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Hippocampus, amygdala and stress: Interacting systems that affect susceptibility to addiction

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Abstract

Stress is one of the major factors in drug abuse, particularly in relapse and drug-seeking behavior. However, the mechanisms underlying the interactions between stress and drug abuse are unclear. For many years, studies have focused on the role of the dopaminergic reward system in drug abuse. Our results show that an increased dopaminergic activity is induced by drug sensitization and different stressors via potentiation of the ventral subiculum-nucleus accumbens (NAc) pathway. Although the role of the NE system in stress is well-known, its involvement in drug abuse has received less attention. This review explores the different mechanisms by which stressors can modulate the ventral subiculum-accumbens pathway, and how these modulations can induce alterations in the behavioral response to drug administration. In particular, we will focus on two main afferents to the NAc, the basolateral amygdala and the ventral subiculum of the hippocampus, and their interactions with the locus coeruleus-norepinephrine system.

Keywords

ventral subiculum of the hippocampus; basolateral amygdala; locus coeruleus-norepinephrine system; mesolimbic system; nucleus accumbens

Investigations into the pathophysiology of drug abuse have traditionally focused on the dopaminergic reward system in the development of addiction, with a particular emphasis on the neural changes in reward-sensitive regions that are induced during addiction, relapse and abstinence ^{1, 2}. Repeated administration of drugs of abuse is believed to induce a pathological response in the neural circuitry involved in processing natural reward, and the mechanisms underlying these allostatic changes have been a topic of extensive research ³. The mesolimbic system formed in part by the ventral tegmental area (VTA) and the nucleus accumbens (NAc) is an integral part of the brain's reward circuit. Mesolimbic dopamine is implicated in the processing of natural and drug-related rewards, mediates the hedonic aspects of rewarding stimuli ⁴, and acts as a learning signal for behavioral reinforcement ⁵. A model has been proposed for brain changes that occur during the development of addiction that explains the persistent vulnerability to relapse, even long after drug taking has ceased. Indeed, drug-induced modifications in synaptic plasticity in the mesolimbic system, especially the VTA and the NAc, and the possible role of dopamine receptors in the development of these neuroadaptations, have been the focus of several studies. The modulation of excitatory synaptic transmission in the limbic regions during and after drug exposure has been shown to play a significant role in drug relapse and reinstatement ¹. Thus morphological as well as synaptic alterations of several neuronal cell types in the limbic

regions of the brain may be responsible for long-term behavioral plasticity driving addiction ⁶. It is now well-established that the most difficult phase in treating drug addiction is not the drug withdrawal, but preventing relapse ^{7, 8}. Relapse to drug addiction is usually associated with craving that accompanies drug-seeking behavior. It has been suggested that even after weeks, if not months of withdrawal, addicts become sensitized to drug-associated environmental cues that act as external stimuli for craving ^{9–11}.

One of the many factors that are known to contribute to relapse to drug abuse is stress. Indeed, numerous clinical as well as animal studies have shown a predominant role of stress in drug abuse and relapse ¹². However the mechanisms underlying this relationship remain unclear. Stress and psychostimulants cross-sensitize, with stress leading to heightened responsivity to psychostimulants and vice versa. One common feature that stress and drug sensitization share is their strong dependence on context. Indeed, animals exposed to a stressor in a specific context show behavioral changes in that same context ^{13, 14}, and psychostimulant sensitization is greater when the animals are tested in the same environment in which the drug has been delivered ^{15, 16}. A region that has been implicated in context-dependent processes is the ventral subiculum of the hippocampus (vSub). The vSub is involved in context-dependent fear conditioning ¹⁷ as well as other context-related processes ^{18–20}. The vSub is also a key structure in stress-related physiological response ²¹ and hyperdopaminergic response to amphetamine ^{22, 23}. Another key structure related to stress is the basolateral amygdala (BLA). Neuronal activity within the amygdala is strongly affected by acute stressors, chronic stress exposure, and conditioned aversive stimuli ^{24, 25}. Synaptic plasticity within the amygdala is also affected by exposure to stress ²⁶. Importantly, the BLA is also involved in drug relapse, in particular by integrating the influences of stress on drug-related memory ²⁷. Moreover, the BLA provides a potent input to the vSub ²⁸. The present review will focus on those two main afferents to the NAc and describe their possible role in drug relapse, drug seeking behavior and their relationship to stress.

