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The Bed Nucleus of the Stria Terminalis in Drug-associated Behavior and Affect: A Circuit-Based Perspective

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Abstract

The bed nucleus of the stria terminalis was first described nearly a century ago and has since emerged as a region central to motivated behavior and affective states. The last several decades have firmly established a role for the BNST in drug-associated behavior and implicated this region in addiction-related processes. Whereas past approaches used to characterize the BNST have focused on a more general role of this region and its subnuclei in behavior, more recent work has begun to reveal its elaborate circuitry and cellular components. Such recent developments are largely owed to methodological advances, which have made possible efforts previously deemed intractable, such as tracing of long-range cell-type specific projections and identifying functional efferent and afferent connections. In this review, we integrate earlier foundational work with more recent and advanced studies to construct a broad overview of the molecular neurocircuitry of the BNST in drug-associated behavior and affect.

Introduction

The bed nucleus of the stria terminalis (BNST) was first anatomically defined in 1923 by Johnston, who described the structure as a “band or ridge of gray matter lying medial to the caudate nucleus” (Johnston, 1923). Nearly a century later, this structure has been identified as a key regulator of several motivational states and affective modalities, including anxiety,

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fear, aversion, stress, and reward (reviewed in (Lebow & Chen, 2016). Although work over the last several decades has implicated the BNST in a broad range of affective states and behaviors, optogenetic and chemogenetic advances have more recently allowed researchers to elucidate the cell-type and circuit-specific mechanisms underlying its involvement. This shift in focus from a broad region-based perspective to a cell type- and circuit-specific understanding of complex behavioral states is largely owed to the advent of modern genetic and viral tools. Thus, a more complex anatomical picture of the BNST has developed and insight into its intrinsic and extrinsic pathways has been gained.

Since the early work of Johnston, the anatomical organization of the BNST has been refined and efforts have been made to characterize its cyto- and chemo-architecture. Surrounding the more caudal aspect of the anterior commissure and forming a major subdivision of the extended amygdala forebrain continuum, the BNST is a dense collection of small yet distinct nuclei (Alheid, 2003; Alheid et al., 1998; De Olmos, Beltramino, & Alheid, 2004). Neuroanatomical studies in the rodent have identified 12–18 distinct subdivisions of the BNST, based on patterns of molecular expression and neuronal composition (Bota, Sporns, & Swanson, 2012; Ju & Swanson, 1989). There is proposed to be a considerable amount of local connectivity among the subregions of the BNST as described by Dong and Swanson (2004, 2006a, 2006b), and studies have just recently started to examine the functional neuroconnectivity of the BNST microcircuitry. In the sections that follow, the intricate neurochemical composition of the BNST and its adjunctive intrinsic and extrinsic circuits, along with their known contributions to diverse behaviors are described, with particular focus on the dorsal lateral and ventral BNST.

Intrinsic Composition of the BNST

The BNST is a diverse structure comprised of many distinct nuclei broadly categorized into an anterior-posterior (initially medial-lateral) division (Bota & Swanson, 2010; Ju & Swanson, 1989; Krettek & Price, 1978) and further subdivided into a dorsal-ventral division along the anterior portion (Ju & Swanson, 1989; Ju, Swanson, & Simerly, 1989). Neurons within these divisions and their subnuclei co-express a variety of signaling molecules, including neuropeptides such as: corticotropin-releasing factor (CRF), dynorphin, enkephalin, neuropeptide Y, neurotensin, relaxin, and somatostatin (Ju et al., 1989; Poulin, Arbour, Laforest, & Drolet, 2009; Walter, Mai, Lanta, & Gorcs, 1991). The majority of BNST neurons are GABAergic in phenotype (Cullinan, Herman, & Watson, 1993; Esclapez, Tillakaratne, Tobin, & Houser, 1993), with modest expression of glutamate cells in the posterior BNST and sparse population in the dorsomedial and fusiform nuclei (Poulin et al., 2009). These BNST neurons are densely innervated by a variety of neuromodulatory centers described below.

