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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).

3.3. Post-traumatic stress disorder (PTSD)

Reduced concentrations of cerebrospinal and plasma NPY have been reported in both individuals with PTSD and those who have been exposed to traumatic stress (Sah et al., 2009; Rasmusson et al., 2000; Morgan et al., 2003). NPY is inversely related to PTSD symptomology, with low NPY correlating specifically to the presence of intrusion symptoms (Sah et al., 2014). Higher NPY is predicative of PTSD symptom improvement and shows a positive association with coping following a traumatic event (Yehuda et al., 2006). Aberrant NPY and norepinephrine function have been linked in PTSD. Yohimbine, an antagonist of the presynaptic α2-adrenergic receptor that increases norepinephrine levels, elicits panic attacks and exacerbates the core symptoms of PTSD (Bremner et al., 1997). Yohimbine has also been shown to stimulate increases in plasma NPY and levels of the norepinephrine metabolite MHPG (3-methyl-4-hydroxy-phenyl-glycol) in healthy subjects. However, yohimbine-stimulated increases in NPY are significantly blunted in persons with PTSD (Rasmusson et al., 2000; Rasmusson et al., 1998). Additionally, baseline concentrations of plasma NPY correlated negatively to yohimbine-induced increases in MHPG in the same study (Rasmusson et al., 2000). This correlation suggests that low basal levels of NPY were associated with an exaggerated increase in MHPG following yohimbine (Rasmusson et al., 2000). Both basal and yohimbine-stimulated levels of NPY were negatively correlated to scores on a combat-exposure scale, indicating that greater combat exposure was associated with blunted levels of NPY (Rasmusson et al., 2000).

4. Potential therapeutic applications of NPY: evidence from animal models

Pathological responses to stress manifest in behaviors that include enhanced anxiety, arousal, and fear. In this section, we review the findings in animal models utilized to examine these three behavioral responses, as well as the effects of NPY in rodent models of PTSD and depression-like behavior. Examples provided in the text are summarized in Table 1.

4.1. Anxiety

Genetic rodent models and pharmacological studies have provided insight into the anxiolytic properties of NPY in multiple paradigms of anxiety-like behavior (Kask et al., 2002; Sajdyk et al., 2004). NPY deficiency is associated with an anxiogenic phenotype in rodents (Bannon et al., 2000), and highly anxious rats are more sensitive to the anxiolytic actions of NPY (Sudakov et al., 2001). Intracerebroventricular (i.c.v.) administration of NPY decreases anxiety-like behavior in the elevated plus maze, Vogel's drinking conflict test (Broqua et al., 1995; Heilig et al., 1989), and other operant conflict tasks (Britton et al., 1997; Heilig et al., 1992). Site specific-studies have revealed the amygdala, locus coeruleus, lateral septum, and hippocampus as regions that are involved in the anxiolytic properties of NPY (Lin et al., 2010; Thorsell et al., 2000; Primeaux et al., 2005; Sajdyk et al., 1999; Heilig et al., 1993; Kask et al., 1998a,b,c; Trent and Menard, 2011). For example, infusion of NPY into the basolateral amygdala decreases social anxiety (Sajdyk et al., 1999), produces anti-conflict effects via the central nucleus of the amygdala (Heilig et al., 1993), and decreases anxiety upon injection into the locus coeruleus (Kask et al., 1998a,b,c). The effects of NPY may be related to interactions with CRF signaling, as NPY attenuates anxiety and avoidance behavior induced by CRF and CRF agonists upon i.c.v. or direct delivery into subregions of the amygdala (Ide et al., 2013; Sajdyk et al., 2006; Britton et al., 2000). An interaction with norepinephrine systems has also been implicated, as pretreatment with idazoxan, an α2-adrenergic receptor antagonist, blocks the anxiolytic effects of NPY (Heilig et al., 1989).

