

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

Yan Lin¹, Soledad Cabeza de Vaca¹, Kenneth D Carr¹ and Eric A Stone*¹

¹Department of Psychiatry, New York University School of Medicine, New York University Medical Center, New York, NY, USA

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.

Neuropsychopharmacology (2007) **32**, 835–841. doi:10.1038/sj.npp.1301145; published online 5 July 2006

Keywords: α_1 -adrenoceptors; locus coeruleus; reward; self-stimulation; medial forebrain bundle

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

*Correspondence: Dr EA Stone, Department of Psychiatry, New York University School of Medicine, New York University Medical Center, MHL HN510, 550 First Ave., New York, NY 10016, USA, Tel: +1 212 263 5740, Fax: +1 212 263 0712, E-mail: eric.stone@nyu.edu
Received 10 November 2005; revised 16 May 2006; accepted 25 May 2006

Online publication: 31 May 2006 at <http://www.acnp.org/citations/Npp053106050673/default.pdf>

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; Miliareisis *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 ($26 \times 26 \times 21$ 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 μ l 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

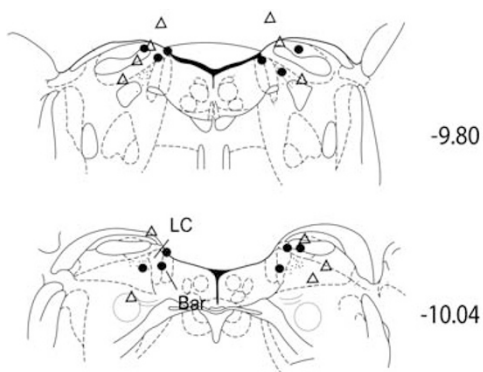


Figure 1 Schematic of rat LC showing locations of cannula tips of animal used in experiments. The solid circles represent the six rats of the TER 10 nmol group, which included animals having at least one cannula within 0.2 mm of the LC core. These rats are representative of the other groups used with 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).

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

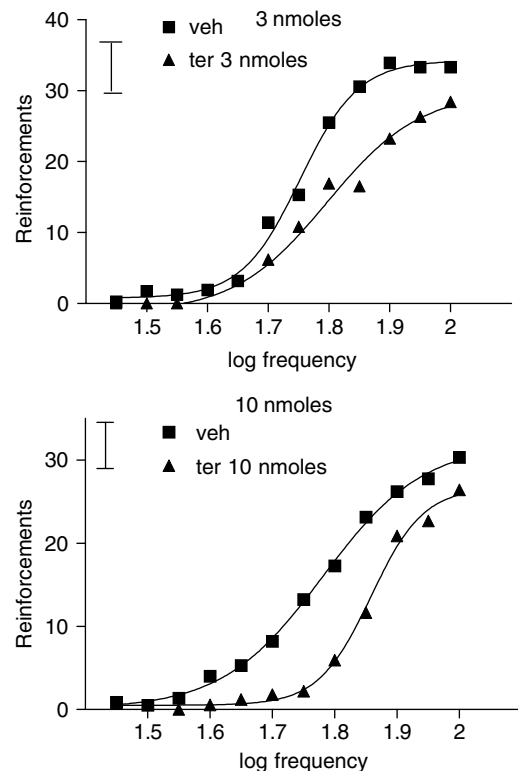


Figure 2 Effects of TER at 3 and 10 nmol on the rate–frequency curves for MFB self-stimulation. Points are the mean numbers of reinforcements for each frequency averaged across six rats for the 10 and 3 nmol doses and their respective saline curves. The average SEM is given by the bar on the left. Curves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

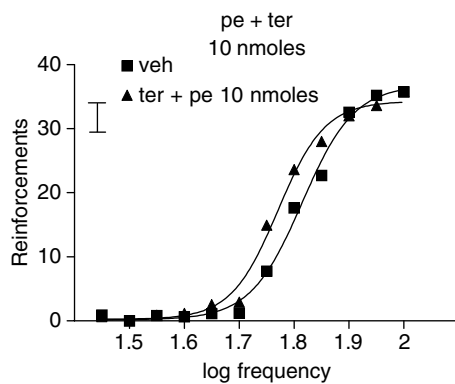


Figure 3 Reversal of effects of TER 10 nmol on rate–frequency curve by addition of the α_1 -agonist, PE, 10 nmol. For details see legend to Figure 2. $N = 6$.

