

# Activation and Inhibition of Neurons in the Hippocampal Ventral Subiculum by Norepinephrine and Locus Coeruleus Stimulation

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The ventral subiculum (vSub) has been implicated in a wide range of neurocognitive functions, including responses to fear, stress, and anxiety. The vSub receives dense noradrenergic (NE) inputs from the locus coeruleus (LC), and the LC-NE system is heavily implicated in attention and is known to be activated by stressors. However, the way in which the neurons in the vSub respond to activation of the LC-NE is not well understood. In this study, the direct LC innervation of the vSub was investigated. The effect of norepinephrine (NE) on single vSub neurons was examined using microiontophoresis combined with electrophysiological recordings in anesthetized rats, and this response compared with the effect of electrical stimulation of the LC. Ionophoretic NE inhibited all vSub neurons tested, whereas LC stimulation inhibited 16% and activated 38% of neurons. Inhibition was mediated primarily by alpha-2 receptors, whereas activation was mediated by beta-adrenergic receptors. Furthermore, this effect was not mediated via the LC-basolateral amygdala (BLA) pathway, because BLA inactivation did not block LC stimulation-evoked activation of the vSub. These results indicate that the LC-NE system is a potent modulator of vSub activity. Based on these findings, stress-induced activation of the LC-NE system is expected to evoke inhibition and activation in the vSub, both of which may contribute to stress adaptation, whereas an imbalance of this system may lead to pathological stress responses in mental disorders.

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## INTRODUCTION

The ventral subiculum (vSub) constitutes a part of the hippocampal formation; however it is distinct in structure and function from the dorsal hippocampus. It is associated with a broad spectrum of neurocognitive functions, including responses to fear (Maren, 1999), stress and anxiety (Mueller *et al*, 2004; Herman and Mueller, 2006), spatial representation (Oswald and Good, 2000), memory formation and recall (Deadwyler and Hampson, 2004), novelty detection (Lisman and Grace, 2005), encoding of context (Maren, 1999; Fanselow, 2000), and regulation of the midbrain dopamine system (Floresco *et al*, 2001, 2003).

The vSub receives dense innervation from noradrenergic neurons of the locus coeruleus (LC) (Oleskevich *et al*, 1989; Schroeter *et al*, 2000). The LC-norepinephrine (NE) system, in turn, has a critical role in regulation of behavioral states, including attention and stress responses (Berridge and Waterhouse, 2003). Indeed, it is activated by a variety of

stressors, including restraint, footshock, and social stress (Valentino and Van Bockstaele, 2008). Furthermore, the behavioral effects of LC activation mimic the effects of stress exposure, and lesions of the LC attenuate neuroendocrine and behavioral stress responses (Ziegler *et al*, 1999). The vSub itself has been identified as a region that is a crucial element in the forebrain's stress response, particularly to psychogenic stressors (Mueller *et al*, 2004; Herman and Mueller, 2006). In rats, multiple stressors, including restraint, swim stress, and novelty stress increase the hippocampal expression of Fos, a marker of neuronal activity (Emmert and Herman, 1999; Figueiredo *et al*, 2003). Indeed, previous studies from our laboratory (Lipski and Grace, 2011) and others (Otake *et al*, 2002) have shown that, in rats, restraint stress activates neurons in the vSub. The vSub is also implicated in processing of contextual information, which is significant, as stress is a context-dependent phenomenon; ie, the context in which the stressor is administered has a major role in the adaptive response of the organism (Bouton and Bolles, 1979). In addition, the vSub potently influences dopaminergic neuron activity (Floresco *et al*, 2001, 2003), and prolonged stress is known to trigger maladaptive responses to acute stress involving dopamine dysregulation, such as relapse in drug

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addiction, schizophrenia, and depression (Belujon and Grace, 2011).

Given that LC noradrenergic neurons are potently activated by stressful stimuli, and that the vSub is one of the most densely innervated targets of the LC (Oleskevich, Descarries and Lacaille, 1989; Schroeter *et al*, 2000), the way in which the vSub processes this input is critical to understanding its role in the brain's stress response. However, it is not known how vSub activity is generated in response to LC activation, and surprisingly few studies have addressed this question. Here, the effects of LC activation on the vSub, and whether this activation is mediated via direct projections from the LC, was evaluated. The response of vSub neurons to local application of NE and to electrical stimulation of the LC was examined. Finally, to test whether the response to LC stimulation was mediated via the basolateral amygdala (BLA), the response of vSub neurons to LC stimulation was tested after BLA inactivation.