The receptor subtypes mediating the anxiolytic properties of NPY are currently under investigation. Studies largely support a role for the activation of Y1R in the attenuation of anxiety-like behavior. For example, the anxiolytic effects of NPY are absent in mice lacking the Y1R (Karlsson et al., 2008; Heilig, 1995), and Y1R knockout mice exhibit an anxiogenic phenotype (Karl et al., 2006; Longo et al., 2014). Selective knockout of Y1R from excitatory forebrain neurons also results in increased anxiety (Bertocchi et al., 2011). Centrally administered Y1R agonists are anxiolytic in a number of behavioral paradigms (Britton et al., 1997; Sorensen et al., 2004), while site-specific examinations implicate the central nucleus of the amygdala and hippocampus as regions of Y1R-mediated anxiolysis (Heilig et al., 1993; Olesen et al., 2012; Lyons and Thiele, 2010). Administration of Y1R antagonists centrally or into the periaqueductal grey produces anxiogenic effects (Kask et al., 1998a,b,c), but has no reported effects when delivered into the locus coeruleus, hypothalamus, or central nucleus of the amygdala (Kask et al., 1998a,b,c). The lack of effect in these regions may be due to their low level of expression of Y1R (Kask et al., 2002). Central blockade of Y1R is also sufficient to elicit conditioned place aversion, supporting the notion that Y1R are necessary for endogenous anxiolytic actions of NPY (Kask et al., 1999). Y1R are found to be preferentially expressed on pyramidal cells in the basolateral amygdala (Rostkowski et al., 2009), therefore it is likely that Y1R mediate anxiolysis here by influencing glutamatergic input to the central nucleus of the amygdala and subsequent output to the brainstem (Gilpin et al., 2011).

The function of Y2R in anxiety is allegedly opposite of the Y1R subtype; however conflicting reports demonstrating both anxiogenic and anxiolytic effects mediated by Y2R make the role of this subtype in anxiety less clear. Y2R are generally considered NPY autoreceptors and evidence for their pre-synaptic localization has been demonstrated in humans and rodents (Stanic et al., 2011; Caberlotto et al., 1998). Central administration of Y2R agonists have failed to alter anxiety-like behavior in a number of studies (Broqua et al., 1995; Heilig et al., 1989; Britton et al., 1997; Sorensen et al., 2004). However, agonism of Y2R in the locus coeruleus and lateral septum produces anxiolytic effects, whereas Y2R are required for NPY-mediated anxiolysis in the hippocampus (Kask et al., 1998a,b,c; Trent and Menard, 2013; Smialowska et al., 2007). Y2R agonism in the basolateral amygdala has bidirectional effects on anxiety in the social interaction test, with low agonist doses generating anxiety and high doses decreasing anxiety (Sajdyk et al., 2002). A recent study indicates that knockout of the Y2R in GABAergic neurons located in the central nucleus of the amygdala was anxiogenic specifically in female mice (McCall et al., 2013). Contrasting reports indicate that Y2R antagonism in the central nucleus of the amygdala is anxiolytic (Kallupi et al., 2013), and that ablation of Y2R in either the basolateral or central nucleus of the amygdala produces an anxiolytic phenotype (Tasan et al., 2010). Global deletion of Y2R reduces anxiety in the elevated plus maze, light–dark, open-field, and marble burying tests (Tasan et al., 2009; Painsipp et al., 2008; Painsipp et al., 2008; Tschenett et al., 2003), and Y2R deficient mice exhibit reduced neuronal activation upon exposure to an anxiogenic environment (Nguyen et al., 2009). Taken together, this evidence suggests that Y2R may function in a regionally specific and neurochemically selective fashion.

The Y4R and Y5R also have putative roles in rodent anxiety-like behavior. Similar to Y2R mutant mice, deletion of the Y4R also reduces anxiety-like behavior in a number of rodent paradigms (Tasan et al., 2009; Painsipp et al., 2008). Knockout of the Y4R with

Table 1
Behavioral observations following pharmacological interventions or genetic manipulations of the NPY system.

