Role of α_1-Adrenoceptors of the Locus Coeruleus in Self-Stimulation of the Medial Forebrain Bundle

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The present experiments were undertaken to clarify the role of central α_1-adrenoceptors in reward processes. Rats, trained to self-stimulate via electrodes in the medial forebrain bundle of the lateral hypothalamus, were administered α_1-selective drugs near the locus coeruleus (LC), a site of a dense concentration of α_1-receptors. Effects on reward potency were assessed from shifts in rate–frequency curves while effects on motor response capacity were judged from changes in the maximal rates of responding. It was found that local blockade of LC α_1-receptors with terazosin produced a significant dose-dependent and site-dependent rightward shift of 0.08 log units and a significant decrease of 16.3% in the maximum response rate. Both effects were completely reversed by coadministration of the α_1-agonist, phenylephrine and were not attributable to terazosin's weak action at α_2-adrenoceptors. It is concluded that LC α_1-adrenoceptors are involved both in reward/motivational processes and operant response elaboration which are postulated to work together to facilitate goal attainment.

INTRODUCTION

It is now well established that a subgroup of CNS α_1-adrenoceptors are necessary for gross behavioral activity in a variety of conditions. Blockade of these receptors produces profound inactivity and catalepsy, whereas stimulation of them leads to hyperactivity (Stone *et al*, 2001; Stone and Quartermain, 2005). The effect of these receptors on behavioral activity may be related to their involvement in reward mechanisms (Hunt *et al*, 1976; Liebman *et al*, 1982; Umemoto and Olds, 1981), or positive motivation (Zhang and Kosten, 2005; Stone and Quartermain, 2005). Increased behavioral activity as a result of rewarding stimulation of these receptors might result from attempts by the organism to obtain more reward or from an enhancement of the potency of secondary reinforcers in the environment.

In support of a reward function, selective blockade of α_1-receptors by peripherally administered antagonists has been found to inhibit self-stimulation of the medial forebrain bundle (MFB) (Hunt *et al*, 1976; Liebman *et al*, 1982; Fenton and Liebman, 1982), to impair conditioned

place preference (CPP) for morphine (Sahraei *et al*, 2004) and to prevent cocaine-induced reinstatement of drug seeking (Zhang and Kosten, 2005) but not to inhibit operant responses that escape aversive brain stimulation (Liebman *et al*, 1982). Furthermore, knockout of the α_{1B}-adrenoceptor has also been shown to disrupt CPP for morphine (Drouin *et al*, 2002), while total blockade of central α_1-receptors with intraventricular terazosin has been found to block all spontaneous movement including eating and drinking while it only partially inhibits movement to aversive stimulation such as forced swimming or struggling in the tail suspension test (Stone *et al*, 1999; Stone and Quartermain, 1999). In addition, α_{1B}-receptors have been found to be necessary for the motor hyperactivity caused by a number of reinforcing drugs including cocaine, amphetamine, modafinil, and morphine (Drouin *et al*, 2002; Stone *et al*, 2002; Duteil *et al*, 1990).

It is presently unclear which brain region may mediate the presumed rewarding effect of α_1-receptors. α_1-Adrenoceptors have a widespread distribution in the CNS and affect behavioral activity from multiple regions. The region whose α_1-receptors have the greatest effect on behavioral activity is the dorsal pons and most likely in the locus coeruleus (LC), which also has one of the highest densities of these receptors in the brainstem (Stone *et al*, 2004b; Jones *et al*, 1985). Furthermore, the LC is a site from which self-stimulation can be elicited (Yadin *et al*, 1983), is highly sensitive to appetitive operant conditioning (Clayton *et al*, 2004) and has efferent connections with dopaminergic neurons in the ventral

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tegmental area (Grenhoff et al, 1993; Mejias-Aponte et al, 2004).

The present experiments were undertaken therefore to examine the effect on reward processes of modifying α_1-receptor activity in the LC. In order to separately assess the roles of motor impairment versus reward, the present experiment studied the effects of these LC receptors on the threshold and maximum response for self-stimulation of the MFB in the lateral hypothalamus. It has been established that changes in self-stimulation threshold are most closely associated with changes in reward potency or motivation whereas changes in maximum response rate are closely related to changes in motor or response capacities (Edmonds and Gallistel, 1974; Miliaressis et al, 1986).