## MATERIALS AND METHODS

### Surgery

All procedures were performed in accordance with the United States Public Health Service *Guide for the Care and Use of Laboratory Animals* and were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. Male Sprague Dawley rats (300–400 g) were housed two per cage with food and water available *ad libitum*. Rats were anesthetized with urethane (1.5 g/kg i.p.), a long-lasting agent known to induce stable LC activity (Murase *et al*, 1994; Verbanac *et al*, 1994; Nishiike *et al*, 1997; Fenik *et al*, 2005). The level of anesthesia was carefully controlled by adjusting the anesthetic dose based on body mass of each animal, and by monitoring the pedal withdrawal reflex and breathing of the animal throughout the experiment. Rats were placed in a stereotaxic device (David Kopf Instruments, Tujunga, CA), the skull was exposed, and holes were drilled in the skull overlying the vSub, the LC, and/or the BLA. Coordinates (rostral from bregma; lateral from midline) were determined using a stereotaxic atlas (Paxinos and Watson, 2007): vSub: –6.0, 4.6; BLA: –3.5, 5.0; LC (see 'LC stimulation' below).

### Extracellular Single-Unit Recording

Recordings were performed using microelectrodes constructed from Omegadot (WPI) borosilicate glass tubing using a microelectrode puller (Narishige, Tokyo, Japan) as previously described (Goto and Grace, 2006). Briefly, microelectrodes were filled with 2% pontamine sky blue dye dissolved in 2 M NaCl. The recording electrode impedance ranged between 6 and 14 MOhms measured *in situ*. Electrical potentials were amplified using an extracellular amplifier (Fintronics, Orange, CT), and monitored on an oscilloscope. Data were fed to a PC and recorded using LabChart software (ADInstruments, Colorado Springs, CO). Recordings were made of long duration, large amplitude extracellular spikes generated by putative vSub pyramidal neurons. Following recording, dye was ejected electrophoretically from the electrode by applying a constant negative current (30  $\mu$ A for 30 min) to mark the recording placement.

### Iontophoresis

NE was applied by microiontophoresis onto vSub neurons using 5-barrel microelectrodes (Activational Systems, Warren, MI) and a 5-channel electrophoresis unit (E104 B/5, Fintronics). One barrel was filled with a NE solution (Sigma-Aldrich; 0.5 M NE, 100 mM NaCl, pH 4.0), two barrels were filled with 3 M NaCl solution for current balancing, and one barrel was filled with a glutamate solution (Sigma-Aldrich; 10 mM Glu, 150 mM NaCl, pH 8.0) to activate neurons with low spontaneous firing rates. NE was applied in a dose-response fashion (5, 10, 20, 40 nA) using current balancing and controlling for warm-up effects (Bloom, 1974) as described previously (Buffalari and Grace, 2007). The response was defined in terms of changes in firing rate.

### LC Stimulation

The LC (A: –12.6, M/L: +1.1, D/V: –6.0 from bregma, at 10°) was stimulated using current pulses (0.25 ms duration) delivered via a bipolar concentric electrode at current amplitudes between 500 and 800 mA. Train stimulation (4 pulses at 20 Hz) was delivered to mimic bursts of spikes normally produced during phasic activation of the LC in behaving animals (Aston-Jones and Bloom, 1981; Akaike, 1982; Florin-Lechner *et al*, 1996; Devilbiss and Waterhouse, 2011). Recordings of responses to LC stimulation consisted of a 4 s pre-stimulation baseline and 4 s following LC stimulation. Stimulation pulses were delivered every 10 s. Average Z-score histograms were calculated for each neuron, based on at least 25 trials, and using 100 ms bins. Responses were characterized in terms of changes in firing rate; activation following train stimulation was defined as Z-scores greater than 2.0 in at least five bins during the 1 s following stimulation. Inhibition was defined as Z-scores below –2.0 in at least 5 bins during the 1 s following stimulation. At the end of LC stimulation experiments, stimulation electrode locations were marked by passing constant current (150  $\mu$ A, 10 s) through the stimulation electrode.

### Drug Application

Once the neuronal response was characterized, the alpha-2 antagonist idazoxan (Sigma-Aldrich; 1.0 mg/kg i.v.), alpha-1: antagonist prazosin (Fluka; 1 mg/kg i.v) or the beta antagonist propranolol (Sigma-Aldrich; 1.0 mg/kg i.v.) was administered at doses known to block NE effects *in vivo* (Buffalari and Grace, 2007) via a lateral tail vein. Drugs were applied systemically to adequately block afferent-evoked input to distal dendrites, which cannot be reliably blocked by local iontophoretic application. Moreover, it is not reliable to block iontophoretic agonist administration with iontophoretic antagonist, given the greater diffusion of the more hydrophilic transmitter.