The dopamine reward system

It is now well-known that mesolimbic dopaminergic neurons have different states of activity. Dopaminergic neurons can be divided into two groups based on their activity: spontaneously active, corresponding to the population activity of DA neurons, and inactive neurons ²⁹. Of the DA neurons that are firing spontaneously, the firing pattern is observed to exist in two activity patterns: a slow, irregular “tonic” firing pattern, and a bursting “phasic” pattern ^{30, 31}. The bursting firing pattern is triggered by external reward-related stimuli in awake-behaving animals, or by stimulation of afferents ^{5, 22}. One of the main efferents of the mesolimbic DA system is the NAc. Thus, irregular firing activity will modulate the tonic DA levels in the NAc whereas burst firing pattern mediates a large phasic, transient peak of dopamine in the synapse ³². These two firing patterns are induced by different types of afferents to the VTA. The bursting firing activity is driven by glutamate release in the VTA by the pedunculopontine tegmentum (PPTg) ^{32, 33}, whereas population firing that mediates the tonic release of dopamine is induced by activation of an indirect pathway consisting of the vSub-NAc-ventral pallidum-VTA (Figure 1). This pathway has been confirmed by the ability of kynurenic acid injected into the NAc and local injection of muscimol/baclofen (specific agonists of GABA_{A/B} receptors) in the ventral pallidum to block the effects of vSub activation on DA neuron firing ³². Interestingly, those two firing patterns have been shown to work synergistically to induce an appropriate behavioral response. Thus, we have shown that the number of DA neurons firing spontaneously determines the numbers of cells that can be driven into burst firing ²². Therefore, stimuli that increase vSub activity increase the amplitude of the DA system response to a particular phasic event.

The ventral subiculum and stress/drug relapse

The vSub is the primary output of the hippocampus, sending projections to many limbic-related regions, especially the NAc ³⁴. The vSub is involved in different context-dependent processes such as fear-conditioning ^{17, 19}, extinction ³⁵, drug sensitization ¹² and stress ³⁶.

Studies have shown that vSub inactivation decreases cocaine and cue-induced reinstatement, highlighting the importance of the vSub in drug-seeking behavior ³⁷. Drug sensitization has been proposed to model drug craving that occurs during the addiction process ³⁸ and may play a significant role in reinstatement and relapse in drug-abstinent subjects. Indeed, context is known to play a large role in recidivism to drug-taking behavior ³⁷. Drug sensitization is described as the repeated administration of psychostimulants, such as cocaine or amphetamine, resulting in a heightened response to a subsequent single drug administration ³⁹. This behavioral sensitization has been compared to the increased drug craving observed in human drug abusers ³⁸. Behavioral sensitization to amphetamine is attributable, at least in part, to an increased mesolimbic DA neuron drive, which is dependent on the vSub-NAc pathway. In fact, inactivation of the vSub in amphetamine-sensitized rats restores the DA population activity to basal levels, and eliminates the behavioral hyper-responsivity to amphetamine ²³. Moreover, cocaine sensitization induces long-term potentiation in the vSub-NAc pathway dependent on D1-receptors activation ⁴⁰. All of these studies support a substantial role of the vSub in drug sensitization.

Drugs of abuse engage similar brain areas as those involved in the response to stress. Stress can be defined as a threat to the maintenance of homeostatic balance, and the stress response inducing adaptive changes modulated by environmental factors ⁴¹. Many studies have shown an increasing role of the vSub in different stress responses ⁴². Thus, hippocampal lesion is linked to increased plasma levels of the adrenocorticotrophic hormone (ACTH) and corticosterone under stressor conditions ⁴³, and a decreased stress threshold in animals ⁴⁴. One of the major stress responses of the vSub is to decrease, via multisynaptic pathways, the response of the hypothalamic-pituitary-adrenal (HPA) axis to stress ⁴⁵. Moreover, other limbic system-associated regions, such as the prefrontal cortex, the amygdala and the NAc, have been shown to regulate the HPA axis ⁴⁵. This suggests that limbic information may affect the activity of the homeostatic systems and dysfunctional stress integration may involve dysregulation in this circuitry.

