Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2009 November 13; 33(8): 1329–1335. doi:10.1016/j.pnpbp.2009.05.022.

Modulation of Glutamatergic Synaptic Transmission in the Bed Nucleus of the Stria Terminalis

Zoé Anastasia McElligott[1] and **Danny G. Winder**[1,2,3]

[1] Vanderbilt Brain Institute, Vanderbilt University Medical Center, Nashville, TN, USA

[2] Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center, Nashville, TN, USA

[3] Kennedy Center For Human Development, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

Glutamate, catecholamine and neuropeptide signaling within the bed nucleus of the stria terminalis (BNST) have all been identified as key participants in anxiety-like behaviors and behaviors related to withdrawal from exposure to substances of abuse. The BNST is thought to serve as a key relay between limbic cognitive centers and reward, stress and anxiety nuclei. Human studies and animal models have demonstrated that stressors and drugs of abuse can result in long term behavioral modifications that can culminate in psychological diseases such as addiction and post-traumatic stress disorder. The ability of catecholamines and neuropeptides to influence synaptic glutamatergic transmission (stemming from cognitive centers) within the BNST may have profound consequences over these behaviors. In this review we highlight studies examining synaptic plasticity and modulation of excitatory transmission within the BNST, emphasizing how such modulation may result in alterations in anxiety and reward related behavior.

Introduction

The ability to integrate and interpret stressful and rewarding situations is necessary for an organism's survival. Evidence suggests that maladaptive processes in brain regions associated with stress and reward may lead to pathological anxiety conditions (generalized anxiety disorder, post-traumatic stress disorder, panic disorder) and addiction. The bed nucleus of the stria terminalis (BNST) – a component of the "extended amygdala" – has been shown to play a role in contextual conditioned and unconditioned fear responses; anxiety-like behaviors; affective behaviors related to drug/alcohol dependence; and, stress-induced reinstatement of drug seeking, a model of stress-induced relapse (Walker and Davis, 1997; Shaham et al., 2000; Sullivan et al., 2004; Fendt et al., 2005; Olson et al., 2006). This is particularly interesting given the ample evidence for the co-morbidity of substance abuse and anxiety disorders (George et al., 1990; Kushner et al., 2000; Breese et al., 2005; Sareen et al., 2006; Vik, 2007; Herrero et al., 2008). Additionally, as many of these behaviors are postulated to involve cortical and limbic regions that provide glutamatergic inputs to the BNST, alterations in the strength

Corresponding Author: Danny G. Winder, Ph.D., Department of Molecular Physiology & Biophysics, Room 724B, RRB 1, Vanderbilt University School of Medicine, Nashville, TN 37232-0615, Phone: (615) 322-1144, Fax: (615) 343-0490, danny.winder@vanderbilt.edu.

of these connections within the BNST are hypothesized to play roles in the pathogenesis of addiction and anxiety disorders. In this review we will explore the current understanding of synaptic physiology in the BNST and begin to form a conceptual framework for beginning to interpret potential behavioral correlates.

