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Synaptic Plasticity in the Bed Nucleus of the Stria Terminalis: Underlying Mechanisms and Potential Ramifications for Reinstatement of Drug- and Alcohol-Seeking Behaviors

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Abstract

The bed nucleus of the stria terminalis (BNST) is a component of the extended amygdala that shows significant changes in activity and plasticity through chronic exposure to drugs and stress. The region is critical for stress- and cue-induced reinstatement of drug-seeking behaviors and is thus a candidate region for the plastic changes that occur in abstinence that prime addicted patients for reinstatement behaviors. Here, we discuss the various forms of long-term potentiation (LTP) and long-term depression (LTD) in the rodent BNST and highlight the way that these changes in excitatory transmission interact with exposure to alcohol and other drugs of abuse, as well as other stressors. In addition, we highlight potential areas for future research in this area, including investigating input- and cell-specific bidirectional changes in activity. As we continue to accrue foundational knowledge in the mechanisms and effects of plasticity in the BNST, molecular targets and treatment strategies that are relevant to reinstatement behaviors will also begin to emerge. Here, we briefly discuss the effects of catecholamine receptor modulators on synaptic plasticity in the BNST due to the role of norepinephrine in LTD and dopamine on the short-term component of LTP as well as the role that signaling at these receptors plays in reinstatement of drug- and alcohol-seeking behaviors. We hope that insights gained on the specific changes in plasticity that occur within the BNST during abstinence from alcohol and other drugs of abuse will provide insight into the biological underpinnings of relapse behavior in human addicts and inform future treatment modalities for addiction that tackle this complex biological problem.

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Notes

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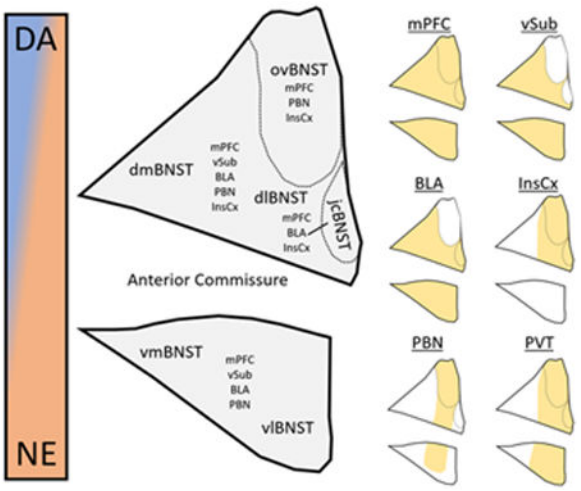

Keywords

BNST; reinstatement behaviors; synaptic plasticity; addiction; glutamate; catecholamines

■ INTRODUCTION: THE BRAIN DURING PROTRACTED ABSTINENCE

Addiction and alcoholism are chronic diseases characterized by bouts of remission and relapse.[1] Only a minority of patients receive treatment; for those that do, relapse to use is a common event; and susceptibility to relapse can last for years into abstinence.[2] These high rates of eventual relapse occur in patients with substance use disorders to all drugs of abuse, including cocaine, alcohol, opiates, nicotine, and others, and even in behavioral addictions such as gambling disorder.[3] Therefore, we consider that the biology underlying these processes has overlapping neural substrates. During the transition from casual drug use to pathologic addiction, brain changes occur that prime the addict or user to reengage in drug use and relapse to addiction.[4,5] It is hypothesized that during this process, as drug use becomes habitual and withdrawal-induced negative affect becomes prominent, the brain recalibrates such that the homeostatic set point of “normalcy” is not reached in the absence of drug and a new allostatic set point is reached only in the presence of drug. This is a useful framework to guide conceptualizing brain changes that occur in the addicted or alcoholic patient. Interestingly, the structural and molecular changes that occur during this transition persist even after the acute physical symptoms of withdrawal have occurred and can last for years after drug use, like susceptibility to relapse. The process of protracted abstinence after extensive drug use has been effectively modeled in rodents as either extinction training or incubation of drug craving after self-administration or other drug conditioning procedures.[6,7] In both humans and rodents, relapse can be triggered by stressful life events,[8–10] re-exposure to the drug,[11] or even exposure to the environment of or cues associated with drug use.[12,13] A better understanding of the neural substrates associated with the priming of the brain to respond to these stimuli with drug-seeking will allow for better treatment of addicted patients in the context of relapse prevention.

The effects of abstinence from drug use on structural changes in the brain have been studied in a number of brain regions. The classical neural pathway for these and related studies is the mesolimbic dopamine system consisting of the projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). This projection is engaged during use of all drugs of abuse and leads to dopamine release in the NAc that is critical for reinforcement of drug use, reinstatement of drug-seeking, and other drug-related behaviors.[14] Compelling evidence supports the notion that drug exposure elicits robust changes in plasticity in projection neurons within the mesocorticolimbic dopamine system.[15–17] However, the long-term changes in synaptic plasticity in amygdalar and other regions that project into the mesolimbic dopamine system are likely important in the longer-term effects of protracted use and abstinence-related relapse but much less studied. The extended amygdala is one such collection of nuclei known to play a key role in addiction-related behaviors.[18−20] Composed of the anatomically related central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the shell of the NAc,[21,22] the extended amygdala functions as an integrator of stress and reward information within the brain and is implicated in the withdrawal and negative affect stage of the addictive cycle described above.[23–26] Specifically, the BNST has a direct projection to the VTA that is critical for and engaged during drug-seeking behavior as well as withdrawal from drugs of abuse.[27] In addition, activity in the BNST is critical for both cue- and stress-induced reinstatement of drug-seeking and has been shown to undergo plastic changes during abstinence from drugs of abuse after extended use.[28–31] For this reason, it will be the subject of the remainder of this review, extending prior analyses of this literature.[32–34]

■ LONG-TERM POTENTIATION OF GLUTAMATERGIC TRANSMISSION IN THE DORSOLATERAL BNST

Early work on synaptic plasticity in the BNST utilized ex vivo brain slices to study changes in neurotransmission after electrical stimulation of glutamatergic afferents within coronal sections. Different stimulation protocols can elicit different changes in activity, with long-term potentiation (LTP) representing enhanced effect to the same stimulation parameters and long-term depression (LTD) diminished effect. Here, we summarize work done on LTP in the BNST before transitioning to LTD. An overview of both LTP and LTD experimental results in the BNST can be seen in Tables 1 and 2, respectively.

Mechanism(s) of LTP in dlBNST.

LTP can be induced in BNST slices using high frequency stimulation (HFS) protocols, often involving two bouts of 100 Hz stimulation for 1 s each, and recorded either in the synaptic component of field potential responses to stimulation or through intracellular recordings using sharp electrodes. Early studies aimed to uncover the molecular mechanisms underlying this effect in ex vivo mouse BNST slices and showed that this LTP was sensitive to NMDAR (*N*-methyl-D-aspartate receptor) inhibition by AP5 and insensitive to inhibition of L-type calcium channels by nimodipine or $GABA_A$ receptors by picrotoxin.[35] Subunit specificity of the effects of NMDAR inhibition was later shown, as GluN2A knockout did not affect LTP,[36] but GluN2B knockout and pharmacological inhibition by Ro25-6981 both reduced LTP.[37] Interestingly, the early phase of LTP (0–5 min post-HFS) was sensitive to

bath application of 100 mM ethanol before but not after HFS through an NMDAR-dependent process.[35] The effects of ethanol on NMDAR-dependent transmission were again later shown to be GluN2B-dependent but GluN2A-independent.[37,38]

Drug Exposure Interactions with dlBNST LTP.

