Published in final edited form as:
Exp Neurol. 2016 October ; 284(Pt B): 196–210. doi:10.1016/j.expneurol.2016.06.020.

Neuropeptide Y (NPY) and Posttraumatic Stress Disorder (PTSD): a translational update

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Abstract

Posttraumatic stress disorder (PTSD) is a trauma-evoked syndrome, with variable prevalence within the human population due to individual differences in coping and resiliency. In this review we discuss evidence supporting the relevance of Neuropeptide Y (NPY), a stress regulatory transmitter in PTSD. We consolidate findings from preclinical, clinical and translational studies of NPY that are of relevance to PTSD with an attempt to provide a current update of this area of research. NPY is abundantly expressed in forebrain limbic and brainstem areas that regulate stress and emotional behaviors. Studies in rodents demonstrate a role for NPY in stress responses, anxiety, fear and autonomic regulation, all relevant to PTSD symptomology. Genetic studies support an association of NPY polymorphisms with stress coping and affect. Importantly, cerebrospinal fluid (CSF) measurements in combat veterans provide direct evidence of NPY association with PTSD diagnosis and symptomology. In addition, NPY involvement in pain, depression, addiction and metabolism may be relevant to comorbidities associated with PTSD. Collectively, the literature supports the relevance of NPY to PTSD pathophysiology, although knowledge gaps remain. The NPY system is an attractive target in terms of understanding the physiological basis of PTSD as well as treatment of the disorder.

I. Introduction

Posttraumatic stress disorder (PTSD) is a function-impairing, trauma-evoked syndrome with an annual prevalence of about 4.7% and a life time prevalence of about 6.1% in the general US adult population (Goldstein et al, 2016). Higher prevalence rates of approximately 13 % are observed in combat veterans (U.S. Department of Veterans Affairs, 2015). Experiencing or witnessing an intense traumatic event or events is a prerequisite to the development of PTSD. However, a significant variability is observed among individuals in susceptibility to PTSD. The ability of the psyche to withstand severe, repeated traumas---or to rebound and recover from them---is the hallmark of psychological resistance or resiliency. Since only a

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fraction of trauma-exposed individuals develop PTSD, there has been considerable interest in the identification of biological factors that may confer resiliency versus susceptibility to PTSD. Mounting evidence suggests a potential role of stress regulatory transmitter, Neuropeptide Y (NPY) in the pathophysiology of PTSD. While previously published reviews have addressed this topic (Enman et al., 2015; Reichmann & Holzer, 2015; Sah & Geracioti, 2013; Wu et al., 2011), the current article attempts to update the field and provide a translational perspective by collating preclinical, clinical and translational models that support an association of NPY with PTSD.

II. Neuropeptide Y (NPY) and NPY receptors: a brief overview

NPY is a 36 amino acid peptide that is widely distributed throughout the central and peripheral nervous system (Adrian et al., 1983; Allen et al., 1983). It is processed from a 97-amino acid precursor, pre-pro-NPY which is processed to the final peptide after catalytic action of prohormone converting enzymes and carboxypeptidase-like enzyme, and subsequently amidated to the biologically active form, NPY1-36 (Grouzmann & Brakch, 2005). The NPY family of peptides includes peptide YY (PYY) and pancreatic polypeptide (PP), two enteric peptides that share a hairpin-like structure called the PP-fold (Gehlert, 2004).

NPY mRNA mapping within the rodent brain identified the hypothalamic arcuate nucleus (ARC), the locus coeruleus (LC), the nucleus tractus solitari (NTS) and the septohippocampal nucleus as major sources of NPY synthesis (Kask et al., 2002). Investigation of NPY mRNA in the human brain tissue reveals abundance in the neocortex, polymorphic layer of the dentate gyrus, basal ganglia and amygdala (Caberlotto et al., 2000). In conjunction with mRNA mapping, high NPY peptide expression is observed in cell bodies and fibers within the amygdala, nucleus accumbens (NAcc), various hypothalamic nuclei, cortex and hippocampus within the human brain (Adrian et al., 1983). In rodents, the highest expression levels are seen in the hypothalamus, amygdala, cortex, hippocampus, NAcc, periaqueductal grey (PAG), dorsal raphe nucleus, the A1-A3 noradrenergic cell groups in the ventral medulla and the LC (Allen et al., 1983; Wahlestedt et al., 1989; Yamazoe et al., 1985).

The biological actions of NPY are mediated by G-protein coupled receptors. To date five different Y receptors (Y1, Y2, Y4, Y5, Y6) have been cloned and characterized in mammals (Michel et al, 1998). While the Y1, Y2, Y4 and Y5 receptors are functional, the Y6 receptor is non-functional in several mammals including humans and is not present in rats (Bromée et al., 2006). NPY shows strong affinity for the Y1, Y2 and Y5 receptors, while PP is the preferential agonist at the Y4 receptor (Alexander et al., 2013).

Most NPY receptors associate with pertussis toxin-sensitive Gi/Go proteins that can trigger hyperpolarization of the cell (Michel 1991, Michel et al, 1998). Intracellular signaling events include inhibition of calcium channels, activation of G protein-coupled inwardly-rectifying potassium (GIRK) channel activity or Ih inhibition via hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Sun et al, 2001; Acuna-Goycolea et al, 2005; Giesbrecht et al, 2010). NPY receptors reduce cyclic adenosine monophosphate (cAMP) via inhibition

of adenylate cyclase and mobilize calcium through phospholipase C/phosphatidylinositol 3-kinase (PLC/PI3K) activity (Härfstrand et al, 1987a, Walker et al, 1988). NPY receptors can also regulate gene transcription via activation of extracellular signal-regulated kinase (ERK) or CREB (cAMP response element--binding protein) signaling (Sheriff et al, 2002; Mullins et al, 2002). Table 1 illustrates Y receptor subtype ligand specificities and recruited signaling pathways (also refer to Brothers and Wahlestedt 2010)

Y1 is the most abundant Y receptor in humans, with highest expression observed in the subcallosal gyrus and insular cortex, and moderate expression in the cingulate, frontal and temporal cortices (Caberlotto et al., 1997). Autoradiographic studies using a Y1-selective positron emission tomography ligand, Y1-973, demonstrate expression of the receptor in the human brain, including the caudate-putamen, dentate gyrus, cortical regions, hypothalamus and thalamus (Hostetler et al., 2011). Co-localized expression of NPY with receptor subtype Y2 is observed in the human cerebral cortex, hippocampus, amygdala, striatum and NAcc (Caberlotto et al., 2000). Recent detailed immunochemical studies in the mouse brain support presynaptic localization of the Y2 receptor, co-localized to NPY and GABAergic (gamma aminobutyric acid) terminals (Stanić et al., 2011). Evidence from site-selective ablation of the Y2 gene in the amygdala further supports a regulatory role of the Y2 receptor in presynaptic release of NPY as well as GABA (Tasan et al., 2010). Autoradiographic studies reveal significant species differences in the distribution of NPY receptor subtypes between mice, rats and primates (Dumont et al., 1998). [^{125}I]-Leu^{31},Pro^{34}-PYY (Y1-preferring)- binding sites are preferentially expressed in the cortex, hippocampus, hypothalamus and brainstem of the rat/mouse brain, whereas low overall expression was evident in the human brain except for the dentate. Y2-preferring-[^{125}I]-PYY3--36 sites are enriched in the hippocampus, cortex and septum in rodent brain, while a preferential distribution in the cortex was observed in human brain.

Most rodent behavioral models pertinent to PTSD have focused on Y1, Y2 and Y5 receptors given their high affinity for NPY and expression in areas regulating stress, anxiety and fear related behaviors. Contributions of each receptor subtype are discussed throughout the review where applicable. The differential, species-specific distribution of NPY receptors needs to be considered when extrapolating data from preclinical rodent models to humans. This becomes especially relevant for inferences drawn from rodent PTSD models where region-specific manipulation with selective NPY receptor agonists and antagonists may not apply to humans.

III. Relevance of NPY in Post-Traumatic Stress Disorder

Accumulating evidence from preclinical and clinical studies conducted over the past decade strongly support a potential role of NPY dysfunction in the pathophysiology of PTSD. Figure 1 illustrates a temporal layout of major observations from preclinical, clinical and translational studies that have facilitated our understanding of a potential association of NPY with PTSD. The following sections discuss these observations lending support to the physiological relevance of NPY in PTSD.