MATERIALS AND METHODS

Subjects and Surgical Procedures

All subjects were 350–400 g male Sprague–Dawley rats housed individually in plastic cages with access to food and water ad libitum. Animals were maintained on a 12 h light/dark cycle with lights on at 07:00 hours, and behavioral testing was always conducted during the light phase. Several days after arrival in the central animal facility, each rat was anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and stereotaxically implanted with a 0.25 mm diameter monopolar stimulating electrode (Plastics One, Roanoke, VA) in the lateral hypothalamic MFB (3.0 mm posterior to bregma, 1.6 mm lateral to the sagittal suture, and 8.6 mm ventral to skull surface). An anterior ipsilateral stainless steel skull screw served as ground. The animals were simultaneously implanted with bilateral 26 ga cannula (Plastics One) targeted so that the protruding inner cannulas would be adjacent or near the border of each LC. The coordinates for the cannulas were −9.8 mm from Bregma, 1.3 mm lateral, and 6.5 mm ventral. Several animals were implanted with cannulas targeted to be approximately 0.4 mm laterally distant from the LC (1.7 mm lateral to midline) as a control for site specificity. Each cannula contained an occlusion stylet. The electrode, ground, and cannula were permanently secured to the skull by flowing dental acrylic around them and three additional mounting screws.

Behavioral Test Apparatus

Electrical brain stimulation. Brain stimulation training and testing were conducted in two standard operant test chambers (26 × 26 × 21 cm) placed within sound-attenuating cubicles. Each chamber had a retractable lever mounted on one wall and a house light mounted on the opposite wall. Two constant current stimulators (PHM-152B/2; Med-Associates, Georgia, VT) were used to deliver trains of 0.1 ms cathodal pulses, which were conducted to implanted electrodes by way of commutators and flexible cables. Electrical stimulation, contingencies, and data recording were controlled through an IBM personal computer and interface (Med-Associates). All stimulation parameters were monitored on a Tektronix (TAS 455) oscilloscope.

Self-Stimulation Training

After 1 week of postsurgical recovery, rats were exposed to the operant chamber and trained to lever press for 0.5 s trains of lateral hypothalamic stimulation at a frequency of 100 pulses per second (pps). The initial stimulation intensity of 120 mA was systematically manipulated to locate the lowest intensity for each rat that would maintain vigorous lever pressing with no signs of aversive or motoric side effects. This initial screening was followed on subsequent days by training in a discrete trials procedure. Each training session consisted of 24 60-s trials. Each trial was initiated by extension of the response lever and a 2 s train of 'priming' stimulation. Each trial was terminated by retraction of the lever and followed by a 10 s intertrial interval. Each lever press produced a 1 s train of stimulation, except for those presses emitted during the 1 s train that did not increase reinforcement density. The number of lever presses and reinforcements were recorded for each trial. Discrete trials training was followed by rate–frequency training, which continued for 2 weeks. Rate–frequency curves were generated by presenting 12 trials in which the frequency of brain stimulation decreased in 0.05 log units over successive trials from an initial frequency of 100 pps to a terminal frequency of 28 pps. Three such series were presented in each training session which lasted 45 min.

Procedure

After rate–frequency curves had stabilized, the effect of drug infusion in the LC on response characteristics was examined. For this, animals were infused bilaterally on separate days (at least 48 h apart) first with saline alone and then with the test drug or drug combination. Each drug test or dose was preceded by a saline test and only one saline–drug test pair was performed on each animal. The test drugs were: the α_1-adrenergic antagonist, terazosin (TER) alone at 3 or 10 nmol/0.5 μl saline in balanced order, the α_1-adrenergic agonist, phenylephrine (PE), 10 nmol, the combination of TER (10 nmol) plus PE (10 nmol), and the selective α_2-antagonist, atipamezole (ATI) at 1 nmol. The α_2-antagonist was used at a lower dose than the α_1-antagonist because TER's affinity at α_2-receptors is less than one-tenth its affinity at α_1-receptors (Hancock et al, 1995). All infusions occurred over 3 min which included 30 s delay before cannula removal. The 36 trial test series began 3 min postcannula removal. Separate groups of six rats each were used for the TER 3 and 10 nmol, PE, TER + PE, ATI, and TER 10 outside the LC (TER 10 OUT) experiments, respectively.

All experiments were conducted in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals (1996) and were approved by the New York University School of Medicine IUCAC. The above numbers of rats per group represented the minimum numbers needed to achieve statistical significance based on a priori estimates of the effect sizes.

