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The homeostatic role of neuropeptide Y in immune function and its impact on mood and behaviour

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Abstract

Neuropeptide Y (NPY), one of the most abundant peptides in the nervous system, exerts its effects via 5 receptor types, termed Y1, Y2, Y4, Y5 and y6. NPY's pleiotropic functions comprise the regulation of brain activity, mood, stress coping, ingestion, digestion, metabolism, vascular and immune function. Nerve-derived NPY directly affects immune cells while NPY also acts as a paracrine and autocrine immune mediator, since immune cells themselves are capable of producing and releasing NPY. NPY is able to induce immune activation or suppression, depending on a myriad of factors such as the Y receptors activated and cell types involved.

There is an intricate relationship between psychological stress, mood disorders and the immune system. While stress represents a risk factor for the development of mood disorders, it exhibits diverse actions on the immune system as well. Conversely, inflammation is regarded as an internal stressor and is increasingly recognized to contribute to the pathogenesis of mood and metabolic disorders. Intriguingly, the cerebral NPY system has been found to protect against distinct disturbances in response to immune challenge, attenuating the sickness response and preventing the development of depression. Thus, NPY plays an important homeostatic role in balancing disturbances of physiological systems caused by peripheral immune challenge. This implication is particularly evident in the brain in which NPY counteracts the negative impact of immune challenge on mood, emotional processing and stress resilience. NPY thus acts as a unique signalling molecule in the interaction of the immune system with the brain in health and disease.

Keywords

Brain; Immune system; Neuropeptide Y

The neuropeptide Y family and its receptors (Y1, Y2, Y4, Y5)

The principal members of the neuropeptide Y (NPY) family of biologically active peptides are NPY, peptide YY (PYY) and pancreatic polypeptide (PP). Like other biologically active peptides, the NPY-related peptides are synthesized as large protein precursors which are

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subsequently cleaved to release the active peptides. All three members of the NPY peptide family are made of 36 amino acids. In addition, NPY, PYY and PP share the PP fold (hairpin fold) tertiary structural motif and the C-terminal tyrosine amide structure. The N-terminal amino acid of NPY and PYY is also tyrosine, which is reflected by the names of peptide YY and neuropeptide Y. The genes encoding NPY, PYY and PP have been identified and found to have very similar base sequences (Cerda-Reverter & Larhammar 2000).

The biological actions of NPY, PYY and PP are mediated by Y receptors. Of the 7 Y receptor types occurring in vertebrates, 5 types are expressed in mammals, namely Y1, Y2, Y4, Y5 and y6 (a pseudogene in humans and rats). The genes encoding the Y receptors have been characterized at the molecular and pharmacological level (Michel *et al.* 1998), and it is remarkable that the various Y receptors display surprisingly low sequence homologies and thus represent one of the most heterogeneous receptor families (Larhammar 1996). All Y receptors are metabotropic receptors that are coupled to pertussis toxin-sensitive $G_{i/o}$ protein transduction mechanisms which decrease cAMP synthesis and protein kinase A activity (Redrobe *et al.* 2004a, Alexander *et al.* 2011). In some cells NPY can also activate pertussis toxin-insensitive G_q proteins activating protein kinase C (PKC) and extracellular signal-regulated kinase 1/2 (Herzog *et al.* 1992, Goldberg *et al.* 1998, Yang *et al.* 2008, Persaud & Bewick 2014).

The Y receptor types exhibit distinct affinities for the different members of the peptide family and their fragments (Cox 2007a, Alexander *et al.* 2011). This is of biological relevance, given that the N-terminus of NPY and PYY is readily cleaved by aminopeptidase P and dipeptidyl peptidase 4 (DP4, CD26), yielding the fragments NPY_{2-36}, NPY_{3-36} and PYY_{3-36} which have distinct pharmacological properties. While there is not much difference in the affinities of NPY and PYY for the Y1, Y2 and Y5 receptor subtypes, NPY_{2-36} is a Y2 agonist, while NPY_{3-36} and PYY_{3-36} are preferential agonists at Y2 and Y5 receptors, and PP displays some selectivity for Y4 receptor (Cox 2007a, Abid *et al.* 2009, Alexander *et al.* 2011). The Y1 and Y2 receptors are the most abundant receptor types in the periphery and the central nervous system (Holzer *et al.* 2012).

PYY and PP are almost exclusively expressed in the digestive system, whereas NPY occurs primarily in the central and peripheral nervous system (Holzer *et al.* 2012). PP is synthesized by endocrine F cells of the pancreatic islets (Ekblad & Sundler 2002) and some enteroendocrine cells of the small and large intestine, these cells differing from PYY-expressing cells (Cox 2007a). Although Y4 receptors, which are preferentially targeted by PP, are expressed in the brain, PP does not seem to be produced in the central nervous system, given that the immunoreactivity which was once believed to reflect cerebral PP turned out to be NPY (Allen *et al.* 1983, DiMaggio *et al.* 1985). PYY is primarily formed by the enteroendocrine L cells which occur most abundantly in the lower gastrointestinal tract (Ekblad & Sundler 2002, McGowan & Bloom 2004, Cox 2007a, Cox 2007b, Ueno *et al.* 2008). Other, but minor sources of PYY are enteric neurons of the stomach (Böttcher *et al.* 1993) and pancreatic endocrine cells (Cox 2007b) while the expression of PYY in the brain is relatively sparse (Ekblad & Sundler 2002, Morimoto *et al.* 2008). Interestingly, while the

major circulating form of PYY is PYY_{3-36}, PYY_{1-36} seems to be predominant in the brain (Gelegen *et al.* 2012).

In contrast to PP and PYY, NPY is widely expressed in the body. Within the brain, NPY is one of the most abundant neuropeptides, being expressed by multiple neuronal systems from the medullary brainstem to the cerebral cortex such as the nucleus of the solitary tract, ventrolateral medulla, periaqueductal grey, locus coeruleus, paraventricular nucleus of the thalamus, hypothalamus (arcuate nucleus, paraventricular nucleus and other regions), septum, hippocampus, amygdala, basal ganglia, nucleus accumbens and cerebral cortex (Wettstein *et al.* 1995, Kask *et al.* 2002, Eaton *et al.* 2007). Due to the absence of specific reuptake mechanisms and their special kinetics of action, neuropeptides have long-lasting effects on target neurons (Heilig 2004). In the periphery, the major cellular sources synthesizing NPY are enteroendocrine cells of the gut (Bär *et al.* 2014), distinct populations of enteric neurons such as secretomotor neurons and inhibitory motoneurons (Schicho *et al.* 2003, Cox 2007a), primary afferent neurons (Brumovsky *et al.* 2007), postganglionic sympathetic neurons supplying the vascular system but also lymphoid tissues (Romano *et al.* 1991, Lomax *et al.* 2010), and immune cells (Dimitrijevic & Stanojevic 2013). Another source of NPY is platelets which, especially in rats, have been reported to release noticeable amounts of NPY into the circulation (Myers *et al.* 1988). The concentration of circulating NPY is in the picomolar range, and levels in the cerebrospinal fluid (CSF) are 3 fold higher compared to plasma levels (Baker *et al.* 2013). The half-life of NPY in plasma is uncommonly long and amounts to 40 min in humans (Ahlborg *et al.* 1992).

In this review, we focus on particular implications of NPY in immune regulation, on the one hand, and its involvement in brain functions underlying mood, emotional processing and stress coping, on the other hand. These implications may, at first glance, appear unrelated with each other, but there is abundant evidence for a close interaction between the immune system and the brain, which has an important bearing on psychiatric diseases including anxiety disorders and major depression (Dantzer *et al.* 2008, Haroon *et al.* 2012). As the review illustrates, the effects of NPY both in the immune and the nervous system are utterly complex. While some aspects of the peripheral immune response may be enhanced, whereas others are inhibited by NPY, the disturbances in brain function and behaviour elicited by peripheral immune challenge are uniformly counteracted by cerebral NPY in a homeostatic fashion.

NPY's pleiotropic actions on immune cells

The first evidence that NPY could exert immunological effects was borne out by the finding that sympathetic neurons innervating lymphoid organs contain NPY (Romano *et al.* 1991) and NPY is co-released with noradrenaline upon stimulation (Lundberg *et al.* 1989). In addition to nerve-derived NPY, it was found that immune cells such as monocytes, macrophages, dendritic cells (DCs) and lymphocytes express NPY and can modulate immune cell function in a paracrine or autocrine manner (Schwarz *et al.* 1994). In addition to NPY, also PYY mRNA has been demonstrated in mouse macrophages (Macia *et al.* 2012b). Collectively, the investigation of the effects of NPY on the immune system has revealed that the peptide is implicated in a variety of inflammatory disorders such as

autoimmunity, asthma, atherosclerosis and cancer (Macia *et al.* 2011, Dimitrijevic & Stanojevic 2013, Jaaskelainen *et al.* 2013).

The expression of various Y receptors on immune cells enables NPY to directly influence immune function (Petitto *et al.* 1994). The Y1 receptor represents the most abundant receptor and has been localized to all immune cells examined thus far (Dimitrijevic & Stanojevic 2013). The effects of Y1 receptor activation on inflammation-associated disorders are summarized in Fig. 1. In contrast, reports regarding the expression of the other Y receptors are scarcer. Thus, in mice, gene expression of Y1, Y2, and Y5 receptors has been reported in macrophages, while the Y4 receptor seems not to be expressed (Singer *et al.* 2013). Similarly, Y1, Y2, and Y5 receptors are expressed on rat granulocytes (Mitic *et al.* 2011). In contrast, human neutrophils express mRNA of all 4 functional Y receptors (i.e. Y1, Y2, Y4 and Y5), and the Y4 receptor is the most abundant, while the Y2 receptor is upregulated upon neutrophil stimulation (Bedoui *et al.* 2008). However, despite the highest expression of the Y4 receptor, the stimulation of this receptor by PP does not elicit any changes in reactive oxygen species production or phagocytosis (Bedoui *et al.* 2008).

