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Catecholamines and Self-Stimulation: The Action of Amantadine and Its Interaction with Amphetamine

L. J. HERBERG AND D. N. STEPHENS

Institute of Neurology, Queen Square, London WC1N 3BG

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HERBERG, L. J. AND D. N. STEPHENS. *Catecholamines and self-stimulation: the action of amantadine and its interaction with amphetamine.* PHARMAC. BIOCHEM. BEHAV. 3(2) 263–269, 1975. – The antiparkinsonian drug amantadine HCl caused a dose-dependent depression of electrical self-stimulation, followed by a dose-dependent enhancement. Neither action was correlated with the differential effects of d- and l-amphetamine at different implantation sites. The initial depression was not prevented by pretreatment with anticholinergic or antiserotonergic agents nor by depression of catecholamine (CA) synthesis. The stimulant effects of amantadine and d-amphetamine summated but did not interact, response rates after d-amphetamine being augmented by pretreatment with amantadine except at intervals at which amantadine was by itself depressant. It is concluded that the initial effect of amantadine is caused by impulse-independent release of a pool of intraneuronal CA, causing dissociation between reinforcement signals and the rat's responses. This is followed by amphetamine-like facilitation of impulse-dependent release; the first action depresses performance, the second enhances it.

Amantadine d-Amphetamine l-Amphetamine α-MPT Noradrenaline Dopamine Self-stimulation Tyramine Parkinsonism Catecholamines Acetylcholine

AMANTADINE hydrochloride (Symmetrel, Geigy) is an antiviral agent recently found to act as a central stimulant and to be effective in the management of Parkinson's disease [34]. During recent months at least six theories have been advanced to account for its unexpected behavioural and therapeutic effects.

(1) Cholinergic activity is known to be enhanced by amantadine, and a anumber of investigators have suggested that striatal cholinergic activity might activate a GABA-based inhibitory mechanism with antiparkinsonian effects [1,3]. Against this idea is the known antiparkinsonian action of anticholinergic agents. (2) Enhancement of dopamine synthesis. The relief of extrapyramidal symptoms sometimes afforded by agents which restore striatal dopamine (DA) suggests that amantadine may act in a similar way, and Scatton and colleagues [23] have confirmed that amantadine speeds up the synthesis of DA from labelled precursors. But the actual increase in DA synthesis is slight, and it may be secondary to accelerated release [9]. (3) DA-sparing. Similar considerations apply also to the sparing action by which amantadine has been reported to increase the amount of (labelled) brain DA available for neurotransmission, possibly by slowing down loss of DA from the brain [29]. (4) Inhibition of CA reuptake. An imipramine-like action is supported by data showing an increased production of 0-methylated (extracellular) catecholamine (CA) metabolites and a corresponding decrease in deaminated (intracellular) metabolites for as long as 12 hr after injection of amantadine [2]. But inhibition of DA reuptake required high drug concentrations, and with usual therapeutic doses the effect is possibly insignificant; amantadine has been shown to be only 1/1250 as potent as d-amphetamine in this respect [32]. (5) Direct stimulation of CA receptors. Locomotor stimulation by amantadine is abolished by drugs such as spiroperidol or phenoxybenzamine which block synaptic receptor sites for DA and noradrenaline (NA); while conversely the cataleptic action of high doses of these blocking agents is antagonized by amantadine [17]. It has accordingly been suggested that amantadine competes with them for the same receptors and that it therefore acts directly on the receptor sites to produce its central stimulant and therapeutic effects [4,17]. This suggestion is supported by reports firstly that the CA content of the brain shows little or no overall change after treatment with amantadine [1,18]; and, secondly, that depleted stores of endogenous CA's are no bar to its stimulant effects: increased locomotor activity ensues even after blockade of NA and/or DA synthesis by alpha-methyl-p-tyrosine (α-MPT) [3, 4, 17, 31]. These findings