Rodent models	Pharmacological intervention or genetic manipulation	Route of administration/region	Direction of behavioral effect	Reference
Anxiety–like Behavior	NPY	i.c.v. BLA, CeA Hippocampus Lateral Septum LC	Decrease	(Broqua et al., 1995; Heilig et al., 1989; Britton et al., 1997; Heilig et al., 1992) (Primeaux et al., 2005; Sajdyk et al., 1999; Heilig et al., 1993) (Lin et al., 2010; Thorsell et al., 2000) (Trent and Menard, 2011) (Kask et al., 1998)
	NPY knockout		Increase	(Bannon et al., 2000)
	Y1R agonists	i.c.v. CeA Hippocampus	Decrease	(Britton et al., 1997; Sorensen et al., 2004) (Heilig et al., 1993; Lyons and Thiele, 2010) (Olesen et al., 2012)
	Y1R antagonists	i.c.v. PAG LC Hypothalamus CeA	Increase No effect	(Kask et al., 1998; Kask et al., 1998a,b,c; Kask et al., 1999) (Kask et al., 1998)
	Y1R knockout		Increase	(Karl et al., 2006; Longo et al., 2014; Bertocchi et al., 2011)
	Y2R agonist	i.c.v. LC Lateral septum BLA (high dose)	No effect Decrease	(Broqua et al., 1995; Heilig et al., 1989; Britton et al., 1997; Sorensen et al., 2004) (Kask et al., 1998) (Trent and Menard, 2013) (Sajdyk et al., 2002)
	Y2R antagonists	CeA	Decrease	(Kallupi et al., 2013)
	Y2R knockout	Global, BLA or CeA GABAergic neurons in CeA	Decrease Increase	(Tasan et al., 2010; Tasan et al., 2009; Painsipp et al., 2008; Painsipp et al., 2008; Tschenett et al., 2003) (McCall et al., 2013)
	Y4R knockout		Decrease	(Tasan et al., 2009; Painsipp et al., 2008)
	Y5R agonist	i.c.v.	Decrease	(Sorensen et al., 2004)
	Y5R antagonist	BLA	Decrease	(Sajdyk et al., 2002)
Arousal	NPY	i.c.v., BLA CeA	Decrease No effect	(Broqua et al., 1995; Gilpin et al., 2011; Gutman et al., 2008) (Gutman et al., 2008)
	NPY knockout		Increase	(Sudakov et al., 2001)
	Y1R agonists	i.c.v.	Decrease	(Broqua et al., 1995)
	Y2R	i.c.v.	No effect	(Broqua et al., 1995)
	Y2R knockout		Increase	(Sudakov et al., 2001)
Fear	NPY	i.c.v., Amygdala	Decrease	(Gutman et al., 2008; Lach de Lima, 2013; Fendt et al., 2009; Pickens et al., 2009)
	NPY knockout		Increase	(Verma et al., 2012)
	Y1R agonists	i.c.v.	Decrease	(Lach de Lima, 2013)
	Y1R antagonists	i.c.v. Amygdala	Block NPY effects Increase	(Lach de Lima, 2013) (Gutman et al., 2008)
	Y1R knockout		Increase	(Fendt et al., 2009)
	Y2R knockout		No effect	(Verma et al., 2012)
Depression–like Behavior	NPY	i.c.v., Hippocampus	Decrease	(Redrobe et al., 2005; Stogner and Holmes, 2000; Redrobe et al., 2002; Ishida et al., 2007)
	Y1R agonists	i.c.v.	Decrease	(Redrobe et al., 2002)
	Y1R antagonists	i.c.v.	Block NPY effects	(Redrobe et al., 2002)
	Y1R knockout		Increase	(Karlsson et al., 2008)
	Y2R antagonists	i.c.v.	Decrease	(Redrobe et al., 2002)
	Y2R knockout		Decrease	(Painsipp et al., 2008)
	Y4R knockout		Decrease	(Tasan et al., 2009; Painsipp et al., 2008)
Depression Models (OBX or FSL)	NPY		Decrease (OBX)	(Goyal et al., 2009)
	Y1R agonist	i.c.v.	Decrease (OBX)	(Goyal et al., 2009)
	Y2R agonist	i.c.v.	Increase (OBX)	(Morales-Medina et al., 2012)
	Y2R antagonist	i.c.v.	Decrease (OBX)	(Morales-Medina et al., 2012)
	Y5R antagonist	i.c.v.	Decrease (FSL)	(Walker et al., 2009)
PTSD models (PSS and SPS	NPY	Intranasal, Hippocampus	Decrease anxiety, arousal, fear, depression-like behaviors	(Cohen et al., 2012; Serova et al., 2013; Serova et al., 2014)
	Y1R antagonist	Hippocampus	Increase anxiety, arousal	(Cohen et al., 2012)

the Y2R enhances the anxiolytic phenotype observed following deletion of either receptor alone (Tasan et al., 2009). Finally, pharmacological studies indicate that Y5R ligands may have promising anxiolytic properties. A Y5R antagonist blocked the anxiolytic effects of a Y2R agonist in the basolateral amygdala (Sajdyk et al., 2002), while i.c.v. delivery of a Y5R agonist produced anxiolytic effects (Sorensen et al., 2004). Y5R can form heterodimers with Y1R (Gehlert et al., 2007), and these receptor subtypes are colocalized in the basolateral amygdala, hippocampus, and hypothalamus (Wolak et al., 2003; Longo et al., 2014; Oberto et al., 2007; Fetissov et al., 2004). Y1 and Y5 receptors act synergistically in the regulation of energy homeostasis (Mashiko et al., 2009). Although the combined effects of Y1 and Y5 receptor agonists have not been tested in the context of anxiety thus far, the notion of co-activating these receptors could be valuable in the development of pharmacotherapeutics for enhanced anxiolytic effects.