In general, it can be stated that NPY serves as a modulator of the immune system, and its distinct effects are strongly context-dependent (Tables 1 – 8). Thus, activation of different Y receptor types can mediate distinct effects of NPY while the same receptor expressed on different immune cell types can exert either pro- or anti-inflammatory actions (Wheway *et al.* 2005). Finally, DP4 cleaving NPY1-36 to the Y2/5 receptor agonist NPY_{3-36} is another regulator of NPY's immunologic actions, being also responsible for some of the controversial effects of NPY reported *in vitro* and *in vivo* (Mitic *et al.* 2011).

The relationship between NPY and the immune system is bidirectional. Thus, the production of NPY by immune cells can be upregulated upon immune stimulation (Singer *et al.* 2013). Likewise, cytokines have been reported to stimulate mouse chromaffin cells to release NPY and catecholamines, which on their own affect the immune system (Rosmaninho-Salgado *et al.* 2007).

NPY's actions on monocytes, macrophages, microglia and cytokine secretion

One of the first studies examining the role of NPY on macrophages found that both NPY and PYY are able to increase adhesion (Table 1), chemotaxis (Table 2), phagocytosis of latex beads and *Candida albicans* (Table 3) as well as production of superoxide anions (Table 4) in resting peritoneal macrophages from male BALB/c mice (De la Fuente *et al.* 1993). In addition to the macrophage activating actions of NPY and PYY, a stimulation of PKC in these cells was observed (De la Fuente *et al.* 1993). Interestingly, in a subsequent study the effects on macrophage function were shown to change with age. Thus, while NPY increased macrophage function in adult mice, it decreased the chemotaxis and phagocytosis capacity of macrophages from old mice which under control conditions display a higher chemotaxis and phagocytosis capacity than adult mice (De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a). Furthermore, NPY potentiated nitric oxide (NO) production of LPS-stimulated resident rat peritoneal macrophages solely in young rats, an effect that was mediated by Y1 and Y2 receptors (Dimitrijevic *et al.* 2008).

Analysis of the receptors involved revealed that *in vitro* NPY potentiated adhesiveness and phagocytosis of peripheral blood granulocytes and monocytes via the Y1 receptor (Mitic *et al.* 2011). In the same study it was found that *in vivo* NPY reduced inflammatory cell accumulation in LPS-induced air-pouch exudates via Y1/Y2 receptor activation, while it decreased their adhesion via Y2/Y5 receptor stimulation (Mitic *et al.* 2011).

NPY produced by endothelial cells has been suggested to be involved in the recruitment of leukocytes at sites of LPS-induced inflammation (Silva *et al.* 2003). Thus, NPY, Y1 and Y2 receptors are expressed in human umbilical venous endothelial cells, while immune challenge with lipopolysaccharide (LPS) has been reported to increase NPY, DP4 activity and to induce Y5 receptor expression, while the Y2 receptor expression is suppressed (Silva *et al.* 2003).

Several reports demonstrate further inhibitory actions of NPY on macrophage function. For instance, NPY inhibits spontaneous activation of human granulocytes and macrophages as well as their chemotaxis (Dureus *et al.* 1993). NPY, PYY, LP-NPY (a Y1/Y5 receptor agonist) and $NPY_{13\text{-}36}$ (a Y2 receptor agonist) decrease peroxide production of thioglycollate-elicited rat peritoneal macrophages (Dimitrijevic *et al.* 2002). In addition, phagocytosis of zymosan by peritoneal macrophages is decreased through an action of the Y2 receptor (Dimitrijevic *et al.* 2005). PYY acting via Y1 receptors has also been demonstrated to decrease the adhesion capacity of elicited peritoneal macrophages of male rats and to suppress phagocytosis and NO production of resident macrophages (Stanojevic *et al.* 2006).

The partly contradicting effects of NPY on macrophage function might be due to species differences between mice and rats and to the different response modes of resident versus elicited macrophages (Stanojevic *et al.* 2006). The differences in phagocytosis may also depend on the activating agent or pathogen. Specifically, while NPY has been reported to increase the phagocytosis of *Candida albicans* (De la Fuente *et al.* 1993), it suppresses phagocytosis and killing of *Leishmania major* parasites by a murine leukaemic monocyte macrophage cell line (Raw 264.7) (Ahmed *et al.* 2001). Further analysis of NPY's effects in Raw 264.7 cells disclosed a suppression of phagocytosis of unopsonized *Escherichia coli* and *Staphylococcus aureus* bioparticles (Phan & Taylor 2013). In addition, NPY decreases FcR-associated generation of reactive oxidative species and phagolysosome activation (Phan & Taylor 2013).

The effects of NPY on cytokine production (Table 5) by immune cells are likewise of a diverging nature. While NPY has been reported to increase the production of interleukin (IL)-1β, IL-6 and tumour necrosis factor-α (TNF-α) of whole blood cells from healthy subjects (Hernanz *et al.* 1996), it decreases TNF-α release in response to LPS as well as IL-1β and IL-2 release in response to concavalin A (Con A) in murine peritoneal macrophages (De la Fuente *et al.* 2001a, Puerto *et al.* 2005). Furthermore, NPY increases the release of the anti-inflammatory transforming growth factor-beta 1 in the Raw 264.7 cell line, a process mediated by the Y1 receptor (Zhou *et al.* 2008a). In addition, NPY is able to inhibit DC maturation and cytokine production *in vitro* (Singer *et al.* 2013). NPY acting via Y1 receptors likewise reduces cytokine release from thioglycollate-elicited peritoneal mouse

macrophages stimulated by interferon-γ and LPS (Macia *et al.* 2012b). While the involvement of Y2 receptors in this effect has been excluded, macrophages of NPY/PYY double-knockout (KO) mice exhibit higher cytokine levels than those of Y1 KO mice, suggesting that Y4 or Y5 receptors could also contribute to the anti-inflammatory effect of NPY in this context (Macia *et al.* 2012b).

Finally, NPY affects microglia function and related neuroinflammatory processes (Malva *et al.* 2012) (Table 6). Murine N9 microglia cells express Y1, Y2, and Y5 receptors and the expression of NPY and the Y1 receptor by microglial cells increases after activation with LPS (Ferreira *et al.* 2010). Furthermore, NPY acting via the Y1 receptor inhibits the release of IL-1β and subsequent NO production in LPS-stimulated microglial cells (Ferreira *et al.* 2010). Subsequent studies from the same group revealed that NPY likewise inhibits LPS- and IL-1β-induced phagocytosis of opsonized latex beads (Ferreira *et al.* 2011) and microglial motility via the Y1 receptor (Ferreira *et al.* 2012). The inhibitory effects of NPY on microglial motility have been confirmed in murine cortex explants (Ferreira *et al.* 2012).

NPY's effects on dendritic cells and lymphocytes

The effects of NPY on natural killer (NK) cells are age- and dose-dependent and differ in NK cells originating from different lymphoid organs (Dimitrijevic & Stanojevic 2013) (Table 7). Thus, NPY has been shown to suppress NK activity of human lymphocytes *in vitro* (Nair *et al.* 1993) and splenic NK activity in adult male rats *in vivo* (Saurer *et al.* 2006). However, the type of effect of NPY on NK cell activity has been shown to differ with age (De la Fuente *et al.* 2001b). Thus, NPY inhibits NK activity in spleen leukocytes of young female mice, while it stimulates NK activity in leukocytes from axillary nodes and thymus of adult and mature female mice which exhibit a decline of NK activity with age (De la Fuente *et al.* 2001b). Apart from age, dose is another factor modulating the type of effect of NPY on NK cell numbers. Thus it has been reported that intravenous administration of high-dose NPY increases the numbers of NK cells, lymphocytes and monocytes in the blood, while low-dose NPY decreases NK cell numbers and B cell counts (Bedoui *et al.* 2001). Analysis of the NPY receptors involved revealed that Y1 receptor activation decreased blood leukocyte counts, while Y5 receptor activation was associated with leukocytosis (Bedoui *et al.* 2002).

NPY is involved in T cell recruitment, proliferation (Table 8) and cytokine secretion. Thus it has been proven that NPY increases adhesion of human T cells to fibronectin via the Y2 receptor (Levite *et al.* 1998). Furthermore, NPY is able to increase spontaneous proliferation of peritoneal lymphocytes while it inhibits proliferation after stimulation with the mitogen Con A or LPS (Puerto *et al.* 2005, Dimitrijevic & Stanojevic 2013). These results suggest that the effects of NPY on lymphocyte proliferation depend on the activation state of these cells. Furthermore, NPY induces cytokine secretion from T cells (Levite 1998) and, interestingly, is able to induce the secretion of Th2 cytokines from Th1 T cell lines and the other way around (Levite 1998). In addition, several studies report that NPY shifts the immune balance towards a Th2 immune response (Kawamura *et al.* 1998, Medina *et al.* 2000a, Puerto *et al.* 2005). Pharmacological analysis attributed the Y1 receptor a role in the effect of NPY to inhibit the activation of T cells in mice (Wheway *et al.* 2005). The same

study, however, also demonstrated that Y1 receptor signalling on DCs promotes antigen-presenting capacity and T cell priming (Wheway *et al.* 2005), thus providing an explanation for the modulatory role of Y1 receptor activation in lymphocyte function.