Although ethanol appeared to have an inhibitory effect on LTP in mouse BNST slices when bath applied, chronic exposure to alcohol using the chronic intermittent ethanol (CIE) paradigm was shown to upregulate GluN2B expression[39] and enhance LTP induction in the BNST through an GluN2B-dependent process.[37] This enhancement was prevented by chronic but not acute corticosterone administration, chronic or acute social isolation,[40] and simultaneous chronic social isolation and chronic unpredictable stress.[41] The CIE paradigm consists of two cycles of 4 days with 16-h ethanol exposure and 8-h recovery with 3 days in between each cycle. This suggests that repeated exposure to ethanol and withdrawal induces structure and molecular changes in the BNST that increase the potential for LTP induction. Similarly, a single injection of cocaine or bath application of cocaine enhances the early phase of high frequency stimulation-induced LTP, defined here as short-term potentiation (STP), in a dopamine- and CRF-dependent process.[42] However, each of these recordings was done on the population level as a field potential and do not give information regarding cell-specific effects on plasticity, which is important in the heterogeneity of the BNST. Parallel cell-specific results were observed, though, in rats undergoing a self-administration procedure for cocaine or food. In both cases, self-administration increased the excitability of anterolateral BNST neurons via an increased AMPAR/NMDAR ratio, an electrophysiological measurement that compares the current passing through the two receptors and is increased upon the synaptic AMPAR insertion that commonly occurs in LTP.[43] This increased excitability is not seen after either acute cocaine injection or passive administration of cocaine or food.[43] Similar results were also obtained in the oval BNST, where sucrose and cocaine self-administration increased AMPAR/NMDAR ratios during the acquisition phase.[44] Interestingly, cocaine-induced excitability changes persisted throughout maintenance and withdrawal and were sensitive to GluN2B blockade, while sucrose-induced changes diminished during maintenance and resulted in increased NMDAR current decay rates, suggesting mechanistic differences. Increased AMPAR/NMDAR ratios were also seen in ventrolateral BNST neurons after chronic treatment with a subcutaneous morphine pellet implant.[45] This effect was specific to VTA-projecting BNST neurons and was elicited only by electrical stimulation of afferents in dorsolateral BNST and not medial stimulation, suggesting input and output specificity.

■ LONG-TERM POTENTIATION OF EXCITATORY TRANSMISSION AND INTRINSIC EXCITABILITY IN THE JUXTACAPSULAR BNST

The juxtacapsular nucleus (jcBNST) is a subnucleus of the BNST located on the lateral aspect of the dorsal BNST and runs parallel to the internal capsule that has received specific focus due to its input from the basolateral amygdala alongside lesser input from the CeA.[46,47] Upon high frequency stimulation of the stria terminalis in ex vivo rat brain slices, LTP of excitatory transmission is observable within the jcBNST as in the dlBNST.[48] This LTP is inhibited by NMDAR, D1R, and mGluR5 antagonism, is enhanced by $GABA_A$ and $GABA_B$

receptor antagonism, and is unaffected by D2R antagonism. In addition, the same stimulation protocol elicits an alternative form of LTP known as LTP of intrinsic excitability (LTP-IE), which consists of reduced inward rectification, depolarized resting membrane potential, and increased membrane resistance, together decreasing the rheobase and firing threshold and increasing temporal fidelity of firing and overall cellular excitability. The mechanism underlying the changes in cellular excitability were shown to involve the postsynaptic D-type K^+ current (I_D). Both of these forms of LTP are disrupted by long-term drug exposure in rats during protracted withdrawal after alcohol dependence as well as in rats self-administering cocaine or heroin with long (23 h) access to the self-administration chamber. LTP is unaffected in a variety of control groups including nondependent rats in protracted withdrawal from ethanol as well as self-administering rats on a short-access schedule of drug access. Occlusion of jcBNST LTP induction by withdrawal is suggested by recent data showing that opioid dependence in self-administering rats elicits LTP-IE specifically in the electrophysiologically defined Type III neurons of the jcBNST but not Type I or Type II neurons.[49,50] Briefly, in an effort to begin to subcategorize neurons within the heterogeneous BNST, Hammack et al. developed a classification system whereby neurons are subdivided based on their electro-physiological response to positive and negative current injections (Type I: hyperpolarization sag and regular firing pattern; Type II: hyperpolarization sag and burst firing pattern; Type III: no hyperpolarization sag and fast inward rectification).[51] This schema was confirmed with follow-up transcriptomic analyses[50] and has proven useful in classifying otherwise unidentified BNST neurons and will thus be used here as appropriate.

In contrast to the observed LTP-IE in Type III jcBNST neurons, protracted withdrawal from four weeks of intermittent alcohol vapor exposure reduces excitability of all three types of rat jcBNST neurons,[52] suggesting a complex interaction between drug exposure and contingency of administration that needs to be further explored. Interestingly, LTP impairment in protracted abstinence can be mimicked by chronic intracerebroventricular (ICV) administration of corticotrophin releasing factor (CRF) and is blocked by the CRFR1 antagonist R121919 but not the CRFR2 antagonist astressin$_2$-B,[53] suggesting a role for this neuropeptide in withdrawal-associated changes in plasticity in the rat BNST. As described above, it was later shown that CRF neurons in the oval subnucleus of the rat BNST can undergo LTP after high frequency stimulation and that this LTP was enhanced by repeated restraint specifically in Type III CRF neurons via a striatal-enriched tyrosine phosphatase (STEP)-dependent mechanism,[54] providing a possible source of the CRF for the observed changes in plasticity within the jcBNST. Future work should aim to determine whether or not changes in plasticity observed in the jcBNST are specific to this subnucleus and, if so, how this system interacts with the other subnuclei of the BNST as well as other nuclei of the extended amygdala and the rest of the brain.

■ EXPANDING THE SCOPE OF LTP IN THE BNST: EFFECTS OF IN VIVO INDUCTION ON BEHAVIOR

Two of the limitations of the work on LTP in the BNST described thus far are (1) the lack of input specificity during high frequency stimulation of afferents in ex vivo brain slices and

(2) a lack of connection to behavioral outcomes in addition to the well-established connection to behavioral history. In two recent rat studies, high frequency stimulation of the ventricular subiculum and CA1 subregion of the hippocampus were shown to induce LTP in the BNST via an NMDAR-dependent mechanism.[55,56] This elicited anxiolysis that was reversed by the NMDAR antagonist AP5 in one study and potentiation of cocaine-induced locomotor activity at a subthreshold dose via LTP in VTA-projecting BNST neurons in the other. Unexpectedly, when the same stimulation protocol was used to stimulate the infralimbic cortex, it induced LTD in the BNST, suggesting that this stimulation protocol differentially affects glutamatergic inputs to the BNST and highlighting the importance of input specificity in studies on BNST plasticity. These two studies provide a framework for future work on BNST LTP in vivo, where the electrophysiological and behavioral effects of high frequency stimulation of cell bodies projecting to the BNST and recording of neuronal effects can inform our understanding of the relevant neural circuitry.