(1) Preclinical Evidence: NPY regulates behavioral and physiological responses pertinent to PTSD

Experiencing or witnessing traumatic events can lead to PTSD, suggesting the relevance of biological systems that are recruited following trauma and stress exposure. NPY and NPY receptors in limbic and brainstem areas play an important role in the regulation of stress and anxiety (Reichmann & Holzer, 2015), fear (Tasan et al., 2016), learning and memory (Gøtzsche & Woldbye, 2015), and cardiovascular regulation (Zukowska-Grojec, 1995). Figure 2 illustrates NPY regulation of PTSD-relevant behavioral and physiological responses, highlighting brain areas that mediate these effects.

(i) NPY and stress—Collective evidence suggests that NPY regulates the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathetic nervous system (SNS), which are responsible for the response and adaptation to stress (Ulrich-Lai & Herman, 2009). The paraventricular nucleus (PVN) of the hypothalamus is densely innervated by NPY terminals, some of which synapse on corticotropin releasing hormone (CRH) neurons (Liposits et al., 1988). NPY administered by intracerebroventricular (ICV) injection or directly into the PVN elevates plasma adrenocorticotropic hormone (ACTH) and corticosterone in rats (Hanson & Dallman, 1995; Härfstrand et al., 1987b). These effects may be mediated by Y1 and Y5 receptors, as central injections of the Y1 agonist [Leu^{31},Pro^{34}] NPY and Y5 agonist [CPP^{1-7}, NPY^{19-23} Ala^{31}, Aib^{32}, Gln^{34}]hPP significantly increased plasma ACTH and corticosterone (Dimitrov et al., 2007; Kakui & Kitamura, 2007). NPY receptors have also been shown to regulate the HPA axis via extrahypothalamic sites. Conditional knockout mice lacking Y1 receptors in Ca^{2+}/calmodulin-dependent kinase II (CaMKII)-expressing forebrain excitatory neurons (primarily hippocampus) have elevated corticosterone and increased NPY and CRH immunoreactivity in the PVN (Bertocchi et al., 2011). Thus, hippocampal Y1 receptors may play a role in inhibition of the HPA axis. However, studies on HPA activity in NPY deficient mice have yielded contradictory results. Chronic restraint stress-evoked HPA activation was increased in NPY-deficient mice (Baldock et al., 2014). Contrary to this, maternal separation stress-evoked HPA activation was attenuated in NPY-deficient mice (Schmidt et al., 2008). Timing, duration or modality of stress may be relevant in this regard. In a recent study, timing of stress exposure within the circadian cycle was found to be a relevant factor in NPY regulation of the HPA axis as well as stress-evoked anxiety and startle behavior. In this study, rats exposed to predator stress prior to the inactive phase demonstrated higher vulnerability to stress-evoked HPA activation, anxiety and startle responses compared to rats exposed prior to the active phase (Cohen et al., 2014). Interestingly, NPY expression showed a higher magnitude of decrease in the inactive versus active cycle. Furthermore, NPY infusion into the PVN rescued stress induced neuroendocrine and behavioral responses associated with the diurnal cycle.

In addition to having direct effects on the HPA axis, the NPY system also operates as a physiological brake to counteract and regulate the activity of pro-stress transmitters such as norepinephrine (NE) and CRH that have been implicated in PTSD (Baker et al., 1999; Geracioti et al., 2001). NPY and CRH are expressed in areas relevant to stress and emotional regulation, such as the amygdala, hypothalamus, and the bed nucleus of stria terminalis (BNST). Behavioral studies suggest that NPY exerts potent anxiolytic effects, whereas CRH

is anxiogenic. Thus, it seems that a balance of these two peptides may exert an important influence on regulation of behavioral state. Direct injection of NPY in the basolateral nucleus of the amygdala (BLA) prior to a CRH agonist injection significantly blocks the development of avoidance behavior in the two floor choice test (Wahlestedt et al., 1990, Sajdyk et al, 2006) and prevents the CRH-induced reduction in social interaction time (Sajdyk et al, 2004). NPY and CRH have been reported to converge on GABA synapses in the central nucleus of the amygdala (CeA) and the BNST, having opposing effects on projection neurons and downstream effector regions impacting stress and anxiety-related behaviors and alcohol consumption (Gilpin et al., 2015; Kash & Winder, 2006; Pleil et al., 2015). Stimulatory effects of NPY on neuroendocrine responses via hypothalamic CRH may appear contradictory to inhibition of CRH responses by NPY in other brain regions, such as in the amygdala and the BNST. The differential effects of NPY on CRH transmission in these regions may be attributed to differential coupling to effector systems or localization of NPY receptors on CRH neurons, as well as, regulatory effects on excitatory versus inhibitory circuits within these regions (Dimitrov et al, 2007, Giesbrecht et al, 2010, Pleil et al, 2015). Interaction of stress and appetite regulatory effects of NPY and CRH in the hypothalamus may also contribute to these differences.

NPY exists as a co-transmitter with NE in central and peripheral noradrenergic neurons (Hendry, 1993) where it regulates the release and activity of NE in sympathetic responses. Central and peripheral NPY regulate cardiovascular responses in association with NE, exerting significant decreases in blood pressure and heart rate when injected ICV and into the brainstem of rats (Morris et al., 1997; Westfall et al., 2006), while exerting potent vasoconstrictor effects in the periphery (Wahlestedt et al., 1990). Mice exposed to six weeks of chronic stress manifest significant attenuation of NE and CRH release in the PVN by NPY neurons in the ARC, an effect that is absent in NPY deficient mice and restored following expression of NPY in NE neurons (Baldock et al., 2014). In addition to the hypothalamus, the LC appears to be another important site for NPY-NE recruitment following stress. Recent studies in the single prolonged stress (SPS) model of PTSD have shown normalization of SPS-evoked increases in HPA activity and elevated dopamine-β hydroxylase expression by intranasal (IN) NPY administration (Sabban et al., 2015; Serova et al., 2013).

Pharmacological and genetic studies in rodents support a pivotal role of NPY in promoting stress adaptation and coping. Transgenic rats overexpressing NPY show insensitivity to the normal anxiogenic-like effect of restraint stress in the elevated plus maze (EPM) (Thorsell et al., 2000). NPY administration into the basolateral amygdala (BLA) significantly reduced restraint stress-evoked anxiety in rats, an effect persistent over weeks (Sajdyk et al., 2008).

(ii) NPY and anxiety—Central administration of NPY has potent anxiolytic effects in multiple models of anxiety-like behavior in rats and mice (Eaton et al, 2007; Kask et al., 2002; Reichmann & Holzer, 2015; Wu et al., 2011). Following ICV NPY treatment, anxiolytic effects were observed in the EPM (Broqua et al., 1995), the social interaction test (Sajdyk et al., 1999) and open field test (Sørensen et al., 2004), as well as models of learned suppression of behavior (e.g., non-operant punished drinking) (Britton et al., 1997). In spontaneously hypertensive rats ICV NPY increased exploratory activity in the light-dark

box (Pich et al., 1993). Site-specific studies have identified the amygdala (Sajdyk et al., 1999), PAG (Kask et al., 1998b), hippocampus, lateral septum (Trent & Menard, 2011) and LC (Kask et al., 1998a) as potential anatomical substrates responsible for anxiolytic effects of NPY (Kask et al., 2002). Pharmacological anti-anxiety effects of NPY agree with data from genetic studies. NPY deficiency is associated with an anxiogenic phenotype in mice (Bannon et al., 2000). Viral-mediated overexpression of NPY in the amygdala (Christiansen et al., 2014; Primeaux et al., 2005) or hippocampus (Christiansen et al., 2014; Lin et al., 2010) is anxiolytic in the EPM and open field test.

