Neuroscience Vol. 7, No. 9, pp. 2217 to 2224, 1982
Printed in Great Britain

0306-4522/82/092217-08$03.00/0
Pergamon Press Ltd

CHANGES IN NORADRENERGIC TERMINAL EXCITABILITY INDUCED BY AMPHETAMINE AND THEIR RELATION TO IMPULSE TRAFFIC

S. NAKAMURA,* J. M. TEPPER, S. J. YOUNG and P. M. GROVES
Department of Psychiatry, University of California, San Diego School of Medicine (M-003), La Jolla, CA 92093, U.S.A.

Abstract—The effects of amphetamine upon the terminal excitability of noradrenergic neurons of the nucleus locus coeruleus were studied in urethane anesthetized rats. Terminal excitability was measured by determining the stimulus currents necessary to evoke antidromic responses in locus coeruleus neurons from terminals in the frontal cortex. In most cases, terminal excitability was decreased following local infusion of amphetamine into the frontal cortex, while intravenous administration of the drug tended to increase terminal excitability. The decreased terminal excitability induced by local infusion of amphetamine appeared to be due to activation of alpha-adrenergic receptors located on the terminals of locus coeruleus neurons, since this effect mimics that of clonidine, a direct acting alpha-adrenergic agonist, and since the effect was abolished by pretreatment with alpha-methyl-*p*-tyrosine which disrupts the catecholamine liberating properties of amphetamine. Phentolamine, a direct acting alpha-adrenergic receptor antagonist was also found to block or reverse the effect of amphetamine. The changes in terminal excitability following intravenous injection of amphetamine appeared to be related to changes in the spontaneous activity of locus coeruleus neurons. A large decrease in spontaneous activity following intravenous administration of amphetamine was associated with increased terminal excitability, whereas when smaller changes in spontaneous activity occurred, terminal excitability was found to be decreased.

These results are discussed with respect to the pharmacological properties of catecholaminergic neurons and the mechanisms of action of amphetamine.

Activation of presynaptic receptors on the terminals of catecholaminergic neurons is thought to be important in the regulation of neurotransmitter biosynthesis and release.[9,10,22,23,30,34] In two recent series of experiments, we have obtained evidence suggesting that activation of presynaptic receptors located on the terminals of catecholaminergic neurons also produces changes in the polarization and/or ionic conductance of the axonal terminal membranes of both noradrenergic[28] and dopaminergic[13] neurons. Thus, intravenous administration of amphetamine, which promotes the extracellular accumulation of dopamine,[33] typically produced a decrease in the excitability of axon terminals of nigro-striatal dopaminergic neurons, as determined by changes in the current necessary to activate the cells antidromically.[13]

The terminal excitability of central noradrenergic neurons of the locus coeruleus was shown to be modified by adrenergic drugs. Local infusion of the alpha-agonist, clonidine, into the frontal cortical terminal fields of locus coeruleus neurons decreased the terminal excitability of these neurons, whereas infusion of the alpha-antagonist, phentolamine, was capable of blocking or reversing the effects of clonidine. Terminal excitability was not affected by a beta-agonist, isoproterenol, but was decreased by a beta-antagonist, propranolol. These results were interpreted to suggest that changes in polarization or conductance affecting terminal excitability could be linked to activation of presynaptic autoreceptors.[27,28]

The present experiment was focused on the effects of amphetamine on the terminal excitability of locus coeruleus neurons. Amphetamine was expected to alter the terminal excitability of locus coeruleus neurons, since amphetamine has been shown to affect the release and re-uptake of catecholamines.[2,3,4,7,11,19,20,29,33,35] Available evidence suggests that the effects of amphetamine on catecholamine release may be partly dependent on impulse activity of the catecholaminergic neurons; ongoing impulse activity of dopaminergic neurons greatly enhances catecholamine release caused by amphetamine, compared to conditions where there is no impulse activity.[33] Thus, changes in terminal excitability caused by amphetamine may also depend on the level of impulse activity of locus coeruleus neurons. To explore this possibility, the effects of the intravenous administration of amphetamine, which at low doses may affect not only the terminal field of locus coeruleus neurons but also the somadendritic membranes resulting in suppression of spontaneous discharges,[8,12,15] were compared to those resulting from the infusion of amphetamine into the frontal cortical terminal fields of locus coeruleus neurons, a procedure which does not alter spontaneous firing rate.

* Present Address: Department of Neurophysiology, Institute of Higher Nervous Activity, Osaka University Medical School, Osaka 530, Japan.

EXPERIMENTAL PROCEDURES

Fifty-two male Sprague-Dawley rats weighing between 250–450 g were anesthetized with urethane (1.3 g/kg, i.p.) and a tracheal intubation performed for the purpose of subsequent artificial ventilation. The left femoral vein was catheterized for the intravenous administration of amphetamine and the rat was placed in a stereotaxic apparatus utilizing blunt, atraumatic ear bars coated with 5% lidocaine ointment (Kopf Instruments). Body temperature was maintained at 37 ± 1°C by a heating pad electronically coupled to a Yellow Springs telethermometer. The electrocardiogram was monitored continuously on an auxillary oscilloscope. Following a subcutaneous injection of lidocaine (2% Xylocaine), the calvarium was exposed and a small hole drilled for the insertion of a bipolar stimulating electrode into the dorsal noradrenergic pathway. The coordinates of this stimulating electrode were 2.0 mm anterior to lambda, 0.8 mm lateral to the midline and 5.9–6.0 mm ventral to the cortical surface. The electrode was affixed to the skull with cyanoacrylate glue and dental cement. For stimulation and infusion of the frontal cortex ipsilateral to the recording site, a hole was drilled at coordinates 3.0 mm anterior to bregma and 2.5 mm lateral to the midline. For recording from the locus coeruleus, a large hole was made at coordinates of 2.0 mm posterior to lambda and 1.0 mm lateral to the midline and the transverse sinus was ligated as previously described.[28]

Bipolar electrodes of insulated stainless steel wire with exposed tips approximately 0.5 mm apart were used for electrical stimulation of both the dorsal noradrenergic pathway and the frontal cortex. Electrical stimuli to frontal cortex were delivered at a rate of 1 Hz with a pulse width of 0.5–2.0 ms and at currents ranging from 0.1–2.0 mA.

