Mol. Cells 2015; 38(1): 1-13
http://dx.doi.org/10.14348/molcells.2015.2261

Molecules and Cells
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Minireview

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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Received 26 September, 2014; accepted 29 September, 2014; published online 4 December, 2014

Keywords: connectivity, CRF, extended amygdala, NPY, signaling

eISSN: 0219-1032

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.

ACKNOWLEDGMENTS

The Authors would like to acknowledge ABMRF, NARSAD, The Bowles Center for Alcohol Studies, and the National Insititute of Health (Grants: AA011605, AA019454, AA020911, AA022280, AA021043, AA021319, AA022549) for their support.

REFERENCES

Adrian, T.E., Allen, J.M., Bloom, S.R., Ghatei, M.A., Rossor, M.N., Roberts, G.W., Crow, T.J., Tatemoto, K., and Polak, J.M. (1983). Neuropeptide Y distribution in human brain. Nature ***306***, 584-586.

Allen, Y.S., Adrian, T.E., Allen, J.M., Tatemoto, K., Crow, T.J., Bloom, S.R., and Polak, J.M. (1983). Neuropeptide Y distribution in the rat brain. Science ***221***, 877-879.

Almli, L.M., Mercer, K.B., Kerley, K., Feng, H., Bradley, B., Conneely, K.N., and Ressler, K.J. (2013). ADCYAP1R1 genotype associates with post-traumatic stress symptoms in highly traumatized African-American females. Am. J. Med. Genet. B Neuropsychiatr. Genet. ***162B***, 262-272.

Aragam, N., Wang, K.S., and Pan, Y. (2011). Genome-wide association analysis of gender differences in major depressive disorder in the Netherlands NESDA and NTR population-based

samples. J. Affect Disord. ***133***, 516-521.
Arzt, E., and Holsboer, F. (2006). CRF signaling, molecular specificity for drug targeting in the CNS. Trends Pharmacol. Sci. ***27***, 531-538.
Aston-Jones, G., and Harris, G.C. (2004). Brain substrates for increased drug seeking during protracted withdrawal. Neuropharmacology ***46***, 167-179.
Beal, M.F., Mazurek, M.F., and Martin, J.B. (1987). A comparison of somatostatin and neuropeptide Y distribution in monkey brain. Brain Res. ***405***, 213-219.
Beal, M.F., Mazurek, M.F., Ellison, D.W., Swartz, K.J., McGarvey, U., Bird, E.D., and Martin, J.B. (1988). Somatostatin and neuropeptide Y concentrations in pathologically graded cases of Huntington's disease. Ann. Neurol. ***23***, 562-569.
Betley, J.N., Cao, Z.F., Ritola, K.D., and Sternson, S.M. (2013). Parallel, redundant circuit organization for homeostatic control of feeding behavior. Cell ***155***, 1337-1350.
Binder, E.B., Kinkead, B., Owens, M.J., and Nemeroff, C.B. (2001). Neurotensin and dopamine interactions. Pharmacol. Rev. ***53***, 453-486.
Blank, T., Nijholt, I., Grammatopoulos, D.K., Randeva, H.S., Hillhouse, E.W., and Spiess, J. (2003). Corticotropin-releasing factor receptors couple to multiple G-proteins to activate diverse intracellular signaling pathways in mouse hippocampus, role in neuronal excitability and associative learning. J. Neurosci. ***23***.
Boom, A., Mollereau, C., Meunier, J.C., Vassart, G., Parmentier, M., Vanderhaeghen, J.J., and Schiffmann, S.N. (1999). Distribution of the nociceptin and nocistatin precursor transcript in the mouse central nervous system. NSC ***91***, 991-1007.
Botchkina, G.I., and Morin, L.P. (1995). Organization of permanent and transient neuropeptide Y-immunoreactive neuron groups and fiber systems in the developing hamster diencephalon. J. Comp. Neurol. ***357***, 573-602.
Browning, J.R., Jansen, H.T., and Sorg, B.A. (2014). Inactivation of the paraventricular thalamus abolishes the expression of cocaine conditioned place preference in rats. Drug Alcohol Depend. ***134***, 387-390.
Bruchas, M.R., Land, B.B., Lemos, J.C., and Chavkin, C. (2009). CRF1-R activation of the dynorphin/kappa opioid system in the mouse basolateral amygdala mediates anxiety-like behavior. PLoS One ***4***, e8528.
Bunzow, J.R., Saez, C., Mortrud, M., Bouvier, C., Williams, J.T., Low, M., and Grandy, D.K. (1994). Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa opioid receptor type. FEBS Lett. ***347***, 284-288.
Burghardt, N.S., and Bauer., E.P. (2013). Acute and chronic effects of selective serotonin reuptake inhibitor treatment on fear conditioning, implications for underlying fear circuits. Neuroscience ***247***, 253-272.
Burroughs, L.F., Fiber, J.M., and Swann, J.M. (1996). Neuropeptide Y in hamster limbic nuclei, lack of colocalization with substance P. Peptides ***17***, 1053-1062.
Caceda, R., Kinkead, B., and Nemeroff, C.B. (2006). Neurotensin, role in psychiatric and neurological diseases. Peptides ***27***, 2385-2404.
Calcagnoli, F., de Boer, S.F., Beiderbeck, D.I., Althaus, M., Koolhaas, J.M., and Neumann, I.D. (2014). Local oxytocin expression and oxytocin receptor binding in the male rat brain is associated with aggressiveness. Behav. Brain Res. ***261***, 315-322.
Carmichael, M.S., Humbert, R., Dixen, J., Palmisano, G., Greenleaf, W., and Davidson, J.M. (1987). Plasma oxytocin increases in the human sexual response. J. Clin. Endocrinol. Metab. ***64***, 27-31.
Carr, J.A. (2002). Stress, neuropeptides, and feeding behavior, A comparative perspective. Integr. Comp. Biol. ***42***, 582-590.
Carty, M.L., Wixey, J.A., Kesby, J., Reinebrant, H.E., Colditz, P.B., Gobe, G., and Buller, K.M. (2010). Long-term losses of amygdala corticotropin-releasing factor neurons are associated with behavioural outcomes following neonatal hypoxia-ischemia. Behav. Brain Res. ***208***, 609-618.
Chiba, T., Kayahara, T., and Nakano, K. (2001). Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, Macaca fuscata. Brain Res. ***888***, 83-101.
Choi, D.C., Furay, A.R., Evanson, N.K., Ostrander, M.M., Ulrich-Lai, Y.M., and Herman, J.P. (2007). Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity, implications for the integration of limbic inputs. J. Neurosci. ***27***, 2025-2034.
Chronwall, B.M., DiMaggio, D.A., Massari, V.J., Pickel, V.M., Ruggiero, D.A., and O'Donohue, T.L. (1985). The anatomy of neuropeptide-Y-containing neurons in rat brain. Neuroscience ***15***, 1159-1181.
Chung, S., Kim, H.J., Kim, H.J., Choi, S.H., Cho, J.H., Cho, Y.H., Kim, D.H., and Shin, K.H. (2014). Desipramine and citalopram attenuate pretest swim-induced increases in prodynorphin immunoreactivity in the dorsal bed nucleus of the stria terminalis and the lateral division of the central nucleus of the amygdala in the forced swimming test. Neuropeptides ***48***, 273-280.
Ciccocioppo, R., Biondini, M., Antonelli, L., Wichmann, J., Jenck, F., and Massi, M. (2002). Reversal of stress- and CRF-induced anorexia in rats by the synthetic nociceptin/orphanin FQ receptor agonist, Ro 64-6198. Psychopharmacology ***161***, 113-119.
Ciccocioppo, R., Cippitelli, A., Economidou, D., Fedeli, A., and Massi, M. (2004). Nociceptin/orphanin FQ acts as a functional antagonist of corticotrophin-releasing factor to inhibit its anorectic effect. Physiol. Behav. ***82***, 63-68.
Ciccocioppo, R., Fedeli, A., Economidou, D., Policani, F., Weiss, F., and Massi, M. (2003a). The bed nucleus is a neuroanatomical substrate for the anorectic effect of corticotrophin-releasing factor and for its reversal by nociceptin/orphanin FQ. J. Neurosci. ***23***, 9445-9451.
Ciccocioppo, R., Fedeli, A., Economidou, D., Policani, F., Weiss, F., and Massi, M. (2003b). The bed nucleus is a neuroanatomical substrate for the anorectic effect of corticotropin-releasing factor and for its reversal by nociceptin/orphanin FQ. J. Neurosci. ***23***, 9445-9451.
Cippitelli, A., Damadzic, R., Hansson, A.C., Singley, E., Sommer, W.H., Eskay, R., Thorsell, A., and Heilig, M. (2010). Neuropeptide Y (NPY) suppresses yohimbine-induced reinstatement of alcohol seeking. Psychopharmacology ***208***, 417-426.
Cummings, S., Elde, R., Ells, J., and Lindall, A. (1983). Corticotropin-releasing factor immunoreactivity is widely distributed within the central nervous system of the rat, an immunohistochemical study. J. Neurosci. ***3***, 1355-1368.
D'Este, L., Casini, A., Pontieri, F.E., and Renda, T.G. (2006). Changes in neuropeptide FF and NPY immunohistochemical patterns in rat brain under heroin treatment. Brain Res. ***1083***, 151-158.
Dabrowska, J., Hazra, R., Guo, J.D., DeWitt, S., and Rainnie, D.G. (2013). Central CRF neurons are not created equal, phenotypic differences in CRF-containing neurons of the rat paraventricular hypothalamus and the bed nucleus of the stria terminalis. Front Neurosci. ***7***, 1-14.
Dale, H.H. (1906). On some physiological actions of ergot. J. Physiol. ***34***, 163-206.
Dautenberg, F.M., and Hauger, R.L. (2002). The CRF peptide family and their receptors, yet more partners discovered. Trends Pharmacol. Sci. ***23***, 71-77.
Davis, M., and Shi, C. (1999). The extended amygdala, are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety? Ann. N Y Acad. Sci. ***877***, 281-291.
Davis, M., and Walker, D.L. (2013). Role of bed nucleus of the stria terminalis and amygdala AMPA receptors in the development and expression of context conditioning and sensitization of startle by prior shock. Brain Struct. Funct. [Epub ahead of print].
Davis, M., Walker, D.L., and Lee, Y. (1997a). Amygdala and bed nucleus of the stria terminalis, differential roles in fear and anxiety measured with the acoustic startle reflex. Philos. Trans. R Soc. Lond. B Biol. Sci. ***352***, 1675-1687.
Davis, M., Walker, D.L., and Lee, Y. (1997b). Roles of the amygdala and bed nucleus of the stria terminalis in fear and anxiety measured with the acoustic startle reflex. Possible relevance to PTSD. Ann. N Y Acad. Sci. ***821***, 305-331.
Dawe, K.L., Wakerley, J.B., and Fulford, A.J. (2010). Nociceptin/orphanin FQ and the regulation of neuronal excitability in the rat bed nucleus of the stria terminalis, Interaction with glucocorticoids. Stress ***13***, 516-527.
de Campo, D.M., and Fudge, J.L. (2013). Amygdala projections to