4.2. Arousal

Hypervigilance is a characteristic symptom of stress-related psychiatric disorders that may reflect dysregulation of brain arousal systems. Startle responses can be measured in rodents using loud acoustic tones, and can be enhanced in fear-potentiated startle, a paradigm in which startle is tested in an environment previously paired with footshocks. Central administration of NPY inhibits both basal acoustic startle and fear-potentiated startle in rodents (Broqua et al., 1995; Gilpin et al., 2011; Gutman et al., 2008). Another study demonstrated that NPY infusion into the basolateral, but not central nucleus, of the amygdala mimics the effects of NPY on acoustic startle and fear-potentiated responses (Gutman et al., 2008). Central administration of a Y1R agonist attenuates fear-potentiated startle, whereas a Y2R agonist was reported to have no effect (Broqua et al., 1995). In genetically modified rodents, knockout of NPY or Y2R enhances acoustic startle (Bannon et al., 2000), whereas deletion of the Y1R yields impaired habituation of startle responses (Karl et al., 2010). These studies indicate a role for NPY in the modulation of startle and potential for NPY as a therapeutic for hyperarousal in stress-related psychiatric disorders. However the receptor subtypes and brain regions dictating NPY-induced resilience to this behavioral response remain unclear. The NE system originating in the locus coeruleus (LC) is a brainstem region contributing to arousal responses (Samuels and Szabadi, 2008; Sara and Bouret, 2012), thus NPY may mediate arousal behavior by directly acting in the LC or by influencing brain regions upstream. Fig. 1 demonstrates putative neurochemical interactions and circuitry that may influence the function of the LC-NE system and arousal behavior. NPY inhibits the firing rate of NE neurons in the LC, and potentiates the effect of NE on presynaptic autoinhibition of neuronal firing (Illes et al., 1993; Finta et al., 1992). This electrophysiological evidence suggests that NPY may act to restrain the activity of noradrenergic neurons, which may have important implications for stress-psychiatric diseases in which the LC-NE system is disrupted. In combination with anatomical evidence demonstrating rich NPY innervation of the LC (Smialowska, 1988) (shown in Fig. 2),these studies suggest that NPY may play an important role in the regulation of noradrenergic stress responses and arousal via NE circuitry.

4.3. Fear

Recent rodent studies suggest that NPY may be useful in the treatment of psychiatric diseases such as PTSD, which is heavily characterized by behavioral sequelae associated with fear. NPY has been found to influence multiple fear-related behaviors including the acquisition, incubation, expression, and extinction of conditioned fear. For example, i.c.v. administration of NPY or a Y1R agonist inhibits freezing behavior in both the acquisition and consolidation phases of fear conditioning, and these effects are blocked by pretreatment with a Y1R antagonist (Lach de Lima, 2013). Y1R may not be necessary for the cued-expression of fear, as intra-amygdalar administration of NPY robustly decreases the expression of conditioned fear, but these effects are not replicated by Y1R agonists and are not blocked by pretreatment with a Y1R antagonist (Fendt et al., 2009). In this particular study, Y1R knockout mice showed slight elevations in freezing behavior during fear conditioning, but did not show an enhanced phenotype upon testing for the cued-expression of fear compared to wildtype mice (Fendt et al., 2009). In addition, NPY was still capable of reducing the cued-expression of fear in these Y1R deficient mice, suggesting that the Y1R may not be involved in this phase (Fendt et al., 2009). NPY can suppress the long-term incubation of conditioned fear, while delivery of NPY prior to extinction training attenuates freezing and enhances retention of extinguished fear memories (Gutman et al., 2008; Lach de Lima, 2013; Pickens et al., 2009). Y1R antagonism blocks NPY-induced reductions in freezing and blockade of amygdalar Y1R leads to deficient extinction retention (Gutman et al., 2008; Lach de Lima, 2013). Consistent with pharmacological studies, NPY knockout mice display accelerated acquisition of conditioned fear, excessive recall of fear, and impaired fear extinction (Verma et al., 2012). Interestingly, deletion of the Y1R has moderately similar effects, whereas knockout of the Y2R has no effect on fear (Verma et al., 2012). However, double Y1R and Y2R knockout mice exhibit a remarkably similar phenotype to NPY deficient mice, indicating that both receptor subtypes do play a role in aspects of fear conditioning (Verma et al., 2012). In an inescapable footshock paradigm, interactions between the NPY and CRF systems were evident as increased amygdalar CRFR1 and

