells in the rat anterior pituitary [607]. P2X2 receptors were identified on corticotropin-releasing and thyrotropin-releasing hormone producing neurons [105]. Corticotrophs and somatotrophs were found not to express P2Y receptors. Cultures of stably transfected GH_4C1 rat pituitary cells express P2X7 receptors [264,348]. Purinergic receptor ligands stimulate pro-opiomelanocortin (POMC) gene expression in AtT-20 mouse pituitary corticotroph cells. ATP, adenosine and corticotrophin-releasing hormone act synergistically to promote the expression of transcription factors of the POMC gene and ACTH synthesis via different intracellular signalling pathways ([617]; see Fig. 1c). mRNA for A_1, A_{2A}, P2X1, P2X3, P2X4, P2X6, P2X7, $P2Y_1$, $P2Y_2$ and $P2Y_4$ receptors was identified in corticotroph cells.

Reviews about purinergic regulation of hypothalamic and pituitary functions are available ([509,513,514]; and see schematic Fig. 2).

Pancreas

The pancreas performs both exocrine and endocrine functions. It regulates the metabolic states of the body by sensing changes in fatty acids and glucose and responds by secreting insulin and glucagon. Most of the pancreas is exocrine, consisting of 70-90 % acinar cells and 5-25 % duct cells, varying between species. Endocrine cells in the islets of Langerhans consist of only 3-5 % of the pancreas. Pancreatic stellate cells consist of less than 5 % of the pancreas mass.

The first reports on the role of purinergic signalling in the endocrine pancreas appeared 50 years ago. Secretion of

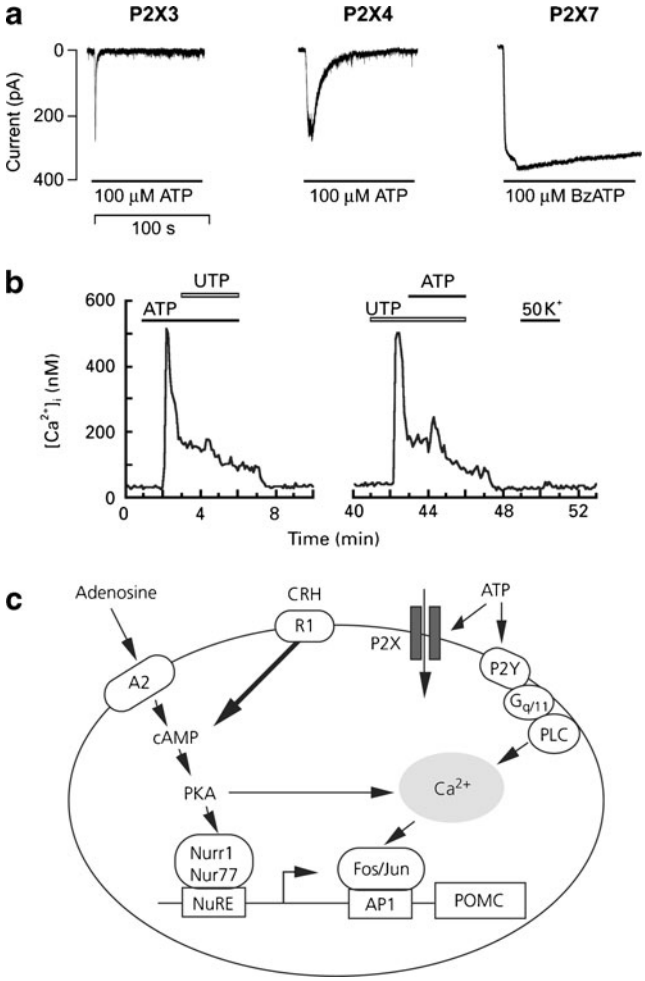

Fig. 1 **a** Characterization of ion-conducting purinergic receptors expressed in pituitary cells. Pattern of current signals in GT1 cells expressing recombinant P2X3, P2X4 and P2X7 receptors. (Reproduced from [510], with permission from Elsevier.) **b** Responses of rat pituitary folliculo-stellate cells in primary culture to ATP (10 μm), UTP (10 μm) and K^+ (50 mm) applied as indicated with *horizontal bars above the traces*. The trace is not shown during 10–40 min. The same cell responded to ATP and to UTP with a 30-min wash. (Reproduced from [558], with permission from Wiley.) **c** Schematic representation of the putative molecular mechanism for the purinergic regulation of pro-opiomelanocortin (*POMC*) gene expression in AtT20 mouse corticotroph cells. ATP, adenosine and corticotrophin-releasing hormone (*CRH*) stimulate the 5′-promoter activity of the POMC gene in a more than additive manner, suggesting an enhancing role of these compounds in CRH-mediated adrenocorticotropic hormone (ACTH) synthesis. The ligands also stimulate the expression of transcription factors of the regulation of the POMC gene, without enhancing ACTH secretion. The effect of adenosine and CRH, but not ATP, can be inhibited by a protein kinase A (*PKA*) inhibitor, indicating mediation via different intracellular signalling pathways. *NuRE* Nurr1/Nur77 response element, *PLC* phospholipase C. (Reproduced from [617], with permission from Blackwell.)

insulin by ATP was reported in 1963 for rabbit pancreas slices [449], confirmed later in primates [304]. Experiments on ATP-induced insulin release were carried out on isolated perfused pancreas (e.g. [150,518]).

ATP released together with insulin from pancreatic secretary granules by exocytosis was reported in 1975, comparable to the release of ATP with noradrenaline (NA) from adrenal chromaffin granules [298]. ATP was next shown to stimulate glucagon and insulin secretion from isolated perfused rat pancreas in 1976, which was dependent on low and high glucose concentrations, respectively [328]. The ATP released from secretary granules is broken down to ADP and adenosine monophosphate (AMP) [517] and ectoATPases are present [303]. Adenosine, resulting from ATP breakdown, inhibited insulin secretion stimulated by glucose [240]. Adenosine, ADP and 5′-AMP elicit release of glucagon in isolated perfused rat pancreas [582].

Early studies on the role of nucleotides on insulin secretion came from the laboratory of Mme Marie-Madelaine Loubatières-Mariani. It was shown, for example, that the relative potencies of nucleotides that caused insulin release induced by glucose was ATP≥ADP>AMP. Adenosine had only weak activity and guanosine triphosphate (GTP), inosine triphosphate, cytosine triphosphate and UTP were virtually inactive [329]. It was shown that 2-2″pyridylisatogen tosylate, a P2 receptor antagonist, inhibited the insulin secreting action of ATP [82]. Stimulation of the secretion of glucagon, but not insulin, by adenosine suggested that α-cells were more sensitive to adenosine than β-cells [330]. There have been some valuable reviews about various aspects of purinergic endocrine signalling in the pancreas over the years [50,66,133,219,228,337,382,411,479,515,524]. A recent one is available about purinergic signalling in diabetes ([67]; Fig. 3).

Both endocrine and exocrine cell activities are regulated by parasympathetic and sympathetic nerves, in addition to hormones, and autocrine and paracrine mediators [350]. Intrapancreatic parasympathetic nerves are present at day 14 of gestation in the foetal rat pancreas, but there was no sympathetic innervation at that stage [119]. ATP and acetylcholine (ACh) act synergistically to regulate insulin release [28] and islet oscillations [207], in keeping with their roles as cotransmitters from parasympathetic nerves. Intrapancreatic ganglia are involved in the regulation of periodic insulin secretions and studies of insulin release from the perfused pancreas after nerve blockade led to the proposal that the islets communicate via non-adrenergic, non-cholinergic neurotransmission [505]. Effector cells are innervated when they form close relationships with axonal varicosities [64]. Such relationships have been shown between sympathetic nerve varicosities and both α- and δ- cells, although less so with β-cells [451]. Sympathetic nerve stimulation inhibited insulin secretion, probably via α_{2A} receptor mediated opening of ATP-dependent K^+ channels [132,324]. Another study showed that over-expression of the α_{2A} adrenoceptor contributed to development of type 2 diabetes [457]. Sympathetic nerve stimulation regulated exocrine ducts and acinar cells via β-adrenergic

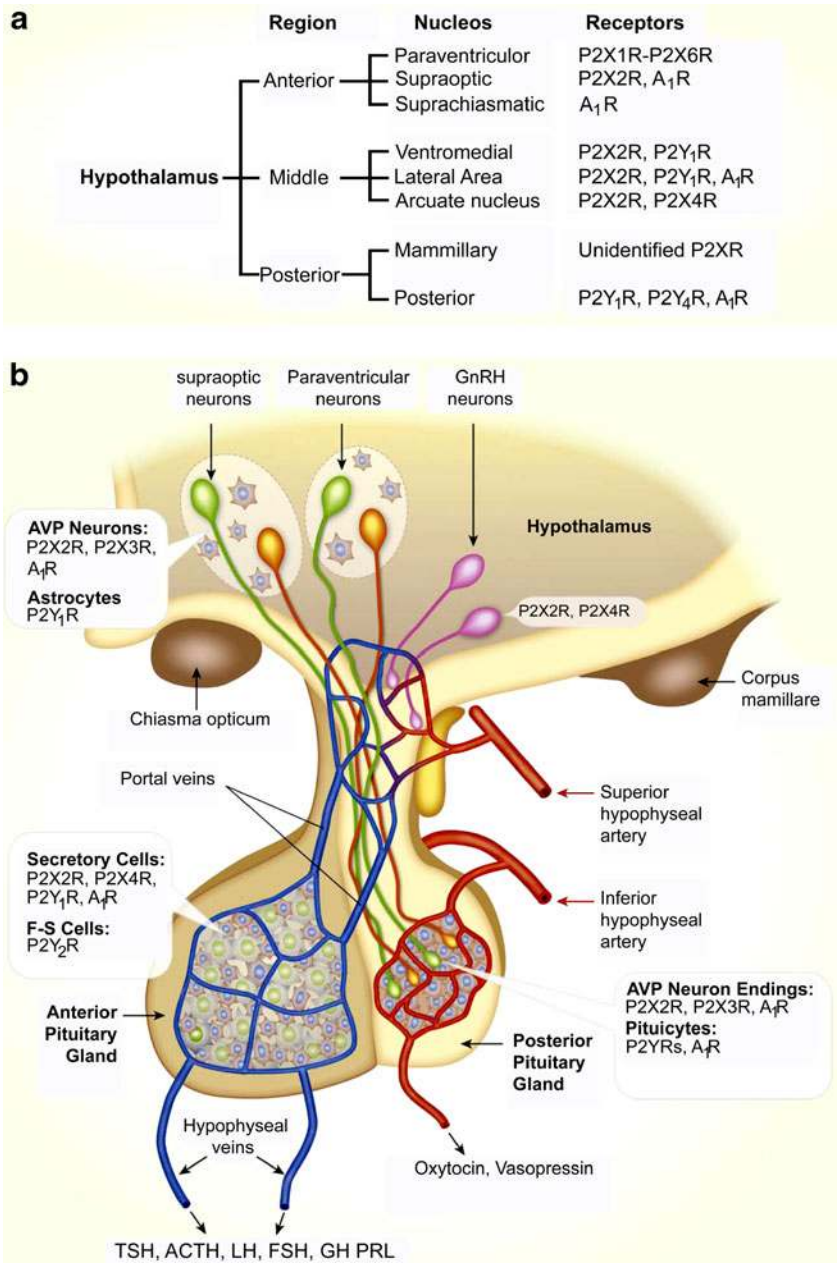

Fig. 2 Expression of purinergic receptors in the hypothalamus and pituitary. **a** Receptors and receptor channels expressed in neurons of nuclei of the hypothalamus. For paraventricular and supraoptic nuclei, receptors expressed in parvocellular areas are listed. **b** Schematic representation of the hypothalamopituitary system. *Insets* indicate expression of purinergic receptors in secretory and supporting cells in three compartments. Note the pattern of expression of purinergic receptors: P2X2R are expressed in a majority of secretory cells (in anterior and middle hypothalamic neurons, vasopressinergic nerve endings and anterior pituitary (AP) cells). Supporting cells (astrocytes in the hypothalamus, pituicytes in the posterior pituitary (PP) and folliculostellate (*F-S*) cells in the anterior lobe) do not express P2XRs. Many cells co-express P2XRs, which facilitate electrical activity, and A1Rs, which silence electrical activity. P2X7R are also expressed in hypothalamopituitary cells, but the cell types expressing these channels have not been identified. In other brain regions, astroglial cells express P2X7Rs. ATP is co-secreted by neurons making synapses with magnocellular neurons in the hypothalamus and by both vasopressin and oxytocin-secreting neurons in the PP. ATP is also released by AP cells through still not well-characterized pathways. Green cells, vasopressin (*AVP*)-secreting neurons; orange cells, oxytocin-secreting neurons; pink cells, GnRH neurons. (Reproduced from [509], with permission from Elsevier.)

receptors [314,315,238,381], although its major effect was on blood vessels where it caused vasoconstriction [238]. Further, sympathetic nerves (releasing NA and ATP as cotransmitters) indirectly regulate pancreatic endocrine and exocrine secretion via actions on parasympathetic ganglionic neurons in the pancreas [605]. Different pancreatic cell types possess a number of purinergic and adenosine receptors and ectonucleotidases, implicating ATP as a parasympathetic/sympathetic cotransmitter.

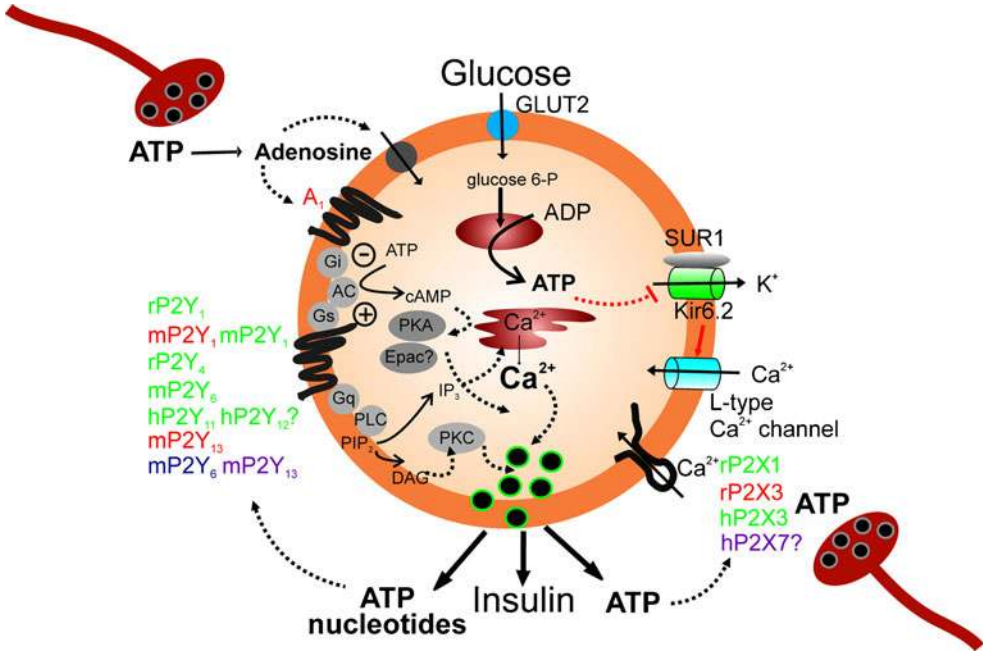

Fig. 3 Role of purinergic receptors in regulation of insulin secretion and β-cell survival. The facilitative GLUT-2 transporter mediates glucose entry. Glucose metabolism results in production of ATP, which closes the ATP-sensitive channel, K_{ATP}. The channel comprises of four Kir6.2 and SUR1 subunits. Closure of K_{ATP} depolarises the cell membrane potential and thus opens voltage-gated L-type Ca^{2+} channels eventually leading to generation of Ca^{2+} action potentials. Exocytosis of secretory vesicles containing insulin (and ATP) is triggered by increases in the cellular Ca^{2+}. ATP can be also released from parasympathetic and sympathetic nerves. P2 receptors can boost and amplify signals associated with the glucose effect on insulin secretion and on proliferation or apoptosis of β-cells. P2X receptors facilitate Ca^{2+}/Na^{+} influx and membrane depolarisation, and as a result, they can elicit insulin secretion even at low glucose concentrations. Some P2Y receptors increase cellular Ca^{2+} and activate protein kinase C (*PKC*) pathways. In addition, other P2Y and adenosine receptors affect the cyclic AMP pathway and possibly Epac signalling. At high adenosine concentrations, adenosine would be transported into the β-cell and exert metabolic effects. Receptors leading to increased insulin secretion are shown in *green*, those inhibiting insulin secretion are in *red*. Receptors affecting cell proliferation are in *blue* and those stimulating apoptosis purple. Receptors depicted here are taken from functional studies and the prefixes refer to rat, mouse or human receptors. (Reproduced from [66], updated from [382], with permission from The Society of Endocrinology.)