BNST: early insights and anatomical positioning

Behavioral studies have highlighted the BNST as a region at the crossroads of reward and stress/anxiety networks. The hypothalamic-pituitary-adrenal (HPA) axis functions to engage the body's stress response. The paraventricular nucleus of the hypothalamus (PVN) releases corticotrophin releasing hormone (CRH) in the pituitary gland, which in turn releases adrenocorticotrophic hormone (ACTH) into the bloodstream where it acts on the adrenal gland to release corticosterone. Although limbic and cortical projections had been shown to regulate HPA axis function, their efferents often terminate prior to the PVN, with strong evidence for the BNST to serve as a key relay between these regions (Cullinan et al., 1993). Early work demonstrated that a portion of the BNST projections to the PVN express GABAergic markers (Cullinan et al., 1993). Additionally, electrical stimulation of the lateral BNST decreases plasma levels of corticosterone following electrical stimulation of the lateral BNST (Dunn, 1987) and glutamate microstimulation in the BNST induces inhibitory postsynaptic potentials in the magno- and parvocellular cells of the PVN (Boudaba et al., 1996)., Swim stress, moreover, increases Fos immunoreactivity in glutamate decarboxylase (GAD, the enzyme that produces GABA) containing BNST-PVN projecting neurons (Cullinan et al., 1996). These data have led researchers to infer that the BNST is a member of a collective group of nuclei that provide a strongly integrated braking mechanism controlling HPA axis induction (Cullinan et al., 2008). In contrast perhaps to these data, BNST lesions reduce interleukin-1β induced Fos activation in the PVN and attenuate ACTH levels (Crane et al., 2003), demonstrating its critical role as a relay for stress axis activation. This may be reconciled by more recent lesion studies that have demonstrated that BNST subregions can potently regulate HPA axis function in divergent ways (Choi et al., 2007). Furthermore, these subregions appear to regulate HPA axis function differently depending on the organisms exposure to an acute stressor following chronic stressors vs. an acute stressor alone suggesting that plastic changes within BNST microcircuitry may have profound influence over HPA axis function (Choi et al., 2008a; Choi et al., 2008b).

In addition to regulation of HPA axis, the BNST also appears to mediate other affective behaviors. Infusion of an AMPA receptor antagonist into the BNST and excitotoxic lesions diminish anxiety-like behavior as measured by light enhanced startle and CRF enhanced startle respectively (Lee and Davis, 1997; Walker and Davis, 1997). Furthermore lesioning the BNST enhanced learned despair during a forced swim task (Schulz and Canbeyli, 2000), impairs fear conditioning with a prolonged stimuli, and reinstatement of conditioned fear (Waddell et al., 2006). Single administration of ethanol (via various routes of administration) also activates Fos in dlBNST neurons (Knapp et al., 2001; Crankshaw et al., 2003) (but see (Herring et al., 2004)). Finally, blocking opiate receptors specifically within the BNST attenuates heroin self-administration (Walker et al., 2000). While these studies raise the question as to how the BNST mediates these behaviors, some of which may seem divergent, together they suggest that as a whole, the BNST may serve as a relay between these limbic, cortical regions, and reward centers and the HPA axis, and may play a key role in behavioral responses to stress, anxiety and substances of abuse.

Closer inspection of the anatomy reveals that the BNST receives glutamatergic inputs from several brain regions that play roles in the manifestation of various types of behavior, notably cognitive and emotional processes; and, furthermore outputs to several regions, notably regions involved with reward, feeding behavior and stress (Dong et al., 2001b; Dong and Swanson,

2004). Of note, the BNST receives inputs from the central (a GABAergic projection), medial and basolateral nuclei of the amygdala, the hippocampus and the prefrontal, insular and limbic cortices (Cullinan et al., 1993; McDonald, 1998; Dong et al., 2001a). These regions have also been identified as plausible contributors to behavioral responses from processive stressors (psychological stressors like restraint stress as opposed to systemic stressors like sepsis) and drugs of abuse.

Ascending modulatory transmitter systems also project heavily to the BNST. The BNST receives one of the most robust noradrenergic innervations in the CNS (Forray and Gysling, 2004). These projections arise mainly from the nucleus of the tractus solitarius (NTS) and the A1 cell groups via the ventral noradrenergic bundle (VNAB), although some of the projections also arise from the dorsal noradrenergic bundle (DNAB) stemming from the locus coeruleus (Ricardo and Koh, 1978; Woulfe et al., 1988; Banihashemi and Rinaman, 2006). The majority of these projections are made in the ventrolateral BNST (vlBNST), however, the dorsolateral BNST (dlBNST) receives innervation as well (Egli et al., 2005; Bienkowski and Rinaman, 2008). The dlBNST also receives dopaminergic innervation arising from both the ventral tegmental area (VTA) as well as the periaqueductal grey (PAG) (Hasue and Shammah-Lagnado, 2002; Meloni et al., 2006). In addition to classic neuromodulators, the BNST also receives input from neuropeptide containing neurons, for example CRF (Sakanaka et al., 1986) and neuropeptide Y (NPY) (Walter et al., 1991; Larriva-Sahd, 2006).