suggest that the CA receptors are stimulated not by endogenous CA but by amantadine itself. (6) Indirect stimulation of CA receptors. Amphetamine-like drugs may bring a prompt (though temporary) relief of Parkinsonian symptoms [13], presumably by facilitating the release of endogenous stores of striatal CA. Several findings suggest that amantadine is another drug acting in this way. Firstly, biochemical [35] and histochemical [9] evidence confirms that it releases labelled DA from the brain and other tissues. Secondly, administration of amantadine to rats or mice with unilateral nigrostriatal lesions elicits a turning response in a direction the same as that produced by indirect, rather than direct stimulants [9, 33, 37]. Thirdly, although the action of amantadine is relatively unaffected by pretreatment with α-MPT alone [3, 4, 17, 31] or reserpine alone [4,17], its stimulant effects are eliminated by simultaneous pretreatment with α-MPT and reserpine [3, 9, 18, 28], i.e. by a combination which prevents the synthesis as well as the storage of CA and thereby obviates the slow replenishment of intraneuronal CA which can otherwise occur [11,27]. Fourthly, it has been shown that the high sensitivity of amphetamine-treated animals to the effects of α-MPT [39] depends in part on a specific interaction between α-MPT and amphetamine [8], so that the lesser sensitivity to α-MPT shown by the amantadine-treated animal [3, 4, 17, 31] does not necessarily imply that amantadine is in any way less dependent than amphetamine on the availability of endogenous CA.

These findings add up to the conclusion that amantadine acts indirectly, by releasing endogenous CA's in a manner similar to that ascribed to the amphetamines [41], a conclusion said to represent a "consensus" held by most investigators [6]. But there are several ways in which amantadine and amphetamine seem to differ: the behavioural stimulant effect of amantadine even at optimal doses is much weaker than that of amphetamine [9,31], and it is sometimes preceded by a period of absolute depression lasting 15 to 20 min [1, 18, 31]. This biphasic effect is not found with amphetamine [31]. Unlike amphetamine [10,22], amantadine at high doses fails to elicit compulsive sniffing, licking, biting, bizarre social behaviour or stereotypy [4]. Amantadine (like apomorphine in the mouse [12], depresses body temperature [42] but amphetamine raises it [38]. Although some amphetamines (e.g., d-amphetamine) are blocked by α-MPT and others (e.g., methylphenidate) are blocked by reserpine [11,24], amantadine (as noted above) is blocked by neither. In addition, various behavioural, metabolic and toxic effects of amphetamine have been reported to be blocked or diminished, rather than intensified, by pretreatment with amantadine [20], and biochemical investigations with intraventricular amantadine in high doses have revealed a dose-related rise in the spontaneous (i.e., impulse-independent) efflux of DA in the CSF lasting up to 6 min after administration [35]; this impulse-independent release of transmitter by amantadine resembled the action of tyramine rather than amphetamine [36].

For the present investigation of the behavioural effects of amantadine we have examined a number of possible explanations for the similarities and differences between amphetamine and amantadine, and sought to interpret our results in terms of recent data on their biochemical effects. For this purpose we have adopted the rate of hypothalamic self-stimulation as a continuous index of the functional activity of brain CA during treatment with amantadine or amphetamine, since involvement of brain CA in self-stimulation is now reasonably well-established [5, 11, 21, 26], and the effects on self-stimulation performance of amphetamine-like agents is known in some detail [11, 21, 41].

METHOD

Animals

Twisted bipolar stainless steel electrodes were permanently implanted in the lateral hypothalamus of adult male Wistar rats, aimed at a point 5.2 mm in front of the De Groot [7] zero plane, 1.4 mm lateral to the midline and 8.8 mm below the surface of the skull. The rats were trained to operate a pedal for 0.5 sec sine-wave reinforcing pulses delivered on a variable interval schedule at a rate of not more than one reinforcement per 10 sec. Use of this schedule ensured a steady, seizure-free rate of responding, on which clear stimulant or depressant effects could be imposed without any appreciable change in the rate of reinforcing stimulation. The stimulating current for each rat was fixed at an intensity between 40 and 100 μA that elicited a pedal-pressing rate of approximately 20 responses per min, and regular training continued until the rate of responding averaged at 2 min intervals on a printout counter had become stable throughout a 2 hr session. Each electrode was then tentatively classified as being lodged in either a dopaminergic or noradrenergic area of the hypothalamus according to the relative effect on self-stimulation of injections of l- and d-amphetamine. The two isomers have been reported to be equally effective in facilitating the action of synaptic DA, but to differ by a factor of 10 in their effects on NA [30]; the interpretation of these findings is open to question [32,36], but comparison of the relative effects of the two isomers on self-stimulation has been suggested to distinguish between electrodes in dopaminergic and noradrenergic pathways [21]. We accordingly determined the maximum percentage increase in self-stimulation in the hour following 0.5 mg/kg injections of l- and d-amphetamine and took a d/l ratio of unity ± 1 as provisional evidence of an electrode in a predominantly dopaminergic locus. At the end of the experiment the anatomical location of the electrode tips was determined from photographic enlargements of unstained frozen sections.

