Norepinephrine in the Extended Amygdala Regulates Stress-Induced Reinstatement

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Abstract

After treatment for drug addiction, patients remain at high risk for relapse into drug-seeking behavior, especially during stress. A region of the brain that plays a key role in stress-induced relapse into drug-seeking behavior is the extended amygdala. The extended amygdala is anatomically positioned to integrate stress and reward circuitry in the brain. In particular, norepinephrine signaling in the extended amygdala plays an integral role in rodent models of stress-induced reinstatement of drug-seeking. Therefore, understanding how norepinephrine modulates synaptic transmission in the extended amygdala may allow for insight into the mechanisms underlying stress-induced reinstatement of drug-seeking, and may lead to the identification of new pharmacological therapies for treating stress-induced relapse in humans.

Keywords

Stress
Addiction
Norepinephrine,
Extended amygdala
Bed nucleus of the stria terminalis
Central nucleus of the amygdala
Stress-induced reinstatement

Introduction

After undergoing initial treatment for addiction to drugs of abuse, an individual's risk of relapse remains high[1]. Exposure to stressful stimuli greatly increases an individual's risk for relapsing into drug- and alcohol-seeking behavior[2-4]. Relapse into substance abuse upon stress exposure suggests a close relationship between the stress-response circuitry and the reward-seeking circuitry of the brain. The extended amygdala is anatomically situated to participate in both stress and reward circuitry[5]. Further, norepinephrine (NE) in the extended amygdala has been shown to play a critical role in rodent behavioral models of stress-induced relapse into drug-seeking behavior, and to modulate neural activity in the extended amygdala[6-12]. Recent clinical trials have shown certain noradrenergic drugs to be effective in attenuating stress-induced drug cravings in humans[13-15]. Therefore, a better understanding of how NE modulates synaptic transmission in the extended amygdala may provide insight into the underlying mechanisms of stress-induced relapse into drug-seeking behavior, and lead to the identification of new pharmacological therapies. This review will discuss previous findings regarding the role of NE in rodent models of stress-induced reinstatement, as well as findings regarding the role of NE in modulating synaptic transmission in the extended amygdala.

Anatomy of the Extended Amygdala and Its Noradrenergic Innervation

The anatomy of the extended amygdala is critical for its ability to engage both reward and stress circuitry in the brain. The central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST) are key components of the extended amygdala[16,17]. The CeA and the BNST are embryologically related[18], and interconnect with one another[19,20], with the CeA exerting inhibitory influence over the BNST[18,21,22]. To participate in stress-response circuitry, the BNST sends an inhibitory projection to the paraventricular nucleus (PVN) of the hypothalamus[20,22-24]. The projection from the BNST to the PVN influences the release of ACTH[25], which in turn leads to the activation of the body's stress response[24,26]. The CeA has some direct connections to the PVN[24], but can also modulate stress activity indirectly through the BNST[24]. The BNST also projects to the nucleus accumbens (NAc)[27] and sends an excitatory projection to the ventral tegmental area (VTA)[28-30]; these projections, along with a projection to the hypothalamus, allow the BNST to modulate reward circuitry [31]. Therefore, the extended amygdala may play a key role in the integration of stress and reward.

The extended amygdala receives an array of synaptic inputs that can modulate its neural activity[6-9]. Modulation of synaptic activity in the extended amygdala can have a profound impact on stress-induced reinstatement[11,12,32]. Two examples of such inputs include excitatory glutamatergic inputs, such as from the basolateral amygdala (BLA)[18], and noradrenergic inputs[6]. The CeA receives its noradren-

ergic input primarily from the A2 cell group of the nucleus tractus solitaris (NTS) through the ventral noradrenergic bundle (VNAB)[33,34], with a small amount of noradrenergic input arising from the locus coeruleus (LC)[35,36]. The BNST receives very dense noradrenergic innervation through the ventral noradrenergic bundle (VNAB) from the A1 and A2 cell groups in the NTS[33,37-39]. The densest noradrenergic input is to the ventral BNST, with the dorsal BNST also receiving noradrenergic input[6]. NE has been shown to be elevated in the extended amygdala during both stress and withdrawal[40-43]; further, NE plays an integral role in stress-induced relapse into drug-seeking behavior[12,44].