### BLA Inactivation

In a subset of experiments, a cannula guide (Plastics One, Roanoke, VA) was lowered into the BLA (from bregma: –3.5 caudal, 5.0 lateral) of urethane anesthetized rats. Once

baseline responses to LC stimulation were established, the effect of BLA inactivation by tetrodotoxin (TTX; Sigma-Aldrich) infusion was tested. A cannula was inserted into the guide, such that the tip of the cannula extended 1 mm past the tip of the cannula guide. 0.5  $\mu$ l of TTX (1.0  $\mu$ M) was infused over 30 s using a Hamilton syringe. At 2 min following the infusion, the response to LC stimulation was again tested.

## Histology

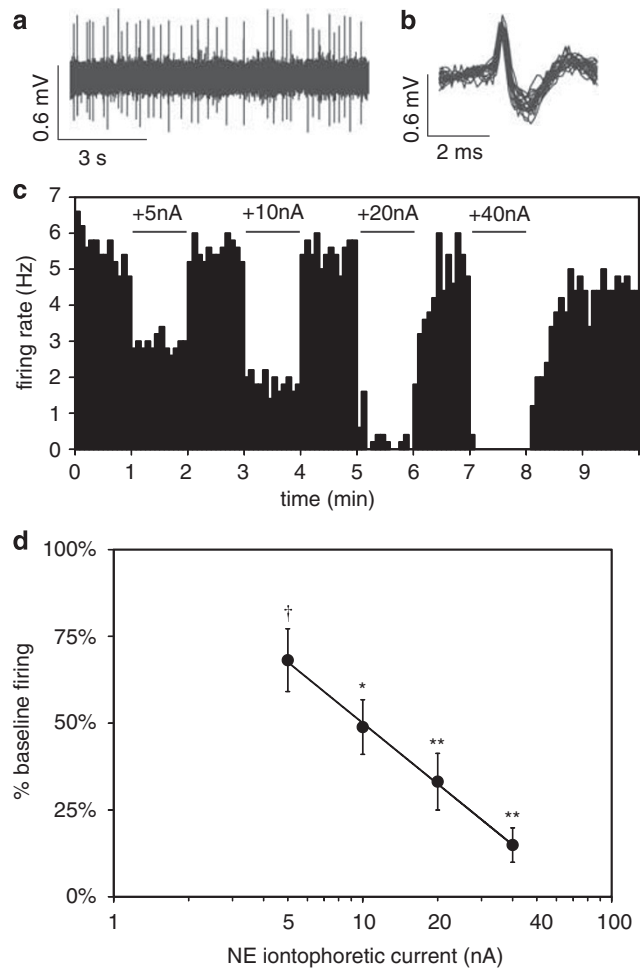
Recording, stimulation, and iontophoresis electrode placements were verified by histological analyses. Following each experiment, rats were euthanized by an overdose of anesthetic, followed by decapitation and brain removal. Brains were fixed in 10% formalin for a minimum of 24 h, and then cryoprotected with 25% sucrose solution in 0.1 M phosphate buffer. Subsequently, brains were frozen and cut into 40  $\mu$ m coronal sections using a microtome, mounted on slides, and stained with cresyl violet. Recording sites were identified by the presence of the Pontamine sky blue dye spot, and the location of the stimulating electrodes was identified by the presence of a small lesion at the end of the electrode track.

## RESULTS

### NE Iontophoresis Inhibits vSub Neurons Primarily via $\alpha$ -2 Receptors

Spontaneously active neurons were isolated in the vSub of 7 rats, and baseline activity was recorded for at least 1 min. Recording placements were confirmed histologically, and were located primarily within the pyramidal layer (PYR;  $N=8$ ), but also within the molecular layer of the vSub (MOL;  $N=2$ ). The spontaneous firing rate of recorded vSub neurons was  $4.9 \pm 1.5$  Hz ( $N=10$ ). For neurons with a spontaneous firing rate of less than 1 Hz, glutamate was allowed to diffuse from the electrode by turning off the glutamate iontophoretic retention current. Subsequently, four doses (5, 10, 20, and 40 nA) of NE were applied iontophoretically. In all neurons tested, NE dose-dependently inhibited spontaneous firing ( $N=10$ ; Figure 1). A two-way repeated ANOVA revealed a significant effect of NE on firing rate compared with baseline ( $p < 0.001$ ), but no main effect of NE dose ( $p = 0.163$ ). However, there was a significant interaction between treatment (NE vs baseline) and NE dose ( $p < 0.001$ ).