A recent study shows that NPY induces migration of human DCs via the Y1 receptor (Buttari *et al.* 2014). Furthermore, NPY is able to promote DC adhesion and a Th2 polarizing profile of the DCs (Buttari *et al.* 2014). These findings led the authors to conclude that NPY, on the one hand, recruits DCs to the inflammatory site but, on the other hand, exerts anti-inflammatory actions by promoting Th2 polarization (Buttari *et al.* 2014). Interestingly, NPY is also able to suppress experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, by inhibiting Th1 responses via the Y1 receptor (Bedoui *et al.* 2003, Brod & Bauer 2012, Dimitrijevic *et al.* 2012).

The interaction of NPY with the immune system may also affect the skin, as exemplified by the depigmenting skin disorder vitiligo, which results from a loss of melanocytes, cells with an embryologic link to the nervous system (Kunisada *et al.* 2014). Autoimmunity and abnormal immune responses are implicated in the pathophysiology of the disease as vitiligo patients present with increased levels of IL-4 (Imran *et al.* 2012), IFN-γ (Dwivedi *et al.* 2013), IL-1β (Laddha *et al.* 2014) and other abnormalities in both humoral and cell-mediated immunity (Kemp *et al.* 2001). Importantly, vitiligo patients also present higher levels of NPY in plasma and skin tissue (Tu *et al.* 2001, Laddha *et al.* 2014). As NPY has been demonstrated to lead to increased release of IFN-γ and IL-4 from T cells (Levite 1998), an interaction between NPY and immune regulatory factors might also occur in vitiligo.

The neuropeptide Y (NPY) family in immune function within the gastrointestinal tract

The gut hormones PYY and PP and the enteric/sympathetic neuropeptide NPY serve multiple regulatory roles in digestion (Cox 2007a, Cox 2007b, Fujimiya & Inui 2000), gastrointestinal immune function (Wheway *et al.* 2007a) and gut-brain-gut communication (Holzer *et al.* 2012). In addition, it is emerging that these peptides play a role in the interaction between the gut microbiota and the gastrointestinal mucosa and immune system (Holzer & Farzi 2014). In order to understand these complex interdependencies it is appropriate to recall the chief functions which NPY-related peptides exert in the gastrointestinal tract.

PP is released from endocrine F cells of the pancreas following a meal and acts preferentially via Y4 and Y5 receptors to inhibit gastric emptying and reduce appetite through a vagus nerve-dependent action (Murphy & Bloom 2006, Field *et al.* 2010). Furthermore, PP inhibits intestinal electrolyte and water secretion (Cox 2007a) as well as intestinal motor activity and peristalsis via an action involving the enteric nervous system (Holzer *et al.* 1986, Fujimiya & Inui 2000).

The vagus nerve also plays a role in the postprandial release of PYY from enteroendocrine L cells in the lower gut (Fu-Cheng *et al.* 1997, Cox 2007b, Field *et al.* 2010). PYY and PYY_{3-36} inhibit gastrointestinal motility and secretion via an action on Y1, Y2, and Y4

receptors (Cox 2007a, Cox 2007b, Field *et al.* 2010, Wang *et al.* 2010). Through these actions, PYY slows gastric emptying and intestinal transit when fat reaches the lower gut, while the antisecretory action of PYY facilitates nutrient absorption (Van Citters & Lin 2006, Cox 2007b).

In the context of this review it is particularly worth noting that short chain fatty acids such as butyrate, which the colonic microbiota generates by fermentation of otherwise indigestible dietary fibre (Cherbut *et al.* 1998), stimulate L cells to release PYY via the G-protein coupled receptor Gpr41 (Samuel *et al.* 2008). In this way, short chain fatty acids can indirectly attenuate gastrointestinal motility as well as electrolyte and water secretion (Cox 2007b). More importantly, short chain fatty acids exert homeostatic actions on the function of the colonic mucosa and immune system (Hamer *et al.* 2008, Tazoe *et al.* 2008, Guilloteau *et al.* 2010, Macia *et al.* 2012a, Smith *et al.* 2013). Whether PYY plays a role in these effects of short chain fatty acids awaits to be investigated, but may be envisaged from the finding that PYY promotes mucosal cell differentiation (Hallden & Aponte 1997).

Apart from its effect to inhibit gastrointestinal motility as well as electrolyte and water secretion (Saria & Beubler 1985, Holzer *et al.* 1987, Holzer-Petsche *et al.* 1991, Cox 2007a), NPY is of distinct relevance to immune function in the gastrointestinal mucosa (Bedoui *et al.* 2007, Wheway *et al.* 2007a, Dimitrijevic & Stanojevic 2013, Chandrasekharan *et al.* 2013b) in which NPY-containing nerve fibres are in close contact with immune cells such as IgA-producing lymphocytes (Shibata *et al.* 2008).

Although the effect of NPY on immune function translates to an antiinflammatory action in many tissues, its effect in the gut needs to be labelled as proinflammatory. The effect of NPY to facilitate colonic inflammation is supported by several lines of evidence (Holzer *et al.* 2012). Thus, mice with a genetic deletion of NPY are to a large degree resistant to the development of dextran sulfate sodium (DSS)-induced colitis (Chandrasekharan *et al.* 2008, Painsipp *et al.* 2011). This observation is reproduced by treatment with a NPY antisense oligodeoxynucleotide (Pang *et al.* 2010) and by KO or antagonism of Y1 receptors (Hassani *et al.* 2005), which attributes Y1 receptors a key role in the proinflammatory action of NPY (Holzer *et al.* 2012). The inflammation-resistant phenotype of NPY and Y1 receptor KO mice results from a defect in antigen-presenting cell function, a reduction of TNF-α and IL-12 production by macrophages, and a decrease in the number of effector T cells (Wheway *et al.* 2005, Chandrasekharan *et al.* 2013a).

An implication of the NPY and Y1 receptor system in controlling colonic inflammation is corroborated by the observations that experimentally induced colitis is associated with an increase in the colonic expression of NPY (Chandrasekharan *et al.* 2008, Pang *et al.* 2010, Baticic *et al.* 2011), a downregulation of colonic Y1 receptors and a defective antisecretory effect of NPY (Klompus *et al.* 2010). The expression of NPY in sympathetic neurons of the mesenteric ganglia is also elevated in pigs with chemically induced ileitis (Pidsudko *et al.* 2011). In contrast, the epithelial levels of NPY and PYY are decreased in rats with DSS-induced colitis (Hirotani *et al.* 2008) and in mice with genetic deletion of carboxypeptidase E, an enzyme involved in the biosynthesis of many neuropeptides including NPY, in which DSS-induced colitis is exacerbated (Bär *et al.* 2014). These experimental data are in keeping

with a decrease of colonic PYY levels in patients with inflammatory bowel disease (Tari *et al.* 1988, El-Salhy *et al.* 1997, Schmidt *et al.* 2005), whereas circulating levels of PYY and NPY are enhanced (Adrian *et al.* 1986, Straub *et al.* 2002). These observations suggest that the epithelial levels of NPY and PYY are exhausted by excessive release of the peptides from enteroendocrine cells and intestinal neurons, although the expression of the peptides in these cells is enhanced.

From these observations it is evident that intestinal inflammation goes along with a remodelling of the NPY system, which has an effect on mucosal permeability, immune cell function, intestinal motor activity and intestinal blood flow (Hirsch & Zukowska 2012, Chandrasekharan *et al.* 2013b). The impact of NPY on gut inflammation involves a heterogeneity of cellular and molecular mechanisms (Holzer *et al.* 2012) which include activation of antigen-presenting cells, altered regulation of T cell function, TNF-α, nuclear factor κ-light-chain-enhancer of activated B-cells (NF-κB) and oxidative stress (Wheway *et al.* 2005, Wheway *et al.* 2007a, Wheway *et al.* 2007b, Dimitrijevic & Stanojevic 2013, Chandrasekharan *et al.* 2013a, Chandrasekharan *et al.* 2013b). There is a close interaction between NPY and TNF-α as, on the one hand, the TNF-α system appears to be downregulated in NPY KO mice while, on the other hand, blockade of TNF-α reduces colonic NPY expression and experimental colitis (Chandrasekharan *et al.* 2013a). In addition, NPY enhances the expression of neuronal NO synthase which is a component of oxidative stress and subsequent inflammation (Chandrasekharan *et al.* 2008). The proinflammatory effect of NPY is likely to be counterregulated by the vasoconstrictor effect of the peptide (Holzer *et al.* 2012), since the sympathetic constriction of splanchnic resistance vessels is co-mediated by the sympathetic triad adenosine triphosphate (ATP), noradrenaline and NPY (Holzer *et al.* 2012). In addition, NPY is able to augment the constrictor effect of noradrenaline and ATP, this effect as well as the vasoconstrictor response to NPY being mediated by postjunctional Y1 receptors (Holzer *et al.* 2012).

The gut microbiota may be another cellular system that is relevant to the proinflammatory action of NPY in the digestive tract. On the one hand, the NPY/PYY system seems to have an impact on the composition and function of the gut microbiota as NPY has been found to exhibit a direct antimicrobial effect against various gut bacteria including *Escherichia coli, Enterococcus faecalis*, and *Lactobacillus acidophilus* (El Karim *et al.* 2008, Augustyniak *et al.* 2012). On the other hand, there is evidence that the gut microbiota has an influence on the NPY/PYY system. Through the generation of short chain fatty acids, the gut microbiota can directly interact with enteroendocrine cells that release PYY, besides glucagon-like peptide-1 (Cani *et al.* 2009, Cani & Delzenne 2011, Delzenne *et al.* 2011). Colonization of the mouse colon with a fermentative human microbial community increases the plasma level of PYY, an effect that is blunted by knockout of the short chain fatty acid receptor Gpr41. Gpr41 deficiency is associated with a reduced expression of PYY, an increase in intestinal transit rate and an attenuation of energy harvest (Samuel *et al.* 2008). Microbiota-fermented short chain fatty acids acting via Gpr41 on PYY-expressing L cells could thus be an important link in microbial-host communication and immune signalling (Holzer & Farzi 2014). The microbiota-NPY link may also have a bearing at other relays of the gut-brain

axis, given that the expression of NPY in the hypothalamus of germ-free mice is higher than in conventionally raised animals (Schele *et al.* 2013).