The Role of Norepinephrine in the Extended Amygdala in Stress-Induced Reinstatement

NE is released into the extended amygdala during times of stress[40-42,45]. Similarly, neurons in the BNST, and noradrenergic inputs to the BNST, are activated during withdrawal from drugs of abuse[43,46], leading to increased levels of NE[43,46,47]. The release of NE during times of stress and withdrawal affects behavior. Rodent behavioral models implicate NE signaling in the aversive symptoms of withdrawal[12,43,46,48], as well as in behavioral responses to stressors[42]. NE also plays a role in reinstatement of reward-seeking[49], as direct injection of NE into the extended amygdala has been shown to reinstate cocaine-seeking behavior[49]. Similarly, mice lacking dopamine-β-hydroxylase (DBH), an enzyme required for NE synthesis, do not demonstrate morphine-induced conditioned place preference (CPP)[44]. Viral restoration of DBH to the NTS, but not the LC, rescued the morphine-induced CPP behavior[44]. At the integration of stress and reward, NE in the extended amygdala has been shown to be a key mediator of stress-induced reinstatement of drug-seeking[49,50]. For example, lesioning of the VNAB blocks stress-induced reinstatement of morphine-seeking[12]. These studies specifically implicate NE inputs to the extended amygdala in reward-seeking and stress-induced reinstatement. Subsequent work has focused on the role of particular noradrenergic receptors in stress-induced reinstatement.

Adrenergic Receptors Modulate Neuronal Signaling

NE is capable of modulating neurotransmitter release[51] through its actions on adrenergic receptors (ARs). There are nine different ARs[52] divided into three major classes: α_1 receptors, α_2 receptors and β receptors[52]. Each type of receptor has three subtypes: α_1-ARs are composed of α_{1a}, α_{1b}, and α_{1d}; the α_2-ARs are α_{2a}, α_{2b}, and α_{2c}; and the β-ARs are β_1, β_2 and β_3[52]. ARs are G-protein coupled receptors that can modulate synaptic transmission through both pre- and post-synaptic mechanisms. α_1-ARs are linked to G_q signaling, α_2-ARs are linked to $G_{i/o}$ signaling, and β-ARs are linked to G_s signaling[53].

α_2-AR Agonists Block Stress-Induced Reinstatement of Drug-Seeking

Activation of the α_2-AR subtype has repeatedly been shown to block stress-induced reinstatement[11,12,54,55]. Peripheral administration of α_2 agonists blocks stress-induced reinstatement of heroin-seeking[48], and cocaine-seeking[11,54,55]. Specifically in the extended amygdala, α_2-ARs can inhibit stress-induced reinstatement, as administration of an α_2 agonist directly into the BNST blocks footshock-induced reinstatement of morphine-seeking[12]. Of note, α_2-ARs have been implicated in stress-induced reinstatement in humans. Patients being treated for drug addiction who are treated with α_2 agonists have improved relapse outcomes, and show decreased stress-induced drug cravings[13-15]. Therefore, activation of α_2-ARs by NE in the extended amygdala appears to play a crucial role in attenuating stress-induced reinstatement of drug-seeking in both rodents and humans, and could provide an effective therapeutic target.

α_1- and β-AR Antagonists Block Stress-Induced Reinstatement of Drug-Seeking

β-ARs and α_1-ARs also play a role in stress-induced reinstatement. Administration of β_1[10] and β_2 antagonists[10,11] into the CeA or BNST blocks stress-induced reinstatement of cocaine-seeking in rodents[11]. Peripheral administration of an α_1 antagonist, prazosin, can block footshock-induced reinstatement of alcohol-seeking[56]. Therefore, while activating α_2-ARs attenuates stress-induced reinstatement, blocking β- and α_1-ARs appears to be necessary for a similar attenuation of stress-induced reinstatement. However, while α_1-ARs in the BNST have been shown to modulate the stress response, β-ARs have not[42]. For example, while injection of either α_1 antagonists or β_1 and β_2 antagonists in the BNST reduces anxiety after stress[42], only the α_1 antagonist reduces plasma ACTH levels following stress[42]. Therefore, α_1-ARs' modulation of the stress response likely does not contribute to attenuation of stress-induced reinstatement.