A large number of studies implicate the Y1 receptor in mediating attenuation of anxiety by NPY. Y1-preferring agonist [Leu^{31},Pro^{34}]NPY produces NPY-like anxiolytic effects in the EPM (Broqua et al., 1995). Furthermore, Y1 receptor-selective antagonists, BIBO3304 and BIBP3226 block anxiolytic effects of NPY in the social interaction test (Sajdyk et al., 1999). Administration of BIBP3226 alone resulted in site-specific effects on anxiety-like behavior on the EPM (Kask et al., 1998b): anxiogenic behaviors were observed following injection into the PAG while no effects were observed in the amygdala, LC and PVN injected animals. Anxiolytic effects of NPY are absent in mice lacking Y1 receptors (Karlsson et al., 2008). Recently, conditional knockdown of Y1 receptor from excitatory forebrain neurons using αCamKII promoter-CRE driver resulted in elevated anxiety in the EPM (Bertocchi et al., 2011). Anti-anxiety effects of NPY possibly result from altered excitability within circuits regulating anxiety. NPY via the Y1 receptor reduces synaptic excitability in the BLA (Giesbrecht et al., 2010; Molosh et al., 2013). Y2 and Y5 receptors may also be recruited in NPY effects on anxiety, although the directionality of receptor actions appear to be region-specific. For example, Y2-agonism in the amygdala produces anxiogenic responses in the social interaction test (Sajdyk et al., 2002), whereas injection of Y2 agonists in the LC and lateral septum produces anxiolysis. Selective knockout of Y2 in GABAergic neurons in the CeA is anxiogenic in female but not male mice (McCall et al., 2013). On the contrary, CeA infusion of Y2 antagonist BIIE0246 reduced anxiety in the EPM in both naïve and alcohol- dependent rats (Kallupi et al., 2014). Global deletion of Y2 was also found to reduce anxiety in multiple tests of anxiety (Painsipp et al., 2008; Tschenett et al., 2003). Initial studies reported no effects of Y5 antagonist, CGP71683A on NPY evoked anxiolysis (Kask et al., 2001). However, subsequent studies using a different Y5 antagonist (Lu AA33810) demonstrated anxiolytic efficacy (Walker et al., 2009). ICV administration of Y5 agonist produced anxiolytic effects in the EPM and open field tests (Sørensen et al., 2004). Interestingly, conditional deletion of Y1 from Y5 expressing neurons results in increased anxiety-like behavior, suggesting a role of Y1-Y5 co-expressing neurons in regulating anxiety (Longo et al., 2015).

Overall, collective evidence from pharmacological and genetic studies suggest an anxiolytic role of NPY mediated primarily via Y1 and potentially Y5 receptors. Role of Y2 receptors in anxiety appears to be region-and circuit dependent, although there is some consensus on anxiogenic effects possibly via auto-receptor mediated reduction in synaptic NPY concentrations.

(iii) NPY, fear learning and memory—NPY is expressed in areas relevant to the processing of fear memories such as the amygdala, hippocampus and prefrontal cortex

(PFC), and modulates neuronal excitability in these areas. These findings have led to investigation of the role of NPY in the regulation of fear conditioning and extinction (see Tasan et al., 2016 for review). The first evidence for fear regulatory effects of NPY came from studies demonstrating inhibition of fear-potentiated startle by NPY and the Y1 agonist, Leu(31), Pro(34)]-NPY (Broqua et al., 1995). More recently, infusion of NPY into the BLA was found to inhibit the expression of fear-potentiated startle as well enhance within session extinction, an effect mediated by Y1 receptor within the BLA (Gutman et al., 2008). In a contextual conditioning paradigm, robust reduction of conditioned fear and facilitated extinction was observed following ICV NPY administration, partially mediated via the Y1 receptor (Lach & de Lima, 2013). In contrast, attenuation of cue-conditioned fear by intra-amygdala NPY infusion was not blocked by Y1 antagonism (Fendt et al., 2009). Recent studies implicate Y2 receptors in the CeA in fear expression and extinction (Verma et al., 2015). ICV NPY significantly inhibited incubation of conditioned fear tested a month following fear acquisition, a model pertinent to delayed onset PTSD (Pickens et al., 2009). Assessment of fear behaviors has been studied in genetic models and parallel pharmacological observations. NPY knockout mice show accelerated acquisition, increased expression of conditioned fear as well as impaired extinction (Verma et al., 2012). These effects are less pronounced in Y1 knockouts and were not observed in Y2-deficient mice. Interestingly, Y1-Y2 deficient mice exhibit the robust fear phenotype observed in NPY knockouts suggesting a synergistic role of these receptors in fear regulation. Interestingly, deletion of Y2 receptors from GABAergic neurons led to increased fear acquisition in female but not male mice (McCall et al., 2013). Rats lacking dipeptidyl peptidase-4 (DPP4), an enzyme that cleaves NPY into $NPY_{3\text{-}36}$, a Y2 receptor agonist, exhibit improved fear extinction, likely due to elevated central NPY concentration and altered activity at Y1 versus Y2 receptors (Canneva et al., 2015).

To date most studies have targeted the amygdala as a site for NPY regulation of fear conditioning. However, NPY and NPY receptors are abundant in cortical regions that regulate fear memory, specifically extinction and retrieval of extinguished fear. Reduced activation in the ventromedial PFC has been reported in PTSD subjects in association with impaired retrieval of extinction (Milad et al., 2009). Recent studies by our group observed a significant impairment in the retrieval of extinction following infralimbic infusion of NPY in rats (Vollmer et al, 2016). Interestingly, carriers of NPY gene polymorphism rs16147 have elevated NPY expression in the medial PFC (Sommers et al, 2010). Prefrontal NPY expression appears to be stress-sensitive, as exposure of rats to chronic stress resulted in a significant increase in this area (McGuire et al, 2011). Elevated prefrontal NPY may compromise top-down regulation of regions such as the amygdala and result in impaired processing of conditioned fear, perhaps leading to increased vulnerability to PTSD.

The evidence suggests that NPY may regulate different aspects of fear learning and memory in a region-selective manner. While inhibitory effects of NPY on conditioned fear are well established, regulation of fear extinction and retrieval may be more complicated. These responses may arise from differential regulation of fear circuits in discrete brain areas by NPY and its receptors. Further investigation using region-circuit-cell specific approaches may be required to carefully tease out the role of NPY in fear memory regulation.

(iv) NPY and control of autonomic responses—NPY regulates autonomic responses in a complex manner via the brain and periphery. NPY injected in the brainstem of rats significantly decreases blood pressure and heart rate (Morris et al., 1997). Transgenic rats overexpressing NPY have reduced blood pressure at baseline and during stress (Michalkiewicz et al., 2003). NPY-evoked hypotension is accompanied by reduced plasma catecholamine concentrations. Intrathecal injections of NPY have also been reported to have depressor effects (Chen et al., 1988). Other studies have reported no differences at baseline but increased sympathetic activity during stress in mice overexpressing NPY in noradrenergic neurons (Ruohonen et al., 2009). However, these effects were attributed to increased NPY release from the adrenal gland following sympathetic activation. In contrast to central effects, NPY released from postganglionic sympathetic neurons is reported to be a potent vasoconstrictor (Han et al., 1998). Chronic peripheral infusion of NPY leads to increased systolic blood pressure and cardiac dysfunction (Zhang et al., 2015). Overall, it appears that central NPY plays a major role in inhibition of the SNS, effects that oppose its peripheral actions. It would be important to consider these disparate effects when therapeutic targeting options and the utility of peripheral NPY as a surrogate biomarker for central NPY is being considered.

2) NPY and PTSD: supporting evidence from human studies

A potential contribution of NPY to PTSD pathophysiology is supported by two lines of investigation in humans: (a) clinical and gene association studies showing a role of NPY in stress coping and resiliency and (b) clinical studies in individuals with PTSD. Based on studies in rodent models, clinical studies were undertaken to assess effects on stress responses and stress coping in humans. An association of NPY with PTSD is supported by several clinical observations as described below:

(i) NPY, stress coping and resilience—Seminal studies in military survival training soldiers (Morgan et al., 2000) reported a negative association between plasma NPY levels with distress and poor performance scores following interrogation stress supporting a role of NPY in the behavioral effects of stress in humans. Individuals with higher NPY were “stress-hardy” and had better performance (in terms of interrogation behavior scores) identified by the Army training laboratory, while lower NPY was related to higher distress and symptoms of dissociation. Plasma NPY is primarily sympathetic and adrenomedullary in origin, and is linked to enhanced sympathetic activation under stressful conditions (see above). In another cohort of US Navy personnel, plasma NPY, cortisol and NE were significantly associated with survival school stress: greater levels of NPY release negatively correlated with psychological distress scores (Morgan et al., 2000).