Drugs

All injections were adjusted to a volume of approximately 0.5 ml of solution and administered intraperitoneally. Amantadine hydrochloride and cyproheptadine hydrochloride were dissolved in distilled water immediately before use. The amphetamines were dissolved in physiological saline. Atropine was dissolved in acetic acid and titrated with 2 M NaOH to pH 5.5.

Test Procedure

Injections were administered only after self-stimulation had been in progress for at least 45 min, and the rate of responding during the last 30 min before injection was taken as a nodrug baseline. Self-stimulation continued for another 120 min after injection, and mean response rates were determined at 10 min intervals. Rats which stopped responding after treatments were encouraged to restart by taps on the lever; if this failed, by the administration of

priming shocks, and then by the experimenter placing the rat bodily on the lever. This sequence was repeated at 20 min intervals until responding returned.

Experiment 1 established a dose-response relationship between amantadine and the rate of self-stimulation. Ten rats were given 12.5, 25 or 50 mg/kg amantadine or a control injection of saline, in random order. Each animal received one injection at each dose. At least 4 days elapsed between successive injections.

Experiment 2 examined the interaction between amantadine and d-amphetamine. Ten rats were run according to a design for an analysis of variance of repeated observations. Each rat was injected in random order with (a) saline, (b) amantadine alone (25 mg/kg), and (c) amantadine followed by d-amphetamine 30 min later. Scores were expressed as a proportion of the preinjection rate, and those submitted to analysis were obtained from the 3rd 10 min period after d-amphetamine alone, the third 10 min period after amantadine-followed-by-amphetamine (i.e., the 6th 10 min period after the amantadine), and the 6th 10 min period after amantadine alone. Five of the rats were additionally tested for a further analysis of variance based on the same data with the exception that all 25 mg/kg doses of amantadine were replaced by doses of 50 mg/kg.

Experiment 3 sought to determine whether serotonin, acetylcholine or CA played a significant role in the depressant action of amantadine. Groups of 3–5 rats (sample sizes are specified in the Results) were given 1.5 mg/kg cyproheptadine, or 4, 20, or 100 mg/kg atropine 10 to 15 min before the administration of 25 mg/kg amantadine or saline, and tested for self-stimulation as in Experiment 1. Four rats were given 150 mg/kg α-MPT 3 hr before being tested with 50 mg/kg amantadine or saline.

RESULTS

Experiment 1

All doses of amantadine caused a significant fall in responding (Wilcoxon T = 7, n = 10, $p<0.05$) followed by a prolonged rise, whereas saline had virtually no effect. Figure 1(A) shows the depressant effect recorded in the first 10 min after each dose. The depth and duration of the initial depression was proportional to the injected dose (Friedman χ^2 = 14.9 and 8.6; $p<0.01$ and $p<0.05$, respectively), and at the highest dose (50 mg/kg) 3 of the 10 rats stopped responding altogether. But depression did not occur in every test, and the probability of its occurrence was unrelated to dose: at each dose one rat (a different one each time) speeded up soon after injection with no demonstrable slowing.

The depressed phase usually ended after 10 to 30 min, and when recovery took place the rate of responding quickly reached a level that was significantly above the preinjection rate (Wilcoxon T = 6, $p<0.05$; see Figs. 1(B), 1(C) and 1(D), the strongest effect again being associated with the highest dose. The translation from the depressed to the excited state was often very rapid: rats which had stopped self-stimulating after injection usually responded at rates well above their preinjection rates within the first 2 or 3 min of recovery.

No dose of amantadine was as effective a stimulant as 0.5 mg/kg d-amphetamine, and at no time period was d-amphetamine followed by a fall in responding (Fig. 1(A)–1(D)).