The locus coeruleus-norepinephrine (LC-NE) system is one the major systems implicated in stress. In fact, corticotropin-releasing factor, a hormone that will induce release of ACTH during stress, has been shown to activate the LC-NE system in response to specific challenges ⁴⁶. Thus, in vivo ⁴⁷ and in vitro ⁴⁸ studies have shown that administration of CRF induced an increase in LC firing rate simultaneously with an increase in NE efflux ⁴⁷. The vSub receives a prominent NE innervation from the LC ⁴⁹, and NE can produce an activation of vSub neurons ⁵⁰. In rats, the vSub is described as having the highest density of beta-adrenergic receptors in the hippocampal formation ⁵¹. Thus, activation of beta adrenergic receptors by NE release into the vSub may induce a strong modulatory effect by increasing responses to glutamatergic afferent input to the vSub ^{52, 53}.

Stress and drug abuse share many common features; in particular the ability to induce dopamine as well as norepinephrine release in limbic regions ⁵⁴ and their strong association with context, implicating the vSub. Moreover, stress cross-sensitizes with psychostimulants. Thus an animal exposed to a stressor will show a heightened responsivity to amphetamine when exposed to a subsequent administration of the drug, and vice versa ¹⁶. We have shown that acute stress caused by a 2h restraint stress protocol induced an increase in the population activity in the VTA, and that this increase is reversed by infusion of the sodium-channel

inhibitor tetrodotoxin (TTX) in the vSub ⁵⁵. The 2hr restraint protocol used in the previous study has been described to induce behavioral sensitization to amphetamine ⁵⁶. Thus, the increased VTA population activity occurs in concert with a sensitized behavioral response to amphetamine; a response that is also reversed by vSub inactivation ⁵⁵.

Taken together, these data demonstrate that the DA hyperactivity described after a stress exposure or psychostimulant sensitization is due to an increase in the tonic firing of VTA DA neurons and is dependent on hyperactivity in the vSub-NAc pathway. Activation of the vSub by norepinephrine could be one possible mechanism that underlies the hyperactivity in the vSub efferent pathway to the NAc.

Norepinephrine and stress/drug relapse

Norepinephrine (NE) is one of the most abundant neurotransmitters in the brain and it plays a significant role in selective attention ⁵⁷ general arousal ⁵⁸, and stress^{59, 60}. The norepinephrine system originates mostly in the locus coeruleus and, as described above, has a central role in the response to stressors. Thus, a large variety of stressors will increase the firing activity of LC neurons ⁶¹ as well as increase the turnover of NE in many projection regions of the LC ⁶². The role of NE in drug abuse has long been neglected, as the dopamine-reward system has been the focus of most of the studies in this field. Nonetheless, NE release is reported to affect the reinstatement of drug-seeking behavior ⁶³. Thus, the LC-NE system has been shown to be activated during withdrawal from drugs ⁶⁴ and it has been suggested that part of the reinforcing properties of the addictive drug morphine derive in part from its ability to decrease stress-induced NE release and the anxiety associated with this release ⁶⁵. Moreover, pharmacological studies using alpha2 adrenergic autoreceptor agonists have highlighted the role of NE in stress-induced reinstatement of drug-seeking ⁶⁶, and alpha-2adrenergic antagonists induce an increase in dopamine-dependent locomotor activity ⁶⁷.

Besides directly activating the LC-NE system, stressors can activate other structures that project to the LC, such as the BLA. Importantly, one structure that plays a major role in the emotional component of the stress response is the BLA ⁶⁸. Thus, stressful stimuli such as footshock or tail-pinch induce activation of the amygdala ^{69, 70}. In addition, synaptic plasticity within the amygdala is also affected by different stressors ^{24, 26}. Moreover, chronic, as well as acute, stressors induced an increase in the activity of BLA neurons ⁷¹. However, the modulation of LC neuron activity by the BLA is indirect, via activation of the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST) that will induce release of CRF in the dendritic pericoerulear regions ⁷². Thus, the BLA sends excitatory inputs to the CeA ⁷⁰, a structure that will then activate the LC-NE system by releasing CRF ⁴⁸. The relation between the LC-NE system and the BLA is reciprocal. Thus, besides sending an indirect projection to the LC, the BLA receives direct afferent projections from the locus coeruleus, and the NE release by the LC modulates the activity of BLA neurons via alpha- and beta-adrenergic receptors ⁷³ (Figure 2).