Several types of nucleotide-/nucleoside-modifying enzymes are expressed in various pancreatic cells. Membrane Mg^{2+}- or Ca^{2+}-activated adenosine triphosphatase activity in rat pancreas has been reported [211,214,283,343]. ATP diphosphohydrolase was identified in pig pancreas, hydrolysing ATP to ADP and AMP [282]. An early study of rat pancreas showed ATPase, ADPase, 5′-nucleotidase and alkaline phosphatase activity in the vasculature, endocrine and exocrine cells [44]. ATPase was present on both endocrine and exocrine cells, while endocrine but not exocrine cells expressed alkaline phosphatase (see [187]). ATP-pyrophosphohydrolase (ecto-NPP) and alkaline phosphatase were shown in isolated mouse pancreatic islets [69]. Later, type-1 ecto-nucleoside triphosphate diphosphohydrolase (denoted NTPDase/CD39) was purified from pig pancreas [480]. A monoclonal antibody was prepared as a specific inhibitor of human NTPDase-3, which was expressed in all Langerhans islet cells [364]. Later, NTPDase-3 was shown to be expressed in endocrine cells of several species, and ecto-5′-nucleotidase (CD73) was expressed in rat, but not in human and mouse [288]. It was also shown that NTPDase-3 modulated insulin secretion.

Islets of Langerhans are situated throughout the pancreas, comprising of four cell types, α-cells containing glucagon, β-cells containing insulin and amylin and δ-cells containing somatostatin and pancreatic polypeptide-containing cells.

β-Cells

Extracellular ATP stimulation of β-cells results in insulin secretion (see [109,411,450]) and ATP released from nerves was proposed to regulate insulin secretion [524]. In 1963, it was reported that ATP added to the medium surrounding pieces of rabbit pancreas increased insulin secretion into the medium [449]. Stimulation of insulin secretion also occured when ATP was applied to the isolated perfused rat pancreas [327–329,518] and hamster pancreas [150]. ATP increases $[Ca^{2+}]_i$ in clonal insulin-producing RINm5F cells [15]. ATP action was found to be glucose-dependent and was exerted via two different types of P2 receptors: P2X receptors on rat pancreatic β-cells transiently stimulated insulin release at low glucose concentrations and P2Y receptors potentiated glucose-stimulated insulin secretion ([410]; see [479]). Electrophysiological and immunocytochemical evidence has been

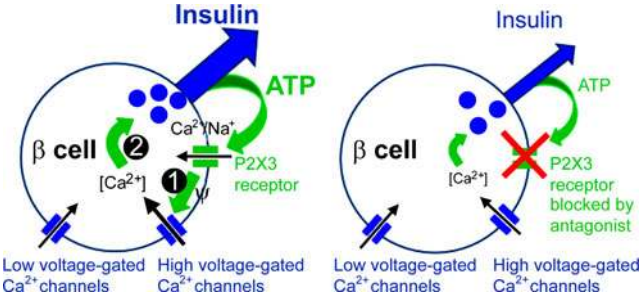

Fig. 4 Proposed model for the positive autocrine feedback loop mediated by ATP in human β cells. *Left hand panel*: ATP, coreleased with insulin, activates ionotropic P2X3 receptors in the β-cell plasma membrane. This opens the cation selective P2X3 channel pore to let Na^+ and Ca^{2+} flow into the cell (1). The resultant membrane depolarization and increase in action potential frequency increases Ca^{2+} flux through high voltage-gated Ca^{2+} channels. Increased $[Ca^{2+}]_i$ (2) stimulates insulin secretion. *Right hand panel*: In the absence of P2X3 activation (using a P2X receptor antagonist), insulin secretion is diminished, revealing a strong contribution of ATP receptor activation to the response. (Modified and reproduced from [242], with permission from the National Academy of Sciences of the United States of America.)

presented that P2X1 and P2X3 receptors are expressed by mouse pancreatic β-cells [484]. It has been shown that the mitochondrial Ca^{2+} uniporter is required for sustained increase in cytosolic ATP/ADP ratio and is essential for glucose-induced ATP increases in pancreatic β-cells [532]. The concentration-response relationship for different P2 receptor agonists with different glucose backgrounds were summarised in a review [411]. Later studies indicated that ATP also had inhibitory effects on insulin release, perhaps via specific P2 receptor subtypes with different binding sites, and/or different intracellular signalling pathways, or even indirectly via adenosine receptors after ATP breakdown. Pancreatic β-cells act as glucose sensors, where intracellular ATP is altered with glucose concentration change. It has been reported that elevated cytosolic ATP enhanced the activity of Na^+ channels, which lead to modulation of β-cell excitability and insulin release when blood glucose concentration increases [621]. There also appear to be significant species differences. ATP, via P2X and/or P2Y receptors, increases $[Ca^{2+}]_i$ in many β-cell preparations and models, including human insulin-secreting β-cells, where ATP enhances sensitivity and responsiveness of β-cells to glucose fluctuations ([242,503]; see Fig. 4). Intracellular signalling pathways, including K_{ATP} channel open/closed state, membrane voltage and Ca^{2+} influx, lead to release of insulin. The initial phase of the biphasic insulin response to glucose was potentiated by endogenous ATP [85]. Comparative effects of ATP and related analogues on insulin secretion in rat pancreas have been reported [86]. ATP triggers synchronization of β-cell rhythmicity after increasing $[Ca^{2+}]_i$ [197].

Insulin granules contain ATP (and ADP) [239,298]. These granules are secreted and were detected as quantal exocytotic release from rat β-cells expressing P2X2 receptors acting as ATP biosensors; ATP concentrations up to 25 μmol/l close to plasma cell membranes have been detected [216,251]. ATP was shown to be released by exocytosis, while insulin was retained in the granule [384], suggesting that basal release of ATP may have a role as an autocrine regulator. The vesicular nucleotide transporter (VNUT) is expressed in pancreatic β-cells and VNUT-mediated ATP release is part of the mechanism that controls glucose-induced secretion [181]. They showed further that P2X receptors are critical in mediating the effect of ATP on insulin secretion when VNUT is overexpressed. Evidence has been presented to suggest that $P2Y_1$ as well as P2X receptors play a role in the modulation of insulin secretion, proliferation and cell viability in mouse pancreatic β-cells [391]. ATP is also co-released with 5-hydroxythryptamine (5-HT), γ-aminobutyric acid, glutamate and zinc, which have further autocrine coregulatory functions on insulin secretion [49,251,444]. Extracellular nucleotides inhibit insulin receptor signalling [87].

The molecular identities of P2 receptors on various preparations of β-cells are summarised in Table 2 and their role in regulation of insulin secretion is shown in Fig. 3. α,β-Methylene ATP (α,β-meATP) mimicked the ATP effects on insulin secretion [408], indicating that P2X1 or P2X3 receptor subtypes might be involved. RT-PCR and Western blots showed that most of the P2X1 - P2X7 receptors were expressed in rat primary islet β-cells and the INS-1 cell line [444,470]. The characteristics of the P2X7-like receptor activated by ATP were described in the hamster β-cell line, HIT-T15 cells [291]. Mouse, human and porcine β-cells express rapidly desensitising P2X1 and P2X3 receptors, and it was proposed that paracrine and/or neural ATP activation of these receptors contribute to the initial outburst of glucose- or ACh-evoked insulin release [484]. Further, ATP liberated together with insulin, might participate in positive feedback control of insulin release [41,116]. P2X3 receptors were shown to constitute a positive autocrine and amplifying signal for insulin release in the human pancreatic β-cell [242]. In the rat INS-1 cell line, the P2X3 receptor inhibited insulin secretion at all glucose concentrations tested [470].

Evidence for P2Y receptors mediating the biphasic response in insulin secretion from β-cells has been presented [29,153,306]. Extracellular ATP increases $[Ca^{2+}]_i$ in β-cells, mainly by triggering Ca^{2+} release from intracellular stores [196,597], implicating P2Y receptors. Adenosine-5′-(β-thio)-diphosphate (ADPβS) was a potent agonist mediating insulin secretion from perfused rat pancreas and isolated islets [34,410], indicating that $P2Y_1$, $P2Y_{12}$ or $P2Y_{13}$ receptors might be involved. This ADP analogue also enhanced insulin secretion and reduced hyperglycemia after oral administration to rats and dogs [227]. β-Cell apoptosis is induced by high glucose and free fatty acids via the autocrine action of ATP acting via $P2Y_{13}$ receptors [531]. Several studies focussed on $P2Y_1$ receptors and pharmacological agents were developed

Table 2 Molecular identity of P2 receptor subtypes expressed in pancreatic β-cells (Reproduced from [66], with permission from the Society of Endocrinology)

Receptor subtype	Tissue origin	Technique	Reference
P2X1	Rat and mouse pancreas (progressively upregulated)	Immunohistochemistry	[109]
	Mouse islet cells	Immunocytochemistry	[484]
	Rat INS-1e	RT-PCR	[470]
P2X2	Rat islets, rat (INS-1) and mouse (βTC3) β-cell models	RT-PCR, Western blot analysis and immunohistochemistry	[444]
	Rat INS-1e	RT-PCR	[470]
P2X3	Mouse islet cells	Immunocytochemistry	[484]
	Rat islets, rat (INS-1) and mouse (βTC3) β-cell models	RT-PCR, Western blot analysis and immunohistochemistry	[444]
	Rat INS-1e	RT-PCR, siRNA	[470]
	Human islets	Immunohistochemistry, RT-PCR, Western blot analysis and in-situ hybridization	[242]
P2X4	Rat islets, RINm5F and HIT-T15 cells	mRNA blot analysis	[579]
	Rat and mouse pancreas (progressively upregulated)	Immunohistochemistry	[109]
	Rat islets, rat (INS-1) and mouse (βTC3) β-cell models	RT-PCR, Western blot analysis and immunohistochemistry	[444]
	Rat INS-1e	RT-PCR	[470]
P2X5	Human islets	in-situ hybridization	[242]
P2X6	Rat islets, rat (INS-1) and mouse (βTC3) β-cell models	RT-PCR, Western blot analysis and immunohistochemistry	[444]
	Rat INS-1e	RT-PCR	[470]
P2X7 $P2Y_1$	HIT-T15 cells	Western blot analysis	[292]
	Rat INS-1e	RT-PCR	[470]
	Human islets	in-situ hybridization	[242]
	Mouse WT and KO islets and pancreas	RT-PCR, Western blot analysis, immunohistochemistry and functional studies	[188]
	Human islets		
	INS-1 β-cells	RT-PCR and Western blot analysis	[332]
	Mouse islets and β-cells	RT-PCR	[405]
	Mouse β-TC6 insulinoma cells	RT-PCR	[390]
	Rat INS-1e	RT-PCR	[470]
	Mouse MIN6	RT-PCR	[17]
	Mouse WT and KO whole body	Functional studies	[301]
$P2Y_2$	INS-1 β-cells	RT-PCR and Western blot analysis	[332]
	Rat INS-1e	RT-PCR	[470]
$P2Y_4$	Pancreatic β-cells (normal and diabetic rats)	Immunohistochemistry	[109]
	Rat islets, INS-1 and RIN cells	RT-PCR and Western blot analysis	[470]
	INS-1 β-cells	RT-PCR and Western blot analysis	[332]
	Rat INS-1e	RT-PCR, siRNA	[470]
$P2Y_6$	INS-1 β-cells	RT-PCR and Western blot analysis	[332]
	Mouse islets and β-cells	RT-PCR	[405]
	Mouse β-TC6 insulinoma cells	RT-PCR	[390]
	Rat INS-1e	RT-PCR	[470]
	Mouse MIN6	RT-PCR	[17]
$P2Y_{11}$	Human β-cells	RT-PCR, Western blot analysis, immunofluorescence	[333]
	HIT-T15 cells	Western blot analysis	[292]
$P2Y_{12}$	INS-1 β-cells	RT-PCR and Western blot analysis	[332]
	Human β-cells	RT-PCR, Western blot analysis, immunofluorescence	[333]
	Rat INS-1e	RT-PCR	[470]
$P2Y_{13}$	Mouse islets and β-cells	RT-PCR	[9]

Other functional and pharmacological evidence for P2 receptors is given in the text

[147,159,230]. $P2Y_1$ receptor knockout mouse experiments indicated that the receptor was involved in glucose homeostasis, although insulin secretion was decreased in islets isolated from $P2Y_1$ knockout mice [301]. Pancreatic β-cells also express other P2Y receptors. The P2U (i.e. $P2Y_2$ or $P2Y_4$) receptor was cloned and characterised from human pancreas [506]. The $P2Y_4$ receptor was demonstrated immunohistochemically in rat β-cells [109,110]. mRNA and protein expression showed that rat insulinoma INS-1 cells express $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$ and $P2Y_{12}$ receptors [332,470]. Further, the $P2Y_4$ receptor stimulated insulin secretion at all glucose concentrations tested [470]. However, mouse β-cells did not express $P2Y_2$ and $P2Y_4$ receptors [390,405].

Although most studies have shown that ATP/ADP increase insulin release, some early studies showed that ADP could also decrease insulin release [409,428]. Later studies showed that P2Y receptors, possibly $P2Y_1$, mediated inhibition of L-type Ca^{2+} channels in rat pancreatic β-cells [194]. Another study showed that in mice β-cells ADP inhibited insulin secretion by activation of $P2Y_{13}$ receptors, but increased insulin secretion via $P2Y_1$ receptors [9].

$P2Y_1$ and $P2Y_6$ receptors in mouse β-cells mediated inhibition of insulin secretion at high glucose concentrations, but were slightly stimulant at 5 mM glucose [390]. Other studies showed clear stimulation of insulin secretion via these receptors at glucose concentrations >8 mM [17,405]. A further two receptors were identified, $P2Y_{11}$ and $P2Y_{12}$, in human pancreatic islets and their involvement in stimulation of insulin secretion was postulated [333]. In the hamster β-cell line HIT-T15, $P2Y_{11}$ receptors stimulated insulin secretion while P2X7 receptors inhibited it; the net effect depending on the glucose concentration [292]. P2X7 receptors mediate IL-1 receptor antagonist secretion and it has been suggested that this in turn regulates β-cell mass and function [188].

P2 receptors are also involved in β-cell survival. Pancreatic islet cells express NTPDase-3 and ecto-5′-nucleotidase is present in some species, leading to accumulation of adenosine [288]. While rat islets express 5′-nucleotidase for breakdown of extracellular ATP to adenosine, mouse islets do not [604]. Microelectrode recordings from mouse pancreatic β-cells showed that theophylline (a non-selective P1 receptor antagonist) depolarised the β-cell membrane leading to insulin release; further, in 10 mM glucose, β-cells exhibited slow waves with bursts of spikes in the plateau and increased insulin secretion [223]. In perfused dog pancreas, the adenosine analogue 5′-N-ethylcarboxamidoadenosine (NECA) inhibited insulin release, the effect being concentration-dependent [16]. A_1 receptors mediating inhibition were pharmacologically identified on β-cells [32,226,572] and in INS-1 cells [543]. A_1 receptor antagonism in rat pancreatic islets potentiates insulin secretion [623]. The ectonucleotidases and A_1 receptors might explain some of the dual effects of ATP.

