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Pharmacology of the Bed Nucleus of the Stria Terminalis

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Abstract The bed nucleus of the stria terminalis (BNST) regulates not only stress-related behaviors but also maternal behavior, pain-related behaviors, and reward-driven behavior. Dysfunction of the BNST leads to physiopathological states like anxiety disorder, post-traumatic syndrome disorder, anorexia, or addiction. Thus, a better understanding of the BNST emerges as an important challenge in order to develop innovative therapeutic strategies. Indeed, to improve our knowledge on the BNST, we first need to understand what shapes its activity. The BNST is strongly innervated by multiple inputs (glutamatergic, GABAergic, noradrenergic, dopaminergic, serotoninergic) giving rise to a part of its complexity. Importantly, under specific conditions (stress exposure, drug-withdrawal), endocannabinoid and neuropeptides can orchestrate the activity of the BNST. Here, we give a brief overview of the main pharmacological approaches targeting the BNST to assess the function of classical neurotransmitters and neuromodulators, from a pharmacological point of view through to behavior.

Keywords Pharmacology · Bed nucleus of the stria terminalis · Neuromodulators · Endocannabinoid · Catecholamine · Neuropeptides

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Introduction

The bed nucleus of the stria terminalis (BNST) belongs to a neuronal network of interconnected limbic regions and is conserved between rodents and humans [1]. For several years, more attention has been directed to understand the role of the BNST in humans [2–4]. The BNST emerges as a critical region that is activated in response to a potential threat or to a stress exposure, in order to develop adaptive strategies. Thus, it gives to the BNST a strong function in the regulation of anxiety and stress exposure [5–9]. Importantly, the BNST has also been presented as key player in motivational and goal directed behavior, through its connections with the reward circuit [7, 8, 10–13]. Dysfunction of the BNST may trigger maladaptive responses to inoffensive cues and physiopathological states such as anxiety disorders or addiction.

The BNST is located posterior to the nucleus accumbens, below the lateral ventricles and surrounding the anterior commissure. The BNST is a heterogeneous structure, not only composed of GABAergic neurons [41, 42] but also contains glutamatergic neurons [7, 41, 43–45]. It can be divided into different subnuclei based on morphological, biochemical, and electrophysiological studies: the antero-medial part of the BNST (amBNST), the antero-lateral part of the BNST (alBNST), the posterior part of the BNST (pBNST), [46–49].

BNST neurons project principally to a fundamental region of the reward system, the ventral tegmental area (VTA), and to a key regulator center of the hypothalamo-pituitary axis, the paraventricular nucleus of the hypothalamus (PVN). In turn, the BNST receives strong glutamatergic inputs mainly arising from the prefrontal cortex, the ventral hippocampus, the basolateral nucleus of the amygdala, and the paraventricular nucleus of the thalamus. In addition, the central nucleus of the amygdala (CeA) and the nucleus accumbens send GABAergic projections to the BNST.

The activity of BNST neurons is modulated by dopamine (DA) and 5-hydroxytryptamine (5-HT) from the ventral periaqueductal gray region (vPAG)/dorsal raphe (DR) [50, 51] and noradrenaline (NA) coming, from the nucleus of the tractus solitarius (A2) and A1 region [52]. Moreover, the activity of BNST neurons can be modulated by distinct neuropeptides such as corticotropin-releasing factor (CRF), pituitary adenylate cyclase-activating peptide (PACAP), neuropeptide Y, and endocannabinoid under certain circumstances [45, 52]. Altogether, these interconnected structures not only constitute a functional connectome consistent with its role in stress and motivation-associated behaviors but also support the complexity and the multifaceted aspects of the regulation of BNST neurons.

Thus, this review will aim to summarize the main pharmacological studies performed in the BNST based on in vitro, in vivo electrophysiology and behavioral data, in order to give a better view of the intriguing regulation of BNST neuron activity (Table 1).