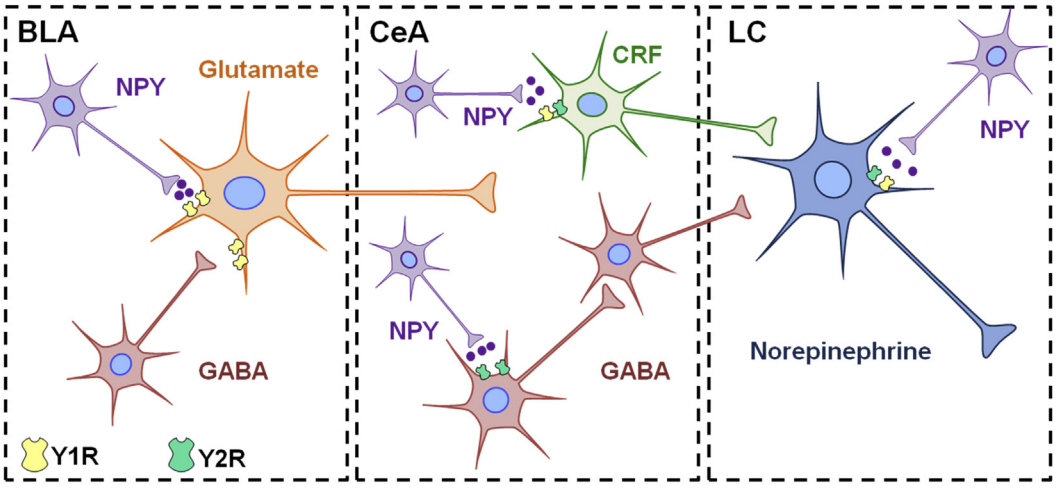

Fig. 1. Putative modulation of arousal behavior by NPY within stress–integrative circuitry. Excitatory glutamatergic (Glu) projections from the basolateral amygdala (BLA) activate the central nucleus of the amygdala (CeA) in response to stress. Subsequent activation of afferents expressing corticotropin-releasing factor (CRF) leads to enhanced activity of norepinephrine (NE) neurons in the locus coeruleus (LC), which then project to and activate regions of the forebrain to regulate arousal behavior. Putative interactions of NPY with stress responsive regions are shown. Activation of Y1 receptors on Glu neurons in the BLA may decrease activation of the CeA in response to stress (Rostkowski et al., 2009). NPY may suppress noradrenergic activation in the LC via Y2R located on NE neurons (Illes et al., 1993; Finta et al., 1992), or suppress Y2R-expressing GABAergic interneurons in the CeA leading to disinhibition of GABA output to the LC (not shown) (Gilpin, 2012). Alternatively, we hypothesize that NPY axon terminals may directly interact with CRF neurons in the CeA to suppress the activity of the LC-NE system in response to stress.

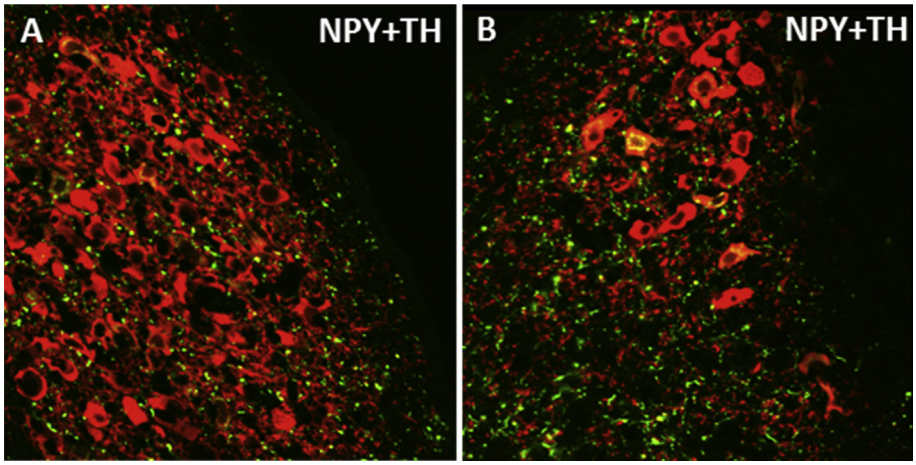

Fig. 2. NPY innervation of the rat locus coeruleus. NPY fibers (green) innervating the nuclear core (A) and the ventral dendritic region (B) of the locus coeruleus are shown. Noreprinephrine neurons in the locus coeruleus are represented by staining of the biosynthetic enzyme tyrosine hydroxylase (TH) (red). Colocalization of NPY and TH can be observed in cell bodies and fibers (yellow). NPY and TH in this high magnification image were visualized by immunofluorescence and confocal laser microscopy. Tissues were obtained from a non-colchicine treated Sprague–Dawley rat, which may contribute to the minimal observation of NPY synthesizing neurons in this image. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