(ii) NPY Genetics relevant to PTSD—Direct associations of NPY or NPY receptor gene polymorphisms with PTSD have not been reported to date. However, a large number of genetic studies on NPY haplotypes and gene polymorphisms have been associated with stress coping, affect, pain sensitivity and addiction, all of which are relevant to PTSD. NPY haplotypes predict low and high expression of NPY messenger RNA in post-mortem brain and lymphoblasts, as well as plasma NPY peptide levels (Zhou et al., 2008). Lower haplotype-driven NPY expression was associated with higher emotion-induced activation

of the amygdala, higher trait anxiety and diminished pain/stress-induced activations of the endogenous opioid neurotransmission in various brain regions (Zhou et al., 2008). While several NPY single gene polymorphisms (SNPs) have been investigated in different human pathologies, rs16147, rs3037354 and -1002 T>G polymorphisms appear to be most relevant to stress-associated responses. In general, all these polymorphisms are associated with lower NPY expression, although tissue-specific differences may exist. NPY SNP rs16147 is reported to account for more than half variation in NPY expression in humans (Zhou et al., 2008). An interaction between NPY gene polymorphism rs16147 and early adversity was found to modulate stress responses in young adults (Witt et al., 2011). Contribution of rs16147 allele associates with stronger bilateral amygdala activation and slower response to treatment in anxious depression patients (Domschke et al., 2010). There appear to be regional differences in the effects of SNP rs16147 on NPY expression. In a study by Sommer et al, (Sommer et al., 2010) NPY SNP rs16147 resulted in higher prefrontal NPY expression in postmortem samples. In the same study, a separate epidemiological sample showed association of SNP rs16147 with negative affect in individuals exposed to high adversity. Differential NPY expression among brain regions may arise from variances in post-transcriptional processing or differences in epigenetic DNA modifications among brain regions (Hannon et al., 2015). Another NPY gene SNP, rs3037354 is reported to associate with elevated stress-evoked cardiovascular responses, higher plasma NPY and altered glucocorticoid receptor (GR) signaling (Zhang et al., 2012). Additionally, a loci in the NPY promoter (1002 T>G) results in lower NPY expression in the CSF and amygdala and higher arousal during stress and alcohol consumption in rhesus macaques (Lindell et al., 2010). Contrary to these findings, one study failed to replicate the contribution of NPY gene haplotypes to trait anxiety (neuroticism) (Cotton et al., 2009).

Interestingly, polymorphisms in NPY receptors have been associated with addictive behaviors. SNPs in the Y2 and Y5 receptor genes associate with alcohol dependence and comorbid cocaine dependence (Wetherill et al., 2008). NPY Y1 receptor polymorphism rs7687423 has been linked with methamphetamine dependence (Okahisa et al., 2009). Although direct evidence of NPY SNPs association with PTSD has not been determined, a pilot prospective study reported greater susceptibility to PTSD in the absence of early intervention in a high risk group expressing combined genetic variants (including NPY rs16147) (Rothbaum et al., 2014). Collectively, these data suggest that genetic variation in NPY expression may promote inter-individual differences in stress and emotional responses to trauma that are relevant in determining PTSD susceptibility or resilience following trauma.

(iii) NPY in PTSD patients—Direct evidence for the relevance of NPY in PTSD pathophysiology comes from measurements of NPY peptide-like immunoreactivity in PTSD subjects. Table 2 compiles clinical studies on NPY measurements in PTSD subjects and other conditions that are often comorbid with PTSD.

Based on preclinical evidence our group tested the hypothesis that cerebrospinal fluid (CSF) NPY concentrations are reduced in PTSD patients. We reported significantly lower CSF NPY levels in Vietnam veterans with combat-related PTSD relative to healthy controls (Sah et al., 2009). In a follow up study we replicated reduced CSF NPY concentrations

in Iraq/Afghanistan combat veterans with PTSD compared to a combat-exposed non-PTSD group (Sah et al., 2014), suggesting that low CSF NPY concentration is a pathophysiological feature of PTSD and not due to combat exposure per se. Moreover, NPY inversely correlated with intrusive symptom and diagnostic CAPS scores but not with combat exposure scale (CES) and comorbid depression score (BDI), suggesting a possible association of reduced CSF NPY with PTSD symptomology. Of relevance to comorbidities related to PTSD, reduced CSF NPY has been observed in individuals with insomnia and substance dependence (Huang et al., 2015; Xu et al., 2012), while elevated CSF NPY was reported in individuals with impulsive aggression (Coccaro et al., 2012).

Plasma NPY concentrations in PTSD have been examined by other groups. Baseline plasma NPY levels were found to be reduced (Rasmusson et al., 2000) or unchanged (Morgan et al., 2002) in PTSD patients as compared with healthy or trauma exposed non PTSD subjects, respectively. Significantly higher plasma NPY levels were reported in individuals with past PTSD but currently recovered, suggesting a potential role of NPY in resilience (Yehuda et al., 2006). High coping and resilience showed positive correlation with NPY levels in these subjects.

Overall, CNS NPY concentrations appear to be associated with PTSD pathophysiology, although the exact contributions of NPY are unknown. Plasma NPY concentrations may be reflective of sympathetic drive, however, given recent studies showing a lack of correlation between CSF and plasma NPY pools (Baker et al, 2013), there is need for caution in extrapolating plasma to predict central brain NPY status. Future studies are required to compare these pools concurrently in PTSD subjects and comparing NPY changes at baseline versus stress conditions.

3) NPY and PTSD: evidence from animal models of PTSD-like behavior

Following clinical observations of central NPY dysregulation in PTSD, numerous studies have investigated NPY regulation and intervention in rodent models simulating PTSD-relevant behaviors, with the objective of investigating potential mechanistic and pharmaco-therapeutic contributions of NPY. Previous studies have shown that exposure to acute and chronic stress regulates NPY expression in the brain, the magnitude and directionality being dependent on stressor modality, duration and brain area being examined (Reichmann & Holzer, 2015). In recent years, several animal models of PTSD have been proposed, primarily in rodents (Daskalakis et al., 2013; Goswami et al., 2013). Most models involve exposure of the animal to acute or chronic stressor/stressors to evoke a phenotype that simulates PTSD-like behaviors and physiology. These include increased fear expression, increased acoustic startle response (ASR), potentiated anxiety-like behavior, increased sympathetic responses, reduced social interaction, and altered sleeping behavior. In the following sections, changes in NPY and NPY receptor protein or mRNA expression as well as behavioral outcomes produced by NPY intervention are described for each model (collated in Table 3).

(i) Predator Stress Models

Predator Scent Stress (PSS) Model

Regulation of NPY in PSS model: This model entails exposure to the scent of a natural predator to mice or rats. Exposure of rats to soiled cat litter for 10 min produced reduced NPY-like immunoreactivity in a wide range of brain areas including posterior cortex, amygdala, hippocampus, and the PAG at 7 days post-PSS exposure (Cohen et al., 2012). Reduced NPY is specific to the subset of animals expressing increased anxiety-like behaviors on the EPM and an increased ASR. In a recent study, NPY expression was associated with differential sensitivity to predator exposure across the circadian cycle (Cohen et al., 2015). Basal expression of NPY specifically in the hypothalamic PVN and the arcuate was significantly lower at the onset of the light phase but not at the dark phase onset (Cohen et al., 2015). Interestingly, rats exposed to PSS at the onset of light cycle (but not the dark cycle) also manifested HPA abnormalities, increased ASR and reduced open arm time in the EPM.

NPY Intervention in PSS model: Based on PSS-evoked reductions in hippocampal NPY, animals were administered 5 or 10 μg bilaterally directly into the dorsal hippocampus, 1 hr post-PSS exposure (Cohen et al., 2012). A significant attenuation of PSS-induced increases in ASR amplitude, contextual fear and anxiety-like behavior was observed in NPY treated animals. Additionally, NPY treatment resulted in elevated NPY and YR1 immunoreactivity in the dentate and BDNF immunoreactivity in the dentate and CA3 regions. In a more recent study, NPY intervention in the PVN normalized PSS-induced increases in ASR, elevated anxiety-like behavior and HPA response (Cohen et al., 2014).

Predator Exposure: Similar to PSS, exposure of rodents to a natural predator constitutes an intense stressor relevant to threat simulation for PTSD, although animals are never in direct contact with the predator (Daskalakis et al., 2013; Goswami et al., 2013; Stam et al., 2007). Typical predators include cats (for rats) or rats (for mice) (Adamec et al., 2004; Cohen & Zohar, 2004). Predator stress-evoked behavioral manifestations such as HPA hyperactivity, anxiety-like behavior on the EPM and light-dark box and exaggerated ASR are measured at delayed intervals ranging from 7d to 30d (Daskalakis et al., 2013; Stam et al., 2007). A recent study investigated NPY alterations in a predator exposure paradigm using captured field mice (Varman & Rajan, 2015). Predator-exposed field mice reared under standard housing conditions exhibited increased anxiety-like behavior and fear. However, field mice reared under enriched conditions were resistant to predator-evoked behavioral impairments. Interestingly, a significant elevation of NPY was observed in the amygdala of enrichment exposed mice that did not express predator stress effects. Furthermore, expression of the Y1 receptor in the amygdala is significantly increased and that of the Y2 receptor significantly decreased in the enriched housing group. This is consistent with the anxiolytic/anti-stress versus anxiogenic role of the Y1 and Y2 receptors, respectively.