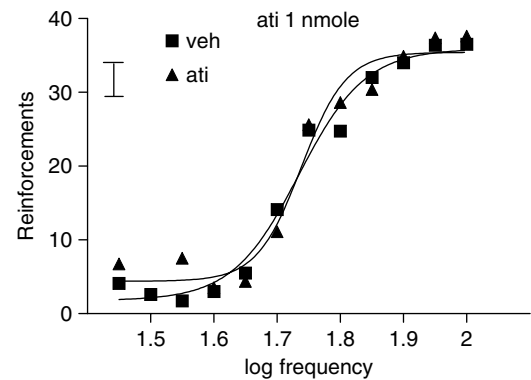


Figure 5 Lack of effect of α_2 -antagonist, ATI 1 nmol, on rate–frequency curve. For details see legend to Figure 2. $N = 6$.

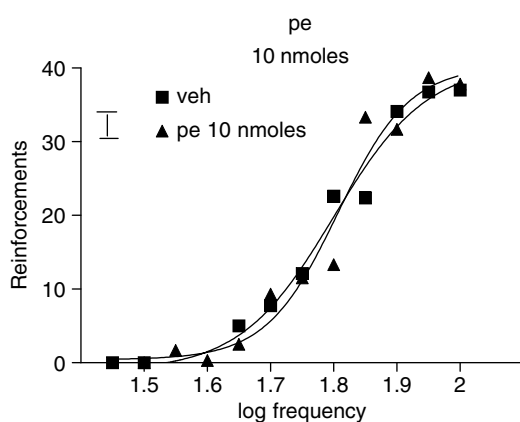


Figure 4 Lack of effect of PE, 10 nmol, alone on rate–frequency curve. $N = 6$.

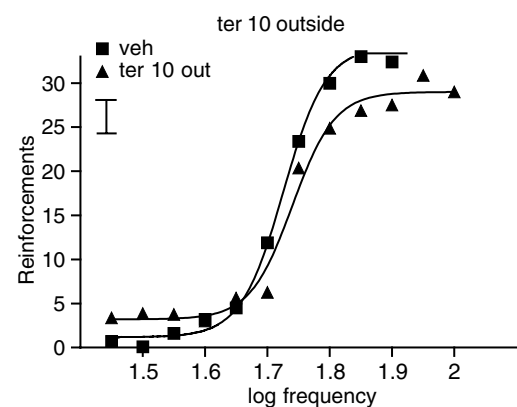


Figure 6 Reduction of effects of TER 10 nmol on rate–frequency curve by displacement of injection site to 0.3–0.6 mm from LC core. $N = 6$.

by the fact that the α_1 -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

α_2 -adrenoceptors can be excluded since the selective α_2 -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 α_2 -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 pedunclopontine tegmentum (Yeomans *et al*, 1993; Yeomans and Baptista, 1997). Thus, projections from the LC and pedunclopontine 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.

ACKNOWLEDGEMENTS

We wish to thank Dr Robert Cancro, Chair of Department of Psychiatry, for his help and encouragement that were essential to these studies. Supported in part by grants MH45265 (EAS), K02 DA00292 (KDC) and Bridging Fund from New York University Medical Center.

