Review

Neuropeptide Y and its role in CNS disease and repair

M. Decressac a,⁎, R.A. Barker b

a Wallenberg Neuroscience Center, Department of Experimental Medical Sciences, Lund University, Lund, Sweden
b Department of Clinical Neurosciences, Cambridge Centre for Brain Repair, University of Cambridge, Forvie Site, Robinson Way, Cambridge, UK

ABSTRACT

Neuropeptide Y (NPY) is widely expressed throughout the CNS and exerts a number of important physiological functions as well as playing a role in pathological conditions such as obesity, anxiety, epilepsy, chronic pain and neurodegenerative disorders. In this review, we highlight some of the recent advances in our understanding of NPY biology and how this may help explain not only its role in health and disease, but also its possible use therapeutically.

© 2012 Elsevier Inc. All rights reserved.

Contents

Introduction .......................................................................................................................... 265
NPY and neurogenesis in the adult brain ........................................................................... 266
  NPY and hippocampal neurogenesis ........................................................................... 266
  NPY and neurogenesis in the subventricular zone ..................................................... 266
NPY in neurodegenerative and neurological diseases ......................................................... 269
  NPY in Alzheimer’s disease ....................................................................................... 269
  NPY and Huntington’s disease .................................................................................... 269
  NPY and Parkinson’s disease ...................................................................................... 269
Conclusions ..................................................................................................................... 270
References ......................................................................................................................... 270

Introduction

It has been 30 years since neuropeptide Y (NPY) was isolated from the porcine brain and subsequently sequenced by Tatemoto et al. to reveal a 36 amino acid long peptide with tyrosine residues (Y) flanking its amino and carboxy terminals (Tatemoto, 1982; Tatemoto et al., 1982). Embryologically it starts to be expressed during early brain development and in the fully mature central nervous system (CNS) is found in many sites but especially the hypothalamus, hippocampus, amygdala and nucleus accumbens (Adrian et al., 1983; Allen et al., 1983, 1986; Woodhams et al., 1985).

As with all neuropeptides, NPY is synthesized in neuronal cell bodies, especially GABAergic neurons, and transported by fast anterograde transport to the synaptic nerve terminal where it can act as a modulator of neurotransmission both pre- and post-synaptically. Four G-protein coupled receptors, Y1, Y2, Y4, Y5 and Y6 receptors, mediate the wide range of physiological effects of this peptide and each of them has a distinct expression pattern in the brain (Dumont et al., 1998; Michel et al., 1998; Naveilhan et al., 1998). At the ultrastructural level, while a post-synaptic localization has been reported for all receptors, only Y2 is described as being pre-synaptic thereby mediating auto-receptor regulation (Colmers et al., 1991; Stanic et al., 2011).

New tools, such as the development of specific NPY receptor agonists and antagonists and the generation of targeted receptor knockouts has led to a resurgence of interest in the action of NPY in physiological and pathological processes. While great progress has
been made into defining the role of this peptide in the regulation of food intake, blood pressure, seizure activity, anxiety, bone formation, pain, depression and drug addiction, new functions for it in the pathogenesis of neurodegenerative disorders have only recently started to be investigated (Chee and Colmers, 2008; Hofkelt et al., 2008; Lin et al., 2004; Pedrazzini et al., 2003). In particular there is now a growing body of literature on its role in neurogenesis and neuroprotection (Xapelli et al., 2006). The present review summarizes these novel findings on the role of NPY.

**NPY and neurogenesis in the adult brain**

Neurogenesis constitutively occurs in two restricted regions of the adult brain: the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ) and during the last decade, several studies have identified NPY as an important regulator of this.

**NPY and hippocampal neurogenesis**

The existence of neural stem cells in the hippocampus has now been shown in most mammalian species and is seen throughout life, although decreases with age. Notably, the continuous renewal and incorporation of neurons in the circuitry of the adult hippocampus is thought to contribute fundamentally to certain learning and memory processes (for review Deng et al., 2010). Neural stem cells located within the subgranular zone give rise to transient amplifying cells that in turn differentiate into neuronal progenitors and from there to immature neurons which migrate through the granule cell layer becoming polarized as they mature. They send axonal projections along the mossy fibre pathways to the CA3 subfield and also extend dendrites in the opposite direction toward the molecular layer. Approximately three weeks after birth, these new mature neurons become fully integrated into the hippocampal circuitry with established afferent and efferent connections within the local neuronal network (for review Suh et al., 2009).