■ LTP IN THE BNST: A SUMMARY

LTP has been shown to occur in BNST neurons after either high frequency stimulation (HFS) of afferent populations or after long-term drug exposures. In both the dorsolateral and juxtacapsular subnuclei of the BNST, HFS-induced LTP is sensitive to NMDAR inhibition. However, the two types of LTP differ in that dlBNST LTP is enhanced by exposure to alcohol in a CIE paradigm and cocaine in vivo or ex vivo, while jcBNST LTP is disrupted by long-term exposures to alcohol, cocaine, and heroin, suggesting regional differences. In the dlBNST, LTP is disrupted by chronic stressors including corticosterone, social isolation, and combined isolation with unpredictable stress, while the effects of these stressors have not been evaluated in the jcBNST. In the jcBNST, LTP of intrinsic excitability is also observed after HFS and during protracted abstinence in opioid withdrawal specifically in Type III neurons, driven by changes in the D-type K^+ current I_D. LTP-IE has not been studied in dlBNST neurons, but anterolateral and ventrolateral BNST neurons show enhanced AMPA/NMDA ratios after cocaine self-administration or chronic morphine pellet implant, which suggest increased excitability to synaptic inputs through a parallel mechanism. Future work should aim to further compare these types of LTP as well as continue to uncover molecular correlates underlying this change in synaptic plasticity. In addition, a future focus on species differences in these forms of LTP would inform this literature due to a lack of direct comparison and substantial points of divergence between rat and mouse BNST.[57,58]

■ METABOTROPIC RECEPTOR-INDUCED LONG-TERM DEPRESSION IN THE BNST: HETEROGENEITY OF STIMULI

Plasticity is bidirectional, with LTP resulting in increased activity and LTD resulting in decreased activity. Classically, the intracellular levels of Ca^{2+} that initiate LTD are lower than the high levels required to initiate LTP.[59] The two most common means of LTD induction are low frequency stimulation protocols or activation of metabotropic signaling cascades, the latter of which has been more extensively studied in the BNST again in ex vivo brain slices. Specifically, LTD of excitatory transmission in the BNST can be initiated by G_q-coupled GPCR signaling cascades downstream of metabotropic glutamate receptors

(mGluR),[60–63] the α_1-adrenergic receptor (α_1-AR),[64,65] and the chemogenetic receptor hM3Dq.[66]

Metabotropic glutamate receptors can be functionally split into three classes: (1) Group I consists of mGluR1 and mGluR5, which are predominantly postsynaptic and stimulate G_q-GPCR signaling cascades; (2) Group II consists of mGluR2 and mGluR3, which are both presynaptic and postsynaptic and stimulate G_i-GPCR signaling cascades; and (3) Group III consists of mGluR4, mGluR6, mGluR7, and mGluR8, all of which are both presynaptic and postsynaptic and also stimulate G_i-GPCR signaling cascades.[67] Both Group I mGluRs and α_1-ARs are G_q-coupled GPCRs. The processes by which they elicit LTD share some features but differ in others. In the mouse BNST, Group I mGluR-dependent LTD was shown to occur via two distinct pathways: (1) an mGluR1 and mGluR5-dependent process that involves presynaptic cannabinoid receptor 1 (CB1R) signaling, and (2) an mGluR5-dependent pathway involving postsynaptic extracellular related kinase 1 (ERK1) but not ERK2 activation.[63] mGluR5-LTD was unaffected by GluA1 inhibition and did not result in a change in calcium-permeable AMPA receptor expression.[64] On the other hand, α_1-AR-dependent LTD was shown to be postsynaptic and dependent on clathrin-dependent endocytosis, GluA1 activity, and L-type voltage-gated calcium channel (VGCC) activation.[64,65] α_1-AR-LTD was independent of NMDAR and mGluR5 activation[65] and resulted in loss of sensitivity to calcium-permeable AMPA receptors.[64] Norepinephrine (100 uM) initiates α_1-AR-dependent LTD after 20 min but not 10 min bath application.

To determine if G_q-GPCR-initiated LTD was translatable beyond the mGluR5 and α_1-AR, hM3Dq-dependent LTD was tested and confirmed in mouse VGAT-expressing BNST neurons.[66] hM3Dq is a modified form of the M3 muscarinic receptor that does not respond to its endogenous ligand acetylcholine but instead responds to the otherwise inert ligand clozapine-*N*-oxide (CNO). In this study, hM3Dq-LTD was sensitive to phospholipase C (PLC) inhibition and CB1R antagonism, induced anxiogenesis not seen with activation of the chemogenetic G*i*-coupled hM4Di receptor, and led to downstream recruitment of the VTA, parabrachial nucleus (PBN), and locus coeruleus (LC), as seen by DREADD-associated metabolic mapping (DREAMM). In addition to extending mGluR5- and α_1-AR-LTD to hM3Dq, this work also highlighted the potential for alternative G_q-GPCR-LTD pathways as VGAT+ BNST neurons also expressed the acetylcholine M_1 muscarinic receptor and the serotonin 5-HT_{2C} receptor.

■ METABOTROPIC RECEPTOR-INDUCED LTD IN THE BNST: INTERACTIONS WITH BEHAVIORAL HISTORY

Analogous to BNST HFS-induced LTP, LTD initiated by G_q-GPCR agonism is also highly sensitive to behavioral and pharmacological history of the animal. mGluR5/ERK1-dependent LTD in mouse BNST is sensitive to a single injection of cocaine, bath application of cocaine, and CIE exposure.[62,63] The duration of disruption of mGluR5/ERK1-LTD is extended with repeated injections of cocaine but is not permanent, as LTD is observable 10 days after final cocaine injection.[62] Cocaine-induced disruption of mGluR5/ERK1-LTD can also be prevented by in vivo mGluR5 antagonism.[62] α_1-AR-dependent LTD is absent after

restraint stress or exposure to either continuous or intermittent alcohol and in various genetic models of affective disorders, including the norepinephrine transporter (NET) and α_{2A}-adrenergeric receptor (α_{2A}-AR) knockout mice.[64,65] While there are many similarities in processes that affect these types of LTD, there are differences. For example, mGluR5-dependent LTD is not affected by restraint stress or by α_{2A}-AR knockout, while α_1-AR-dependent LTD is not affected by a single exposure to cocaine.[64,65]

■ LOW FREQUENCY STIMULATION-INDUCED LTD IN THE BNST

Low frequency stimulation (LFS; 15 min 10 Hz stimulation) of glutamatergic afferents in ex vivo rat BNST slices is also capable of inducing LTD of excitatory transmission.[44] This LTD is NMDAR- and GluN2B-dependent and is unaffected by sucrose self-administration but occluded by cocaine self-administration in a GluN2B-dependent process, again connecting plasticity changes with drug history. Honing in on a specific population of afferents, a similar stimulation protocol (5 min 10 Hz stimulation) within prefrontal cortex in vivo has also been shown to lead to LTD of firing in mouse BNST neurons.[68] After stress, though, this LTD switches to LTP in a glucocorticoid receptor-independent fashion.[68] In both cases, CB1R antagonism, full knockout, or glutamatergic neuron-specific knockout blocks both the LTD and the stress-induced transition to LTP. Similarly, after extended nicotine self-administration in rats, LTP is observed broadly in BNST neurons and specifically in VTA-projecting BNST neurons after stimulation of the infralimbic cortex.[69,70] This LTP was NMDAR- and CB1R-dependent and was absent in extinguished but not abstinent mice and induced nicotine-seeking in trained animals. Prior rat ex vivo work highlighted the role of CB1R agonism in the BNST in both depolarization-induced suppression of excitation (DSE) and LTD, dissociating the 2-arachidonylglycerol-mediated L-type calcium channel-dependent short-term depression (STD) and the mGluR5-initiated anandamide-mediated TRPV1-dependent LFS LTD.[71] More mechanistic work on in vivo endocannabinoid modulation of BNST plasticity will inform our understanding of endocannabinoid mediated LTD and the molecular correlates underlying the transition from LTD to LTP.

As can be seen here, BNST neurons are highly susceptible to long-term depression after activation of subtypes of metabotropic receptors to glutamate and norepinephrine or low frequency stimulation of afferent populations, and that these forms of plasticity are differentially affected by stress and drug exposure. The behavioral correlates and molecular under-pinnings, in addition to species differences, alternative targets, and effect specificity, remain to be fully elucidated.