decreased Y1R mRNA were found concurrently in animals displaying enhanced freezing time, and all of these effects were reversed in parallel following re-exposure to the footshock-paired environment (Hendriksen et al., 2012). Indirect evidence for NPY interactions with norepinephrine was obtained using auditory fear conditioning, in which centrally administered NPY and a Y1R agonist blunted fear-induced tachycardia (Tovote et al., 2004). These effects were blocked by a Y1R antagonist (Tovote et al., 2004).

4.4. Rodent models of depression

NPY is implicated in depression-like behavior and produces antidepressant effects. For example, central administration of NPY dose-dependently reduces immobility and increases swimming time in the forced swim test (Redrobe et al., 2005; Stogner and Holmes, 2000; Redrobe et al., 2002), a screening paradigm for pharmacological anti-depressant activity. Y1R agonists and Y2R antagonists also produce anti-depressant effects in forced swim (Redrobe et al., 2002), whereas Y1R antagonists block the anti-depressant effects of NPY (Redrobe et al., 2002). Intra-hippocampal infusion of NPY has anti-depressant properties in a learned helplessness paradigm, which is blocked by co-administration of a Y1R, but not a Y2R antagonist (Ishida et al., 2007). Y1R knockout mice display increased immobility in the forced swim test, indicative of a depression-like phenotype (Karlsson et al., 2008). Both Y2R and Y4R knockout mice exhibit reduced depression-like behavior in the tail suspension test, another common screening assay for antidepressant potential (Tasan et al., 2009; Painsipp et al., 2008; Painsipp et al., 2008). Knockout of both Y2R and Y4R results in augmented anti-depressant effects compared to single-knockout of either receptor (Tasan et al., 2009). Anti-depressant strategies including imipramine and electroconvulsive stimuli increase NPY immunoreactivity or receptor mRNA and binding sites, respectively (Heilig et al., 1988; Madsen et al., 2000). The anti-depressant properties of NPY may be mediated through interactions with the serotonin system, as administration of a tryptophan hydroxylase inhibitor blocked the anti-depressant effects of NPY in the forced swim test (Redrobe et al., 2005).

The Flinders-sensitive line (FSL) is a transgenic model of depression in which abnormalities in NPY, serotonin, and catecholaminergic systems have been identified (Overstreet et al., 2005; Serova et al., 1998). Depression-like behavior has been associated with impaired hippocampal neurogenesis, and enhanced NPY and serotonin activities been shown to increase cell proliferation in the dentate gyrus of the hippocampus (Husum et al., 2006). Hippocampal and amygdalar NPY immunoreactivity is lower in FSL rats compared to Flinders-resistant controls (Jimenez Vasquez et al., 2000; Jimenez-Vasquez et al., 2000; Zambello et al., 2008), and aging is associated with exacerbated loss of hippocampal NPY immunoreactivity in the FSL line (Husum et al., 2006). In FSL rats, Y5R antagonism produces anti-depressant effects in the forced swim test (Walker et al., 2009). Electroconvulsive stimuli and the selective serotonin reuptake inhibitor fluoxetine increase NPY mRNA or immunoreactivity in the hippocampus and hypothalamus, and upregulate amygdalar Y1R binding sites in FSL rats (Caberlotto et al., 1998; Caberlotto et al., 1999). Exercise and escitalopram are associated with similar alterations in hippocampal NPY and Y1 receptor mRNA (Bjornebekk et al., 2010). NPY has also been examined in olfactory bulbectomized rats (OBX), which are utilized as a rodent model due to depression-like disruptions in behavior, physiology, and neurochemistry (Song and Leonard, 2005; Kelly et al., 1997). Anti-depressant effects are observed following chronic treatment with NPY, a Y1R agonist, and a Y2R antagonist in OBX rats (Goyal et al., 2009; Morales-Medina et al., 2012). In contrast, chronic administration of a Y2R agonist enhanced depression-like behavior in OBX rats in the forced swim test (Morales-Medina et al., 2012).