In five additional neurons recorded from five rats, after the response to three doses of NE (5, 10, and 20 nA) was recorded, the  $\alpha$ -2 receptor antagonist idazoxan was injected (1.0 mg/kg i.v.), and the response to NE was re-tested. Idazoxan eliminated the inhibitory effect of iontophoretic NE. Before drug application, NE significantly inhibited firing rate compared with baseline (two-way RM-ANOVA,  $p < 0.05$ ); systemic idazoxan blocked this inhibition (two-way RM ANOVA/ Holm-Sidak test,  $p < 0.05$ ; Figure 2a). In another five neurons recorded from five rats, the effect of the  $\alpha$ -1 receptor antagonist prazosin (1.0 mg/kg i.v.) was tested on three doses of NE (5, 10, and 20 nA). Prazosin only partially blocked the inhibitory effect of NE applied at 5 nA,

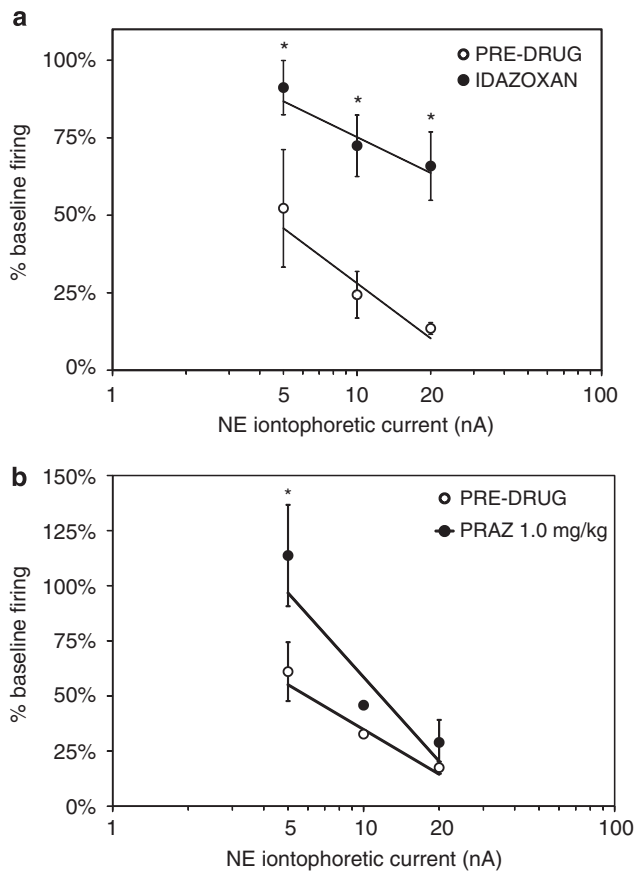


**Figure 1** Iontophoretically applied norepinephrine (NE) dose-dependently inhibits the firing of ventral subiculum (vSub) neurons. (a) A representative extracellular voltage trace recorded in the vSub. (b) The corresponding overlay of 15 discriminated spike waveforms corresponding to a single neuron. (c) A firing rate histogram from a representative neuron showing dose-dependent inhibition by NE. Horizontal black bars on top of the figure indicate NE ejection, with current amplitudes shown above each bar. (d) Group data showing inhibition as a percentage of baseline firing.  $^{\dagger}p = 0.065$ ;  $*p < 0.01$ ,  $**p < 0.001$ .

at the lowest iontophoretic current of NE (two-way RM ANOVA/ Holm-Sidak test,  $p < 0.05$ ; Figure 2b).

### LC Stimulation Produced Excitatory and Inhibitory Effects on vSub Neurons

In a separate cohort of animals, spontaneously active vSub neurons were isolated using single barrel recording electrodes and responses to electrical stimulation of the LC were tested. Recording placements were confirmed histologically, and were located within the pyramidal layer, and molecular layer of the vSub. Of 32 vSub neurons tested in 24 rats, 38% showed activation within 1 s following LC burst stimulation (baseline firing rate (FR) =  $3.55 \pm 1.4$  Hz, LC stimulation FR =  $9.98 \pm 3.3$  Hz;  $p < 0.05$ , paired  $t$ -test; Figure 3a), 16% showed inhibition within this period (baseline FR =  $4.1 \pm 2.3$  Hz, LC stimulation FR =  $1.2 \pm 0.7$  Hz;  $p < 0.05$ , paired  $t$ -test; Figure 3b), whereas the remaining