■ INPUT SPECIFICITY: WHERE TO LOOK AND WHY

Through the processes of LTP and LTD detailed above, BNST neurons increase or decrease their response to glutamatergic input. However, in most cases, it is unclear whether these effects occur in response to all glutamatergic afferents or whether it is input- and synapse-specific. In the basolateral nucleus of the amygdala (BLA), for example, auditory fear conditioning initiates changes in plasticity in an input-specific manner.[72] In auditory fear conditioning, an auditory stimulus functions as the conditioned stimulus (CS) that is eventually learned to be a signal of a forthcoming footshock, which is the aversive

unconditioned stimulus (US). After learning has taken place, LTP of input from the auditory thalamus and auditory cortex to the BLA is specifically observed, consistent with the strengthened connection between the CS and US-mediated behaviors such as freezing.[73] In the context of protracted abstinence-induced plasticity in the BNST, the corollary of these inputs is unclear, as the source of withdrawal stimuli-associated activity has not been clearly elucidated. In addition, one of the key points of differentiation between the amygdala and the BNST in stress and anxiety is that the former is engaged during acute, predictable stressors while the latter is engaged during chronic, diffuse stressors that may lack a specific unitary source.[24] However, with projection-specific optogenetic technology and other recently developed tools that can differentiate specific inputs to or populations of neurons of interest, this is an experimentally testable hypothesis. Here, we provide rationale for investigations of plasticity at specific glutamatergic inputs to the BNST that play a role in reinstatement behaviors and attempt to connect these inputs to the LTP and LTD experiments described above. For an overview of the anatomy of these inputs with respect to subnucleus divisions of the BNST as well as relationships to catecholamine input (discussed below), see Figure 1.

Medial Prefrontal Cortex.

Input-specificity of abstinence-associated changes in synaptic plasticity has been performed on infralimbic cortical input to the BNST, as previously described. LTP of this input occurs in nicotine self-administration in rats, and low frequency stimulation in drug-naïve mice elicits LTD of this input that transitions to LTP with stress exposure in a CB1R-dependent fashion.[68,69] This suggests that drug exposure correlates with a strengthening of this input and thus may underlie some of the behavioral changes associated with increased drug exposure. Indeed, in humans, increased glucose metabolism is observed in the related orbitofrontal cortex (OFC) one week into withdrawal, and metabolism within the OFC and the prefrontal cortex (PFC) correlates with drug craving in abstinent patients.[74] In the context of stress, stress-induced changes in PFC activity by functional magnetic resonance imaging (fMRI) was associated with greater number of days since last cocaine exposure and shorter time to relapse.[75] In rodent models, prefrontal cortex activity has been shown a number of times to be critical for stress-induced reinstatement of drug-seeking and incubation of drug craving.[76–78] PFC neurons have also been shown to undergo changes in plasticity and enhancement of activity during either protracted abstinence from drugs of abuse or after acute or chronic stress exposure.[77,79–82] The BNST mediates an interaction between medial PFC activity and recruitment of the paraventricular nucleus of the hypothalamus (PVN) during psychological stressors, suggesting a role of this nucleus as a relay between cortical input and behavioral output that may translate from stress circuitry to drug and reward circuitry.[83–86] This collection of work highlights the potential for a PFC-BNST circuit to mediate aspects of stress-induced reinstatement of drug- and alcohol-seeking behaviors. However, the PFC is a heterogeneous collection of nuclei consisting of at least the infralimbic cortex, prelimbic cortex, and orbitofrontal cortex, each of which project to the BNST[87] and are known to engage differently in addiction-related and other behaviors. It will be important to parse out these differences as plasticity in this circuit is investigated.

Ventral Subiculum.

Long-term potentiation induced by in vivo high frequency stimulation of the ventral subicular (VSub) input to the BNST was determined to be anxiolytic in mice and potentiating of the locomotor response to cocaine via BNST-VTA projections in rats.[55,68] Similar to the input to the BNST from the PFC, this projection is known to act as an inhibitory relay between the ventral hippocampus and the PVN to dampen the stress response.[88,89] This suggests that engagement of this pathway, as occurs during stressful stimuli, would attempt to counteract the effects of stress. Chronic engagement of this pathway, though, could lead to loss of potential for plasticity. However, with chronic or juvenile exposure to stress, we see enhanced LTP within the ventral hippocampus, suggesting otherwise.[90–93] The cocaine-potentiating effects of high frequency stimulation of the ventral subicular input to the BNST via projections to the VTA suggests that interactions between stress and cocaine may also occur via this circuit. Supporting this hypothesis, cocaine conditioning also increased[90] and induced structural changes that support increased activity in the region.[94,95] These data suggest that protracted abstinence may lead to increased plasticity at VSub-BNST projections, and that this projection may contribute to susceptibility to reinstatement. Specifically, the ventral subiculum is critical for cocaine-, cue-, and context-induced reinstatement of cocaine-seeking behaviors.[96–99] Interestingly, electrical stimulation of the ventral subiculum itself is capable of reinstating drug-seeking behaviors.[100] In human patients, though, we see decreased hippocampal volume in alcoholics[101] and after childhood maltreatment,[102] suggesting a loss of activity with these chronic stressors. Future studies will inform whether or not changes in plasticity occur at VSub-BNST projections during protracted abstinence and, if they do, whether the projection still elicits anxiolysis as it does in naïve animals.

Basolateral Amygdala.

The BLA sends a glutamatergic projection to the BNST that has also previously been shown to induce anxiolysis and decrease respiratory rate.[103] Although this projection has not been directly investigated in the context of abstinence-induced changes in plasticity, the BLA sends a portion of its BNST projections to the juxtacapsular subnucleus (jcBNST),[104] where high frequency stimulation of the stria terminalis induces LTP-IE that is occluded by prolonged drug exposure. Consistent with a potential role in abstinence-induced changes in plasticity, extensive evidence has linked the BLA with reinstatement of drug-seeking behaviors. Specifically, the BLA is shown to be critical for context-, cue-, and drug-induced reinstatement of drug-seeking behaviors in some but not all studies.[105–108] Furthermore, a history of drug exposure and re-exposure to drug-associated stimuli leads to robust activation and activity-dependent changes in the BLA in both rodent models[109,110] and humans,[111,112] supporting the hypothesis that BLA-BNST connectivity may be enhanced in protracted abstinence. However, given the anxiolysis induced by stimulation of this pathway and that withdrawal induces anxiogenesis in addicted patients, it is also a candidate pathway for input-specific LTD of glutamatergic transmission in the BNST. Consistent with this hypothesis, BLA lesions did not affect footshock-induced reinstatement of cocaine-seeking behavior dependent on BNST activity,[29] and direct administration of NMDAR antagonists into the BLA to block development of NMDAR-dependent plasticity did not affect conditioned reward or reinstatement of cocaine self-administration.[113] In addition, human

imaging studies show that a reduced amygdalar volume is consistent with high risk for the development of alcoholism and other neuropsychiatric disorders.[114,115] It will be important for future studies to determine the presence, directionality, behavioral relevance, and subnucleus specificity of plasticity at glutamatergic synapses originating in the BLA projecting to the BNST.

Insular Cortex.