NPY's involvement in obesity-associated inflammation and inflammation-induced metabolic disturbances

An excess of nutrients leading to obesity initiates a state of low-grade inflammation which contributes to metabolic dysfunctions such as insulin resistance (Gregor & Hotamisligil 2011). In this context it is noteworthy that NPY is regarded as one of the most potent orexigenic neuropeptides, the hypothalamus and its nuclei such as the arcuate nucleus being the crucial centres in which these effects are brought about (Zhang *et al.* 2014). Emerging evidence indicates that Y1 receptors on cells of the hematopoietic compartment mediate a protective effect against obesity-associated inflammation, given that deletion of the Y1 receptor promotes inflammation in adipose tissue and development of insulin resistance in response to a high-fat diet (Macia *et al.* 2012b). Y1 receptor deletion also leads to an increase of the proinflammatory cytokine monocyte chemotactic protein 1 (Macia *et al.* 2012b). A further study confirms the anti-inflammatory role of NPY by showing that, in lean mice, exogenous NPY decreases adipose tissue macrophage numbers and suppresses monocytes and, in obese mice fed a high-fat diet, NPY from hematopoietic cells decreases adipose tissue macrophages (Singer *et al.* 2013). In contrast, the Y2 receptor has been implicated in the exaggeration of diet-induced obesity by stress, which also results in macrophage infiltration (Kuo *et al.* 2007).

Both NPY and PYY play important roles in metabolism and energy homeostasis (Herzog 2003). NPY promotes energy storage by promoting adipogenesis and inhibiting lipolysis (Kuo *et al.* 2007), and its expression is increased in the adipose tissue of obese mice and other species (Zhang *et al.* 2014). However, lipolysis caused by β-adrenoceptor stimulation is rather augmented by NPY, pointing to another context-dependent modulatory role of NPY (Li *et al.* 2012). The differential effects of NPY on lipolysis may be mediated by different second messenger systems coupled to the Y1 receptor (Li *et al.* 2012).

Furthermore, PYY is able to regulate function and survival of islet cells of the pancreas, which also express NPY receptors (Upchurch *et al.* 1994, Sam *et al.* 2012, Persaud & Bewick 2014). Exogenous PYY inhibits glucose-induced insulin secretion (Böttcher *et al.* 1993) whereas PYY KO mice display hyperinsulinaemia (Boey *et al.* 2006). In contrast, PYY_{3-36} is able to improve glucose tolerance by indirect stimulation of insulin release (Chandarana *et al.* 2013). In addition, PYY exerts anti-inflammatory actions in the pancreas and inhibits several transcription factors such as NF-κB (Vona-Davis & McFadden 2007). Recent studies revealed complex interactions between NPY and PYY in regulating various aspects of energy balance and glucose homeostasis by using NPY/PYY single- and double-KO mice as well as Y2 and Y4 receptor KO mice (Zhang *et al.* 2012). Thus, NPY/PYY double-KO mice and Y2 receptor KO mice display a reduction in spontaneous food intake (Edelsbrunner *et al.* 2009a, Edelsbrunner *et al.* 2009b), and both PYY KO and NPY/PYY KO mice show impaired hypoglycaemic responses to insulin, suggesting that the impairment of insulin action by PYY deficiency cannot be corrected by NPY deletion (Zhang *et al.* 2012). In line with these complex interactions of NPY and PYY, deletion of either peptide

(NPY or PYY) or both peptides (NPY plus PYY) aggravates and prolongs the weight loss induced by immune challenge with Bacille Calmette-Guérin (BCG) (Painsipp *et al.* 2013). Importantly, the weight loss observed in the KO mice outlasted the BCG-induced decrease in food intake. Thus, alterations of food intake cannot explain the aggravated weight loss in the KO mice. Also, circulating IL-6 levels did not significantly differ between groups. These results therefore indicate that in addition to their basal effects on food intake and energy homeostasis, NPY and PYY play an important physiological role in maintaining energy homeostasis in response to infection and immune challenge (Painsipp *et al.* 2013).

Effects of NPY on brain function and behaviour

There is abundant evidence that NPY has antiepileptic effects and triggers neuroprotective pathways (Malva *et al.* 2012) (Fig. 3). In addition, NPY exerts mitogenic actions, inducing neuroproliferation and neurogenesis, an effect taking place in an Y1 receptor- and PKC-dependent manner (Hansel *et al.* 2001, Decressac *et al.* 2011). Furthermore, NPY is able to prevent neuronal apoptosis (Thiriet *et al.* 2005). Interestingly, NPY has also been reported to exert protective actions during murine retrovirus-induced neurological disease (Du *et al.* 2010). Specifically, NPY KO mice presented an earlier onset of histological changes together with higher virus levels in brain tissue, while the neuroinflammatory response and neuronal apoptosis were not markedly different compared to wild-type (WT) mice (Du *et al.* 2010). Further, NPY contributes to the control of anxiety, depression and cognition. Thus, NPY and its receptors are widely expressed in cerebral areas regulating anxiety, mood, cognition and stress resilience, such as the cortex, hippocampus, and amygdala (Heilig 2004, Morales-Medina *et al.* 2010, Holzer *et al.* 2012). In rodents, central administration of NPY reduces anxiety and depression-like behaviour (Sajdyk *et al.* 1999b, Stogner & Holmes 2000). In line with these pharmacological studies, central over-expression of NPY reduces anxiety-like behaviour (Thorsell *et al.* 2000), while NPY KO mice display an anxious and depressive-like phenotype (Bannon *et al.* 2000, Painsipp *et al.* 2011). In PYY KO mice a depression-like phenotype has been observed (Painsipp *et al.* 2011).

Although not entirely consistent, the majority of clinical studies demonstrate decreased levels of NPY in plasma or CSF of patients suffering from major depression, and increased NPY levels following antidepressant treatment (Morales-Medina *et al.* 2010). In addition, there is evidence that a polymorphism in the NPY gene leading to a low NPY expression genotype is associated with decreased stress resilience, a risk factor for major depression, and reduced responsiveness to antidepressant treatment (Zhou *et al.* 2008b, Domschke *et al.* 2010, Mickey *et al.* 2011). Likewise, there is evidence for altered NPY signalling in schizophrenia (Stadlbauer *et al.* 2013).

The effect of NPY on mood is determined by an interaction with multiple Y receptors in the brain. Although genetic studies revealed partially controversial data, most results indicate that the Y1 receptor mediates an anxiolytic effect (Morales-Medina *et al.* 2010). In contrast, the Y2 receptor is involved in increasing anxiety- and depression-like behaviours (Tschenett *et al.* 2003, Painsipp *et al.* 2008a, Tasan *et al.* 2010), which can be related to its presynaptic localization and function as an inhibitory autoreceptor reducing NPY release (Caberlotto *et al.* 2000).

Despite the limited distribution of the Y4 receptor in the brain, KO of this receptor is associated with reduced anxiety- and depression-related behaviours (Painsipp *et al.* 2008b, Tasan *et al.* 2009). In contrast, the involvement of the Y5 receptor in mood and stress resilience is rather inconclusive as judged from the available findings (Kormos & Gaszner 2013).

NPY has also been proposed to affect memory processing in rodents. Thus, central administration of NPY leads to an improvement of memory in rodent amnesia models induced by either anisomycin or scopolamine (Flood *et al.* 1987). While NPY KO mice do not show any gross abnormalities in learning tests (Bannon *et al.* 2000), Y2 deficient mice have been reported to display cognitive deficits (Redrobe *et al.* 2004b, Greco & Carli 2006, Painsipp *et al.* 2008b). Interestingly, a recent study provided evidence for altered Y2 receptor signalling in symptoms associated with schizophrenia, as administration of $PYY_{3\text{-}36}$ to male mice induces behavioural abnormalities relevant to schizophrenia (Stadlbauer *et al.* 2013).

Involvement of NPY in behavioural disturbances caused by peripheral immune challenge

Immune challenge has been demonstrated to disturb homeostasis of many physiological systems and to contribute to the development of mood disorders such as major depression (Dantzer *et al.* 2008, Haroon *et al.* 2012) and other disturbances of brain function (Figs. 2 + 3). Cytokine-induced depression can be modelled in rodents by administration of proinflammatory cytokines or bacterial components such as LPS (Dantzer *et al.* 2008, Farzi *et al.* 2014). In this context, proinflammatory cytokines cause acute sickness behaviour by exciting afferent neurons (e.g. in the vagus nerve) and by inducing the expression of cytokines within the brain (Dantzer *et al.* 2008). The acute sickness response (sedation, social withdrawal, anorexia) is followed by signs of depression-like behaviour which has been demonstrated to be mediated by activation of the enzyme indoleamine-2,3-dioxygenase by proinflammatory cytokines, leading to the production of kynurenine (O'Connor *et al.* 2009). Interestingly, peripheral immune challenge has an impact on several brain nuclei that express NPY and various Y receptors, and there is evidence that the NPY system protects against various disturbances caused by immune activation (Holzer *et al.* 2012) (Figs. 2 and 3).

