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Minireview

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Neuropeptide Regulation of Signaling and Behavior in the BNST

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Recent technical developments have transformed how neuroscientists can probe brain function. What was once thought to be difficult and perhaps impossible, stimulating a single set of long range inputs among many, is now relatively straight-forward using optogenetic approaches. This has provided an avalanche of data demonstrating causal roles for circuits in a variety of behaviors. However, despite the critical role that neuropeptide signaling plays in the regulation of behavior and physiology of the brain, there have been remarkably few studies demonstrating how peptide release is causally linked to behaviors. This is likely due to both the different time scale by which peptides act on and the modulatory nature of their actions. For example, while glutamate release can effectively transmit information between synapses in milliseconds, peptide release is potentially slower [See the excellent review by Van Den Pol on the time scales and mechanisms of release (van den Pol, 2012)] and it can only tune the existing signals via modulation. And while there have been some studies exploring mechanisms of release, it is still not as clearly known what is required for efficient peptide release. Furthermore, this analysis could be complicated by the fact that there are multiple peptides released, some of which may act in contrast. Despite these limitations, there are a number of groups making progress in this area. The goal of this review is to explore the role of peptide signaling in one specific structure, the bed nucleus of the stria terminalis, that has proven to be a fertile ground for peptide action.

THE BED NUCLEUS OF THE STRIA TERMINALIS (BNST)

The bed nucleus of the stria terminalis (BNST) is a limbic structure in the brain situated medial to the striatum and later to the septum. Because of its rich connectivity (discussed below) its role in regulation of behavior has been extensively studied. Broadly, this region has been shown to play a role in stress or aversion related behaviors, however there is also evidence that it can regulate appetitive responses. Numerous pharmacological studies targeting different peptide systems as well as monoaminergic systems have found that the BNST plays a key role in anxiety. For example, the Davis group has found that CRF in the BNST can potently enhance anxiety (Walker et al., 2009b) and the Hammack group has found that PACAP signaling can alter stress responses (Kocho-Schellenberg et al., 2014; Lezak et al., 2014a; 2014b). In support of this, recent findings from several groups using optogenetic approaches have shown the BNST plays a role in anxiety (Jennings et al., 2013a; Kim et al., 2013), however these manuscripts also found that there were potent anxiolytic pathways in the BNST. This highlights one of the major positive aspects of optogenetic approaches, the ability to probe genetically and anatomically defined circuits allows a glimpse in to processes that may play subtle roles in regulation of behavior.

In addition to anxiety, several reports have suggested that the BNST is involved fear learning. A study by Sullivan et al., found that lesions of the BNST can alter contextual fear conditioning, but not cued fear conditioning (Sullivan et al., 2004). This is not inconsistent with the data from the Davis group demonstrating that inactivation of the BNST can alter the fear response to a long duration (8 min) cue, suggesting that the BNST plays a role in responding to more diffuse stimuli (Davis and Shi, 1999; Davis and Walker, 2013, Davis et al., 1997a; 1997b; Gewirtz et al., 1998; Walker and Davis 1997; Walker et al., 2009a). Interesting, a recent paper from Duvarci et al., found that lesioning the BNST could alter fear generalization in a fashion that suggests the BNST is involved in safety learning (Duvarci et al., 2009). This appears to contrast with the previous BNST fear learning data, however, it is important to note that the Duvarci paper used the Lewis rat strain. This particular strain exhibits altered HPA function and noradrenergic function in the BNST, so it is possible that these results are due to aberrant plasticity (McElligott et al., 2013). Interestingly, there have been several recent papers demonstrating that acute fluoxetine can increase cue-induced fear recall via its actions in the BNST (Burghardt and Bauer, 2013; Ravinder et al., 2013). This raises an intriguing possibility that during 'basal' states, the BNST plays no role in cued fear learning, however during states of altered biogenic amine levels, it then turns 'online' and plays a role in cued fear learning.

The BNST is a site of integration of stress and reward information and may mediate the negative affective state associated with chronic alcohol/drug use. The BNST mediates stress-

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induced relapse to drug seeking (Erb et al., 2001). While less is known about the role of the BNST specifically in self-administration of abused drugs, there have been several studies demonstrating that pharmacological manipulations in the BNST can alter alcohol drinking (Eiler et al., 2003) and cocaine self administration behaviors (Epping-Jordan et al., 1998). Additionally, there is a body of evidence suggesting that BNST neuronal function is altered by exposure to drugs of abuse. In particular, several studies have found that chronic alcohol exposure and withdrawal alters the function and glutamatergic plasticity of BNST neurons (Kash et al., 2009; Wills et al., 2012). The BNST has also been implicated in feeding related behaviors (Betley et al., 2013; Jennings et al., 2013b). This is not surprising, as stress and anxiety can exert powerful effects on feeding behaviors. Briefly, as these particular ideas will be discussed below in the sections of individual peptides, the BNST has been shown to play potent roles in both the inhibition and stimulation of feeding related behaviors.