The insular cortex is another glutamatergic input to the BNST, including but not limited to the jcBNST,[116] that has the potential to either enhance or inhibit reinstatement of drug-seeking behaviors and thus could undergo bidirectional changes in plasticity with increased drug exposure and protracted abstinence. Broadly, the insular cortex functions in integrating interoceptive processes and translating that information into conscious feelings and behavioral decisions regarding risk and reward.[117] The insula has received substantial interest since the observation that nicotine-dependent patients who had stroke-associated damage to the insula reported substantially decreased craving and high rates of success in quitting smoking.[117] This clinical finding has been well-replicated in humans[118,119] and modeled in rodents.[120,121] Insular activity is also critical for addiction-like behaviors to other drugs of abuse, as inactivation blocks conditioned place preference (CPP) for amphetamine,[122,123] cue-induced reinstatement to cocaine-seeking,[124] and operant responding for alcohol.[125] Consistent with a potentiating role in the development and maintenance of addiction-like behaviors during abstinence, the insula is engaged during cue or context presentations in humans[126] and rodents[122] and shows increased dendritic complexity after chronic nicotine exposure and withdrawal in rodents.[127] Although the case for a hyperactive insula in addiction is compelling, there is also a case for loss of insular activity with chronic drug exposure and abstinence. Reduced gray matter volume is observed in the insula cortex of drug users as well as decreased regional activity during decision-making processes,[128] and stimulation of the insula in rodent models decreases nicotine self-administration.[129] The only study to evaluate the potential function of insula—BNST connectivity shows that inactivation of either population blocks the ability of safety signals to decrease stress-associated decrements in social interaction,[130] although the authors do not test the projection directly and posit that it occurs via a relay in the BLA. This hypothesis will need to be tested in future studies.

Parabrachial Nucleus.

The parabrachial nucleus (PBN) provides a dense glutamatergic input to the BNST that extends from the oval to the ventrolateral subnuclei but remains largely unexplored.[131] These synapses tend to be axosomatic in structure and likely instructive in functionality,[132,133] as introduction of channelrhodopsin and elicitation of light-evoked currents is capable of initiating action potentials or hyperpolarizing BNST neurons recorded in whole-cell electro-physiology.[134] The behavioral relevance of PBN-BNST projections has yet to be evaluated, yet PBN neurons and specifically those projection neurons positive for the neuropeptide calcitonin-gene related peptide (CGRP) have been implicated in a number of behaviors, including pain, thirst, taste, and other physiologic processes.[135] Specifically, CGRP+ PBN neurons are activated by diverse events such as noxious stimulation (both internal and external), satiation, consumption of novel foods, and auditory cues in a fear

conditioning paradigm, and are critical for food neophobia and conditioned fear responses.[136] Together, these data suggest that the PBN plays a role both in the processing of danger signals and engaging those adaptive responses that will limit resultant harm.[136] CGRP corelease with glutamate from PBN afferents in the BNST mimics the actions of intracerebroventricular (ICV) administration of CGRP in the induction of anxiety and leads to recruitment of other brain regions involved in the stress response,[137] suggesting relevance to abstinence-induced negative affect and stress-induced reinstatement. The parallel CGRP+ projection from the PBN to the CeA encodes the affective components of pain[138] and is critically involved in pain-associated plasticity and excitatory transmission in this region,[139–142] providing a framework for PBN circuits in the extended amygdala interacting with chronic stressors. Interestingly, though, CGRP appears to have excitatory actions in the CeA but potentiate $GABA_A$-mediated currents in the BNST, potentially leading to increased inhibition, highlighting potential regional differences.[143]

Paraventricular Nucleus of the Thalamus.

The paraventricular nucleus of the thalamus (PVT) also provides a dense glutamatergic input to the lateral BNST that has been extensively studied by anatomical methods but minimally by functional methods.[144] Preclinical data support a role for the PVT in drug-seeking behaviors, as activity within the subnucleus has been shown to be critical for expression of cocaine conditioned place preference as well as cue- and drug-induced reinstatement of cocaine-seeking.[145–148] In humans, the thalamus is activated by drug cues but shows reduced activity during response inhibition,[149] suggesting a role in addiction-related processes. The projection from the PVT to the NAc has been heavily investigated as the nexus for connections between PVT activity and drug-seeking behavior. Consistent with this notion, drug exposure increases excitability and induces synaptic plasticity in neurons projecting from PVT to NAc,[150–152] and in vivo depotentiation of this pathway by an LTD protocol can limit the expression of withdrawal-associated symptomatology.[153] Interestingly, there is heavy collateralization between PVT projections to the NAc, the BNST, and the central nucleus of the amygdala (CeA), suggesting that the same synaptic plasticity that is occurring in projections from the PVT to the NAc might also be occurring in projections to the BNST.[144] Furthermore, PVT fibers appose with extended amygdala neurons positive for the neuropeptide corticotropin releasing factor (CRF), suggesting an interaction that may underlie abstinence-induced changes in plasticity and behavior.[154] Future studies should aim to explore the function of this projection in the context of reinstatement behaviors.

Together, the glutamatergic inputs from the prefrontal cortex, ventral subiculum, basolateral amygdala, insular cortex, parabrachial nucleus, and paraventricular nucleus of the thalamus are potential candidates for mediating the changes in input-specific synaptic plasticity in the BNST that occur with protracted abstinence from drugs of abuse that prime the brain for relapse to drug-seeking behaviors. Future experiments should aim to connect changes in the strength of these inputs to the different types of plasticity observed in the BNST and determine the directionality (i.e., LTP or LTD) and behavioral relevance of these effects. This increased understanding of the input specificity underlying abstinence-induced changes in plasticity will open the door to more focused pharmacological studies aimed at protecting against these maladaptive changes.

■ CELL-TYPE SPECIFICITY: PROJECTION TARGETS AND GENETIC MARKERS

Studies of plasticity in the BNST have mostly focused on effects within neuronal populations through field potential recordings or unidentified neurons through in vivo or ex vivo electro-physiology. Although determining the source of input to a defined neuronal population will be important for circuit-based interventions, the outcome of LTP or LTD will converge on increased or decreased likelihood of neuronal firing and neurotransmitter release in the BNST neurons themselves. Then, depending on the projection target and the neuro-transmitter packaged for release, this change in activity will be translated into increased or decreased likelihood of reinstatement of drug-seeking or related behaviors. Differentiating cell-specific mechanisms of plasticity in the BNST will be especially important due to the known heterogeneity of and complex inter-relationships among cells within the BNST.[155,156]

Within the rat BNST, neurons positive for the neuropeptide CRF undergo HFS-induced LTP that is further potentiated by repeated restraint stress specifically in Type III CRF neurons that are defined by their electrophysiological response to positive and negative current injection.[54] This process was determined to be dependent on a lack of expression of striatal-enriched tyrosine phosphatase (STEP), an enzyme that shows downregulation with repeated restraint stress. LTP in CRF neurons would thus be expected to increase CRF release either in the BNST from interneurons or in projection targets. As CRF signaling is critical for cocaine-induced enhancement of short-term potentiation,[42] stressful stimuli that engage LTP of this population may exacerbate changes in excitatory transmission within the region as a result of extended drug exposure and have long-term effects on BNST plasticity. Extrahypothalamic CRF is critical for stress-induced reinstatement of drug-seeking behavior, as CRF itself can act as a stimulus for reinstatement, and CRFR1 antagonists reduce stress-induced reinstatement when injected systemically or directly to the BNST.[157,158] The role of CRF is independent of the drug of abuse, the type of stressor, or the experimental procedure used.[159] CRF levels in the BNST are elevated during withdrawal from alcohol and normalize after re-exposure,[31] a process that will lead to increased engagement of a BNST-VTA projection population via enhancement of excitatory transmission.[160] Thus, LTP of BNST CRF neurons and enhancement of this process by chronic stressors may drive reinstatement behaviors. Both the connection between CRF and LTP as well as the role of other neuropeptides and genetic markers expressed in the BNST, including but not limited to neuropeptide Y (NPY), somatostatin (SST), and protein kinase Cδ (PKCδ), remain to be further explored (for a review of neuropeptide signaling in the BNST, see Kash et al.[161] and Daniel and Rainnie[162]).