The first piece of evidence for a role for NPY in this process came from the observation that NPY and its receptors, especially Y1, Y2 and Y5, are heavily expressed both in the developing and adult hippocampal regions (Allen et al., 1983; Naveilhan et al., 1998; Woodhams et al., 1985). In particular within the DG, NPY is stored in GABAergic interneurons located in the hilus, which send long processes through-out the granule cell layer in close proximity to the DG neuronal precursor cells (Sperk et al., 2007). Since a tonic GABAergic input is known to play an important role in the kinetics of the proliferation and maturation of DG progenitors, it seemed logical to assume that the co-release of NPY could have a similar function.

Howell et al. (2003) were the first to provide functional evidence for such an effect of NPY on DG neuronal precursor cell proliferation. Using primary hippocampal cultures from early post-natal and adult wild type and Y1 receptor knockout mice, they demonstrated that NPY exerts a proliferative action on both nestin- and β-tubulin-positive precursors. This effect is specifically mediated via the Y1 receptor that is expressed by these cells, and involves an ERK1/2 signaling pathway. Notably, Y1 receptor knockout mice exhibit reduced proliferation of both precursor cells and the generation of immature doublecortin-positive neuroblasts in the DG compared to wild-type mice. Furthermore, NPY treatment not only promoted the differentiation of newly generated cells towards a neuronal fate (Howell et al., 2003, 2005, 2007), but directly stimulated the proliferation of hippocampal progenitors. Furthermore it has now also been shown that NPY potentiates the pro-neurogenic effect of fibroblast growth factor-2 on these progenitors, by increasing the expression of its receptor FGFR1 (Rodrigo et al., 2010).

Using transgenic mice and pharmacological approaches, our group further confirmed this property in vivo, ICV delivery of NPY in wild-type animals stimulated, through the Y1 receptor, the proliferation of DG precursors and promoted their differentiation into mature granule neurons (Decressac et al., 2011b) (Figs. 1A–B). In this study we did not look at hippocampal dependent behaviors so it is not possible to say how these NPY-induced changes in neurogenesis affect the cognitive functions of the hippocampus, if at all.

Animal models of brain pathologies where adult neurogenesis is altered have also provided interesting information about a role for NPY in this process. In the transgenic R6/2 mouse model of Huntington’s disease there is an impairment of hippocampal neurogenesis (Phillips et al., 2005) and we found in parallel a significant reduction in the number of NPY-immunoreactive neurons in the DG, although infusion of NPY in this model did not rescue this deficit (Decressac et al., 2010a). This suggests that the loss of this population of NPY cells in this model of HD is not critical in regulating neurogenesis. In line with this is the finding that in Alzheimer’s disease the NPY neurons are also severely affected by the neurodegenerative disease process (Chan-Palay et al., 1986), but in this case neurogenesis is increased in the DG (Jin et al., 2004).

While the exact role of NPY in neurogenesis and neurodegeneration remains somewhat obscure, its role in epilepsy seems clearer. Firstly its anti-epileptic action through the inhibition of glutamate release is well known (Colmers et al., 1988, 1991; Sorensen et al., 2008) and in addition there is an up-regulation of NPY and NPY receptor expression in the DG after seizures and this may be important in seizure-induced neurogenesis (Furtinger et al., 2001, 2002; Kokaia, 2011). In support of this role for NPY in epilepsy, studies have shown that mice lacking NPY or the Y1 receptor have a reduced basal and seizure-induced proliferation in the DG (Howell et al., 2007; Laskowski et al., 2007). Overall therefore NPY seems to be intimately associated with diseases that affect the hippocampus and this includes it having a possible role in modulating neurogenesis in some pathological conditions.