the lateral bed nucleus of the stria terminalis in the macaque, comparison with ventral striatal afferents. J. Comp. Neurol. ***521***, 3191-3216.
Desai, S.J., Upadhya, M.A., Subhedar, N.K., and Kokare, D.M. (2013). NPY mediates reward activity of morphine, via NPY Y1 receptors, in the nucleus accumbens shell. Behav. Brain Res. ***247***, 79-91.
Desai, S.J., Borkar, C.D., Nakhate, K.T., Subhedar. N.K., and Kokare, D.M. (2014). Neuropeptide Y attenuates anxiety- and depression-like effects of cholecystokinin-4 in mice. Neuroscience ***277C***, 818-830.
Dong, H.W., Petrovich, G.D., and Swanson, L.W. (2001a). Topography of projections from amygdala to bed nuclei of the stria terminalis. Brain Res.***earch.*** Brain Res. Rev. ***38***, 192-246.
Dong, H.W., Petrovich, G.D., Watts, A.G., and Swanson, L.W. (2001b). Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain. J. Comp. Neurol. ***436***, 430-455.
Dore, R., Iemolo, A., Smith, K.L., Wang, X., Cottone, P., and Sabino, V. (2013). CRF mediates the anxiogenic and anti-rewarding, but not the anorectic effects of PACAP. Neuropsychopharmacology ***38***, 2160-2169.
du Vigneaud, V., Ressler, C., and Trippett, S. (1953). THE SEQUENCE OF AMINO ACIDS IN OXYTOCIN, WITH A PROPOSAL FOR THE STRUCTURE OF OXYTOCIN. J. Biol. Chem. ***205***, 949-957.
Dumont, Y., Fournier, A., St-Pierre, S., and Quirion, R. (1996). Autoradiographic distribution of [125I]Leu31,Pro34]PYY and [125I]PYY3-36 binding sites in the rat brain evaluated with two newly developed Y1 and Y2 receptor radioligands. Synapse ***22***, 139-158.
Duvarci, S., Bauer, E.P., and Pare, D. (2009). The bed nucleus of the stria terminalis mediates inter-individual variations in anxiety and fear. J. Neurosci. ***29***, 10357-10361.
Eiler, W.J., 2nd, Seyoum, R., Foster, K.L., Mailey, C., and June, H.L. (2003). D1 dopamine receptor regulates alcohol-motivated behaviors in the bed nucleus of the stria terminalis in alcohol-preferring (P) rats. Synapse ***48***, 45-56.
Elharrar, E., Warhaftig, G., Issler, O., Sztainberg, Y., Dikshtein, Y., Zahut, R., Redlus, L., Chen, A., and Yadid, G. (2013). Overexpression of corticotropin-releasing factor receptor type 2 in the bed nucleus of stria terminalis improves posttraumatic stress disorder-like symptoms in a model of incubation of fear. Biol. Psychiat. ***74***, 827-836.
Epping-Jordan, M.P., Markou, A., and Koob, G.F. (1998). The dopamine D-1 receptor antagonist SCH 23390 injected into the dorsolateral bed nucleus of the stria terminalis decreased cocaine reinforcement in the rat. Brain Res. ***784***, 105-115.
Erb, S. (2010). Evaluation of the relationship between anxiety during withdrawal and stress-induced reinstatement of cocaine seeking. Progr. Neuro-psychoph. ***34***, 798-807.
Erb, S., and Stewart, J. (1999). A role for the bed nucleus of the stria terminalis, but not the amygdala, in the effects of corticotrophin-releasing factor on stress-induced reinstatement of cocaine seeking. J. Neurosci. ***19***, RC35.
Erb, S., Salmaso, N., Rodaros, D., and Stewart, J. (2001). A role for the CRF-containing pathway from central nucleus of the amygdala to bed nucleus of the stria terminalis in the stress-induced reinstatement of cocaine seeking in rats. Psychopharmacology ***158***, 360-365.
Fallon, J.H., and Leslie, F.M. (1986). Distribution of dynorphin and enkephalin peptides in the rat brain. J. Comp. Neurol. ***249***, 293-336.
Flavin, S.A., and Winder, D.G. (2013). Noradrenergic control of the bed nucleus of the stria terminalis in stress and reward. Neuropharmacology ***70***, 324-330.
Francesconi, W., Berton, F., Repunte-Canonigo, V., Hagihara, K., Thurbon, D., Lekic, D., Specio, S.E., Greenwell, T.N., Chen, S.A., Rice, K.C., et al. (2009). Protracted withdrawal from alcohol and drugs of abuse impairs long-term potentiation of intrinsic excitability in the juxtacapsular bed nucleus of the stria terminalis. J. Neurosci. ***29***, 5389-5401.
Fu, Y., and Neugebauer, V. (2008). Differential mechanisms of CRF1 and CRF2 receptor functions in the amygdala in pain-related synaptic facilitation and behavior. J. Neurosci. ***28***, 3861-3876.
Funk, C.K., O'Dell, L.E., Crawford, E.F., and Koob, G.F. (2006a). Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rat. J. Neurosci. ***26***, 11324-11332.
Funk, D., Li, Z., and Lê, A.D. (2006b). Effects of environmental and pharmacological stressors on c-fos and corticotropin-releasing factor mRNA in rat brain, Relationship to the reinstatement of alcohol seeking. Neuroscience ***138***, 235-243.
Gafford, G.M., Guo, J.D., Flandreau, E.I., Hazra, R., Rainnie, D.G., and Ressler, K.J. (2012). Cell-type specific deletion of GABA(A)α1 in corticotrophin-releasing factor-containing neurons enhances anxiety and disrupts fear extinction. Proc. Natl. Acad. Sci. USA ***109***, 16330-16335.
García-Carmona, J.A., Milanés, M.V., and Laorden, M.L. (2013). Brain stress system response after morphine-conditioned place preference. Int. J. Neuropsychopharmacol. ***16***, 1999-2011.
Gaspar, P., Berger, B., Lesur, A., Borsotti, J.P., and Febvret, A. (1987). Somatostatin 28 and neuropeptide Y innervation in the septal area and related cortical and subcortical structures of the human brain. Distribution, relationships and evidence for differential coexistence. Neuroscience ***22***, 49-73.
Gass, J.T., Trantham-Davidson, H., Kassab, A.S., Glen, W.B., Jr., Olive, M.F., and Chandler, L.J. (2014). Enhancement of extinction learning attenuates ethanol-seeking behavior and alters plasticity in the prefrontal cortex. J. Neurosci. ***34***, 7562-7574.
Gaszner, B., Kormos, V., Kozicz, T., Hashimoto, H., Reglodi, D., and Helyes, Z. (2012). The behavioral phenotype of pituitary adenylate-cyclase activating polypeptide-deficient mice in anxiety and depression tests is accompanied by blunted c-Fos expression in the bed nucleus of the stria terminalis, central projecting Edinger-Westphal nucleus, ventral lateral septum, and dorsal raphe nucleus. Neuroscience ***202***, 283-299.
Gavioli, E.C., Rizzi, A., Marzola, G., Zucchini, S., Regoli, D., and Calo, G. (2007). Altered anxiety-related behavior in nociceptin/orphanin FQ receptor gene knockout mice. Peptides ***28***, 1229-1239.
Gewirtz, J.C., McNish, K.A., and Davis, M. (1998). Lesions of the bed nucleus of the stria terminalis block sensitization of the acoustic startle reflex produced by repeated stress, but not fear-potentiated startle. Prog. Neuropsychopharmacol. Biol. Psychiatry ***22***, 625-648.
Gimpl, G., and Fahrenholz, F. (2001). The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. ***81***, 629-683.
Girard, B.A., Lelievre, V., Braas, K.M., Razinia, T., Vizzard, M.A., Ioffe, Y., El Meskini, R., Ronnett, G.V., Waschek, J.A., and May, V. (2006). Noncompensation in peptide/receptor gene expression and distinct behavioral phenotypes in VIP- and PACAP-deficient mice. J. Neurochem. ***99***, 499-513.
Gray, T.S., and Magnuson, D.J. (1992). Peptide immunoreactive neurons in the amygdala and the bed nucleus of the stria terminalis project to the midbrain central gray in the rat. Peptides ***13***, 451-460.
Guo, J.D., Hammack, S.E., Hazra, R., Levita, L., and Rainnie, D.G. (2009). Bi-directional modulation of bed nucleus of stria terminalis neurons by 5-HT, molecular expression and functional properties of excitatory 5-HT receptor subtypes. Neuroscience ***164***, 1776-1793.
Hammack, S.E., Cheung, J., Rhodes, K.M., Schutz, K.C., Falls, W.A., Braas, K.M., and May, V. (2009). Chronic stress increases pituitary adenylate cyclase-activating peptide (PACAP) and brain-derived neurotrophic factor (BDNF) mRNA expression in the bed nucleus of the stria terminalis (BNST), roles for PACAP in anxiety-like behavior. Psychoneuroendocrinology ***34***, 833-843.
Hammack, S.E., Cooper, M.A., and Lezak, K.R. (2012). Overlapping neurobiology of learned helplessness and conditioned defeat, implications for PTSD and mood disorders. Neuropharmacology ***62***, 565-575.
Harmar, A.J., Arimura, A., Gozes, I., Journot, L., Laburthe, M., Pisegna, J.R., Rawlings, S.R., Robberecht, P., Said, S.I., Sreedharan, S.P., et al. (1998). International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. Pharmacol. Rev. ***50***, 265-270.
Hashimoto, H., Nogi, H., Mori, K., Ohishi, H., Shigemoto, R.,