GABA and Glutamate afferents

The central amygdala (CeA) provides the predominate source of GABAergic input to BNST (Dong, Petrovich, Watts, & Swanson, 2001; Li et al., 2012). Conversely, excitatory glutamatergic input to the BNST is derived from widespread limbic, paralimbic, and cortical origins. These regions include the basolateral amygdala, entorhinal cortex, insular cortex,

olfactory bulb, parabrachial nucleus, prefrontal cortex (orbital, infralimbic, and prelimbic cortices), and ventral subiculum of the hippocampus (Cullinan et al., 1993; Hurley, Herbert, Moga, & Saper, 1991; McDonald, 1998; Takagishi & Chiba, 1991; Vertes, 2004). Notably, alcohol exposure can directly alter glutamatergic synaptic plasticity within the BNST as discussed below.

Multiple forms of plasticity are regulated by non-contingent and contingent exposure to alcohol to produce functional changes within the BNST that may contribute to alcohol use disorders. Studies using male C57BL/6J mice have shown dynamic intra-BNST regulation of the NMDA receptor subunit GluN2B by acute and chronic non-contingent alcohol administration (Wills et al., 2012, 2013; Kash et al., 2008, 2009). Specifically, chronic intermittent ethanol enhanced LTP within the BNST, an effect that was dependent upon GluN2B (Wills et al., 2012). In addition, studies have shown that GluN2B is upregulated within the BNST following chronic intermittent ethanol (Kash et al., 2009). Application of ethanol to BNST brain slices inhibited the early phase of LTP in a NMDA and not GABA_A manner (Weitlauf et al., 2004; Kash et al., 2008). In addition, acute ethanol only affected GABAergic transmission in adolescent, but not adult animals (Wills et al., 2013). This suggests that alcohol use disorders, may in part be dependent on increased glutamatergic tone within the BNST. However, it is important to note, that no studies have set to identify the specific glutamatergic inputs that are modulated following alcohol exposure. This is an important goal, which can provide insight in to the aberrant information flow and plasticity induced by alcohol.

The core hypothesis that has emerged from multiple studies is that chronic alcohol consumptions changes synaptic plasticity within the BNST to regulate affective states, and promote alcohol use disorders. Studies have found that mice exposed to 4 days of chronic intermittent exposure to ethanol vapor led to an upregulation of the GluN2B-containing NMDA receptors, which was not seen in chronic continuous ethanol vapor exposure (Kash et al., 2009). The NMDA receptor antagonist ketamine has been shown to have anti-depressive like properties in both preclinical and clinical models of depression (Berman et al., 2000; Holleran et al., 2016). Interestingly, deletion of the GluN2B subunit of the NMDA receptor within the BNST reduced latency to approach liquid ensure in the novelty-induced hypophagia task in male C57BL/6J mice (Louderback et al., 2013), and administration of ketamine, an NMDA receptor antagonist, reversed alcohol-induced behavioral phenotypes in female mice (Holleran et al., 2016). In addition, chronic alcohol exposure in Wistar rats has been shown to lead to a dampening of LTP of intrinsic excitability within the lateral juxtacapsular nucleus of the BNST that could be blocked with a CRFR1 antagonist (Francesconi et al., 2009), this suggests that the CRF system is sensitive to alcohol, and other drugs of abuse such as cocaine, and heroin (Francesconi et al., 2009). This data suggests that ethanol exposure may drive behavioral alterations through changes in glutamatergic dependent long-term potentiation, and interactions with the CRF system within the BNST.

Dopamine afferents

Dopamine inputs originating in the ventral tegmental area (VTA) and periaqueductal gray project primarily into the dorsolateral subdivision of the BNST (dlBNST) and synapse directly onto CRF neurons (Meloni, Gerety, Knoll, Cohen, & Carlezon, 2006). It has been hypothesized that dopamine inputs to BNST underlie the stimulant action of abused drugs, as cocaine, ethanol, morphine, and nicotine dose-dependently increase extracellular BNST dopamine concentrations (Carboni, Silvagni, Rolando, & Di Chiara, 2000). Increased release of dopamine in the BNST has also been reported following exposure to natural reward (sucrose) and reward-predictive cues (Park et al., 2013; Park et al., 2012). Notably, intra-BNST antagonism of D1-like receptors has been shown to reduce ethanol self-administration and sucrose self-administration, though to a lesser extent in both male and female alcohol-preferring P rats (Eiler, Seyoum, Foster, Mailey, & June, 2003). However, to date there has been no rigorous examination of which of the two major dopaminergic inputs to the BNST drives this behavior.