Properties of BNST neurons

As with the neighboring central nucleus of the amygdala and shell of the accumbens, the majority of the neurons within the BNST are GABAergic, however, there does appeart to be a distinct glutamatergic population of projection neurons as well as evidenced by functional assays and the presence of mRNA of multiple vesicular glutamate transporter genes (Georges and Aston-Jones, 2002; Allen Institute for Brain Science, 2008). In addition, they express a variety of neuropeptides including CRF, enkephalin, NPY and substance P (Malsbury and McKay, 1987; Arluison et al., 1990; Walter et al., 1991; Champagne et al., 1998). While the majority of neurons appear somewhat similar in morphology to medium spiny neurons, Golgi-impregnation studies reveal an impressive array of cellular morphologies (McDonald, 1983; Larriva-Sahd, 2006). This diversity combined with strong evidence for a number of subnuclei within the BNST suggests a complex neurocircuitry.

To begin to attempt to understand the neurophysiology of this circuitry, we and others have begun characterizing the electrical properties of neurons within the BNST. The neurons in the BNST appear very heterogeneous between the dorsal and ventral subdivisions and even within the subdivisions. Various BNST neurons have been shown to have low threshold spiking (likely mediated via T-type calcium current), I_h, I_A and inward rectifying potassium currents, and a persistent sodium current (Rainnie, 1999; Egli and Winder, 2003; Hammack et al., 2007). This suggests that synaptic input to these cells may be differentially integrated, which may have an important effect on subsequent behavior. Recently it has been shown using retrograde tracers that neurons projecting from the BNST to the VTA have distinct physiological properties. Neurons projecting to the VTA have lower capacitance, higher input resistance, inward rectifying potassium currents and lack I_h currents (Dumont and Williams, 2004; Kash et al., 2008a). These properties could suggest that these cells are more easily excited by synaptic input and the low threshold spike activity in the ventral BNST may result in increased bursting phenomena (Egli and Winder, 2003). Additionally, dorsal BNST neurons, as opposed to these VTA projection neurons which mainly reside in the ventral BNST, appear to be under tonic inhibition in the *ex vivo* slice preparation (Egli and Winder, 2003). Furthermore, anatomical data suggests that portions of the dorsal BNST project to subnuclei within the ventral BNST (Dong et al., 2000). Tonic inhibition of presumably inhibitory dorsal BNST neurons, therefore,

could potentially disinhibit ventral BNST neurons which may have profound impact on the functional output of the nucleus as a whole. Examining the physiological properties of BNST neurons targeting other nuclei, the paraventricular nucleus of the hypothalamus (PVN) for example, and intrinsic BNST projections will no doubt prove useful to future studies examining synaptic integration and modulation.

Homosynaptic modulation

The modification and remodeling of glutamatergic synapses have long been postulated to play a role in classical learning and memory. Studies have correlated plasticity at glutamate synapses to learning paradigms by demonstrating that interfering with or potentiating the induction/expression of the plasticity in various brain regions can disrupt or enhance several learned behaviors (Malenka and Bear, 2004), as well as demonstrating that plasticity at these synapses is induced by behavioral stimulation that promotes learning (Whitlock et al., 2006).

More recently these concepts have been explored in the context of reward and substance abuse. Interfering with glutamatergic transmission alters behavioral paradigms of addiction (Wolf, 1998). Several drugs of abuse with differing pharmacological targets and stress have been shown to increase AMPA/NMDA ratios (suggesting an induction of long term potentiation – LTP) in the ventral tegmental area (VTA) (Ungless et al., 2001; Saal et al., 2003). Moreover, mice lacking the GluR1 subunit of the AMPA receptor (AMPAR) do not exhibit increases in AMPA/NMDA ratios to cocaine or stress challenges in the dopaminergic neurons of the VTA (Dong et al., 2004). These findings have led to the theory that addiction is a pathological hijacking of learning-like cellular correlates in reward centers (Kauer and Malenka, 2007).