Glutamatergic Pharmacology of the BNST

The amBNST receives excitatory inputs primarily from the ventral subiculum of the hippocampus (vSUB) and infralimbic cortex [42, 60, 61]. The lateral part of the BNST mainly received excitatory inputs from the insular cortex [61] and the paraventricular nucleus of the thalamus [62]. Our understanding of the functional role of these pathways mainly stems from local glutamatergic pharmacology studies.

First, activation of metabotropic glutamatergic receptors (mGluR) in the BNST diminishes the glutamatergic transmission. For example, an agonist of the group I mGluR -3,5-Dihydroxyphenylglycine (DHPG) decreases the frequency of the miniature excitatory postsynaptic currents (mEPSCs) and triggers long-term depression (LTD) in the BNST [14, 15]. In addition, bath application of an agonist of the group II of the mGluR (LY354740) diminishes the field response and the EPSC in the BNST [53]. It has been shown that bath application of an agonist of the group III of mGluR (3,4-Dicarboxyphenylglycine (DCPG)) decreases the frequency and the amplitude of the spontaneous excitatory post-synaptic current (sEPSCs) [54]. Together, these studies indicate that activation of mGluR results in a wide range of inhibitory responses in the BNST that have been associated to anxiety and stress-related behaviors [63].

On the other hand, an infusion of ionotropic glutamatergic antagonist (CNQX ((6-cyano-7-nitroquinoxaline-2,3-dione) + AP5 (2-amino-5-phosphonovaleric acid) reduces the excitatory response in the BNST evoked by the infralimbic cortex stimulation *in anesthetized rats* [13]. Interestingly, blocking glutamatergic transmission within the BNST in mice (local infusion of CNQX and AP5) can induce anxiolytic effect [8]. In addition, projections from neurons of the BNST to the VTA are crucial not only to behaviors related to reward and motivation but also aversion [7]. One particularly important glutamatergic output of the BNST is the VTA. BNST neurons control the activity of VTA DA neurons; chemical stimulation of the ventral part of the BNST (vBNST) with glutamate infusion increases the bursting activity of VTA DA neurons [11]. Infusing AP5, an N-methyl-D-aspartate (NMDA) receptor antagonist, in the BNST blocks the LTP in BNST neurons projecting to the VTA induced by high-frequency stimulation in the vSUB and the concomitant potentiation of VTA DA neurons [16]. This NMDA-dependent LTP in the BNST enhances the locomotor activity induced by a low threshold of cocaine [16]. The NMDA receptor is a heterotetrameric complex composed of two obligatory GluN1 subunits and two GluN2 and/or GluN3 subunits. The use of NMDA receptor subunit-specific pharmacology have demonstrated a key role of the extrasynaptic populations of GluN2B-containing NMDA receptors in tuning LTP after chronic ethanol exposure [64]. All together, these BNST studies show that glutamate acting on specific NMDA, AMPA, or mGluR receptor subtypes not only can modulate fear and anxiety but also regulate behaviors related to substances of abuse.

GABAergic Pharmacology of the BNST

The amBNST receives GABAergic innervation mainly from intra-BNST connections (from the oval nucleus), from local interneurons or collaterals [48, 65], and from the central amygdala [60]. First, it has been shown that bath application of an antagonist of GABAA receptor (Picrotoxin) enhances the resting membrane potential of dorsal part of the BNST neurons [66]. Moreover, BNST infusion of an agonist of GABAA receptors (Muscimol) inhibits freezing behavior following an exposure to a predator odor [17]. In addition, anxiety behavior and decrease in social behavior have been noted in animals that had received a GABA synthesis inhibitor (L-allyglycine) in the BNST [18]. An important role attributed to the BNST is the integration of sensory information from a situation perceived as stressfull [67]. Lines of evidence coming from different branches of neuroscience indicate that GABAergic neurotransmission in the BNST is a preferred candidate for modulation of anxiety-related and innate-defensive responses, with evidently clinically relevant effect with benzodiazepine [68]. Together, these data support a strong impact of the GABAergic transmission in the BNST on anxiety-related behaviors.