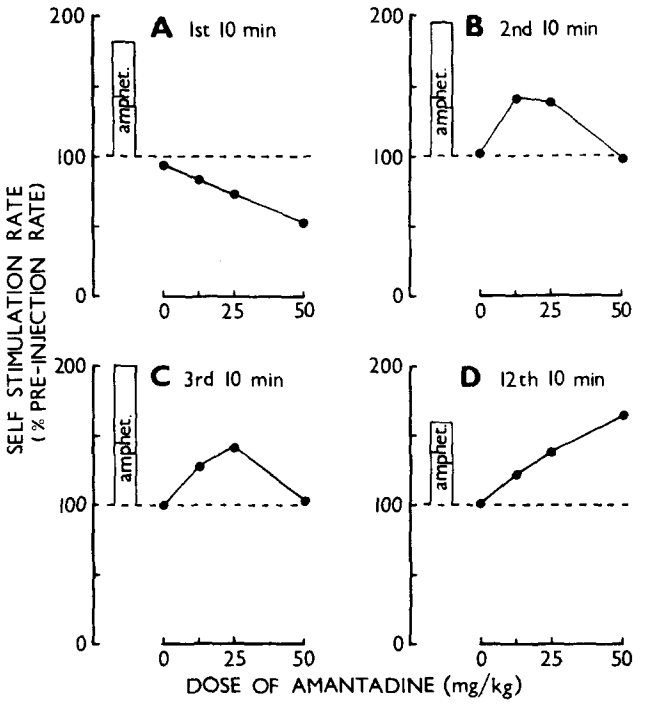

FIG. 1. Effect on self-stimulation of 3 doses of amantadine (12.5, 25 and 50 mg/kg) and of a control injection of saline (0 mg/kg) at 4 different time intervals after injection. Each plotted point is the mean of the percentage changes from the respective preinjection rates in 10 rats. The vertical bar in each figure indicates the stimulant effect of d-amphetamine (0.5 mg/kg) at the indicated time interval. Test sessions after saline injections were stopped after 1 hr, and the zero mg/kg point in D, on the 2 hr curve, is a no-injection control score derived from the corresponding stage of the final training session.

Experiment 2

Low-dose amantadine. Figure 2 shows that amantadine (25 mg/kg) was again depressant at first, but that all 3 drug treatments (amantadine, d-amphetamine, and amantadine plus d-amphetamine) were eventually followed by a rise in responding above the preinjection level. In the 3rd 10 min period the stimulant effect was stronger after amphetamine-following-amantadine than after d-amphetamine alone (t = 2.7, df = 18, $p<0.02$), and this difference became even more pronounced during the hour that followed. Analysis of variance showed that the stimulant effects of amantadine alone, F(1,9) = 5.6, $p<0.05$, and of d-amphetamine alone, F(1,9) = 27.4, $p<0.01$, showed no interaction when the two drugs were given in combination, F(1,1) = 0.36. This result indicates that with the doses used the stimulant effects of d-amphetamine and amantadine were purely additive.

High-dose amantadine. The 50 mg/kg dose was again found to cause a more prolonged depression than 25 mg/kg (Fig. 3A) and in some rats response rates were still depressed 30 min after injection, when the amphetamine came to be administered. Even at the 6th 10 min period amantadine alone was still not stimulant (Fig. 3A; F(1,4, = 0.33, n.s.), and it produced a non-significant reduction in the stimulant effect of d-amphetamine (Fig. 3C; t = 1.6, df = 8, $p<0.1$). Once again there was no sig-

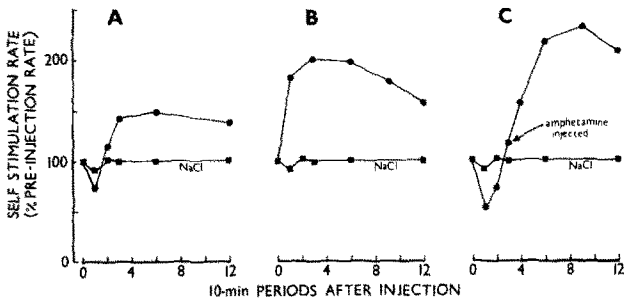

FIG. 2. Self-stimulation scores in 10 rats after a control injection of saline and (A) 25 mg/kg amantadine, (B) 0.5 mg/kg d-amphetamine, and (C) 25 mg/kg amantadine followed by 0.5 mg/kg d-amphetamine 30 min later. Response rates are expressed as the mean of the percentage change from the preinjection rates. Mean preinjection rates in (A), (B) and (C) were respectively 136, 139 and 139 responses per 10 min. The 12th 10 min point on the NaCl curve in each figure includes no-injection scores.