Long Term Potentiation

To begin to assess the ability of neurons within the BNST to undergo synaptic remodeling our group first described an extracellularly recorded synaptic response to local stimulation and demonstrated that two 100 Hz trains of stimuli (1 second each) can produce an NMDA receptor (NMDAR) dependent long term potentiation (LTP) in this region (Weitlauf et al., 2004; Weitlauf et al., 2005). Interestingly, the early portion of this LTP was found to be attenuated by acute, *in vitro* application of ethanol in a manner that was dependent on $GABA_A$ signaling and mimicked by incomplete NMDAR blockade. Furthermore it was noted that ethanol reversibly attenuates NMDAR currents by directly acting on receptors that containe the NR2B subunit (Weitlauf et al., 2004; Kash et al., 2008a). Previously, it had been proposed in the hippocampus and cortex that the NR2A subunit was responsible for the induction of NMDAR dependent LTP (Liu et al., 2004; Massey et al., 2004; Mallon et al., 2005), however, our group demonstrated that LTP in the dlBNST was intact in mice lacking NR2A subunits and that the pharmacological blocker used to previously confirm NR2A dependence in mediating LTP was not selective in brain slices at the concentration previously used by other researchers (Weitlauf et al., 2005).

Long Term Depression

In addition to ionotropic receptors, glutamate also exerts its actions through G-protein coupled receptors (GPCRs) known as metabotropic glutamate receptors (mGluRs). Although mGluRs are not direct pharmacological targets of drugs of abuse, mGluR5 knockout mice do not self-administer cocaine nor do they exhibit locomotor responses to psychostimulants (Chiamulera et al., 2001). Moreover the mGluR5 antagonist MPEP has been shown to reduce the locomotor properties of cocaine and reduce conditioned place preference to cocaine, morphine and amphetamine (McGeehan and Olive, 2003; Herzig and Schmidt, 2004; Herzig et al., 2005). The BNST has been shown to express all three families of mGluRs and stimulation of all three mGluR families reduces glutamatergic transmission in the dlBNST (Grueter and Winder,

2005; Grueter et al., 2006). Activation of group I (specifically mGluR5) and group II mGluRs can induce long term depression (LTD) of glutamatergic synapses in the dlBNST, albeit via different mechanisms. Typically coupled to $G_{i/o}$, group II mGluRs depress synaptic transmission via a presynaptic mechanism (Grueter and Winder, 2005). mGluR5 activation, which typically couples to G_q, however, induces LTD via extracellular regulated kinase 1 (ERK1) signaling (Grueter et al., 2007; Grueter et al., 2008)). Further experiments using postsynaptic delivery of GTP-γ-S and a dynamin inhibitory peptide suggests that the mGluR5 receptor is on the postsynaptic cell and that the LTD is maintained by postsynaptic modifications; and, requires clathrin-dependent endocytosis and actin remodeling thus suggesting a loss of AMPAR at the synaptic cleft by receptor internalization (Grueter et al., 2008). Furthermore, expression of this LTD following mGluR5 stimulation, but not the initial decrease in glutamatergic efficacy observed in the time course, is prevented by *in vivo* administration of cocaine. This occlusion can be rescued by prior administration of the mGluR5 antagonist, MPEP *in vivo* (Grueter et al., 2008). This suggests that cocaine signals through mGluR5 *in vivo* to exert effects over this plasticity in the dlBNST.

Cocaine administration can also regulate other forms of plasticity within the BNST. Dumont and colleagues found that self-administration of cocaine or palatable food, but not yoked administration, increased AMPA/NMDA current ratios (an indirect measure of LTP) in VTA-projecting neurons in the vlBNST (Dumont et al., 2005; Dumont et al., 2008), thus suggesting a requirement for active drug seeking. Additionally it has recently been shown that chronic morphine administration can also increase AMPA/NMDA ratios in neurons projecting from the BNST to the VTA (Dumont et al., 2008). Interestingly, this was shown to be specific to the location of the stimulating electrode, suggesting that this morphine-induced plasticity may be input specific.