Neuropeptide afferents

Neuropeptides, such as CRF, not only innervate the BNST but also modulate local excitability and synaptic function (See Kash et al 2014). CRF cell bodies projecting into the BNST can arise from the central nucleus of the amygdala, the paraventricular nucleus of the hypothalamus, or an internal population of BNST CRF interneurons all of which have been suggested to modulate cell excitability, and behavioral output. Nevertheless, CRF plays an important role in the addiction process, including stress-induced reinstatement of drug seeking (for review see Mantsch et al., 2015). CRF and CRF receptor activation within the BNST have been shown to promote anxiety, and reinstatement to cocaine in rats (Cummings et al., 1988; Dong and Swanson, 2006; Erb and Stewart, 1999). Studies have shown that CRF infusion within the lateral ventricle of male Sprague-Dawley rats increases a startle response that could be blocked by either lesioning the BNST or by the infusion of alpha-helical CRF (a non-specific CRF antagonist) into the BNST (Lee and Davis, 1997). Other behaviors are also observed when CRF is infused into the BNST; for example, male Long-Evans rats spent more time in the closed compartment of an elevated plus maze, an indicator of anxiety (Sahuque et al., 2006), increased the duration of conditioned place aversion (Sahuque et al., 2006), and reinstated to extinguished-cocaine seeking (Erb and Stewart, 1999; Vranjkovic et al., 2014).

Within the BNST, CRF signaling has been implicated in alcohol drinking behavior, and alcohol use disorders (Silberman and Winder, 2015; Vendruscolo et al., 2012). For instance, neuropeptide Y receptor 1 activation has been shown to suppress binge alcohol drinking by enhancing inhibitory drive onto CRF neurons in adult male C57BL/6J mice (Pleil et al., 2015). Other studies have indicated that through the actions of CRFR1, glutamate release is enhanced in mice exposed to chronic intermittent ethanol vapor (Silberman et al., 2013, Silberman and Winder 2013). This suggests that ethanol exposure and withdrawal drives distinct forms of plasticity with changes in CRF-dependent glutamatergic and GABAergic signaling.

Electrophysiological studies have shown that CRF exerts multiple actions in the BNST including enhancement of GABAergic transmission, glutamatergic signaling by increasing the frequency of spontaneous excitatory postsynaptic currents (sEPSC) (Kash, Nobis et al., 2008), and increasing cell firing. Several potential extrinsic sources of CRF exist, but a large population of CRF neurons are present within the BNST. Data suggest that these CRF BNST neurons are exclusively GABAergic, and these GABAergic CRF neurons are highly interconnected with CRF negative neurons within the BNST (Marcinkiewicz, Mazzone et al 2016, Partridge et al., 2016). Recent data from Marcinkiewicz, and colleagues have shown that serotonin (5-HT) from the dorsal raphe nucleus is involved in driving enhanced fear and anxiety-like behavior by engaging a CRF and GABAergic inhibitory microcircuitry through the actions of the 5-HT_{2C} receptor; specifically, activation of this pathway leads to an inhibitions of the anxiolytic output into the VTA and the lateral hypothalamus (Marcinkiewicz et al., 2016). This suggests that alterations in BNST microcircuitry may affect negative reinforcement based alcohol intake, anxiety, and depression. Also, these studies not only illustrate the heterogeneity of the BNST, but also highlighted the importance of understanding the plasticity that occurs within the BNST that promote anxiety which can directly drive alcohol use.