Noradrenergic Receptors Modulate Excitatory and Inhibitory Transmission

Evidence suggests that the actions of NE in the extended amygdala influence stress-induced reinstatement of drug-seeking behavior; therefore it is important to understand how NE modulates synaptic transmission to elucidate underlying mechanisms. There has been substantial

evidence to support a heterosynaptic role for ARs in modulating glutamatergic transmission[7-9,57] and inhibitory transmission[30] in the extended amygdala. The effect of NE on synaptic transmission in the BNST appears to depend on duration of NE action[8], previous alterations in noradrenergic signaling[8,58], as well as type of adrenergic receptor activated[6]. Studies have shown α_1-ARs and α_2-ARs to depress excitatory synaptic transmission[6-8,30] as well as to modulate inhibitory transmission[7], while β-ARs are capable of enhancing both excitatory transmission[6,57] and inhibitory transmission[30]. Work has suggested that α_2-ARs are capable of differentially regulating glutamatergic inputs to the extended amygdala[9](unpublished data). The activation of ARs relies on many factors, such as duration of NE action, previous alterations in NE signaling, and activation of other receptors[6,57]. Further, ARs are capable of complex modulations of synaptic transmission in the extended amygdala, such as enhancement or depression of excitatory or inhibitory transmission, and differential regulation of individual excitatory inputs to the BNST. Therefore, ARs can intricately modulate synaptic transmission in the extended amygdala in response to diverse stress and reward stimuli, and these modulations may underlie stress-induced reinstatement.

α_1-ARs Modulate Excitatory Transmission in a Time-Dependent Manner

Noradrenergic modulation of synaptic transmission in the extended amygdala depends on duration of NE action. Extended application of NE to the BNST has been observed to result in an α_1-AR-dependent long term depression (LTD) of glutamatergic transmission in the BNST[8] through a postsynaptic mechanism[8]. However, with a shorter application of NE, only a transient depression or enhancement is seen[6,8]. This LTD is disrupted in mice with chronic alternations in adrenergic signaling, such as α_{2A}-AR- or NET-knockout mice[8], or mice that have undergone chronic stress or chronic ethanol exposure[58]. The absence of α_1-mediated LTD in the context of chronic disruption of noradrenergic signaling suggests that α_1-ARs may be important for long-term regulation of excitatory transmission in the extended amygdala, with prolonged dysregulation of noradrenergic signaling interfering with the α_1-ARs' ability to regulate transmission. Further, evidence suggests α_1-ARs dominate regulation of synaptic transmission after prolonged exposure to NE by ultimately inducing LTD[8], regardless of whether the initial response to NE is a β_2-AR-mediated increase in excitatory transmission, or an α_2-AR-mediated decrease of excitatory transmission[6]. In addition to transient depression in excitatory signaling, acute application of NE to α_1-ARs causes a transient increase of inhibitory transmission through a presynaptic mechanism[30]. Perhaps with prolonged stimulation by NE, α_1-ARs switch from a short-term presynaptic mechanism that enhances inhibitory transmission, to a long-term postsynaptic mechanism that depresses excitatory transmission[8,58]. α_1-ARs would then have the ability to depress activity in the BNST both short-term, through enhancement of $GABA_A$ inhibitory postsynaptic currents (IPSCs), and well as long term, through LTD. The ability of α_1-ARs to induce LTD in the extended amygdala suggests a possible mechanism for α_1-ARs in modulating the stress-response after exposure to a prolonged stressor. α_1-ARs in the extended amygdala have been shown to be capable of modulating the stress response, with injection of α_1 antagonists into the BNST decreasing levels of plasma ACTH[42]. By modulating excitatory or inhibitory transmission in the BNST, α_1-ARs may modulate the stress response by affecting the strength of the BNST's inhibitory projection to the PVN.