REFERENCES

- Aston-Jones G, Astier B, Ennis M (1992). Inhibition of noradrenergic locus coeruleus neurons by C1 adrenergic cells in the rostral ventral medulla. *Neuroscience* **48**: 371–381.
- Auclair A, Cotecchia S, Glowinski J, Tassin JP (2002). D-amphetamine fails to increase extracellular dopamine levels in mice lacking alpha 1b-adrenergic receptors: relationship between functional and nonfunctional dopamine release. *J Neurosci* **22**: 9150–9154.
- Borsody MK, Weiss JM (2005). The subdiaphragmatic vagus nerves mediate activation of locus coeruleus neurons by peripherally administered microbial substances. *Neuroscience* **131**: 235–245.
- Boudaba C, Di S, Tasker JG (2003). Presynaptic noradrenergic regulation of glutamate inputs to hypothalamic magnocellular neurones. *J Neuroendocrinol* **15**: 803–810.
- Bouret S, Sara SJ (2005). Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci* **28**: 574–582.
- Cedarbaum JM, Aghajanian G (1976). Noradrenergic neurons of the locus coeruleus: inhibition by epinephrine and activation by the α -antagonist piperoxane. *Brain Res* **112**: 413–419.
- Chamba G, Weissmann D, Rousset C, Renaud B, Pujol JF (1991). Distribution of alpha-1 and alpha-2 binding sites in the rat locus coeruleus. *Brain Res Bull* **26**: 185–193.
- Clayton EC, Rajkowski J, Cohen JD, Aston-Jones G (2004). Phasic activation of monkey locus coeruleus neurons by simple decisions in a forced-choice task. *J Neurosci* **24**: 9914–9920.
- De Sarro G, Masuda Y, Ascioff C, Audino M, Nistico G (1990). Behavioural and ECoG spectrum changes induced by intracerebral infusion of interferons and interleukin 3 in rats are antagonized by naloxone. *Neuropharmacology* **29**: 167–179.
- De Sarro GB, Ascioff C, Froio F, Libri V, Nistico G (1987). Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha-1 and alpha-2-adrenoceptors affect sleep and arousal mechanisms. *Brit J Pharmacol* **90**: 675–685.
- Deutch A, Goldstein M, Roth R (1986). Activation of the locus coeruleus induced by selective stimulation of the ventral tegmental area. *Brain Res* **363**: 307–314.
- Drouin C, Darracq L, Trovero F, Blanc G, Glowinski J, Cotecchia S et al (2002). 1b-Adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. *J Neurosci* **22**: 2873–2884.
- Duteil J, Rambert FA, Pessonier J, Hermant J-F, Gombert R, Assous E (1990). Central α_1 -adrenergic stimulation in relation to the behaviour stimulating effect of modafinil; studies with experimental animals. *Eur J Pharmacol* **180**: 49–58.
- Edmonds D, Gallistel C (1974). Parametric analysis of brain stimulation reward in the rat. *J comp physiol Psychol* **87**: 876–883.
- Ennis M, Aston-Jones G (1988). Activation of locus coeruleus from nucleus paragigantocellularis: a new excitatory amino acid pathway in brain. *J Neurosci* **8**: 3644–3657.
- Ennis M, Aston-Jones G, Shiekhattar R (1992). Activation of locus coeruleus neurons by nucleus paragigantocellularis or noxious sensory stimulation is mediated by intracoeular excitatory amino acid neurotransmission. *Brain Res* **598**: 185–195.