**NPY and neurogenesis in the subventricular zone**

In addition to the DG, the generation of new neurons in adulthood is also seen in the subventricular zone (SVZ). The SVZ lies immediately beneath the lateral wall of the lateral ventricles, where proliferation of resident neural precursors is influenced by several factors present in the cerebrospinal fluid (CSF), adjacent ependymal cells, and innervation from striatal cells or more distally from nigral dopaminergic neurons (O’Keeffe et al., 2009; Suh et al., 2009). SVZ stem cells give rise to transient amplifying cells that subsequently differentiate into immature neurons that migrate in chains, along the rostral migratory stream (RMS), to the olfactory bulb (OB) where they differentiate into granular neurons or periglomerular neurons, establish synaptic connections and become electrophysiologically active (for review see Suh et al., 2009). Since olfaction is essential in rodents, replacement of OB neurons from the SVZ precursors is a critical and continuous process and is thought to be important in certain forms of olfactory memory. Its role in humans is less clear-cut (Sanai et al., 2011).

NPY, like several growth factors and neurotransmitters, is now known to play a role in SVZ neurogenesis both during development and adult life. At embryonic days 13 and 14, a period corresponding to the peak of cellular proliferation in the rodent SVZ, high levels of this peptide are found in this region (Woodhams et al., 1985) although no direct association has been demonstrated so far between these two events.

In the adult brain while NPY-containing GABAergic neurons are scattered throughout the adjacent striatum, the density of the NPY-positive fibres increases markedly around the SVZ (Figs. 1C–D). Moreover, NPY-expressing cells, which also display markers of neural progenitors such as Sox2- and Nestin, lie in close proximity to the proliferating doublecortin-positive neuroblasts (Thiriet et al., 2011) (Fig. 1D). All of which suggests a possible role for NPY in regulating SVZ neurogenesis, a process that may also be dependent on the levels of NPY present in the CSF (Maeda et al., 1994).

Although the expression of NPY in the striatal/SVZ region has been known for years, its direct involvement in the regulation of SVZ progenitor cell proliferation has only emerged over the last few years.
Hansel et al. (2001) first reported the neuroproliferative effect of NPY in the olfactory epithelium and demonstrated that it promoted the proliferation of postnatal neuronal precursor cells without affecting cell death, while having no effect on gliogenesis. This effect was mediated through the Y1 receptor and the downstream activation of the protein kinase C-dependant ERK1/2 pathway. In addition, mice with targeted deletion of NPY display a significant reduction in the number of olfactory neurons, and recently it has been shown that ATP initiates neuronal proliferation in the olfactory epithelium via NPY up-regulation, release, and Y1 receptor activation (Jia and Hegg, 2010). This data supports the hypothesis that NPY is important in the maintenance of olfactory epithelium under physiological conditions as well as after injury (Jia and Hegg, 2011).

More recently, using SVZ cell cultures, Agasse et al. (2008) showed that NPY stimulates SVZ precursor cell proliferation and that this pro-neurogenic effect was mediated by activation of the Y1 receptor. Moreover, NPY had a dual action since it promoted both neurogenesis through an ERK1/2 signalling pathway and axonogenesis through the activation of a JNK cascade. This effect was further investigated and it was shown that endogenous NPY produced by SVZ cells may act in an autocrine/paracrine manner to fine tune neurogenesis. In particular it appeared to exert a chemokinetic and mitogenic action on SVZ

![Fig. 1. Pro-neurogenic effect of NPY in the adult rodent brain. A–B: BrdU immunostaining illustrating the proliferative effects of NPY on hippocampal progenitors. More BrdU-positive cells are observed in the DG 48 h after ICV injection of NPY compared to saline injection. C: NPY-expressing cells and a dense NPY innervation are observed in the adult SVZ. D: NPY-positive fibres (green) are in close contact to SVZ doublecortin (DCX)-positive neuroblasts and stimulate their proliferation. E–F: BrdU immunohistochemistry showing the proliferative effect of NPY on SVZ neurogenesis. The number of BrdU-positive proliferating cells is increased 48 h after ICV injection of NPY (F) compared to saline injection (E). E–F: 3 weeks after a single ICV injection of NPY (H), a marked proliferation of DCX-positive cells (red) is observed in the SVZ compared to saline treatment (G) (blue: ToPro-3; green: GFAP).](image-url)
progenitor cells while not affecting the self-renewal of SVZ stem cells (Thiriet et al., 2011).