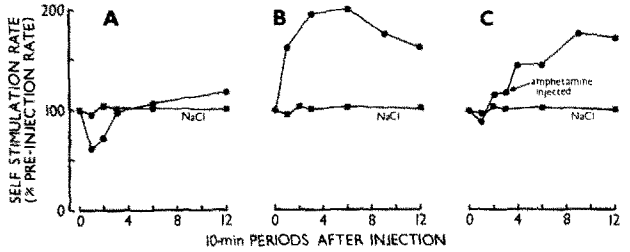

FIG. 3. Self-stimulation scores obtained as for Fig. 2 after injection of (A) 50 mg/kg amantadine, (B) 0.5 mg/kg d-amphetamine, and (C) 50 mg/kg amantadine followed by 0.5 mg/kg d-amphetamine 30 min later.

nificant interaction between the amantadine and d-amphetamine, F(1,1, = 3.3 n.s., their combined effects again being algebraically additive (i.e., in this case, subtractive).

Experiment 3

Table 1 shows that pretreatment with atropine, cyproheptadine or α-MPT had little or no effect on the depression of self-stimulation recorded during the first three 10 min periods after amantadine.

Cyproheptadine caused no discernible change in the depressant effect of amantadine even though the dose administered (1.5 mg/kg) was slightly larger than a dose (1.0 mg/kg) known to antagonize the motivational effects of centrally injected serotonin [15].

Atropine at the lowest dose tested (4.0 mg/kg) was similarly ineffective, while higher doses, which were depressant in their own right, tended to enhance rather than reduce the depressant effect.

α-MPT caused an appreciable fall in the rate of self-stimulation recorded 3 hr after administration, but the injection of amantadine at this point caused an immediate further fall superimposed on that due to α-MPT.

Electrode Localisation

Effects of d- and l-amphetamine. The ratio between the percentage increase in self-stimulation rate after d- and after l-amphetamine ranged from 0.7 to 17.9 in different rats. Three electrode placements yielded d/l ratios of less than 2.0 and on that basis were classified as predominantly dopaminergic, but the ratio values were not significantly correlated with the depressant or the stimulant effects of amantadine at any of the doses tested (Spearman $r_s<0.5$, n = 10, $p>0.05$.)

TABLE 1

THE EFFECT OF ATROPINE, CYPROHEPTADINE AND α-MPT ON SELF-STIMULATION AND ON THE DEPRESSION OF SELF-STIMULATION BY AMANTADINE

Pretreatment	Dose (mg/kg)	N	Amantadine Dose (mg/kg)	Postamantadine Rate* 1st 10 min	2nd 10 min	3rd 10 min
Nil	–	10	25	74.7	114.9	143.3
	–	10	50	52.8	72.8	103.3
Atropine†	4.0	4	–	107.8	101.0	101.0
	4.0	5	25	60.9	123.1	136.2
	20.0	4	–	75.9	78.8	73.5
	20.0	3	25	72.5	68.8	65.0
	100.0	4	–	81.5	81.3	77.6
	100.0	3	25	60.4	57.5	60.1
Cyproheptadine†	1.5	4	–	98.3	96.9	105.2
	1.5	4	25	69.3	117.5	143.9
α-MPT‡	150.0	4	–	68.9	59.6	35.4
	150.0	4	50	31.6	28.7	36.4

*Self-stimulation scores are expressed as a percentage of the response rate recorded in the 30 min before administration of the first injection.

†Administered 15 min before injection of amantadine.

‡Administered 3 hr before injection of amantadine.