Yamamoto, K., Matsuda, T., Mizuno, N., Nagata, S., and Baba, A. (1996). Distribution of the mRNA for a pituitary adenylate cyclase-activating polypeptide receptor in the rat brain, an in situ hybridization study. J. Comp. Neurol. ***371***, 567-577.

Hashimoto, H., Shintani, N., Tanaka, K., Mori, W., Hirose, M., Matsuda, T., Sakaue, M., Miyazaki, J., Niwa, H., Tashiro, F., et al. (2001). Altered psychomotor behaviors in mice lacking pituitary adenylate cyclase-activating polypeptide (PACAP). Proc. Natl. Acad. Sci. USA ***98***, 13355-13360.

Hashimoto, R., Hashimoto, H., Shintani, N., Chiba, S., Hattori, S., Okada, T., Nakajima, M., Tanaka, K., Kawagishi, N., Nemoto, K., et al. (2007). Pituitary adenylate cyclase-activating polypeptide is associated with schizophrenia. Mol. Psychiatr. ***12***, 1026-1032.

Hasue, R.H., and Shammah-Lagnado, S.J. (2002). Origin of dopaminergic innervations of the central extended amygdala and accumbens shell, a combined retrograde tracing and immunohistochemical study in the rat. J. Comp. Neurol. ***454***, 15-33.

Hattori, S., Takao, K., Tanda, K., Toyama, K., Shintani, N., Baba, A., Hashimoto, H., and Miyakawa, T. (2012). Comprehensive behavioral analysis of pituitary adenylate cyclase-activating polypeptide (PACAP) knockout mice. Front Behav. Neurosci. ***6***, 58.

Hawley, D.F., Bardi, M., Everette, A.M., Higgins, T.J., Tu, K.M., Kinsley, C.H., and Lambert, K.G. (2010). Neurobiological constituents of active, passive, and variable coping strategies in rats, integration of regional brain neuropeptide Y levels and cardiovascular responses. Stress ***13***, 172-183.

Heilig, M. (2004). The NPY system in stress, anxiety and depression. Neuropeptides ***38***, 213-224.

Heilig, M., and Thorsell, A. (2002). Brain neuropeptide Y (NPY) in stress and alcohol dependence. Rev. Neurosci. ***13***, 85-94.