β-ARs Enhance Excitatory and Inhibitory Transmission in the BNST

Prior alterations in noradrenergic signaling can influence which ARs are recruited by NE. For example, with brief application of NE, α_1-ARs have been shown to enhance IPSC frequency in the BNST[30]; during acute withdrawal from morphine, NE-treated slices also demonstrate increased IPSC frequency through β-ARs[30]. Therefore, although the overall outcome of enhanced inhibitory transmission is the same whether through α_1- or β-ARs, the physiological circumstances under which NE is released in the extended amygdala seem to influence whether or not β-ARs are recruited. Brief application of NE to a slice might mimic a brief stressor that predominantly acts through α_1-ARs. In contrast, withdrawal may lead to long-term changes in NE signaling that effect the basal activity of β-ARs, and thus their likelihood of recruitment by subsequent NE signaling. Further evidence suggests that the recruitment of β-ARs by NE depends on their initial state of activity before NE application[6]. If enhanced excitatory transmission does not occur with initial NE application, subsequent treatment with β-AR agonists will not lead to β-AR-mediated enhancement of excitatory transmission[6]. However, if excitatory transmission does enhance with initial NE application, subsequent β-AR agonists will cause a similar enhancement of excitatory transmission[6]. Withdrawal may therefore influence the initial state of β-ARs, increasing their likelihood of recruitment by NE signaling. In other studies, β-ARs have been shown to enhance excitatory synaptic transmission through

processes that rely on the activity of other receptors, such as α_2-ARs[6] and CRFR1 receptors[57]. Therefore, the initial state of the β-ARs may also rely on signaling through other receptors. As a result, β-ARs may be poised to integrate stress and reward information received from inputs that signal though different neurotransmitters, for example integrating NE neurotransmission with CRF neurotransmission. The ability of β-ARs to enhance synaptic transmission in the extended amygdala may rely on both prior noradrenergic signaling, and on activation of other receptors.

α_2-ARs Mediate Short-term Depression of Excitatory and Inhibitory Transmission

Like α_1-ARs, α_2-ARs depress synaptic transmission in the BNST through heterosynaptic mechanisms[7,9]. Distribution of α_{2A}-ARs in the BNST suggests a prominent role for α_{2A}-ARs in modulating glutamatergic transmission. Immunohistochemical studies reveal that α_{2A}-ARs in the BNST are more broadly distributed than noradrenergic terminals, and instead closely resemble distribution of glutamatergic terminals[7]. Functionally, activation of α_2-ARs in the BNST leads to a decrease in excitatory transmission[6,7]. In a later study, application of a specific α_{2A}-AR agonist to BNST slices led to a decrease in both excitatory and inhibitory synaptic transmission[7]. Unlike α_1-ARs, the depression of synaptic transmission by α_2-ARs occurs through a presynaptic mechanism[7]. Also in contrast to α_1-ARs, α_2-ARs may play a greater role in short term depression of synaptic transmission[6] (unpublished data). Studies have not yet shown α_2-ARs to be capable of modulating plasticity of the BNST through LTD.

α_2-ARs Differentially Modulate Individual Inputs to the Extended Amygdala

α_2-ARs may differentially regulate synaptic transmission from individual inputs to the extended amygdala[9,59](unpublished data). As in the BNST, NE signaling in the CeA has been shown to heterosynaptically modulate glutamatergic transmission through α_2-ARs[9]. Further, NE has differential effects on the modulation of the glutamatergic inputs to the CeA from the parabrachial nucleus and the BLA[9]. Application of NE depresses glutamatergic transmission from the parabrachial nucleus to the CeA, but had no effect on transmission between the BLA and the CeA, with this effect depending on α_2-AR activation[9]. The differential modulation of glutamatergic transmission by NE is a particularly interesting finding, as it suggests that NE action through the α_2-AR, for a similar duration of time, could lead to afferent-specific effects on excitatory transmission. Differential excitatory modulation has important implications for understanding the circuitry underlying the relationship between stress and reward-seeking, as specific glutamatergic inputs could have a stronger influence on synaptic transmission in the extended amygdala, contingent on activation of α_2-ARs. Further evidence of differential regulation of glutamatergic inputs to the extended amygdala through α_2-ARs has been shown by increased c-fos expression after treatment with an α_{2A} agonist[59]. C-fos expression following treatment with an α_{2A}-AR agonist may indicate an excitatory role for α_{2A}-ARs in modulating glutamatergic transmission, which contrasts with previous work showing α_{2A}-ARs depress excitatory transmission[7]. Unpublished data using optogenetic approaches has also provided evidence for α_{2A}-AR-mediated enhancement of excitatory transmission. Behaviorally, guanfacine, an α_{2A} agonist, was recently shown to be less effective than prazosin at blocking yohimbine-induced reinstatement of alcohol-seeking[56]. The decreased effectiveness of guanfacine could result from guanfacine enhancing excitatory transmission from certain inputs while depressing others, therefore having less of an overall effect on synaptic transmission in the extended amygdala. However, work still needs to be done to determine if glutamatergic inputs to the extended amygdala are indeed differentially regulated by α_2-ARs, and if so, how α_2-ARs modulate each of these inputs. Optogenetic approaches may provide a powerful tool to resolve the effect of α_2-AR activation on specific inputs to the extended amygdala.