Tracing studies have shown that the BNST receives cortical inputs from the infralimbic and prelimbic regions of the prefrontal cortex (Chiba et al., 2001; Hurley et al., 1991; Takagishi and Chiba 1991; Vertes, 2004) that may be important for fear responses. The infralimbic and prelimbic prefrontal cortices are involved in both the expression and extinction of fear and drug seeking behaviors (Gass et al., 2014) perhaps through via recruitment of the BNST (Bruchas et al., 2009). Thalamic inputs from the paraventricular nucleus may also govern fear behavior (Li et al., 2014) in addition to aspects of addiction (Browning et al., 2014; Matzeu et al., 2014) and stress responses (Heydendael et al., 2011). Biogenic amine inputs to the BNST originate from discrete cell populations. Noradrenergic inputs to the BNST arising from the nucleus of the solitary tract, ventrolateral medulla, locus coeruleus and parabrachial nucleus (Myers et al., 2005) may modulate behaviors related to addiction, stress and mood (Flavin and Winder, 2013, McElligott et al., 2013; McReynolds et al., 2014; Nagai et al., 2013; Wenzel et al., 2014). Serotonin inputs from the dorsal raphe nucleus (Peyron et al., 1998, Shin et al., 2008) and dopaminergic inputs from the ventral periaqueductal gray and ventral tegmental areas (Hasue and Shammah-Lagnado, 2002; Herr et al., 2012) likely modulate similar behaviors. In turn, the BNST orchestrates complex behavioral responses related to addiction, mood and stress via outputs to the hypothalamus, amygdala, nucleus accumbens, dorasl raphe and ventral tegmental area (Choi et al., 2007; Dong et al., 2001a; 2001b). With the advent of new technologies allowing pathway-specific modulation of neuronal function, the contribution of specific BNST projections to behavioral responses can be evaluated. For example, recent investigations using ***in vivo*** optogenetics demonstrate that BNST outputs to the lateral hypothalamus, parabrachial nucleus and ventral tegmental area govern distinct aspects of anxiety and motivational responses (Jennings et al., 2013a; Kim et al., 2013). Importantly, beyond the anatomical framework for how the BNST functions, there is a neurochemical heterogeneity that plays a major role in regulation of behavior. In terms of classical neurotransmistters, while the majority of neurons are GABAergic, expressing the vesicular GABA transporter (vGAT), there is also a small subpopulation of glutamate neurons expression the vesicular glutamate tranporter 2 (vGlut2). Finally, there is a small subpopulation of neurons that expresses vGlut3, however these appear to be GABAergic as well. In addition to these different neurotransmitter releasing populations of neurons, there is a tremendous amount of diversity of peptides expressed in the BNST. This includes, but is not limited to the peptides that are discussed below. It is tempting to speculate that these diverse populations of neurons are engaged and encode different signals that allow for fine-tuning of behavior.

CORTICOTROPIN RELEASING FACTOR (CRF)

Corticotropin releasing factor (CRF) belongs to a family of neuropeptides that includes CRF, urotensis-1, urocortin, and sauvagine (Lovejoy and Balment, 1999). CRF is a 41-amino-acid peptide that is predominantly expressed in the paraventricular nucleus of the hypothalamus (PVN), where it acts as a hormone that triggers a neuroendocrine response to stress which ultimately releases glucocorticoids into circulation. However, extrahypothalamic sites of CRF action can be found in the extended amygdala, including the BNST, where it acts as a peptide neurotransmitter that can robustly shape circuit function and behavior (Huang et al., 2010; Kash and Winder, 2006; Silberman et al., 2013). Within the BNST, CRF neurons are clustered in the dorsolateral and ventrolateral aspects (Phelix et al., 1992; Silberman et al., 2013), with a high concentration found in the oval and fusiform nuclei (Cummings et al., 1983; Morin et al., 1999). Dense CRF terminals are also found in the oval nucleus of the BNST, which may originate from local CRF neurons in the BNST or from CRF neurons projecting from the CeA (Cummings et al., 1983; Morin et al., 1999; Sakanaka et al., 1986).

CRF neurons in the BNST colocalize with serotonin (5HT) terminals, suggesting that inputs from the dorsal raphe nucleus (DRN) may interact with CRF neurons in the BNST (Phelix et al., 1992). Previous work in 5HT2c-R knockout mice also suggests that CRF neurons in the BNST express 5HT2c receptors (5HT2c-Rs), which have excitatory post-synaptic effects (Guo et al., 2009). This raises the possibility that the well-documented anxiety-provoking aspects of 5HT2c-R signaling may be at least partially mediated by its actions in this specific cell population. Interestingly, dopamine and norepinephrine (NE) also depolarize CRF neurons in the BNST (Silberman et al., 2013), suggesting a common pathway for biogenic amine signaling in the BNST. These direct actions of norepinephrine and dopamine on CRF neurons suggest that projections from the noradrenergic projections from the locus coeruleus (LC) and dopaminergic projections from the periaquaductal grey (PAG) (Hasue and Shammah-Lagnado, 2002; Meloni et al., 2006) synapse directly on CRF neurons in the BNST.

A substantial body of evidence supports the role of CRF signaling in the BNST in general anxiety (Gafford et al., 2012; Sahuque et al., 2006; Sink et al., 2013), social anxiety (Lee et al., 2008), acoustic startle responses (Sink et al., 2013; Walker et al., 2009b) anxiety generated by stress (Heisler et al., 2007; Tran et al., 2014) retention of emotional memory (Liang et al., 2001) and anxiety during withdrawal from drugs of abuse (Huang et al., 2010; Overstreet et al., 2003). The direction of these responses is receptor type dependent, as CRF1-R and CRF2-Rs in the BNST exert opposing roles on stress-induced anxiety, neuroendocrine response, and pain threshold, with CRF1-Rs augmenting these responses and CRF2-Rs inhibiting them (Tran et al., 2014). The oval nucleus, a rich source of CRF neurons and terminals, may be a critical site of action for these behavioral effects. In an elegant study by Deisseroth and colleagues, selective activation of the oval nucleus was shown to generate anxiety-like behavior (Kim et al., 2013), which may be mediated by CRF neurons or terminals within this region. However, a recent study also identified the anterolateral portion of the BNST as an important locus for CRF1R signaling in stress-induced anxiety (Tran et al., 2014), indicating that CRF

may have a more ubiquitous role in generating anxiety within the BNST.