Histology

On the completion of behavioral testing, rats were overdosed with sodium pentobarbital (100 mg/kg, i.p.), and

brains were removed. After a minimum of 48 h in 10% buffered formalin, 30 μ-thick frozen coronal sections were cut on a minotome cryostat (International Equipment Co.) and stained with cresyl violet.

Data Analysis

Average rate–frequency curves for each saline or drug condition were constructed by averaging response rates across all rats in a group at each stimulation frequency. The curves were analyzed for the two LHSS parameters that can be used to distinguish between changes in reward potency and performance capacity. These were the reward threshold, which is defined as that stimulation frequency which maintains the response rate at one-half its maximum value, and the maximum rate. Both parameters were calculated by nonlinear regression (Prism, GraphPad) using fixed slope and no constraints on the bottom and top of each curve. In addition, the slopes of the curves were calculated in order to determine if the saline and drug curves were parallel. Significance at $\alpha = 0.05$ was calculated from the nonoverlap of the 95% confidence intervals for each variable.

RESULTS

With the exception of the TER-10 OUT group, which had both cannula tips located from 0.3 to 0.6 mm distant to the LC nucleus core, all the animals used in the study were chosen on the basis of having at least one cannula tip within 0.2 mm of the nucleus core. We and others have shown that in awake animals, unilateral blockade of LC activity with either TER or with the α_2-agonist, clonidine, is sufficient to induce profound behavioral inactivity in rodents (De Sarro et al, 1987; Stone et al, 2004b). Figure 1 shows the implantation sites of the TER 10 nmol and TER-10-OUT groups. The former group is representative of the remaining groups used.

The effects of TER at 3 and 10 nmol on the rate–frequency curve are shown in Figure 2 and Table 1. As can be seen, TER produced a dose-dependent increase in threshold
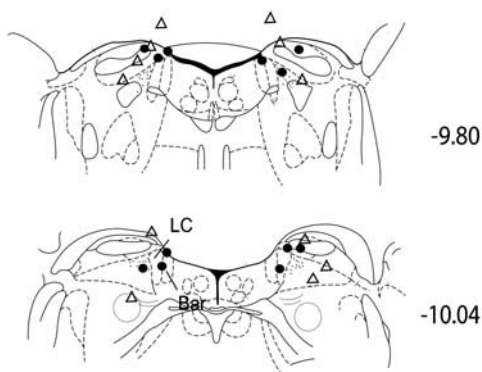
frequency and a dose-dependent reduction in maximum response rate both of which were significant at the 10 nmol dose (Table 1). At this dose the changes amounted to a shift of 0.08 log units for the threshold and a drop of 16.5% for the maximum rate. No effect on the slopes of the curve was found. The effect of addition of the α_1-agonist, PE at 10 nmol to TER 10 nmol is shown in Figure 3. As can be seen the agonist totally reversed both effects of 10 nmol TER and produced a small leftward shift in the curve. Infusing PE, 10 nmol, by itself had no effect on any parameter (Figure 4). The effect of infusion of the α_2-antagonist, ATI, 1 nmol, are shown in Figure 5. This procedure also had no effect on the threshold, maximum rate or slope of the curve. The effects of Infusion of 10 nmol of TER at a distance of 0.3–0.5 mm from the LC are shown in Figure 6. At this distance, TER failed to significantly alter the threshold and but continued to produce a reduction in the maximum response rate.

DISCUSSION

The results support the hypothesis that α_1-adrenoceptors in the LC are involved in the rewarding or motivational effects of MFB stimulation. Injection of an α_1-antagonist near or within the LC produced a significant and dose-dependent rightward shift in the rate–frequency curve for MFB stimulation. As noted above, rightward shifts in this curve have been shown to reflect reductions in reward efficacy or motivation. That this effect of TER is due to its α_1-antagonism and not to some nonspecific effect was shown
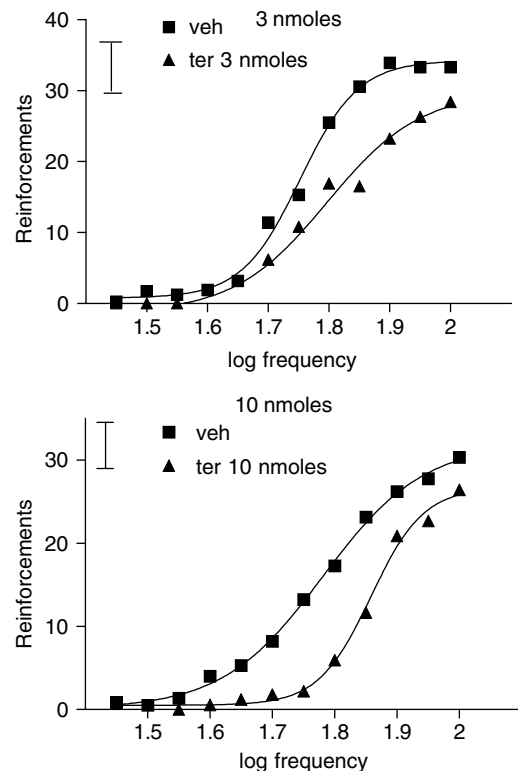