- Ericson E, Ahlenius S (1999). Suggestive evidence for inhibitory effects of galanin on mesolimbic dopaminergic neurotransmission. *Brain Res* **822**: 200–209.
- Eshel G, Ross SB, Kelder D, Edis LE, Jackson DM (1990). α_1 (but not α_2)-adrenoreceptor agonists in combination with the dopamine D2 agonist quinpirole produce locomotor stimulation in dopamine-depleted mice. *Pharmacol Toxicol* **67**: 123–131.
- Fenton H, Liebman J (1982). Self-stimulation response decrement patterns differentiate clonidine, baclofen and dopamine antagonists from drugs causing performance deficit. *Pharmacol Biochem Behav* **17**: 1207–1212.
- Gordon GRJ, Bains JS (2003). Priming of excitatory synapses by α_1 adrenoceptor-mediated inhibition of group III metabotropic glutamate receptors. *J Neurosci* **23**: 6223–6231.
- Grenhoff J, Nisell M, Ferre S, Aston-Jones G, Svensson TH (1993). Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat. *J Neural Transm* **93**: 11–25.
- Hancock AA, Buckner SA, Ireland LM, Knepper SM, Kerwin Jr JF (1995). Actions of terazosin and its enantiomers at subtypes of alpha 1- and alpha 2-adrenoceptors *in vitro*. *J Recept Signal Transduct Res* **15**: 863–885.
- Hirakawa N, Tershner SA, Fields HL, Manning BH (2000). Bi-directional changes in affective state elicited by manipulation of medullary pain-modulatory circuitry. *Neuroscience* **100**: 861–871.
- Hunt GE, Atrens DM, Chesher GB, Becker FT (1976). Alpha-noradrenergic modulation of hypothalamic self-stimulation: studies employing clonidine, 1-phenylephrine and alpha-methyl-p-tyrosine. *Eur J Pharmacol* **37**: 105–111.
- Hunt GE, McGregor IS (1998). Rewarding brain stimulation induces only sparse Fos-like immunoreactivity in dopaminergic neurons. *Neuroscience* **83**: 501–515.
- Ivanov A, Aston-Jones G (1995). Extranuclear dendrites of locus coeruleus neurons: activation by glutamate and modulation of activity by alpha adrenoceptors. *J Neurophysiol* **74**: 2427–2436.
- Jones LS, Gauger LL, Davis JN (1985). Anatomy of brain alpha-1 adrenergic receptors: *in vitro* autoradiography with [¹²⁵I]-heat. *J Comp Neurol* **231**: 190–208.
- Liebman J, Hall N, Prowse J (1982). Effect of various catecholamine receptor antagonists, muscle relaxation and physical hindrance on shuttlebox self-stimulation. *Pharmacol Biochem Behav* **16**: 785–790.
- Marek G, Aghajanian G (1999). 5-HT_{2A} receptor or α_1 -adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. *Eur J Pharmacol* **367**: 197–206.
- Mejias-Aponte C, Zhu Y, Aston-Jones G (2004). Noradrenergic innervation of midbrain dopamine neurons: prominent inputs from A1 and A2 cell groups. *Abstract Viewer/Itinerary Planner*. Society for Neuroscience: Washington, DC. Program No. 465.4.
- Miliaressis E, Rompre P, Laviolette P, Philippe L, Coulombe D (1986). The curve-shift paradigm in self-stimulation. *Physiol Behav* **37**: 85–91.
- Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR et al (1998). Exposure to acute stress induces brain interleukin-1 β protein in the rat. *J Neurosci* **18**: 2239–2246.
- Nicoll RA, Malenka RC, Kauer JA (1990). Functional comparison of neurotransmitter receptor subtypes in mammalian central nervous system. *Physiol Rev* **70**: 513–565.