Specifically, NPY increases the survival of rats from septic shock induced by high doses of LPS (Hauser *et al.* 1993). This beneficial effect might to some extent be explained by NPY's counterbalancing effects on the cardiovascular system. Thus, in contrast to other vasoconstrictors, the pressor response to NPY is not reduced by LPS and NPY is able to attenuate LPS induced-hypotension (Hauser *et al.* 1993, Felies *et al.* 2004, Kuncova *et al.* 2011). Furthermore, NPY is able to partially reverse the suppressed responsiveness to other vasoconstrictors in response to LPS (Hauser *et al.* 1995). A further mechanism whereby NPY attenuates effects of immune challenge is its ability to stabilize body temperature in endotoxaemic rats (Felies *et al.* 2004).

Pain is another hallmark of inflammation and NPY's antinociceptive effects also extend to the inhibition of inflammatory pain (Taylor *et al.* 2014). Specifically, NPY is up regulated in the spinal cord during inflammation and exerts anti-hyperalgesic actions via the Y1 receptor by inhibiting the release of substance P (Taylor *et al.* 2014).

Finally, the beneficial effects of NPY against disturbances caused by immune activation might be mediated directly by its effects on the immune system (Nave *et al.* 2004). Thus, NPY is able to attenuate LPS-induced leukopenia and to stabilize granulocyte and T-lymphocyte numbers (Nave *et al.* 2004). Furthermore, NPY increases adhesion of monocytes to the endothelium via Y2 receptor stimulation (Nave *et al.* 2004) (Fig. 2). The beneficial effect of Y2 receptor activation in response to LPS is further related to an attenuation of TNF-α levels (Stadler *et al.* 2011).

In view of the involvement of NPY in the control of appetite and food intake it is not totally unexpected that NPY is able to attenuate cytokine-induced anorexia (Fig. 3), one aspect of the sickness response to immune activation. NPY concentrations have been reported to be increased, decreased or unchanged in hypothalamic nuclei in response to immune stimulation (McCarthy *et al.* 1995, Gayle *et al.* 1997, Gayle *et al.* 1998, Ilyin *et al.* 1998, Gayle *et al.* 1999, Kim *et al.* 2007, Carlson *et al.* 2009, Iwasa *et al.* 2010). Central administration of NPY has repeatedly been reported to block or reverse anorexia induced by immune activation (Sonti *et al.* 1996, McMahon *et al.* 1999, Kim *et al.* 2007).

NPY has also been implicated in other manifestations of the sickness response to immune activation such as immobility/sedation and impaired mood (Fig. 3). Y2 and Y4 receptor KO mice are particularly susceptible to the acute action of LPS to attenuate locomotion (Painsipp *et al.* 2008a, Painsipp *et al.* 2010). Intriguingly, decreased locomotion in Y4 KO mice is still evident 4 weeks after treatment with LPS (Painsipp *et al.* 2010). In addition, Y2 and Y4 KO mice display depression-like behaviour 4 weeks after administration of LPS, while such an effect is absent in WT mice (Painsipp *et al.* 2010). From these results it has been concluded that NPY acting via Y2 and Y4 receptors attenuates the development of long-term sickness- and depression-like behaviour induced by immune challenge (Painsipp *et al.* 2010).

Immune activation and neuroinflammation can also lead to cognitive impairment and there is evidence for the involvement of immune activation in neurodegenerative diseases such as Alzheimer's disease (Czerniawski & Guzowski 2014, Lueg *et al.* 2014). While reports regarding the effects of NPY on cognitive impairment induced by peripheral immune activation are lacking, there is evidence for beneficial effects of NPY in the pathophysiology of Alzheimer's disease (Malva *et al.* 2012).

Calorie restriction has been demonstrated to suppress LPS-induced cytokine release, microglial activation, fever, and sickness behaviour (MacDonald *et al.* 2014). In addition, calorie restriction is able to upregulate the expression of NPY in the arcuate nucleus (McShane *et al.* 1999). Therefore, a recent study examined the relationship between calorie restriction, LPS-stimulated microglial activation and NPY (Radler *et al.* 2014). A strong correlation was demonstrated between NPY and body temperature on the one side, and body

temperature and microglial morphology, on the other side (Radler *et al.* 2014). In contrast, the authors did not find an association between NPY and microglial morphology. These results led the authors to conclude that NPY may indirectly attenuate LPS-induced microglial activation through its effects on body temperature (Radler *et al.* 2014).

As NPY protects from behavioural sequelae of stress, exerts neuroprotective actions and counteracts disturbances caused by immune activation via several mechanisms, it is very likely that its effects on brain function converge with its effects on the immune system in order to have a beneficial influence on mood and behaviour. However, further systematic studies are required to untangle to which extent the immunomodulating and stress-buffering actions of the NPY family contribute to the attenuation of behavioural disturbances caused by peripheral immune challenge.

NPY, stress and stress resilience

A large body of evidence has identified NPY as a crucial factor counteracting stress-induced disturbances of homeostasis (Heilig 2004). During stress exposure, NPY strongly interacts with corticotrophin-releasing hormone (CRH), a principal regulator of the hypothalamic-pituitary-adrenal (HPA) axis (Heilig *et al.* 1994, Sajdyk *et al.* 2004). A fibre tract between the hypothalamic arcuate nucleus, a major source of NPY, and the hypothalamic paraventricular nucleus (PVN), a major source of CRH, allows a crosstalk between these two neuropeptide systems (Broberger *et al.* 1999). In face of a stressful challenge, parvocellular neurons of the PVN respond rapidly with the transcription of CRH (Imaki *et al.* 1996). CRH promotes the production of adrenocorticotropic hormone, which in turn regulates adrenal glucocorticoid release.

Like CRH, NPY is also regulated by stress exposure. Depending on type and duration of stress as well as brain region examined, stress modifies the expression of NPY to counteract the biological actions of CRH (Thorsell *et al.* 1998, Thorsell *et al.* 1999, de Lange *et al.* 2008, McGuire *et al.* 2011). Moreover, NPY alters the stress response in a gender-dependent manner, given that HPA axis reactivity to stress differs between male and female mice in a NPY-related fashion (Forbes *et al.* 2012). Thus, stress-induced corticosterone levels are higher in male NPY KO mice than in male WT mice, an effect absent in female mice. Furthermore, stress-induced reduction of food intake is observed in female NPY KO, but not in male NPY KO mice (Forbes *et al.* 2012).

An important interaction between NPY and CRH with special relevance for emotional regulation takes place in the basolateral amygdala, which expresses receptors for both neuropeptides (Van Pett *et al.* 2000, Kask *et al.* 2002). Intraamygdalar CRH application induces anxiety, while NPY is anxiolytic (Sajdyk *et al.* 1999b, Sajdyk *et al.* 1999a). A direct interaction is suggested by the finding that intraamygdalar pretreatment with NPY blocks the anxiogenic action of CRH receptor stimulation (Sajdyk *et al.* 2006) (Fig. 3).

The behavioural effects of NPY and its ability to revert the effects of CRH raise the question whether NPY has a role in stress resilience, i.e. the ability to cope with stress. Indeed, hippocampal NPY overexpression protects from the anxiety-producing effects of stress (Thorsell *et al.* 2000), and repeated administration of NPY into the basolateral amygdala

generates resilient mice that are protected from the negative consequences of stress (Sajdyk *et al.* 2008). A study by Cohen et al. (Cohen *et al.* 2012) describes a correlation between behavioural disruption of animals after predator scent stress and brain NPY levels. Animals whose behaviour is extremely disrupted by stress have the lowest brain NPY levels.

Furthermore, treatment of animals with NPY shortly after stress exposure significantly reduces the prevalence of behavioural maladaptation (Cohen *et al.* 2012). In line with these observations, recent evidence suggests a therapeutic potential of intranasal NPY to reverse stress-induced neuropsychiatric disorders. Intranasal NPY infusion, which avoids potential peripheral side effects, attenuates stress-induced anxiety and depression-like behaviour when applied before or 1 week after prolonged stress exposure (Serova *et al.* 2013, Serova *et al.* 2014). The anti-stress and anxiolytic properties of NPY are very likely related to the peptide's action within the amygdala (Fig. 3): NPY acting on Y1 receptors reduces excitability of amygdalar neurons by decreasing NMDA-mediated excitatory currents and increasing GABA-mediated inhibitory currents via 2 divergent signal-transduction pathways (Molosh *et al.* 2013).

NPY is further considered a resilience factor as individuals with a low NPY-expressing haplotype show disturbed emotionality and diminished stress resilience (Zhou *et al.* 2008b, Mickey *et al.* 2011). Accumulating evidence also suggests that NPY is a protective factor preventing post-traumatic stress disorder (PTSD) development (Sah & Geracioti 2013). Thus, veterans suffering from PTSD have lower plasma and cerebrospinal NPY levels than healthy control subjects (Rasmusson *et al.* 2000, Sah *et al.* 2009). Moreover, combat veterans without PTSD have higher cerebrospinal NPY levels than combat veterans with PTSD (Sah *et al.* 2014). However, other reports suggest that the exposure to trauma, but not the associated PTSD, is responsible for the decrease in NPY levels (Morgan *et al.* 2003, Yehuda *et al.* 2006). A recent study of the relationship between NPY and PTSD after severe motor vehicle accidents found no difference in NPY levels between the study groups (Nishi *et al.* 2014). It appears that accident-related PTSD has different biological features than combat-related PTSD.