Animals were immobilized with gallamine triethiodide (Flaxedil, 50 mg/kg, i.p.) and artificially respired on a Harvard Apparatus Rodent respirator at 80–90 strokes/min. Single unit discharges of locus coeruleus neurons were recorded extracellularly with glass micropipettes filled with 3M KCl or 3M NaCl with impedances of from 6–12 Megohms. Single unit activity was amplified by a Grass preamplifier (Model P-15C), displayed on a Tektronix 565 oscilloscope and simultaneously recorded on magnetic tape for later analysis. As described previously, the location of the locus coeruleus was determined by the appearance of an extracellularly recorded antidromically-evoked field potential from dorsal pathway stimulation. Single unit antidromic discharges of locus coeruleus neurons in response to dorsal pathway stimulation were found to be superimposed upon the field response.[25,26] Locus coeruleus neurons exhibited a relatively low rate of spontaneous firing (0.5–8 spikes/s) and a long duration action potential (2–5 ms).

Responses elicited by electrical stimulation of the dorsal pathway and frontal cortex were considered to be antidromic in nature provided that they were extinguished following collision with spontaneously occurring action potentials. In both the frontal cortex and dorsal pathway, the antidromic threshold was defined as the minimum current sufficient to elicit an antidromic response on 100% of the non-collision trials. In addition, the proportion of antidromic response to several lower currents was determined.

d-Amphetamine sulfate (*dextro*-amphetamine sulfate, Smith, Klein & French) was administered either intravenously or by local infusion into the frontal cortex. The doses ranged from 0.25–1.0 mg/kg in a volume of 0.9% saline corresponding to 1.0 ml/kg for intravenous injection, and 5 μM or 50 μM in 0.9% saline in a volume of 0.31 μl for local infusion. In some cases, phentolamine (Regitine HCl, Ciba-Geigy Corp.), 10 μM, was infused locally into the same site prior to the infusion of amphetamine. Clonidine (Catapres, Boehringer-Ingelheim) was administered intravenously at doses ranging from 0.02–0.08 mg/kg in 1.0 ml/kg of 0.9% saline. In some experiments a racemic mixture of alpha-methyl-*p*-tyrosine methyl ester (Sigma) was administered at a dose of 200 mg/kg i.p. in 2.0 ml/kg of 0.9% saline. For local infusion, drugs were delivered through 32 gauge cannulae situated approximately 50 μm from the exposed tips of a bipolar stimulating electrode. The cannulae plus the stimulating electrode were positioned in the frontal cortex at a depth of 1–1.5 mm. The drugs were infused by means of infusion pumps (Harvard Apparatus Co., Model No. 975) equipped with 10 μl Hamilton syringes at a speed of 0.0625 μl/min for 5 min. In some subjects the terminal fields of more than one cell were infused per animal. In these cases, the stimulating electrode and infusion cannulae were moved to a new site, at least 2.0 mm distant from the original site of stimulation and infusion. As described previously,[28] in control experiments utilizing two stimulating electrodes separated by 2.0 mm, it was found that whereas the thresholds obtained from the infusion site were reliably altered by the local infusion of noradrenergic agents, those obtained from the second stimulation site, 2.0 mm from the infusion site, remained unchanged.[28]

RESULTS

Amphetamine at concentrations of 5 μM or 50 μM was infused directly into the frontal cortical terminal fields of 32 locus coeruleus neurons. Amphetamine infusion was followed by a dose-related decrease in terminal excitability in 20 cells ($\bar{X}$ ± S.E.M. = 31.9% ± 6.1%), an increase in terminal excitability in 7 cells (27.8 ± 7.0%), and no effect (a change of less than 10%) in the remaining 5 cells, as summarized in Table 1. Figure 1 illustrates typical antidromic responses of locus coeruleus neurons to stimulation of the frontal cortex before and after the infusion of 50 μM amphetamine. Figure 1A shows a pre-drug, control antidromic action potential obtained at 0.36 mA, the threshold, or minimum current sufficient to elicit antidromic activation in 100% of the non-collision trials. Following the local infusion of amphetamine, no antidromic response is evoked even at a higher current of 0.54 mA, and the new threshold is 0.59 mA. These data are shown in Figs 1B and C, respectively. The decrease in antidromic excitability induced by local infusion of amphetamine was often accompanied by a slight increase in the antidromic response latency (0.5–1.0 ms), and in latency variability (Figs 1D and 1E).

The latency to the onset of drug effects from local infusion was, on the average, approximately 2 min from the start of the infusion, with the range extending from 1–4 min. Spontaneous firing rate and amplitude or waveform of action potentials of locus coeruleus neurons were not affected by local infusion of amphetamine. Changes in terminal excitability following local infusion of amphetamine were dose-related.

Table 1. The effects of amphetamine, amphetamine plus phentolamine, and amphetamine plus alpha-methyl-*p*-tyrosine upon terminal excitability of locus coeruleus neurons

	Local infusion				Intravenous injection
	Amphetamine		Phentolamine + Amphetamine	Alpha-methyl-*p*-tyrosine + Amphetamine	
Excitability	5 μM	50 μM	50 μM	50 μM	Amphetamine
Decreased	2 (12.0 $\pm$ 0.5)*	18 (36.2 $\pm$ 6.6)	0	0	2 (14.6 $\pm$ 2.1)
Increased	1 (10.5)	6 (30.7 $\pm$ 7.6)	1 (13.0)	0	12 (18.2 $\pm$ 1.5)
No Effect	3	2	4	5	0
Total	6	26	5	5	14

* The numbers in parentheses indicate mean percent change $\pm$ S.E.M. in terminal excitability. In phentolamine and amphetamine cases, local infusion of 10 μM phentolamine was followed by local infusion of amphetamine into the same site. In alpha-methyl-*p*-tyrosine plus amphetamine cases, 200 mg/kg alpha-methyl-*p*-tyrosine was administered i.p. 3–6 h prior to amphetamine infusion.