Anxiety precipitated by drug withdrawal was recently proposed as a significant motivating factor in stress-induced reinstatement of drug-seeking behavior, with CRF1R signaling in the BNST providing a key link (Erb, 2010; Erb and Stewart 1999). The BNST is ideally position to integrate stress and reinforced behavior given its reciprocal connections with the extended amygdala and mesocorticolimbic systems that process reward, particularly the ventral tegmental area (VTA) (Aston-Jones and Harris, 2004). In fact, a recent study has shown that acute withdrawal from chronic intermittent ethanol (CIE), which provokes a robust anxiety phenotype in rodents (Lowery-Gionta et al., 2014; Overstreet et al., 2003), also enhances excitatory transmission on VTA projecting neurons in a CRF1-R dependent fashion (Silberman et al., 2013). This BNST-to-VTA pathway has been implicated in both anxiety and motivated behavior (Jennings et al., 2013a), suggesting a potential mechanism of action for CRF in both drug-related anxiety and reinstatement. Although Erb and colleagues argue that the CRF projections from the CeA are primary source of CRF in these behaviors (Erb et al., 2001), emerging evidence indicates that local CRF neurons in the BNST may play a critical role. Stress activates neurons in the LC that release NE, which was recently shown to depolarize CRF neurons in the BNST (Silberman et al., 2013). In a recent study, β2-adrenergic receptors (β2-AR) antagonists blocked stress-induced reinstatement to cocaine-conditioned reward and stress-induced increases in CRF mRNA in the BNST but not the CeA (McReynolds et al., 2014). Taken together, these data indicate that NE acting at CRF neurons in the BNST induces reinstatement behaviors.

Stress-induced inhibition of feeding behavior was traditionally thought to be mediated by hypothalamic CRF (Carr, 2002), but evidence for an extrahypothalamic role of CRF has also begun to emerge (Ciccocioppo et al., 2003a; 2004). In a recent study, it was found that GABAergic projections from the BNST to LH hypothalamus robustly enhance feeding (Jennings et al., 2013b), raising the possibility that CRF may exert its anorexic effects by inhibiting this projection. This CRF-mediated suppression of feeding appears to mediated by CRF-2Rs (Ohata and Shibasaki, 2011), suggesting that CRF2R may enhance GABAergic drive onto LH projecting neurons in the BNST in a manner similar to the laterocapsular division of the CeA (Fu and Neugebauer, 2008). Conversely, binge eating induced by frustration stress in female rats (e.g. the sight of palatable food before allowing access), was attenuated by CRF1-R antagonists infused in the BNST (Micioni Di Bonaventura et al., 2014), suggesting that stress-induced hyperphagia, but not hypophagia, is mediated by CRF1-R signaling.

Cellular effects

CRF binds to CRF-1 and CRF-2 receptors (CRF-1Rs and CRF-2Rs), which are G-protein coupled receptors (GPCRs) acting through a Gs-cAMP-PKA signaling mechanism (Arzt and Holsboer, 2006; Blank et al., 2003; Dautenberg and Hauger, 2002; Reul and Holsboer, 2002). Despite their common signal transduction mechanisms, CRF1- and CRF-2Rs appear to have opposing actions on stress responsiveness, pain perception. startle response, and anxiety (Fu and Neugebauer, 2008; Takahashi, 2001; Tran et al., 2014). In the laterocapsular division of the CeA, CRF1-Rs increase excitability in a postsynaptic fashion, while CRF2-Rs act presynaptically to increase GABA release. However, the cellular actions of CRF in the BNST appear to be a bit more convoluted. CRF1-R signaling in the BNST enhances glutamatergic drive on neurons projecting to the VTA in a presynaptic fashion (Silberman et al., 2013) while enhancing GABAergic transmission in a postsynaptic manner (Kash and Winder, 2006). Given that CRF neurons in the BNST are GABAergic (Dabrowska et al., 2013), CRF released from the same neuron may enhance responses to GABA via postsynaptic CRF1Rs. On the other hand, glutamatergic terminals likely express presynaptic CRF1Rs that enhance glutamate release. Taken together, these data suggest that CRF can enhance both inhibitory and excitatory transmission in the BNST, albeit through distinct signaling mechanisms. The behavioral outcomes of this are unclear, although if CRF1-R signaling in the BNST is strictly anxiogenic, then we might expect CRF to increase GABAergic transmission in anxiolytic circuits and glutamatergic transmission in anxiogenic circuits.

Early life stress or repeated, uncontrollable stress has been associated with a myriad of neuropsychiatric conditions ranging from post-traumatic stress disorder (PTSD), general anxiety disorder (GAD), social anxiety disorder (SAD) and Major Depression (MD). For this reason, stress is often used to recapitulate the neuroendocrine and physiological events that lead to the behavioral disturbances characteristic of these disorders in animal models of psychiatric disease. Social defeat stress, which induces both anhedonia and learned helplessness that are the hallmarks of depression (Hollis et al., 2011; Rygula et al., 2005; 2006) as well as anxiety-like behavior (Kinsey et al., 2007; Patki et al., 2014), has also been shown to increase CRF mRNA in the BNST (Funk et al., 2006b). Likewise, novel environment stress activates CRF neurons in the BNST (Heisler et al., 2007), which were previously implicated in local, CRF1-R dependent modulation of anxiety circuity.