Conclusion

Evidence implicates ARs in the extended amygdala as being important in stress-induced reinstatement of drug-seeking. In the BNST, activation of α_1-ARs depresses excitatory synaptic transmission, enhances inhibitory synaptic transmission, and modulates the stress response following prolonged exposure to stressors. Depressing excitatory transmission or enhancing inhibitory transmission in the BNST could lead to decreased strength of the inhibitory projection from the BNST to the PVN, and therefore decreased inhibition of the PVN and an enhanced stress response in the body. Therefore, α_1-AR antagonists in the extended amygdala may attenuate these effects on excitatory and inhibitory transmission, thus attenuating the stress response of the body, which is consistent with previous findings of decreased plasma ACTH upon injection of α_1-AR antagonists into the BNST[42]. This attenuation of the stress response likely does not contribute to α_1-AR antagonists' ability to block stress-induced reinstatement in the BNST, as β-AR antagonists injected into the BNST also block re-

instatement, but do not decrease plasma ACTH[42]. Perhaps instead, block of stress-induced reinstatement is mediated through changes in strength of the BNST projection to the VTA. α_2- and β-ARs seem to influence negative symptoms of withdrawal, as α_2-AR agonists and β-AR antagonists can block withdrawal-mediated conditioned place aversion[43], perhaps implicating reward, as opposed to stress, circuitry in attenuating stress-induced reinstatement. Further, β- and α_2-ARs may be critical in integrating information from different inputs to the extended amygdala. β-ARs may integrate signals from different neurotransmitters, as β-AR-mediated increases in excitatory transmission rely on signaling through other receptors, such as α_2-AR[6] and CRFR1[57]. Activation of these other receptors may help to determine the initial state of β-AR responsiveness to NE, thus determining subsequent response to β-AR agonists[6]. Finally, α_2-ARs play a role in transient depression of excitatory transmission, and may differentially modulate excitatory inputs to the extended amygdala. Differential modulation would allow for certain inputs to dominate regulation of synaptic transmission in the extended amygdala, depending on the neural context of information reaching the BNST. Integration of inputs to the extended amygdala, and modulation of neural activity within the region, may allow noradrenergic receptors to regulate stress-induced reinstatement to drug-seeking.

References

1. Weiss F and Koob GF (2001). Drug addiction: functional neurotoxicity of the brain reward systems. Neurotoxicity research. 3 (1): 145-156.

2. Brown S, Vik PW, Patterson TL, Grant I and Shuckit MA (1995). Stress, Vulnerability and Adult Alcohol Relapse. Journal of Studies on Alcohol. 56: 538-545.

3. Sinha RDC and O'Malley S (1999). Stress-induced craving and stress resoponse in cocaine dependent individuals. Psychopharmacology. 142: 343-351.

4. Sinha R, Shaham Y and Heilig M (2011). Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacology.

5. Egli RE and Winder DG (2003). Dorsal and ventral distribution of excitable and synaptic properties of neurons of the bed nucleus of the stria terminalis. Journal of neurophysiology. 90 (1): 405-414.

6. Egli RE, Kash TL, Choo K, Savchenko V, Matthews RT, Blakely RD and Winder DG (2005). Norepinephrine modulates glutamatergic transmission in the bed nucleus of the stria terminalis. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 30 (4): 657-668.