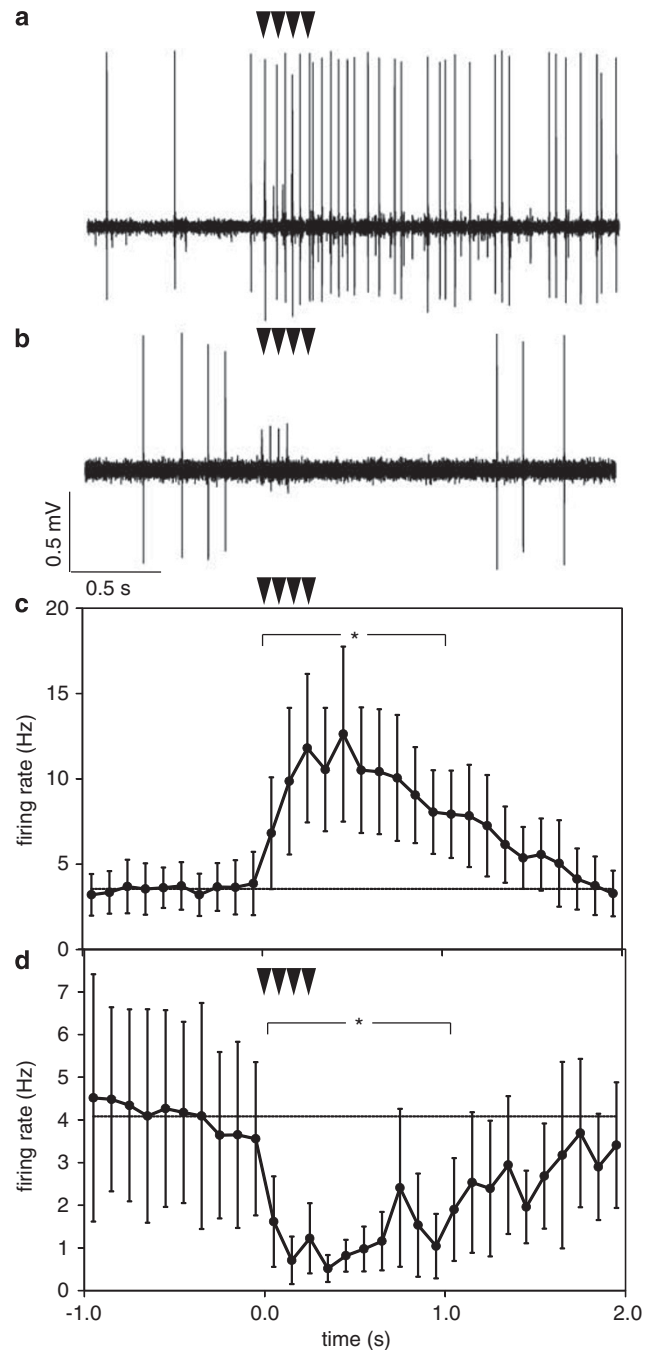


**Figure 2** Norepinephrine (NE) inhibits ventral subiculum (vSub) neurons primarily via alpha-2 receptors. NE-induced inhibition of vSub neuron firing is (a) blocked by systemic alpha-2 antagonist idazoxan (1 mg/kg) at all currents, and (b) partially attenuated by systemic alpha-1 antagonist prazosin (PRAZ) (1 mg/kg) at the lowest iontophoretic current. (\* indicates difference between pre- and post-drug condition,  $p < 0.05$ ).

neurons did not alter their firing. Location within the vSub did not predict the response to LC stimulation, with neurons activated ( $N=10$  PYR,  $N=2$  MOL), inhibited ( $N=4$ ,  $N=1$  MOL), and unaffected by LC stimulation ( $N=12$  PYR,  $N=3$  MOL) in both the PYR and MOL. Both activation and inhibition was long lasting, persisting for an average of  $0.8 \pm 0.3$  s after LC stimulation. The mean pre-LC stimulation baseline firing of vSub neurons was not different between neurons showing inhibition and suppression to LC stimulation (Mann-Whitney rank sum test).

