Neuropeptides 56 (2016) 19–24

Contents lists available at ScienceDirect

Neuropeptides

journal homepage: www.elsevier.com/locate/npep

Potential of neuropeptide Y for preventing or treating post-traumatic stress disorder

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ARTICLE INFO

Article history:
Received 28 July 2015
Received in revised form 11 November 2015
Accepted 11 November 2015
Available online 12 November 2015

Keywords:
Intranasal
Resilience
PTSD
Depression
Single prolonged stress

ABSTRACT

There is extensive evidence that NPY in the brain can modulate the responses to stress and play a critical role in resistance to, or recovery from, harmful effects of stress. Development of PTSD and comorbid depression following exposure to traumatic stress are associated with low NPY. This review discusses putative mechanisms for NPY's anti-stress actions. Recent preclinical data indicating potential for intranasal delivery of NPY to brain as a promising non-invasive strategy to prevent a variety of neuroendocrine, molecular and behavioral impairments in PTSD model are summarized.

Contents

1. Neuropeptide Y and its receptors

Neuropeptide Y (NPY), so named for the abundance of tyrosine (Y) residues (5/36 amino acids, including the amino and carboxyl terminal residues), has widespread functions in CNS and periphery. These include regulation of feeding behavior, blood pressure, circadian rhythm, reproductive behavior, learning, memory, vascular remodeling, cell proliferation, angiogenesis, as well as behavioral responses to stress, mood disorders and alcoholism (Eaton et al., 2007; Heilig, 2004; Heilig et al., 1989; Hirsch and Zukowska, 2012).

In the periphery NPY is expressed primarily in sympathetic ganglia, the adrenal medulla and in platelets. NPY is one of the most widely distributed and abundant neuropeptides in the mammalian brain. NPY immunopositive cell bodies and fibers are generally found in cortical, limbic, hypothalamic, and brainstem regions. Expression of

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http://dx.doi.org/10.1016/j.npep.2015.11.004
0143-4179/

NPY in the human and rodent brain is similar, with abundant NPY mRNA or immunoreactivity located in the neocortex, amygdala, hippocampus, basal ganglia, hypothalamus, periaqueductal gray, dorsal raphe nucleus, and the A1-3 and A6 noradrenergic cells groups in the brainstem [reviewed in (Kask et al., 2002)].

The biological effects of NPY are mediated by activation of at least four G-protein coupled receptor subtypes: Y1, Y2, Y4, and Y5 (Michel et al., 1998; Hirsch and Zukowska, 2012; Redrobe et al., 2002). The Y6 subtype is not present in the rat while the human analog is truncated and non-functional. Y1, Y2 and Y5 receptors exhibit dense and overlapping gene expression in brain areas implicated in anxiety and depression including the hippocampus, bed nucleus of stria terminalis, hypothalamus, amygdala, locus coeruleus and prefrontal cortex. The distribution of the Y4 receptor is much more limited in brain areas involved in stress. All NPY receptors are G protein-coupled receptors that can regulate several signaling cascades leading to rapid responses as well as changes in gene transcription. Receptors associate with Gi/Go proteins, which trigger hyperpolarization by inhibiting calcium channels, activating GIRK (G protein-coupled inwardly rectifying potassium) channel activity or I_H channels. They inactivate adenylyl cyclase and thus cAMP dependent pathways and mobilize intracellular calcium by phospholipase C and phosphatidyl inositol kinase. They can lead to changes in gene expression by way of ERK or CREB signaling [reviewed in (Brothers and Wahlestedt, 2010; Sah and Geracioti, 2013)].

2. Neuropeptide Y and resilience to harmful effects of stress

There is now abundance of evidence that neuropeptide Y (NPY) can modulate the responses to stress and may play a critical role in resilience to harmful effects of stress. This information is covered in a number of excellent review articles, which show how NPY is inversely related to stress associated neuropsychiatric disorders, including PTSD and comorbid depression, and as well as the selective NPY receptor subtypes implicated in mediating these effects (Eaton et al., 2007; Wu et al., 2011; Sah and Geracioti, 2013; Enman et al., 2015; Heilig, 2004; Kask et al., 2002; Rasmusson et al., 2010; Kormos and Gaszner, 2013; Bowers et al., 2012; Pedrazzini et al., 2003; Reichmann and Holzer, 2015).

In soldiers or in trauma exposed veterans increased plasma NPY levels are associated with positive coping mechanisms (Morgan et al., 2001; Morgan et al., 2002; Yehuda et al., 2006). Significantly lower plasma and CSF concentrations of NPY were found in individuals with combat-related PTSD than in control subjects (Sah et al., 2009; Rasmusson et al., 2000). Depression is commonly co-morbid with PTSD and about half the patients with PTSD also have symptoms of depression. In this regard, decreased NPY levels in CSF (Heilig and Widerlöv, 1990; Hou et al., 2006) and plasma (Nilsson et al., 1996) are also observed in depressed patients.