This paper demonstrates that norepinephrine applied to the BNST is capable of either enhancing or depressing excitatory transmission. The enhancement of excitatory transmission was shown to occur through β-ARs, with depression of excitatory transmission being mediated by α_2-ARs.

7. Shields AD, Wang Q and Winder DG (2009). alpha2A-adrenergic receptors heterosynaptically regulate glutamatergic transmission in the bed nucleus of the stria terminalis. Neuroscience. 163 (1): 339-351.

This paper demonstrates the heterosynaptic role of α_{2A}-ARs in depressing glutamatergic synaptic transmission. It also provides evidence that α_{2A}-ARs may also depress inhibitory transmission in the BNST. Finally, the paper provides immunohistochemical evidence for the heterosynaptic role of α_2-ARs in regulating glutamatergic transmission in the BNST.

8. McElligott ZA and Winder DG (2008). Alpha1-adrenergic receptor-induced heterosynaptic long-term depression in the bed nucleus of the stria terminalis is disrupted in mouse models of affective disorders. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 33 (10): 2313-2323.

9. Delaney AJ, Crane JW and Sah P (2007). Noradrenaline modulates transmission at a central synapse by a presynaptic mechanism. Neuron. 56 (5): 880-892.

This paper demonstrates interesting evidence for the differential modulation of individuals inputs to the extended amygdala by α_2-ARs. α_2-AR activation is shown to depress the excitatory input from the parabrachial nucleus to the CeA, but α_2-AR activation has no effect on the excitatory input from the BLA to the CeA. My studies will look at the differential modulation of excitatory inputs to the BNST by α_2-ARs.

10. Leri F, Flores J, Rodaros D and Stewart J (2002). Blockade of stress-induced but not cocaine-induced reinstatement by infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala. The Journal of neuroscience : the official journal of the Society for Neuroscience. 22 (13): 5713-5718.

11. Mantsch JR, Weyer A, Vranjkovic O, Beyer CE, Baker DA and Caretta H (2010). Involvement of noradrenergic neurotransmission in the stress- but not cocaine-induced reinstatement of extinguished cocaine-induced conditioned place preference in mice: role for beta-2 adrenergic receptors. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 35 (11): 2165-2178.

12. Wang X, Cen X and Lu L (2001). Noradrenaline in the bed nucleus of the stria terminalis is critical for stress-induced reactivation of morphine-conditioned place preference in rats. Eur J Pharmacol. 432 (2-3): 153-161.

13. Sinha R, Kimmerling A, Doebrick C and Kosten TR (2007). Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. Psychopharmacology. 190 (4): 569-574.

14. Jobes ML, Ghitza UE, Epstein DH, Phillips KA, Heishman SJ and Preston KL (2011). Clonidine blocks stress-induced craving in cocaine users. Psychopharmacology.

15. Sallee FR and Eaton K (2010). Guanfacine extended-release for attention-deficit/hyperactivity disorder (ADHD). Expert opinion on pharmacotherapy. 11 (15): 2549-2556.