Heilig, M., Koob, G.F., Ekman, R., and Britton, K.T. (1994). Corticotropin-releasing factor and neuropeptide Y, role in emotional integration. Trends Neurosci. ***17***, 80-85.

Heisler, L.K., Zhou, L., Bajwa, P., Hsu, J., and Tecott, L.H. (2007). Serotonin 5-HT(2C) receptors regulate anxiety-like behavior. Genes Brain Behav. ***6***, 491-496.

Herr, N.R., Park, J., McElligott, Z.A., Belle, A.M., Carelli, R.M., and Wightman, R.M. (2012). ***In vivo*** voltammetry monitoring of electrically evoked extracellular norepinephrine in subregions of the bed nucleus of the stria terminalis. J. Neurophysiol. ***107***, 1731-1737.

Heydendael, W., Sharma, K., Iyer, V., Luz, S., Piel, D., Beck, S., and Bhatnagar, S. (2011). Orexins/hypocretins act in the posterior paraventricular thalamic nucleus during repeated stress to regulate facilitation to novel stress. Endocrinology ***152***, 4738-4752.

Hollis, F., Duclot, F., Gunjan, A., and Kabbaj, M. (2011). Individual differences in the effect of social defeat on anhedonia and histone acetylation in the rat hippocampus. Horm. Behav. ***59***, 331-337.

Hooker, J.M., Patel, V., Kothari, S., Schiffer, W.K. (2009). Metabolic changes in the rodent brain after acute administration of salvinorin A. Mol. Imaging Biol. ***11***, 137-143.

Huang, M.M., Overstreet, D.H., Knapp, D.J., Angel, R., Wills, T.A., Navarro, M., Rivier, J., Vale, W., Breese, G.R. (2010). Corticotropin-Releasing Factor (CRF) sensitization of ethanol withdrawal-induced anxiety-like behavior is brain site specific and mediated by CRF-1 receptors, Relation to stress-induced sensitization. J. Pharmacol. Exp. Ther. ***332***, 298-307.

Hurley, K.M., Herbert, H., Moga, M.M., and Saper, C.B. (1991). Efferent projections of the infralimbic cortex of the rat. J. Comp. Neurol. ***308***, 249-276.

Ide, S., Hara, T., Ohno, A., Tamano, R., Koseki, K., Naka, T., Maruyama, C., Kaneda, K., Yoshioka, M., and Minami, M. (2013). Opposing roles of corticotropin-releasing factor and neuropeptide Y within the dorsolateral bed nucleus of the stria terminalis in the negative affective component of pain in rats. J. Neurosci. ***33***, 5881-5894.

Ikeda, K., Watanabe, M., Ichikawa, T., Kobayashi, T., Yano, R., and Kumanishi, T. (1998). Distribution of prepro-nociceptin/orphanin FQ mRNA and its receptor mRNA in developing and adult mouse central nervous systems. J. Comp. Neurol. ***399***, 139-151.

Ingram, C.D., and Moos, F. (1992). Oxytocin-containing pathway to the bed nuclei of the stria terminalis of the lactating rat brain, Immunocytochemical and ***in vitro*** electrophysiological evidence. Neuroscience ***47***, 439-452.

Ingram, C.D., Cutler, K.L., and Wakerley, J.B. (1990). Oxytocin excites neurones in the bed nucleus of the stria terminalis of the lactating rat ***in vitro***. Brain Res. ***527***, 167-170.

Insel, T.R. (1992). Oxytocin--a neuropeptide for affiliation, evidence from behavioral, receptor autoradiographic, and comparative studies. Psychoneuroendocrinology ***17***, 3-35.

Insel, T.R., and Shapiro, L.E. (1992). Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc. Natl. Acad. Sci. USA ***89***, 5981-5985.

Ishihara, T., and Shigemoto, R., Mori, K., Takahashi, K., Nagata, S. (1992). Functional expression and tissue distribution of a novel receptor for vasoactive intestinal polypeptide. Neuron ***8***, 811-819.

Jaworski, D.M., and Proctor, M.D. (2000). Developmental regulation of pituitary adenylate cyclase-activating polypeptide and PAC(1) receptor mRNA expression in the rat central nervous system. Brain Res. Dev. Brain Res. ***120***, 27-39.

Jennings, J.H., Sparta, D.R., Stamatakis, A.M., Ung, R.L., Pleil, K.E., Kash, T.L., and Stuber, G.D. (2013a). Distinct extended amygdala circuits for divergent motivational states. Nature ***496***, 224-228.

Jennings, J.H., Sparta, D.R., Stamatakis, A.M., Ung, R.L., and Stuber, G.D. (2013b). The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding. Science ***341***, 1517-1521.

Kalamatianos, T., Faulkes, C.G., Oosthuizen, M.K., Poorun, R., Bennett, N.C., and Coen, C.W. (2010). Telencephalic binding sites for oxytocin and social organization, A comparative study of eusocial naked mole-rats and solitary cape mole-rats. J. Comp. Neurol. ***518***, 1792-1813.

Kash, T.L., and Winder, D.G. (2006). Neuropeptide Y and corticotropin-releasing factor bi-directionally modulate inhibitory synaptic transmission in the bed nucleus of the stria terminalis. Neuropharmacology ***51***, 1013-22.

Kash, T.L., Baucum, A.J., 2nd, Conrad K.L., Colbran, R.J., and Winder, D.G. (2009). Alcohol exposure alters NMDAR function in the bed nucleus of the stria terminalis. Neuropsychopharmacology ***34***, 2420-2429.

Kempadoo, K.A., Tourino, C., Cho, S.L., Magnani, F., Leinninger, G.M., Stuber, G.D., Zhang, F., Myers, M.G., Deisseroth, K., de Lecea, L., et al. (2013). Hypothalamic neurotensin projections promote reward by enhancing glutamate transmission in the VTA. J. Neuroscience ***33***, 7618-7626.

Kendrick, K.M., Keverne, E.B., Hinton, M.R., and Goode, J.A. (1992). Oxytocin, amino acid and monoamine release in the region of the medial preoptic area and bed nucleus of the stria terminalis of the sheep during parturition and suckling. Brain Res. ***569***, 199-209.

Kim, S.Y., Adhikari, A., Lee, S.Y., Marshel, J.H., Kim, C.K., Mallory, C.S., Lo, M., Pak, S., Mattis, J., Lim, B.K., et al. (2013). Diverging neural pathways assemble a behavioural state from separable features in anxiety. Nature ***496***, 219-223.

Kimura, C., Ohkubo, S., Ogi, K., Hosoya, M., Itoh, Y., Onda, H., Miyata, A., Jiang, L., Dahl, R.R., Stibbs, H.H., et al. (1990). A novel peptide which stimulates adenylate cyclase: molecular cloning and characterization of the ovine and human cDNAs. Biochem. Biophys. Res. Commun. ***166***, 81-89.

Kinsey, S.G., Bailey, M.T., Sheridan, J.F., Padgett, D.A., and Avitsur, R. (2007). Repeated social defeat causes increased anxiety-like behavior and alters splenocyte function in C57BL/6 and CD-1 mice. Brain Behav. Immun. ***21***, 458-466.

Kocho-Schellenberg, M., Lezak, K.R., Harris, O.M., Roelke, E., Gick, N., Choi, I., Edwards, S., Wasserman, E., Toufexis, D.J., Braas, K.M., et al. (2014). PACAP in the BNST produces anorexia and weight loss in male and female rats. Neuropsychopharmacology ***39***, 1614-1623.

Koob, G.F. (2003). Alcoholism, allostasis and beyond. Alcohol. Clin. Exp. Res. 27, 232-243.