Figure 1 Schematic of rat LC showing locations of cannula tips of animal used in experiments. The solid circles represent the six rats of the TER 10 nmol group, which included animals having at least one cannula within 0.2 mm of the LC core. These rats are representative of the other groups used with the exception of the TER 10 OUT group which included animals having both cannulas at least 0.3 mm distant from the LC and which are represented by the open triangles. Figures are modifications of those in Paxinos and Watson (1986).


Figure 2 Effects of TER at 3 and 10 nmol on the rate–frequency curves for MFB self-stimulation. Points are the mean numbers of reinforcements for each frequency averaged across six rats for the 10 and 3 nmol doses and their respective saline curves. The average SEM is given by the bar on the left. Curves were generated by nonlinear regression.

Table 1 Effects of α-Adrenergic Drugs in LC on MFB Self-Stimulation Rate–Frequency Curve Parameters

	Log$_{10}$ threshold	Maximum response	Hill slope
Saline	1.75 (1.74–1.77)	34.25 (32.18–36.32)	9.06 (6.56–11.55)
TER 3	1.80 (1.75–1.84)	29.87 (22.98–36.75)	5.67 (2.46–8.87)
Saline	1.78 (1.77–1.80)	31.96 (29.71–34.21)	5.39 (4.36–6.42)
TER 10	1.86 (1.84–1.87)*	26.68 (24.23–29.12)*	10.31 (7.47–13.15)
Saline	1.80 (1.76–1.84)	40.56 (32.51–48.61)	5.87 (2.93–8.82)
PE 10	1.81 (1.76–1.85)	40.24 (31.30–49.18)	7.69 (2.37–13.00)
Saline	1.82 (1.80–1.83)	36.82 (33.66–39.97)	9.20 (6.49–11.92)
TER 10+PE 10	1.77 (1.76–1.79)*	34.30 (31.84–36.76)	10.17 (6.88–13.46)
Saline	1.74 (1.71–1.76)	35.91 (32.26–39.55)	8.26 (4.27–12.25)
ATI 1	1.74 (1.71–1.77)	35.42 (31.69–39.16)	12.32 (3.99–20.65)
Saline	1.73 (1.72–1.73)	34.17 (33.33–35.01)	12.78 (9.89–15.66)
TER 10 OUT	1.74 (1.73–1.75)	29.00 (27.71–30.30)*	17.26 (11.44–23.08)