The physiological roles of all these P1 and P2 receptor subtypes and their different effects on insulin secretion are being investigated. Studies of both in vivo and in vitro pancreas and in isolated islets with coupled β-cells showed that secretion of insulin (and glucagon and somatostatin) is pulsatile. Pulsatility is reflected by intracellular Ca^{2+} oscillations and membrane potential changes. It has been suggested that purinergic signalling is one of the coordinating mechanisms [219,221,382]. Activation of P2Y receptors enhanced insulin release from β-cells by triggering the cyclic AMP (cAMP)/PKA pathways [98]. Inhibition of the $P2Y_1$ receptor attenuated glucose-induced insulin oscillations, but increased the total amount of insulin secreted [466]. Glucose stimulation of mouse β-cells triggers oscillations of the ATP concentration in the sub-plasma membrane space and it was suggested that a dynamic interplay between ATP and $[Ca^{2+}]_i$ in β-cells may be important for the generation of pulsatile insulin secretion [307]. A_1 receptor deletion increased insulin pulses and prolonged glucagon and somatostatin pulses and they lost their antisynchronous action [245,468]. Endothelial cells in the islets had a tonic inhibitory action on β-cell P2 receptors, resulting in impaired synchronisation of the insulin release pulses [222]. Figure 3 illustrates the pulsatility of ATP release and differential regulation via various P2 receptors and shows that P1 receptors could contribute to the pattern of insulin release [11]. It was claimed that adenosine inhibited insulin release from rat β-cells [31].

It has been suggested that P2Y receptors mediating stimulation of Gs proteins could have similar roles as incretins, glucagon-like peptide and gastric inhibitory peptide, both by augmenting insulin release and by maintaining the β-cell number [601]. An important signalling pathway of incretin action involves Epac (exchange proteins activated by cAMP). Whether P2Y or adenosine receptors also stimulate Epac in β-cells has not yet been investigated.

α-Cells

ATP stimulated secretion of glucagon from α-cells in isolated perfused rat pancreas in one study, though in another study adenosine and ADP, but not ATP, were effective [328,582]. The presence of A_2 receptors on glucagon-secreting α-cells was reported in several studies [16,83,84]. Adenosine stimulation of glucagon secretion via A_2 receptors was potentiated by an α_2-adrenergic agonist [203]. NECA, an A_2 receptor agonist, potentiated ACh-induced glucagon secretion [30]. Both A_1 and A_{2A} receptors on mouse α-cells were shown by immunohistochemistry and stimulation of A_{2A} receptors with CGS-21680 to increase glucagon release, while adenosine decreased it [554]. Pulses of glucagon (and somatostatin) were prolonged in A_1 receptor knockout mice, indicating that these α-cells (and δ-cells) possessed A_1 receptors [468].

Diadenosine tetraphosphate stimulated glucagon and insulin secretion in perfused rat pancreas [486]. Studies on mice α-cells showed that they expressed P2 receptors. $P2Y_6$ receptors, activated by uridine 5′-O-thiodiphosphate, increased glucagon release [405]. In contrast, $P2Y_1$ receptors mediated inhibition of Ca^{2+} signalling and glucagon secretion in mice α-cells [554]. In the presence of high concentrations of glucose, insulin secretion was significantly greater in islets from $P2Y_1$ receptor knockout mice, indicating that $P2Y_1$ receptors play a physiological role in the maintenance of glucose homeostasis, at least in part, by regulating insulin secretion [198,301]. Glucagon secretion in rat islets was inhibited by the selective $P2Y_1$ receptor antagonist MRS 2179 [198]. P2X7 receptors are expressed on α-cells, perhaps responding to ATP released from β-cells [109]. P2X7 receptors were shown to be expressed early in a subpopulation of glucagon- and insulin-immunopositive cells in developing islets, which later became restricted to glucagon-expressing α-cells [97,109].

δ-Cells

It was recognised early that δ-cells had local inhibitory effects, via somatostatin, on the release of insulin and glucagon from adjacent α- and β-cells [220]. Stimulation of somatostatin secretion by P2 receptor agonists from dog pancreas was reported [33], especially by ADPβS [229]. Pulses of somatostatin (and glucagon) were removed by addition of the $P2Y_1$ receptor antagonist MRS 2179, although the regularity of insulin secretion was maintained [467].

Thyroid gland

The thyroid gland is a large endocrine gland situated at the base of the neck, consisting of two lobes on each side of the trachea. The thyroid gland is concerned with regulation of the metabolic rate, by the secretion of thyroid hormone, which is stimulated by TSH from the pituitary gland and requires trace amounts of iodine. Sympathetic nerves supply blood vessels in the thyroid and various nerve terminals have also been seen in close apposition to the bases of thyroid follicular epithelial cells [540,559]. Parasympathetic and sensory nerves are also present in the thyroid gland [204].

An early paper reported that ATP stimulated, while adenosine inhibited, PK activity in bovine thyroid [252]. Adenosine was shown to inhibit thyroidal T4 release, through receptor-mediated cAMP activated PK [166,335,591].

The in vitro action of thyroid-releasing hormone (TRH) on iodine metabolism in dog thyroid appears to be modulated by adenosine, but not ATP [122]. Intralysosomal hydrolysis of thyroglobulin, which promotes thyroid hormonal secretion, requires an acidic pH. Addition of ATP to the incubation medium prevented alkalinization and it was argued that an ATP-driven proton pump is present in the membranes of thyroid lysosomes [165].

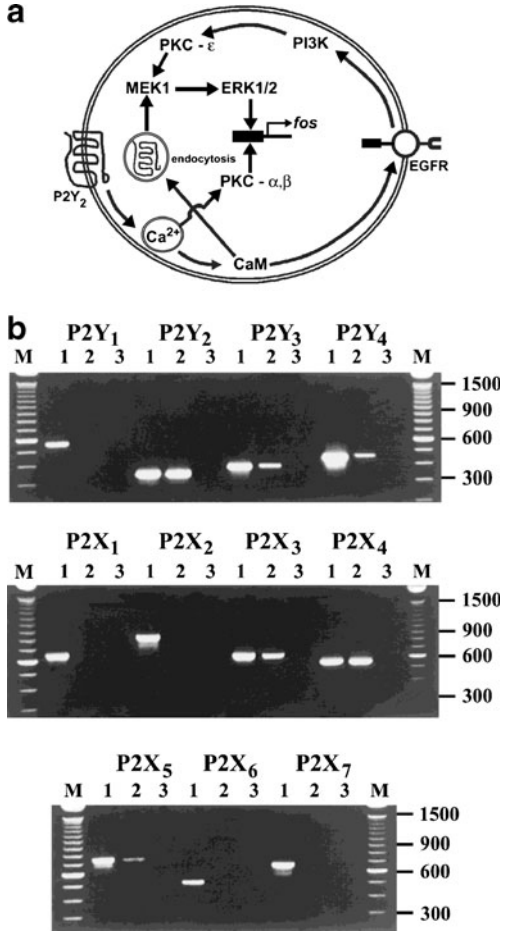

Fig. 5 **a** A proposed model for the control of ERK1/2 phosphorylation and fos induction by thyroid $P2Y_2$ receptors in PC Cl3 cells. The $P2Y_2$ activation provokes intracellular Ca^{2+} signalling and activation of calmodulin (*CaM*) and calcium-dependent PKCs. CaM is responsible for the epidermal growth factor receptor (*EGFR*) transactivation and $P2Y_2$ endocytosis. These two events coordinate the phosphorylation of ERK1/2 through the activity of phosphoinositide 3-kinase (*PI3K*), novel PKC-ε and mitogen-activated protein kinase (*MEK*). ERK1/2 and PKCα/β induce the expression of fos protein. (Reproduced from [141], with permission from Elsevier.) **b** RT-PCR analysis of P2 receptor transcripts present in thyroid FRTL5 cells. Agarose gel electrophoresis of PCR products. *M* size markers: 100 bp ladder (Gibco), appropriate sizes are indicated. For each receptor amplification, *lane 1* is a PCR reaction using the appropriate plasmid construct as template, *lanes 2 and 3* incorporated cDNA synthesis where reverse transcriptase was present or absent, respectively. PCR amplifications with no added template were also carried out for each primer set and resulted in no amplification products (data not shown). The figure is representative of three independent experiments. (Reproduced from [137], with permission from Wiley.)

ATP has been claimed to activate Ca^{2+}-dependent nicotinamide adenine dinucleotide phosphate-oxidase, generating hydrogen peroxide in thyroid plasma membranes, which regulates hormone synthesis through the activation of H_2O_2 production, a substrate for peroxidase [368]. Signals arising

from ATP occupation of P2 receptors on rat FRTL-5 thyrocyte cell line leads, via PLC and adenylate cyclase, to iodide efflux [393]. ATP increases $[Ca^{2+}]_i$ in dog thyroid cells [432], suggestive of P2 receptor involvement. P2 receptor stimulation also led to arachidonate release from FRTL-5 thyroid cells [395]. ATP, as well as TRH, regulates $[Ca^{2+}]_i$ in human thyrocytes in primary culture [434]. However, extracellular ATP has been shown to completely reverse the TSH-induced morphological change in FRTL-5 cells [369]. P2Y receptors have been identified on the PC-C13 rat thyroid cell line that mediates increase in $[Ca^{2+}]_i$ via PLC activation, Ca^{2+} store depletion and L-type voltage-dependent Ca^{2+} channel activation [340]. In a later study by this group, $P2Y_2$ receptor mRNA was shown on both PC-C13 cells and a transformed cell line (C-ElAraf) derived from PC-C13 cells [140]. However, no mitogenic selective $P2Y_2$ receptor activation occurred in PC-C13 cells ([141]; Fig. 5a).

Atrial natriuretic peptide-induced cyclic guanosine monophosphate accumulation by purinergic agonists occurs in FRTL-5 thyroid cells [392]. Porcine thyroid cells produced H_2O_2, but not O_2, when stimulated by extracellular ATP [367]. ATP increased the generation of inositol phosphates in dog thyrocytes [435,436], again suggesting that P2Y receptors might be involved. From a pharmacological study, it was concluded that a G protein is involved in the nucleotide-induced activation of FRTL-5 cells [394]. ATP activates a Ca^{2+}-dependent Cl^- current in rat FRTL-5 cells [341]. In an electrophysiological study, it was shown that depolarisation of rat thyroid FRTL-5 cells decreased the ATP-induced Ca^{2+} influx [544,545], raising the possibility that P2X receptors are also present.

An important advance was made when it was suggested that at least three different purinergic receptors were involved in the responses of FRTL-5 thyroid cells to ATP and probably also its breakdown product, adenosine, coupled to different signal transduction systems, namely activation of PLC, inhibition and activation of adenylate cyclase [473]. The relative order of potencies of nucleotides on the P2 receptors located on FRTL-5 cells was: adenosine-5′-(γ-thio)-triphosphate (ATPγS)≥ATP≫ADP≫GTP [125] perhaps suggestive of a P2X receptor subtype. ATP as low as 10^{-7} M specifically increased $[Ca^{2+}]_i$; this was duplicated by ATPγS, but not by adenosine, AMP, ADP or α,β-meATP [7]. The ATP-induced rise in $[Ca^{2+}]_i$ was biphasic, with the second component related to the opening of a channel, since it required extracellular Ca^{2+} and was abolished by SC38249, an inhibitor of voltage operated channels [39], consistent with a P2X receptor subtype. On the other hand, P2 receptor stimulation of iodide efflux from FRTL-5 rat thyroid cells involves parallel activation of PLC and PLA_2 [488], a clear indication of P2Y receptor involvement. Since extracellular UTP as well as ATP increase $[Ca^{2+}]_i$ in single human thyrocytes [478], this suggests that $P2Y_2$ and $P2Y_4$ receptors are involved. A UTP sensitive receptor has also been located on the apical membrane of thyroid epithelial cells that mediates inhibition of Na^+ absorption [47]. RT-PCR analysis and pharmacological studies revealed the presence of $P2Y_2$, $P2Y_4$, $P2Y_6$, P2X3, P2X4 and P2X5 receptor mRNA on rat FRTL-5 cells involved in control of DNA synthesis ([137]; Fig. 5b). An immunohistochemical study of the localisation of P2X receptor subtype proteins in adult rat thyroid showed that: P2X1, P2X2 and P2X6 receptors were found exclusively on vascular smooth muscle, endothelial cells stained for P2X3, P2X4 and P2X7 and thyroid follicular cells showed immunoreactivity for P2X3, P2X4 and P2X5 receptors [189]. No immunostaining of P2X receptors was observed on C-cells. P2X7 receptors mediate stimulation of plasma membrane trafficking and internalisation in rat FRTL cells [271,272].

It has been suggested that extracellular ATP, in the presence of insulin, may be a cofactor (comitogen) in the regulation of thyroid cell proliferation, probably by phosphorylating MAPK and stimulating the expression of c-fos [546]. ATP regulates PLA_2 activation by a G_i/G_o protein-dependent mechanism and Ca^{2+}, PKC and MAPK are also involved in its regulatory process [136].

Sympathetic nervous control of thyroid hormone secretion has been reported [201]. ATP released as a cotransmitter with NA from sympathetic nerves is likely to stimulate P2 receptors on thyroid follicular cells. Another source of ATP may be calcitonin-secreting C-cells, which stain with quinacrine that recognises high levels of ATP bound to peptides in vesicles [135]. ATP may also be released from thyroid follicular epithelial cells by paracrine or autocrine mechanisms [271].

Adenosine A_1 receptors were identified on rat FRTL-5 thyroid cells [279,603] and P2 receptor activation of phosphoinositide turnover shown to be potentiated by A_1 receptor stimulation of thyroid cells [370]. The P1 receptor agonist phenyliospropyladenosine strongly inhibited thyrotropin (TSH)-induced cAMP accumulation and H_2O_2 generation in FRTL-5 cells [40]. Adenosine is a potent stimulator of endothelin-1 secretion from rat thyroid FRTL-5 cells [562]. P1 receptor-mediated modulation of TSH actions on FRTL-5 thyroid cells has also been described [273].Thyroid-specific expression of the A_2 adenosine receptor transgene promoted gland hyperplasia and severe hyperthyroidism, causing premature death in mice [290]. Adenosine inhibits DNA synthesis stimulated with TSH, insulin or phorbol 12-myristrate 13-acetate in rat thyroid FRTL-5 cells [563]. Extracellular adenosine increased Na^+/iodide (I^-) supporter gene expression in rat thyroid FRTL-5 cells and stimulates I^- transport via the adenosine A_1 receptor [212]. Thyrotropin regulates A_1 receptor expression in FRTL-5 cells [564]. Thyroid hormone stimulates 5′-ectonucleotidase (CD73) of neonatal rat ventricular myocytes [73] and in cultured vascular smooth muscle cells [529].

The parafollicular cell of the mammalian thyroid gland is a neural crest derivative, which is capable of expressing neural characteristics when stimulated by nerve growth factor. Parafollicular cells produce 5-HT, which is stored in the same secretary granules as the peptide hormone, calcitonin. There is ATP-dependent uptake of 5-HT by secretary granules isolated from sheep thyroid parafollicular cells [104].