16. Alheid GF and Heimer L (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience. 27 (1): 1-39.

17. Alheid GF (2003). Extended amygdala and basal forebrain. Annals of the New York Academy of Sciences. 985: 185-205.

18. Walker D (2003). Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. European Journal

of Pharmacology. 463 (1-3): 199-216.
19. Dong HW and Swanson LW (2006). Projections from bed nuclei of the stria terminalis, anteromedial area: cerebral hemisphere integration of neuroendocrine, autonomic, and behavioral aspects of energy balance. The Journal of comparative neurology. 494 (1): 142-178.
20. Shammah-Lagnado SJ, Beltramino CA, McDonald AJ, Miselis RR, Yang M, de Olmos J, Heimer L and Alheid GF (2000). Supracapsular bed nucleus of the stria terminalis contains central and medial extended amygdala elements: evidence from anterograde and retrograde tracing experiments in the rat. The Journal of comparative neurology. 422 (4): 533-555.
21. Dong HW, Petrovich GD and Swanson LW (2001). Topography of projections from amygdala to bed nuclei of the stria terminalis. Brain research. Brain research reviews. 38 (1-2): 192-246.
22. Choi DC, Furay AR, Evanson NK, Ostrander MM, Ulrich-Lai YM and Herman JP (2007). Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity: implications for the integration of limbic inputs. The Journal of neuroscience : the official journal of the Society for Neuroscience. 27 (8): 2025-2034.
23. Cullinan WE, Herman JP and Watson SJ (1993). Ventral subicular interaction with the hypothalamic paraventricular nucleus: evidence for a relay in the bed nucleus of the stria terminalis. The Journal of comparative neurology. 332 (1): 1-20.
24. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC and Cullinan WE (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Frontiers in neuroendocrinology. 24 (3): 151-180.
25. Herman JP, Cullinan WE and Watson SJ (1994). Involvement of the bed nucleus of the stria terminalis in tonic regulation of paraventricular hypothalamic CRH and AVP mRNA expression. Journal of neuroendocrinology. 6 (4): 433-442.
26. Harris GW (1948). Neural control of the pituitary gland. Physiological reviews. 28 (2): 139-179.
27. Dong HW, Petrovich GD, Watts AG and Swanson LW (2001). Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain. The Journal of comparative neurology. 436 (4): 430-455.
28. Georges F and Aston-Jones G (2001). Potent regulation of midbrain dopamine neurons by the bed nucleus of the stria terminalis. The Journal of neuroscience : the official journal of the Society for Neuroscience. 21 (16): RC160.
29. Georges F and Aston-Jones G (2002). Activation of ventral tegmental area cells by the bed nucleus of the stria terminalis: a novel excitatory amino acid input to midbrain dopamine neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience. 22 (12): 5173-5187.
30. Dumont EC and Williams JT (2004). Noradrenaline triggers GABAA inhibition of bed nucleus of the stria terminalis neurons projecting to the ventral tegmental area. The Journal of neuroscience: the official journal of the Society for Neuroscience. 24 (38): 8198-8204.
31. White FJ (1996). Synaptic regulation of mesocorticolimbic dopamine neurons. Annual review of neuroscience. 19: 405-436.
32. Briand LA, Vassoler FM, Pierce RC, Valentino RJ and Blendy JA (2010). Ventral tegmental afferents in stress-induced reinstatement: the role of cAMP response element-binding protein. The Journal of neuroscience: the official journal of the Society for Neuroscience. 30 (48): 16149-16159.
33. Forray MI and Gysling K (2004). Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. Brain research. Brain research reviews. 47 (1-3): 145-160.
34. Zardetto-Smith AM and Gray TS (1990). Organization of peptidergic and catecholaminergic efferents from the nucleus of the solitary tract to the rat amygdala. Brain research bulletin. 25 (6): 875-887.
35. Fallon JH and Moore RY (1978). Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. The Journal of comparative neurology. 180 (3): 545-580.
36. Moore RY and Bloom FE (1979). Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. Annual review of neuroscience. 2: 113-168.
37. Ricardo JA and Koh ET (1978). Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. Brain research. 153 (1): 1-26.
38. Woulfe JM, Hrycyshyn AW and Flumerfelt BA (1988). Collateral axonal projections from the A1 noradrenergic cell group to the paraventricular nucleus and bed nucleus of the stria terminalis in the rat. Experimental neurology. 102 (1): 121-124.
39. Banihashemi L and Rinaman L (2006). Noradrenergic inputs to the bed nucleus of the stria terminalis and paraventricular nucleus of the hypothalamus underlie hypothalamic-pituitary-adrenal axis but not hypophagic or conditioned avoidance responses to systemic yohimbine. The Journal of neuroscience: the official journal of the Society for Neuroscience. 26 (44): 11442-11453.
40. Pacak K, McCarty R, Palkovits M, Kopin IJ and Goldstein DS (1995). Effects of immobilization on in vivo release of norepinephrine in the bed nucleus of the stria terminalis in conscious rats. Brain research. 688 (1-2): 242-246.
41. Cecchi M, Khoshbouei H and Morilak DA (2002). Modulatory effects of norepinephrine, acting on alpha1 receptors in the central nucleus of the amygdala, on behavioral and neuroendocrine responses to acute immobilization stress. Neuropharmacology. 43 (7): 1139-1147.
42. Cecchi M, Khoshbouei H, Javors M and Morilak DA (2002). Modulatory effects of norepinephrine in the lateral bed nucleus of the stria terminalis on behavioral and neuroendocrine responses to acute stress. Neuroscience. 112 (1): 13-21.
43. Delfs JM, Zhu Y, Druhan JP and Aston-Jones G (2000). Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. Nature. 403 (6768): 430-434.
44. Olson VG, Heusner CL, Bland RJ, During MJ, Weinshenker D and Palmiter RD (2006). Role of noradrenergic signaling by the nucleus tractus solitarius in mediating opiate reward. Science. 311 (5763): 1017-1020.
45. Ma S and Morilak DA (2005). Norepinephrine release in medial amygdala facilitates activation of the hypothalamic-pituitary-adrenal axis in response to acute immobilisation stress. Journal of neuroendocrinology. 17 (1): 22-28.
46. Aston-Jones G, Delfs JM, Druhan J and Zhu Y (1999). The bed nucleus of the stria terminalis. A target site for noradrenergic actions in opiate withdrawal. Annals of the New York Academy of Sciences. 877: 486-498.
47. Fuentealba JA, Forray MI and Gysling K (2000). Chronic