Monoamine Pharmacology of the BNST

A characteristic of the BNST is its high contents and diversity of neuromodulators. Indeed, both glutamatergic and

Table 1 Main pharmacological studies in the BNST

Pharmacology	Molecular and in vitro electrophysiology	In vivo electrophysiology	Behaviors	References
Glutamate		In the vBNST, increases the bursting of VTA DA neurons		Georges and Aston-Jones [11]
DHPG mGLURI agonist	Decreases frequency of mEPSCs Promotes LTD			Grueter et al. [14]; Grueter et al. [15]
LY354740; DCPG mGLURII and mGLURIII agonist	Decreases field response and EPSC Decreases frequency and amplitude of sEPSC in dBNST			Grueter et al. [53], Gosnell et al. [54]
NBQX + AP5 antagonist			Anxiolytic (EPM)	Kim et al. [8]
CNQX + AP5 antagonist		Decreases excitatory evoked response to ILCx		Massi et al. [13]
AP5 NMDAR antagonist		Decreases LTP induced by HFS in vSUB in BNST neurons projecting to VTA and blocks the potentiation of VTA DA neurons	Increases locomotor activity induced by a threshold dose of cocaine	Glangetas et al. [16]
Muscimol $GABA_AR$ agonist			Inhibits freezing behavior induced by an exposure to a predator odor	Fendt et al. [17]
L-allyglycine GABA synthesis inhibitor			Enhances anxiety behavior (EPM) and decreases the social behavior	Sajdyk et al. [18]
DA	Increases the frequency of sEPSCs in dlBNST via D_1R and D_2R Decreases $GABA_A$-IPSC amplitude in the ovBNST via D_1R and D_2R			Kash et al. [55], Krawczyk et al. [19]
NA	Increases the $GABA_AR$ inhibition in control and in acute morphine withdrawal via α_1R			Dumont and Williams [20]
UK-14,304 Isoproterenol (α and β) agonist NA	Diminishes field recordings and EPSC via $\alpha_{2A}R$ or increases the excitatory transmission if β adrenergic receptors are activated			Egli et al. [21]
Propanolol β R antagonist	Reduces number of FOS in BNST after opiate withdrawal		Decreases drug-withdrawal-induced conditional place aversion Decreases stress-induced reinstatement of cocaine seeking behavior Decreases the behavioral response to stressor Decreases in the run away in the avoidance test after session of i.p. cocaine	Aston-Jones et al. [22] Leri et al. [23] Cecchi et al. [56] Wenzel et al. [57]
5-HT	Inhibits via $5HT_{1A}R$ Excits via $5HT_{2A,2C,7}$		Anxiolytic effect; (startle behavior)	Rainnie et al. [58] Levita et al. [24]
Win 55,212-2 CB_1R agonist	Diminishes the fEPSCP, the EPSC and the frequency of sEPSC in the alBNST, increases the PPR	Decreases the excitatory responses in the BNSTneurons and in the VTA DA neurons evoked by ILCx stimulation		Massi et al. [13], Puente et al. [25]

Table 1 (continued)

Pharmacology	Molecular and in vitro electrophysiology	In vivo electrophysiology	Behaviors	References
AM251 CB_1R antagonist		Blocks LTP-induced by 10-Hz stimulation of ILCx after stress exposure or after 60 days of nicotine self-administration	Decreases cue-induced reinstatement	Glangetas et al. [26]; Reisiger et al. [27]
D-Phe CRF_1R antagonist			Blocks stress-induced reinstatement of drug seeking behavior	Erb and Stewart [28], Erb [29]
CRF	Increases the amplitude of mIPSC in dlBNST via CRF_1R			Kash and Winder [30]
Urocortin 1 CRF_1R agonist	Enhances sEPSC frequency			Nobis et al. [31]
$Astressin_2B$ CRF_2R antagonist			Anxiogenic effect, (EPM)	Tran et al. [32]
CRF			Influences maternal behavior	Klampfl et al. [33]
CRF			Anxiogenic effect	Erb and Stewart [28], Sahuque et al. [34]
PACAP	Chronic stress elevates the expression of PACAP transcript and PAC_1R in the dBNST		Anxiogenic effect persistent 7 days after infusion, (startle reflex)	Hammack et al. [35], Lezak et al [36, 37], Roman et al. [38]
PACAP			Reduces weight and food intake 24 h after, mediated by the posterior BNST	Kocho-Schellenberg et al. [39]
PACAP	PACAP38 increases the level of corticosterone 30 min after acute stress			Lezak et al. [36, 37]
NPY	Decreases mIPSC amplitude and frequency in vlBNST and increases the PPR			Kash et al. [30]
NPY	Increases frequency of mIPSC		Y1 agonist decreases the binge alcohol drinking behavior whereas Y2 agonist enhances this behavior	Pleil et al. [40]