Future studies investigating the efficacy of NPY in depression-like behavior induced by chronic psychosocial stress using the resident-intruder model of social defeat would be interesting. Social defeat reproduces behavioral and physiological indices of depression including disruption of CRF and NE systems (Wood et al., 2010; Wood, 2014; Chaijale et al., 2014; Chaijale et al., 2013; Russo et al., 2012), and would likely yield important information regarding the role of NPY in depressive behavior and disorders.

4.5. Rodent models of PTSD

Several rodent models of PTSD indicate that NPY expression in the brain following stress may be associated with susceptibility to

PTSD-associated impairments. For example, rats displaying extreme anxiety and arousal following exposure to predator scent stress (PSS) had lower NPY protein levels in the cortex, amygdala, hippocampus, and periaqueductal grey compared to rodents that were less impaired or to unstressed controls (Cohen et al., 2012). Injection of NPY into the hippocampus 1 h after PSS reduced the development of anxiety-like behavior, hyperarousal, and cue-elicited freezing. Additionally, NPY administration reduced the prevalence of an extreme behavioral response (Cohen et al., 2012).

Delivery of NPY to the brain by intranasal (IN) infusion has been used to examine its efficacy in the single prolonged stress (SPS) model of PTSD (Serova et al., 2013; Laukova et al., in press; Serova et al., 2014). Intranasal NPY can elevate CSF concentrations to a range that reduces anxiety behavior after i.c.v. administration, while also reaching multiple stress responsive brain regions and leaving plasma NPY levels unchanged (Serova et al., 2013; Laukova et al., in press). Pretreatment with IN NPY slowed the development of immobility during the forced swim portion of SPS, and reduced the induction of gene expression of the NE biosynthetic enzymes, tyrosine hydroxylase and dopamine beta hydroxylase, in the locus coeruleus shortly after SPS (Serova et al., 2013). SPS-induced increases in plasma corticosterone and ACTH were also attenuated by IN NPY, suggesting either less activation or more rapid recovery of the hypothalamic-pituitary-adrenal (HPA) axis (Serova et al., 2013). Intranasal NPY administered prior to or immediately after SPS led to pronounced and long-lasting effects on the development of behavioral, neuroendocrine, and molecular impairments associated with PTSD. NPY greatly attenuated, and in many cases prevented, increases in anxiety, hyperarousal, and depression-like behavior observed 1–2 weeks after exposure to traumatic stress (Serova et al., 2013). NPY prevented SPS-triggered induction of CRF, glucocorticoid receptor (GR), and FKBP5 mRNAs and the reduction in phosphorylated-GR in the mediobasal hypothalamus (Laukova et al., in press). NPY also increased the expression and phosphorylation of GR in the hippocampus (Laukova et al., in press). These studies suggest that early intervention with intranasal NPY may prevent dysregulation of the HPA axis by restoring proper negative feedback inhibition by GR. Intranasal NPY also attenuated long-term changes in the central noradrenergic system induced by SPS, including the development of increased sensitization of the LC to re-experiencing the forced swim (Serova et al., 2013). Taken together, PSS and SPS studies indicate that a single treatment with NPY near the time of the traumatic stress could provide long-lasting resilience to the development of PTSD and co-morbid impairments such as depression. Moreover, recent work also suggests that NPY may be efficacious as a treatment once PTSD-like symptoms have already manifested. Rats given IN NPY one week after SPS, when PTSD-like symptoms have manifested, exhibit anxiety-like behavior similar to unstressed controls up to 2 days later (Serova et al., 2014). Rats administered NPY after SPS also had reduced depression-like behavior (Serova et al., 2014). Further studies are necessary to determine if intranasal NPY reverses other impairments associated with PTSD, as well as the duration and sustainability of the improvements.

5. Therapeutic implications

The examples presented herein demonstrate that pharmacological interventions targeting the NPY system display much promise for the treatment of numerous stress-related psychiatric disorders. Future pharmacotherapeutic studies should consider targeting the central NPY system in stress-related emotionality and resilience. The preponderance of data suggests that NPY itself has significant therapeutic potential as a mediator of stress resilience. There are two major challenges associated with the development of NPY as a drug for psychiatric disorders; it is a peptide and it has a broad range of activities that may result in undesirable side-effects. The attractiveness and challenges of peptide therapeutics for CNS disorders has recently been reviewed (McGonigle, 2012). Peptides do not accumulate in tissues and are effectively metabolized by endogenous enzymes; therefore they have limited potential for drug–drug interactions. However, peptides have short half-lives and several methods have been introduced to prolong their stability *in vivo*. Encouragingly, as demonstrated in rodent models (Serova et al., 2013; Laukova et al., in press; Serova et al., 2014), NPY may confer long-lasting benefits for stress resilience despite its short half-life.