Noradrenergic afferents

The BNST receives dense noradrenergic inputs from the ventral noradrenergic bundle, and sparse innervation from the locus coeruleus. Studies have shown that the alpha-2 adrenergic receptor agonist such as clonidine, and guanfacine ameliorates withdrawal symptoms from alcohol, and other drugs of abuse. In addition, chronic alcohol partially attenuated alpha-1 receptor-mediated long-term depression within the BNST, while chronic restraint stress occluded long-term depression (McElligott et al., 2010). This suggests that noradrenergic signaling in the BNST is upregulated during periods of withdrawal, and this upregulation may promote an increase in glutamatergic signaling. In addition, studies have shown that activation of beta-adrenergic receptors leads to activation of CRFR1 signaling via possible local release of CRF (Nobis et al., 2011). Taken together with upregulation of NR2B signaling, this coordinated increase in glutamatergic activity may drive dysphoric behavioral states such as anxiety and depression during withdrawal.

Behavioral studies have suggested that noradrenergic BNST signaling promotes anxiety, especially during withdrawal from alcohol or cocaine. Day and colleagues have shown that predator odor, which promotes anxiety and fear increase Fos expression within the BNST and the nucleus solitary tract, indicating the involvement of the noradrenergic system in the fear response (Day et al., 1999). In addition, exposure to predator odor elicits an increase in norepinephrine release specifically within the ventral BNST (vBNST) of Sprague Dawley rats (Fendt et al., 2005, 2003). Exposure to cocaine has been shown to elicit both rewarding and delayed anxiogenic effects. Recent studies have shown that intra-vBNST cocktail injection of the beta- one and -two adrenergic receptor antagonists, Betaxolo and ICI 118,551 respectively, attenuated the negative and anxiogenic effects of cocaine (Wenzel et al., 2014). This suggests that noradrenergic activity; through the actions of beta-adrenergic receptors within BNST promote anxiety like behavior.

Similar results have been shown in human studies. Clinical data has suggested that the non-specific beta-adrenergic receptor antagonist propranolol and the alpha 2a agonist guanfacine may decrease cocaine-withdrawal induced anxiety, and lower cocaine-craving (Fox and Sinha, 2014; Fox et al., 2012, 2008; Kampman et al., 2011, 2001). Similar data was obtained in a preclinical setting in which antagonism of the beta receptors within the BNST blocks anxiety like behavior following an immobilization stressor (Cecchi et al., 2002). In addition, intra vBNST injections of the beta-adrenergic receptor antagonist timolol dose-dependently increased intraplantar-formalin-induced conditioned place aversion; while the nonspecific beta- adrenergic receptor agonist isoproterenol increased conditioned place aversion in the absences of a noxious stimulus (Deyama et al., 2008). In regards to stress-induced drug seeking, numerous studies have indicated the involvement of beta-adrenergic receptors within the BNST (Mantsch et al., 2015). Studies have shown that antagonism of beta-2 adrenergic receptors with ICI 118,551 (Vranjkovic et al., 2014) or a mixture of betaxolol and ICI 118,551 (Leri et al., 2002) in the vBNST blocks stress-induced reinstatement. In addition, peripheral administration of ICI 118,551 was able to attenuate forced swim induced increases in BNST *crf* transcript in cocaine conditioned place preference mice (McReynolds et al., 2014). Interestingly, rats infused with the beta-2 receptor agonist clenbuterol showed reinstatement of extinguished cocaine-seeking behavior. (Vranjkovic et al., 2014). Furthermore, early studies suggested that reinstatement to cocaine seeking occurs in a pathway whereby activation of the noradrenergic system precedes activity of the CRF system (Brown et al., 2011); this was later shown to be partly dependent within the BNST, in which beta2-adrenergic receptor activation acted upstream from CRFR1 to promote relapse to a footshock stressor (Vranjkovic et al., 2014). These studies suggest that anxiety and drug seeking behavior arise from noradrenergic and CRF interactions within the BNST.

While both CRF and the noradrenergic system regulate behavior within the dorsal BNST, studies have shown that both systems regulate glutamatergic signaling with the BNST. Studies have shown that spontaneous excitatory postsynaptic currents (sEPSCs) are controlled by beta-1 adrenergic receptors within the dorsal BNST (Nobis et al., 2011), since application of the nonspecific beta-adrenergic agonist isoproterenol increased the frequency of sEPSC (Nobis et al., 2011; Silberman et al., 2013). Furthermore, Silberman and colleagues showed that isoproterenol could directly depolarize CRF neurons with in the dorsal BNST (Silberman et al., 2013) suggesting that beta-adrenergic receptor activation within the BNST can lead to CRF release, from either local CRF-interneurons or CRF projecting neurons to facilitate glutamatergic transmission. This glutamatergic projection into the BNST can arise from the basolateral amygdala, or from the parabrachial nucleus (Flavin et al., 2014).