CRF2-R signalingin the BNST, previously shown to have important implications for feeding behavior, have been recently implicated in the pathophysiology of PTSD (Elharrar et al., 2013; Lebow et al., 2012). In a recent study, exposure to trauma-related cues provoked elevations in CRF1R expression coupled with persistent downregulation of CRF2-Rs in rats susceptible to PTSD-like behavior, which was rescued by overexpression of CRF2-Rs in the medial posterointermediate BNST (Elharrar et al., 2013). In a mouse model of PTSD involving repeated exposure to a traumatic series of shocks, mice exhibiting a PTSD-like phenotype had long-lasting upregulation of CRFR-2 mRNA in the BNST, while genetic knockdown of CRF2-R in the posterior medial BNST was protective against the development of PTSD-like characteristics (Lebow et al., 2012). These data corroborate the bidirectionality of CRF1-R and CRF2-R responses seen in models of anxiety and pain perception (Tran et al., 2014).

The core features of addiction recapitulated in animal models of drug dependence typically include anxiety, reinforcement, and dysphoria. During withdrawal from chronic intermittent ethanol (CIE), which elicits anxiety (Lowery-Gionta et al., 2014; Overstreet et al., 2003) and enhanced ethanol seeking behavior (Lopez et al., 2012), CRF peptide levels were elevated in the BNST and normalized by subsequent ethanol intake (Olive et al., 2002). Furthermore, direct infusion of CRF1-R antagonists into the BNST alleviates anxiety associated with CIE withdrawal in rats (Huang et al., 2010). Together, these data indicate that ethanol-induced reductions in CRF signaling in the BNST following CIE may alleviate anxiety and lead to escalated drinking behavior, a hallmark of ethanol dependence. However, this view is confounded by the fact that CRF1-R antagonists infused in the CeA, but not the BNST, block enhanced ethanol self-administration in ethanol-withdrawn rats (Funk et al., 2006a).

Thus, although CRF actions in the BNST are principally involved in the anxiety-provoking aspects of ethanol withdrawal, the transition to dependence marked by enhanced ethanol seeking behavior may involves a complex interplay between CRF systems in the BNST and CeA that involve direct or indirect crosstalk between the two. The juxtacapsular BNST (jcBNST), a region that sends inhibitory projections to the CeA, shows marked reductions in excitability after protracted withdrawal from CIE (Szücs et al., 2012). Similarly, protracted withdrawal from an ethanol self-administration regimen that leads to escalated responding after reintroduction of ethanol impairs the long-term potentiation of intrinsic excitability (LTP-IE) in the jcBNST (Francesconi et al., 2009). CRF1-R antagonists normalized this response, while repeated administration of CRF mimicked the effect of protracted withdrawal on LTP-IE in the jcBNST. Thus, CRF actions in the jcBNST may in effect disinhibit the CeA, leading to long-term adaptation in ethanol sensitivity and patterns of ethanol consumption. Further modulation by CRF at the level of the CeA may also play a role in these behaviors. The adaptations in CRF signaling in the BNST observed in models of ethanol dependence also general to other drugs of abuse, including cocaine (Erb and Stewart, 1999; McReynolds et al., 2014; Nader et al., 2011; 2012) and morphine (García-Carmona et al., 2013; Wang et al., 2006).

DYNORPHIN

Dynorphin, a member of the opioid peptide family, is thought to mediate dysphoria and may be a key component of stress and drug withdrawal (Koob and Le Moal, 2008). Though dynorphin and its endogenous receptor, the kappa opioid receptor (KOR) are known to exist in the BNST (Li et al., 2012), little work has been done assessing this crucial peptide. While the precise projection pattern and innervation of these neurons in the BNST has not been demonstrated, some molecular and anatomical work has been done, providing a potential clue to their function. Dynorphin-A (Poulin et al., 2009) and Dynorphin-B (Fallon and Leslie, 1986) are expressed throughout the anterior-posterior regions of the BNST, with dense concentrations of Dynorphin-A in the oval nucleus. Interestingly, dynorphin and substance P may be co-localized in some of these neurons in some species (Neal et al., 1989). In addition to local dynorphin neurons, GABAergic neurons co-expressing dynorphin in the central amygdala (CeA) send a projection to the BNST (Marchant et al., 2007). KOR activation inhibits GABA transmission from the CeA (Li et al., 2012). There is therefore a potential for multiple sources of dynorphin in the BNST, and complex interactions between these neurons.

Some work has been done addressing the potential role of dynorphin in the BNST and stress. proDynorphin mRNA increased following forced swim (Chung et al., 2014). Metabolic activation in the BNST is evident after administration of the KOR agonist Salvinorin-A (Hooker et al., 2009). The dynorphin and CRF systems have long been though to mediate stress and anxiety (Bruchas et al., 2009); specifically, the Chavkin lab has hypothesized some of CRF's key actions may be through the KOR system, though this interaction has not been demonstrated in the BNST.

In addition, recent literature has focused on sex differences and the KOR system. Females displayed conditioned place aversion at a low (2.5 mg/kg) dose of a KOR agonist, U-50488, while males displayed CPA at a higher (10 mg/kg) dose (in addition, the higher dose decreased social interaction in both sexes) (Robles et al., 2014). Interestingly, the larger dose also increased the number of pERK neurons in the ventral BNST, a sub-region of the BNST associated with aggressive behavior. Another study by the Chartoff lab (Russell et al., 2014) demonstrated that female mice are less-sensitive to the reward-decreasing effects of U-50488 in a intracranial self-stimulation (ICSS) paradigm. In addition, though U-50488 induced in C-Fos positive cells in both males and females, the increase in females was dependent on estrus cycle (interestingly, the C-Fos positive neurons appeared to be CRF negative, further highlighting the potential interaction between the dynorphin-CRF systems).