In addition to defining neuronal populations by their expression pattern of genetic markers, BNST neurons can also be defined based on their projection target. Although not directly applied to plasticity changes in the BNST or with abstinence and reinstatement, this approach allowed for distinction of projection-specific functions that contribute to the various phenotypes associated with anxiety-like behavior in rodent models. Specifically, optogenetic excitation of BNST afferents in the lateral hypothalamus (LH) elicits reduced

risk avoidance in the elevated plus maze, while those in the PBN elicits reduced respiratory rate and those in the VTA elicits increased positive valence.[103] Although these responses have not been fully translated into the behaviors seen with reinstatement of drug-seeking, nor have the behaviors seen with reinstatement of drug-seeking been elegantly dissected in this manner, one could imagine parallels of these effects in the rodent undergoing protracted abstinence from drugs of abuse.

Finally, the data presented thus far suggest that experience-dependent or stimulation-induced LTP in either CRF+ neurons or anxiogenesis-inducing projections from the BNST to the VTA, LH, and PBN would likely increase the probability of reinstatement. This begs the question of whether the LTD observed through a variety of mechanisms described above could represent a therapeutic end-goal for reducing the ability of stress or other factors to re-engage the circuitry necessary for reinitiating drug-seeking behaviors. However, G_q-mediated LTD initiated by the hM3Dq DREADD in VGAT+ BNST neurons elicited anxiety-like behaviors and lead to increased engagement of downstream neuronal activity in the VTA, the PBN, and the locus coeruleus (LC), suggesting that either LTD occurs in interneurons in the BNST and leads to disinhibition of BNST projection neurons, or that decreased firing of BNST neurons leads to disinhibition of downstream target neurons in the VTA and other regions of interest. New genetic tools like INTRSECT (Intronic Recombinase Sites Enabling Combinatorial Targeting) will allow for populations like interneurons to be isolated with or without the use of a genetic marker and studied to answer questions such as these.[163]

■ MODULATION OF PLASTICITY: CATECHOLAMINE RECEPTOR MODULATION

As more information is gained on the mechanism and specificity of LTP and LTD, molecular targets for modulation of these processes are likely to emerge. Currently, much focus has been placed on NMDAR antagonists such as Ro25-6981, as they have been shown to attenuate ex vivo and in vivo LTP in the BNST.[37,55,56] This work has promising applications related to the clinical use of ketamine and other similar drugs but may be limited due to off-target as well as undesired on-target effects. Due to the complex and bidirectional actions on BNST synaptic plasticity and neurotransmission in general, targeting of the receptors for the catecholamines dopamine and norepinephrine represents a potential therapeutic modality for these synaptic changes as well as their resultant behavioral outcomes. Dopamine and norepinephrine input to the BNST spans the dorsoventral extent of the nucleus with a patterned distribution where dopamine input is more prominent in the dorsal aspect and norepinephrine in the ventral (Figure 1).[164]

Dopamine.

Release of dopamine in the BNST through stimulant action or exogenous drug actions at dopamine receptors is permissive and enhancing of the molecular changes that underlie STP and LTP in the region. Many drugs of abuse, including morphine, nicotine, cocaine, and alcohol, lead to increased extracellular levels of dopamine in the BNST as they do in the nucleus accumbens.[19] Palatable substances like sucrose also increase dopamine, while

aversive stimuli such as quinine reduce these levels, a profile opposite that of norepinephrine.[165] Once released, dopamine initiates excitatory actions in the BNST, enhancing glutamatergic transmission via signaling at D1 and D2 receptors in an activity- and CRFR1-dependent manner in the mouse[42] and inhibiting GABAergic transmission via D2Rs in the rat oval subnucleus.[166] Potentiating these excitatory actions, dopamine enhances the short-term component of high frequency stimulation-induced LTP in the mouse BNST.[42] Upon contingent drug exposure paradigms, however, these excitatory actions become inhibitory, with upregulation of the D1R leading to enhancement and LTP of $GABA_a$ inhibitory postsynaptic currents (IPSCs) not seen in control, sucrose self-administering, cocaine self-administration acquiring, and cocaine-yoked rats.[167] This $GABA_A$ LTP involves c-Srk tyrosine kinase and neurotensin receptor signaling pathways and is independent of canonical G-protein and other tyrosine kinase signaling pathways. Further, the magnitude $GABA_A$ LTP is proportional to the break-point on the progressive ratio schedule of cocaine reinforcement, a measure that defines motivation for reward-seeking behaviors. Inhibitory actions of dopamine can also be seen on NMDAR currents in ex vivo brain slices from cocaine self-administering rats via D1Rs and D2Rs via activation of PLC and protein phosphatases[168] as well as on LTP of excitatory transmission in the rat jcBNST in a D1-dependent manner.[48] Regardless of the directionality of effects on neurotransmission in the region, blockade of dopamine signaling at D1Rs in the BNST alters drug-seeking behaviors as evidenced by decreased alcohol-motivated responding[20] and decreased cocaine reinforcement,[18] suggesting that targeting dopamine-mediated transmission and its downstream effects on plasticity represents a therapeutic modality for drug- and alcohol-seeking behaviors.

Norepinephrine.

Norepinephrine receptor modulators are specifically known to modulate stress-induced reinstatement of drug-seeking behavior and also to affect BNST plasticity. Specifically, disruption of the norepinephrine input to the BNST as well as inhibition of β- and α_1-adrenergic receptor signaling and agonism of α_2-adrenergic receptors inhibits stress-induced reinstatement of drug-seeking behaviors.[28,169,170] In ex vivo brain slices, 20 but not 10 min application of norepinephrine (100 μM) initiates LTD mimicking α_1-AR-LTD,[65] and α_1-AR-LTD is disrupted as a result of aberrant norepinephrine signaling in the norepinephrine transporter (NET) and α_{2A}-AR knockout mouse model.[65] In the BLA, norepinephrine is known to gate LTP via decreased inhibitory tone on pyramidal projection neurons likely via actions on local inhibitory interneurons, enabling the plastic changes that occur with fear conditioning paradigms.[73] If norepinephrine-mediated α_1-AR-LTD were to occur in BNST inhibitory interneurons and decrease their inhibition of BNST-VTA projection neurons, for example, a similar process may control BNST-dependent reinstatement behaviors.

Modulation of norepinephrine action and potential effects of norepinephrine on abstinence-induced changes in plasticity represents a promising therapeutic strategy for addiction. These effects could be due to direct inhibition of norepinephrine release via autoreceptor α_2-ARs or via blockade of norepinephrine actions at α_1-ARs, β-ARs, or heteroceptor α_2-ARs. Direct administration of β_1- and β_2-AR antagonists or α_2-AR agonists to the BNST blocks stress-induced reinstatement of cocaine- and morphine-seeking behaviors,[171–174]

highlighting a role for these receptors in the process that we hypothesize is connected to abstinence-induced changes in plasticity. Similarly, direct administration of α_1-, β_1-, and β_2-AR antagonists to the BNST elicits anxiolysis.[175] With respect to changes in activity, briefly, β-ARs broadly enhance BNST neuronal activity via a postsynaptic mechanism, while α_1-ARs elicit LTD and α_2-ARs inhibit both norepinephrine and glutamate release (for a more detailed review, see Flavin and Winder[176]). β-AR activity specifically enhances BNST activity through a microcircuit involving CRF signaling, while BNST α_{2A}-ARs inhibit glutamate release in an input-specific manner at PBN but not BLA terminals,[134,177] highlighting the potential for actions that can be targeted to specific BNST inputs and outputs as more information is gleaned from work on the specificity of changes in plasticity as described above. In addition, G_q-coupled LTD-mediated activation of downstream components of addiction-related neurocircuitry[178] and potential excitatory actions of α_{2A}-ARs within the BNST[134,179] highlight the possibility that activation of inhibitory signaling cascades and their effects on neuronal activity, and thus neuronal plasticity, are not always direct and thus may inform future work in the area of plasticity.