Serotonergic afferents

Serotonin (5-HT) inputs to the BNST arise from caudal regions of the dorsal raphe nucleus (DRN) and target the more dorsal portion of the BNST (Commons, Connolley, & Valentino, 2003; Lowry et al., 2008; Phelix, Liposits, & Paull, 1992). Within the BNST, multiple 5-HT receptor subtypes are differentially distributed and serve to modulate the responses of multiple cell types (Guo, Hammack, Hazra, Levita, & Rainnie, 2009; Hazra, Guo, Dabrowska, & Rainnie, 2012). However, most highly expressed are the excitatory (Gs-

coupled) 5-HT₇ receptor (46%) and inhibitory (Gi-coupled) 5-HT_{1A} (41%) receptors, which prime the BNST for bidirectional modulation by 5-HT (Guo et al., 2009).

Activation of BNST 5-HT receptor subtypes have been shown to produce direct and opposing effects on behavior. For example, activation of 5-HT_{1A} in the BNST reduces anxiety-like behavior, potentially serving to counter anxiogenic signaling through 5HT_{2C}-R. Notably, one week exposure to chronic intermittent ethanol vapor lead to an upregulation of 5HT_{2C}-R function in the BNST. Furthermore, animals exposed to the same ethanol vapor paradigm exhibited reduced social interactions, which was reversed by administration of a 5HT_{2C}-R antagonist. This does not provide unequivocal evidence that BNST 5HT_{2C}-R can drive alcohol induced disruptions in behavior, it does support the possibility. Future studies will need to explore this with more precision.

BNST Efferents to the Ventral Tegmental Area

As mentioned above, the BNST comprises multiple different subnuclei and genetically distinct cell types. Previous studies examining output regions of the BNST has been extremely challenging since electrical stimulation of the BNST often resulted in indirect stimulation of other brain regions and other passing projections (Sparta et al, 2013). Optogenetic-assisted circuit mapping allows for site-specific circuit mapping in heterogeneous structure such as the BNST. Using this approach, multiple studies have indicated that the BNST sends projects into the parabrachial nucleus (PBN), the lateral hypothalamus (LH), the periaqueductal gray (PAG), the central nucleus of the amygdala (CeA), and the VTA (Jennings et al., 2013; Kim et al., 2013). Since the VTA integrates multiple modalities that regulate reward behavior, the next section will focus on studies examining how stress and anxiety are regulated by BNST projections into the VTA.

The BNST sends dense projections GABAergic and glutamatergic projections into the VTA (Dong & Swanson, 2004, 2006a, 2006b; Kudo et al., 2012) that directly act on dopamine and GABA cells within the VTA (Georges & Aston-Jones, 2001, 2002; Jalabert, Aston-Jones, Herzog, Manzoni, & Georges, 2009; Jennings et al., 2013; Kudo et al., 2012). Of the BNST neurons that project to the VTA, 90% have been identified as GABAergic/non-glutamatergic (Kudo et al., 2012). Despite the prevalence of inhibitory outputs from BNST to VTA, early work suggested a primarily excitatory control of the VTA by BNST afferents. Specifically, stimulation of the vBNST potently and consistently activated VTA dopamine neurons (Georges and Aston-Jones, 2002; Yetnikoff et al., 2014). It is important to note that these data sets are not incongruent, it is possible, and likely that BNST GABA neurons preferentially synapse on to VTA GABA neurons leading to disinhibition of VTA DA neurons.

