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Targeting the neuropeptide Y system in stress-related psychiatric disorders

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ABSTRACT

Repeated, extreme, or traumatic stressors can elicit pathological effects leading to many negative physical and psychological outcomes. Stressors can precipitate the onset of psychiatric diseases, or exacerbate pre-existing disorders including various anxiety and mood disorders. As stressors can negatively impact human psychiatric health, it is essential to identify neurochemicals that may confer protection from the negative sequelae of repeated or extreme stress exposure. Elucidating the neurobiological underpinnings of stress resilience will enhance our ability to promote resilience to, or recovery from, stress-related psychiatric disease. Herein, we will review the evidence for neuropeptide Y as an endogenous mediator of resilience and its potential relevance for the treatment of stress-related psychiatric diseases.

1. Introduction

Stressors elicit a cascade of neuronal, endocrine, and behavioral responses that promote homoeostatic adaptation to changing or threatening environments. Stressors maintained over prolonged periods of time or perceived as extreme can lead to maladaptive responses within stress-integrative circuitry. Pathological neurochemical and behavioral mechanisms can then manifest in the form of stress-related psychiatric diseases including anxiety disorders, post-traumatic stress disorder (PTSD), and depression. Neuropeptides have been shown to be influential neuromodulators of stress-related emotionality (Kormos and Gaszner, 2013). A growing body of evidence supports a role for neuropeptide Y (NPY) as a protective neurochemical that mediates stress resilience. NPY is a 36-amino acid peptide derived from preproNPY and belonging to a family that also includes pancreatic polypeptide (PP) and peptide YY (PYY) (Larhammar et al., 1993). NPY is highly conserved across mammalian species and is expressed throughout the central nervous system (CNS) (Larhammar et al., 2001; Adrian et al., 1983; Allen et al., 1983; Lundberg and Hokfelt, 1986; Hirsch and Zukowska, 2012). In the periphery, NPY is expressed primarily in sympathetic ganglia, the adrenal medulla, and in platelets (Larhammar et al., 2001; Adrian et al., 1983; Allen et al., 1983; Lundberg and Hokfelt, 1986; Hirsch and Zukowska, 2012). NPY is the most abundant and widely distributed neuropeptide in the human brain (Adrian et al., 1983), and has been shown to have a significant impact on brain activity. In the CNS, NPY and its receptors (Y1, Y2, Y4, Y5) play important roles in the control of food intake, energy homeostasis, pain, and many behavioral and physiological processes associated with stress and stress resilience (Hirsch and Zukowska, 2012; Brothers and Wahlestedt, 2010). In this review, we will discuss the role of NPY in stress-related behaviors and its relevance to select psychiatric disorders.

2. Neuropeptide Y (NPY)

2.1. NPY and NPY receptor subtypes in the brain

NPY immunopositive cell bodies and fibers are generally found in cortical, limbic, hypothalamic, and brainstem regions (Allen et al., 1983). Expression of 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 grey, dorsal raphe nucleus, and the A1-3 and A6 noradrenergic cells groups in the brainstem (Adrian et al., 1983; Allen et al., 1983; Caberlotto et al., 2000; Wahlestedt et al., 1989; Yamazoe et al., 1985; de Quidt and Emson, 1986; de Quidt and

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Emson, 1986). The effects of NPY are mediated by at least four subtypes of G-protein coupled receptors termed Y1, Y2, Y4, and Y5. Y6 receptors are expressed in the mouse brain, but this isoform is absent in the rat and nonfunctional in human and non-human primates (Larhammar and Salaneck, 2004). Autoradiographic and immunohistochemical examinations indicate that Y1 and Y2 receptors (Y1R and Y2R) exhibit the greatest expression in the brain, whereas lower levels of Y4 and Y5 receptors (Y4R and Y5R) are also present (Dumont et al., 1993; Stanic et al., 2006; Stanic et al., 2011; Dumont et al., 1998; Kask et al., 2002; Wolak et al., 2003). Significant differences in the distribution of NPY receptors are detectable between the rodent and human brain, warranting caution in the generalization of the role of NPY receptors from preclinical animal models to humans (Dumont et al., 1998). NPY receptors can couple to various effectors systems by associating with inhibitory $G_{i/o}$ proteins (see review (Sah and Geracioti, 2013)). NPY receptors inhibit adenylyl cyclase and the accumulation of cAMP, mobilize calcium through phospholipase C and phosphatidylinositol 3-kinase activity, and have effects on multiple ion channels (Sah and Geracioti, 2013). Within stress responsive brain regions such as the cortex, amygdala, hypothalamus, and locus coeruleus, NPY receptors are localized on or impact the function of neurons expressing GABA, glutamate, corticotropin-releasing factor (CRF), and norepinephrine (NE) (Grove et al., 2000; Dimitrov et al., 2007; Giesbrecht et al., 2010; Rostkowski et al., 2009; Illes et al., 1993; Eaton et al., 2007). It has been hypothesized that NPY serves as a functional "brake" to tone down the excitatory effects of pro-stress neurotransmitters such as CRF and NE (Sah and Geracioti, 2013; Eaton et al., 2007; Heilig et al., 1994). This hypothesis is supported by studies demonstrating that NPY is frequently contained within the same neuroanatomical brain structures as CRF and NE, and the function of NPY is often physiologically and behaviorally opposite to pro-stress neurotransmitters (reviewed in (Kask et al., 2002; Sah and Geracioti, 2013; Sajdyk et al., 2004)). Although clear interactions between NPY and pro-stress systems in the regulation of stress-related emotionality still need to be established, it is likely that the balance of these neuropeptides and transmitters in stress-related circuits plays a pivotal role in mediating resilience to stress-associated responses discussed in this review.