(ii) Single Prolonged Stress (SPS) model

Regulation of NPY in SPS model: The SPS model involves exposure of animals to a 2 hr. restraint stress, a 20 min forced swim (24°C) and ether exposure, consecutively. This

model is reproducible in multiple laboratories, making it a popular PTSD animal model (Liberzon et al, 1997; Lee et al., 2014; Nedelcovych et al., 2015; Sabban et al., 2015; Serova et al., 2013; Yamamoto et al., 2009). SPS evokes a delayed onset HPA dysregulation, marked by enhanced negative feedback inhibition of ACTH responses to corticosterone injection or re-stress in the form of restraint (Liberzon et al, 1997). Attenuated NPY mRNA expression in the amygdala (Nedelcovych et al., 2015), and reduced NPY peptide immunoreactivity in the PVN (Lee et al., 2014) are observed at 7 and 9 days post-SPS, respectively. Significant SPS-evoked decrease in NPY Y2 receptor mRNA in the LC has also been reported (Sabban et al., 2015). In contrast, one study observed a significant increase in NPY immunoreactive fibers and terminals specific to the BLA (not CeA) at 7d post SPS exposure in rats (Cui et al, 2008). In this study double immunostaining by fluorescence and electron microscopy revealed that NPY immunoreactive terminals were closely associated with CaMKII (a marker for pyramidal neurons)-positive neurons in the BLA, which were also immunopositive for GR and mineralocorticoid receptor (MR). Since no other endpoints were investigated, it is not evident how these SPS-evoked morphological changes relate to PTSD-relevant physiology and behavior. Collectively, SPS evoked changes in NPY expression appear to be dependent on brain region. Assessment of behavioral outcomes in conjunction with morphological measurements may be necessary for correct interpretation of stress-evoked NPY changes.

NPY Intervention in SPS model: Intranasal administration of NPY in the SPS model has proved to be effective at reducing behavioral and neurochemical changes induced by SPS (Serova et al., 2013; Serova et al., 2014). One study compared IN NPY treatment in SPS treated animals either 30 min before or immediately after SPS exposure (Serova et al., 2013). IN administration of NPY prior to SPS improved PTSD- and depression-related behaviors (reduced ASR, increased open arm time on the EPM, and reduced immobility in forced swim test (FST)) tested at 7d post-SPS. IN NPY blocked the expression of many SPS-evoked neurochemical changes, including elevated mRNA expression of CRH, FK506-binding protein 5 (FKBP5) and GR in the hypothalamus and GR protein in the hippocampus (Laukova et al., 2014). In a separate study, IN NPY increased tyrosine hydroxylase (TH) protein in the LC and increased CRH receptor mRNA and protein in the CeA (Sabban et al., 2015). In addition to its efficacy as a preventive treatment for PTSD-like behaviors, the same team tested whether IN NPY can reverse SPS-evoked behavioral impairments in a follow up study. When IN NPY was administered after the 7d recovery period (when behavioral impairments are evident), significant changes were observed on several PTSD-relevant behavioral endpoints (attenuated ASR, reduced anxiety and depression-like behaviors). These data suggest that IN administration of NPY may reverse behavioral impairments triggered by the traumatic stress of SPS, suggesting a possible therapeutic potential for treatment of PTSD (Serova et al., 2014).

(iii) Chronic Stress Model

Regulation of NPY by chronic stress: Models using chronic stress exposure are relevant to PTSD, given evidence that the cumulative effects of chronic trauma such as combat stress may contribute to the disorder. We used chronic variable stress (CVS), composed of multiple, single episode events occurring in an unpredictable fashion, to simulate prolonged

stress (McGuire et al., 2010; McGuire et al., 2011). CVS consists of a 7d, twice daily exposure to physical and psychological stressors administered in an unpredictable manner. In a recent study, a final inescapable foot shock stressor within the CVS was included to simulate a stressful event that could later tested for post-recovery fear recall (Schmeltzer et al., 2015). The 7 day CVS exposure produces a pronounced deficit in HPA axis stress reactivity that emerges 4 days after cessation and persists for at least 30 days (Ostrander et al., 2006), consistent with reduced HPA drive seen in PTSD (Yehuda, 2001). Region-specific alteration in NPY is observed within key stress and fear-regulatory brain areas. At the 7d post CVS recovery period, animals exposed to CVS showed differential regulation of NPY with a significant reduction in the amygdala but a significant increase in the PFC (McGuire et al., 2011). These changes temporally associate with exaggerated fear memory and arousal behaviors observed in these animals, including enhanced freezing in response to a reminder stimulus (McGuire et al., 2010). NPY alterations are consistent with maladaptive emotional responses due to the nature of NPY signaling within these respective regions as well as the reciprocal connectivity between the amygdala and the PFC. In a later study, inclusion of inescapable foot shocks within the CVS resulted in a significant reduction of hippocampal NPY at the 7d post recovery time point (Schmeltzer et al., 2015). Thus adaptive changes in NPY may be dependent on stressor modality and intensity within the CVS paradigm. Studies on NPY intervention in chronic traumatization models of PTSD has not been performed to date.

(iv) Inescapable foot shock (IFS) stress model

Regulation of NPY in IFS model: Foot shocks encompassing a wide range of intensity, duration and frequency have been commonly used as “traumatic stimuli” in PTSD animal models (Daskalakis et al., 2013; Goswami et al., 2013). Using a light dark box, where animals received 10 foot shocks upon crossover to the dark compartment, enhanced context –associated fear and generalized anxiety is observed post recovery (Hendriksen et al., 2012). While one can argue whether the concept of ‘trauma’ can be ascribed to rats and mice, like other models this method produces late emerging and lasting changes in behavior reminiscent of PTSD symptoms. A significant reduction of NPY Y1 receptor mRNA (but not NPY) was observed in the amygdala of shock-exposed animals at 22 d post-IFS exposure (Hendriksen et al., 2012). Interestingly, this reduction is rescued if animals are re-exposed to the shock context (without shocks) for 8 consecutive days (extinction) suggesting recruitment of amygdala Y1 receptor in PTSD-relevant behaviors in this model.

NPY Intervention in the IFS model: Based on observations of Y1 receptor recruitment in the IFS model (see above) the Y1 receptor agonist [Leu^{31},Pro^{34}]-NPY was administered into the BLA 20 minutes prior to behavioral testing at 21d post exposure to IFS. Infusion of Y1 agonist normalized the enhanced sensitivity to stress observed in IFC exposed animals when tested in the sudden silence test (SOS), a test where animals are placed in the open field with 85dB background noise, which is suddenly turned off after 5 min. Y1 agonist treatment decreased freezing and increased locomotion compared to vehicle treated animals. Freezing behavior was positively correlated with the distance of the cannula tip from the BLA, highlighting the specificity of the BLA to this effect (Hendriksen et al., 2012).

In conclusion, the weight of evidence suggests that significant region-selective changes in NPY expression may correlate temporally with PTSD- relevant physiological and behavioral responses in most paradigms, although directionality of effects may not resonate among studies. It is evident from most models that the hippocampus, amygdala and the hypothalamus may be key areas where stress-sensitive effects of the NPY system are observed. Another area is the PFC, where NPY regulation of extinction retrieval has been reported and may be relevant to PTSD (Vollmer et al, 2016). More investigation on prefrontal NPY in rodent PTSD models is warranted. Importantly, intracranial NPY intervention into the hippocampus and hypothalamus or via IN administration appears to be effective in reducing enhanced anxiety-like behavior and ASR, normalizing HPA reactivity and fear related behaviors evoked by traumatic stress exposure. Collectively, these preclinical studies support the potential attractiveness of NPY intervention in PTSD prevention and treatment. An important consideration for extrapolating from rodent models to humans is the differential NPY receptor expression between the two species (see section II).

(IV) Relevance of NPY in PTSD comorbid conditions

The evidence presented in preceding sections strongly supports an association of NPY with PTSD pathophysiology. In addition to the regulation of stress, anxiety and fear by NPY, as well as clinical studies on NPY in PTSD, it is important to note that NPY regulates other physiological responses that may contribute to comorbidities that are often associated with PTSD. These include the regulation of metabolism, nociception, addiction and depression-associated behaviors. Comorbidity of PTSD with physical illnesses and other psychiatric disorders has been identified. While it is beyond the scope of the current article to discuss each of these areas in detail, excellent reviews are referenced where applicable.