NPY

Neuropeptide Y (NPY) is a 36-amino acid protein with five known receptors (Y1R-Y5R) located throughout the central and peripheral nervous system. Central signaling of the endogenous "anti-stress" NPY system is recruited acutely to help maintain or reachieve homeostasis in the presence of stressors (e.g., Heilig et al., 1994). NPY also protects organisms from the negative behavioral consequences of chronic exposure to stressors, including anxiety, depression, and compulsive reward, drug, and alcohol-seeking behavior (Cippitelli et al., 2010; Heilig, 2004; Heilig and Thorsell, 2002; Pandey et al., 2003).

NPY mRNA and protein have been identified in the BNST of many species. Specifically, a number of immunohistochemical studies have characterized a moderate level of cell body expression of NPY and dense expression of NPY in fibers in the BNST of rodents including laboratory rats and mice (Allen et al., 1983; Chronwall et al., 1985; O'Donohue et al., 1985; Pleil et al., 2012; Shen 1987), hamsters (Botchkina and Morin, 1995; Burroughs et al., 1996; Reuss and Olcese, 1995), and ground squirrels (Reuss et al., 1990, Smith et al., 1985), as well as avian species (Kuenzel and McMurtry, 1988), sheep (Pompolo et al., 2005), and human and non-human primates (Adrian et al., 1983; Beal et al., 1987; Gaspar et al., 1987; Walter et al., 1991). Dense NPY expression in the BNST and co-expression with markers for the inhibitory neurotransmitter GABA (Pompolo et al., 2005) are rather conserved phenomena across species, indicating its potential importance in the regulation of conserved, basic animal behaviors. However, co-expression of NPY with other peptides and molecules varies; for example, NPY neurons in the BNST densely co-express somatostatin in rodents (McDonald, 1989) but do so to a much lesser degree in humans (Gaspar et al., 1987) and non-human primates (Beal et al., 1987). Neurons within the BNST that synthesize NPY have also been shown to project to downstream targets including those in the hypothalamus, such as the preoptic area (Pompolo et al., 2005).

The high density of NPY-positive fibers in the BNST is likely due to a combination of axons from NPY interneurons within the BNST, as well as projections from other brain regions rich with NPY neurons. The most dense NPY input to the BNST that has been identified is that from agouti-related protein (AgRP) neurons in the arcuate nucleus of the hypothalamus (ARC), which co-release NPY (Betley et al., 2013; Nilsson et al., 2005). Interestingly, the density of NPY-containing neurons in the BNST increases across development and adolescence to reach its peak by early adulthood (Carty et al., 2010), and AgRP density in the ARC follows a similar timeline (Nilsson et al., 2005), together suggesting that NPY function in the BNST is fully mature by this time. In addition, several NPY receptors known to mediate the functional behavioral properties of NPY are densely expressed in the BNST, including Y1R, Y2R, and Y5R (Dumont et al., 1996; Kash and Winder 2006; Pleil et al.,

2012; Sparrow et al., 2012; Weinberg et al., 1996), further implicating NPY signaling within the BNST as a potentially relevant mechanism for the regulation of emotional and reward-seeking behaviors.

Very few studies have examined the behavior and functional modulatory roles of NPY in the BNST. One study showed that NPY and CRF have opposing functional modulatory roles on inhibitory transmission in the BNST, with NPY inhibiting GABA transmission via presynaptic Y2Rs (Kash and Winder, 2006). Further examination showed that chronic restraint stress increases NPY and Y2R expression in the BNST and reduces the Y2R-mediated effect of NPY on inhibitory synaptic transmission in a stress-susceptible mouse strain (DBA/2J), but not a stress-resilient strain (C57BL/6J) (Pleil et al., 2012). In addition to these studies, several studies have examined the impact of behavioral or systemic/central pharmacological challenges on NPY expression in the BNST, implicating the involvement of NPY signaling in the BNST involvement in stress responsivity, drug/reward seeking behaviors, pain, and neurodegenerative diseases. For example, behavioral flexibility in a stress coping response to chronic variable stressors has been associated with increased NPY expression in the BNST (Hawley et al., 2010). Another study showed that intracerebroventricular (i.c.v.) administration of the peptide fragment cholecystokinin-4 (CCK-4) produced anxiety-like and depressive-like behavior and a decrease in NPY expression in the BNST; behavioral effects of CCK-4 could be attenuated by NPY via Y1R, suggesting a role for BNST NPY via Y1R in anxiety and depression (Desai et al., 2014). Interestingly, another group has shown that binding of presynaptic Y2R in the BNST is correlated with anxiety-like and depressive-like behavior induced by Y2R deletion from GABAergic inputs from the CeA (Tasan et al., 2010), suggesting another potential receptor-mediated synaptic mechanism for NPY signaling in the BNST in anxiety and depressive behaviors. NPY binding to Y2R in the BNST has also been shown to play a role in the attenuation of pain-induced conditioned place aversion, potentially via direct functional antagonism of CRF on excitability of Type II BNST neurons (Ide et al., 2013).