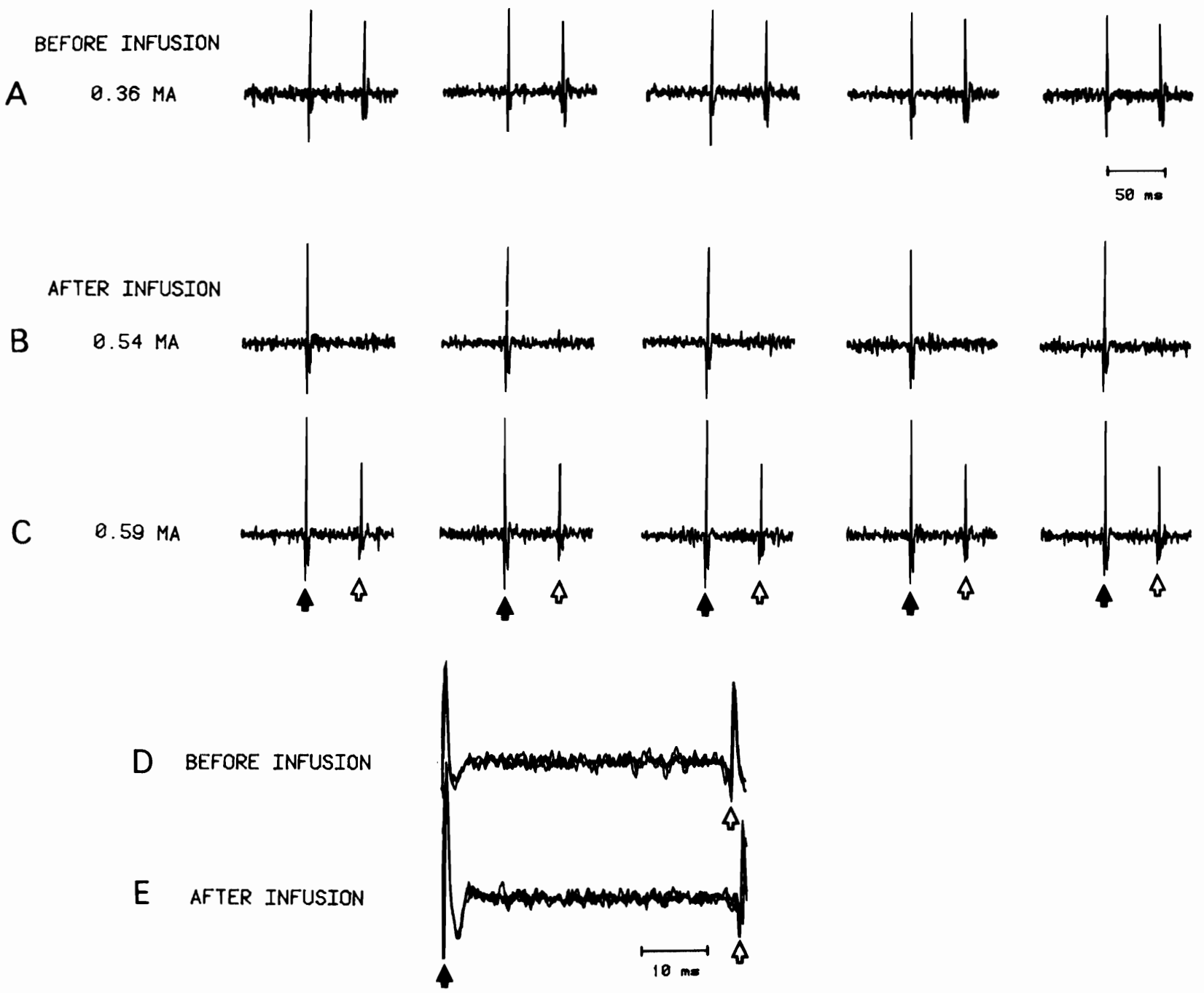

Fig. 1. Antidromic responses to electrical stimulation of the terminal field of a locus coeruleus neuron before (A) and after (B, C) local infusion of amphetamine into the frontal cortex. Before the infusion a stimulus current of 0.36 mA was sufficient to evoke 100% antidromic responses on non-collision trials (A), whereas after the infusion 0.54 mA was totally ineffective (B) and 0.59 mA was required to produce 100% activation (C). In D and E, the increased latency and variability of the antidromic response following the infusion are shown. Black arrows indicate the stimulus artifact and white arrows the antidromic responses.