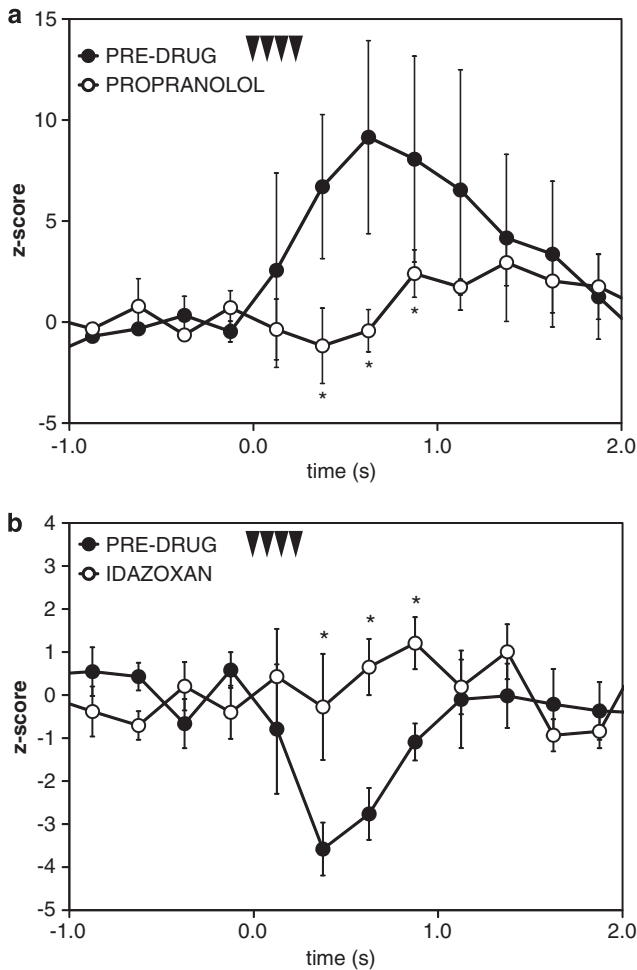
In five additional neurons activated by LC stimulation, recorded from five rats, the  $\beta$  receptor antagonist propranolol (1 mg/kg i.v.) was injected after the baseline response was established. Propranolol blocked the LC-evoked activation (two-way RM ANOVA/ Holm-Sidak test,  $p < 0.05$ ; Figure 4a). In another six neurons, recorded from six rats, the effect of the  $\alpha$ -2 receptor antagonist idazoxan was tested on LC-evoked inhibition. Idazoxan blocked the inhibitory effect of LC stimulation (two-way RM ANOVA/ Holm-Sidak test,  $p < 0.05$ ; Figure 4b).

In addition to its direct projections to the vSub, LC stimulation also will affect neuron activity in BLA (Buffalari and Grace, 2007); a region that also innervates and excites the vSub (Lipski and Grace, 2009). To determine whether part of the response to LC stimulation was mediated via



**Figure 3** Locus coeruleus (LC) stimulation resulted in activation or inhibition of neurons in the ventral subiculum (vSub). Representative voltage traces from extracellular single-unit recording showing activation (a) and inhibition (b) by LC stimulation (arrowheads). Overall, LC stimulation resulted in activation in 38% (c), and inhibition in 16% (d) of vSub neurons tested. Plots in (c) and (d) show the mean firing rate (FR) of the neurons in response to burst stimulation of the LC (delivered at  $t=0$ ). (\* indicates difference between baseline and post-LC stimulation FR,  $p < 0.05$ ). In this and subsequent figures, LC stimulation occurs at  $t=0$  and indicated by arrowheads.

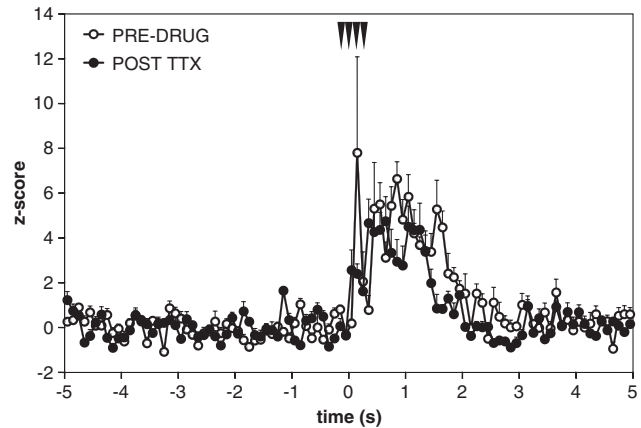
BLA-vSub afferents, the response of vSub neurons to LC stimulation was tested before and after TTX infusion in the BLA, in five neurons recorded from five rats. BLA inactivation did not affect activation of vSub neurons by LC stimulation (Figure 5).