PTSD patients are at risk for developing obesity and type 2 diabetes (Farr et al., 2015; Vaccarino et al., 2014). Furthermore, PTSD has also been associated with obesity, particularly in women subjects (Kubzansky et al., 2014; Perkonigg et al., 2009). Given the interactions between stress and metabolism and a role of NPY in both appetite regulation (Stanley et al., 1986) and stress (see above), it is possible that NPY dysregulation in PTSD impacts metabolic outcomes. A recent review discusses this topic and the impact of NPY systems on body weight and metabolism in association with stress (Rasmusson et al, 2010)

Presence of chronic pain is observed in approximately 10-50% of PTSD patients suggestive of high comorbidity between the two conditions (Sharp & Harvey, 2001). PTSD-pain comorbidity is sustained by the perception of pain as a recurring trauma reminder increasing the individual's level of perceived pain, emotional distress and disability. A close association with ongoing anxiety as an exacerbating factor for pain has also been proposed (Brennstuhl et al., 2015). Anti-nociceptive actions of NPY have been widely studied in several rodent models of pain (reviewed in Brumovsky et al, 2007). Pain/stress- induced activation of the endogenous opioid system, as measured by positron emission tomography (PET), was higher in individuals with greater NPY expression (Zhou et al., 2008); this finding is consistent with better suppression of pain and stressful stimuli in this population. NPY in the BNST inhibits the affective component of pain by opposing CRH induced conditioned

place aversion (Ide et al., 2013). Reduced NPY tone in PTSD subjects may contribute to pain hypersensitivity, although these associations remain to be investigated.

Substance abuse comorbidity is present in nearly half of all PTSD patients (Breslau et al., 2003). A three-to five-fold higher incidence has been reported compared to healthy controls. Among individuals diagnosed with PTSD, the highest comorbidity is observed for alcohol dependence, followed by other substances such as opioids and cannabinoids, although stimulants like cocaine are also abused (Jacobsen et al., 2001). Conversely, approximately 25% of individuals with some addiction may suffer from some form of PTSD (Driessen et al., 2008). Regulation of the neurobiological response to addictive substances by NPY, including drugs of abuse (such as psychostimulants), nicotine and alcohol (including alcohol consumption, dependence, and withdrawal) is well established (reviewed in Gilpin & Roberto, 2012; Gonçalves et al., 2015; Thorsell, 2007). The current consensus is that NPY deficiency is associated with increased sensitivity to cocaine, elevated alcohol consumption and nicotine dependence (Wetherill et al, 2008; Bhaskar et al, 2013). Interestingly, the rs16147 polymorphism described above for stress and anxiety is also associated with increased risk for tobacco dependence (Mutschler et al., 2012). It is possible that maladaptive NPY function contributes to both PTSD and addiction physiology in individuals expressing comorbid symptoms.

Preclinical and clinical studies over the past several years support an association of NPY in the pathophysiology of depression (extensively reviewed in Eaton et al., 2007; Kormos & Gaszner, 2013; Morales-Medina et al., 2010; Wu et al., 2011)). Significant comorbidity is observed between depression and PTSD, with about 36-43 % of traumatized subjects expressing comorbid PTSD and depressive symptomology (Campbell et al., 2007; Stein & Kennedy, 2001). As for PTSD, stress has a pivotal role in the pathophysiology of depression. Stress has been identified as a risk factor for both major depressive disorder and PTSD, and together with genetic contributions results in psychopathological outcomes (Smoller, 2015). Measurements of CSF NPY in subjects with major depression have yielded inconsistent results. Initial reports showed significantly reduced CSF NPY levels in major depression (Heilig, 2004; Nikisch et al., 2005; Widerlöv et al., 1988) In contrast, other studies report no differences or significantly higher CSF NPY concentration in depressive subjects (Martinez et al., 2012; Soleimani et al., 2015). These inconsistencies may be explained by different subgroups within depression that may express higher NPY as either an adaptive response or due to genetic history (Soleimani et al., 2015). Recently, IN NPY was found to reverse depressive-like behavior evoked by SPS, a rodent model of PTSD (Serova et al., 2014). Studies on NPY association with comorbid PTSD and depression are lacking. In a recent study we reported an inverse correlation of CSF NPY with PTSD diagnostic CAPS scores, but no associations with Beck Depression Inventory (BDI) scores in PTSD subjects with depression symptoms (Sah et al., 2014).

Evidence reported in the preceding paragraphs suggests that various PTSD comorbid conditions may also be associated with NPY dysregulation reported in PTSD. However, association studies in patient populations as well as the development of animal models simulating comorbid phenomena are required to understand specific contributions of NPY to PTSD and comorbidities.

(V) Therapeutic Implications

There is a reasonable amount of evidence from ‘bench and bedside’ observations supporting NPY and NPY receptors as potential therapeutic targets for PTSD (reviewed in Brothers and Wahlestedt 2010; Sabban et al 2016). Targeting the NPY system to enhance NPY function in vulnerable individuals prior to predictable trauma (e.g. combat exposure) may facilitate resiliency and reduce the likelihood of developing PTSD. Preclinical evidence suggests that central NPY supplementation following traumatic stress can prevent the development of PTSD-like behaviors. Most data indicate that an increased availability of CNS NPY may be beneficial for several physiological responses relevant to PTSD. In this regard, administration of NPY peptide /Y1 agonists /Y2 antagonists may be effective treatments. In mice, NPY administered intravenously can enter the brain by diffusion across the blood brain barrier (Kastin and Akerstrom 1999), although NPY distribution and dynamics in humans is less well understood. Use of blood-brain barrier penetrant non-peptide NPY Y2 receptor antagonists is an interesting option (see Saldanha et al., 2010 for review). Several potent Y2 antagonists with desirable brain penetrant properties have been synthesized (Brothers and Wahlestedt, 2010, Shoblock et al, 2010, Mittapalli et al., 2012), although preclinical studies have been limited. Compound JNJ- 31020028 elicited anxiolytic and antidepressant effects in rodent models (Cippitelli et al 2011; Morales-Medina et al, 2012). This therapeutic approach has limitations: while Y2 antagonists may promote anxiolysis, they are likely to have adverse effects on the processing of fear memories, given recent evidence showing reduced fear expression via Y2 receptors (Verma et al., 2015). Moreover, systemic administration of NPY modulators may have undesirable side effects, given the modulatory effects of NPY on vasoconstriction, inflammation, angiogenesis and adipogenesis (Hirsch and Zukowska, 2012). Intranasal NPY delivery is an interesting option, as it has the potential to increase peptide concentration directly in the CNS without significant effects in the periphery. This approach has worked successfully in the SPS and PSS rodent models of PTSD (Cohen et al., 2015; Serova et al., 2013). Investigators at Mount Sinai are using this approach to study whether effective concentrations of NPY can be delivered to the human CNS (Clinical trial NCT00748956 and ongoing studies). While the IN route has worked in rodents there are several unknowns to consider before translation to humans. Differences in blood brain barrier architecture, permeability, peptide uptake and degradation mechanisms between rodents and humans are important in assessing how much peptide needs to be delivered via the IN route to reach effective CNS concentrations.

Thus, translation of NPY therapeutics from preclinical studies to humans has limitations and challenges despite the efficacy of NPY in rodent models. It would also be important to consider regional disparity in beneficial versus adverse effects of NPY on PTSD-relevant behaviors. This is especially relevant for the regulation of fear conditioning, as differential effects of NPY in the amygdala versus PFC have been reported.

(VI) Conclusions, gaps and future directions

Figure 3 illustrates a potential link between NPY dysregulation and PTSD. A combination of genetic and environmental factors, such as early adversity or chronic stress exposure, may result in maladaptive functioning of the NPY system. This may promote anxiety,

hyperarousal or impaired processing of fear memories, increasing a risk to develop PTSD. Although studies support a potential relevance of NPY in PTSD, there are several knowledge gaps in our understanding of how NPY may associate with posttraumatic physiology. So far, research groups have taken a highly fragmented view of the NPY system focusing on specific brain areas and behaviors. It would be useful to employ an interconnected, circuit level approach to start investigating how NPY and NPY receptors in different brain regions regulate circuits and transmitters impacting PTSD-relevant outcomes. For example, there is evidence of a dysfunctional connectivity and crosstalk between the amygdala and PFC in PTSD. Gaining insights on how NPY regulates PFC/amygdala circuits and its impact on behavioral outcomes (primarily fear) will be useful. Currently, information on CNS NPY in PTSD has been restricted to analysis in the CSF. While providing valuable information, NPY concentration in discrete brain areas remain unknown. Since the uptake and dynamics of NPY across CSF and regional brain compartments is unclear, we cannot assume a global reduction of NPY in the brain based on CSF analysis. Postmortem studies in healthy versus PTSD subjects are warranted in this regard. Based on evidence suggesting an interaction between early adversity and NPY gene polymorphisms, it would be important to investigate epigenetic modifications in segments around SNPs identified in NPY and NPY receptor genes in association with PTSD diagnosis. These studies may potentially lead to the development of biomarkers for PTSD risk and susceptibility. In conclusion, the NPY system is of relevance to PTSD pathophysiology. However, the applicability of NPY and NPY receptors in the development, diagnosis and treatment of PTSD still remains to be demonstrated.