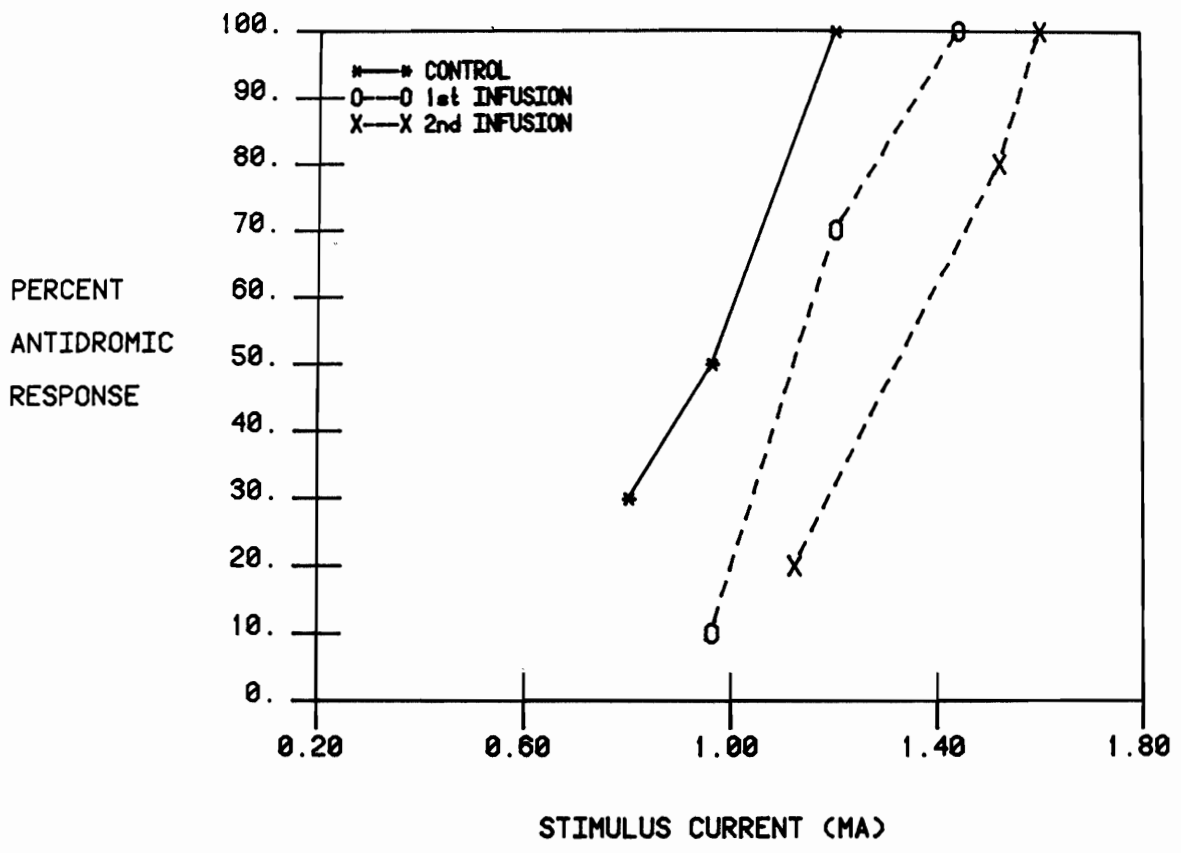

Fig. 2. Dose-related effects of local infusion of amphetamine into the frontal cortex upon the terminal excitability of a locus coeruleus neuron. Following the first infusion of 10 μM amphetamine the stimulus currents necessary to evoke antidromic responses increased (O), and further increases in current were necessary following an additional infusion of 10 μM amphetamine ($\times$).

In several cases where successive amphetamine infusions into a site were attempted, the second infusion consistently led to a further reduction in terminal excitability, as illustrated for one representative case in Fig. 2.

In the seven cases where amphetamine infusion led to an increase in terminal excitability, the increase in excitability was typically accompanied by a small decrease (0.5–1.0 ms) in the latency of antidromic response, and the variability in antidromic latency was seen to decrease slightly.

In five additional cases, rats were given an i.p. injection of 200 mg/kg of a racemic mixture of alpha-methyl-*p*-tyrosine methyl ester, a procedure that appears to block the amphetamine-induced release of dopamine from dopaminergic terminals in the neostriatum and presynaptic dendrites in the substantia nigra.[18,24] 0.50 μM amphetamine was infused into the frontal cortical terminal fields of five cells between 3 and 6 h after alpha-methyl-*p*-tyrosine administration. In all cases the typical effects of amphetamine infusion on terminal excitability were totally blocked, and the terminal excitability remained unchanged.

In five cases, the frontal cortex was pretreated with a 10 μM phentolamine infusion. Five min after the completion of the phentolamine infusion, the level of antidromic excitability was determined, 50 μM amphetamine was infused into the same site, and the level of antidromic excitability was re-established. As reported previously, phentolamine infusion resulted in an increase in terminal excitability.[28] In one of the five cases, 50 μM amphetamine caused a small increase (13%) in terminal excitability, while in the remaining four cases, amphetamine infusion had no effect on the level of antidromic excitability. In sharp contrast to the cases without phentolamine pretreatment, none of the amphetamine infusions resulted in a decrease in terminal excitability. In order to control for various non-specific effects of local drug infusion such as pressure or osmotic changes at the infusion site, local infusion of the vehicle (0.9% saline) was performed in eight cases as detailed previously.[28] Local infusion of the vehicle resulted in no change in terminal excitability in seven cases, and a small (10%), long-latency increase in terminal excitability in the remaining case.

A total of 14 animals received between 0.25 mg/kg and 1.0 mg/kg amphetamine i.v. As noted by previous authors,[8,12] 20–30 s following the injection the spontaneous firing rate of most locus coeruleus units recorded decreased dramatically. Eight of 14 cells showed a complete cessation of spontaneous activity and in the remaining six cases, spontaneous activity decreased between 13% and 65% relative to baseline values. Concomitantly, the amplitude of both the spontaneous and antidromically-activated action potentials increased by approximately 10–30%. In addition, B spike (somadendritic spike) failure was occasionally observed in the antidromic responses from frontal cortex stimulation. This is a rare event under control conditions.[25]

As summarized in Table 1, in these 14 cells, the threshold for antidromic activation decreased in 12 cases, ranging from 11.8% to 28.8% ($\bar{X} \pm$ S.E.M. = 18.2%). In the remaining two cases, the threshold increased by 12.5% and 16.7%. These effects also occurred beginning 20–30 s post-injection. In Fig. 3A, antidromic stimulation at a current of 0.67 mA only activates the neuron in about 20% of non-collision trials, while the threshold current was approximately