■ CONCLUDING REMARKS AND FUTURE DIRECTIONS

Chronic exposure to drugs and stress leads to changes in neurotransmission and synaptic plasticity in the bed nucleus of the stria terminalis, a component of the extended amygdala critical for reinstatement of drug- and alcohol-seeking behaviors. We hypothesize that long-term changes in activity in this region prime the addict or alcoholic for relapse during protracted abstinence. Here, we discuss the mechanisms underlying long-term potentiation and depression in the region and highlight how these changes interact with a history of stress and drug exposure in rodent models. In addition, we highlight important future directions including input- and cell-specific bidirectional changes in activity. A better understanding of the molecular correlates and mechanisms underlying synaptic plasticity will lead to more effective treatment strategies that have the ultimate goal of decreasing the emergence of reinstatement behaviors during abstinence. Here, we discuss the role of catecholamine receptor modulators in the process, as inhibition of both dopamine and norepinephrine receptors affect reinstatement behaviors, while activation enhances or initiates LTP and LTD, respectively. We hope that the insights gained from studying the specific changes that underlie synaptic plasticity in the BNST during protracted abstinence from alcohol and other drugs of abuse will provide insight into the biology underlying relapse behavior in human addicts and alcoholics and inform future treatment modalities for this complex biological problem.

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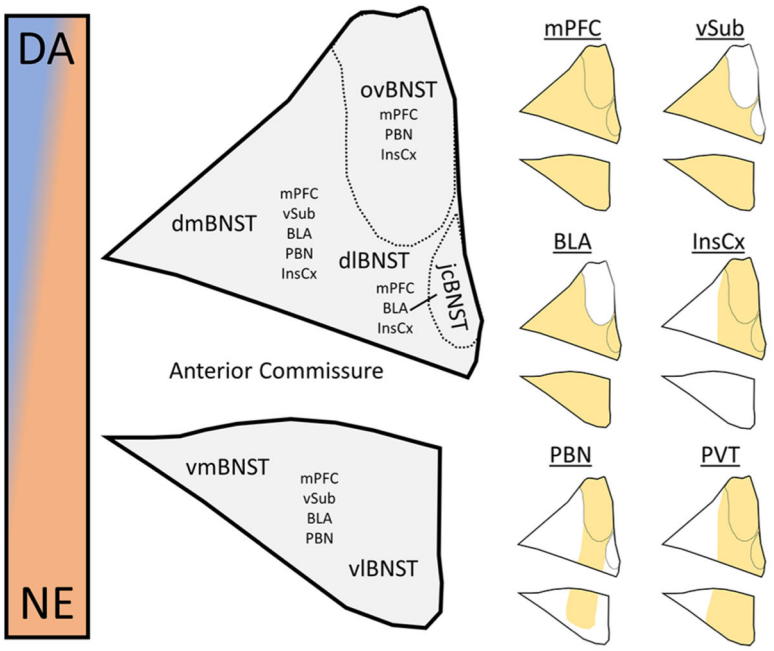

Figure 1.

Anatomy of glutamatergic and catecholaminergic input to the bed nucleus of the stria terminalis. (Left) Anatomical depiction of BNST subnuclei shows location of the oval (ovBNST), juxtacapsular (jcBNST), dorsomedial (dmBNST), dorsolateral (dlBNST), ventromedial (vmBNST), and ventrolateral (vlBNST) subnuclei (Allen Reference Atlas). In addition, glutamatergic afferent populations are noted within the subnuclei, and catecholaminergic input is represented as a gradient from high prevalence of dopaminergic (blue) to noradrenergic terminals (orange). (Right) Terminal field afferent populations from each of the six glutamatergic inputs, including the ventral subiculum (VSub), medial prefrontal cortex (mPFC), para-brachial nucleus (PBN), basolateral amygdala (BLA), insular cortex (InsCx), and paraventricular nucleus of the thalamus (PVT). The topography of afferent population terminal fields are adapted from McDonald et al. 1996[87] for the mPFC, Dong et al. 2001[104] for the VSub, Kim et al. 2013[103] for the BLA, Yasui et al. 1991[116] for the InsCx, Saper and Loewy 1980[131] for the PBN, and Li and Kirouac 2008.[154]

Table 1.

Overview of LTP Studies in the BNST[a]

type of LTP	notes	reference
LTP of excitatory transmission in dlBNST	Induced by HFS (2× 100 Hz for 1 s)	Weitlauf et al. 2004[35]
	Recorded by field potentials or sharp electrode recordings in ex vivo BNST slices (mouse)	Weitlauf et al, 2005[36]
	Blocked by NMDAR inhibition, GluN2B KO, GluN2B inhibition	Wills et al. 2012[37]
	Inhibited by prestimulation 100 mM ethanol (only 0–5 min)	
	Unaffected by L-type Ca^{2+} channel inhibition, $GABA_A$ inhibition, GluN2A KO, poststimulation 100 mM ethanol	
CIE-induced enhancement of LTP of excitatory transmission in dlBNST	Induced by HFS (2× 100 Hz for 1 s)	Conrad et al. 2011[40]
	Recorded by field potentials in ex vivo BNST slices (mouse)	Conrad et al. 2011[41]
	Blocked by GluN2B KO, GluN2B inhibition, chronic or acute social isolation, simultaneous chronic social isolation and chronic unpredictable stress	Wills et al. 2012[37]
	Unaffected by acute corticosterone administration	
DA-induced enhancement of STP of excitatory transmission in dlBNST	Induced by HFS (2× 100 Hz for 1s)	Kash, Nobis et al. 2008[42]
	Recorded by field potentials in ex vivo BNST slices (mouse)	
	Blocked by NMDAR inhibition, CRFR1 antagonist, pan-dopamine receptor antagonist (flupenthixol), D1R KO	
LTP of excitatory transmission in oval BNST CRF cells	Induced by HFS (5× 100 Hz 1s, interval = 20 s)	Dabrowska et al. 2013[54]
	Recorded by whole cell electrophysiology in ex vivo BNST slices (rat)	
	Occurs in all CRF+ BNST neurons	
	Enhanced by repeated restrain stress (only in Type III)	
	Blocked by intracellular STEP (only in Type III)	
LTP of VSub-amBNST projections	Induced and recorded in vivo by HFS (500 pulses at 400 Hz, 250 μs duration) in VSub and electrophysiological recordings in amBNST (rat)	Glangetas et al. 2015[55]
	Blocked by NMDAR inhibition	Glangetas et al. 2017[56]
	Induces: potentiation of cocaine-induced locomotor activity (via BNST-VTA projections), anxiolysis (NMDAR-dependent)	
LTP of ILC-BNST projections in nicotine self-administration	Induced and recorded in vivo by LFS (10 Hz for 1 min) in ILC and electrophysiological recordings in BNST (rat) during protracted abstinence	Reisiger et al. 2014[69]
	Does not occur in saline self-administration or yoked nicotine controls	
	Blocked by NMDAR inhibition, extinction training, CB1R antagonism	
	Results in enhanced nicotine seeking	
Increased AMPAR/NMDAR ratio in vlBNST	Observed after cocaine self-administration or with chronic subcutaneous morphine pellet implant in whole-cell recordings from ex vivo rat BNST slices	Dumont et al. 2005[43]
	Not seen after: acute cocaine injection, passive administration of cocaine or food	Dumont et al. 2008[45]
Increased AMPAR/NMDAR ratio in ovBNST	Observed after acquisition in cocaine and sucrose self-administration in whole-cell recordings from ex vivo rat BNST slices.	deBacker et al. 2015[44]