Genetic studies in humans and rodents found that lower NPY levels are associated with more anxiety and higher reactivity to emotional and stressful challenges (Bannon et al., 2000; Heilig, 2004; Zhou et al., 2008; Mickey et al., 2011; Domschke et al., 2010). Conversely, overexpression of NPY in hippocampus or amygdala in transgenic rats or with viral vectors produced anxiolytic-like effects (Thorsell et al., 2000; Christiansen et al., 2014).

A number of pharmaceutical studies have demonstrated that injections of NPY into the brain ventricles or locally into hippocampus, amygdala or locus coeruleus, has anxiolytic and anti-depressive effects, and inhibits many stress induced behaviors (Kask et al., 2002; Sajdyk et al., 2002a; Sajdyk et al., 2002b; Primeaux et al., 2005; Kask et al., 1998). Overall the studies suggest that NPY acts with a high potency on core mechanisms of emotionality and behavioral stress responses (Heilig and Thorsell, 2002).

This review will concentrate on discussing the potential mechanisms for NPY's anti-stress actions and summarize recent data indicating its potential for preventing PTSD and comorbid disorders.

3. Putative mechanisms for NPY's anti-stress effects

3.1. Counteracting actions of pro-stress transmitters in various brain regions

A number of brain areas are implicated in mediating NPY's anti-stress effects. It has been proposed that NPY is needed to adequately terminate corticotrophin releasing hormone (CRH) triggered responses to stress (Heilig, 2004; Palkovits, 2008). NPY and CRH co-localize in stress regulatory brain regions, such as the amygdala, hypothalamus and bed nucleus of stria terminalis. NPY can compete with CRH reducing its anxiogenic effect in the extrahypothalamic regions involved in regulation of anxiety and fear [reviewed in (Thorsell, 2010; Heilig et al., 1994; Sajdyk et al., 2004)].

3.1.1. Amygdala

Functional antagonism between NPY and CRH has been observed in amygdala (Kask et al., 2002; Giesbrecht et al., 2010) where both peptides regulate GABA neurotransmission in an opposite manner via their respective receptors (Kash and Winder, 2006). The balance of NPY and CRH in the amygdala may be important in fear modulation and anxiety.

3.1.2. Hypothalamus

The relationship between CRH and NPY in the hypothalamus may be more complex. The hypothalamic CRH producing paraventricular nucleus (PVN) has a high density of NPY-containing nerve terminals (Liposits et al., 1988). NPY projections from both the brain stem and arcuate nucleus are in close apposition to CRH cell bodies and fibers. Under certain conditions NPY increases CRH gene expression and release (Dimitrov et al., 2007; Wahlestedt et al., 1987; Suda et al., 1993; Pronchuk et al., 2002). However its inhibitory effects on the CRH-producing neurons in the PVN have also been demonstrated (Horvath et al., 1997). Accordingly, NPY administered continuously for 3 days into the cerebral ventricle reduced CRH mRNA in the PVN (Füzesi et al., 2007). Our studies revealed that intranasal NPY given at end of traumatic stressors in single prolonged stress (SPS) rodent PTSD model prevented the SPS-elicited rise of CRH and FKBP5 mRNAs in the mediobasal hypothalamus measured a week later, a time for manifestation of behavioral impairments (See table). Thus NPY may enable proper HPA feedback regulation (Laukova et al., 2014; Serova et al., 2013). Overall, NPY may elicit diverse effects on the HPA axis depending upon the origin of NPY input and nature of the specific physiological stimuli (Palkovits, 2008).

3.1.3. Hippocampus

NPY may also be acting via modulation of expression of glucocorticoid receptors (GR) and as a consequence GR dependent regulation of transcription of GR responsive genes. In the hippocampus, a key region in controlling learning and memory, GR mRNA and protein levels are up-regulated after exposure to severe traumatic stress (Liberzon et al., 1999; Kohda et al., 2007; Li et al., 2011; Serova et al., 2013) and intranasal infusion of NPY (Serova et al., 2014) (see table) or injections of NPY or NPY-Y1 agonist directly into the hippocampus (Cohen et al., 2011) attenuated the rise in GR.

3.1.4. Locus coeruleus

NPY may likewise be able to alter the response of the noradrenergic system to stress. This effect of NPY is at least partially mediated by activation of pre-synaptic Y2 receptors therefore depressing the post-synaptic potential of the noradrenergic locus coeruleus (LC) neurons (Finta et al., 1992; Illes et al., 1993; Kask et al., 2002). Attenuation of LC activation will lead to decreased activity of numerous regions innervated by the LC which are implicated in arousal, memory acquisition, attention, vigilance, etc. in response to stress (Foote et al., 1983; Valentino and Van Bockstaele, 2008).