In addition to LTD, activation of group I mGluRs in the BNST can also induce the release of endocannabinoids from the postsynaptic cell to act on presynaptic cannabinoid type 1 receptors (CB1Rs) (Grueter et al., 2006). Activation of these receptors decreases release probability, thus reducing glutamatergic efficacy. Recently Georges and colleagues showed that glutamatergic projections from the infralimbic cortex can stimulate BNST neurons (both dorsally and ventrally) to excite approximately 80% of the dopamine neurons in the VTA (Massi et al., 2008). The majority of this excitability was then demonstrated to be blunted by the addition of CB1R antagonists infused into the BNST which may demonstrate a mechanism for cannabinoid signaling to decrease the positive valance behaviors (such as pleasurable feelings) mediated by VTA activation.

Heterosynaptic modulation

Dopaminergic modulation

For many years, dopaminergic signaling has been the focal point of substance abuse research. Common features of addictive substances include increasing dopaminergic tone in the NAc; increasing synaptic plasticity on mesolimbic dopamine neurons in the VTA; and, animals will reliably perform intracranial self-stimulation (ICSS) of dopaminergic processes (Wise, 1998). It is important to note, however, that such dopamine transmission is not limited to the classical mesolimbic dopamine system. DiChiara and colleagues demonstrated that drugs of abuse can increase dopamine concentrations in the BNST (Carboni et al., 2000). Further, administration of addictive substances, but not non-addictive drugs activate extracellular regulated kinase (ERK) via dopaminergic signaling (Valjent et al., 2004) in the BNST. Additionally disruption of dopamine D1 receptor (D1R) signaling in the BNST can attenuate psychostimulant and ethanol reinforcement (Epping-Jordan et al., 1998; Eiler et al., 2003). These studies are additionally interesting because, as stated above, it has been shown that the

BNST makes excitatory projections to VTA dopamine neurons possibly demonstrating a feed-forward loop for reinforcing drugs (Georges and Aston-Jones, 2002).

As a result of the importance of dopamine in reward, our group has begun investigations into regions with high dopaminergic innervation. Focusing on the BNST, NAc and the dorsal striatum Healey et al. (2008) examined expression levels of tyrosine hydroxylase (TH, the rate limiting enzyme in the production of dopamine) and the dopamine transporter (DAT) following either chronic or chronic intermittent exposure to ethanol vapor (Healey et al., 2008). In this study, 4-6 hours following chronic ethanol exposure there was a significant reduction in DAT, but conversely, 4-6 hours following chronic intermittent ethanol exposure there was a significant increase in DAT expression in the NAc. Interestingly, however, there was no change in DAT expression in the BNST, in either condition, in tissue samples taken from the same exposed mice. This may be of functional significance as the BNST receives dopaminergic innervation from the PAG as well as the VTA. Competing forms of modification in the VTA and the PAG may have resulted in a lack of effect in the BNST in general.