GABAergic transmission within the BNST can be modulated by stress-elicited release of neuromodulators such as monoamines, neuropeptides, and endocannabinoid. Overall, the effects of these neuromodulators in the BNST seem to participate to a multistep control of the autonomic and psychoneuroendocrine impacts of stress.

Noradrenaline

Noradrenergic fibers arising from the A1 and A2 noradrenergic cell groups (nucleus of the tractus solitarius) [69, 70] mainly project to the vBNST [71]. Threatening or stressful stimuli activate these noradrenergic inputs which thereafter promote the release of NA in the BNST [72, 73]. In addition, noradrenergic system may be activated in response to a reward stimulus. For example, an increase of NA release in the vBNST has been noted after intracranial self-stimulation of the VTA/SNc [74]. NA can act on three different classes of adrenergic receptors: α, β_1, and β_2 receptors (see for more details review [75]). Intra-BNST infusion of β_1 and β_2 receptor antagonist decreases footshock-induced reinstatement of cocaine seeking behaviors [23] and diminishes drug withdrawal-induced conditional placed aversion [22].

NA can affect both excitatory and inhibitory transmission in the BNST [20, 63, 66]. The action of noradrenaline onto the glutamatergic transmission in the BNST depends on the type of receptor activated. Indeed, it has been demonstrated that application of NA can trigger both enhancement and decrease of the excitatory transmission in the BNST [66]. Notably, bath application of an agonist of the α2A adrenergic receptors (UK-14,304) decreases the EPSC in the BNST whereas a β adrenergic receptor agonist (isoproterenol) increases the excitatory transmission in the dBNST [21]. Furthermore, NA can increase the $GABA_A$ inhibitory postsynaptic currents (IPSC) in the vlBNST [20]. Thus, these data suggest that noradrenaline can modulate the glutamatergic and the GABAergic transmission in the BNST.

Dopamine

Dopaminergic fibers originating from the vPAG/DR and the VTA principally innervate the anterodorsolateral part of the BNST [50]. It has been shown that DA bath application increases the frequency of sEPSCs in the dlBNST which was blocked by D1R and D2R antagonists, SCH23390, and sulpiride, respectively [76]. This study suggests that DA enhances the glutamatergic drives onto dlBNST neurons. To extend that work, Krawczyck et al. [19] specify that catecholamines have bidirectional effect onto the oval BNST, a subregion of the anterodorsolateral part of the BNST. In particular, DA diminishes the evoked $GABA_A$-IPSCs through D_2R whereas NA decreases the AMPAR-EPSCs through the α_2 adrenergic receptor. Therefore, this result may propose that DA reduces the inhibitory influence onto oval BNST neurons whereas the NA downregulates the excitatory drive specifically onto them. Thus, DA may regulate differentially anterodorsolateral part of BNST neurons depending on their specific localization.

In the future, better characterization of DA's modulation of the different subnuclei of the alBNST may help to better understand the regional specificity of neurons in the dlBNST and their control by dopamine released from multiple origins. Catecholamines may be an important signal that triggers information related to stressful situations or reward-related situation to the dlBNST.