Acknowledgments

Support from VA Merit Award grants (I01BX001075 and 2I01BX001075) to Dr. Renu Sah and MH049698 to Dr. James Herman is acknowledged.

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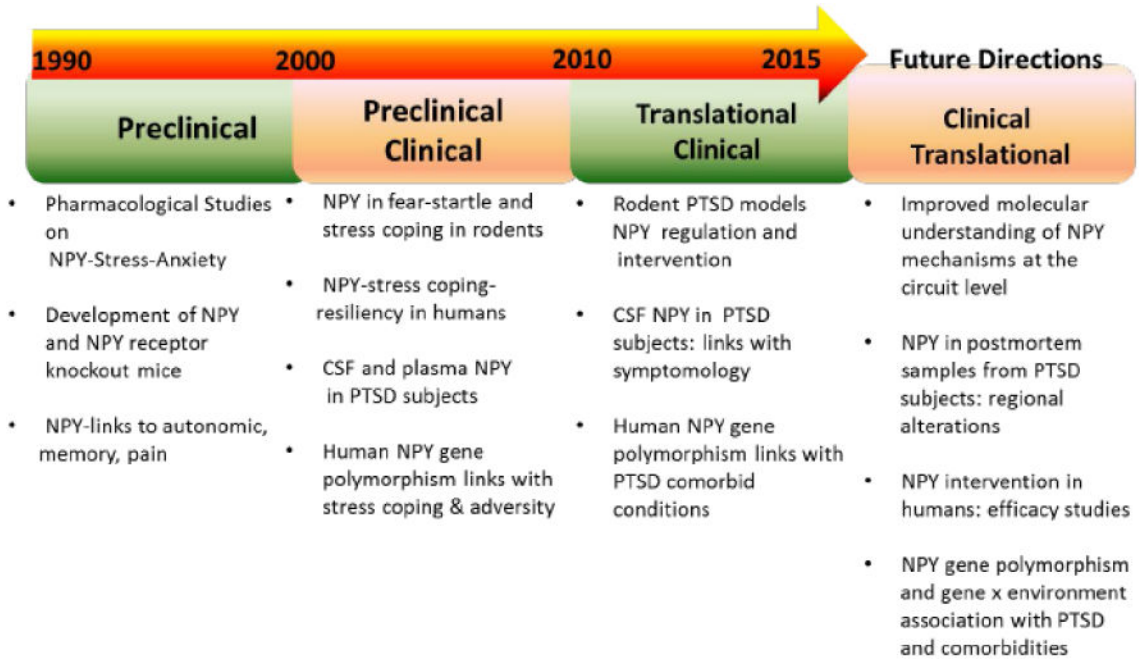

Figure 1.

Temporal trajectory of scientific observations from preclinical, clinical and translational animal models supporting an association of NPY with PTSD pathophysiology. Note the transition from preclinical studies to clinical and PTSD animal model studies forming a cycle of “bench” to “bedside” to “bench”. Preclinical observations supporting NPY regulation of stress, anxiety, autonomic regulation, memory and pain led to human trials on NPY and stress resiliency and coping. These observations were followed by CSF studies reporting NPY dysregulation in PTSD patients and genetic studies linking NPY polymorphisms with stress coping and resiliency. Ongoing preclinical studies on NPY and fear suggested potential links to PTSD symptomology. Clinical findings on NPY deficiency in PTSD prompted translational studies in animal models testing therapeutic potential of NPY intervention. Future studies are required on regional and circuit-based approaches to understand molecular mechanisms linking NPY to PTSD physiology. Preclincal observations on regional disparity in NPY function further necessitate the investigation of regional NPY status in postmortem brain tissue in PTSD. Human intervention studies will require an improved understanding of blood brain barrier permeability, CSF dynamics and novel NPY analogs for efficacious NPY targeting to the brain.

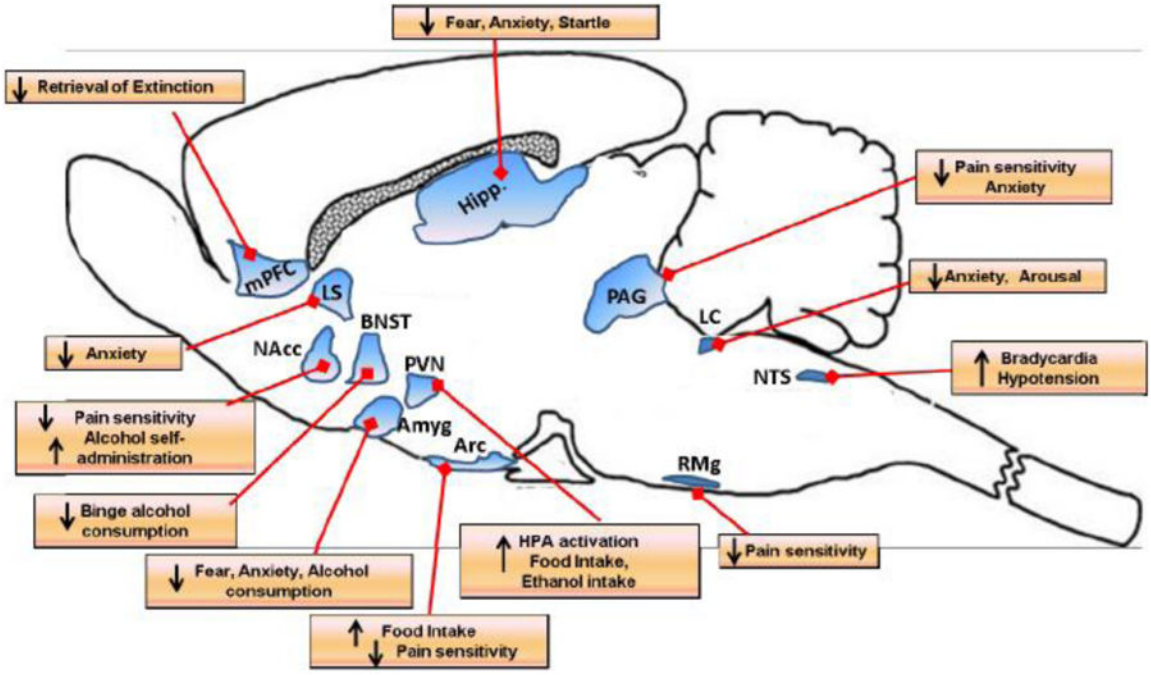

Figure 2.

Potential sites for the regulation of behavioral and physiological responses relevant to PTSD and other comorbid conditions by NPY. Selection of target sites and responses are based on preclinical studies described in the text. (↑= increase; ↓= decrease).

mPFC=medial prefrontal cortex, LS=lateral septum, Nacc=nucleus accumbens, Hipp=hippocampus, BNST=bed nucleus of the stria terminalis, PVN=paraventricular nucleus of the hypothalamus, Amyg.=amygdala, Arc=arcuate nucleus of the hypothalamus, PAG=periaqueductal grey, RMg=nucleus raphe magnus, LC=locus coeruleus, NTS=nucleus of the solitary tract