Koob, G.F. (2013). Addiction is a Reward Deficit and Stress Surfeit Disorder. Front Psychiatry ***4***, 72.

Koob, G.F., and Le Moal, M. (2008). Review. Neurobiological mechanisms for opponent motivational processes in addiction. Philos. Trans. R Soc. Lond. B Biol. Sci. ***363***, 3113-3123.

Köster, A., Montkowski, A., Schulz, S., Stübe, E.M., Knaudt, K., Jenck, F., Moreau, J.L., Nothacker, H.P., Civelli, O., and Reinscheid, R.K. (1999). Targeted disruption of the orphanin FQ/nociceptin gene increases stress susceptibility and impairs

stress adaptation in mice. Proc. Natl. Acad. Sci. USA ***96***, 10444-10449.
Kotagale, N.R., Walke, S., Shelkar, G.P., Kokare, D.M., Umekar, M.J., and Taksande, B.G. (2014). Agmatine attenuates nicotine induced conditioned place preference in mice through modulation of neuropeptide Y system. Behav. Brain Res. ***262***, 118-124.
Kozicz, T., Vigh, S., and Arimura, A. (1997). Axon terminals containing PACAP- and VIP-immunoreactivity form synapses with CRF-immunoreactive neurons in the dorsolateral division of the bed nucleus of the stria terminalis in the rat. Brain Res. ***767***, 109-119.
Kozicz, T., Vigh, S., and Arimura, A. (1998). The source of origin of PACAP- and VIP-immunoreactive fibers in the laterodorsal division of the bed nucleus of the stria terminalis in the rat. Brain Res. ***810***, 211-219.
Krawczyk, M., Mason, X., DeBacker, J., Sharma, R., Normandeau, C.P., Hawken, E.R., Di Prospero, C., Chiang, C., Martinez, A., Jones, A.A., et al. (2013). D1 dopamine receptor-mediated LTP at GABA synapses encodes motivation to self-administer cocaine in rats. J. Neurosci. ***33***, 11960-11971.
Kuenzel, W.J., and McMurtry, J. (1988). Neuropeptide Y, brain localization and central effects on plasma insulin levels in chicks. Physiol. Behav. ***44***, 669-678.
Lebow, M., Neufeld-Cohen, A., Kuperman, Y., Tsoory, M., Gil, S., and Chen, A. (2012). Susceptibility to PTSD-like behavior is mediated by corticotropin-releasing factor receptor type 2 levels in the bed nucleus of the stria terminalis. J. Neurosci. ***32***, 6906-6916.
Lee, Y., Fitz, S., Johnson, P.L., and Shekhar, A. (2008). Repeated stimulation of CRF receptors in the BNST of rats selectively induces social but not panic-like anxiety. Neuropsychopharmacology ***33***, 2586-2594.
Lee, H.J., Macbeth, A.H., Pagani, J.H., and Young, W.S., 3rd. (2009). Oxytocin, the great facilitator of life. Prog. Neurobiol. ***88***, 127-151.
Leinninger, G.M., Opland, D.M., Jo, Y.H., Faouzi, M., Christensen, L., Cappellucci, L.A., Rhodes, C.J., Gnegy, M.E., Becker, J.B., Pothos, E.N., et al. (2011). Leptin action via neurotensin neurons controls orexin, the mesolimbic dopamine system and energy balance. Cell Metabol. ***14***, 313-323.
Leventhal, L., Mathis, J.P., Rossi, G.C., Pasternak, G.W., and Bodnar, R.J. (1998). Orphan opioid receptor antisense probes block orphanin FQ-induced hyperphagia. Eur. J. Pharmacol. ***349***, R1-3
Lezak, K.R., Roelke, E., Harris, O.M., Choi, I., Edwards, S., Gick, N., Cocchiaro, G., Missig, G., Roman, C.W., Braas, K.M., et al. (2014a). Pituitary adenylate cyclase-activating polypeptide (PACAP) in the bed nucleus of the stria terminalis (BNST) increases corticosterone in male and female rats. Psychoneuroendocrinology ***45***, 11-20.
Lezak, K.R., Roman, C.W., Braas, K.M., Schutz, K.C., Falls, W.A., Schulkin, J., May, V., and Hammack, S.E. (2014b). Regulation of bed nucleus of the stria terminalis PACAP expression by stress and corticosterone. J. Mol. Neurosci. ***54***, 477-484..
Li, C., Pleil, K.E., Stamatakis, A.M., Busan, S., Vong, L., Lowell, B.B., Stuber, G.D., and Kash, T.L. (2012). Presynaptic inhibition of gamma-aminobutyric acid release in the bed nucleus of the stria terminalis by kappa opioid receptor signaling. Biol. Psychiatry ***71***, 725-732.
Li, Y., Dong, X., Li, S., and Kirouac, G.J. (2014). Lesions of the posterior paraventricular nucleus of the thalamus attenuate fear expression. Front. Behav. Neurosci. ***8***, 94.
Liang, K.C., Chen, H.C., and Chen, D.Y. (2001). Posttraining infusion of norepinephrine and corticotrophin releasing factor into the bed nucleus of the stria terminalis enhanced retention in an inhibitory avoidance task. Chin. J. Physiol. ***44***, 33-43.
Lopez, M.F., Griffin, W.C.3rd., Melendez, R.I., and Becker, H.C. (2012). Repeated cycles of chronic intermittent ethanol exposure leads to the development of tolerance to aversive effects of ethanol in C57BL/6J mice. Alcohol. Clin. Exp. Res. ***36***, 1180-1187.
Lovejoy, D.A., and Balment, R.J. (1999). Evolution and physiology of the corticotrophin-releasing factor (CRF) family of neuropeptides in vertebrates. Gen. Comp. Endocrinol. ***115***, 1-22.
Lowery-Gionta, E.G., Marcinkiewcz, C.A., and Kash, T.L. (2014). Functional alterations in the dorsal raphe nucleus following acute and chronic ethanol exposure. Neuropsychopharmacology [Epub ahead of print].
Lutz, E.M., Sheward, W.J., West, K.M., Morrow, J.A., Fink, G., and Harmar, A.J. (1993). The VIP2 receptor, molecular characterisation of a cDNA encoding a novel receptor for vasoactive intestinal peptide. FEBS Lett. ***334***, 3-8.
Marchant, N.J., Densmore, V.S., and Osborne, P.B. (2007). Coexpression of prodynorphin and corticotrophin-releasing hormone in the rat central amygdala, evidence of two distinct endogenous opioid systems in the lateral division. J. Comp. Neurol. ***504***, 702-715.
Martinez, L.A., Albers, H.E., and Petrulis, A. (2010). Blocking oxytocin receptors inhibits vaginal marking to male odors in female Syrian hamsters. Physiol. Behav. ***101***, 685-692.
Martinez, L.A., Levy, M.J., and Petrulis, A. (2013). Endogenous oxytocin is necessary for preferential Fos expression to male odors in the bed nucleus of the stria terminalis in female Syrian hamsters. Horm. Behav. ***64***, 653-664.
Matsushita, H., Ishihara, A., Mashiko, S., Tanaka, T., Kanno, T., Iwaasa, H., Ohta, H., and Kanatani, A. (2009). Chronic intracerebroventricular infusion of nociceptin/orphanin FQ produces body weight gain by affecting both feeding and energy metabolism in mice. Endocrinology ***150***, 2668-2673.
Matzeu, A., Zamora-Martinez, E.R., and Martin-Fardon, R. (2014). The paraventricular nucleus of the thalamus is recruited by both natural rewards and drugs of abuse, recent evidence of a pivotal role for orexin/hypocretin signaling in this thalamic nucleus in drug-seeking behavior. Front. Behav. Neurosci. ***8***, 117.
McDonald, A.J. (1989). Coexistence of somatostatin with neuropeptide Y, but not with cholecystokinin or vasoactive intestinal peptide, in neurons of the rat amygdala. Brain Res. ***500***, 37-45.
McElligott, Z.A., Fox ME, Walsh PL, Urban DJ, Ferrel MS, Roth BL, and Wightman RM. (2013). Noradrenergic synaptic function in the bed nucleus of the stria terminalis varies in animal models of anxiety and addiction. Neuropsychopharmacology ***38***, 1665-1673.
McReynolds, J.R., Vranjkovic O, Thao M, Baker DA, Makky K, Lim Y, and Mantsch JR. (2014). Beta-2 adrenergic receptors mediate stress-evoked reinstatement of cocaine-induced conditioned place preference and increases in CRF mRNA in the bed nucleus of the stria terminalis in mice. Psychopharmacology ***231***, 3953-3963.
Meloni, E.G., Gerety, L.P., Knoll, A.T., Cohen, B.M., and Carlezon, W.A. (2006). Behavioral and anatomical interactions between dopamine and corticotrophin-releasing factor in the rat. J. Neurosci. ***26***, 3855-3863.
Micioni, D.i. Bonaventura, M.V., Ciccocioppo, R., Romano, A., Bossert, J.M., Rice, K.C., Ubaldi, M., St Laurent, R., Gaetani, S., Massi, M., et al. (2014). Role of bed nucleus of the stria terminalis corticotrophin-releasing factor receptors in frustration stress-induced binge-like palatable food consumption in female rats with a history of food restriction. J. Neurosci. ***34***, 11316-11324.
Miyata, A., Arimura, A., Dahl, R.R., Minamino, N., Uehara, A., Jiang, L., Culler, M.D., and Coy, D.H. (1989). Isolation of a novel 38 residue-hypothalamic polypeptide which stimulates adenylate cyclase in pituitary cells. Biochem. Biophys. Res. Commun. ***164***, 567-574.
Miyata, A., Jiang, L., Dahl, R.D., Kitada, C., Kubo, K., Fujino, M., Minamino, N., and Arimura, A. (1990). Isolation of a neuropeptide corresponding to the N-terminal 27 residues of the pituitary adenylate cyclase activating polypeptide with 38 residues (PACAP38). Biochem. Biophys. Res. Commun. ***170***, 643-648.
Moga, M.M., and Gray, T.S. (1985a). Evidence for corticotropin-releasing factor, neurotensin, and somatostatin in the neural pathway from the central nucleus of the amygdala to the parabrachial nucleus. J. Comp. Neurol. ***241***, 275-284.
Moga, M.M., and Gray, T.S. (1985b). Peptidergic efferents from the intercalated nuclei of the amygdala to the parabrachial nucleus in the rat. Neurosci. Lett. ***61***, 13-18.
Moga, M.M, Saper, C.B, and Gray, T.S. (1989). Bed nucleus of the stria terminalis, cytoarchitecture, immunohistochemistry, and projection to the parabrachial nucleus in the rat. J. Comp. Neurol. ***283***, 315-332.
Mollereau, C., Simons, M.J., Soularue, P., Liners, F., Vassart, G., Meunier, J.C., and Parmentier, M. (1996). Structure, tissue distribution, and chromosomal localization of the prepronociceptin gene. Proc. Natl. Acad. Sci. USA ***93***, 8666-8670.