- Osborne PB, Vidovic M, Chieng B, Hill CE, Christie MJ (2002). Expression of mRNA and functional alpha(1)-adrenoceptors that suppress the GIRK conductance in adult rat locus coeruleus neurons. *Brit J Pharmacol* 135: 226–232.
- Paxinos G, Watson C (1986). *The Rat Brain in Stereotaxic Coordinates*. Academic Press: Sydney.
- Pieribone VA, Aston-Jones G (1991). Adrenergic innervation of the rat nucleus locus coeruleus arises predominately from the c1 adrenergic cell group in the rostral medulla. *Neuroscience* 41: 525–542.
- Pudovkina OL, Westerink BHC (2005). Functional role of alpha1-adrenoceptors in the locus coeruleus: A microdialysis study. *Brain Res* 1061: 50–56.
- Rampello L, Chiechio S, Nicoletti G, Alvano A, Vecchio I, Raffaele R et al (2004). Prediction of the response to citalopram and reboxetine in post-stroke depressed patients. *Psychopharmacology* 173: 73–78.
- Sahraei H, Ghazzaghi H, Zarrindast MR, Ghoshooni H, Sepehri H, Haeri-Rohan A (2004). The role of alpha-adrenoceptor mechanism(s) in morphine-induced conditioned place preference in female mice. *Pharm Biochem Behav* 78: 135–141.
- Stone E, Cotecchia S, Lin Y, Quartermain D (2002). Role of brain α_{1B} -adrenoceptors in modafinil-induced behavioral activity. *Synapse* 46: 269–270.
- Stone E, Lehmann M, Lin Y, Quartermain D (2006). Depressive behavior in mice due to immune stimulation is accompanied by reduced neural activity in brain regions involved in positively motivated behavior. *Biol Psychiatry*, in press.
- Stone E, Lin Y, Ahsan M, Quartermain D (2004a). α_1 -Adrenoceptors in the Locus Coeruleus Stimulate Gross Behavioral Activity Abstract Viewer/Itinerary Planner. Society for Neuroscience: Washington, DC. Program No.: 954.6-00.
- Stone E, Lin Y, Ahsan M, Quartermain D (2005). 1 and α_2 -adrenergic balance in the dorsal pons and gross behavioral activity of mice in a novel environment. *Psychopharmacology* 183: 127–132.
- Stone E, Lin Y, Ahsan R, Quartermain D (2004b). Role of locus coeruleus α_1 -adrenoceptors in motor activity in rats. *Synapse* 54: 164–172.
- Stone E, Quartermain D (1999). Alpha 1-noradrenergic neurotransmission, corticosterone and behavioral depression. *Biol Psychiatry* 46: 1287–1300.
- Stone E, Quartermain D (2005). Brain epinephrine-stimulated α_1 -adrenoceptor system in behavioral activation and depression. *Curr Psychiat Revs* 1: 33–43.
- Stone E, Rosengarten H, Lin Y, Quartermain D (2001). Pharmacological blockade of brain alpha 1-adrenoceptors as measured by *ex vivo* [3 H]prazosin binding is correlated with behavioral immobility. *Eur J Pharmacol* 420: 97–102.
- Stone E, Zhang Y, Rosengarten H, Yeretsian J, Quartermain D (1999). Brain α_1 -adrenergic neurotransmission is necessary for behavioral activation to environmental change in mice. *Neuroscience* 94: 1245–1252.
- Tse WS, Bond AJ (2002). Difference in serotonergic and noradrenergic regulation of human social behaviours. *Psychopharmacology* 159: 216–221.
- Umemoto M, Olds M (1981). Presynaptic alpha-adrenergic mediation of self-stimulation in locus coeruleus in rats treated neonatally with 6-hydroxydopamine. *Brain Res* 219: 107–119.
- Weiss JM, Boss-Williams KA, Moore JP, Demetrikopoulos MK, Ritchie JC, West CHK (2005). Testing the hypothesis that locus coeruleus hyperactivity produces depression-related changes via galanin. *Neuropeptides* 39: 281–287.
- Williams J, Surprenant A, North R (1988). Adrenergic neuron electrophysiology and behavior. In: Stolk JM, U'Prichard, DC, Fuxe K (eds). *Epinephrine in the Central Nervous System*. Oxford: New York. pp 252–257.
- Wu MF, Gulyani SA, Yau E, Mignot E, Phan B, Siegel JM (1999). Locus coeruleus neurons: cessation of activity during cataplexy. *Neuroscience* 91: 1389–1399.
- Yadin E, Guarini V, Gallistel CR (1983). Unilaterally activated systems in rats self-stimulating at sites in the medial forebrain bundle, medial prefrontal cortex, or locus coeruleus. *Brain Res* 266: 39–50.
- Yeomans J, Baptista M (1997). Both nicotinic and muscarinic receptors in ventral tegmental area contribute to brain-stimulation reward. *Pharmacol Biochem Behav* 57: 915–921.
- Yeomans JS, Mathur A, Tampakeras M (1993). Rewarding brain stimulation: role of tegmental cholinergic neurons that activate dopamine neurons. *Behav Neurosci* 107: 1077–1087.
- Zhang XY, Kosten TA (2005). Prazosin, an α_1 adrenergic antagonist, reduces cocaine-induced reinstatement of drug-seeking. *Biol Psychiatry* 57: 1202–1204.