Hypothyroidism occurs with subnormal activity of the thyroid gland with low testosterone levels. If present at birth and untreated, it leads to cretinism. In adult life, it causes mental and physical slowing, undue sensitivity to cold, slowing of the pulse, weight gain and coarsening of the skin; this can be treated with thyroxine (T4). Thyroid hormones have profound effects on cardiovascular function in both hypothyroidism and hyperthyroidism [23]. It has been suggested that in hyperthyroidism, increase in ATP hydrolysis by E-NTPDase 3 and subsequent decrease in extracellular ATP levels is an important factor for prevention of the excessive contractility of cardiomyocytes induced by an overproduction of triiodothyronine (T3) [22]. Hyperthyroidism increases platelet 5′-nucleotidase activity, while hypothyroidism decreases it [54]. Hyperthyroidism reduces ecto-nucleotidase activity in synaptosomes from hippocampus and cerebral cortex of rats [53,55]. Evidence has been presented to suggest that both excess and deficiency of thyroid hormones can modulate the activities of both diphosphohydrolase (CD39) and CD73 ectoenzyme activities in rat blood serum with effects on vascular activity [56]. It has been claimed that both purinergic signalling and reactive oxygen species participate in thyroid hormone-induced vasorelaxation, and that there is a diminution of $P2Y_6$ receptor expression in hyperthyroid rats [24]. Hypothyroidism has been shown to lead to impotence in some men. In an experimental rabbit model of hypothyroidism, relaxations to ATP, α,β-meATP and electrical field stimulation of corpus cavernosum strips were reduced, while relaxation to adenosine was unchanged [606].

Purinergic stimulation by ATP is able to induce rapid cytoplasm to nucleus translocation of APEI Ref-I protein initially and its neosynthesis later in a human thyroid tumour cell line (ARO) which expresses high levels of the APEI Ref-I protein involved in both base excision repair pathways of DNA lesions and in eukaryotic transcriptional regulation of gene expression [418]. In thyroid papillary carcinoma cells, P2X7 receptor mRNA and protein was increased and it was suggested that it may be a useful marker for this disease [491]. A recent review discusses the role of purinergic signalling in thyroid hormone activities in both heath and disease [485].

Parathyroid gland

Two pairs of parathyroid glands are situated behind or sometimes embedded within the thyroid gland. They are stimulated to produce parathyroid hormone by a decrease in the amount of calcium in the blood. A high level of parathyroid hormone causes transfer of calcium from bones to the blood. A deficiency lowers blood calcium levels causing tetany, a condition relieved by treatment with the hormone. ATP and ATPγS mobilise cellular Ca^{2+} and inhibit parathyroid hormone secretion [371]. It has been suggested that the ATP may be released from sympathetic nerve terminals in the parathyroid gland and/or by autocrine release from parathyroid secretory vesicles [106]. Parathyroid hormone potentiates nucleotide-induced $[Ca^{2+}]_i$ in rat osteoblasts; it is suggested that this may explain how systemic parathyroid hormone can initiate bone remodelling [57]. Human parathyroid hormone secretion is inhibited by caffeine, suggesting that P1 receptors are also involved [331].

Adrenal gland

Adrenal chromaffin cells

Co-storage and release of NA and ATP from chromaffin cells

Chromaffin cells of the adrenal medulla can be regarded as a highly specialised form of sympathetic nerve cell, both have a common embryological origin in the neural crest. Well before NA and ATP were recognised as cotransmitters in sympathetic nerves, NA and ATP were shown to be co-stored in a ratio of about 4:1 [42,46,232,280,587] and coreleased [72,74,507] from adrenal chromaffin cells by vesicular exocytosis [205,237]. It was also suggested that chromagranines and dopamine-β-hydroxylase were stored together with NA and ATP in these cells [422,589,590]. NA and ATP were shown to be localised in chromaffin granules within the chromaffin cells [589] and the ATP stored in the granules is not synthesised in them, but is taken up from the cytoplasm [278,407].

Early studies considered that the major role of ATP was to regulate the synthesis, storage and release of catecholamines (CA) from chromaffin cells (see [231,262,360,536,588]). It was only later that it was recognised as an equal partner in hormonal activities by analogy with the roles of NA and ATP as cotransmitters in sympathetic neurotransmission (see [62]). ATP and CA are released in parallel from adrenal chromaffin cells in response to stimulation by ACh, K^+ or Ba^{2+} ([253]; Fig. 6a and b). ACh and nicotine caused exocytotic release of both CA (mainly adrenaline) and ATP from bovine adrenal chromaffin cells [454,583]. This response was blocked by mecamylamine, a nicotine receptor blocker [186]. Later it was shown that methacholine, a selective muscarinic agonist, as well as nicotine, induced CA and ATP secretion, via increasing $[Ca^{2+}]_i$, in porcine adrenal chromaffin cells, indicating that both nicotinic and muscarinic receptors were expressed by chromaffin cells [600]. Diadenosine

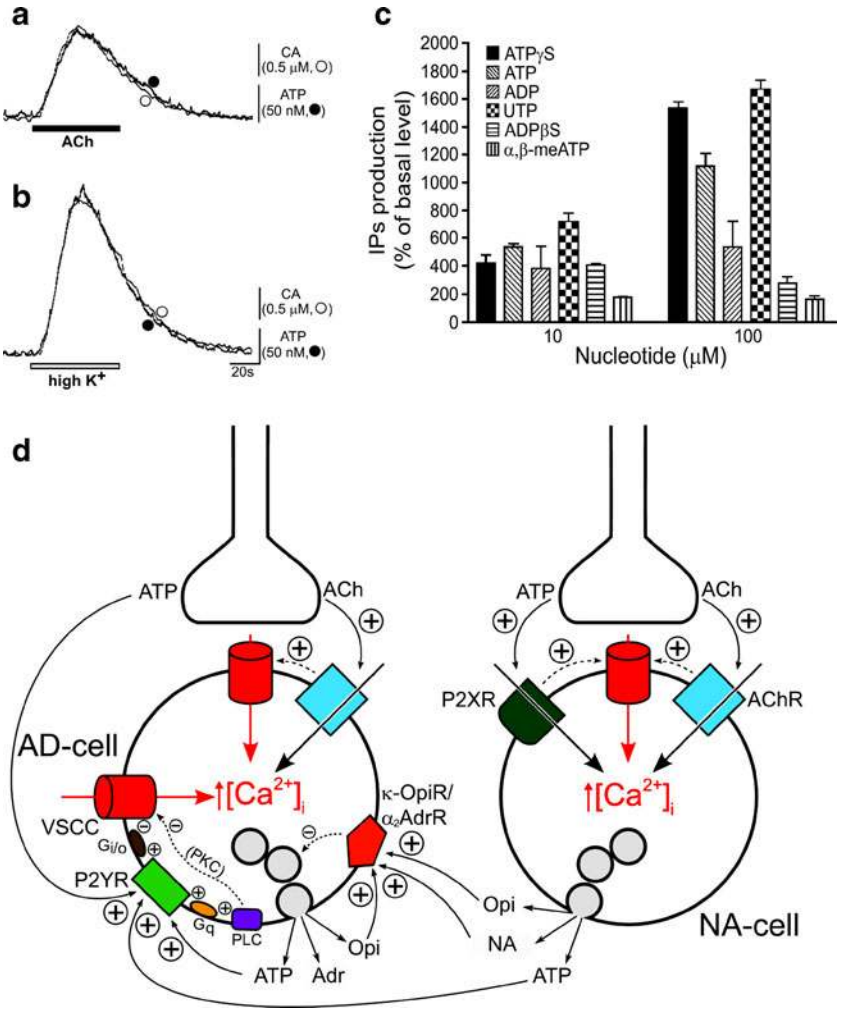

Fig. 6 **a** and **b** Typical recordings of on-line measurement of ATP and catecholamine (CA) released from cultured adrenal chromaffin cells in response to ACh and high K^+. ACh (a, 100 mM, ■) or high K^+ (b, 60 mM, □) was applied for 1 min. The responses of ATP (*filled circle*) and CA (*open circle*) are superimposed. *Vertical bars* indicate the amplitude of peak oxidative currents and luminescence induced by ATP (50 nM) and NA (0.5 mM). (Reproduced from [253], with permission from Elsevier.) **c** Effect of nucleotides on production of inositol phosphates in bovine adrenocortical fasciculata cells. (Reproduced from [379], with permission from Elsevier.) **d** Simplified model for inhibitory regulation of adrenaline secretion involving transmitters released from both nerve terminals and chromaffin cells of bovine adrenal gland. Auto-inhibitory feedback loops related to cholinergic transmission are not considered for simplicity. Inhibitory transmitters acting on receptors preferentially located to adrenergic chromaffin cells (i.e. P2Y receptors and κ-opioid receptors) have been considered, as well as nor adrenaline, which inhibits adrenaline release via α_2-adrenoceptors. Activation of P2Y, κ-opioid and α_2-adrenergic receptors inhibits voltage-sensitive Ca_{2+} channels (*VSCCs*) via $G_{i/o}$ proteins (not depicted for the latter two receptors for simplicity) and, consequently, exocytosis. Protein kinase C (*PKC*) is negatively coupled to VSCCs in an isoform-specific fashion. *AD-cell* adrenergic chromaffin cell, *NA-cell* noradrenergic chromaffin cell, *ACh* acetylcholine, *VSCC* voltage-sensitive Ca^{2+}channels, *AChR* nicotinic cholinergic receptors, *P2XR* P2X receptors, *P2YR* P2Y receptors, *κ-OpiR*/*α_2AdrR* κ-opioid and α_2-adrenergic receptors (represented as a single entity for simplicity), *PLC* phospholipase C, *PKC* protein kinase C, *G_q and $G_{i/o}$* G proteins, *Adr* adrenaline, *NA* noradrenaline, *Opi* opioid peptides. For simplicity, and because $[Ca^{2+}]_i$ rises induced by PLC activation do not evoke catecholamine secretion from bovine chromaffin cells, they are not made explicit in the scheme. Also for simplicity, granule exocytosis is not depicted as occurring preferentially in the vicinity of VSCC hot-spots. Positive and negative signs indicate stimulatory and inhibitory interactions, respectively. (Reproduced from [541], with permission.)

tetraphosphate (Ap_4A) is co-released with ATP and CA from bovine adrenal medulla [75,483].

In bovine chromaffin cells, the Ca^{2+} channels involved in exocytosis are effectively inhibited by ATP and opioids that are coreleased with CA during cell activity [70]. Uptake of met-enkephalin by chromaffin cells was shown to be dependent on the presence of ATP in the incubation medium [528]. Chromaffin cells take up adenosine and convert it into ATP [352]. Tricyclic antidepressants block cholinergic nicotinic receptors and ATP secretion in bovine chromaffin cells [241].

Purinoceptor subtypes in adrenal chromaffin cells

ATP was shown early to depolarise adrenal chromaffin cells and it was suggested that this may be related to hormone release from granules and regulation of CA secretion in vivo

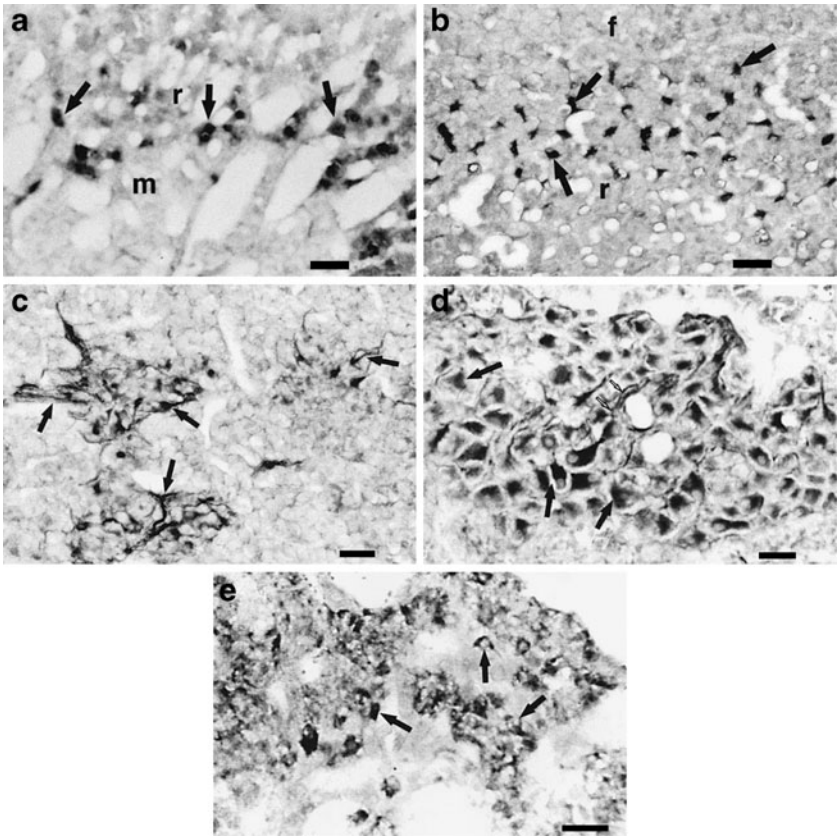

Fig. 7 **a** and **b** Guinea pig adrenal gland sections immunoreacted with P2X1 or P2X2 receptor antibodies. **a** P2X1 receptor-immunoreactive cortical cells (*arrows*) of the inner part of the zona reticularis (*r*) at corticomedullary junction (*m* medulla). **b** P2X2 receptor-immunoreacted section showing immunoreactive elements (*arrows*) located in the outer region of the zona reticularis. Note the irregular shape of the immunoreactive elements and their location between groups of non-immunoreactive cortical cells (*f* zona fasciculata). Note that whereas the two panels are at the same magnification, **a** appears of higher magnification due to the presence of large vascular plexus and a more network-like arrangement of the cortical cells in the inner region of zona reticularis. **c**–**e** Sections of guinea pig adrenal medulla immunoreacted with P2X5 or P2X6 receptor antibodies. **c** P2X5 receptor-immunoreactive nerve fibres that form plexuses (*arrows*) around the chromaffin cells. **d** P2X5 receptor-immunoreactive intrinsic neurones (*black arrows*) located in the adrenal medulla. Note the proximal parts of processes (*small white arrows*) projecting out of some of the cells, which indicate their neural identity. **e** P2X6 receptor-immunoreactive chromaffin cells (*arrows*). All scale bars=40 μm. (Reproduced from [3], with permission from Karger.)

[313,385,427] via cAMP [236]. CA secretion from bovine chromaffin cells can also be inhibited by extracellular ATP, probably after being converted to adenosine [96].

The presence of P2 receptors on adrenal chromaffin cells was first suggested in 1990 [6]. ATP can produce at least three different effects on adrenal chromaffin cells: inhibition of voltage-gated Ca^{2+} channels [113,127,225,311], release of Ca^{2+} from internal stores [441] and activation of a non-selective cation channel [402]. While the first two effects are most probably mediated by P2Y receptors, the third effect has the characteristics for the activation of P2X receptors. A biphasic rise in $[Ca^{2+}]_i$ was shown in response to extracellular ATP, one phase due to release of Ca^{2+} from intracellular sites, the other from extracellular sites which was lost in Ca^{2+}-free solutions [347]. This important study was a clear hint for the recognition that both P2X and P2Y receptors are expressed by chromaffin cells [127,402,441].

The P2 receptors on adrenaline-containing chromaffin cells were claimed to differ from those found on NA-containing chromaffin cells ([79,541]; Fig. 6d). The suggestion was that the inhibitory effect of ATP on NA-containing cells appeared to be largely mediated by P2X receptors, while the adenosine-containing cells were activated by both UTP and ATP and appeared to be largely mediated by P2U (probably $P2Y_2$ or $P2Y_4$) receptors. It was proposed that P2Y receptors on adrenal chromaffin cells mediate negative feedback of hormone secretion and that ATP inhibited both N- and P/Q-type Ca^{2+} channels [113,311]. Neuropeptide Y (NPY) and ATP may be co-modulators of this feedback pathway [618].

In one of the first immunohistochemical studies of P2X receptors, P2X1 and P2X2 immunoreactivity on chromaffin cells of the adrenal medulla was reported [577]. Later immunohistochemical studies ([2,3]; Fig. 7) showed limited expression of P2X5 and P2X7 receptors in rat chromaffin cells, while

P2X6 immunoreactivity was detected in the guinea-pig. Brake et al. [48] cloned the P2X2 receptor from PC12 cells and detected weak expression of the mRNA in the adrenal gland by Northern blotting. P2X4 mRNA has also been detected [43]. However, in both studies, it was not certain whether the mRNA was present in the medullary or cortical cells.