**Figure 4** Locus coeruleus (LC) stimulation excited ventral subiculum (vSub) neurons via an action on beta norepinephrine receptors. (a) LC stimulation-induced excitation is blocked by propranolol. (b) LC stimulation-induced inhibition is blocked by idazoxan. (\* indicates difference in firing rate between pre- and post-drug condition,  $p < 0.05$ ).

## DISCUSSION

The LC-NE system was found to have multiple effects on vSub neurons. Microiontophoretic application of NE was found to potently inhibit the firing of vSub neurons, and this inhibition was mediated primarily by the activation of alpha-2 receptors. In addition, the alpha-1 receptor antagonist prazosin partially blocked the inhibition produced by iontophoretic NE, suggesting that alpha-1 receptors contribute substantially less to the inhibition compared with other adrenergic receptors. This result is consistent with the action of iontophoretic NE, as reported in the dorsal hippocampus. Experiments examining the action of NE on dorsal CA1 and CA3 neurons revealed that NE potently suppressed neuron firing; and that idazoxan, and to a lesser extent prazosin, block this effect (Curet and de Montigny, 1988a), at the same doses of the antagonists (1 mg/kg) used in the present study. Alpha-1 receptors are thought to be expressed primarily by inhibitory GABAergic interneurons in the hippocampus, and alpha-1 receptor activation depolarizes these neurons, thereby presumably



**Figure 5** Locus coeruleus (LC)-basolateral amygdale (BLA) inactivation does not block LC-induced excitation of ventral subiculum (vSub) neurons.

increasing inhibition of hippocampal pyramidal cells (Hillman *et al*, 2005a, 2005b).

NE is released in the vSub during stress from terminals of LC neurons, which densely innervate this region. Therefore, the effect of electrically stimulating this input was examined. In contrast to iontophoretically applied NE, LC stimulation resulted in inhibition of firing in 16% of neurons and activation in 38%, while not significantly affecting the firing in the remaining neurons. These effects were apparently mediated through NE release from the LC, as both activation and inhibition was blocked by specific noradrenergic receptor antagonists. Thus, administration of the alpha-2 antagonist idazoxan blocked the inhibitory responses, and the beta antagonist propranolol blocked the excitatory responses to LC stimulation. Given that antagonists in these experiments were applied systemically, their site of action cannot be determined definitely. However, the fact that both increasing NE concentration in the vSub through iontophoresis and LC stimulation caused alpha-2 mediated inhibition suggests that the inhibitory effects of LC stimulation are mediated by alpha-2 receptors located in the vSub. On the other hand, LC stimulation-induced activation was not mimicked by iontophoretic NE in the vSub. This suggests that the activation results from NE acting on beta noradrenergic receptors located either outside the vSub, or along the distal portion of vSub neuron dendrites where beta receptors would be less likely to be activated by iontophoretically applied NE. Although the subcellular localization of adrenergic receptors has not been studied in the vSub, beta receptors in the hippocampal in the dentate gyrus have been observed primarily post-synaptically on the dendrites of granule cells (Milner *et al*, 2000). Alpha-2 receptors, on the other hand, have been observed both pre-synaptically on axon terminals, and post-synaptically on dendrites and somata of pyramidal cells in the CA1 (Milner *et al*, 1998). Regardless of their site of action, the current study confirmed previous findings showing that beta adrenoreceptors are the primary mediators of excitatory responses to LC-evoked NE release in the vSub (Curet and de Montigny, 1988b).

In addition to differential localization of noradrenergic receptor subtypes, it is possible that other factors may account for differences in vSub neuron responses to

iontophoretically applied and synaptically released NE. First, electrical stimulation of the LC may result in the recruitment of a variable number and location of noradrenergic fibers, depending on exact-stimulating electrode placement, whereas iontophoretic NE results in high concentrations of NE locally around the recording site that rapidly diminish with distance. This may account for the large variability in responses to LC stimulation. Second, LC fibers may differentially innervate individual vSub neurons, perhaps accounting for why some neurons were not responsive to LC stimulation. Finally, individual neurons within the vSub may vary in noradrenergic receptor expression and localization.