NPY signaling in the BNST has also been indicated in feeding behavior, as positive modulation of AgRP/NPY projections from the ARC to the BNST stimulates feeding behavior (Betley et al., 2013), as well as drug-seeking behavior via interactions with other peptide systems. I.c.v. administration of nicotine increases conditioned place preference and decreases NPY-IR in the BNST, which can both be prevented by concurrent i.p. administration of the neuromodulator agmatine (Kotagale et al., 2014). In another study, rats trained to self-stimulate the medial forebrain bundle had increased NPY-IR in the BNST, however intra-accumbens administration of morphine, which potentiated self-stimulation, decreased NPY-IR in the BNST (Desai et al., 2013). In contrast, others have shown that systemic heroin administration in drug-naïve rats decreases NPY expression in the BNST, while heroin administration in drug-sensitized rats increases it (D'Este et al., 2006). Together, these data suggest that NPY interacts with the endogenous opioid system in the BNST to regulate reward-related behaviors. Given the density of NPY and its receptors in the BNST, as well as observed changes in the NPY system in related and connected brain regions after chronic alcohol drinking and in alcohol dependence (Roy and Pandey, 2002; Slawecki et al., 1999; Sparrow et al., 2012), it is likely that NPY modulation of BNST function is involved in alcohol drinking behavior and becomes dysregulated during the transition to alcohol dependence (Koob, 2003; 2013). However, no research to date has reported on the specific role of BNST NPY in alcohol-related behaviors.

In addition to its potential roles in stress and motivated behaviors and altered signaling in addiction, NPY in the BNST may also undergo aberrant plasticity in other disease states, particularly in neurodegenerative conditions. For example, NPY-IR in the BNST is greater in people with Huntington's Disease (Beal et al., 1988). And, NPY innervation of the BNST and other limbic structures is reduced in a rat model of Alzheimer's disease, and central administration of NPY potentiates nicotine-induced improvement of learning and memory in this disease model (Rangani et al., 2012). Altogether, behavioral data available to date indicate the potential importance of NPY in the BNST in the regulation of a number of behaviors, and they highlight the critical need for further characterization of NPY anatomy, signaling, and functional effects in the BNST.

PACAP

Pituitary adenylate cyclase-activating polypeptide (PACAP), named for its cyclic AMP (cAMP) stimulating activity, was discovered and isolated from ovine hypothalamic tissue in 1989 (Miyata et al., 1989). Since then, PACAP and its cognate G protein-coupled receptor, PAC1 (Harmar et al., 1998; Pisegna and Wank 1993), have been implicated in stress-related psychiatric illnesses, particularly post-traumatic stress disorder (PTSD) (Almli et al., 2013; Ressler et al., 2011; Uddin et al., 2013; Wang et al., 2013). Functionally, PACAP is an α-amidated peptide that exists in two forms following cleavage of a prohormone precursor: PACAP38, and its C-terminally truncated form, PACAP27, consisting of 38 and 27 amino acid residues, respectively (Miyata et al., 1989; 1990). As a member of the vasoactive intestinal peptide (VIP)/secretin/glucagon superfamily, PACAP27 shares 68% sequence homology with VIP (Miyata et al., 1989). Like VIP, PACAP has high affinity for the Gs protein-coupled receptors VPAC1 (Harmar et al., 1998; Ishihara et al., 1992) and VPAC2 (Harmar et al., 1998; Lutz et al., 1993) in addition to the PAC1 receptor. Intriguingly, the PAC1 receptor has five splice variants that allow for differential coupling of Gα subunits and the engagement of various second messenger systems (Spengler et al., 1993; Vaudry et al., 2009). Within the BNST, fibrous PACAP expression is observed throughout the dorsolateral subdivision (Piggins et al., 1996), and in close proximity to CRF-expressing neurons (Kozicz et al., 1997). Retrograde tracing analysis indicates that PACAP-containing fibers in the BNST originate from the paraventricular nucleus of the hypothalamus (PVN) and the dorsal vagal complex (Kozicz et al., 1998). Because the BNST contains high expression of the PAC1 receptor (Hashimoto et al., 1996; Jaworski and Proctor 2000), and little expression of VPAC1 (Ishihara et al., 1992) or VPAC2 (Sheward et al., 1995) receptors, PAC1 is the likely postsynaptic target of PACAP in the BNST.

Behaviorally, PACAP and PAC1 receptor null mice display reduced anxiety-like behavior and increased locomotor activity (Gaszner et al., 2012; Girard et al., 2006; Hashimoto et al., 2001; Hattori et al., 2012; Otto et al., 2001). In keeping with PACAP's role as a pro-stress peptide, intracerebroventricular (ICV) administration of PACAP increases anxiety-like behavior and body weight loss (Dore et al., 2013). Further, infusion of PACAP38 into the BNST elevates plasma corticosterone levels up to an hour post infusion (Lezak et al., 2014a), corresponding with increases in anxiety-like behavior that persist up to one week (Hammack et al., 2009; Roman et al., 2014). These effects are likely attributable to the PAC1 receptor, as local BNST infusion of a PAC1 receptor agonist, and not the VPAC receptor ligand VIP, also induces anxiety-related behavior (Roman et al.,

2014). Interestingly, exposure to chronic stress elevates both PACAP and PAC1 receptor expression in the BNST (Hammack et al., 2009; Lezak et al., 2014b; Roman et al., 2014). As repeated systemic corticosterone treatment is sufficient to increase PAC1 receptor expression in the dorsal BNST, but does not alter PACAP transcript levels, stress-induced corticosterone increases alone do not account for increased BNST PACAP expression following chronic stress exposure (Lezak et al., 2014b). Further, antagonism of the PAC1 receptor in the BNST throughout chronic stress exposure can blunt subsequent stress-induced increases in corticosterone and anxiety-like behavior, thus demonstrating the role of PACAP as a "master regulator" of the stress response (Roman et al., 2014; Stroth et al., 2011). In addition to alterations in acute and stress-induced anxiety, local infusion of PACAP to the BNST reduces food and water intake, resulting in weight reduction (Kocho-Schellenberg et al., 2014; Roman et al., 2014). Recent evidence also suggests PACAP activity in the BNST may increase learned helplessness behavior (Hammack et al., 2012).