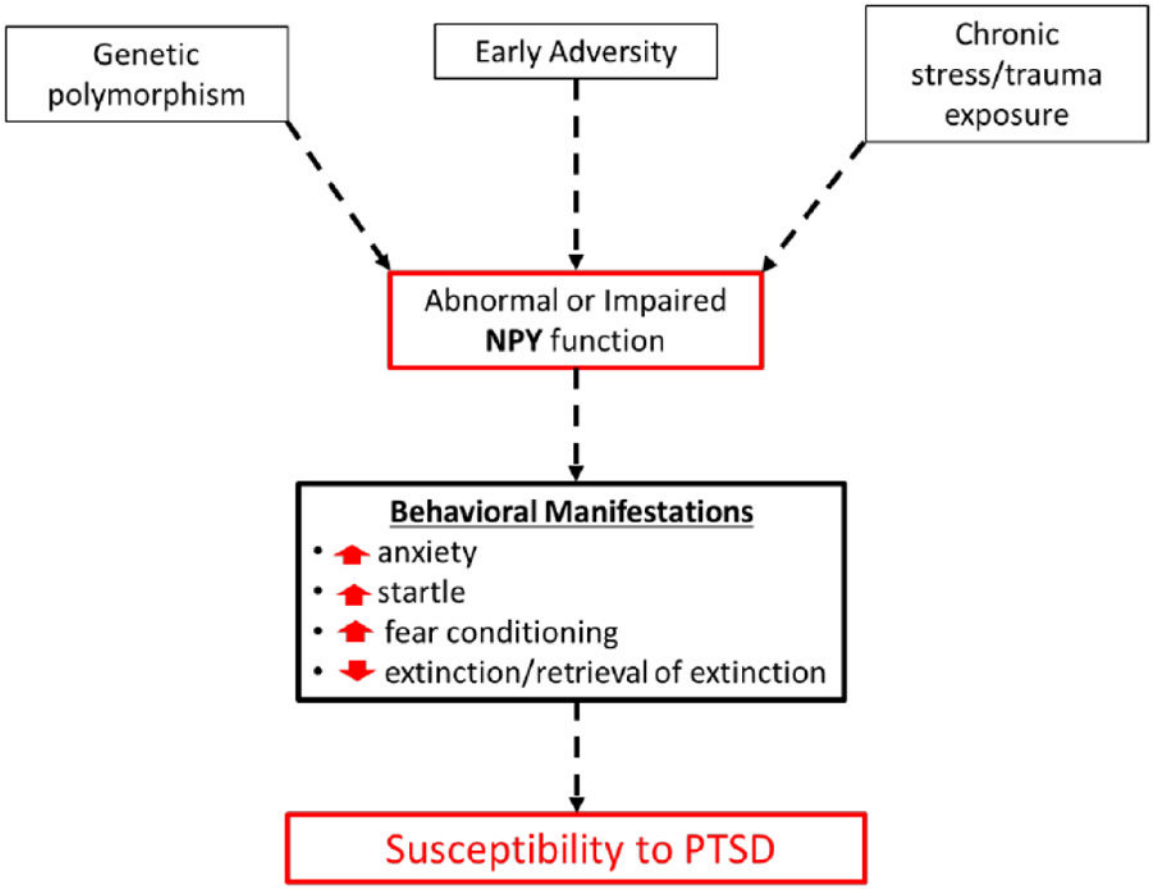

Figure 3.

Potential links of NPY with PTSD susceptibility. A combination of genetic and environmental factors such as early adversity or chronic stress exposure may result in maladaptive functioning of the NPY system. This may promote anxiety, hyperarousal and impaired processing of fear memories promoting the development of PTSD.

Table 1

Y receptor subtype	Ligand preference	Agonists [antagonists]	Cell Signaling ** (coupled to Gi/Go/Gq)
Y1	NPY>PYY⋙PP	[Leu^{31}, Pro^{34}]NPY (Y1/Y5) *, F^{7}P^{34} NPY [BIBO3304,BIBP3226,1229U91, GR231118 *, J-104870, J-115814, BW1911U90, BMS193885]	cAMP/PKA/PLC-IP3-Ca^{2+} GIRK channel I_H current (HCN channel)
Y2	NPY=PYY⋙PP	PYY/NPY(3–36), PYY/NPY(13–36), [ahx$^{5-24}$]NP, [BIIE0246, JNJ-3102008, JNJ-5207787, SF-11]	cAMP-PKA PLC-IP3-Ca^{2+} PI3K-ERK Ca^{2+} channel
Y4	PP⋙PYY=NPY	PP, BVD-74D, 1229U91 [GR231118 *, Obinepitide (TM30338) (UR-AK49)]	PLC-IP3-Ca2 cAMP-PKA
Y5	NPY>PYY>PP	[CPP$^{1-7}$, NPY$^{19-23}$ Ala^{31}, Aib^{32},Gln^{34}] hPP, Velneperit, L152,804, 2-36[K4,RYYSA(19-23)]PP [CGP71683A, MK-0577, HTS hit 1-derivative 4i, Lu AE00654]	cAMP-PKA PI3K-ERK

*Y1 preferring;

**Refer to text for references

Table 2

Cerebrospinal fluid (CSF) and plasma NPY alterations in PTSD and PTSD-comorbid conditions

Condition	Pool	Alteration in NPY	Reference
PTSD	CSF	↓NPY vs healthy volunteers	Sah et al, 2009
PTSD	CSF	↓CSF NPY vs combat-no PTSD group	Sah et al, 2014
PTSD	Plasma	↓baseline NPY ↓yohimbine-stimulated NPY vs healthy volunteers	Rasmusson et al, 2000
PTSD	Plasma	↓baseline NPY in combat-PTSD and combat-no PTSD group vs healthy volunteers	Morgan et al, 2003
PTSD	Plasma	↑baseline NPY in combat cohort with past PTSD vs combat cohort with no PTSD	Yehuda et al, 2006
Primary Insomnia	Plasma	↓NPY (morning levels)	Huang et al, 2015
Substance Dependence	Plasma	↓Stress-induced increases in plasma NPY (compared to healthy controls)	Xu et al, 2012
Impulsive Aggression	CSF	↑CSF NPY-like immunoreactivity correlates with ↑Impulsive aggression scores	Coccaro et al, 2012

↓= decrease; ↑= increase

Table 3

Animal Models of PTSD: Regulation of NPY / NPY receptor expression and outcomes of NPY Intervention

Model (Species)	NPY Expression	NPY Intervention	Intervention Outcomes	Reference
Predator Scent Stress (PSS) (rat)	(7d post-PSS) ↓ NPY peptide ELISA (posterior cortex, mygdala hippocampus, PAG) ↓ NPY (immunohistochem) (hippocampal CA1, dentate))	NPY dorsal hippocampus (I hr. post-PSS)	Compared to aCSF (7d post-PSS) ↑ EPM Open arm time ↓ startle amplitude ↑ NPY and Y1R in DG ↑ BDNF in CA3 and DG ↓ contextual freezing	Cohen et al, 2012
	(8d post-PSS) PSS (prior to light cycle) ↓ NPY (immunohistochem) (Arcuate nucleus, CA1, dentate, BLA) PSS (prior to dark cycle) ↓ NPY (immunohistochem) (CA1, dentate, BLA)	NPY PVN (30 min. prior to PSS)	Compared to aCSF (7d post-PSS) ↑ EPM open arm time ↓startle amplitude ↑ PVN NPY, Y1r immunoreactivity	Cohen et al, 2014
Single Prolonged Stress (SPS) (rat)	(7d post-SPS) ↑ NPY peptide (amygdala) ↑ NPY (immunohistochem) (BLA)	ND	ND	Cui et al, 2008
	ND	NPY Intranasal (30 min prior to SPS) NPY Intranasal (immediately post-SPS)	Compared to vehicle (7d post SPS) ↓ immobility in FST ↑ EPM open arm entries and risk assessment ↓ acoustic startle amplitude ↓ TH mRNA ↓ immobility in FST	Serova et al 2013
	(9d post-SPS) ↓ NPY immunoreactivity (PVN)	ND	ND	Lee et al 2014
	ND	Intranasal NPY (immediately post-SPS)	Compared to vehicle: (7d post SPS) ↓ baseline ACTH/CORT ↓ CRH mRNA (hypothalamus, hippocampus) ↓ FKBP5 mRNA (hypothalamus hippocampus)	Laukova et al, 2014
	ND	Intranasal NPY (7 d post-SPS)	Compared to vehicle: (2d post treatment) ↑ open arm entry (EPM)) ↑ Risk Assessment (EPM) ↓ immobility in FST	Serova et al, 2014
	(7d post-SPS) ↓ NPY mRNA (amygdala)	ND	ND	Nedelcovych et al 2015
	(9d post-SPS)	Intranasal NPY (immed. post-SPS)	Compared to vehicle (7d post SPS): ↓ TH protein and immunoreactivity (LC) ↓ CRH R1 mRNA (LC) ↓ CRH peptide (CeA) ↑ Y2 receptor mRNA (LC)	Sabban et al,. 2015
Chronic Variable Stress (CVS) (rat)	(7 days post-CVS) ↓ NPY peptide (amygdala) ↑ NPY peptide (PFC)	ND	ND	McGuire et al, 2011
Chronic Variable Stress-Shock (CVS-S) (rat)	(9 days post CVS-S) ↓ NPY peptide (Hippocampus)	ND	ND	Schmeltzer et al, 2015
Inescapable Foot Shock (IFS) (rat)	(22 days post-IFS) ↓ Y1R mRNA (amygdala)	NPY-Y1 agonist [Leu31, Pro34] BLA (21d post-IFS)	(21d post-IFS) ↑ locomotion in SOS test ↓ freezing in SOS test (SOS =stress of sudden silence)	Hendriksen et al, 2012
Predator Exposure (PE) (mice)	(7h post PE) ↑ Y1 mRNA (amygdala) ↑ Y2 mRNA (amygdala)	ND	ND	Varman et al, 2015

Abbreviations: ↓= decrease; ↑= increase; ND= not determined;