Values are derived from nonlinear regression of curves in Figures 2–5. Parameters are shown with 95% confidence intervals.
*$p < 0.05$ compared to corresponding saline group.
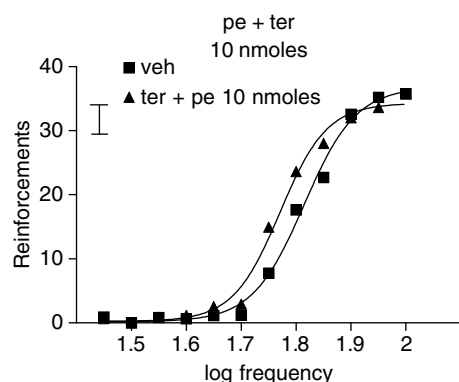
Figure 3 Reversal of effects of TER 10 nmol on rate–frequency curve by addition of the α₁-agonist, PE, 10 nmol. For details see legend to Figure 2. $N = 6$.
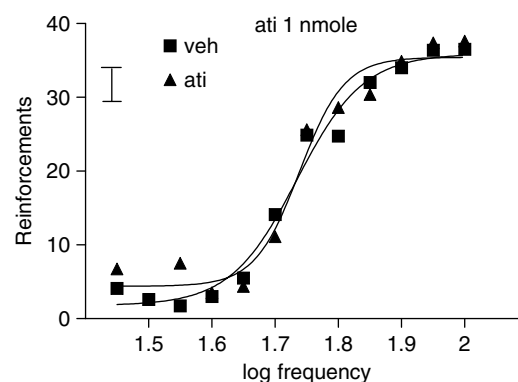
Figure 5 Lack of effect of α₂-antagonist, ATI 1 nmol, on rate–frequency curve. For details see legend to Figure 2. $N = 6$.
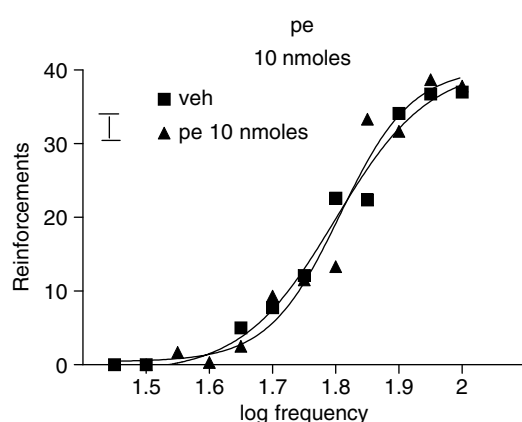
Figure 4 Lack of effect of PE, 10 nmol, alone on rate–frequency curve. $N = 6$.
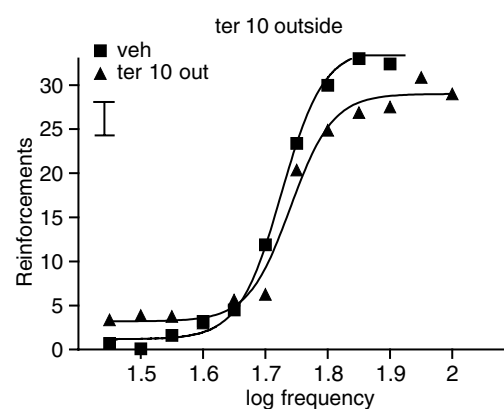
Figure 6 Reduction of effects of TER 10 nmol on rate–frequency curve by displacement of injection site to 0.3–0.6 mm from LC core. $N = 6$.

by the fact that the α₁-agonist, PE, completely abolished the shift. PE by itself had no effect on the dose–response curve suggesting that the receptors are being maximally stimulated at these frequencies of brain stimulation in the absence of the antagonist. Furthermore, an effect of TER on

α₂-adrenoceptors can be excluded since the selective α₂-antagonist, ATI, also had no effect on the position of the curve when given at a dose comparable to the lower affinity of TER for α₂-receptors. We have shown that the dose of ATI used (1 nmol) is sufficient to locally

block α_2-receptors in the mouse and rat brainstem judging from its ability to reverse α_2-receptor-induced behavioral inactivity (Stone et al, 2005).

That the effect of TER on the threshold frequency was due to its action on the LC and not some neighboring nucleus is supported by the fact that the infusion of the drug some distance away from the LC (0.3 mm or greater) greatly attenuated its effects. This is consistent with the fact that the LC possesses the greatest concentration of α_1-receptors by far in the rodent dorsal pons (Jones et al, 1985; Stone et al, 2004a). However, this does not mean that α_1-receptors in other brain regions are not involved in positive reinforcement; in fact, α_1-agonists injected in the rostral ventrolateral medulla have been found to support CPP (Hirakawa et al, 2000).

In addition to its action on threshold frequency, TER injection also significantly reduced the maximum rate of responding by 16%. This effect occurred with cannulas in as well as outside of the area of the LC, which indicates that it may not be an effect specific to the LC, or that maximum rate is more sensitive to α_1-receptor blockade than threshold frequency. As noted above, maximum response rate has been shown to be most closely associated with response capacity. This suggests that LC or neighboring α_1-receptors may also be involved in nonreward related motor functions or motor coordination. This is in agreement with recent findings that LC neuronal activity is highly correlated with operant response execution in positively motivated tasks (Clayton et al, 2004; Bouret and Sara, 2005). The behavioral activation found in previous studies after stimulation of LC α_1-receptors may therefore be due to a combination of both motivational and motor effects. A close association between these two functions is not an unexpected since, if an organism experiences reward or enhanced motivation, it may then increase motor function in an attempt to maximize reward. Therefore, the close integration of these systems may facilitate goal attainment.