In vivo, the pro-neurogenic effects of NPY on SVZ progenitors was initially shown using mice lacking either the Y1 or Y2 receptor (Stanic et al., 2008). Notably, these transgenic mice had fewer Ki-67-positive proliferative cells and doublecortin-positive neuroblasts in the SVZ and RMS compared to wild-type animals. They also exhibited less calbindin- (a marker of interneurons in the glomerular layer of the OB), calretinin- (a widely distributed neuronal marker in the OB), and TH-positive interneurons in the OB compared to wild-type animals. Subsequently, it was shown that ICV injection of exogenous NPY had a robust proliferative effect on SVZ neuroblasts (Decressac et al., 2009) (Figs. 1E–H). Using pharmacological approaches and transgenic mice knocked out for Y1 or Y2 receptor, we confirmed that this effect was due to the specific activation of the Y1 receptor on doublecortin-positive neuronal precursors in the SVZ. We also showed that, upon NPY stimulation, the new neurons generated out of the SVZ migrate not only the OB, via the RMS, but also toward the striatum where they preferentially differentiate into DARPP-32-positive GABAergic neurons (Fig. 2). However, it remains unknown whether these striatal-like neurons can integrate within the host network, establish synaptic connections and exert any functional effects. Therefore, in contrast to its role in the DG, NPY is clearly implicated in SVZ neurogenesis by acting in an autocrine/paracrine fashion with a pro-neurogenic effect on neural cells both in vitro and in vivo as well as stimulating the migration of newborn neuroblasts.

This pro-neurogenic function has been further explored in the context of pathologies affecting the striatal/SVZ regions such as in

---

**Fig. 2.** The possible neuroprotective effects of NPY in the diseased striatum. A schematic figure illustrating the hypothetical actions of NPY on neuronal and glial cells in the adult brain and their implications for pathological conditions. In the striatum, NPY is expressed by medium-sized aspiny GABAergic neurons that receive inputs from both cortical glutamatergic and nigral dopaminergic neurons, and establish connections with a variety of neighbouring cells. Since NPY-expressing neurons are spared in HD, NPY may be neuroprotective for striatal neurons in this pathological condition. In PD, NPY may also exert a neuroprotective effect on midbrain dopamine neurons. Considering the potent effect of this peptide on the inhibition of glutamate release, it could reduce glutamate excitotoxicity that may be contributing to some of the pathology in PD and HD. Non-autonomous cell death may also be counteracted by its action on suppressing inflammatory processes resulting from the activation of glial cells, which occur in both disorders. NPY has a pro-neurogenic effect on SVZ neural stem cells and enhances the migration of newborn neuroblasts toward the striatum. By recruiting the endogenous pool of progenitors, NPY could promote the self-repair capacity of the adult brain. SVZ: subventricular zone; DA: dopamine.
Huntington’s disease (see below) as well as other conditions such as brain trauma, inflammation and stroke; disorders which are all known to trigger endogenous repair mechanisms through the recruitment of SVZ progenitors (Fig. 2).

**NPY in neurodegenerative and neurological diseases**

While clinical manifestations such as motor or cognitive deficits associated with neurodegenerative diseases usually reflect widespread neuronal dysfunction and death in the CNS, it is now recognized that the pathological processes leading to this cellular loss involve both cell-autonomous and non cell-autonomous mechanisms. Although many of these conditions have unknown aetiologies, it is clear that a cascade of pathological processes including inflammation, epigenetic and transcriptional deficits, oxidative stress, protein aggregation or genetic mutations may synergistically contribute to the development of these conditions (for review see Glass et al., 2010; Lee et al., 2011; Sananbenesi and Fischer, 2009).

In addition in several neurodegenerative and neurological disorders, it is postulated that the loss of neurons may, at least in part, relate to excitotoxicity caused by excessive levels of extracellular glutamate (Fig. 2). Therefore molecules capable of buffering this amino acid or inhibiting its release, such as NPY, could have neuroprotective actions. To date, this property of NPY has been mostly studied in the context of epilepsy. Extensive work carried out in rodent models of epilepsy has revealed a pro-epileptic effect for the Y1 receptor, while both Y2 and Y5 receptors, when activated by NPY, have anti-epileptic actions consequent upon their inhibition of glutamate release (Noe et al., 2008; Waldbye et al., 2010). In addition, NPY knockout mice more frequently develop spontaneous seizures and are more sensitive to convulsive agents (Baraban et al., 1997; Erickson et al., 1996). These observations suggest that NPY, or more specifically Y2/Y5 receptor specific agonists may be promising molecules for the treatment of epilepsy (Ribon et al., 2009). In contrast to this well-characterized effect of NPY, only few studies have explored the potential of this peptide in other CNS disorders including Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD) and amyotrophic lateral sclerosis (ALS).