Studies examining the effects of NE on CA3 pyramidal neurons of the dorsal hippocampus (Curet and de Montigny, 1988b) reported that electrical stimulation of the LC also inhibited neuronal firing. However, in contrast to the current results, administration of idazoxan increased the effectiveness of this inhibition, rather than blocking it. Although the reason for this difference is not readily apparent, there are several potential factors that could account for it. Thus, in our studies the LC was activated phasically with a burst of pulses, whereas Curet and de Montigny (1988b) applied continuous 1 Hz stimulation to the LC, which would be expected to facilitate NE accumulation and presynaptic inhibition of NE release. Second, we recorded spontaneously active vSub neurons, whereas the CA3 neurons in the Curet and de Montigny study were activated by iontophoretic application of acetylcholine. Finally, it may be that the discrepancy may be related to differences between the vSub and the dorsal hippocampus. The increase in inhibition caused by idazoxan in the dorsal hippocampus suggests that this effect is mediated by the blockade of pre-synaptic alpha-2 autoreceptors, which control the release of NE into the synaptic cleft (Arima *et al*, 1998). On the other hand, the reversal of inhibition by idazoxan in the vSub suggests that blockade of presynaptic inhibition of NE release may not have as significant of a role. Indeed, whereas most studies of the effects of alpha-2 receptors have addressed the presynaptic alpha-2 autoreceptor located on NE terminals that inhibits NE release (Arima *et al*, 1998), alpha-2 receptors have also been identified at postsynaptic sites in the central nervous system (U'Prichard *et al*, 1980; Freedman and Aghajanian, 1985; Buffalari and Grace, 2007). The fact that idazoxan blocked the inhibition caused by both iontophoretic NE as well as by LC stimulation in the vSub supports the conclusion that LC stimulation-induced inhibition is mediated by the action of NE released from LC terminals onto post-synaptic alpha-2 receptors.

The current study showed that beta adrenoreceptors are the primary mediators of excitatory responses to LC-evoked NE release in the vSub. Indeed, beta receptors are typically excitatory in nature and are positively linked to adenylyl cyclase via activation of Gs proteins (Pfeuffer, 1977; Ross *et al*, 1978). Moreover, NE stimulation of beta receptors has also been shown to mediate excitatory responses of hippocampal neurons to NE in the slice preparation (Dunwiddie *et al*, 1992) and of BLA neurons *in vivo* (Buffalari and Grace, 2007). In the majority of neurons described in the Curet and de Montigny (1988b) study, LC-evoked inhibition was followed by a period of activation in dorsal hippocampal

neurons (Curet and de Montigny, 1988b). Similar to the LC-evoked activation of vSub neurons in our experiments, this activation of CA3 neurons was blocked by systemic application of propranolol. However, in the vSub, LC stimulation evoked inhibition or activation in separate populations of neurons. This suggests that, in the vSub, post-synaptic alpha-2 and beta receptors may be either differentially distributed among separate neural populations, or the effect on interneurons may not be homogeneous throughout this region.

The BLA receives a strong LC projection, and is known to be activated during stress (Cullinan *et al*, 1995; Rosen *et al*, 1998; Chowdhury *et al*, 2000; Akirav *et al*, 2001; Dayas *et al*, 2001). In addition, the vSub is activated by BLA inputs (Lipski and Grace, 2011). To evaluate whether part of the excitatory response of the vSub to LC stimulation occurred via the BLA, the BLA was inactivated by TTX microinfusion. BLA inactivation did not block the increase in firing caused by LC stimulation, suggesting that this response is mediated by beta receptors distal to the site of NE iontophoresis. This result is not surprising, as in unstressed rats, NE release from the LC in the BLA has been reported to primarily inhibit this region, with only a small proportion of neurons being activated through a beta-adrenergic mechanism (Buffalari and Grace, 2007). However, chronic cold stress was reported to increase the excitatory effects of NE in the BLA (Buffalari and Grace, 2009), suggesting this input to the vSub may play a role in responses to LC stimulation under chronic stress conditions.

The modulation of vSub activity by NE has important implications for understanding central responses to stressors and how stress can influence regulation of the dopamine system. As reviewed above, context-dependent vSub activity drives dopamine neuron population activity in the ventral tegmental area (VTA) via a projection involving the NAc-pallidal-VTA circuit. As stress-induced LC activation causes NE release in the vSub as well as other forebrain regions, knowledge of the downstream impact of this release is critical to our understanding of this system. Our findings suggest that stress-induced LC activation can cause inhibition of some vSub neurons, and activation of others. This shift may represent an adaptive response between contextual representations, with alpha-2 receptor-mediated inhibition suppressing ongoing hippocampal activity, and beta receptor stimulation providing a context-selective activation of a subset of the network. Such a broad inhibition overlaid with a selective activation may contribute to the adaptive nature of the response to stressors.

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## DISCLOSURE

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