Functional studies have demonstrated the presence of P2X receptors on bovine [441] and guinea-pig [316,402] chromaffin cells. However, these receptors appear to be absent in the rat [237,316]. The P2X receptor present on chromaffin cells can be activated by ATP and 2-methylthio ATP, but is much less sensitive or insensitive to α,β-meATP [316,441]. To date, the only detailed pharmacological study of P2X receptors on chromaffin cells has been carried out on the guinea-pig. Here, the receptor is antagonised by pyridoxalphosphate-6-azonphenyl-2′,4′-disulphonic acid, but suramin and Cibacron blue are quite weak antagonists. The response is potentiated by low pH, but inhibited by Zn^{2+}. Thus, while this receptor has some properties in common with the rat P2X2 receptor (agonist profile, effect of pH), the lack of potentiation by Zn^{2+} and the low sensitivity to the antagonists suramin and Cibacron blue are not. Although three spliced variants of the guinea-pig P2X2 receptor have been cloned, and some pharmacological characterisation has been carried out, there is at present insufficient information to identify the native P2X receptor present on guinea-pig chromaffin cells. The pharmacological properties of the P2X receptor present on guinea-pig chromaffin cells are very similar to that of the α,β-meATP-insensitive receptor found on pelvic ganglion neurons. It therefore seems likely that it is in fact the homomeric P2X2 receptor. Evidence has been presented that voltage-dependent Ca^{2+} channels are regulated in a paracrine fashion by ATP acting on P2X receptors in porcine adrenal chromaffin cells [389].

P2Y receptors mediate inhibition of exocytotic release of CA from adrenal chromaffin cells by modulation of voltage-operated Ca^{2+} channels, rather than by a direct effect on the secretory machinery [213,429,560]. Exposure of bovine chromaffin cells to NPY results in a long-lasting increase in subsequent stimulation of inositol phosphate formation by ATP acting on P2Y receptors [130]. $P2Y_2$ receptors have been identified immunohistochemically on rat chromaffin cells [5], which is consistent with this effect. ATP stimulation also appears to act through adenylate cyclase to stimulate cAMP formation in bovine chromaffin cells [616], so it is interesting that $P2Y_{12}$ receptors which use this second messenger system, have since been demonstrated in these cells [142].

Second messenger transduction mechanisms

Extracellular ATP leads to increase in $[Ca^{2+}]_i$ and accumulation of inositol 1,4,5-trisphosphate ($InsP_3$) in cultured adrenal chromaffin cells [471]. A recent paper suggests that UTP and ATP acting through $P2Y_2$ receptors increase extracellular signal-regulated kinase 1/2 phosphorylation in bovine chromaffin cells through epithelial growth factor receptor (EGFR) transactivation [334]. The EGFR inhibitor, AG1478, decreased ATP-mediated extracellular-signal-regulated kinase (ERK)1/2 phosphorylation.

Ectonucleotidases

ATPase activity in hydrolysing ATP in chromaffin cells was implicated in the uptake of CA [535] and the release of both amines and ATP from the chromaffin granules membrane [413]. The presence of ecto-nucleotidases responsible for the hydrolysis of released ATP was first described in cultured chromaffin cells [547] and were later localised and characterised in intact pig adrenal glands [27]. ARL 67156 is an effective inhibitor of ecto-nucleotidase activity in bovine chromaffin cells [131].

Diadenosine polyphosphates

Ap_4A, diadenosine pentaphosphate (Ap_5A) and diadenosine hexaphosphate have been identified on bovine adrenal medullary tissue [421,452]. More recently diadenosine diphosphate, adenosine guanosine polyphosphate (Ap_nG) and diguanosine polyphosphates (Gp_nG) have also been identified in chromaffin granules [243]. CA secretion evoked by K^+-rich solutions was further enhanced by diadenosine triphosphate and Ap_5A, while Ap_4A inhibited it [76]. It was speculated that P2Y receptors were likely to mediate the extracellular action of Ap_4A [77,419]. Carbachol-induced release of Ap_4A and Ap_5A from perfused bovine adrenal medulla and isolated chromaffin cells was reported [420]. Ecto-dinucleotide polyphosphate hydrolase was identified, in addition to ecto-nucleotidases, in cultured chromaffin cells [453].

Medullary endothelial cells

CA and ATP and other factors released by chromaffin cells must pass through an endothelial cell barrier to enter the bloodstream. ATP has been shown to stimulate prostacyclin formation via production of the second messenger $InsP_3$ [164]. An intracellular Ca^{2+}-releasing P2U receptor (probably $P2Y_2$ or $P2Y_4$) has been identified on adrenal endothelial cells [78].

Purinergic signalling in development and ageing

There is abundant expression of $P2Y_2$ receptors in NA-containing adrenal chromaffin cells and very little on adrenaline-containing cells in mature rats. However, in newborn rats, $P2Y_2$ receptors are expressed equally on both NA

and adrenaline-containing cells and by one week the majority of P2Y receptor labelled cells contain adrenaline [5]. There is a dramatic loss of $P2Y_2$ receptor expression on both NA- and adrenaline-containing cells in the adrenal gland of old (22 month) rats compared to newborn animals. ATP, acting via $P2Y_2$ receptors, may influence the phenotypic expression of chromaffin cells into NA- or adrenaline-containing cells during early development and ageing. Age-related changes in the localisation of P2X receptors in the rat adrenal gland have also been reported [4].

Adrenocortical cells

Extracellular ATP stimulates steroidogenesis in bovine adrenocortical cells via P2Y receptors and Ca^{2+} mobilization [256]. In contrast, adenosine inhibits secretion of corticosteroids [598]. Calcium is essential for ATP-induced steroidogenesis in bovine adrenocortical fasciculata cells [375]. Later UTP and ADP, as well as ATP, were shown to stimulate cortisol secretion in these cells, suggesting more than one P2 receptor subtype is involved [235]. The mechanism of ATP-stimulated cortisol secretion depends on depolarization-dependent Ca^{2+} entry and may be linked to stress-induced chromaffin cell secretion to corticosteroid production [599].

The rat adrenal cortex is more densely innervated in the capsule-glomerulosa and in the juxta-medullary regions. Electron microscopic studies have shown autonomic axons supplying adrenal cortical tissue, which sometimes penetrate the basal lamina of the cortical cells and come with close (200 nm) contact with their plasma membranes [448,561]. It has been suggested that the nerve fibres in the superficial cortex are mainly of extrinsic origin in contrast to a major contribution of intrinsic neurons in the medulla [401].

Activation of the splanchnic sympathetic innervation strongly potentiates the steroidogenic action of ACTH from the anterior pituitary and there is compelling evidence that the innervation normally plays an important part in cortisol secretion [134]. Neural release of ATP acting on cortical cells has been considered [247], although the possibility that there is a paracrine non-synaptic modulatory role for CA and ATP in the regulation of adrenocortical steroid secretion has also been raised [520]. It has been suggested that the suprachiasmatic nucleus utilises neuronal pathways to spread its time of the day message, not only to the pineal to control melatonin secretion, but also to the adrenal cortex to influence corticosterone secretion [58]. The cotransmitters released by nerve varicosities influence the production of aldosterone [520]. ATP potentiates both ACTH- and angiotensin II-induced steroidogenesis in bovine adrenocortical fasciculata cells [257].

Both ATP and NA were released in response to electrical field stimulation in superfused rat adrenal capsule-glomerulosa preparations and ecto ATPases identified around nerve profiles at the border of capsule and zona glomerulosa tissue [247]. Angiotensin II and ATP provoke K^+ efflux from perfused bovine glomerulosa cells and quinine and apamin significantly reduce the effect of ATP [319].

Two different P2Y receptors (one likely to be a $P2Y_2$ or $P2Y_4$ receptor since it was activated by both UTP and ATP) have been shown to be linked to steroidogenesis in bovine adrenocortical cells [377]. They showed further that mRNA for $P2Y_2$, but not $P2Y_4$ receptors, or for $P2Y_1$, $P2Y_{11}$ and $P2Y_{12}$ receptors, although ADP did stimulate steroidogenesis, perhaps via an unidentified P2Y receptor subtype ([378,379]; Fig. 6c). In a recent study, a human adrenal cortex-derived cell line, NCl-H295R, which expresses all the key enzymes needed for steroidogenesis, was shown to express receptor mRNA and protein for A_{2A} and A_{2B}, P2X5 and P2X7, and $P2Y_1$, $P2Y_2$, $P2Y_6$, $P2Y_{12}$ $P2Y_{13}$ and $P2Y_{14}$ subtypes [380]. They claimed further that the $P2Y_1$ receptor was linked to Ca^{2+}-mobilization and cortisol secretion.

Adenosine-stimulated adrenal steroidogenesis involves A_{2A} and A_{2B} receptors, activation of which triggers the Janus kinase 2-MAPK-activated PK-ERK signalling pathway [90]. Foetal cortisol concentrations are suppressed by A_1 receptor activation and restrict the increase in ACTH during moderate hypoxia [244].

Ovary

Ovaries produce oocytes and are the principal source of oestradiol and a source of progesterone and androgens in females. In addition to oocytes of different stages of maturation, there are specialised mesenchymal granulose and theca cells that engulf oocytes to form ovarian follicles. Oocyte maturation in the mouse is stimulated by a surge of LH 12 hours prior to ovulation. ATP was shown to inhibit LH-stimulated testosterone accumulation by isolated ovarian follicles from rabbits [325]. Adenosine produced a seven-fold amplification of LH-stimulated cAMP accumulation and progesterone secretion in rat luteal cells, but did not show a similar effect on LH-stimulated cAMP accumulation and androgen secretion in luteal cells [208]. Adenosine exerts predominantly inhibitory actions on hormone-induced granulosa cell differentiation [266]. Adenosine stimulates adenylate cyclase in rat ovarian membrane preparations and preovulatory granulosa cells via A_2 receptors [36]. AMP-activated PK regulates progesterone secretion in rat granulose cells [548]. It was suggested that adenosine and prostaglandin $F_{2\alpha}$ may be regulators of luteal cell function by acute and local control of the action of LH [25]. In a later study, this group showed that there was no effect of adenosine on androgen secretion in Leydig cells, but that adenosine produced a marked amplification of FSH-stimulated cAMP accumulation and steroid secretion from granulosa cells from rat and human ovaries [26,425].

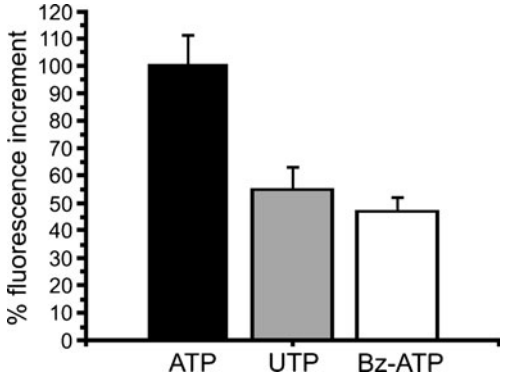

Fig. 8 Purinergic agonist-evoked $[Ca^{2+}]_i$ increase in porcine ovarian theca cells. Cultured theca cells were loaded with fluo-4/AM, and $[Ca^{2+}]_i$ was monitored with fluorescence microscopy. Plots show the mean (±SEM) of maximum fluorescence increase in response to 1 mM ATP, UTP, or 250 μM Bz-ATP (20 sec applications). (Reproduced from [568], with permission from Wiley Liss.)

LH rapidly depletes luteal cell ATP, which appears to be a physiological action, since it occurs during functional luteolysis at the end of the pseudopregnant cycle [501]. The authors suggest that during functional luteolysis, the rising levels of LH that occurs during follicular development and ovulation cause depletion of luteal ATP levels to ensure irreversible regression and eventual death of the corpora lutea of the previous cycle. ATP levels in granulosa-luteal cells can be influenced by gonadotrophins as well as by adenosine [35]. Recognition of the presence of P_{2U} receptor mRNA in the human granulosa cells followed and ATP/UTP was shown to cause rapid and transient increase in $[Ca^{2+}]_i$ [526]. ATP was shown to have an antigonadotrophic action in human granulosa cells [525]. In a later publication from this group, they showed that ATP induced nuclear translocation of phosphorylated ERKs and the induction of egr-1 and c-raf-i expression in the human ovary, supporting the notion that the MAPK signalling pathway plays a role in mediating the effects of ATP on gonadotrophin-induced progesterone secretion in the human ovary [527]. P2, but not P1, receptors were also identified on chicken granulosa cells [361]. $P2Y_2$ and/or $P2Y_4$ receptors in human granulosa-luteal cells mediate calcium oscillations [294,504]. Granulosa cells in contact with the oocyte, respond to ATP via a mechanism that involves $P2Y_2$ receptor stimulation and the participation of ryanodine receptors [357]. Regulation of proliferation of cultured thecal/interstitial cells and steroidogenesis via UTP-sensitive P2Y receptors is relevant in ovarian pathophysiology, since theca hyperplasia is involved in polycystic ovarian syndrome [569]. Purinergic signalling to ovarian perifollicular smooth muscle changed from P2X2 to P2X1 receptors during pregnancy, while there was an increase in P2X2 receptor expression on ovarian vascular smooth muscle [255]. Menopause is associated with decline in ovarian function. P2X2 receptor protein levels were shown to increase with ageing (menopause model), perhaps contributing changes in ageing-relates decline in ovarian function [620]. The theca (or ovarian surface epithelium) is the external layer surrounding the ovarian follicle involved in the synthesis of androgens, the substrate for oestradiol and progesterone synthesis in granulosa cells. ATP causes apoptotic cell death of porcine ovarian theca cells via P2X7 receptor activation ([568]; Fig. 8).

The mammalian ovary is directly innervated by sympathetic nerves, which appear to play major roles in regulating ovarian functions, such as follicular maturation, steroid secretion and ovulation [286]. There are also intrinsic neurons in the rat ovary, but it is not known which cells they innervate or whether ATP is a cotransmitter [115]. Ovarian sympathetic activity increases during the ovulatory process, but the neuronal content of NA and ATP decreases after ovulation. ATP evokes Ca^{2+} oscillations in isolated human granulosa-luteal cells [504]. Granulosa cells secrete oestradiol and luteal cells secrete both oestradiol and progesterone. P2Y receptors are expressed by human and porcine granulosa–luteal cells; ATP has been shown to decrease the production of progesterone and oestradiol and the authors favoured a neuronal origin of ATP [526]. It has been proposed that $P2Y_2$ and $P2Y_4$ receptors on granulosa cells modulate Cl^- permeability by regulating Ca^{2+} release [37]. ATP, probably released from sympathetic nerves, has been shown to activate nuclear translocation of kinases (MAPKs) leading to the induction of early growth response 1 and Raf expression in human granulosa-luteal cells [527].

At least 99 % of follicles in the mammalian ovary undergo follicular atresia, a cellular degeneration that involves apoptosis in both somatic and germinal follicular cells. ATP-induced apoptotic cell death in porcine ovarian theca cells has been shown to be mediated by P2X7 receptors [568], which is part of the regulation of folliculogenesis, known to be modulated by sympathetic cotransmitters. ATP suppresses the K^+ current responses to FSH or adenosine in monolayers of the small follicular cells surrounding a single large oocyte of *Xenopus* [176]. The follicular cells of *Xenopus* have a P2 receptor [265,356] and since UTP and ATP are equipotent, this may be a $P2Y_2$ or $P2Y_4$ receptor subtype [176].

Ovariectomy and oestradiol replacement therapy significantly decreased the hydrolysis of ATP and ADP [423]. Ovarian tumours appear to arise mainly from the ovarian surface epithelium, which is a simple squamous-to-cuboid mesothelium that covers the ovary. ATP stimulates mitogen-activated kinase in pre-neoplastic and neoplastic surface epithelial cells and it was suggested that co-released ATP from sympathetic nerves may play a role in regulating cell proliferation in both normal and neoplastic ovarian surface epithelial cells [99]. Ovarian stimulation is a significant risk factor for arterial and venous thrombosis. It has been shown that FSH has a stimulatory effect on ATP release and platelet aggregation [19]. Functional phosphodiesterase 8 has been identified in

the mammalian ovarian follicle and it was suggested that it is involved in hormonal regulation of folliculogenesis, indicating a potential application of inhibitors as novel contraceptives [472].