Morin, S.M., Ling, N., Liu, X.J., Kahl, S.D., and Gehlert, D.R. (1999). Differential distribution of urocortin- and corticotrophin-releasing factor-like immunoreactivities in the rat brain. Neuroscience ***92***, 281-291.

Myers, E.A., Banihashemi, L., and Rinaman, L. (2005). The anxiogenic drug yohimbine activates central viscerosensory circuits in rats. J. Comp. Neurol. ***492***, 426-441.

Nader, J., Chauvet, C., Rawas, R.E., Favot, L., Jaber, M., Thiriet, N., and Solinas, M. (2012). Loss of environmental enrichment increases vulnerability to cocaine addiction. Neuropsychopharmacology ***37***, 1579-1587.

Nagai, M.M., Gomes, F.V., Crestani, C.C., Resstel, L.B., and Joca, S.R. (2013). Noradrenergic neurotransmission within the bed nucleus of the stria terminalis modulates the retention of immobility in the rat forced swimming test. Behav. Pharmacol. ***24***, 214-221.

Neal, C.R.Jr., Swann, J.M., and Newman, S.W. (1989). The colocalization of substance P and prodynorphin immunoreactivity in neurons of the medial preoptic area, bed nucleus of the stria terminalis and medial nucleus of the amygdala of the Syrian hamster. Brain Res. ***496***, 1-13

Neal, C.R., Mansour, A., Reinscheid, R., Nothacker, H.P., Civelli, O., and Watson, S.J. (1999). Localization of orphanin FQ (nociceptin) peptide and messenger RNA in the central nervous system of the rat. J. Comp. Neurol. ***406***, 503-547.

Nilsson, I., Johansen, J.E., Schalling, M., Hokfelt, T., and Fetissov, S.O. (2005). Maturation of the hypothalamic arcuate agouti-related protein system during postnatal development in the mouse. Brain Res. Dev. Brain Res. ***155***, 147-154.

Nobis, W.P., Kash, T.L., Silberman, Y., and Winder, D.G. (2011). β-Adrenergic receptors enhance excitatory transmission in the bed nucleus of the stria terminalis through a corticotrophin-releasing factor receptor-dependent and cocaine-regulated mechanism. Biol. Psychiat. ***69***, 1083-1090.

O'Donohue, T.L., Chronwall, B.M., Pruss, R.M., Mezey, E., Kiss, J.Z., Eiden, L.E., Massari, V.J, Tessel, R.E, Pickel, V.M., DiMaggio, D.A., et al. (1985). Neuropeptide Y and peptide YY neuronal and endocrine systems. Peptides ***6***, 755-768.

Ogi, K., Kimura, C., Onda, H., Arimura, A., and Fujino, M. (1990). Molecular cloning and characterization of cDNA for the precursor of rat pituitary adenylate cyclase activating polypeptide (PACAP). Biochem. Biophys. Res. Commun. ***173***, 1271-1279.

Ohata, H., and Shibasaki, T. (2011). Involvement of CRF2 receptor in the brain regions in restraint-induced anorexia. Neuroreport ***22***, 494-498.

Olive, M.F., Koenig, H.N., Nannini, M.A., and Hodge, C.W. (2002). Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. Pharmacol. Biochem. Behav. ***72***, 213-220.

Otto, C., Martin, M., Wolfer, D.P., Lipp, H.P., Maldonado, R., and Schutz, G. (2001). Altered emotional behavior in PACAP-type-I-receptor-deficient mice. Brain Res. Mol. Brain Res. ***92***, 78-84.

Overstreet, D.H., Knapp, D.J., Moy, S.S., and Breese, G.R. (2003). A 5-HT1A agonist and a 5-HT2c antagonist reduce social interaction deficit induced by multiple ethanol withdrawals in rats. Psychopharmacology ***167***, 344-352.

Palkovits, M., Somogyvari-Vigh, A., and Arimura, A. (1995). Concentrations of pituitary adenylate cyclase activating polypeptide (PACAP) in human brain nuclei. Brain Res. ***699***, 116-120.

Pandey, S.C., Carr, L.G., Heilig, M., Ilveskoski, E., and Thiele, T.E. (2003). Neuropeptide y and alcoholism, genetic, molecular, and pharmacological evidence. Alcohol. Clin. Exp. Res. ***27***, 149-154.