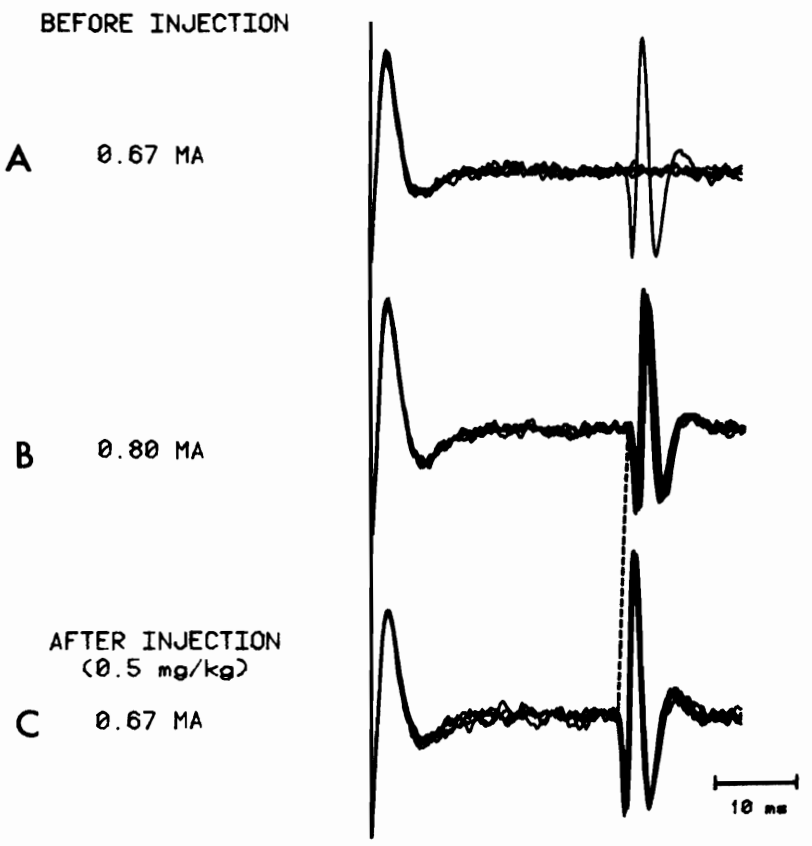

Fig. 3. Antidromic responses to electrical stimulation of the frontal cortex before (A, B) and after (C) intravenous administration of amphetamine. Each Figure is the superimposition of five traces. Before the drug, a stimulus current of 0.67 mA failed to evoke 100% antidromic response (A) and 0.80 mA was required to obtain 100% antidromic response (B). After intravenous injection of amphetamine (0.5 mg/kg), 0.67 mA was sufficient to produce 100% antidromic response (C). Decreases in the antidromic latency and in the variability of the antidromic latency as well as increases in the amplitude of the action potentials are seen following intravenous administration of amphetamine.

0.80 mA, as illustrated in Fig. 3B. After intravenous administration of amphetamine, the threshold current was decreased to 0.67 mA as shown in Fig. 3C. This increased antidromic excitability was accompanied by a decrease in the antidromic latency (1–3 ms) and a decrease in the variability of the antidromic response latency (compare Fig. 3B with Fig. 3C).

In order to determine if changes in terminal excitability induced by intravenously administered amphetamine were specific to the terminal fields of locus coeruleus neurons, the excitability of noradrenergic axons in the dorsal noradrenergic pathway was measured simultaneously for several neurons, as illustrated for one case in Fig. 4. Intravenous administration of 0.5 mg/kg amphetamine led to a decrease in excitability to stimulation of frontal cortex of approximately 29%, and this was accompanied by a decrease in the spontaneous firing rate of from 4.2 spikes/s to 2.4 spikes/s. The second injection (0.5 mg/kg i.v.) led to a further decrease in threshold (58%) and in spontaneous firing rate (1.8 spikes/s) compared to the control values. Excitability of the axon of this cell in the dorsal pathway was not affected by amphetamine injection. In six additional cases, none of the thresholds to dorsal pathway stimulation was altered by intravenously administered amphetamine.

A relation between changes in the rate of spontaneous discharges induced by intravenously administered amphetamine and antidromic threshold is shown in Fig. 5.

In the eight cases in which spontaneous discharges were completely suppressed in response to amphetamine injection, all revealed increased terminal excitability following the drug. In the remaining six cases in which spontaneous discharges were only partially suppressed, four exhibited increased terminal excitability and two exhibited decreased excitability. It is of interest to note that in the two cases that showed decreased terminal excitability, the changes in spontaneous discharge were small (13% to 23% decrease)