Very recently our group investigated the possibility that dopamine may act by modulating glutamatergic transmission in the BNST (Kash et al., 2008b). Dopamine was found to increase excitability in a subset of neurons; and, in an activity dependent fashion, dopamine increased the frequency of spontaneous EPSCs in the dlBNST via signaling at D1 and D2 receptors. Due to reported anatomical and functional interactions between dopamine and corticotrophin releasing factor (CRF) in other brain regions (Riegel and Williams, 2008; Wanat et al., 2008) as well as the presence of CRF containing neurons and terminals within the BNST (Champagne et al., 1998), Kash, Nobis and colleagues sought to determine if dopamine was acting though CRF to increase glutamatergic transmission. Consistent with a dopamine-CRF interaction blocking CRF1 receptors can prevent the effects of dopamine, and CRF or Urocortin application alone can cause an increase in the miniature EPSC frequency. One possibility, therefore, is that dopamine likely acts through the D1 and D2 receptors to excite CRF containing cells within the BNST, thus releasing CRF in the BNST. In fact, dopamine can increase firing in neurons in the BNST recorded in current clamp (Kash et al., 2008b). Another possibility is that dopamine is acting on CRF afferents stemming from the CeA to cause the release of CRF. Additionally, Kash, Nobis et al. (2008B) demonstrated that cocaine (*in vivo* and *in vitro*) and the specific dopamine transporter blocker GBR12909 could produce an NMDAR dependent enhancement of short term potentiation (STP) following tetanus. The increase in STP was prevented by both a pan-dopamine and a CRF-R1 antagonist and was absent in the D1R knockout mouse. In other brain regions, both CRF and dopamine have been demonstrated to modulate LTP (Thompson et al., 2005; Fu et al., 2007), and it has been demonstrated that CRF can modulate dopaminergic neurons in the VTA (Riegel and Williams, 2008; Wanat et al., 2008); however, these data demonstrate for the first time that dopamine can trigger a CRF dependent modulation of STP. The CRF dependent STP enhancement of excitatory transmission in the BNST by dopamine and CRF therefore may lead to increased excitatory tone in the dopaminergic neurons of the VTA via both glutamate release and CRF, now stemming from BNST afferents (Rodaros et al., 2007), enhancement of firing. This plasticity may perhaps serve as a mechanism by which cognitive and limbic centers can create a feed forward loop on midbrain dopamine neurons to enhance dopaminergic tone in several brain regions.

Adrenergic Modulation

Although dopaminergic signaling has been the focal point for substance abuse research for the past three decades, norepinephrine (NE) was originally thought to be a central player in mediating reward. In the 1970's it was shown that animals could perform ICSS of noradrenergic nuclei and pathways, interfering with NE signaling disrupted ICSS, and disruption of NE

signaling was shown to inhibit opiate and ethanol self-administration. (For an in-depth review see Schroeder and Weinshenker 2007.) Recently NE, especially the projections from the ventral noradrenergic bundle (VNAB), has reemerged as a player in both reward and reinstatement to drug seeking. Olson and colleagues demonstrated that mice lacking the enzyme that produces NE (dopamine-β-hydroxylase or DBH) did not show a condition place preference to morphine, but this effect could be rescued by viral introduction of DBH to the nucleus of the tractus solitarius (NTS) (Olson et al., 2006). The BNST receives one of the densest projections of norepinephrine in the CNS stemming from the ventral noradrenergic bundle that is composed of the NTS and A1 cell groups (Ricardo and Koh, 1978; Woulfe et al., 1988; Forray and Gysling, 2004). Alteration of this projection, either by pharmacology (targeting individual ARs), or ablation, has demonstrated that this modulation can impact stress induced reinstatement to drug seeking, withdrawal aversion, fear behavior to predator stress and HPA axis regulation to a systemic stressor (yohimbine injection) (Delfs et al., 2000; Erb et al., 2000; Shaham et al., 2000; Wang et al., 2001; Fendt et al., 2005; Banihashemi and Rinaman, 2006). Furthermore blocking α_1-ARs in the BNST reduces anxiety after a processive stressor (restraint) and decreases adrenocorticotrophic hormone (ACTH) suggesting that NE in the BNST can regulate HPA axis output to an anxiety inducing phenomena (Cecchi et al., 2002).

Our group, therefore, began a detailed investigation as to how norepinephrine modulates glutamatergic synapses in the BNST. Interestingly in different experiments in the dorsolateral BNST (dlBNST) norepinephrine could produce both an increase and decrease in glutamatergic efficacy in fEPSPs. Using pharmacology to dissect which receptors were responsible, Egli et al. showed that α_2-AR stimulation resulted in a strong, but transient, suppression of glutamatergic signaling. β-AR stimulation, however, resulted in a transient increase in glutamatergic signaling (Egli et al., 2005). Intriguingly, stimulating β-AR could not account for the entire observed increase in transmission and the increase could be subsequently blocked by an α_2-AR antagonist, suggesting a synergistic mechanism between β-ARs and α_2-ARs. This data is further complicated by recent data examining the actions of α_2-ARs (see below (Davis et al., 2008)). In the vlBNST however, norepinephrine only produced the transient decrease in fEPSPs which was shown to be mediated via the α_{2A}-AR.