Involvement of NPY in the interaction of stress with the immune system

Stress, mood disorders and the immune system are in an intricate relationship. Thus, psychosocial stress has been reported to activate inflammatory responses via the sympathetic nervous system (Haroon *et al.* 2012). Activation of the HPA axis in response to stress and the subsequent release of glucocorticoids exert, on the one side, immunosuppressive effects but under certain conditions can also stimulate the immune system, in particular within the brain (Bellavance & Rivest 2014). For instance, NK cell activity is decreased in depressed patients, while the plasma levels of NPY are increased, attesting to an inverse correlation between the two factors (Irwin *et al.* 1991). On the other hand, patients with major depression present an exaggerated immune response in stressful situations (Pace *et al.* 2006), and psychological stress and depression are often associated with an aggravation of intestinal inflammation (Mittermaier *et al.* 2004, Ghia *et al.* 2009). Vice versa, an experimental study has shown that iodoacetamide-evoked gastritis induces an increase of anxiety in female mice (Painsipp *et al.* 2007), while DSS-induced colitis induces anxiety-

and depression-related behaviour in a gender-dependent manner (Painsipp *et al.* 2011). The effects of colitis on behaviour seem to be modified by KO of NPY or PYY (Painsipp *et al.* 2011). Thus, genetic depletion of PYY prevents the anxiogenic effects of colitis in male mice, while in female mice NPY or PYY KO blocks depression-like behaviour induced by colitis (Painsipp *et al.* 2011). NPY and PYY thus seem to have distinct effects on the impact of intestinal inflammation on mood and behaviour.

While stress is generally believed to be harmful, certain types and intensities of stress such as predictable chronic mild stress can exert beneficial effects on behaviour (Parihar *et al.* 2011). In line with this contention, a repeated chronic stressor (water avoidance stress) has been demonstrated to attenuate colitis-induced behavioural disturbances in male mice (Hassan *et al.* 2014). Intriguingly, the behavioural resilience was however associated with an increase of hypothalamic NPY and a rise of circulating corticosterone, which points to a possible involvement of hypothalamic NPY in the protective effect of repeated stress against colitis-induced behavioural disturbances (Hassan *et al.* 2014). In contrast, colitis severity, levels of circulating IL-6 and IL-18, and cerebral cyclooxygenase-2 mRNA expression were not modulated by the combination of WAS and DSS. Further studies are warranted to investigate whether hypothalamic NPY induces resilience by affecting immune-related parameters not yet investigated or by interacting with the HPA axis, which also acts on the immune system.

Conclusion

The NPY family of peptides and its receptors exert diverse effects in the context of neuroimmune interactions. The effects of NPY on immune cells are complex and comprise modulation of leukocyte trafficking, regulation of macrophage function, modulation of DCs and T cell priming as well as attenuation of neuroinflammation. It is also emerging that members of the NPY peptide family impact the microbiota gut-brain axis and exhibit pro-inflammatory activities in the intestine.

Within the brain, the effects of NPY can in general be considered as protective and homeostatic as NPY can counteract the detrimental influence of immune challenge on mood, emotional processing, cognition, pain sensitivity and ingestion (Fig. 3). As psychological stress can also activate the immune system, its adverse impact on brain function resembles that of immune challenge in several aspects. NPY is likewise able to buffer many detrimental effects of psychological stress. Another disease associated with an inflammatory state is obesity in which NPY has also been shown to have a modulatory influence. Finally, the NPY system plays a major role in metabolism and has been demonstrated to maintain energy homeostasis in response to infection and immune challenge.

Since NPY is not only expressed in immune cells and cerebral neurons but also in primary afferent as well as sympathetic neurons, it would seem that this peptide participates in the reciprocal interaction between the brain and immune system.

Taken all findings together, NPY emerges to play a unique homeostatic role in immune-brain interaction, which leads us to hypothesize that, on the one hand, aberrant expression

and /or function of NPY and its receptors may be a pathophysiological factor in inflammation- and stress-associated disorders and, on the other hand, Y receptors may be relevant pharmacological targets in these disorders.

The discovery of the pleiotropic effects of NPY in these systems calls for an in-depth investigation of its physiological and pathological implications in neuroimmune communication. While this review highlights some of the pathological disturbances of the NPY system, there is a need for systematic studies – both experimental and clinical – to define the Y receptors that could be targeted by selective ligands to prevent and treat a multitude of the adverse effects which immune challenge and stress have on the brain.

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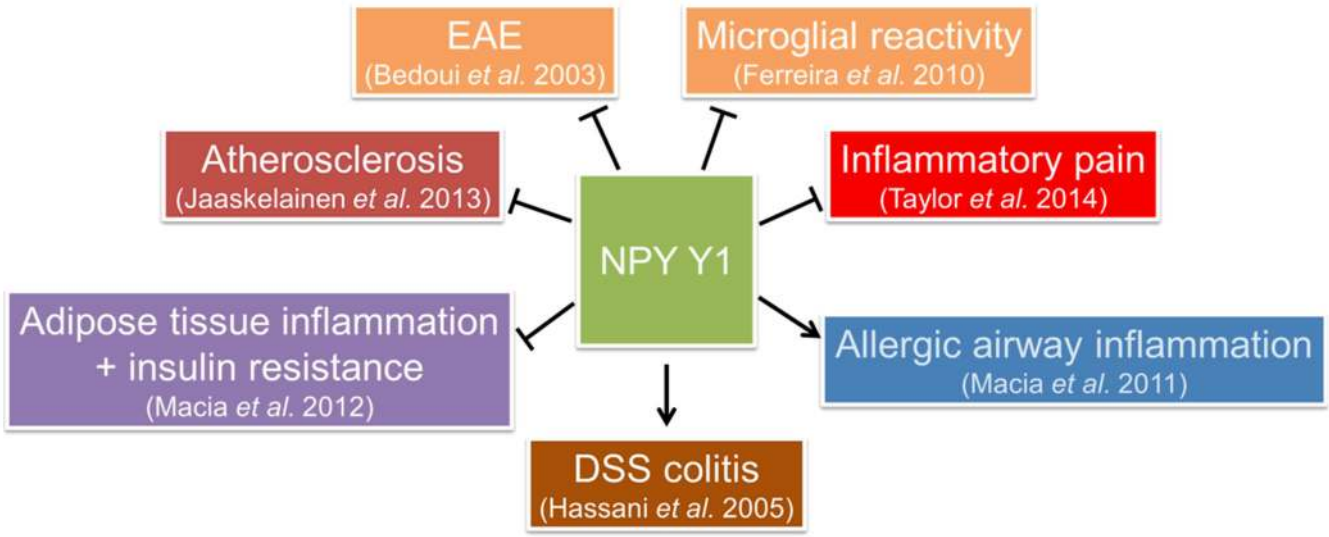

Figure 1. Involvement of the Y1 receptor in inflammation-associated disorders

The arrow symbols denote stimulation, the tack symbols denote inhibition. Abbreviations: DSS, dextran sulfate sodium; EAE, experimental autoimmune encephalomyelitis.

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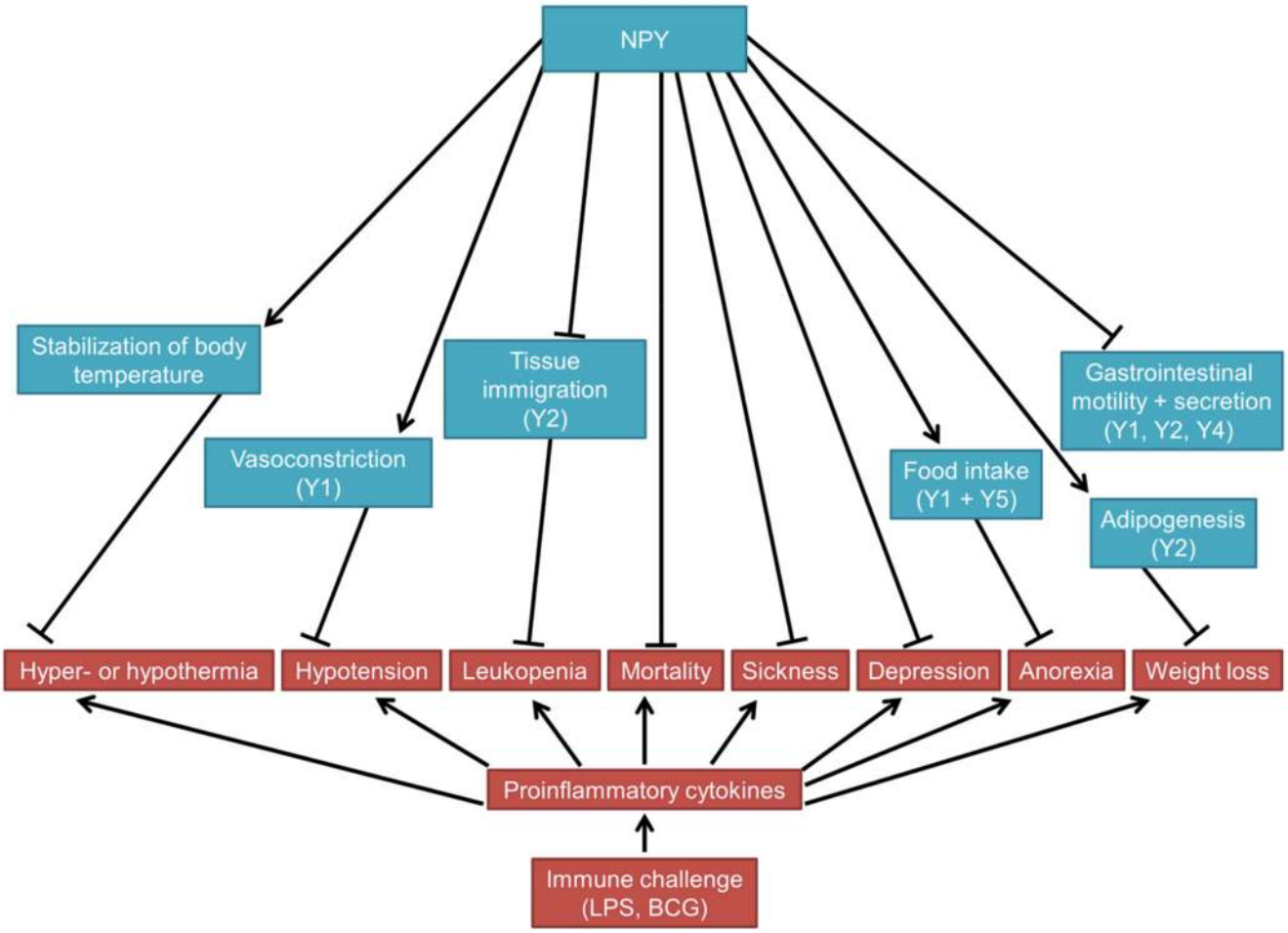

Figure 2. Homeostatic roles of NPY in disturbances of physiological systems caused by peripheral immune challenge

Major receptors involved are bracketed. The arrow symbols denote stimulation, the tack symbols denote inhibition.