PD and HD are neurodegenerative diseases affecting a range of neuronal populations including selective ones within the basal ganglia. After AD, PD is the most prevalent neurodegenerative disorder, while HD is an order of magnitude less common. Both PD and HD share some common features such as prominent motor signs, dysfunction of the nigro-striato-cortical axis, and aggregation of disease-causing proteins (i.e. alpha-synuclein and huntingtin). In AD, neurodegeneration primarily affects association cortices and perihippocampal areas, with defects in protein handling (tau and A-beta peptide) resulting in the formation of the pathological hallmarks of this condition. Unfortunately, no cure is currently available for any of these diseases and current treatments only provide a temporary symptomatic relief.

**NPY in Alzheimer’s disease**

AD is an age-related neurodegenerative disease that impairs cognitive functions, primarily episodic memory, and is characterized pathologically by the formation of amyloid plaques and tau neurofibrillary tangles. Profound morphological changes in the NPY-positive neurons within the brain are seen and this includes a reduction in their number in the cortex and hippocampus at post-mortem (Beal et al., 1986c; Chan-Palay et al., 1985, 1986; Minthon et al., 1990). Martel et al. also reported a marked reduction in NPY binding sites in the temporal cortex and hippocampus of post-mortem AD brains as compared to age-matched controls. In transgenic mouse models of AD, it has been shown that hippocampal and cortical NPY-expressing neurons are the first neuronal populations to exhibit neuropathological features suggesting that they are one of most vulnerable to the disease process (Ramos et al., 2006; Rancillac et al., 2010; Wilcock et al., 2008). Despite contradictory reports, it appears that plasma and CSF levels of NPY are reduced during the course of the disease compared to control patients. While this does not prove a role for this peptide in AD pathogenesis or physiopathology, it does suggest that it could be an interesting biomarker to monitor the progression of the disease and may be linked to its evolution in some way (Edvinsson et al., 1993). However, how the variations in CSF NPY correlate to NPY cell loss is unclear as is its relationship to the disease stage of the patient.

In an attempt to link NPY to disease pathogenesis, Rose et al. (2009) have recently demonstrated that the infusion of NPY fragments derived from neprilysin processing can have a neuroprotective effect in the APP transgenic mouse model of AD and on primary cultures of human neurons. This finding was confirmed in another in vitro study showing that NPY prevents cell loss due to the toxic effect of Aβ(25–35) in SH-SY5Y neuroblastoma cells and cortical neurons through the stimulation of neurotrophin expression, i.e. nerve growth factor and brain-derived neurotrophic factor (Croce et al., 2011, 2012).

**NPY and Huntington’s disease**

Huntington’s disease (HD) is an inherited autosomal dominant disorder that is defined clinically by abnormal movements, changes in mood and cognitive impairment. The genetic basis of this disorder is a CAG repeat expansion in the first exon of the huntingtin gene leading to an abnormally long polyglutamine repeat in the protein promoting its aggregation. Although the exact mechanisms underlying disease pathogenesis remains unclear, the pathological process leads over time to neuronal dysfunction and death especially in the striatum (Imarisio et al., 2008). Interestingly, striatal somatostatin/NPY-co-expressing neurons are selectively spared and in fact in post-mortem human HD brain, the number of NPY-positive cells is increased in the basal ganglia, including the putamen and caudate nucleus (Dawbarn et al., 1985). In addition, if the number of NPY-positive neurons is correlated against the pathological grade of disease in the striatum, then there is a threefold increase of NPY-immunoreactivity in mild and severe grade cases (Beal et al., 1986b, 1988; Mazurek et al., 1997). NPY striatal neurons are also shown to be spared in the R6/2 transgenic mouse model of HD at a manifest stage (14 weeks old) (Decressac et al., unpublished data).