The studies by Egli et al. suggested that norepinephrine modulated excitatory synapses in the BNST via the α_2- and β-AR alone, excluding a role for the α_1-AR. It has been shown, however, that α_1-ARs can modulate glutamatergic transmission in other nuclei. They have, in fact, been demonstrated to act in a promiscuous manner: increasing glutamatergic tone in the hypothalamus (Gordon and Bains, 2003; Gordon et al., 2005; Gordon and Bains, 2005) and decreasing glutamatergic tone in the hippocampus and visual cortex (via a LTD mechanism) (Kirkwood et al., 1999; Scheiderer et al., 2004). mRNAs for the α_1-AR subtypes are expressed in the BNST (Day et al., 1997), activation of α_1-ARs can cause increases in GABAergic tone (Dumont and Williams, 2004) and early evidence suggested that α_1-ARs could depress glutamatergic transmission (Sawada and Yamamoto, 1981). Utilizing the α_1-AR agonist methoxamine we demonstrated that α_1-AR activation can cause an LTD of glutamatergic transmission in the BNST (McElligott and Winder, 2008). A very intriguing aspect of this LTD was that it was dependent on the duration of exposure to NE. This observation may play a critical role of adrenergic modulation within the BNST as various groups have shown that using restraint as a psychological stressor can significantly increase noradrenergic tone in the BNST (via microdialysis) for several minutes following the termination of the stressor (Pacak et al., 1995; Cecchi et al., 2002). Therefore, it may be beneficial to the organism to only engage this type of plasticity only under extreme conditions of psychological stress when NE levels are most robust to perhaps disinhibit projections to nuclei like the PVN or inhibit projections to the VTA.

We next characterized the induction of α_1-AR LTD and were surprised to find that unlike the hippocampus and visual cortex, where it has also been described (Kirkwood et al., 1999; Scheiderer et al., 2004), α_1-AR LTD in the BNST is expressed independently of NMDARs, but it is dependent on L-type voltage gated calcium channels. This suggests that α_1-AR LTD is induced independently of presynaptic glutamatergic control coming from limbic and cortical inputs which could have physiological and psychological impact over animal behavior. For instance, this form of LTD could dissociate stress responses and drug craving from cognitive processes. This sort of disconnect is often alluded to by those with anxiety disorders and pathological substance abuse who are conscious of their pathological conditions yet are unable to overcome them. Although additional research would need to be performed to solidify this hypothesis, however we can envision a scenario where in these pathological conditions there is insufficient input from cognitive decision making domains to override more base feelings of anxiety or drug craving. Additionally, we found in two animal models, the α_{2A}-AR and norepinephrine transporter knockout mice, with various affective disorder phenotypes ranging from depression/anxiety to altered reward profiles (Bohn et al., 2000; Xu et al., 2000; Schramm et al., 2001; Hall et al., 2002; Lahdesmaki et al., 2002; Dziedzicka-Wasylewska et al., 2006; Keller et al., 2006), that α_1-AR LTD could not be induced under our conditions. It is likely that these two animal models lack the ability to induce α_1-AR LTD due to receptor desensitization from chronically elevated levels of NE (Bohn et al., 2000; Xu et al., 2000; Lahdesmaki et al., 2002; Dziedzicka-Wasylewska et al., 2006).

Due to the robust reinstatement data involving noradrenergic signaling, our group's previous data examining α_2-AR modulation of glutamatergic processes and the reported involvement of α_2-ARs in the facilitation of extinction behaviors following fear conditioning (Cain et al., 2004), we probed the ability for α_2-AR antagonism (with yohimbine) to facilitate extinction to the positive valence of cocaine. Surprisingly yohimbine impaired extinction to conditioned place preference to cocaine, and this impairment could not be mimicked with a more selective α_2-AR antagonist (Davis et al., 2008). Furthermore, we showed that yohimbine robustly reduced glutamatergic transmission in the BNST independently of signaling via α_2-ARs. While it is well known that yohimbine is not a selective drug, with off target effects mainly described at serotonin 5HT-1A receptors (Newman-Tancredi et al., 1998; Powell et al., 2005), it is often used for its anxiety inducing properties that are presumably evoked via enhanced adrenergic signaling via blockade of presynaptic ARs. We have demonstrated, however, that “off-target” effects of yohimbine have significant behavioral and physiological ramifications.