morphine treatment and withdrawal increase extracellular levels of norepinephrine in the rat bed nucleus of the stria terminalis. Journal of neurochemistry. 75 (2): 741-748.
48. Shaham Y, Highfield D, Delfs J, Leung S and Stewart J (2000). Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of locus coeruleus noradrenergic neurons. The European journal of neuroscience. 12 (1): 292-302.
49. Brown ZJ, Nobrega JN and Erb S (2011). Central injections of noradrenaline induce reinstatement of cocaine seeking and increase c-fos mRNA expression in the extended amygdala. Behavioural brain research. 217 (2): 472-476.
50. Shaham Y, Shalev U, Lu L, De Wit H and Stewart J (2003). The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology. 168 (1-2): 3-20.
51. Carter AJ (1997). Hippocampal Noradrenaline Release in Awak, Freely Moving Rats Is Regulated by Alpha-2 Adrenoceptors but Not be Adenosinse Receptors. The Journal of Pharmacology and Experimental Therapeutics. 281 (2): 648-654.
52. Bylund DB ED, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, Molinoff PB, Ruffolo RR, Trendelenburg U (1994). International Union of Pharmacology Nomenclature of Adrenoreceptors. Pharmacology Reviews. 46 (2): 121-136.
53. Hein L (2006). Adrenoceptors and signal transduction in neurons. Cell and tissue research. 326 (2): 541-551.
54. Highfield D, Yap J, Grimm JW, Shalev U and Shaham Y (2001). Repeated lofexidine treatment attenuates stress-induced, but not drug cues-induced reinstatement of a heroin-cocaine mixture (speedball) seeking in rats. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 25 (3): 320-331.
55. Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y and Stewart J (2000). Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 23 (2): 138-150.
56. Le AD, Funk D, Juzytsch W, Coen K, Navarre BM, Cifani C and Shaham Y (2011). Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. Psychopharmacology.
57. Nobis WP, Kash TL, Silberman Y and Winder DG (2011). beta-Adrenergic receptors enhance excitatory transmission in the bed nucleus of the stria terminalis through a corticotrophin-releasing factor receptor-dependent and cocaine-regulated mechanism. Biological psychiatry. 69 (11): 1083-1090.
58. McElligott ZA, Klug JR, Nobis WP, Patel S, Grueter BA, Kash TL and Winder DG (2010). Distinct forms of Gq-receptor-dependent plasticity of excitatory transmission in the BNST are differentially affected by stress. Proceedings of the National Academy of Sciences of the United States of America. 107 (5): 2271-2276.
59. Savchenko VL and Boughter JD, Jr. (2011). Regulation of Neuronal Activation by Alpha2A Adrenergic Receptor Agonist. Neurotoxicity research. 20 (3): 226-239.
This paper provides further evidence for a potential excitatory role for α_{2A}-ARs' modulation of glutamatergic transmission, as measured by c-fos staining. This paper is interesting because it contradicts with previous findings that show α_{2A}-ARs as depressing excitatory transmission.

Further Information
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