The BLA plays also an important role in relapse to drug-seeking behavior, since inactivation of this nucleus affects the conditioned-cued reinstatement without modulating the effect of drug administration ⁷⁴. Moreover, a disconnection study has shown that a strong interaction exists between the dopaminergic system and the BLA inducing cue-evoked firing of neurons from the NAc that will promote reward-seeking behavior ⁷⁵.

Inputs from the BLA and the vSub have been described to converge on the same NAc neurons ²⁸. Reciprocal connections between the BLA and the vSub have also been described ²⁸ suggesting that BLA and vSub can interact with each other independent of their connectivity in the NAc. As mentioned above, the vSub is proposed to mediate the effects of

stress in part via the vSub-NAc pathway. Moreover, the vSub receives numerous inputs from stress-related regions such as the LC-NE system, as well as the BLA ²⁸. We have recently found that stimulation of the LC-NE system and the BLA activate vSub neuronal activity ⁵⁰, and both acute and chronic stressors induce an increase of activity in those two inputs ^{24, 76}. Thus, one hypothesis underlying drug sensitization and its modulation by stressors may involve the activation of the vSub-NAc pathway by the LC-NE system and/or the BLA leading to an increase in DA population activity, which mediates the increased behavioral response to psychostimulants.

Conclusion

Relapse to drug-seeking behavior depends on a complex array of factors: environmental context engaging the vSub, cue-induced reinstatement involving the BLA, and stressful events activating a widespread neural circuit including the vSub and BLA. Stressful events and drug abuse have common substrates. They both induce sensitization, which is a context-dependent event that involves hyperactivation of the mesolimbic DA system. The vSub is a pivotal structure that plays a major role in coordinating the response to stressful events and in drug-seeking behavior. We have shown that the vSub, in particular the vSub-NAc pathway, is responsible for the hyperactivity of the DA system in response to a stressor and to drug sensitization. This structure receives two main inputs known to be activated by different stressors and involved in drug-seeking behavior: the LC-NE system and the BLA.

To better understand how drug administration can induce drug-relapse and drug-seeking behavior, it is important to study the pathophysiological alterations occurring in the stress-vSub-limbic system circuit. Such information is important in guiding future pharmacotherapy and treatment for addiction, via pharmacological intervention in one or several structures of this circuitry, such as the vSub or the BLA.

References

1. Chen BT, Hopf FW, Bonci A. Synaptic plasticity in the mesolimbic system: therapeutic implications for substance abuse. *Ann N Y Acad Sci.* 2010; 1187:129–39. [PubMed: 20201850]
2. Deadwyler SA. Electrophysiological correlates of abused drugs: relation to natural rewards. *Ann N Y Acad Sci.* 2010; 1187:140–7. [PubMed: 20201851]
3. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology.* 2001; 24:97–129. [PubMed: 11120394]
4. Wise RA, Rompre PP. Brain dopamine and reward. *Annu Rev Psychol.* 1989; 40:191–225. [PubMed: 2648975]
5. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol.* 1998; 80:1–27. [PubMed: 9658025]
6. Russo SJ, et al. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. *Trends Neurosci.* 2010
7. O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *Am J Psychiatry.* 2005; 162:1423–31. [PubMed: 16055763]
8. Shaham Y, et al. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl).* 2003; 168:3–20. [PubMed: 12402102]
9. Gawin FH, Kleber HD. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations *Arch Gen Psychiatry.* 1986; 43:107–13.
10. Lu L, et al. Cocaine seeking over extended withdrawal periods in rats: different time courses of responding induced by cocaine cues versus cocaine priming over the first 6 months. *Psychopharmacology (Berl).* 2004; 176:101–8. [PubMed: 15071719]
11. Neisewander JL, et al. Fos protein expression and cocaine-seeking behavior in rats after exposure to a cocaine self-administration environment. *J Neurosci.* 2000; 20:798–805. [PubMed: 10632609]

12. Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl)*. 2001; 158:343–59. [PubMed: 11797055]
13. Bouton ME, Bolles RC. Role of conditioned contextual stimuli in reinstatement of extinguished fear. *J Exp Psychol Anim Behav Process*. 1979; 5:368–78. [PubMed: 528893]
14. Bouton ME, King DA. Contextual control of the extinction of conditioned fear: tests for the associative value of the context. *J Exp Psychol Anim Behav Process*. 1983; 9:248–65. [PubMed: 6886630]
15. Piazza PV, Le Moal M. The role of stress in drug self-administration. *Trends Pharmacol Sci*. 1998; 19:67–74. [PubMed: 9550944]
16. Antelman SM, et al. Interchangeability of stress and amphetamine in sensitization. *Science*. 1980; 207:329–31. [PubMed: 7188649]
17. Fanselow MS. Contextual fear, gestalt memories, and the hippocampus. *Behav Brain Res*. 2000; 110:73–81. [PubMed: 10802305]
18. Jarrard LE. What does the hippocampus really do? *Behav Brain Res*. 1995; 71:1–10. [PubMed: 8747170]
19. Maren S. Neurotoxic or electrolytic lesions of the ventral subiculum produce deficits in the acquisition and expression of Pavlovian fear conditioning in rats. *Behav Neurosci*. 1999; 113:283–90. [PubMed: 10357453]
20. Sharp PE. Complimentary roles for hippocampal versus subicular/entorhinal place cells in coding place, context, and events. *Hippocampus*. 1999; 9:432–43. [PubMed: 10495024]
21. Mueller NK, Dolgas CM, Herman JP. Regulation of forebrain GABAergic stress circuits following lesion of the ventral subiculum. *Brain Res*. 2006; 1116:132–42. [PubMed: 16979601]
22. Lodge DJ, Grace AA. The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology*. 2006; 31:1356–61. [PubMed: 16319915]
23. Lodge DJ, Grace AA. Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. *J Neurosci*. 2008; 28:7876–82. [PubMed: 18667619]
24. Correll CM, Rosenkranz JA, Grace AA. Chronic cold stress alters prefrontal cortical modulation of amygdala neuronal activity in rats. *Biol Psychiatry*. 2005; 58:382–91. [PubMed: 16023619]
25. Rosenkranz JA, Grace AA. Dopamine-mediated modulation of odour-evoked amygdala potentials during pavlovian conditioning. *Nature*. 2002; 417:282–7. [PubMed: 12015602]
26. Vouimba RM, et al. Effects of inescapable stress on LTP in the amygdala versus the dentate gyrus of freely behaving rats. *Eur J Neurosci*. 2004; 19:1887–94. [PubMed: 15078562]
27. Wang XY, et al. Stress impairs reconsolidation of drug memory via glucocorticoid receptors in the basolateral amygdala. *J Neurosci*. 2008; 28:5602–10. [PubMed: 18495894]
28. French SJ, Hailstone JC, Totterdell S. Basolateral amygdala efferents to the ventral subiculum preferentially innervate pyramidal cell dendritic spines. *Brain Res*. 2003; 981:160–7. [PubMed: 12885437]
29. Grace AA, Bunney BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons--2. Action potential generating mechanisms and morphological correlates. *Neuroscience*. 1983; 10:317–31. [PubMed: 6633864]
30. Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: single spike firing. *J Neurosci*. 1984; 4:2866–76. [PubMed: 6150070]
31. Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: burst firing. *J Neurosci*. 1984; 4:2877–90. [PubMed: 6150071]
32. Floresco SB, et al. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat Neurosci*. 2003; 6:968–73. [PubMed: 12897785]
33. Lodge DJ, Grace AA. The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. *Proc Natl Acad Sci U S A*. 2006; 103:5167–72. [PubMed: 16549786]
34. Groenewegen HJ, et al. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. *Neuroscience*. 1987; 23:103–20. [PubMed: 3683859]