type of LTP	notes	reference
	Blocked by in vivo GluN2B inhibition (cocaine only)	
	Results in no effects on lever pressing for sucrose or cocaine, potentially disrupts reinstatement behaviors	
HFS LTP of excitatory transmission and intrinsic excitability of jcBNST neurons	Induced by HFS (100 Hz for 1 s at 10 s intervals) in ex vivo BNST slices (rat)	Francesconi et al. 2009[48]
	LTP-IE characteristics: reduced inward rectification, depolarized RMP, increased membrane resistance, decreased rheobase, decreased firing threshold, increased temporal fidelity of firing	Francesconi et al. 2009[53]
	Blocked by NMDAR inhibition, mGluR5 inhibition, D1R inhibition, alcohol dependence and 4–6 week protracted withdrawal (see below), long-access cocaine self-administration, long-access heroin self-administration	
	Enhanced by $GABA_A$ and $GABA_B$ inhibition	
	Unaffected by D2R inhibition, alcohol dependence and 0–4 week protracted withdrawal, short-access cocaine self-administration, short-access heroin self-administration	
ethanol withdrawal-induced disruption of LTP of excitatory transmission in jcBNST	Induced by HFS (100 Hz for 1 s at 10 s intervals) in ex vivo BNST slices (rat)	Francesconi et al. 2009[53]
	Observed in animals with escalated dependent alcohol intake induced by exposure to alcohol vapors Mimicked by chronic ICV CRF (alcohol naivïe animals)	
	Blocked by CRFR1 antagonist	
	Unaffected by CRFR2 antagonist	
LTP-IE in jcBNST neurons	Observed after self-administration of opioids in ex vivo rat BNST slices (only in Type III jcBNST neurons)	Francesconi et al. 2009[53]
	Does not occur in Type I or Type II jcBNST neurons	

[a] amBNST = anteromedial BNST; BNST = bed nucleus of the stria terminalis; CIE = chronic intermittent ethanol; CRF = corticotropin releasing factor; CRFR1 = CRF receptor 1; CRFR2 = CRF receptor 2; DA = dopamine; D1R = DA receptor 1; D2R = DA receptor 2; dlBNST = dorsolateral BNST; $GABA_A$ = gamma-aminobutyric acid receptor A; $GABA_B$ = GABA receptor B; GluN2A = glutamate NMDAR subunit 2A; GluN2B = glutamate NMDAR subunit 2B; HFS = high frequency stimulation; ICV = intracerebroventricular; KO = knockout; LTP = long-term potentiation; LTP-IE = LTP of intrinsic excitability; mGluR5 = metabotropic glutamate receptor 5; NMDAR = *N*-methyl-D-aspartate receptor; RMP = resting membrane potential; STEP = striatal enriched protein tyrosine phosphatase; STP = short-term potentiation; vlBNST = ventrolateral BNST; VTA = ventral tegmental area.

Table 2.

Overview of LTD Studies in the BNST[a]

type of LTD	notes	references
Group I mGluR-LTD in dlBNST	Observed in whole-cell recordings from ex vivo BNST mouse slices	Grueter et al. 2006[63]
	Blocked by CB1R inhibition (mGluR1/5), ERK1 inhibition (mGluR5-only), single injection of cocaine (blocked by in vivo mGlu5 antagonism), bath application of cocaine, chronic intermittent ethanol exposure	Grueter et al. 2008[62]
	Unaffected by ERK2 inhibition, GluA1 inhibition, 10 days withdrawal from single cocaine injection, restraint stress, α2A-AR KO	McElligott et al. 2010[64]
α_1-AR-LTD in dlBNST	Observed in whole-cell recordings from ex vivo mouse BNST slices	McElligott et al. 2010[64]
	Blocked by clathrin-dependent endocytosis inhibition, GluA1 inhibition, L-type VGCC, restraint stress, continuous or intermittent ethanol exposure, NET KO, α_{2A}-AR KO	McElligott and Winder 2008[65]
	Unaffected by NMDAR inhibition, mGluR5-inhibition, single exposure to cocaine	
	Mimicked by 20 min (but not 10 min) 100 uM norepinephrine application	
hM3Dq-LTD in dlBNST	Observed in whole-cell recordings from ex vivo mouse BNST slices	Mazzone et al. 2016[66]
	Blocked by PLC inhibition, CB1R inhibition	
	Results in anxiogenesis, activation of VTA/PBN/LC	
LFS of ILC-aBNST projection-induced LTD	Induced by 5 min 10 Hz stimulation of prefrontal cortex cell bodies in vivo and recorded in aBNST neurons (mouse)	Glangetas et al. 2013[68]
	After stress, switches to LTP (glucocorticoid-independent)	
	Blocked by NMDAR inhibition, CB1R antagonism, CB1R KO, glutamatergic neuron-specific CB1R KO (both LTD alone and LTD transition to LTP)	
	Occurs in VTA-projection neurons as well as unidentified BNST neurons	
HFS of ILC-BNST projection-induced LTD	Induced and recorded in vivo by HFS (500 pulses at 400 Hz, 250 μs duration pulse) in ILC and electrophysiology recordings in BNST (rat)	Glangetas et al. 2017[56]
	Same protocol induces LTP of VSub-BNST projections	
	Enhanced by NMDAR inhibition	
LFS LTD in BNST neurons	Induced by LFS (10 min 10 Hz) and recorded by whole cell electrophysiology in ex vivo BNST neurons (rat)	Puente et al. 2011[71]
	Blocked by CB1R antagonism, mGluR5 inhibition, TRPV1 inhibition, MAGL inhibition, PLC inhibition, sarcoplasmic/endoplasmic Ca^{2+} channel blockade	
	Occluded by TRPV1 agonism	
	Enhanced by FAAH inhibition (subthreshold induction protocol)	
	Unaffected by NMDAR inhibition, L-type Ca^{2+} channel inhibition, DAGL inhibition	
LFS LTD in ovBNST neurons	Induced by LFS (15 min 1 Hz) and recorded by whole cell electrophysiology in ex vivo BNST neurons (rat)	deBacker et al. 2015[44]
	Blocked by NMDAR inhibition, GluN2B inhibition, cocaine self-administration (maintenance)	
	Rescued by GluN2B inhibition (rescue blocked by NMDAR inhibition)	
	Unaffected by sucrose self-administration (maintenance)	

type of LTD	notes	references
DSE/STD in BNST neurons	Induced by 10 s depolarization in whole cell electrophysiology recordings of ex vivo BNST neurons (rat)	Puente et al. 2011[71]
	Blocked by CB1R antagonism, DAGL inhibition, L-type Ca^{2+} channel inhibition, PLC inhibition, sarcoplasmic/endoplasmic Ca^{2+} channel blockade	
	Enhanced by MAGL inhibition	
	Unaffected by FAAH inhibition, TRPV1 inhibition, mGluR5 inhibition, mGluR1 inhibition	

[a]2AG = 2-arachidonyl glycerol; aBNST = anterior BNST; α_1-AR = alpha-1-adrenergic receptor; α_{2A}-AR = alpha-2a-adrenergic receptor; BNST = bed nucleus of the stria terminalis; CB1R = cannabinoid receptor 1; DAGL = diacylglyercol lipase; DSE = depolarization-induced suppression of excitation; ERK1 = extracellular related kinase 1; FAAH = fatty acid amide hydrolase; GluA1 = glutamate AMPAR subunit A1; hM3Dq = human M3 muscarinic receptor Gq-coupled DREADD; LC = locus coeruleus; LFS = low frequency stimulation; LTD = long-term depression; KO = knockout; MAGL = monoacylglycerol lipase; mGluR = metabotropic glutamate receptor; NET = norepinephrine transporter; NMDAR = *N*-methyl-D-aspartate receptor; PBN = parabrachial nucleus; PLC = phospholipase C; STD = short-term depression; TRPV1 = transient receptor potential cation channel subfamily V member 1; VGCC = voltage-gated Ca^{2+} channel; VSub = ventral subiculum; VTA = ventral tegmental area.