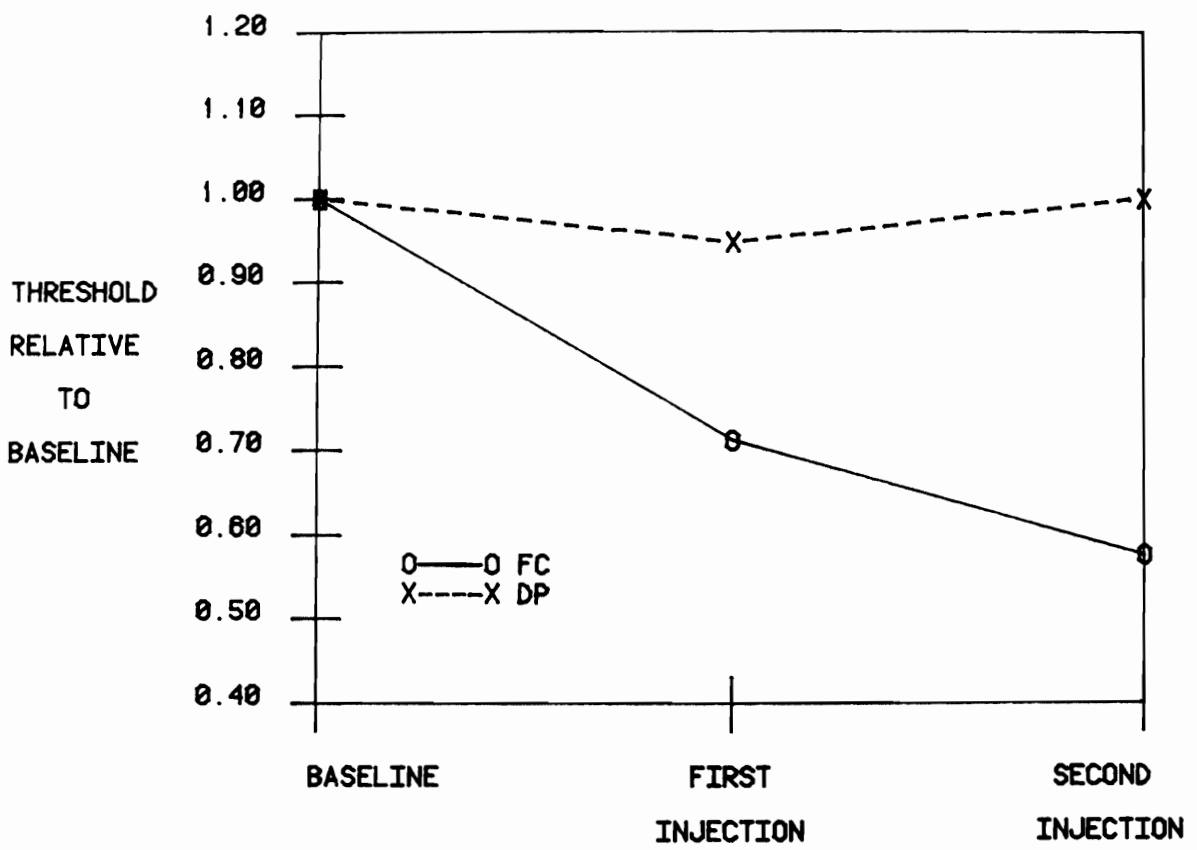

Fig. 4. The effects of intravenous amphetamine administration on terminal (FC) *versus* dorsal pathway (DP) excitability. Two successive amphetamine injections (0.5 mg/kg) produced a dose-related increase in the excitability of terminals in the frontal cortex but not in the axon.

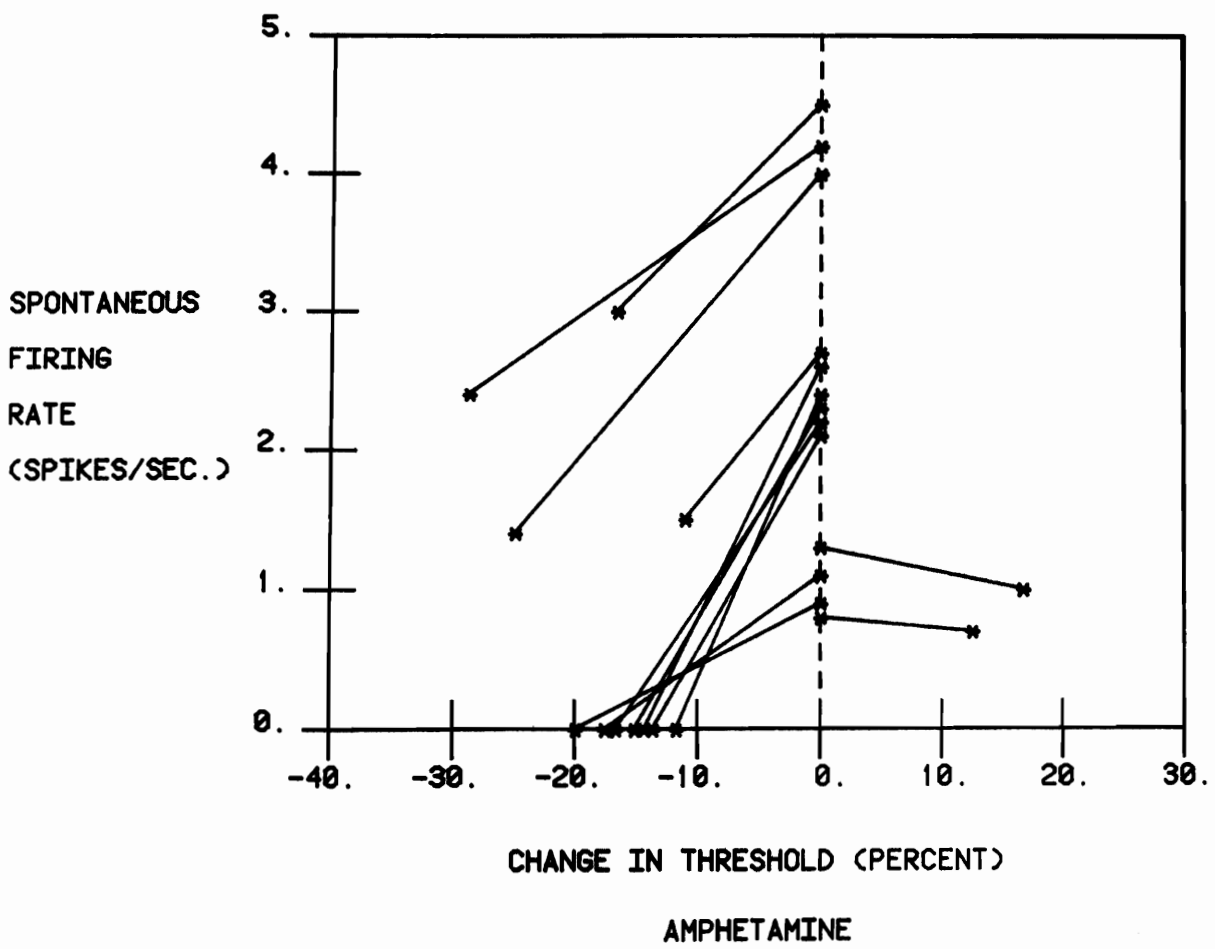

Fig. 5. A relationship between changes in rate of spontaneous activity and terminal excitability of locus coeruleus neurons following intravenous administration of amphetamine. The points on the dashed line represent baseline firing rate. Terminal excitability was increased when amphetamine caused a large change in the rate of spontaneous discharges (left side) but was decreased when the change in rate of spontaneous discharges was small (right side).

as compared to those in the former group (33% to 65% decrease).

Since amphetamine is thought to act indirectly on noradrenergic receptors by promoting the extracellular accumulation of norepinephrine, it was of interest to compare the effects of intravenously administered amphetamine to those of the direct acting alpha-receptor agonist, clonidine. Clonidine was administered intravenously in incremental doses of 0.02 mg/kg to six animals. In three cases excitability decreased to the initial and subsequent doses ($\bar{X} \pm$ S.E.M. = 45% ± 16%). In one case excitability increased to the first dose (14%) and then decreased to a subsequent dose (17%). In the remaining two cases, excitability increased to successive doses of clonidine (total = 0.08 mg/kg). In accordance with previous reports,[5,31,32a] the spontaneous discharges of locus coeruleus neurons were totally inhibited immediately after intravenous injection of clonidine in four cases, and partially suppressed in two others in which the spontaneous activity decreased to 56% and 19% of their control levels, respectively.