Testis

The testis is the primary source of testosterone production. It consists of seminiferous tubules, within which spermatogenesis takes place, and interstitial spaces between these tubules, containing Leydig cells (testosterone-producing cells), as well as supporting tissue and blood or lymphatic vessels. Germ cells and Sertoli cells are the only cell types present within the seminiferous tubules and they are in close contact with each other. The germ cells migrate within the seminiferous tubules and differentiate from stem spermatogonia, through spermatocytes, to spermatids. The changes in Sertoli cell and germ cell morphology during the repetitive cycle of germ cell development in the rat have been categorised into the 14 different developmental stages. P2X2 and $P2Y_2$ receptors have been described on mouse Sertoli cells and a paper identifies mitochondria as essential components of Sertoli cell signalling that control the purinergic-mediated Ca^{2+} responses [570]. Activation of AMP-activated PK by adenosine promotes lactate offer to germ cells, thus contributing to successful spermatogenesis [178]. There is sympathetic innervation of the testis with predominant supply to blood vessels; sensory nerve fibres are also present.

There is ultrastructural evidence for sympathetic innervation of Leydig and interstitial cells, which secrete androgens in the testis of various animals and hormones [430]. ATP was shown to act via P2 receptors to increase $[Ca^{2+}]_i$ in mouse Leydig cells [412]. P2X2 receptors were later described on Leydig cells [426] and ATP shown to increase testosterone secretion [163]. Leydig cells express pannexin hemichannels, which may account for ATP release [555]. Various P2X receptor subtypes, namely, P2X1, P2X2, P2X3, P2X5 and P2X7 (but not P2X4 or P2X6) receptors, are expressed on germ cells during spermatogenesis [191]. No evidence for a role of sympathetic innervation in the control of sperm development has been presented. Multiple purinergic receptors lead to intracellular calcium increases in rat Sertoli cells [270].

A_1 receptors were identified in rat testis [365,508] and adenosine caused steroid production in isolated Leydig cells [455]. The A_1 receptors were also localised in Sertoli cells of the seminiferous tubules [354]. Pertussis toxin treatment of cultured Sertoli cells reversed the adenosine-mediated inhibition of cAMP accumulation and potentiated the cAMP response to FSH [249,355].

The Sertoli cells from the mammalian testis are multifunctional cells that release several proteins and fluid into the lumen of the seminiferous tubules and play a key role in germ

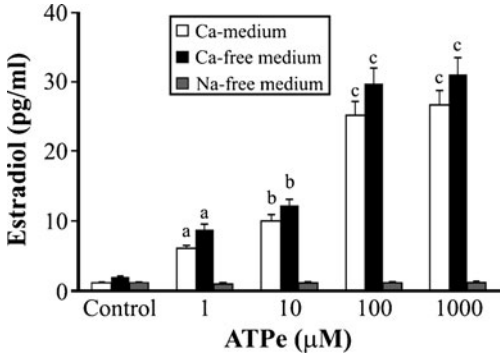

Fig. 9 Effects of extracellular ATP (ATPe) on oestradiol production in rat Sertoli cells: cells were cultured for 4 days in control medium. On the fourth day in culture, cells were stimulated with ATPe (1, 10, 100 and 1000 μM). After 24 h, media were collected and oestradiol production determined by radioimmunoassay. For evaluation of ATPe-induced oestradiol secretion, Sertoli cells were incubated in different experimental conditions as reported in figure legend. Values are expressed as mean ± S.D. of three separate experiments performed in duplicate: *a* $p<0.05$; *b* $p<0.01$; *c* $p<0.001$ vs. control and Na^+-free medium. (Reproduced from [459], with permission from Elsevier.)

cell development. FSH is the main messenger of the response of immature Sertoli cells. When Sertoli cells were exposed to ATP, a fast and biphasic increase in $[Ca^{2+}]_i$ was obtained [281]. Sertoli cells express P2 receptors that are associated with phosphoinositide turnover and are activated equally by ATP and UTP suggesting that $P2Y_2$ or $P2Y_4$ receptors are involved; they have profound effects on FSH responsiveness [157]. ATP stimulates accumulation of $InsP_3$ in primary cultures of rat and mouse Sertoli calls, consistent with $P2Y_2$ or $P2Y_4$ receptor activation [162,463]. Extracellular ATP stimulates oestradiol secretion in rat Sertoli cells via both P2X and P2Y receptors, which leads to increases in both $[Ca^{2+}]_i$ and $[Na^+]_i$ and membrane depolarisation leading to oestradiol secretion ([459]; Fig. 9). RT-PCR studies revealed mRNA for $P2Y_1$, $P2Y_2$ and P2X4 and P2X7 receptors in cultured rat Sertoli cells [270].

Leydig cells are interposed between the seminiferous tubules in the testis. They secrete androgens in response to LH from the anterior pituitary gland. Rat Leydig cells express P2 receptors and their activation by ATP leads to testosterone secretion via a mechanism dependent on the influx of Ca^{2+} from the external medium [163], consistent with mediation via a P2X receptor subtype. The pharmacological features suggested that the P2X2 receptor subtype was involved [426]. Production of androgens by Leydig cells is dependent on androstenedione, the precursor of testosterone synthesis and the activation of the microsomal enzyme 17β-hydroxysteroid dehydrogenase (17βHSD). ATP generation is required for the activation of 17βHSD in the final step of androgen biosynthesis [260]. The activity of 17βHSD is modulated by extracellular pyridine dinucleotides and adenosine [152]. Evidence for sympathetic innervation of human Leydig cells has been presented and their influence on the secretion of testosterone,

perhaps involving ATP release as a cotransmitter with NA [162].

Thyroid hormones are regulators of the male reproductive system. They modulate extracellular ATP levels in hypothyroid cultured Sertoli cells and congenital hypothyroidism and thyroid hormone supplementation on NTPDase activities in Sertoli cells can influence the actions of ATP and adenosine on reproductive functions during development [611].

There is sympathetic and sensory innervation of the rodent testicular artery and the pampiniform plexus, a venous network that surrounds it. The innervation is largely restricted to the capsule of the testes and most superficial blood vessels, suggesting a role in the control of temperature. The testicular capsule of the rat, mouse, rabbit and man all contain contractible smooth muscle. ATP released as a cotransmitter from sympathetic nerves can stimulate contraction of testicular smooth muscle, probably mediated through P2X1 and/or P2X2 receptors [18]. Mouse Leydig cells express P2X4, P2X6 and P2X7 receptor subunits as well as P2X2 receptors and it was suggested that heteromeric P2X2/4/6 receptors may also be present [12].

Pineal gland

The pineal gland is a pea-sized mass of tissue attached by a stalk to the third ventricle of the brain, deep between the cerebral hemispheres at the back of the skull. It contains neurons, glia and special secretary cells called pinealocytes. It functions as an endocrine gland, synthesising, storing and secreting the hormone melatonin.

Endogenous adenosine was shown to be involved in the regulation of melatonin output in the chick pineal gland [145]. Adenosine, acting by A_2 receptors, elevated both *N*-acetylserotonin and melatonin in rat pineal gland [182], probably via A_{2B} receptors [183,372]. A_1 receptors and later A_{2A} receptors were identified in the pineal of sheep [146,602]. A_{2B} and A_3 receptors were both claimed to be present on mouse pineal tumour cells [516].

It was believed for many years that pineal function was regulated by release of NA from sympathetic nerve terminals. However, when it was established that ATP was released as a cotransmitter with NA from sympathetic nerves (see [62]), evidence was presented that ATP was also involved in regulation of pineal activities by sympathetic nerves [362,376]. The presence of P2 receptors in the rat pineal gland was later reported, and claimed that their main role was to mediate potentiation of the effect of NA-induced N′-acetyl-5-HT production [155]. A $P2Y_1$ receptor was identified in cultured rat pineal glands [154] and later shown to mediate enhancement of the rate of pinealocyte-induced extracellular acidification via a calcium-dependent mechanism [156].

Chick pineal glands exhibit persistent circadian rhythms in the rate of formation of melatonin. It has been claimed that purinergic receptors play no major role in control of this circadian rhythm in the rate of thymidine uptake [578].

Thymus

The thymus is a bilobed organ in the base of the neck, above and in front of the heart. It is enclosed in a capsule and divided internally by cross walls into many lobules, each full of T-lymphocytes. It doubles in size by puberty, after which it gradually shrinks, being replaced by adipose tissue. In infancy, the thymus controls the development of lymphoid tissue and immune responses related to autoimmunity. The thymus is important in immunological function because it contains the active hormone thymosin, which helps to stimulate the production and development of T-lymphocytes. The purine degradation enzymes adenosine deaminase and purine nucleoside phosphohydrolase are linked to lymphocyte differentiation and formation and there is evidence for deficiencies in these enzymes in some combined immunodeficiency diseases. T-lymphocytes migrate from the bone marrow to the thymus, where they mature and differentiate until activated by antigen. The thymus gland is innervated by sympathetic nerves that supply the subcapsular cortex, particularly the major blood vessels that run to the corticomedullary junction, but are sparse in the medulla, although there is an increase in β-adrenoceptor expression in the medulla during maturation. There is also evidence that nerve fibres containing ACh and VIP also supply the thymus. There is an increase in sympathetic innervation of the thymus with age, suggesting that these nerves may play a role in age-associated immune dysregulation.

Evidence for stimulation of thymocytes by adenosine, leading to increase in cAMP was presented early [45,172], to enhance DNA synthesis [202] and regulate thymocyte proliferation [469]. The adenosine receptor involved was claimed to be the A_2 subtype, based on agonist potencies [168]. There is cross-talk between A_{2A} receptors and T cell receptors in both directions, supporting a possible role of A_{2A} receptors in the mechanism of immunosuppression in vivo, under adenosine deaminase deficiency and hypoxic conditions such as solid tumours [275].

ATP stimulates calf thymus DNA α-polymerase [584] and enhances calcium influx in intact thymocytes [139,312], suggesting the involvement of P2X receptors. Extracellular ATP increases $[Ca^{2+}]_i$ in mouse thymocytes, but they vary in sensitivity depending on the degree of maturation [458]. It was suggested that extracellular ATP may be involved in the processes that control cellular proliferation within the thymus. P2X4 receptor mRNA was identified in the rat thymus [43]. ATP and adenosine are selective in targeting different

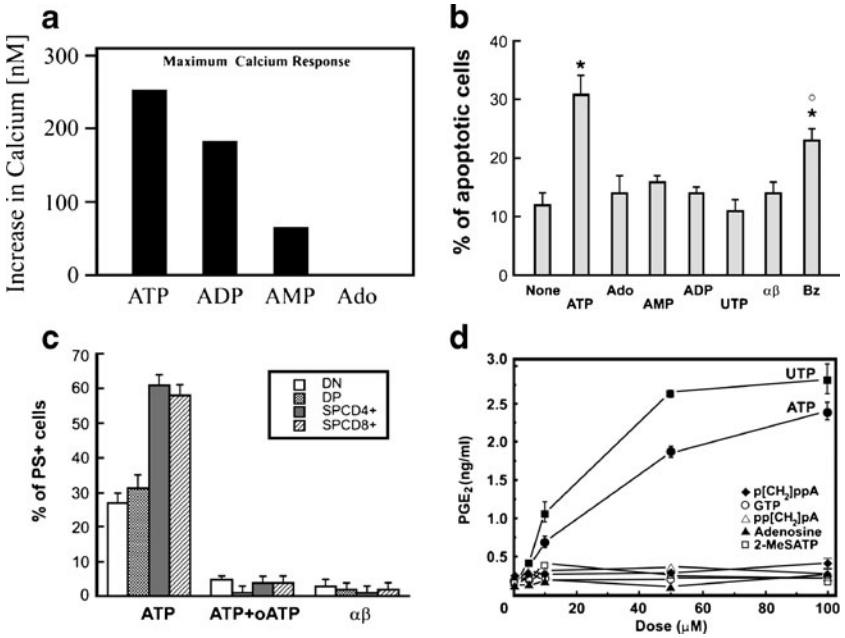

Fig. 10 **a** Extracellular ATP increases intracellular $[Ca^{2+}]_i$ in mouse thymocytes in culture. Comparison of effects of ATP with effects of its catabolites [ADP, AMP and adenosine (*Ado*)] on elevation of $[Ca^{2+}]_i$. Thymocytes were loaded with the $[Ca^{2+}]_i$-sensitive indicator indo-I and incubated with (1 mM) or without nucleotides, and the concentration of $[Ca^{2+}]$, was continuously measured. (Reproduced from [13], with permission from the American Association of Immunologists.) **b** and **c** ATP-induced apoptosis is mediated by P2X7 receptors in thymocytes from BALB/c mice. **b** Thymocytes were incubated for 5 h with purinoceptor agonists. Apoptosis was evaluated from the percentage of cells with apoptotic nuclei (means ± S.E. of four to five experiments). ATP and the P2X7 receptor agonist 2′(3′)-*O*-(4-benzoylbenzoyl) adenosine 5′-triphosphate (*BzATP*) were the most potent agonists. *Significantly different from corresponding control, °significantly different from ATP. **c** Thymocytes were incubated for 30 min with 1 mM ATP or 5 μM α,β-methylene ATP (αβ), for 2 h with 500 μM oxidised ATP (*oATP*), followed by 30 min with 1 mM ATP. Data shown are the percentages of phosphatidylserine (*PS*)+propidium iodide (*PI*) cells (treated minus control), determined from fluorescence microscopy after the binding of annexin-V-FITC in PI-cells (means ± S.E. of three to four experiments). The most mature thymocytes, the single positive cells (SP: CD4+CD8- and CD4-CD8+), were the most sensitive to ATP, whereas the double positive (DP: CD4+CD8+) and double negative (DN: CD4-CD8-) cells exhibited a lower sensitivity. (Reproduced from [302], with permission from Elsevier.) **d** Dose-dependent increase in prostaglandin E_2 (*PGE_2*) production by ATP and UTP in TEA3A1 rat thymic epithelial cells. Confluent TEA3A1 cells were incubated for 15 min at 37 °C with increasing doses of adenosine 5′-[βγ-methylene]triphosphate (p[CH2]ppA), guanosine 5′-triphosphate (*GTP*), adenosine 5′-[αβ-methylene]triphosphate (pp[CH2]pA) and 2-methylthioadenosine triphosphate (*2-MeSATP*). At the end of the experiment, media were collected and the level of PGE_2 produced by the cells was determined by radioimmunoassay. Each point represents the mean+S.D. ($n=3$). (Reproduced from [317], with permission from Portland Press.)

thymocyte subsets and they have additive and/or antagonistic effects with T cell receptor- and steroid-induced thymocyte death ([13]; Fig. 10a).

ATP has been shown to produce apoptotic cell death of thymocytes [366,619], implicating the presence of P2X7 receptors, which were later identified on phagocytic cells of the thymic reticulum [108]. It has been suggested that P2X7 receptor-mediated signalling is involved in the regulation of differentiation as well as cell death in the thymus and purified T, but not B, lymphocytes [102]. P2X7 receptor-mediated apoptosis of thymocytes involves de novo ceramide synthesis and mitochondria alterations ([302]; Fig. 10b and c). P2X1 receptors have also been claimed to play a role in apoptosis of thymocytes [103].

ATP had a biphasic effect on mouse thymocyte consisting of hyperpolarisation followed by depolarisation [345]. There is transient upregulation of $P2Y_2$, but not P2X1, receptor mRNA expression in mouse thymocytes after the addition of steroid hormone [274]. It was suggested that there may be a common early event in responses of T cells to different activating stimuli. mRNA for P2X1, P2X2, P2X6 and P2X7 receptors has been described on mouse thymocytes [173].