The neuronal mechanism by which α_1-receptors in the LC affect the rewarding effects of MFB stimulation are not presently known. α_1-Receptors, which are known to excite neurons in most other brain regions (Nicoll et al, 1990), are believed to excite LC neurons as well based on the findings that pharmacological blockade of α_1-receptors either in brain slices from adult rats (Ivanov and Aston-Jones, 1995) or in vivo in awake dogs (Wu et al, 1999) significantly reduces resting LC unit firing rate by approximately 50%. α_1-Agonists also produce attenuation of α_2-adrenoceptor-induced hyperpolarization and GIRK-induced conductance in LC neurons in brain slices (Osborne et al, 2002). α_1-Receptors in the LC appear to be located in part on its noradrenergic neurons (Osborne et al, 2002), and in part on other structures (Chamba et al, 1991), including potentially glutamatergic (Marek and Aghajanian, 1999; Gordon and Bains, 2003; Boudaba et al, 2003), adrenergic (Pudovkina and Westerink, 2005) and dopaminergic nerve endings (Auclair et al, 2002).

The LC excitatory effect of α_1-agonist stimulation may therefore be due to a direct postsynaptic action at its receptors and/or a potentiation of the presynaptic release or postsynaptic action of glutamate as these mechanisms have been observed in other brain regions (Gordon and Bains, 2003; Marek and Aghajanian, 1999; Boudaba et al, 2003;

Ivanov and Aston-Jones, 1995). α_1-Agonists also may prime glutamate release for several hours after stimulation by activation of protein kinase C (Gordon and Bains, 2003). It should be noted that in previous work by others, epinephrine (EPI) and norepinephrine (NE) were reported to depress LC neuron firing rate via α_2-adrenoceptors. However, this was observed only under conditions that reduce basal glutamatergic neurotransmission including anesthesia (Cedarbaum and Aghajanian, 1976), anesthesia plus an NMDA receptor blocker (Aston-Jones et al, 1992), and brain slice preparations (Williams et al, 1988). However, if glutamate and EPI were released together in the LC of anesthetized rats by electrical or chemical stimulation of the C1/paragigantocellularis nucleus, the source of both LC glutamatergic and adrenergic nerve endings (Ennis et al, 1992; Pieribone and Aston-Jones, 1991), a very marked increase in LC firing rate was observed (Ennis et al, 1992; Ennis and Aston-Jones, 1988). The role of EPI stimulation of α_1-receptors in this excitation has not yet been established however.

An enhanced LC firing rate has been shown to potentiate dopaminergic neurotransmission in the ventral tegmental area (VTA)—nucleus accumbens circuit via α_1-adrenoceptors in the VTA and accumbens (Grenhoff et al, 1993; Eshel et al, 1990). VTA neurons are also excited by MFB self-stimulation via cholinergic fibers arising in the laterodorsal and pedunculopontine tegmentum (Yeomans et al, 1993; Yeomans and Baptista, 1997). Thus, projections from the LC and pedunculopontine tegmentum might summate or synergize at the VTA to enhance self stimulation from the lateral hypothalamus.

Previous studies have shown that self-stimulation of the MFB also markedly increased fos expression in the LC (Hunt and McGregor, 1998). Although, the neuronal mechanism of this effect is not known, it possibly results from retrograde activation via the dorsal noradrenergic bundle, which travels in the MFB in the lateral hypothalamus. LC activation may also result from stimulation of the VTA by the above pathway (Deutch et al, 1986). The fact that neural activity in the LC was elevated during MFB self-stimulation may have facilitated detection of an inhibitory effect of blockade of α_1-receptors in the present study.

The present results provide further support for the notion that the LC is involved in positive motivational processes. This is of interest because a number of antidepressant drugs that act via noradrenergic mechanisms may be particularly effective in restoring positive motivation to depressives (Tse and Bond, 2002; Rampello et al, 2004). However, the LC is also known to be one of the primary stress-responsive nuclei of the CNS, and it is not obvious how stress and reward functions coexist in the same nucleus. In this regard, it has been proposed that at high rates of LC neuron firing, which occur primarily during stressful stimulation, noradrenergic neurons may release galanin, a peptide cotransmitter of NE that has potent neuronal hyperpolarizing and depressing behavioral actions (Weiss et al, 2005; Ericson and Ahlenius, 1999). This is consistent with the findings that cytokines, which are released during severe stress (Nguyen et al, 1998) excite LC neurons (Borsody and Weiss, 2005) but appear to inhibit excitatory noradrenergic transmission at postsynaptic targets (De Sarro et al, 1990; Stone et al, 2006). However, as noted above, the LC shows

marked neuronal activation during MFB self stimulation, which entails heightened positively motivated behavior. Clearly, therefore, more research will be necessary to clarify how the LC functions differentially in positive motivational as opposed to stressful states.

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