Patki, G., Solanki, N., Atrooz, F., Ansari, A., Allam, F., Jannise, B., Maturi, J., and Salim, S. (2014). Novel mechanistic insights into treadmill exercise based rescue of social defeat-induced anxiety-like behavior and memory impairment in rats. Physiol. Behav. ***130***, 135-144.

Peyron, C., Tighe, D.K., van den Pol, A.N., de Lecea, L., Heller, H.C., Sutcliffe, J.G., and Kilduff, T.S. (1998). Neurons containing hypocretin (orexin) project to multiple neuronal systems. J. Neurosci. ***18***, 9996-10015

Phelix, C.F., Liposits, Z., and Paull, W.K. (1992). Monoamine innervation of the bed nucleus of stria terminalis, an electron microscopic investigation. Brain Res. Bull. ***28***, 949-965.

Piggins, H.D., Stamp, J.A., Burns, J., Rusak, B., and Semba, K. (1996). Distribution of pituitary adenylate cyclase activating polypeptide (PACAP) immunoreactivity in the hypothalamus and extended amygdala of the rat. J. Comp. Neurol. ***376***, 278-294.

Pisegna, J.R., and Wank, S.A. (1993). Molecular cloning and functional expression of the pituitary adenylate cyclase-activating polypeptide type I receptor. Proc. Natl. Acad. Sci. USA ***90***, 6345-6349.

Pleil, K.E., Lopez, A., McCall, N., Jijon, A.M., Bravo, J.P., and Kash, T.L. (2012). Chronic stress alters neuropeptide Y signaling in the bed nucleus of the stria terminalis in DBA/2J but not C57BL/6J mice. Neuropharmacology ***62***, 1777-1786.

Polidori, C., de Caro, G., and Massi, M. (2000). The hyperphagic effect of nociceptin/orphanin FQ in rats. Peptides ***21***, 1051-162.

Pomonis, J.D., Billington, C.J., and Levine, A.S. (1996). Orphanin FQ, agonist of orphan opioid receptor ORL1, stimulates feeding in rats. Neuroreport ***8***, 369-371.

Pompolo, S., Ischenko, O., Pereira, A., Iqbal, J., and Clarke, I.J. (2005). Evidence that projections from the bed nucleus of the stria terminalis and from the lateral and medial regions of the preoptic area provide input to gonadotropin releasing hormone (GNRH) neurons in the female sheep brain. Neuroscience ***132***, 421-436.

Poulin, J.F., Arbour, D., Laforest, S., and Drolet, G. (2009). Neuroanatomical characterization of endogenous opioids in the bed nucleus of the stria terminalis. Prog. Neuropsychopharmacol. Biol. Psychiatry ***33***, 1356-1365.

Rangani, R.J., Upadhya, M.A., Nakhate, K.T., Kokare, D.M., and Subhedar, N.K. (2012). Nicotine evoked improvement in learning and memory is mediated through NPY Y1 receptors in rat model of Alzheimer's disease. Peptides ***33***, 317-328.

Ravinder, S., Burghardt, N.S., Brodsky, R., Bauer, E.P., and Chattarji, S. (2013). A role for the extended amygdala in the fear-enhancing effects of acute selective serotonin reuptake inhibitor treatment. Transl. Psychiatry ***3***, e209.

Reinscheid, R.K., Nothacker, H.P., Bourson, A., Ardati, A., Henningsen, R.A., Bunzow, J.R., Grandy, D.K., Langen, H., Monsma, F.J., and Civelli, O. (1995). Orphanin FQ, a neuropeptide that activates an opioidlike G protein-coupled receptor. Science ***270***, 792-794.

Ressler, K.J., Mercer, K.B., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., Norrholm, S.D., Kilaru, V., Smith, A.K., Myers, A.J., et al. (2011). Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature ***470***, 492-497.

Reul, J.M., and Holsboer, F. (2002). On the role of corticotropin-releasing hormone receptors in anxiety and depression. Dialogues Clin. Neurosci. ***4***, 31-46.

Reuss, S., and Olcese, J. (1995). Neuropeptide Y, distribution of immunoreactivity and quantitative analysis in diencephalic structures and cerebral cortex of dwarf hamsters under different photoperiods. Neuroendocrinology ***61***, 337-347.

Reuss, S., Hurlbut, E.C., Speh, J.C., and Moore, R.Y. (1990). Neuropeptide Y localization in telencephalic and diencephalic structures of the ground squirrel brain. Am. J. Anat. ***188***, 163-174.

Robles, C.F., McMackin, M.Z., Campi, K.L., Doig, I.E., Takahashi, E.Y., Pride, M.C., and Trainor, B.C. (2014). Effects of kappa opioid receptors on conditioned place aversion and social interaction in males and females. Behav. Brain Res. ***262***, 84-93.

Rodi, D., Zucchini, S., Simonato, M., Cifani, C., Massi, M., and Polidori, C. (2007). Functional antagonism between nociceptin/orphanin FQ (N/OFQ) and corticotropin-releasing factor (CRF) in the rat brain, evidence for involvement of the bed nucleus of the stria terminalis. Psychopharmacology ***196***, 523-531.

Roman, C.W., Lezak, K.R., Hartsock, M.J., Falls, W.A., Braas, K.M., Howard, A.B., Hammack, S.E., and May, V. (2014). PAC1 receptor antagonism in the bed nucleus of the stria terminalis (BNST) attenuates the endocrine and behavioral consequences of chronic stress. Psychoneuroendocrinology ***47***, 151-165.

Roy, A., and Pandey, S.C. (2002). The decreased cellular expression of neuropeptide Y protein in rat brain structures during ethanol withdrawal after chronic ethanol exposure. Alcohol Clin. Exp. Res. ***26***, 796-803.

Russell, S.E., Rachlin, A.B., Smith, K.L., Muschamp, J., Berry, L., Zhao, Z., and Chartoff, E.H. (2014). Sex differences in sensitivity to the depressive-like effects of the kappa opioid receptor agonist U-50488 in rats. Biol. Psychiatry ***76***, 213-222.

Rygula, R., Abumaria, N., Flügge, G., Fuchs, E., Rüther, E., and Havemann-Reinecke, U. (2005). Anhedonia and motivational