Serotonin

It has been described that serotonin (also known as 5-hydroxytryptamine (5-HT)) application in the alBNST induces complex neuronal responses. It can drive both excitatory and inhibitory responses [35, 58]. One hypothesis is that the inhibition of BNST neurons elicited by 5-HT may be triggered by an activation of 5-HT type 1 receptor whereas the excitation of BNST neurons may be mediated through another type of 5-HT receptor, the $5\text{-}HT_{2A}$ or $5\text{-}HT_7$. In addition, a recent study highlights a key role of BNST 5-HT2C receptors in promoting anxiety through a specific activation of a subpopulation of CRF neurons [77]. Moreover, bilateral injection of an agonist of the $5\text{-}HT_1R$ (5-CT), in the BNST reduced the acoustic startle responses, which suggests an anxiolytic effect [24]. Thus, activation of the $5HT_{1A}R$ in the lBNST may contribute to anxiolytic behavior whereas the activation of the $5HT_2R$ may drive anxiogenic effect. Indeed, 5-HT reuptake inhibitor is used as therapeutic tool to treat anxiety trouble disorder. 5-HT is an important neuromodulator that can bidirectionally modulate anxiety depending on the targeted receptor. Additional works may be required to further dissect the action of 5-HT within the BNST.

Endocannabinoid Pharmacology of the BNST

The endocannabinoid (eCB) system exerts a powerful control onto BNST neurons activity. The eCB system acts as a retrograde signaling by releasing on demand anandamide or 2-arachidonoyl-glycerol (2-AG) that targets cannabinoid type 1 receptor (CB_1R). Activation of CB_1R leads to a temporary or prolonged decrease of the neurotransmitter release. CB_1R have been localized on glutamatergic inputs from medial prefrontal cortex (mPFC) [13, 25] and GABAergic fibers innervating the BNST [25], but have also been proposed to modulate aversive behaviors through its action on noradrenergic transmission in the BNST [78].

The BNST integrates information from stress input pathways, and subsequently regulates both stress output and reward

pathways [11, 79]. The endocannabinoid system participates in these functions, since it has been shown that intra-BNST infusion of a CB_1R agonist, (Win 55,212–2) induces a decrease of excitatory response in BNST neurons evoked by infralimbic cortex (ILCx) electrical stimulation in anesthetized rats [13], which was reversed by i.p. injection of CB_1R antagonist (SR1416A). In addition, this intra-BNST infusion also decreases ventral tegmental area (VTA) dopamine neurons excitatory evoked activity induced by ILCx stimulation. Moreover, bath application of CB_1R agonist, (Win 55,212–2), promotes the decrease of fEPSCs, EPSCs and of the frequency of sEPSCs in the alBNST [25]. One of the main functions of the eCB system is to modulate stress response since it acts as an inhibitory tone on the hypothalamo-pituitary axis [80].

We have previously shown that acute restraint stress induced an eCB dependent long term potentiation (LTP) in the amBNST after a 10 Hz stimulation in the mPFC since it was blocked by intra- BNST infusion of an antagonist of CB_1R, (AM251) [26]. Moreover, 10 Hz stimulation in the mPFC also promotes eCB dependent LTP in the amBNST after 60 days of nicotine self-administration in rats [27]. Intra-BNST infusion of AM251 blocked this LTP and decreased the cue-induced reinstatement in these nicotine self-administrated rats.

All together, these data convey a key function of the eCB system in the regulation on BNST neurons activity notably after stress or drug exposure. Further investigations are required to better tackle the role of this complex eCB system in the BNST and their behavioral outcomes.

Neuropeptides Pharmacology of the BNST

In this part, we will give a brief overview of the different neuropeptides encountered in the BNST and their effects, please for more details (see review [81]).