In humans, PACAP is expressed in BNST tissue (Palkovits et al., 1995) and shares identical sequence homology with rat and ovine PACAP (Kimura et al., 1990; Ogi et al., 1990). Single nucleotide polymorphisms (SNPs) in the gene encoding human PACAP or the PAC1 receptor have been associated with schizophrenia (Hashimoto et al., 2007), major depressive disorder (Aragam et al., 2011), and PTSD (Almli et al., 2013; Ressler et al., 2011; Uddin et al., 2013; Wang et al., 2013). Taken together with rodent behavioral data, these results highlight that alterations in PACAP-PAC1 receptor signaling may have profound effects on human affective behavior, potentially leading to pathological states. Ongoing studies detailing the effects of PACAP on stress-induced plasticity within the BNST, and its interactions with other BNST neuropeptides, will provide exciting targets for the treatment of these disorders.

NOCICEPTIN

Nociceptin (NOC) is an opiate-like neuropeptide that is expressed widely throughout the brain. Originally isolated from hypothalamic porcine extracts in a screen for ligands that activate a previously identified orphan like receptor 1 (ORL1 or NOP)(Bunzow et al., 1994), NOC (or Orphanin FQ) decreased forskolin-induced cAMP production in heterologous cells, displayed amino acid sequence similarity to other opiate peptides, and induced hyperalgesia in behavioral measurements of pain like the hot plate and tail flick assays (Reinscheid et al., 1995). NOC protein is a heptadecapeptide encoded within the c-terminus of the prepronociceptin gene that is highly conserved throughout phylogeny (Mollereau et al., 1996).

Similar to the expression pattern of NOP, initial analysis of NOC mRNA presence in various rodent tissues demonstrated that this gene is predominantly expressed in the central nervous system. Detailed analysis of NOC mRNA and protein expression in rodents using quantitative ***in situ*** hybridization and immunohistochemistry revealed that NOC and NOP are expressed within distinct ensembles of cells that, while being spread throughout the CNS, display striking enrichment in specific brain structures like the lateral septum, various hypothalamic nuclei, and the bed nucleus of the stria terminalis (BNST) (Boom et al., 1999; Ikeda et al., 1998; Neal et al., 1999). NOC is expressed in neurons throughout the BNST, but a heavy concentration of NOC+ immunoreactive and mRNA-containing cell bodies are present in the laterodorsal portion (Neal et al., 1999). Additionally, the BNST contains high levels of NOP mRNA and application of NOC peptide during ***ex vivo*** slice electrophysiological analyses of BNST neurons confirmed that more than half of BNST neurons (either dorsal or ventral) contain functional NOP (Dawe et al., 2010).

The advent of pharmacological tools for the study of NOC signaling revealed a critical role for the neuropeptide in the BNST in the regulation of feeding. Multiple groups have now demonstrated that injection of NOC peptide or NOP agonists into either the lateral ventricle or third ventricle produces naloxone or naltrexone-sensitive hyperphagia (Ciccocioppo et al., 2002; Leventhal et al., 1998; Matsushita et al., 2009; Polidori et al., 2000; Pomonis et al., 1996). Ciccocioppo and colleagues later demonstrated that local injections of NOC into the BNST (and not other brain regions) can block CRF-induced anorexia even at doses that are not hyperphagic when administered alone (Ciccocioppo et al., 2003b). Although the details are still unclear, these studies demonstrate that one potential mode by which NOC promotes feeding is via inhibition of anorexigenic signaling pathways. As new anorexigenic neurons are identified in the brain, new genetic targeting strategies will be necessary to study how NOC-expressing neurons modulate these neurons at a synaptic level.

In addition to its role in feeding, antagonism of CRF signaling by NOC has an anxiolytic effect. At a global level Koster et al. demonstrated that the genetic deletion of NOC in mice results in elevated anxiety and impairs stress adaptation (Gavioli et al., 2007; Köster et al., 1999), whereas systemic injections of a NOP agonist SCH 221510 decrease anxiety (Varty et al., 2008). Additionally, stress and anxiety are sensitive to modulation by CRF signaling as injection of CRF throughout the brain is anxiogenic and is blocked by local microinjection of NOC into the BNST (Rodi et al., 2007).

OXYTOCIN

Oxytocin is a neuropeptide hormone that was originally believed to function exclusively in the peripheral nervous system to promote maternal behaviors (Lee et al., 2009). In fact, oxytocin derives its name from its original proposed function, to stimulate uterine contractions (Dale, 1906). Shortly thereafter, it was found that the same hormone, released from the pituitary gland, promoted milk secretion (Schafer and Mackenzie, 1911). Based on these early studies and others, it was long believed that the main function of oxytocin release was to promote appropriate maternal care in mammals. It has only been in the past several decades that research has shown oxytocin to be a neuropeptide that is active in the central nervous system, functioning to promote appropriate social behaviors and social affiliation (Insel, 1992).