In line with the effect of NPY on SVZ neurogenesis discussed above, the SVZ of HD patients is enriched for NPY-positive cells consistent with an increase in neurogenesis (Curtis et al., 2007). Furthermore, the degree of cell proliferation correlates with the pathological severity and the number of CAG repeats in the htt gene (Curtis et al., 2003). In contrast in R6/2 transgenic mice, where striatal degeneration is very limited, neurogenesis in the SVZ is probably not up-regulated, although the data on this is not clear-cut (Batista et al., 2006; Decressac et al., a, 2010b; Phillips et al., 2005). These findings all suggest that variations in NPY expression associated with HD pathology may promote the generation of new cells from the SVZ which could potentially replenish those lost within the striatum to the disease process (Fig. 2). However, while ICV delivery of NPY in the R6/2 mice has been shown to extend lifespan, ameliorate motor performances and cerebral atrophy, it does not appear to promote cell replacement despite promoting SVZ neurogenesis (Decressac et al., 2010a) (Fig. 2). In this case NPY may be having a neuroprotective mechanism that targets more protein aggregation, or the astrocytic and microglial reaction (Fig. 2). Further work is needed to look at this specifically, but again highlights the potential role for NPY in HD.

**NPY and Parkinson’s disease**

Parkinson’s disease is classically characterized by the progressive loss of dopamine neurons in the substantia nigra and the presence of alpha-synuclein-containing inclusions, i.e. Lewy bodies, in the surviving neurons (although the disease clearly has pathology that extends outside this system). Depletion in striatal dopamine causes the development of some of the clinical features of PD including...
bradykinesia and rigidity and to date, no disease-modifying therapy that halts the disease process is available, and pharmacological and surgical treatments only provide symptomatic relief.

Anatomical and functional studies have revealed that NPY interacts with the dopaminergic system (Fig. 2). Vuillet et al. (1989) examined the ultrastructural relationship between the nigro-striatal projections and NPY neurons in the rat striatum and observed direct synaptic contacts. This fits with the earlier observation that following dopamine deafferentation of the striatum using 6-hydroxydopamine (6-OHDA) there was a marked increase in the number of NPY neurons in the striatum and nucleus accumbens (Kerkerian et al., 1986; Salin et al., 1990). Using another toxin that is commonly employed to model PD, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Obachowicz et al. (2003) observed a similar increase in the number of NPY neurons in the striatum in mice. When treated with deprenyl (a monoamine oxidase-B inhibitor) or after transplantation of ventral mesencephalic tissue, NPY immunoreactivity in the striatum was normalized in these lesioned animals (Moukhles et al., 1992; Obachowicz et al., 2003).

While these studies show that the nigrostriatal dopaminergic pathway regulates striatal NPY neurons, for a role to be shown in PD, the converse needs to be demonstrated and pharmacological studies have done just that. ICV injection of NPY induces a dose-dependent increase in the striatal dopamine release, monitored in freely moving rats by voltammetry, as well as an alteration in the extracellular concentrations of glutamate and GABA (Kerkerian-Le Goff et al., 1992). These findings have been further confirmed by administrating NPY directly into the striatum or onto striatal organotypic slices, and showing that it promotes the synthesis and release of dopamine through the Y2 receptor, while the activation of the Y1 receptor had an opposite effect (Adewale et al., 2005, 2007; Beal et al., 1986a) (Fig. 2). All of which fits with the fact that Y1 and Y2 receptor subtypes are highly expressed in the developing and adult striatum and have a role in dopaminergic neurotransmission (Kopp et al., 2002; Naveilhan et al., 1998). Using a functional autoradiographic method, Shaw et al. (2003) observed that both Y1 and Y2 receptors are also expressed by dopaminergic neurotransmission (Kopp et al., 2002; Naveilhan et al., 1998). Using a functional autoradiographic method, Shaw et al. (2003) observed that both Y1 and Y2 receptors are also expressed by dopaminergic neurotransmission (Kopp et al., 2002; Naveilhan et al., 1998).

In PD patients, changes in NPY expression have been reported. In line with the observations made in the toxin models, post-mortem PD brains exhibit an increase in the number of NPY-expressing cells, especially in the caudate nucleus and putamen, compared to controls (Cannizzaro et al., 2003). Modifications of NPY expression in other regions such as the cortex and the hippocampus are more controversial (Beal et al., 1988). Similarly, measurement of NPY levels in the CSF of PD patients has produced contradictory results (Martignoni et al., 1992; Yaksh et al., 1990).

These changes in NPY expression observed in patients and animal models of PD may:

(1) reflect an endogenous, but ineffective, neuroprotective response of the brain against the neurodegenerative process;

(2) contribute to the pathogenic process, or

(3) be simply downstream and secondary to the loss of dopaminergic tone.