PACAP

Pituitary adenylate cyclase activating peptide (PACAP) is a neuropeptide that can be synthetized in two possible isoforms PACAP38 and PACAP27. PACAP has been detected in fibers from the PVN and dorsal vagal complex [82]. The BNST is enriched in PAC1 receptor, which is the main postsynaptic target of PACAP. PACAP infusion in the BNST induces anxiogenic behavior which can persist for up to 7 days after [83]. An increase in the level of corticosterone has been observed after acute PACAP 38 infusion in the BNST [36]. Indeed, repeated stress exposure promotes an increase in PACAP transcript specifically in the dlBNST [37, 83]. In addition, PACAP antagonist infusion in the BNST blocks anxiogenic effect of repeated stress and deficit in novel objet test [38]. In addition, 14 h after PACAP infusion in the posterior part of the BNST, there is a loss of weight and food intake [38, 39]. Thus, these results suggest that PACAP may be released in the BNST after stress exposure to participate to the stress response, and therefore promotes anxiogenic effect. Further electrophysiological studies will be really helpful to understand the neuronal mechanisms of PACAP within the BNST.

CRF

CRF is a neuropeptide that is mainly produced by the PVN, BNST neurons, or CeA [46, 84] which notably participates to the initiation of stress responses through two different type of receptors CRF type: CRF type 1 receptor (CRFR1) and CRF type 2 receptor R (CRFR2) (for more details, see the review [81]). CRF signaling modulates both glutamatergic and GABAergic transmission within BNST and modulates the subpopulation of neurons projecting to the VTA [85]. For example, CRFR1 activation enhances the frequency of sEPSCs in the BNST [31]. In addition, CRF application increases the amplitude of miniature IPSCs in the BNST through CRFR1 [30].

A number of studies have drawn links between CRF signaling in the BNST with several aspects of aversive and anxiogenic behavioral phenotypes. CRFR1 antagonist infused in the BNST block stress-induced reinstatement of drug seeking behavior [28, 86]. CRF infusion in the BNST induces anxiogenic effect mediated by CRFR1 and drives conditional place aversion [34]. However, the effect of CRF depends not only on the type of receptor activated but also on the region of the BNST studied. Indeed, intra-alBNST injection of CRFR2 antagonist also induces an anxiogenic effect [32]. In addition, CRF system within the BNST influences maternal behavior. Notably, it has been shown that CRFR1 activation in the BNST impaired maternal care [33] and participated to the control of autonomic and neuroendocrine function [87].

Neuropeptide Y

Neuropeptide actions on the BNST are nevertheless much more complex; we do not discuss the action of other neuropeptides in the BNST such as dynorphin, nociceptin, oxytocin, and neurotensin (see, [81] for more details) nor their concomitant actions.

In the BNST, the neuropeptide Y (NPY) can mainly modulate inhibitory GABAergic transmission in the BNST through two distinct receptors: Y1R and Y2R. NPY reduces miniature Inhibitory Postsynaptic Current (mIPSC) amplitude and frequency in the vlBNST via the Y2R [76] More recently, it has been demonstrated that NPY can increase the frequency of mIPSC in the BNST through the Y1R both in mice and monkey [40]. Together, these studies suggest that NPY promote anxiolysis and anti-depressive effects, notably after stress exposure [81, 88, 89].

The NPY system in the BNST has also been implicated in addiction. Interestingly, intra-BNST infusion of Y1R agonist decreases binge alcohol drinking behavior, whereas Y2R agonist increases binge drinking behavior. Further investigations on the function of NPY in vivo in the BNST will be helpful and may provide a new pharmaceutical target strategy for anxiety and addiction disorder.

Conclusion

Thus, understanding how the activity of BNST neurons is regulated represents still a great challenge. Indeed, classical pharmacological approach is an important first step that helps to better tackle these questions. However, as exposed previously, to have a more detail view of the BNST and its complexity, we have also to take into account its different subregions, cell subpopulations, and input specificity. Optogenetic and pharmacogenetic approaches provide good perspectives to further dissect mechanisms and functions of BNST neurons. One other potent question to address is also to define how informations from such different synapses can convey and be integrated at the single cell level in the BNST and how these informations will then be transferred to the VTA and/or to the PVN. The BNST develops powerful plasticity properties under certain circumstances to cope with drastic changes in homeostasis induced by stressful situations or reward experience for example. Further investigations on the BNST and its ability to undergo onto plasticity may be required and would give another alternative approach to treat pathology such as anxiety disorder, anorexia, and addiction.

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Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interests.

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