Abbreviations: BCG, Bacille Calmette-Guérin; LPS, lipopolysaccharide.

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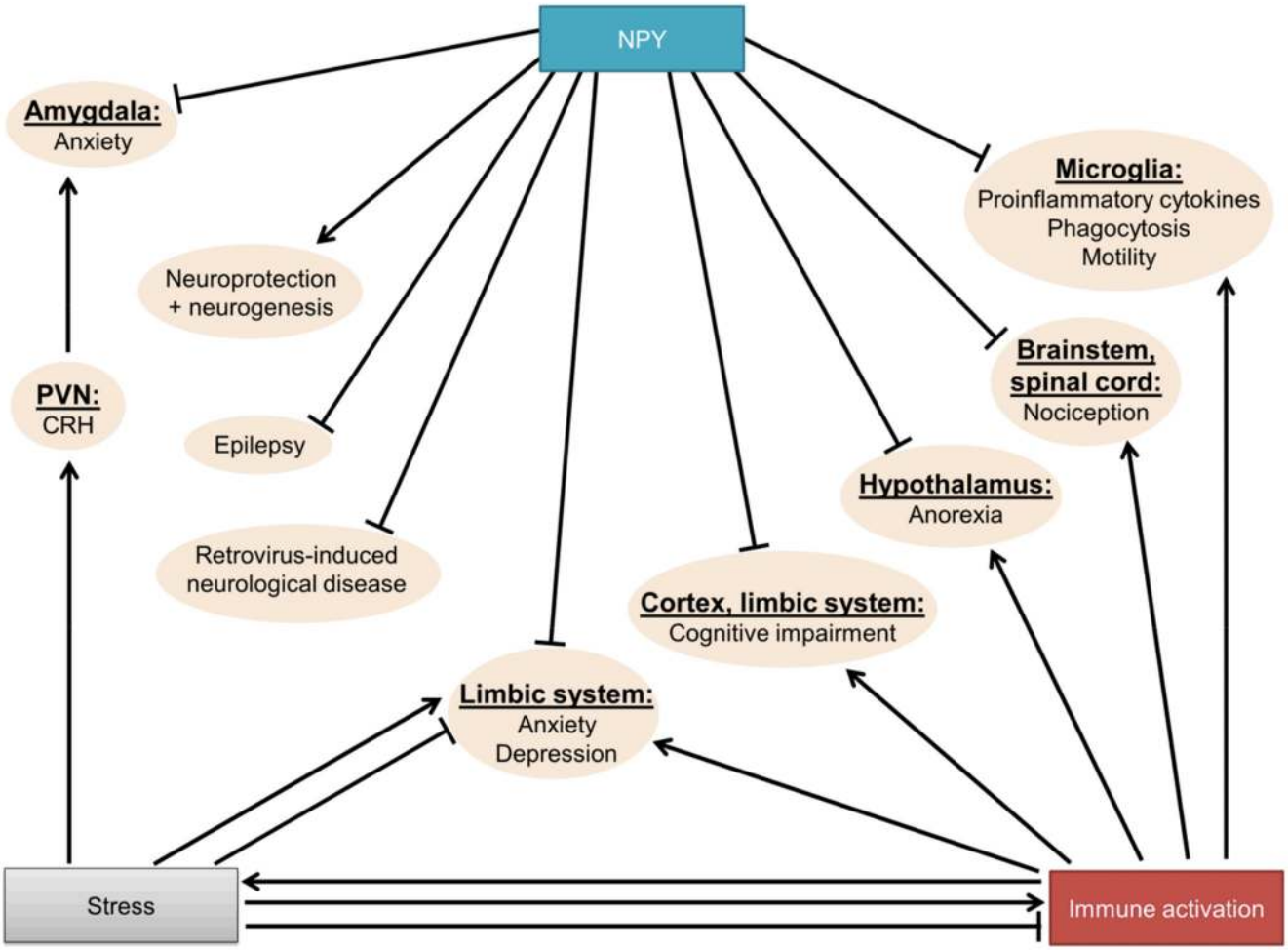

Figure 3. Homeostatic roles of NPY in the central nervous system

The arrow symbols denote stimulation, the tack symbols denote inhibition.

Abbreviations: PVN, paraventricular nucleus of the hypothalamus.

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Table 1

Effects of NPY on adion of immune cells

Cells	Sp	Specification	Rec	Effect	Age	Signal	Ref
Monocytes	H	U937 cell line		↑			(Sung *et al*. 1991)
Macrophages	**M**	Peritoneal resident cells (macrophages +lymphocytes)		↑		PKC	(De la Fuente *et al.* 1993, De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a)
Macrophages	R	Peritoneal, thioglycollate-elicited	Y2	↑ LPS-stimulated			(Nave *et al.* 2004)
Macrophages	R	Peritoneal, thioglycollate-elicited	Y1	↓ by PYY	adult		(Stanojevic *et al.* 2006)
Monocytes + Granulocytes	R	Blood	Y1	↑ LPS-stimulated			(Mitic *et al.* 2011)
Granulocytes	R	Air pouch, carrageenan-elicited	Y1	↑	adult		(Dimitrijevic *et al*. 2010)
Monocytes + Granulocytes	R	Air pouch, LPS-elicited	Y2+Y5	↓			(Mitic *et al.* 2011)
Neutrophils	H	Blood		↑			(Sung *et al*. 1991)
DCs	H	Blood		↑			(Buttari *et al.* 2014)
T cells	H	Blood	Y2	↑		PI3K / PKC	(Levite *et al*. 1998)
Leukocytes	**M**	Peritoneal, spleen, thymus, axillary node		↑ spleen, axillary node, thymus ↓ young: peritoneal; ↓ adult: thymus	young		(Medina *et al*. 2000b)

Abbreviations: H, human; LPS, lipopolysaccharide; M, mouse; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PYY, peptide YY; R, rat; Rec, receptor; Sp, species.

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Table 2

Effects of NPY on cti of immune cells

Cells	Sp	Specification	Rec	Effect / Chemoattractant	Age	Signal	Ref
Monocytes	H	Blood		↑ fetal calf serum			(Straub *et al.* 2000a)
Macrophages	**M**	Peritoneal resident cells (macrophages +lymphocytes)		↑ f-MLP	adult	PKC	(De la Fuente *et al.* 1993, De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a)
Macrophages	**M**	Peritoneal resident cells (macrophages +lymphocytes)		↓ f-MLP	old		(De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a)
Monocytes / Macrophages	**M**	RAW 264.7 cell line		↓ Leishmania major			(Ahmed *et al.* 1998)
Macrophages + Granulocytes	H			↓ f-MLP			(Dureus *et al.* 1993)
Monocytes + Granulocytes	R	Air pouch, LPS-elicited	Y1 + Y2	↓ migration to air pouch			(Mitic *et al.* 2011)
Granulocytes	R	Air pouch, carrageenan-elicited		↓ migration to air pouch			(Dimitrijevic *et al.* 2006, Dimitrijevic *et al.* 2010)
DCs	H	Blood	Y1	↑		ERK/MAPK	(Buttari *et al.* 2014)
Lymphocytes	**M**	Peritoneal resident cells (macrophages +lymphocytes) / axillary node leukocytes		↑ f-MLP	adult		(Medina *et al.* 1998b)
Lymphocytes	**M**	Thymus		↓ f-MLP			(Medina *et al.* 1998b)
Leukocytes	**M**	Peritoneal, spleen, thymus, axillary node		↑ axillary node, peritoneal, f-MLP			(Medina *et al.* 2000b)
Leukocytes	**M**	Peritoneal, spleen, thymus, axillary node		↓ thymus, f-MLP			(Medina *et al.* 2000b)

Abbreviations: DCs, dendritic cells; ERK, extracellular signal regulated kinases; f-MLP, N-formyl-methionyl-leucyl-phenylalanine; H, human; LPS, lipopolysaccharide; M, mouse; MAPK, mitogen-activated protein kinases; PKC, protein kinase C; R, rat; Rec, receptor; Sp, species.