In an immunohistochemical and in situ hybridization study of P2 receptors in the rat thymus, it was confirmed that P2X4 receptors were expressed in thymocytes and P2X1 and $P2Y_2$ receptors on subpopulations of lymphocytes (see [65]). It was also shown that P2X1, P2X2 and P2X4 receptors were present in thymic blood vessel smooth muscle, P2X3 receptors on endothelial cells and P2X5 receptors on fibroblasts in the adventitia ([190]; Fig. 11a). Further, P2X2 and P2X3 receptors were abundant on medullary epithelial cells, while P2X6 receptors were prominent in Hassall's capsules. P2X2 receptors were found on subcapsular and perivascular epithelial cells and P2X2, P2X6 and P2X7 receptors on epithelial cells along the thymic septa. In a functional study of three preparations of thymic epithelial cells: 2BH4 murine cell line, IT45-

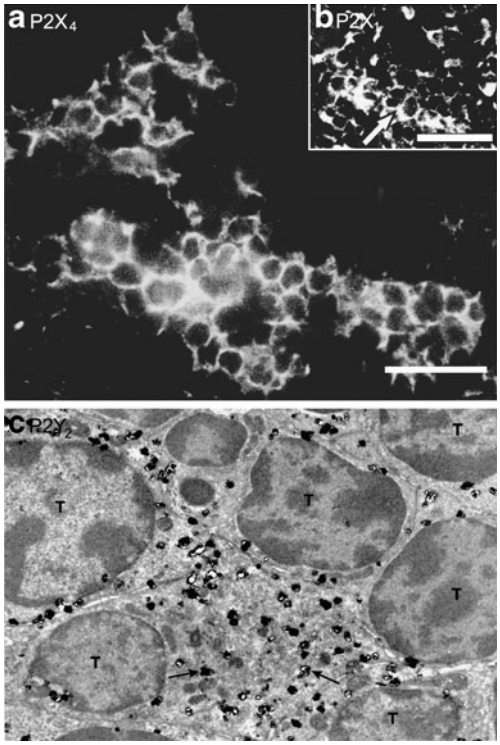

Fig. 11 **a** and **b** P2X4 and P2X1 receptor immunoreactivity in rat thymocytes: immunofluorescence with Texas Red. **a** Clusters of P2X4 receptor-expressing thymocytes along the cortico-medullary junction and within the medulla. **b** Thymocytes staining for P2X1 in the subcapsular area. Scale bar in **a** 20 μm and **b** 40 μm. **c** Ultrastructural identification of $P2Y_2$ receptor mRNA in the cortex of rat thymus. Note intense labelling (numerous 'black' gold-silver grains: *arrows*) localised in the cytoplasm of resting T-cells (*T*) of the specimen that was hybridised to the DIG-labelled rat $P2Y_2$ receptor antisense oligonucleotide probe. ×11,000. (**a** and **b** Reproduced from [190] with permission from Springer. c Reproduced from [322], with permission from Karger.)

R1 rat cell line, and primary murine cells derived from the Nurse cell lympho-epithelial complex, it was shown that extracellular ATP increases $[Ca^{2+}]_i$ probably largely via $P2Y_2$ receptors activated by both ATP and UTP [38]. They showed further that murine 2BH4 cells also expressed P2X7 receptors. $P2Y_2$ receptor mRNA was identified at the electron microscopic level in the rat thymus and shown to be localised on cortical T cells and endothelial cells of thymic blood vessels ([322]; Fig. 11b).

In the thymus, prostaglandin E_2 (PGE_2) is produced and maintained at a high level, largely by thymic epithelial cells. ATP, acting via P2Y receptors, leads to production of PGE_2 and it has been suggested that ATP released as a cotransmitter from sympathetic and parasympathetic nerves may be responsible for the high levels of PGE_2 in the thymus ([317,318]; Fig. 10d).

IL-6 is an important factor for thymic proliferation and differentiation, produced by thymic epithelial cells. It has been suggested that ATP released as a cotransmitter from sympathetic nerves leads to IL-6 production [576], implicating the presence of P2X7 receptors. Extracellular ATP induces phosphatidylserine externalisation earlier than nuclear apoptotic events in thymocytes [107]. Intercellular calcium waves have been identified between thymic epithelial cells and shown to depend on both gap junctions and P2 receptors [374].

Adenosine triphosphatase was localised histochemically intracellularly in thymocytes and shown to be more prominent in thymocyte precursors than in mature thymocytes [363]. ATP, and to a lesser extent ADP, but not AMP, GTP or inosine triphosphate, increased $[Ca^{2+}]_i$ and initiated blastogenesis [138]. Adenosine deaminase was localised in the human thymus [88]. Phorbol esters regulate adenosine deaminase mRNA in human thymocytes [344]. Studies of transgenic mice over-expressing CD73, suggest that adenosine accumulation may play a role in adenosine deaminase-deficiency severe combined immunodeficiency [442]. It is known that the thymus and other lymphoid tissues react to nutritional disorders more rapidly than most other organs. Re-feeding with a 20 % protein diet for 9 days is enough to reverse the effect produced by severe protein malnutrition and adenosine deaminase and purine nucleoside phosphorylase activities [151]. Adenosine deaminase deficiency increases thymic apoptosis and causes defective T cell receptor signalling [14].

There is a valuable review discussing the roles of extracellular ATP in the neuroendocrine control of the thymus [8].

Neuroendocrine hypothalamus

Mg^{2+}ATP has been shown to stimulate the release of luteinising hormone-releasing hormone (LHRH) from isolated hypothalamic granules [68]. ATP facilitates the action of chelated copper, perhaps released endogenously, to stimulate the release of LHRH from explants of the median eminence via interaction with a purinergic receptor [21]. ATP stimulated LHRH release and increased $[Ca^{2+}]_i$ levels in both neurons and glia; LHRH neurons express P2X2 and P2X4 receptors, while glia express $P2Y_1$ and $P2Y_2$ receptors and interactions between neurons and glia appear to be involved in the initiation of Ca^{2+} oscillations and pulsatile LHRH release in vivo in primates [537]. P2X2, P2X4, P2X5 and P2X6 receptor subunits were shown by immunohistochemistry to be expressed on the perykarya of LHRH-producing neurons, and P2X2 and P2X6 receptors on the axon terminals [175,320,321,595]. NTPDase3 has been identified in the neuroendocrine hypothalamus and it has been suggested that it plays a role in the initiation of the LH surge and ATP involvement in the regulation of pituitary LH release [622].

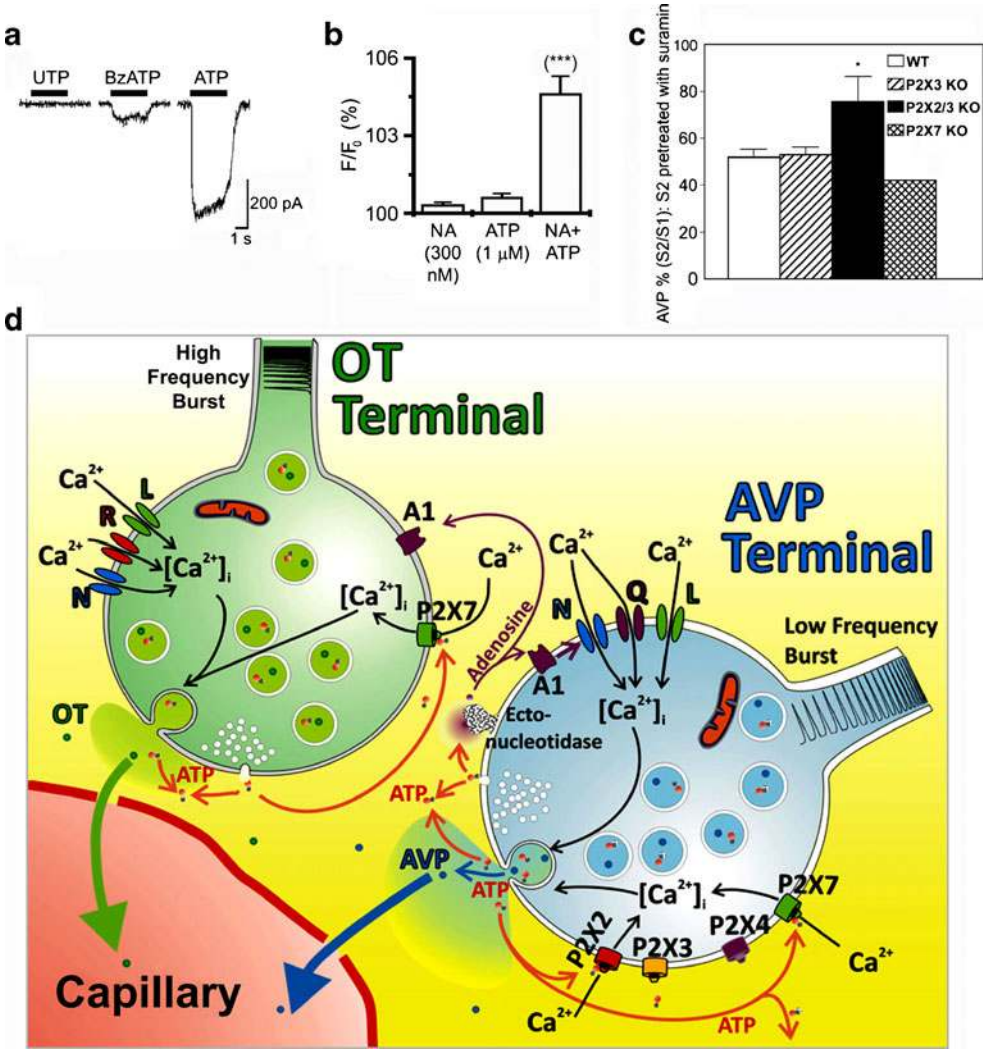

Fig. 12 **a** Patch-clamp analysis of ATP-induced currents in rat supraoptic nucleus (SON) neurons. Representative current responses to UTP (10^{-3} M), BzATP (10^{-4} M) and ATP (10^{-3} M) obtained from a single SON neuron. The breaks in the trace are 3–5 min. The holding potential was −80 mV. The major salt in the pipette used in experiments shown in this figure was caesium methanesulphonate. (Reproduced from [481], with permission from Wiley.) **b** Rat SON astrocytes respond to ATP and noradrenaline (*NA*) and the response is synergistic. Averaged values show that the amplitude of the response to the co-application of the two transmitters is significantly greater than the sum of the responses to individual applications (*** $P<0.001$, $n=22$). (Reproduced from [143], with permission from Elsevier.) **c** Summary of effects of suramin on electrically-stimulated vasopressin (*AVP*) release from wild-type (*WT*), P2X3, P2X2/3 and P2X7 receptor knockout (*KO*) mice. These data indicate that P2X2 is the primary receptor responsible for the facilitation of electrically-stimulated AVP release by endogenous release of ATP. The inhibitory effect of suramin on endogenous ATP facilitation of AVP release was significantly ($P<0.05$) reduced only in the P2X2/3 KO mice. * Indicates significant difference $P<0.05$ compared to WT control. (Reproduced from [114], with permission from Wiley.) **d** Model of the established exogenous and the proposed endogenous purinergic effects on neurohypophysial terminals. Different physiological burst patterns regulate oxytocin (*OT*; high frequency) vs. AVP (low frequency) release. The biophysical properties of the VGCC (N, L, R on OT and N, L, Q on AVP terminals) alone, however, cannot explain the differential effects of such bursts. Thus, we propose that endogenous co-released ATP activates P2X2, P2X3, P2X4 and P2X7 receptors localised on AVP terminals, while activating only P2X7 receptors on OT terminals. The flux of Ca^{2+} through these receptors increases $[Ca^{2+}]_i$ and, thus, neuropeptide release. The ATP is then broken down to adenosine by ecto-nucleotidases, which are present only on AVP terminals. Adenosine, which acts on A_1 receptors, present on both terminal types, directly inhibits N-type Ca^{2+} channels and subsequent neuropeptide release. (Reproduced from [300], with permission from Elsevier.)

ATP injected into the paraventricular and supraoptic nuclei leads to a release of the antidiuretic hormone, arginine-vasopressin (AVP) [358,359]. It was later proposed that ATP was released as a cotransmitter with NA from neurons in the caudal medulla that project to supraoptic VP cells [118]. Application of ATP and UTP (but not adenosine) produced depolarisations of supraoptic neurosecretory cells in superfused explants of rat hypothalamus, via P2X and $P2Y_2$ receptors [233]. ATP appears to act via P2X receptors both on the cell bodies and dendrites of vasopressinergic neurons in the supraoptic nucleus of the hypothalamus [481]. ATP produces inward currents in isolated vasopressinergic

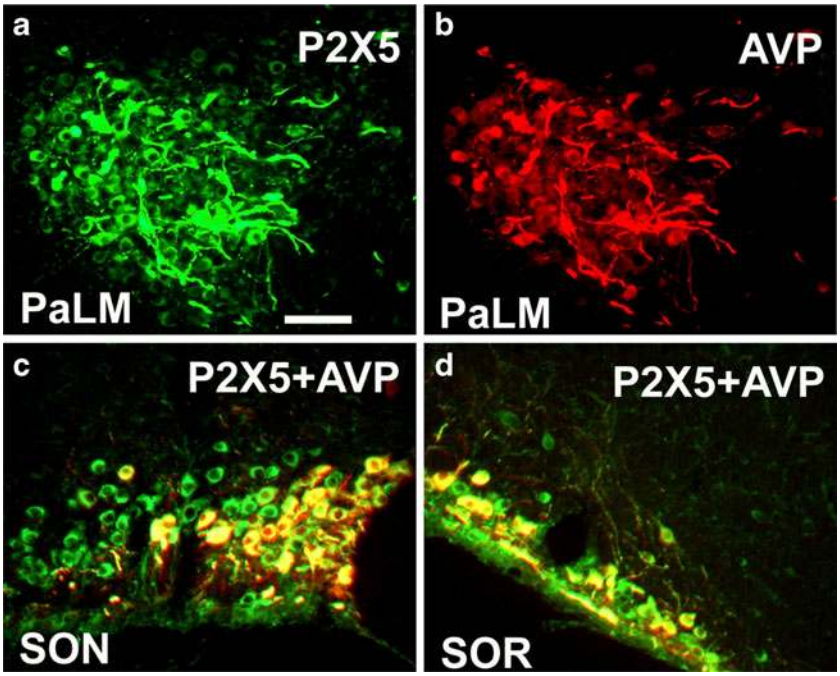

Fig. 13 Coexistence of P2X5 receptor immunoreactivity and vasopressin (*AVP*) in rat hypothalamus. **a** P2X5 receptor-immunoreactive (*ir*) neurons and fibers in the paraventricular hypothalamic nucleus, lateral magnocellular area (PaLM; *green*). **b** AVP-ir neurons and fibers in the PaLM at the same section of a (*red*). **c** Coexistence of P2X5 receptor-ir and AVP-ir in the supraoptic nucleus (*SON*). Note that nearly all the AVP-ir neurons also expressed P2X5 receptor immunoreactivity (*yellow*), but a number of the P2X5 receptor-ir neurons (*green*) did not express AVP. **d** Coexistence (*yellow*) of P2X5 receptor immunoreactivity (*green*) and AVP (*red*) in the retrochiasmatic part of supraoptic nucleus (*SOR*). Scale bar for all figures 80 μm. In each figure, the dorsal aspect of the nuclei is at the top and the ventral aspect of the nuclei is at the bottom. (Reproduced from [596], with permission from Elsevier.)

neurohypophysial terminals via P2X2 and P2X3 receptors [267]. RT-PCR studies showed that mRNAs for P2X3, P2X4 and P2X7 receptors were predominant in rat supraoptic nucleus and functionally expressed, leading to increase in $[Ca^{2+}]_i$ ([481]; Fig. 12a). Evidence has been presented that ATP-induced currents in AVP neurons in the supraoptic nucleus may be mediated, at least in part, by pannexin channels associated with P2X receptors [386]. Adenosine, probably resulting from the breakdown of ATP released from nerves in the supraoptic nucleus, inhibits the release of γ-aminobutyric acid and glutamate via activation of presynaptic A_1 receptors leading to modulation of AVP and OT release [396].