DISCUSSION

An inhibition of neuronal firing of neurons in nucleus locus coeruleus following amphetamine administration was first noted by Graham & Aghajanian.[12] Since amphetamine acts indirectly by facilitating the release and/or blocking the re-uptake of synaptic catecholamines (see review by Groves & Rebec[14]),[3,4,11,19] it was originally believed that the extracellular accumulation of catecholamine produced a compensatory decline in neuronal activity by means of a long postsynaptic feedback loop originating with noradrenergic stimulation of postsynaptic targets of locus coeruleus neurons. More recent anatomical and neuropharmacological evidence, however, suggests that amphetamine acts within the locus coeruleus itself, by facilitating release or blocking re-uptake of catecholamines at noradrenergic recurrent axon collaterals,[1] as well as extrinsic catecholaminergic projections to locus coeruleus and presynaptic noradrenergic dendrites.[6,15,16,17,21]

Neuronal activity in locus coeruleus appears to be extraordinarily sensitive to this intrinsic action of intravenously-administered amphetamine, since even at the very low doses used in these experiments, a complete suppression of spontaneous discharges was commonly seen. In addition, our observations that the action potentials were sometimes increased in amplitude, and that failure of the antidromically-elicited action potentials to invade the soma was seen more frequently after amphetamine, are consistent with the view that the local extracellular accumulation of norepinephrine hyperpolarizes locus coeruleus neurons to produce an inhibition of firing rate.

Changes in the excitability of noradrenergic terminals can be attributed to stimulation of presynaptic alpha-receptors by catecholamines released from the synaptic ending.[28] When amphetamine was infused directly into the frontal cortical terminal fields of locus coeruleus neurons, it typically resulted in a decrease in terminal excitability, an effect that could be

blocked by infusion of the alpha-adrenergic antagonist, phentolamine, or abolished by a pretreatment with alpha-methyl-*p*-tyrosine. These results are consistent with the hypothesis that amphetamine exerts its effects on terminal excitability indirectly by promoting the release and/or blocking the re-uptake of norepinephrine which acts back on the presynaptic alpha-adrenergic receptor. Other treatments which promote norepinephrine release and thereby stimulate presynaptic alpha-receptors also lead to a decline in noradrenergic terminal excitability.[28]

When terminal excitability was examined following intravenous administration of the drug, however, an increase in terminal excitability was most commonly seen. The difference in the effect of these two modes of administration may be attributed to the marked decline in neuronal activity following intravenous administration of amphetamine, since local administration of the drug did not alter firing rate. We have previously shown that terminal excitability is related to spontaneous firing rate, a decline in firing rate leading to increased terminal excitability and increased firing rate leading to the opposite.[28] This interpretation is supported by our observation that whereas increased terminal excitability occurred in those cases where intravenously-administered amphetamine resulted in a considerable or total suppression of neuronal activity, decreases in terminal excitability resulted when smaller decreases in firing rate occurred. These data are consistent with the view that the catecholamine-liberating properties of amphetamine are enhanced by impulse traffic *in situ*.[33] Thus, when spontaneous activity is only partially suppressed by intravenously-administered amphetamine, the overall effect at the axon terminal is to increase norepinephrine release which results in an alpha-receptor mediated decrease in terminal excitability. However, when neuronal firing is largely or completely suppressed, the net effect at the terminal is a decrease in norepinephrine release, and a reduction in autoreceptor stimulation leading to a disinhibition of the terminal, which is observed as an increase in terminal excitability. In further support of this view is our evidence that intravenously-administered clonidine, a direct-acting alpha-receptor agonist, tended to decrease terminal excitability. Since clonidine was as effective as amphetamine in inhibiting spontaneous activity, the preponderance of inhibitory effects on noradrenergic terminal excitability may be attributed to its direct action and relative independence on impulse traffic for activation of the presynaptic receptor.

Our evidence further supports the idea that catecholamines released from the synaptic ending influence the excitability of the presynaptic terminal, probably by means of activation of presynaptic receptors located on the terminals themselves.[13,28] Our evidence also supports the view that the effects of systemically-administered amphetamine on terminal excitability involve a balance between its ability to reduce impulse traffic and to promote the accumulation of extracellular catecholamines at the synaptic terminal. To the extent to which measurement of terminal excitability reflects concurrent changes in the amount of neurotransmitter released, our data would seem to indicate that the overall effect of systemic amphetamine administration at low doses is to reduce the postsynaptic activation of locus coeruleus target cells in the frontal cortex.

Acknowledgements—Supported in part by grant DA 02854 and Research Scientist Development Award, KO2 DA 00079 from the National Institute on Drug Abuse (to P.M.G.).

REFERENCES

1. Aghajanian G. K., Cedarbaum J. M. & Wang R. Y. (1977) Evidence for norepinephrine-mediated collateral inhibition of locus coeruleus neurons. *Brain Res.* **136,** 570–577.
2. Arnold E. B., Molinoff P. B. & Rutledge C. O. (1977) The release of endogenous norepinephrine and dopamine from cerebral cortex by amphetamine. *J. Pharmac. exp. Ther.* **202,** 544–557.
3. Carlsson A., Fuxe K., Hamberger B. & Lindqvist M. (1966) Biochemical and histochemical studies on the effects of imipramine-like drugs and (+)-amphetamine on central and peripheral catecholamine neurons. *Acta physiol. scand.* **67,** 481–497.
4. Carr L. A. & Moore K. E. (1969) Norepinephrine: release from brain by *d*-amphetamine *in vivo*. *Science, N.Y.* **164,** 322–323.
5. Cedarbaum J. M. & Aghajanian G. K. (1977) Catecholamine receptors on locus coeruleus neurons: pharmacological characterization. *Eur. J. Pharmac.* **44,** 375–385.
6. Cedarbaum J. M. & Aghajanian G. K. (1978) Afferent projections to the rat locus coeruleus as determined by a retrograde tracing technique. *J. comp. Neurol.* **178,** 1–16.
7. Chiueh C. C. & Moore K. E. (1974) *In vivo* release of endogenously synthesized catecholamines from the cat brain evoked by electrical stimulation and by *d*-amphetamine. *J. Neurochem.* **23,** 159–168.
8. Engberg G. & Svensson T. H. (1979) Amphetamine-induced inhibition of central noradrenergic neurons: a pharmacological analysis. *Life Sci.* **24,** 2245–2254.
9. Farnebo L.-O. & Hamberger B. (1971) Drug-induced changes in the release of [^{3}H]-noradrenaline from field stimulated rat iris. *Br. J. Pharmac.* **43,** 97–106.
10. Farnebo L.-O. & Hamberger B. (1971) Drug-induced changes in the release of [^{3}H]-monoamines from field stimulated rat brain slices. *Acta physiol. scand.* **Suppl. 371,** 35–41.