Several lines of evidence support a role for BNST-VTA projections in regulating stress and reward-related behaviors. For instance, VTA-projecting BNST neurons are activated by stress (Briand, Vassoler, Pierce, Valentino, & Blendy, 2010) and cocaine-associated cue presentation (Mahler & Aston-Jones, 2012; Sartor & Aston-Jones, 2012). Pharmacological studies have shown that disconnection of BNST transmission to the VTA interferes with cocaine-induced conditioned place preference (CPP) (Sartor & Aston-Jones, 2012) as well

as stress-induced cocaine seeking (Vranjkovic et al., 2014). Several recent studies using chemogenetic strategies have also shown that ethanol-induced CPP is blocked by BNST inhibition via a direct projection to the VTA (Pina & Cunningham, 2017; Pina, Young, Ryabinin, & Cunningham, 2015) and binge-like alcohol drinking is attenuated by inhibition of BNST CRF inputs to the VTA (Rinker et al., 2016). Other more recent work has also helped to elucidate the involvement of distinct VTA-projecting BNST nuclei and cell-types in motivated and affective behavioral states. Most notably, Jennings & Sparta et al (2013) have demonstrated that vBNST glutamate and GABA inputs to the VTA differentially impact anxiety and motivation. In fact, stimulation of vBNST glutamate inputs to the VTA produces an aversive and anxiogenic state, whereas vBNST GABA to VTA stimulation elicits a rewarding and anxiolytic state. In a similar vein, work by Kim et al (2013) showed that optogenetic stimulation of the oval nucleus (ovBNST) and anterodorsal BNST (adBNST) produced opposing effects on anxiety, with ovBNST promoting an anxious state and adBNST promoting an anxiolytic state. Interestingly, the states produced by ovBNST and adBNST further varied by the terminal site of the stimulation. In fact, optical stimulation of adBNST terminals in VTA produced a reward-like state as measured by the development of a real-time place preference without reducing anxiety-like behavior. Interestingly, through chemogenetic mapping recent findings have indicated that anxiety is regulated, in part, by either presynaptic or postsynaptic Gq signaling on BNST GABAergic efferent to the VTA, the locus coeruleus, and the parabrachial nucleus (Mazzone et al., 2016).

While these studies have established a role for this circuit in driven fundamental behaviors, the signaling driving this process in vivo is yet unclear. One potential important player is CRF. For example, both central and peripheral antagonism of the CRFR1 have been shown to decrease binge-like alcohol consumption (Sparta et al., 2009; Lowery et al., 2010). Furthermore, studies have shown that binge-like ethanol drinking increased CRF protein levels within the VTA (Lowery-Gionta et al., 2012) while antagonism of CRFR1 within the VTA reduced escalated ethanol consumption, and blunt binge-like ethanol drinking (Hwa et al., 2013; Sparta et al., 2013). CRF cell bodies project into the VTA from the BNST, CeA, and PVN (Silberman et al., 2013; Vranjkovic et al., 2014; Rodaros et al., 2007); and CRF cell bodies may also be expressed within the VTA (Grieder et al., 2014). This suggests that the increased VTA CRF immunoreactivity as observed by binge-like drinking (Lowery-Gionta et al. 2012) could originate from structures such as the BNST. Studies have also shown that in acute withdrawal from the chronic intermittent ethanol paradigm, VTA-projecting BNST neurons become more sensitive to glutamatergic signaling, and less sensitive to CRFR1 (Silberman et al., 2013). Overall, these studies indicate that chronic alcohol administration may alter CRF signaling with both the BNST and the VTA to promote alcohol use disorders. This work also highlights the importance of BNST-VTA connectivity in varying affective and motivational states.

Conclusion

The studies described in this review have begun to delineate mechanisms by which environmental stimuli regulate BNST circuitry to alter animal behavior, and begin to point to the involvement of specific neuronal populations and efferents, particularly to the VTA. Future studies will need to focus on the many additional neuronal populations within this

structure, along with efferents to other key downstream pathways such as the lateral parabrachial nucleus and the nucleus of the solitary tract as examples, to begin to develop a more complete picture of the coordinated circuits that run through this structure.

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Highlights

The BNST plays complex roles in alcohol and drug seeking behavior.

New tools now enable previously unparalleled specificity for testing the roles of specific BNST neuronal and afferent/efferent populations in alcohol and drug seeking behavior.

Figure 1. Schematic of rodent bed nucleus of the stria terminalis in coronal (top) and sagittal planes (bottom).