In keeping with the features of cotransmission, ATP (via P2X receptors) and phenylephrine (via α_1 adrenoceptors) act synergistically to stimulate AVP release [487,497,500]. Synergistic activation of astrocytes by ATP and NA in the rat supraoptic nucleus has also been described ([143]; Fig. 12b). ATP, acting via P2X2 receptors (which do not show desensitization), caused rapid, sustained release of AVP and OT into perfused explants of the rat hypothalamus-neurohypophysial system [193], while substance P potentiated these responses [250]. P2X5 receptors were shown to be expressed on neurons containing AVP and NOS in the rat hypothalamus ([596]; Fig. 13). Evidence was presented to show that P2Y as well as P2X receptors mediate ATP-stimulated increase in $[Ca^{2+}]_i$ in the supraoptic nucleus, the $P2Y_1$ receptor subtype being more prominent than the $P2Y_2$, $P2Y_4$ or $P2Y_6$ subtypes [498]. In a later paper from this group, it was suggested that $P2Y_1$ receptors may regulate VP release by mediating stretch-inactivated cation channels [499]. A recent study has shown that AVP-containing neurons to the rat paraventricular nucleus expressed P2X4, P2X5 and P2X6 receptors, while OT-containing neurons only expressed P2X4 receptors; in the supraoptic nucleus, AVP neurons expressed P2X2, P2X4, P2X5 and P2X6 receptors and OT-containing neurons expressed P2X2, P2X4 and P2X5 receptors [206]. It was concluded in recent papers that P2X4 receptors were found only on AVP terminals, while P2X7 receptors were expressed on both AVP and OT terminals and somata and this suggested that this is controlled by hypothalamic neurohypophysial neurons to form a positive feedback mechanism for hormone release (Fig. 12c) [114,269]. A model was proposed to explain how purinergic and/or opioid feedback modulation during bursts can mediate differences in the control of neurohypophysial AVP and OT release ([300]; Fig. 12d). Adenosine, acting via P1 receptors, reduces ATP-stimulated AVP release from hypothalamo-neurohypophysial explants [496].

Orexin/hypocretin neurons in the hypothalamus, involved in arousal and feeding behaviours, express A_1 adenosine

receptors [538,594]. P2X2 receptor mRNA has also been shown to be expressed on orexin/hypocretin neurons in the rat perifornical hypothalamus [160] and ATP, released from neurons and/or glia, leads to increased activity of the hypocretin arousal system via P2X2 receptors [592].

Placenta

The placenta and umbilical vessels are involved in steroidogenesis as well as regulation of blood flow and control of transport of materno-foetal fluid and solutes.

NO, released from endothelial cells following occupation of P2 receptors in response to ATP, ADP and UTP, may regulate the release of corticotrophin-releasing hormone from human placental syncytiotrophoblast cells. An increase in placental 5′-nucleotidase was described in late human pregnancy and duration of labour and it was suggested that this may reflect enhanced oestrogen synthesis and facilitation of uterine contractions during labour [61]. Immunocytochemical localisation of 5′-nucleotidase was shown on the external surface of the microvillous plasma membrane of the syncytiotrophoblast, where it may play a role in regulating foeto-placental-maternal microcirculation in the human term placenta [346]. P2X7 receptors mediate regulation of PLD in human placental trophoblasts [126].

P2X1, P2X4, P2X5, P2X6 and P2X7 receptor mRNA has been described in human placental vessels, which contribute to humoral regulation of placental blood flow [565]. The syncytiotrophoblast is the solute-transporting epithelium of the human placenta that facilitates maternal-foetal nutrient exchange. Since the human placenta is not innervated, autocrine, paracrine and endocrine modulation of syncytiotrophoblast transport function is of pivotal importance. Functionally active P2X4, P2X7, $P2Y_2$ and $P2Y_6$ receptors have been identified on human placental syncytiotrophoblast cells [446]. This group showed later that post-translational modifications of the syncytiotrophoblast P2X4 receptor are altered in preeclampsia [447].

Neuroendocrine cells

The neuroepithelial bodies (NEBs) consist of pulmonary neuroendocrine cells that are usually arranged in innervated clusters in the airway mucosa. They are O_2 sensors, of particular importance in early life before the carotid body O_2 sensory system is fully established. They also appear to mediate reflex activities in response to hyperventilation and noxious substances, by releasing ATP to act on P2X3 receptors on sensory nerves arising from the nodose ganglia, which innervate NEBs [51,52]. Parasympathetic efferent fibres also innervate NEBs [1].

Merkel cells in the skin are also regarded as neuroendocrine cells. They are innervated largely by sensory nerves, which are likely to be activated by ATP, which is stored in high concentrations and probably released from these cells by mechanical distortion [112].

Rat prostate neuroendocrine cells express both P2X and P2Y receptor subtypes, which mediate marked increase in $[Ca^{2+}]_i$ [59,261]. The authors speculate ATP is released as a cotransmitter with NA in sympathetic reviews innervating the prostate.

The gastrointestinal tract is, in size at least, the largest endocrine organ in the body. Endocrine cells in the intestinal mucosa release a number of putative hormones [259,476]. For example, the intestinal hormone cholecystokinin acts on primary afferent nerve fibres in the vagal trunk [128]. OT is expressed by intrinsic sensory and secretomotor neurons in the guinea-pig enteric nervous system, suggesting that OT in the gut is involved in both motility and the balance of absorption and secretion of water and electrolytes [608].

Adipocytes

Adipocytes were long considered to be an inert tissue for fat storage, but it is now recognised that it has endocrine functions [80,224,263,456]. Adipocytes secrete adipokines, including adiponectin, leptin, tumour necrosis factor-α and IL-6, as well as adenosine and fasting-induced adipose factor. Leptin is produced by white adipocytes and acts on the brain to maintain body weight by suppressing food intake [431]. Adiponectin has an anti-inflammatory role, protecting against insulin resistant type 2 diabetes, fatty liver disorder and atherosclerosis.

P1 receptors

Adenosine was shown to inhibit adenylate cyclase activity in fat cell ghosts [144,323] and lipolysis in adipose cells stimulated by NA or sympathetic nerve stimulation [169,234,493,556]. Insulin and adenosine are both antilipolytic; they are additive, but not synergistic [494]. Both insulin and adenosine have major roles in regulating adipose tissue mobilisation [351]. Adenosine also plays a role in the regulation of adipose tissue blood flow [342,492,557]. Fat cell plasma membranes were shown to contain sites which bind [^{3}H]adenosine with high affinity [339]. Adenosine receptors on fat cells that mediate inhibition of cAMP accumulation and lipolysis were identified [553]. CD73-derived adenosine is an insulin-independent modulator of lipolysis in fat tissue under in vivo conditions [60]. They were claimed first to be R_a, R_i and then P receptors [179] and later as A_1 receptors in rats [199,406], pigs [349] and humans [200,287,534]. Adenosine inhibited lipolysis in vivo in obese premenopausal women

[180]. White adipocytes were found to be more responsive than brown adipocytes to inhibition of lipolysis by A_1 receptor agonists [464]. Lipolysis of mature brown fat cells is significantly increased by activation by A_{2A} receptor agonists or by A_1 receptor antagonists [192]. The A_2 receptor subtype, which is positively coupled to adenylate cyclase, is expressed in adipocyte precursor cells, but not mature adipocytes [567]. However, in later papers A_1 receptors expressed in human preadipocytes were shown to initiate differentiation while A_{2B} receptors mediated inhibition of apidogenesis [185,533]. Adipocyte A_1 receptors are tonically activated by endogenous adenosine at nanomolar concentrations [310]. A partial agonist of the A_1 receptor was identified and evidence presented that the rat epididymal A_1 receptors are a homogenous receptor population with regard to affinities for ligands [148]. There is a deficient lipolytic response to CA in hypothyroidism and it was suggested that this may be due to an increased influence of adenosine [170]. Short-term hyperthyroidism modulates the expression of adenosine receptors in adipocytes [433].

In subcutaneous abdominal fat cells from obese subjects, the antilipolytic effect of an adenosine analogue was markedly attenuated [387,388], with decreased adenosine receptor numbers [248]. Insulin resistance in Obese Zucker rats is tissue specific and signalling via adenosine receptors may be a factor contributing to tissue specific insulin resistance [111]. Overexpression of A_1 receptors in adipose tissue protects mice from obesity-related insulin resistance [129]. Data has been presented to suggest that inhibition of lipolysis by adenosine is greater in obese African-American women and this may explain why obese African-American women have more difficulty in losing weight than obese Caucasian women [20]. It has been claimed recently that promotion of brown adipose tissue development in white adipose tissue by physiological activation of AMP kinase may have potential for treating obesity [573]. Adenosine had different effects on the actions of OT and insulin on glucose oxidation and lipogenesis [195]. Adenosine greatly enhanced lipolysis in isolated fat cells from streptozotocin-diabetic rats compared to controls [495]. The maximal rate of lipolysis of adipocytes from exercise-trained rats was increased compared to controls, but inhibition by adenosine was comparable in the two groups [482]. Lactation results in an increased responsiveness of adipocytes to β-agonists which stimulate lipolysis and paradoxically, to adenosine which inhibits lipolysis [571]. Activation of A_1 receptors, which have a dominant expression in adipocytes, increases leptin secretion [95,443], as well as inhibition of lipolysis and protection against obesity-related insulin resistance [185]. They suggest that targeting A_1 and A_{2B} receptors could be considered for the management of obesity and diabetes (see also [123,124]). Leptin-induced lipolysis opposes the tonic inhibition by endogenous adenosine in white adipocytes [174]. AMP kinase has been claimed to have fat-reducing effects on adipose tissue [177]. In a study using A_1 receptor knockout mice, increase in lipolysis and decrease in lipogenesis was expected, but in fact an increased fat mass was observed [246]. The authors suggested that this might indicate that other actions of A_1 receptors, possibly outside adipose tissue, may also be important. However, partial antagonism of A_1 receptors increased lipolysis in cells incubated with adrenaline and adenosine with insulin [523]. It was concluded that the adenosine that accumulates in human adipocyte suspensions is almost exclusively derived from ATP released from cells [254]. A_1 receptor signalling contributes to insulin-controlled glucose homeostasis and insulin sensitivity and is involved in the metabolic regulation of adipose tissue [149]. An early review about adenosine and lipolysis is available [167]. AMP is a selective inhibitor of brown adipocyte non-selective cation channels [209].

There is recent interest in the differentiation of mesenchymal stem cells (MSCs) into adipocytes and purinoceptors appear to be involved. For example, differentiation of MSCs into adipocytes was accompanied by significant increases in A_1 and A_{2A} receptor expression and their activation was associated with adipogenesis [184].

P2 receptors

ATP inhibition of insulin-stimulated glucose transport in fat cells was recognised early [81,158,210]. ATP also inhibited insulin-stimulated glucose oxidation [530]. Insulin-stimulated D-allose transport, into or out of the cell, but not basal transport, is inhibited by brief exposure of isolated fat cells to exogenous ATP and ADP [326]. It was suggested that ATP blocks transmission of signal from the insulin receptor to the carrier system. Sympathetic nerve stimulation induces a rapid fall in ATP in subcutaneous adipose tissue, perhaps secondary to the hypoxia produced by vasoconstriction [171]. Evidence was presented to suggest that extracellular ATP may partially inhibit the binding of insulin to its surface receptor and, at the same time, may strongly block the degradative pathways for the processing of insulin [215]. Chronic inflammation in adipose tissue is an important etiologic factor for the development of insulin-resistance, particularly in obesity. In a recent paper, it has been shown that high doses of ATP induce inflammatory responses and insulin resistance in rat adipocytes [610]. The authors suggest that defects in ATP-induced insulin signalling play a major role for the impaired glucose uptake in response to insulin treatment. Echinocytosis by glucose depletion, where erythrocytes shrink, has been attributed to ATP depletion, although other mechanisms may also be involved [593].

High fat diets are associated with a reduction in sympathetic activity in brown adipose tissue [465], bearing in mind that it is now well established that ATP is released as a cotransmitter from sympathetic nerves (see [63]). In obesity, sympathetic nerve activity is increased relating to obesity

hypertension, while sympathetic nerve activity to adipose tissue is reduced and unresponsive to stimulation by feeding [289]. It was further suggested that local sympathetic nerve dysfunction may contribute to abnormal adipose tissue behaviour in obesity and body fat accumulation.

From a study of brown adipocytes of rats it was suggested that secretion, mobilization of membrane transporters, and/or membrane expression of receptors may be regulated by ATP released as a cotransmitter from sympathetic nerves acting via P2Y receptors [295,404]. In a later study, these authors concluded that white adipocytes are very similar to brown adipocytes in their response to extracellular ATP [296]. ATP, acting via P2 receptors, is involved in the regulation of the key enzyme of oestrogen biosynthesis, aromatase, in stromal cells from human adipose tissue [475]. They suggest that P2 receptors might provide a direct link between sympathetic nerve activity and oestrogen biosynthesis. ATP not only mobilises Ca^{2+} from intracellular stores (probably via P2Y receptors), but also exerts a potent inhibitory effect on the store-operated Ca^{2+} entry process in adult rat brown adipocytes [397,398]. ATP, probably released from sympathetic nerves, modulates via P2 receptor activation, the amount and voltage dependence of voltage-gated K^+ currents in brown adipocytes [585], and increases membrane conductance in single rat adipocytes [100].

ATP also mediates long-term signalling, for example it modulates proliferation of brown adipocytes [586]. Evidence has been presented that extracellular ATP redistributes actin filaments towards the plasma membrane of brown adipocytes via P2 receptors [399].

Genes expressing P2X1, P2X4, P2X5 and P2X7, in addition to $P2Y_1$, $P2Y_2$, $P2Y_4$ and $P2Y_6$ receptor mRNA identified by RT-PCR, have been described in rat adipocytes [398]. $P2Y_2$ and $P2Y_{11}$ receptors have been identified on white adipocytes and it has been suggested that $P2Y_{11}$ receptors might be involved in inhibition of insulin-mediated leptin production and stimulation of lipolysis [293]. In a more recent paper, leptin production by white adipocytes was decreased in $P2Y_1$ receptor knockout mice [285]. It was suggested that the $P2Y_1$ receptor may regulate plasma leptin in lean mice, but is overcome in obese mice. $P2Y_2$, $P2Y_6$ and $P2Y_{12}$ receptors, and all P2X receptor subtypes except P2X6, were identified as the nucleotide receptors on brown fat cells [297]. Human adipocytes express functionally active P2X7 receptors that mediate release of inflammatory cytokines; adipocytes from patients with metabolic syndrome show enhanced P2X7 receptor expression [336].

ATP enhanced 3 T3-L1 pre-adipocyte cell migration into fat cell clusters, one of the essential processes of adipose tissue development, by activating P2Y receptors, as well as enhancing the differentiation of adipocytes by adipogenic hormones [400]. Deficits in receptor regulation, transporter mobilization and adipocyte hormone secretion are all thought to contribute to the pathology of obesity. Stimulation of lipogenesis in rat adipocytes by ATP, which regulates fat stores independently from established hormones, has been reported [477].

Ca^{2+} ATPase in mitochondria, that is brown adipose tissue-specific, has been described that can generate heat in the presence of Ca^{2+} concentrations similar to those generated by adrenergic stimulation [120]. Resveratrol and genistein, naturally occurring plant-derived compounds present in red wine and said to have anti-adipogenic effects, deplete ATP from adipocytes [521].

Increase in release of ATP in adipocytes appears to be an important factor increasing leptin gene expression and enhancing leptin secretion after a meal (see [522]).

Concluding comments

In most other areas, the recent emphasis has been on the pathophysiology and therapeutic potential of purinergic signalling. Surprisingly, this has not yet happened in relation to endocrine biology, but hopefully with the recent development of purinoceptor subtype antagonists that are orally bioavailable and stable in vivo, this aspect will be explored.

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