11. Glowinski J., Axelrod J. & Iversen L. L. (1966) Regional studies of catecholamines in the rat brain—IV. Effects of drugs on the disposition and metabolism of [^{3}H]-norepinephrine and [^{3}H]-dopamine. *J. Pharmac. exp. Ther.* **153,** 30–41.
12. Graham A. W. & Aghajanian G. K. (1971) Effects of amphetamine on single cell activity in a catecholamine nucleus, the locus coeruleus. *Nature, Lond.* **234,** 100–102.
13. Groves P. M., Fenster G. A., Tepper J. M., Nakamura S. & Young S. J. (1981) Changes in dopaminergic terminal excitability induced by amphetamine and haloperidol. *Brain Res.* **221,** 425–431.
14. Groves P. M. & Rebec G. V. (1976) Biochemistry and behavior: some central actions of amphetamine and antipsychotic drugs. *A. Rev. Psychol.* **27,** 91–127.
15. Groves P. M., Staunton D. A., Wilson C. J. & Young S. J. (1979) Sites of action of amphetamine intrinsic to catecholaminergic nuclei: catecholaminergic presynaptic dendrites and axon terminals. *Prog. Neuropsychopharmac.* **3,** 315–335.
16. Groves P. M. & Wilson C. J. (1980) Fine structure of rat locus coeruleus. *J. comp. Neurol.* **193,** 841–852.
17. Groves P. M. & Wilson C. J. (1980) Monoaminergic presynaptic axons and dendrites in rat locus coeruleus seen in reconstructions of serial sections. *J. comp. Neurol.* **193,** 853–862.
18. Groves P. M., Young S. J. & Wilson C. J. (1976) Self-inhibition by dopaminergic neurones: disruption by (±)-alpha-methyl-*p*-tyrosine pretreatment or anterior diencephalic lesions. *Neuropharmacology* **15,** 755–762.
19. Hanson L. C. F. (1966) Evidence that the central action of amphetamine is mediated *via* catecholamines. *Psychopharmacologia* **9,** 78–80.
20. Heikkila R. E., Orlansky H., Mytilineou C. & Cohen G. (1975) Amphetamine: evaluation of *d*- and *l*-isomers as releasing agents and uptake inhibitors for [^{3}H]-dopamine and [^{3}H]-norepinephrine in slices of rat neostriatum and cerebral cortex. *J. Pharm. exp. Ther.* **194,** 47–56.
21. Hökfelt T., Fuxe K., Goldstein M. & Johansson O. (1974) Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain. *Brain Res.* **66,** 235–251.
22. Kehr W., Carlsson A., Lindqvist M., Magnusson T. & Atack C. (1972) Evidence for a receptor-mediated feedback control of striatal tyrosine hydroxylase activity. *J. Pharm. Pharmac.* **24,** 744–747.
23. Langer S. Z. (1977) Presynaptic receptors and their role in the regulation of transmitter release. *Br. J. Pharmac.* **60,** 481–497.
24. Moore K. E. (1977) The actions of amphetamine on neurotransmitters: a brief review. *Biol. Psychiat.* **12,** 451–462.
25. Nakamura S. (1977) Some electrophysiological properties of neurons of rat locus coeruleus. *J. Physiol., Lond.* **267,** 641–658.
26. Nakamura S. & Iwama K. (1975) Antidromic activation of the rat locus coeruleus neurons from hippocampus, cerebral and cerebellar cortices. *Brain Res.* **99,** 373–376.
27. Nakamura S., Tepper J. M., Young S. J. & Groves P. M. (1980) Modifications in the excitability of locus coeruleus synaptic terminals by adrenergic agents. *Neuroscience Abs.* **6,** 449.
28. Nakamura S., Tepper J. M., Young S. J. & Groves P. M. (1981) Neurophysiological consequences of presynaptic receptor activation: changes in noradrenergic terminal excitability. *Brain Res.* **226,** 155–170.
29. Rutledge C. O., Azzaro A. J. & Ziance R. J. (1972) The importance of neuronal uptake for the release of [^{3}H]-norepinephrine by *d*-amphetamine. *Fedn Proc. Fedn Am. Socs. exp. Biol.* **31,** 601.
30. Starke K., Taube H. D. & Borowski E. (1977) Presynaptic receptor systems in catecholaminergic transmission. *Biochem. Pharmac.* **26,** 259–268.
31. Svensson T. H., Bunney B. S. & Aghajanian G. K. (1975) Inhibition of both noradrenergic and serotonergic neurons in brain by the alpha-adrenergic agonist, clonidine. *Brain Res.* **92,** 291–306.
32. Svensson T. H. & Usdin T. (1978) Feedback inhibition of brain noradrenaline by tricyclic antidepressants: alpha receptor mediation. *Science N.Y.* **202,** 1089–1091.
33. Von Voigtlander P. F. & Moore K. E. (1973) Involvement of nigrostriatal neurons in the *in vivo* release of dopamine by amphetamine, amantadine and tyramine. *J. Pharmac. exp. Ther.* **184,** 542–552.
34. Walters J. R. & Roth R. H. (1976) Dopaminergic neurons: an *in vivo* system for measuring drug interactions with presynaptic receptors. *Naunyn-Schmiedeberg's Arch. Pharmac.* **296,** 5–14.
35. Ziance R. J., Azzaro A. J. & Rutledge C. O. (1972) Characteristics of amphetamine-induced release of norepinephrine from rat cerebral cortex *in vitro*. *J. Pharmac. exp. Ther.* **182,** 284–294.

(*Accepted* 23 *March* 1982)