3. NPY in stress-related psychiatric disorders: insight from human studies

3.1. Stress and anxiety

Human studies have identified associations between NPY and stress resilience. In healthy human subjects, plasma NPY levels have been shown to rise in response to stress (Morgan 3rd et al., 2001; Morgan et al., 2000; Morgan et al., 2002). For example, when military soldiers underwent an interrogation model of extreme psychological stress to mimic the captive experience of prisoners of war, higher levels of NPY following interrogation were present in soldiers displaying lower psychological distress or belonging to special operations forces (Morgan et al., 2000; Morgan et al., 2002). NPY levels were positively associated with feelings of dominance and self-confidence, and superior performance under interrogation stress (Morgan et al., 2001; Morgan et al., 2000; Morgan et al., 2002).

Genetic variants of the preproNPY gene have been associated with differential stress responses and emotionality (Mickey et al., 2011; Zhou et al., 2008). Specific NPY haplotypes have been correlated to postmortem levels of NPY mRNA in the brain, plasma NPY concentrations, and brain activity in response to stressful challenges (Zhou et al., 2008). Individuals possessing a genotype associated with low NPY expression report more negative emotional experiences during a painful stressor, exhibit greater amygdalar reactivity in response to threat-related facial images, and exhibit low stress resilience compared to high NPY genotype carriers (Mickey et al., 2011; Zhou et al., 2008). Haplotype-driven NPY expression is also inversely correlated to trait anxiety in healthy individuals (Zhou et al., 2008).

Studies in humans with stress-related psychiatric disorders have also revealed a role for NPY in resilience (Eaton et al., 2007; Morales-Medina et al., 2010; Sah et al., 2009; Rasmusson et al., 2000; Morgan et al., 2003), although the evidence stems primarily from populations with PTSD and depression. Rodent studies have provided a wealth of evidence for NPY in resilience to anxiety (see below), but few human studies have been conducted to determine the profile of NPY in generalized anxiety, obsessive compulsive, social anxiety, and panic disorders. One study found an association between a single-nucleotide polymorphism of the NPY gene and increased risk for generalized anxiety disorder in individuals exposed to high stress (Amstadter et al., 2010). Genetic variants of the Y5 receptor gene have been significantly associated with panic disorder (Domschke et al., 2008). Elevated plasma NPY was detected in a study of individuals with panic disorder, in which the authors suggest that an increase in NPY may be compensatory to buffer enhanced sympathetic activation in this disorder (Boulenger et al., 1996). Other studies have not detected differences in NPY levels between healthy controls and persons with obsessive compulsive, social anxiety, or panic disorders (Stein et al., 1996; Altemus et al., 1999), or have failed to identify genetic associations between NPY and anxiety disorders (Lindberg et al., 2006).

3.2. Depression

Clinical investigations have revealed that the plasma and CSF of depressed individuals contain decreased concentrations of NPY compared to healthy controls (Hashimoto et al., 1996; Heilig et al., 2004; Hou et al., 2006; Nilsson et al., 1996; Widerlov et al., 1988). Additional studies have shown lower NPY in clinically depressed patients with a history of suicide attempts compared to healthy persons, and that NPY levels are lowest in individuals with a recent suicide attempt (Westrin et al., 1999). Likewise, low NPY immunoreactivity has been found in postmortem brain tissue of suicide victims, with the most robust reductions in NPY occurring in the brains of persons with a history of depression (Widdowson et al., 1992). Low levels of NPY mRNA expression are also found in persons with bipolar disorder (Caberlotto and Hurd, 1999; Kuromitsu et al., 2001). Genetic variants of the preproNPY gene have been associated with resilience or vulnerability to depression (Heilig et al., 2004; Wang et al., 2013; Sjoholm et al., 2009). For instance, a genetic polymorphism resulting in higher levels of mature NPY appears to be protective against depression despite exposure to environmental risk factors (Sjoholm et al., 2009), and the presence of this polymorphism is less frequent in depressed patients (Heilig et al., 2004). In another study, a genotype associated with low NPY expression was found to be overrepresented in persons with major depression compared to healthy controls (Mickey et al., 2011). Interestingly, antidepressant strategies are associated with parallel elevations in NPY and decreases in corticotropin-releasing hormone (CRH), thereby supporting peptidergic interactions in the mechanisms underlying clinically efficacious treatments for depression. For example, CSF levels of NPY are elevated in depressed patients following electroconvulsive therapy, while levels of corticotropin-releasing hormone decrease concurrently (Mathé et al., 1995; Nikisch and Mathe, 2008). Increased NPY after treatment with the selective serotonin reuptake inhibitor citalopram is associated with a reduction in depression severity and the levels of CRH (Nikisch et al., 2005).