Although this review has concentrated on the beneficial effects of NPY in the CNS, NPY also has multiple actions in the periphery (Hirsch and Zukowska, 2012; Held et al., 2006; Pedrazzini et al., 2003). For example, NPY is a co-transmitter in sympathetic nerves, plays a role in vascular tone, and contributes to cardiovascular remodeling (Zukowska-Grojec, 1995; Edvinsson et al., 1984; Schuerch et al., 1998; Abe et al., 2007). Rodent studies have demonstrated NPY-induced disruption of metabolic homeostasis, as chronic NPY administration in rodents leads to abnormal baroreflex sensitivity, abdominal obesity, and dyslipidemia (Xie et al., 2012). NPY release from sympathetic nerves also stimulates fat angiogenesis, macrophage infiltration, and proliferation and differentiation of new adipocytes leading to abdominal obesity and a metabolic syndrome in rodents (Kuo et al., 2007). NPY also plays a role in bone physiology, gastrointestinal function, and cancer progression (Brothers and Wahlestedt, 2010). Peripheral administration of NPY may result in undesirable side effects on these physiological processes, increasing the value and necessity for strategies of NPY administration to the brain. Moreover, peptides do not typically cross the blood–brain barrier unless carried by specific transporters. Although no such transporter is known to exist for NPY, studies have shown that NPY can enter the brain to some extent (Kastin and Akerstrom, 1999).

Intranasal (IN) infusion represents a clinically relevant and non-invasive approach for the delivery of NPY to the brain. IN administration allows peptides to rapidly and directly enter the CNS via intracellular neuronal olfactory and extracellular trigeminal-associated pathways bypassing the blood–brain barrier to affect multiple sites within the brain (Dhuria et al., 2010; Ionescu et al., 2012; Thorne et al., 1995; Thorne et al., 2004). As demonstrated in rodent models (Serova et al., 2013; Laukova et al., in press; Serova et al., 2014), NPY delivered to the brain by IN infusion has beneficial effects on stress-related emotionality and pathology, which is likely achieved by influencing NPY responsive systems in all regions regulating stress responses. A potential disadvantage of IN infusion is the lack of selective targeting and potential for CNS-mediated side effects. For example, NPY is also a powerful orexigenic agent and regulates circadian rhythms (Brothers and Wahlestedt, 2010; Gehlert, 1999). Although not used for stress-related implications, studies have administered NPY by IN infusion in humans (Lacroix and Mosimann, 1996; Lacroix et al., 1996; Cervin et al., 1999; Hallschmid et al., 2003; Hallschmid et al., 2004). One small clinical trial aimed to test the effect of IN NPY on mood and anxiety (NCT 00748956) (U.S. National Institutes of Health, 2000a,b) while another is currently underway to investigate the safety of IN NPY using a dose escalation in PTSD (NCT 01533519) (U.S. National Institutes of Health, 2000a,b). To date no side effects have been reported. The viability of this route of administration makes it much more feasible to consider clinical proof of concept studies for severe stress-related disorders such as PTSD, for which there are no truly effective treatments and the initiating stress is often known. In the event that CNS-mediated side effects prove to be significant obstacles to the chronic use of NPY as a therapeutic, it is possible

that the selective activation or inhibition of individual receptor subtypes may be a safer yet still effective alternative. There is already considerable preclinical data demonstrating the therapeutic potential of Y1R agonists and Y2R antagonists for the treatment of stress-related disorders and these targets clearly merit additional study.

6. Future directions

Elucidating the neuroanatomical interactions of the NPY system with other neurotransmitters and peptides within stress-integrative circuitry would greatly advance our knowledge regarding the role of NPY in stress resilience and emotionality in future studies. In addition, future studies should consider the impact of sex differences on NPY-mediated effects. Human and rodent studies indicate that females may be more vulnerable to stress and stress-related psychiatric diseases than males (Bangasser and Valentino, 2014). Psychiatric symptomology and treatments responses also vary based on sex (Kokras and Dalla, 2014). Future studies examining the efficacy of NPY on stress and emotionality in females with direct comparisons to males would advance our understanding of sex differences in stress resilience. Neuroanatomical and molecular studies conducted across sexes would reveal potential mechanisms underlying effective coping to stress and intervention strategies for stress-induced psychiatric diseases.

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