We recently tried to address this issue by testing the effect of NPY in cell culture and mouse models of PD. The use of pharmacological agonists and antagonists as well as transgenic mice revealed that NPY protected dopaminergic neurons from 6-OHDA-induced toxicity in vitro and in vivo. This effect was mediated through the Y2 receptors and involved ERK1/2 and Akt pathways, but did not influence the expression of BDNF and glial cell line-derived neurotrophic factor (Decressac et al., 2011a) (Fig. 2).

A role for NPY in PD may not only relate to its neuroprotective action on the dopamine neurons, but also through an inhibitory effect on glutamate release (Fig. 2). NPY striatal cells are targets for cortical glutamatergic neurons (Kerkerian et al., 1990b; Vuillet et al., 1989) and deafferentation of the striatum from its glutamatergic input results in a significant increase in the number of striatal NPY-expressing cells. Combined nigral and cortical lesions counteract the effects of each other, and this may be mediated via the NPY system (Kerkerian et al., 1990a).

Interestingly if NPY can inhibit glutamate release in the striatum, it would be interesting to see what effect this agent has on L-dopa-induced dyskinesias (LID), a troublesome side-effect observed in PD patients given chronic L-DOPA therapy. This clinical complication is known to be caused, at least in part, by excessive striatal glutamate release and studies have demonstrated that administration of inhibitors of the glutamate system (e.g. amantadine) or specific metabotropic receptors, especially the mGluR5, have an effect in reducing LID (Rylander et al., 2010). Therefore, inhibiting the release of glutamate from the cortico-striatal projections using NPY could potentially impact on L-DOPA-induced dyskinesia.

Conclusions

While being highly expressed in the hypothalamus and intensively studied for its role in feeding regulation, NPY is also present in many other brain regions where it undoubtedly plays other important roles. In this respect there is emerging evidence that it plays a role in the regulation of neural stem cell proliferation in the two constitutive neurogenic niches of the adult brain. In addition, it acts as a neuromodulator and affects the release of several neurotransmitters such as dopamine and glutamate and by so doing may underlie some of the features and pathophysiological pathways of some chronic disorders of the CNS. Finally, NPY appears to have some neuroprotective actions in cell culture and in animal models of disease although it remains to be determined which pathological mechanisms NPY acts on in a significant way. In this respect, the effects on neurogenesis and glutamate release may be important, as might its reported actions on suppressing inflammation and encouraging the production of neurotrophic factors (Ferreira et al., 2010; Ferreira et al., 2011; Ferreira et al., 2012) (Fig. 2).

While the field of NPY research benefits from the availability of powerful tools (e.g. transgenic mice, viral vectors, specific NPY receptors agonists and antagonists), little is known about the physiological actions of this peptide in many human brain regions in health and disease.

In summary, NPY biology is emerging as an exciting and dynamic area of research where key regulatory processes in the normal and diseased brain are being revealed, and through which novel therapies for treating CNS diseases may emerge.

References


Beal, M.F., Mazeruk, M.F., Battista, C.M., Ransmayr, G., Speck, G., 2002. Altered expression of neuropeptide Y (NPY) Y1 and Y2 receptors in the hippocampus of patients with mesial temporal lobe epilepsy. Epilepsia 43 (Suppl. 5), 152.


Beal, M.F., Mazeruk, M.F., Battista, C.M., Ransmayr, G., Speck, G., 2002. Altered expression of neuropeptide Y (NPY) Y1 and Y2 receptors in the hippocampus of patients with mesial temporal lobe epilepsy. Epilepsia 43 (Suppl. 5), 152.


Beal, M.F., Mazeruk, M.F., Battista, C.M., Ransmayr, G., Speck, G., 2002. Altered expression of neuropeptide Y (NPY) Y1 and Y2 receptors in the hippocampus of patients with mesial temporal lobe epilepsy. Epilepsia 43 (Suppl. 5), 152.


Rodrigo, C., Zaben, M., Lawrence, T., Laskowski, A., Howell, O.W., Gray, W.P., 2010. NPY augments the proliferative effect of FGF2 and increases the expression of FGFR1 on nestin positive postnatal hippocampal precursor cells, via the Y1 receptor. J. Neurochem. 113, 615–627.