deficits in rats, impact of chronic social stress. Behav. Brain Res. ***162***, 127-134.
Rygula, R., Abumaria, N., Domenici, E., Hiemke, C., and Fuchs, E. (2006). Effects of fluoxetine on behavioral deficits evoked by chronic social stress in rat. Behav. Brain Res. ***174***, 188-192.
Sahuque, L.L., Kullberg, E.F., McGeehan, A.J., Kinder, J.R., Hicks, M.P., Blanton, M.G., Janak, P.H., and Olive, M.F. (2006). Anxiogenic and aversive effects of corticotrophin-releasing factor (CRF) in the bed nucleus of stria terminalis in the rat, role of CRF receptor subtypes. Psychopharmacology ***186***, 122-132.
Sakanaka, M., Shibasaki, T., and Lederis, K. (1986). Distribution and efferent projections of corticotrophin-releasing factor-like immunoreactivity in the rat amygdaloid complex. Brain Res. ***382***, 213-238.
Schafer, E.A., and Mackenzie, K. (1911). The Action of Animal Extracts on Milk Secretion. Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character ***84***, 16-22.
Shen, C.L. (1987). Distribution of neuropeptide Y immunoreactivity in the forebrain of the rat. Proc. Natl. Sci. Counc. Repub. China B ***11***, 115-127.
Sheward, W.J., Lutz, E.M., and Harmar, A.J. (1995). The distribution of vasoactive intestinal peptide2 receptor messenger RNA in the rat brain and pituitary gland as assessed by ***in situ*** hybridization. Neuroscience ***67***, 409-418.
Shin, J.W., Geerling, J.C., and Loewy, A.D. (2008). Inputs to the ventrolateral bed nucleus of the stria terminalis. J. Comp. Neurol. ***511***, 628-657.
Silberman, Y., Matthews, R.T., and Winder, D.G. (2013). A corticotrophin releasing factor pathway for ethanol regulation of the ventral tegmental area in the bed nucleus of stria terminalis. J. Neurosci. ***33***, 950-960.
Sink, K.S., Walker, D.L., Freeman, S.M., Flandreau, E.I., Ressler, K.J., and Davis, M. (2013). Effects of continuously enhanced corticotrophin releasing factor expression within the bed nucleus of the stria terminalis on conditioned and unconditioned anxiety. Mol. Psychiatr. ***18***, 308-319.
Slawecki, C.J., Somes, C., and Ehlers, C.L. (1999). Effects of chronic ethanol exposure on neurophysiological responses to corticotropin-releasing factor and neuropeptide Y. Alcohol. Alcohol. ***34***, 289-299.
Smith, Y., Parent, A., Kerkerian, L., and Pelletier, G. (1985). Distribution of neuropeptide Y immunoreactivity in the basal forebrain and upper brainstem of the squirrel monkey (Saimiri sciureus). J. Comp. Neurol. ***236***, 71-89.
Sparrow, A.M., Lowery-Gionta, E.G., Pleil, K.E., Li, C., Sprow, G.M., Cox, B.R, Rinker, J.A., Jijon, A.M., Pena, J., Navarro, M., et al. (2012). Central neuropeptide Y modulates binge-like ethanol drinking in C57BL/6J mice via Y1 and Y2 receptors. Neuropsychopharmacology ***37***, 1409-1421.
Spengler, D., Waeber, C., Pantaloni, C., Holsboer, F., Bockaert, J., Seeburg, P.H., and Journot, L. (1993). Differential signal transduction by five splice variants of the PACAP receptor. Nature ***365***, 170-175.
Stroth, N., Holighaus, Y., Ait-Ali, D., and Eiden, L.E. (2011). PACAP, a master regulator of neuroendocrine stress circuits and the cellular stress response. Ann. N Y Acad. Sci. ***1220***, 49-59.
Sullivan, G.M., Apergis, J., Bush, D.E., Johnson, L.R., Hou, M., and Ledoux, J.E. (2004). Lesions in the bed nucleus of the stria terminalis disrupt corticosterone and freezing responses elicited by a contextual but not by a specific cue-conditioned fear stimulus. Neuroscience ***128***, 7-14.
Szücs, A., Berton, F., Sanna, P.P., and Francesconi, W. (2012). Excitability of jcBNST neurons is reduced in alcohol-dependent animals during protracted alcohol withdrawal. PLoS One ***7***, e42313.
Takagishi, M., and Chiba, T. (1991). Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat, an anterograde tracer PHA-L study. Brain Res. ***566***, 26-39.
Takahashi, L.K. (2001). Role of CRF(1) and CRF(2) receptors in fear and anxiety. Neurosci. Biobehav. Rev. ***25***, 627-636.
Tasan, R.O., Nguyen, N.K., Weger, S., Sartori, S.B., Singewald, N., Heilbronn, R., Herzog, H., and Sperk, G. (2010). The central and basolateral amygdala are critical sites of neuropeptide Y/Y2 receptor-mediated regulation of anxiety and depression. J. Neurosci. ***30***, 6282-6290.
Tran, L., Schulkin, J., and Greenwood-Van Meerveld, B. (2014). Importance of CRF receptor-mediated mechanisms of the bed nucleus of the stria terminalis in the processing of anxiety and pain. Neuropsychopharmacology ***39***, 2633-2645.
Uddin, M., Chang, S.C., Zhang, C., Ressler, K., Mercer, K.B., Galea, S., Keyes, K.M., McLaughlin, K.A., Wildman, D.E., Aiello, A.E., et al. (2013). Adcyap1r1 genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. Depress Anxiety ***30***, 251-258.
van den Pol, A.N. (2012). Neuropeptide transmission in brain circuits. Neuron ***76***, 98-115.
Varty, G.B., Lu, S.X., Morgan, C.A., Cohen-Williams, M.E., Hodgson, R.A., Smith-Torhan, A., Zhang, H., Fawzi, A.B., Graziano, M.P., Ho, G.D., et al. (2008). The anxiolytic-like effects of the novel, orally active nociceptin opioid receptor agonist 8-[bis(2-methylphenyl)methyl]-3-phenyl-8-azabicyclo[3.2.1] octan-3-ol (SCH 221510). J. Pharmacol. Exp. Ther. ***326***, 672-682.
Vaudry, D., Falluel-Morel, A., Bourgault, S., Basille, M., Burel, D., Wurtz, O., Fournier, A., Chow, B.K., Hashimoto, H., Galas, L., et al. (2009). Pituitary adenylate cyclase-activating polypeptide and its receptors, 20 years after the discovery. Pharmacol. Rev. ***61***, 283-357.
Vertes, R.P. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse ***51***, 32-58.
Walker, D.L., and Davis, M. (1997). Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in startle increases produced by conditioned versus unconditioned fear. J. Neurosci. ***17***, 9375-9383.
Walker, D.L., Miles, L.A., and Davis, M. (2009a). Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. Prog. Neuropsychopharmacol. Biol. Psychiatry ***33***, 1291-1308.
Walker, D.L., Yang, Y., Ratti, E., Corsi, M., Trist, D., and Davis, M. (2009b). Differential effects of the CRF-R1 antagonist GSK876008 on fear-potentiated, light- and CRF-enhanced startle suggest preferential involvement in sustained vs phasic threat responses. Neuropsychopharmacology ***34***, 1533-1542.
Walter, A., Mai, J.K., Lanta, L., and Gorcs, T. (1991). Differential distribution of immunohistochemical markers in the bed nucleus of the stria terminalis in the human brain. J. Chem. Neuroanat. ***4***, 281-298.
Wang, J., Fang, Q., Liu, Z., and Lu, L. (2006). Region-specific effects of brain corticotropin-releasing factor receptor type 1 blockade on footshock-stress- or drug-priming-induced reinstatement of morphine conditioned place preference in rats. Psychopharmacology ***185***, 19-28.
Wang, L., Cao, C., Wang, R., Qing, Y., Zhang, J., and Zhang, X.Y. (2013). PAC1 receptor (ADCYAP1R1) genotype is associated with PTSD's emotional numbing symptoms in Chinese earthquake survivors. J. Affect Disord. ***150***, 156-159.
Weinberg, D.H., Sirinathsinghji, D.J., Tan, C.P., Shiao, L.L., Morin, N., Rigby, M.R., Heavens, R.H., Rapoport, D.R., Bayne, M.L., Cascieri, M.A., et al. (1996). Cloning and expression of a novel neuropeptide Y receptor. J. Biol. Chem. ***271***, 16435-16438.
Wenzel, J.M., Cotton, S.W., Dominguez, H.M., Lane, J.E., Shelton, K., Su, Z.I., and Ettenberg, A. (2014). Noradrenergic beta-receptor antagonism within the central nucleus of the amygdala or bed nucleus of the stria terminalis attenuates the negative/anxiogenic effects of cocaine. J. Neurosci. ***34***, 3467-34674.
Wills, T.A., Klug, J.R., Silberman, Y., Baucum, A.J., Weitlauf, C., Colbran, R.J., Delpire, E., and Winder, D.G. (2012). GluN2B subunit deletion reveals key role in acute and chronic ethanol sensitivity of glutamate synapses in bed nucleus of the stria terminalis. Proc. Natl. Acad. Sci. USA ***109***, E278-287.