35. Sinden JD, Jarrard LE, Gray JA. The effects of intra-subicular ibotenate on resistance to extinction after continuous or partial reinforcement. *Exp Brain Res*. 1988; 73:315–9. [PubMed: 3215307]
36. Herman JP, Mueller NK. Role of the ventral subiculum in stress integration. *Behav Brain Res*. 2006; 174:215–24. [PubMed: 16876265]
37. Sun W, Rebec GV. Lidocaine inactivation of ventral subiculum attenuates cocaine-seeking behavior in rats. *J Neurosci*. 2003; 23:10258–64. [PubMed: 14614084]
38. Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction*. 2000; 95(Suppl 2):S91–117. [PubMed: 11002906]
39. Post RM, Rose H. Increasing effects of repetitive cocaine administration in the rat. *Nature*. 1976; 260:731–2. [PubMed: 944382]
40. Goto Y, Grace AA. Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. *Neuron*. 2005; 47:255–66. [PubMed: 16039567]
41. Pacak K, Palkovits M. Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. *Endocr Rev*. 2001; 22:502–48. [PubMed: 11493581]
42. O'Mara S. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. *J Anat*. 2005; 207:271–82. [PubMed: 16185252]
43. Fendler K, Karmos G, Telegdy G. The effect of hippocampal lesion on pituitary-adrenal function. *Acta Physiol Acad Sci Hung*. 1961; 20:293–7. [PubMed: 13892267]
44. Kant GJ, Meyerhoff JL, Jarrard LE. Biochemical indices of reactivity and habituation in rats with hippocampal lesions. *Pharmacol Biochem Behav*. 1984; 20:793–7. [PubMed: 6330767]
45. Lowry CA. Functional subsets of serotonergic neurones: implications for control of the hypothalamic-pituitary-adrenal axis. *J Neuroendocrinol*. 2002; 14:911–23. [PubMed: 12421345]
46. Valentino RJ, Van Bockstaele EJ. Functional interactions between stress neuromediators and the locus coeruleus–noradrenaline system. *Handbook of Stress and the Brain*. 2005:465–486.
47. Curtis AL, et al. Activation of the locus coeruleus noradrenergic system by intracoeular microinfusion of corticotropin-releasing factor: effects on discharge rate, cortical norepinephrine levels and cortical electroencephalographic activity. *J Pharmacol Exp Ther*. 1997; 281:163–72. [PubMed: 9103494]
48. Jedema HP, Grace AA. Corticotropin-releasing hormone directly activates noradrenergic neurons of the locus ceruleus recorded in vitro. *J Neurosci*. 2004; 24:9703–13. [PubMed: 15509759]
49. Loy R, et al. Noradrenergic innervation of the adult rat hippocampal formation. *J Comp Neurol*. 1980; 189:699–710. [PubMed: 7381046]
50. Lipski, WJ.; Grace, AA. Program No 1951, 2008 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience; 2008. Neurons in the ventral subiculum are activated by noxious stimuli and are modulated by noradrenergic afferents.
51. Duncan GE, et al. Beta-adrenergic receptor distribution in human and rat hippocampal formation: marked species differences. *Brain Res*. 1991; 561:84–92. [PubMed: 1665753]
52. Jurgens CW, et al. Beta1 adrenergic receptor-mediated enhancement of hippocampal CA3 network activity. *J Pharmacol Exp Ther*. 2005; 314:552–60. [PubMed: 15908512]
53. Raman IM, Tong G, Jahr CE. Beta-adrenergic regulation of synaptic NMDA receptors by cAMP-dependent protein kinase. *Neuron*. 1996; 16:415–21. [PubMed: 8789956]
54. Snyder SH. Putative neurotransmitters in the brain: selective neuronal uptake, subcellular localization, and interactions with centrally acting drugs. *Biol Psychiatry*. 1970; 2:367–89. [PubMed: 4320227]
55. Valenti, O.; Grace, AA. 2008 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience; 2008. Acute and repeated stress induce a pronounced and sustained activation of VTA DA neuron population activity. Program no 47911
56. Pacchioni AM, et al. A single exposure to restraint stress induces behavioral and neurochemical sensitization to stimulating effects of amphetamine: involvement of NMDA receptors. *Ann N Y Acad Sci*. 2002; 965:233–46. [PubMed: 12105099]
57. Aston-Jones G, Rajkowski J, Cohen J. Role of locus coeruleus in attention and behavioral flexibility. *Biol Psychiatry*. 1999; 46:1309–20. [PubMed: 10560036]

58. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci.* 2005; 28:403–50. [PubMed: 16022602]
59. Smagin GN, Swiergiel AH, Dunn AJ. Corticotropin-releasing factor administered into the locus coeruleus, but not the parabrachial nucleus, stimulates norepinephrine release in the prefrontal cortex. *Brain Res Bull.* 1995; 36:71–6. [PubMed: 7882052]
60. Valentino RJ, Foote SL, Page ME. The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. *Ann N Y Acad Sci.* 1993; 697:173–88. [PubMed: 7903030]
61. Abercrombie ED, Keller RW Jr, Zigmond MJ. Characterization of hippocampal norepinephrine release as measured by microdialysis perfusion: pharmacological and behavioral studies. *Neuroscience.* 1988; 27:897–904. [PubMed: 3252176]
62. Korf J, Aghajanian GK, Roth RH. Increased turnover of norepinephrine in the rat cerebral cortex during stress: role of the locus coeruleus. *Neuropharmacology.* 1973; 12:933–8. [PubMed: 4750561]
63. Weinshenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology.* 2007; 32:1433–51. [PubMed: 17164822]
64. Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiatry.* 1999; 46:1167–80. [PubMed: 10560023]
65. Aston-Jones G, Harris GC. Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology.* 2004; 47(Suppl 1):167–79. [PubMed: 15464135]
66. Erb S, et al. Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacology.* 2000; 23:138–50. [PubMed: 10882840]
67. Villegier AS, et al. Stimulation of postsynaptic alpha1b- and alpha2-adrenergic receptors amplifies dopamine-mediated locomotor activity in both rats and mice. *Synapse.* 2003; 50:277–84. [PubMed: 14556232]
68. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci.* 2009; 10:423–33. [PubMed: 19469026]
69. Rosen JB, et al. Immediate-early gene expression in the amygdala following footshock stress and contextual fear conditioning. *Brain Res.* 1998; 796:132–42. [PubMed: 9689463]
70. Rosenkranz JA, Buffalari DM, Grace AA. Opposing influence of basolateral amygdala and footshock stimulation on neurons of the central amygdala. *Biol Psychiatry.* 2006; 59:801–11. [PubMed: 16373067]
71. Buffalari DM, Grace AA. Chronic cold stress increases excitatory effects of norepinephrine on spontaneous and evoked activity of basolateral amygdala neurons. *Int J Neuropsychopharmacol.* 2009; 12:95–107. [PubMed: 18647435]
72. Van Bockstaele EJ, Colago EE, Valentino RJ. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. *J Neuroendocrinol.* 1998; 10:743–57. [PubMed: 9792326]
73. Buffalari DM, Grace AA. Noradrenergic modulation of basolateral amygdala neuronal activity: opposing influences of alpha-2 and beta receptor activation. *J Neurosci.* 2007; 27:12358–66. [PubMed: 17989300]
74. See RE, et al. Drug addiction, relapse, and the amygdala. *Ann N Y Acad Sci.* 2003; 985:294–307. [PubMed: 12724166]
75. Ambroggi F, et al. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. *Neuron.* 2008; 59:648–61. [PubMed: 18760700]
76. Jedema HP, Grace AA. Chronic exposure to cold stress alters electrophysiological properties of locus coeruleus neurons recorded in vitro. *Neuropsychopharmacology.* 2003; 28:63–72. [PubMed: 12496941]

Figure 1.

Dopaminergic neurons from the ventral tegmental area (VTA) display two firing patterns regulated by distinct pathways. The phasic burst firing pattern is induced by direct excitatory inputs (red arrows) from the pedunculopontine tegmentum (PPTg) to the VTA, whereas the tonic firing pattern (population firing) is mediated by activation of the indirect ventral subiculum (vSub)-nucleus accumbens (NAc)-ventral pallidum (VP)-VTA pathway. Interactions between these two pathways are involved in decision-making regarding appropriate behavioral responses. Blue arrows: GABAergic inhibitory inputs; red arrows: glutamatergic excitatory inputs; green arrow: dopaminergic (DA) inputs.