Recently, the BNST is gaining appreciation as a region involved in mediating the affective component of pain. Painful stimuli increase dialysis levels of NE in the BNST (Deyama et al., 2008a). Lesioning the BNST, blocking β-ARs and interfering with PKA signaling there reduces conditioned place aversion (CPA) to painful stimuli independently of nociception (Deyama et al., 2007; Deyama et al., 2008b). Interestingly, activating β-ARs and PKA in the BNST induced CPA independently of painful stimulation. Future studies in this area may aid in the development of non-narcotic analgesics for chronic pain.

GABA and Neuropeptides

Although the focus of this review is on glutamatergic transmission in the BNST, it is relevant to consider the importance of GABAergic (γ-aminobutyric acid) transmission within this nucleus. The majority of neurons within the BNST are thought to be GABAergic and the BNST receives a robust GABAergic projection from the central nucleus of the amygdala (CeA) which also can release CRF (Sakanaka et al., 1986). Another neuropeptide, neuropeptide Y (NPY) is expressed in adrenergic terminals and can be released upon high frequency stimulation of adrenergic neurons (Sawchenko et al., 1985; Pernow, 1988). In the vlBNST, NPY and CRF were found to respectively inhibit and increase GABAergic transmission within the BNST

(Kash and Winder, 2006). NPY appeared to decrease transmission presynaptically via the Y2 receptor, while CRF increased inhibitory transmission postsynaptically via CRF-R1. The integration of CRF's effects on inhibitory transmission with the actions of CRF on glutamatergic transmission in the dlBNST (which projects to the vlBNST as well as other nuclei) will most likely shape the output to stress and reward nuclei.

NE has also been shown to modulate inhibitory transmission within the BNST. In neurons projecting to the VTA, NE can increase spontaneous inhibitory post synaptic current (sIPSC) frequency (Dumont and Williams, 2004). In conjunction with NE's inhibitory effect on glutatmatergic signaling, both acutely (Egli et al., 2005) and LTD (McElligott and Winder, 2008), this suggests that NE may globally reduce BNST output to several nuclei.

Conclusions

The BNST serves as an important relay between limbic inputs and stress and reward nuclei in the brain, where synaptic modification can dramatically alter the flow of information, and can be liable to the influence of stressors and drugs of abuse. Synaptic integration in this nucleus is undoubtedly a very complex phenomenon of which researchers have only begun to scratch the surface. Studies that have investigated the physiological properties and glutamatergic modulation within the BNST, however, have begun making progress towards reconciling animal behavior with the underlying molecular mechanism. Glutamatergic transmission is potently modified by stressors and drugs of abuse in this region. In particular, catecholamines may be released in the BNST under both stressful and rewarding conditions and they may engage alterations in glutamatergic transmission that could alter functional output behavioral responses to these experiences. The data suggesting that LTP can occur when a rewarding substance is self-administered, but not passively, administered strongly suggests that this plasticity may underlie learned associations with reward (Dumont et al., 2005) that have the potential to affect the entire reward circuitry. While at this time, the ramifications of this modulation as well as the other forms of plasticity in the BNST are unknown, future studies that strive to discover additional links between environmental influences and synaptic modulation will broaden our understanding of the importance of such modulation in behavioral output. For example, behavioral experiments involving paradigms of stress and reward in varying strains of mice can lead to candidate mRNAs and, ultimately proteins that may be involved in synaptic modulation manifesting as changes at the behavioral level. In such a way, using genetics, bioinformatics, behavioral studies, biochemistry and physiology to address the role of the BNST the field will hopefully contribute to the long term goals of eradicating substance abuse and anxiety disorders.

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