Oxytocin is a 9 amino amino acid neuropeptide that shares a similar structure to a related neuropeptide vasopressin (du Vigneaud et al., 1953). Importantly, both the structure and social affiliation function of oxytocin release is conserved across many species, including rats (Calcagnoli et al., 2014), voles (Insel and Shapiro, 1992; Kalamatianos et al., 2010), hamsters (Martinez et al., 2010; 2013), sheep (Kendrick et al., 1992), and humans (Carmichael et al., 1987). Oxytocin has one known receptor, a G protein coupled receptor that when bound, stimulates the activity of phospholipase C (Gimpl and Fahrenholz, 2001). Within the brain, oxytocin is synthesized in the mangocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and most of the hormone is transported to the pituitary gland to be released throughout the body (Insel, 1992; Lee et al., 2009). Some of these neurons project to other areas of the brain to

promote oxytocin release within the central nervous system, including projections to the BNST. Through in situ hybridization and autoradiography techniques, the oxytocin receptor has been shown to be distributed throughout the BNST in many different species, and this distribution has been is related to the social affilation function of oxytocin (Insel and Shapiro, 1992; Kalamatianos et al., 2010; Kendrick et al., 1992; Martinez et al., 2010; 2013).

Although oxytocin activity within the BNST has been associated with a wide variety of behaviors, these behaviors are all related to one general function: social affiliation and care of offspring. Some of the most striking studies of oxytocin function within the BNST have evaluated behavioral differences between species of voles that show very distinct social affiliation behaviors. Interestingly, prairie voles, which display monogamous pair bonding, show increased receptor distribution in the BNST compared to polygamous vole species, suggesting a role in monogamous pair bonding behaviors (Insel and Shapiro, 1992). Further, exposure to odors of the opposite sex preferentially activated oxytocin neurons in the PVN, while appropriate sexual interactions were dependent on oxytocin release within the BNST (Martinez et al., 2013). Finally, during both birth and maternal feeding behaviors, oxytocin release is increased within the BNST, providing further support for the role of oxytocin in social bonding and maternal behaviors. Interestingly, oxytocin release in the BNST is also important for behaviors opposite of social affiliation, namely aggression. Specifically, excessively aggressive male rats have been shown to have increased oxytocin receptor binding within the BNST (Calcagnoli et al., 2014). While much research has focused on the behavioral function of oxytocin release within the BNST, relatively little is known about the cellular functions of BNST oxytocin. To date, only extracellular recordings of BNST neurons in response to oxytocin administration have been completed. These studies have shown that application of oxytocin to the BNST results in excitations of a subpopulation (roughly 50%) of BNST neurons that is blocked in the presence of oxytocin antagonists (Ingram and Moos, 1992; Ingram et al., 1990). This data suggests that oxytocin release in the BNST functions as a neuromodulator to promote increased activation of BNST neurons. Future studies can begin to evaluate how this cellular activation is related to the social behavioral functions.

NEUROTENSIN

The neuropeptide neurotensin (NTS) is expressed in several brain regions and in the periphery. There are three cloned NTS receptors. Two are 7-TM GPCRs , NTSR1 and NTSR2, while interestingly, one receptor, NTSR3, is a cytosolic protein also known as sortilin (Caceda et al., 2006). In addition the dorsal lateral and oval nucleus of the BNST (both in rodent, human and non-human primate) contains a population of neurons expressing the 13 amino acid peptide neurotensin (de Campo and Fudge 2013; Walter et al., 1991). These cells are known to project to a number of hindbrain structures including the periaqueductal grey and the parabrachial nuclei (Gray and Magnuson 1992; Moga and Gray 1985a; 1985b; Moga et al., 1989). Earlier studies have mainly focused on the interactions of NTS with the Dopamine system and the roles that NTS may play in the pathology of addiction, schizophrenia and Parkinson's Disease [for review see (Binder et al., 2001)]. Recently, however, there has been a renewed focus on NTS signaling within subcortical structures particularly in areas associated with natural rewards and addiction (Kempadoo et al., 2013; Leinninger et al., 2011). Recently, the Dumont group has shown that cocaine self-administration results in a D1 mediated LTP of inhibitory transmission within the BNST that is dependent on NTS signaling (Krawczyk et al., 2013). The long-term exposure to cocaine resulted in an increased D1 signaling mechanism that presumably enhanced NTS release as NTS could increase IPSCs equally in both cocaine and control rats.They suggest that NTS may be released as a retrograde signal to impinge on presynaptic terminals to increase GABA release. Indeed a train of depolarizing pulses in the post-synaptic cell was sufficient to induce the enhancement of GABA release and this effect was blocked by a pan NTSR1 and R2 antagonist.

CONCLUSION

In this article we reviewed several prominent neuropeptides and their role in influencing both neuronal signaling and behavior in the BNST. Additionally, this review highlights the complexity of this structure as well as of peptidergic signaling in the brain. The majority of these peptides are co-expressed with classical neurotransmitters, as well as potentially other neuropeptides. Because of this, while optogenetic approaches can be applied to determine how endogenous peptides can modulate known circuits, determining the role of peptide release in these same populations is more challenging. The first step is determining what the potential overlap in neuropeptide expression is in these populations of neurons. While classical approaches such as dual in situ have provided some basic framework regarding this, given the complexity, this is likely to require cell type specific genetic profiling methods, such as the TRAP approach. Once this is performed, the next question is to develop a functional understanding of what these peptides in these specific neurons are altering behavior. For this, a floxed peptide mouse that allows deletion of the peptide expression in the presence of Cre recombinase would be helpful. Beyond that, there is the need to draw a direct measure of how peptide release can influence behavior. This is a more challenging question that can be probed with optogenetic and chemical genetic approaches, but it requires a rigorous understanding how these individual peptides are released. While this multi-tiered approach requires more steps than probing classical transmitter function in a circuit, it is important, as peptide receptors, and modulatory function in general, represents a key strategy for treatment of psychiatric disorders.

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