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Table 3

Effects of NPY on phagocytosis of immune cells

Cells	Sp	Specification	Rec	Effect / Activating agent	Age	Signal	Ref
Macrophages	**M**	Peritoneal resident cells (macrophages +lymphocytes)		↑ latex beads, Candida albicans	adult	PKC	(De la Fuente *et al.* 1993, De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a)
Macrophages	**M**	Peritoneal resident cells (macrophages +lymphocytes)		↓ latex beads	old		(De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a)
Macrophages	**M**	Purified peritoneal		↓ latex beads	adult		(De la Fuente *et al.* 2001a)
Macrophages	**M**	Purified peritoneal		↑ latex beads	old		(De la Fuente *et al.* 2001a)
Monocytes / Macrophages	**M**	RAW 264.7 cell line		↓ Leishmania major			(Ahmed *et al.* 2001)
Monocytes / Macrophages	**M**	RAW 264.7 cell line		↓ unopsonized E. coli + Staph. aureus			(Phan & Taylor 2013)
Monocytes / Macrophages	**M**	RAW 264.7 cell line		↓ phagolysosome activation			(Phan & Taylor 2013)
Monocytes + Granulocytes	R	Blood	Y1	↑ zymosan			(Mitic *et al.* 2011)
Monocytes + Granulocytes	R	Air pouch, LPS-elicited	Y1+Y2	↓ zymosan			(Mitic *et al.* 2011)
Granulocytes	R	Air pouch, carrageenan-elicited	Y1	↓ zymosan	adult		(Dimitrijevic *et al.* 2006, Dimitrijevic *et al.* 2010)
Neutrophils	H	Blood		↑ E. coli (low dose)			(Bedoui *et al.* 2008)
Neutrophils	H	Blood	Y1+Y2	↓ E. coli (high dose)			(Bedoui *et al.* 2008)

Abbreviations: H, human; LPS, lipopolysaccharide; M, mouse; PKC, protein kinase C; R, rat; Rec, receptor; Sp, species.

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Table 4

Effects of NPY on ROS and NO production of immune cells

Cells	Sp	Specification	Rec	Effect	Age	Signal	Ref
Macrophages	M	Peritoneal resident cells (macrophages + lymphocytes)		↑ ROS (NBT reduction)	adult	PKC	(De la Fuente *et al.* 1993, De la Fuente *et al.* 2000, De la Fuente *et al.* 2001a)
Macrophages	R	Peritoneal, thioglycollate-elicited	Y1+Y2	↑ ROS (PMA-stimulated)		PKC	(Dimitrijevic *et al.* 2005)
Macrophages	R	Peritoneal, thioglycollate-elicited	Y2	↓ ROS (zymosan-stimulated)			(Dimitrijevic *et al.* 2005)
Macrophages	R	Peritoneal, thioglycollate-elicited	Y5	↓ ROS (PMA + zymosan-stimulated)			(Dimitrijevic *et al.* 2005)
Macrophages	R	Peritoneal resident cells		↓ ROS by PYY (zymosan-stimulated)	adult		(Stanojevic *et al.* 2006)
Monocytes / Macrophages	M	RAW 264.7 cell line		↓ ROS (FcR-associated)			(Phan & Taylor 2013)
Granulocytes	R	Air pouch, carrageenan-elicited	Y2+Y5	↓ ROS (PMA-stimulated)			(Dimitrijevic *et al.* 2006)
Neutrophils	H	Blood	Y5	↑ ROS (f-MLP-induced)			(Bedoui *et al.* 2008)
Macrophages	R	Peritoneal resident cells	Y1+Y2	↑ NO (LPS-stimulated)	young		(Dimitrijevic *et al.* 2008)
Macrophages	R	Peritoneal resident cells		↓ NO by PYY (LPS-stimulated)	old		(Stanojevic *et al.* 2006)
Granulocytes	R	Air pouch, carrageenan-elicited	Y1	↑ NO (LPS-stimulated)			(Dimitrijevic *et al.* 2006, Dimitrijevic *et al.* 2010)

Abbreviations: FcR, Fc receptor; f-MLP, N-formyl-methionyl-leucyl-phenylalanine; H, human; LPS, lipopolysaccharide; M, mouse; NBT, nitroblue tetrazolium; NO, nitric oxide; PKC, protein kinase C; PMA, phorbol myristate acetate; PYY, peptide YY; R, rat; Rec, receptor; ROS, reactive oxygen species; Sp, species.

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Table 5

Effects of NPY on n production of immune cells

Cells	Sp	Specification	Rec	Effect	Age	Signal	Ref
Macrophages	**M**	Peritoneal resident cells (macrophages+lymphocytes)		↓ TNF-α (LPS-stimulated)			(De la Fuente *et al.* 2001a)
Macrophages	**M**	Peritoneal resident cells (macrophages+lymphocytes)		↑ IL-1β (Con A-stimulated)	adult		(De la Fuente *et al.* 2001a)
Macrophages	**M**	Peritoneal resident cells (macrophages+lymphocytes)		↓IL-1β (Con A-stimulated)	old		(De la Fuente *et al.* 2001a)
Macrophages	**M**	Peritoneal, thioglycollate-elicited	Y1	↓ MCP-1 + TNF (LPS- stimulated)			(Macia *et al.* 2012b)
Monocytes / Macrophages	**M**	RAW 264.7 cell line	Y1	↑ TGF-β1		PI3K	(Zhou *et al.* 2008a)
Macrophages	**M**	Spleen tissue slice	Y1	↓ IL-6 (spontaneous, α2 adrenoceptor agonist)			(Straub *et al.* 2000b)
Macrophages	**M**	Spleen tissue slice	Y1	↑ IL-6 (β adrenoceptor agonist)			(Straub *et al.* 2000b)
Macrophages	**M**	Peritoneal, thioglycollate-elicited	Y1	↑ high-mobility group box 1 secretion	young	PKC/ERK	(Zhou *et al.* 2013)
DCs	H	Blood		↑ IL-6 + IL-10 (Th2 polarization)			(Buttari *et al.* 2014)
Leukocytes	**M**	Peritoneal resident cells (macrophages+lymphocytes)		↓ IL-2 (Con A-stimulated)	adult		(Puerto *et al.* 2005)
Leukocytes	H	Blood		↑ IL-βp, IL-6, TNF-α			(Hernanz *et al.* 1996)
Leukocytes	**M**	Peritoneal resident cells (macrophages+lymphocytes)		↓TNF-α (LPS-stimulated)	adult		(Puerto *et al.* 2005)
Lymphocytes	**M**			↓ IL-2 (Con A-stimulated)	adult		(Medina *et al.* 2000a)
T cells	**M**	Nonadherent splenocytes + T cell clones		↓ IFN-α + ↑ IL-4 (Th2 polarization)			(Kawamura *et al.* 1998)
T cells	**M**	T cell lines		↑ IL-2, IFN-γ, IL-4			(Levite 1998)
T cells	**M**	Spleen	Y1	↓ IFN-γ (anti-CD3 Ab-stimulated)			(Bedoui *et al.* 2003)

Abbreviations: Ab, antibody, Con A, concanavalin A; DCs, dendritic cells; ERK, extracellular signal regulated kinases; H, human; IFN, interferon; IL, interleukin, LPS, lipopolysaccharide; M, mouse; MCP-1, monocyte chemotactic protein-1; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; Rec, receptor; Sp, species; TGF, transforming growth factor; TNF, tumor necrosis factor.

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Table 6

Effects of NPY on microglia

Cells	Sp	Specification	Rec	Effect	Ref
Microglia	M	N9 cell line	Y1	↓ motility (LPS-stimulated)	(Ferreira *et al*. 2012)
CD11b+ cells	M	Brain cortex explants	Y1	↓ motility (LPS-stimulated)	(Ferreira *et al*. 2012)
Microglia	M	N9 cell line	Y1	↓ phagocytosis (IgG-opsonized latex beads, LPS-stimulated)	(Ferreira *et al*. 2011)
Microglia	M	N9 cell line	Y1	↓ IL-1β, NO (LPS-stimulated)	(Ferreira *et al*. 2010)
Microglia	R	Primary, cultured from cortex	Y1	↓ IL-1β, TNF-α (LPS-stimulated)	(Li *et al*. 2014)

Abbreviations: LPS, lipopolysaccharide; M, mouse; NO, nitric oxide; R, rat; Rec, receptor; Sp, species.

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Table 7

Effects of NPY on natural killer cells

Cells	Sp	Specification	Effect	Age	Signal	Ref
NK cells	H	Blood	↓ activity			(Nair *et al*. 1993)
NK cells	M	spleen, thymus, axillary node	↓ activity (spleen)	young		(Medina *et al*. 1998a, De la Fuente *et al*. 2001b)
NK cells	M	spleen, thymus, axillary node	↑ activity (axillary node + thymus)	adult	cAMP	(Medina *et al*. 1998a, De la Fuente *et al*. 2001b)
NK cells	M	Peritoneal resident cells (macrophages+lymphocytes)	↑ activity	adult		(Puerto *et al*. 2005)

Abbreviations: cAMP, cyclic adenosine monophosphate; H, human; M, mouse; Sp, species.

Table 8

Effects of NPY on lymphoproliferation

Cells	Sp	Specification	Effect	Age	Ref
Lymphocytes	M	Peritoneal resident cells (macrophages +lymphocytes)	↑ spontaneous lymphoproliferation		(Puerto *et al*. 2005)
Lymphocytes	M	Peritoneal resident cells (macrophages +lymphocytes)	↓ lymphoproliferation (Con A- or LPS-stimulated)	adult	(Puerto *et al*. 2005)
Lymphocytes	M	Spleen	↑ spontaneous proliferation	adult	(Medina *et al*. 1999, Medina *et al*. 2000a)
Lymphocytes	M	Spleen, thymus, axillary node	↓ lymphoproliferation (Con A-stimulated)	adult	(Medina *et al*. 1999, Medina *et al*. 2000a)

Abbreviations: Con A, concanavalin A; LPS, lipopolysaccharide; M, mouse; Sp, species.