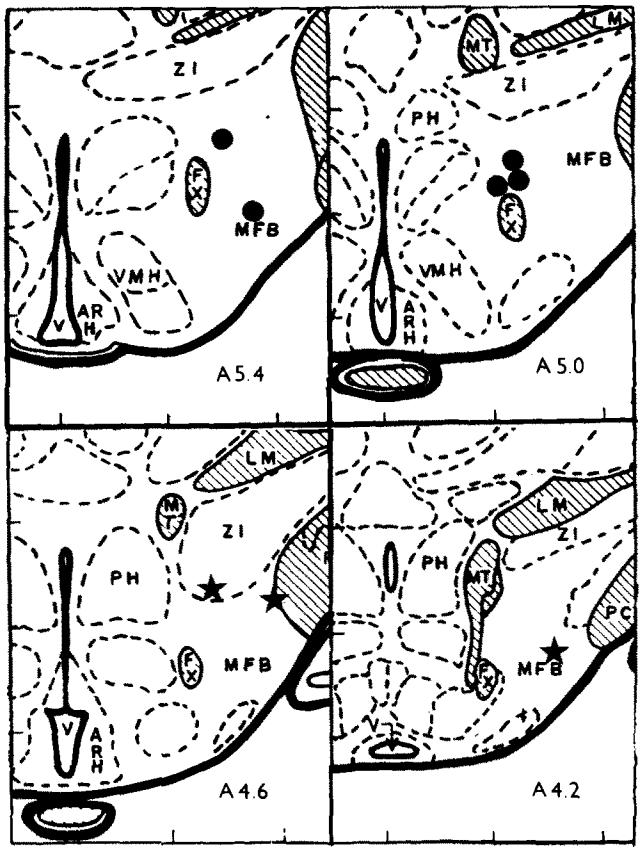

FIG. 4. Coronal sections of rat diencephalon [7] showing location of electrode tips. Stars indicate predominantly dopaminergic placements at which the increment in self-stimulation after d-amphetamine was less than twice that after l-amphetamine; filled circles indicate sites classified as noradrenergic.

Histology. Two brains were lost, and Fig. 4 shows the location of the electrodes in the remaining 8. Placements ranged between the medial and far-lateral quadrants of the medial forebrain bundle, but there was no apparent relationship between any coordinate and the intensity of the depressant or the stimulant action of amantadine.

DISCUSSION

Depressant and Stimulant Effects

In Experiment 1 three different dose levels of amantadine were all followed by an increase in the rate of self-stimulation. Since self-stimulation is sensitive to changes in the availability of brain CA [5, 11, 21, 26], this result is consistent with prevailing views that the stimulant action of amantadine depends on a facilitation of central catecholaminergic mechanisms. But the initial slowing that nearly always followed each injection is less simply accounted for, and raises several further questions.

The depressant action is unlikely to have been caused by overstimulation by supraoptimal levels of the drug in the minutes following injection, since this would not account for the finding that when responding eventually recovered the ensuing rebound was strongly dose-dependent; if the doses that caused depression were all supraoptimal for the reinforcement mechanism they should all have elicited maximal and equal reinforcing effects as the drug was cleared and concentrations passed through the optimal range. Moreover, depression occurred as often with doses of 12.5 mg/kg as with 50 mg/kg.

Another possible explanation of the initial depression is that amantadine might act not only on a reinforcing catecholaminergic pathway but also, transiently, on some other, inhibitory system. Two obvious candidates are the diencephalic cholinergic and ascending serotonergic tracts, both said to exercise an inhibitory control over operant responding or self-stimulation [19,40]; amantadine is known moreover to have serotonergic [16], and strong cholinergic [3] properties. Experiment 3 failed, however, to demonstrate any protective action by the respective blocking agents, cyproheptadine and atropine, and so did not implicate either transmitter in the depressant effect. Nor is there evidence implicating DA or some transient imbalance between DA and NA, since the depression recorded at different placements proved unrelated to the relative effects of d- and l-amphetamine.

The possibility remains that the initial depression results from 'reinforcement' receptors being stimulated in a way that disrupts, rather than enhances, the reinforcement process. This would happen if amantadine generated a continuous stream of reinforcement signals, dissociated from the pedal-pressing response [14]. This could occur either as a result of direct stimulant action (as depicted in Fig. 5A), or indirectly, through an impulse-independent (i.e., noncontingent) release of endogenous transmitter (as in Fig. 5C). A direct action by amantadine seems unlikely, for the reasons cited earlier [3, 9, 18, 28, 37], and because one would not expect its effects to pass off sharply soon after injection. On the other hand, depression due to an indirect action would last only until the pool of endogenous transmitter capable of being displaced by a particular dose of amantadine was exhausted. If this pool was small, depression would be brief; and since the depressant effect survived pretreatment with α-MPT (in Experiment 3), the necessary transmitter is unlikely to be derived from the intraneuronal pool mediating the action of amphetamine [39]. Biochemical evidence of impulse-independent release of CA by amantadine [35] has already been referred to. In this respect the action of amantadine resembled that of tyramine (without necessarily involving a similar mechanism of extracellular transfer), and unpublished results (Franklin and Herberg, in preparation) have confirmed that intraventricular injections of tyramine depress or abolish hypothalamic self-stimulation in the rat. It is not known to what extent non-contingent reinforcement may disrupt other forms of motivated behaviour, but some reports [1, 18, 31] indicate that locomotor or general activity may show similar brief periods of depression on some types of measurement.

The hypothesised exhaustion of a depressant pool of CA by low or high doses of amantadine did not prevent the ensuing enhancement of self-stimulation which followed without further dosage. Thus the depressant and the

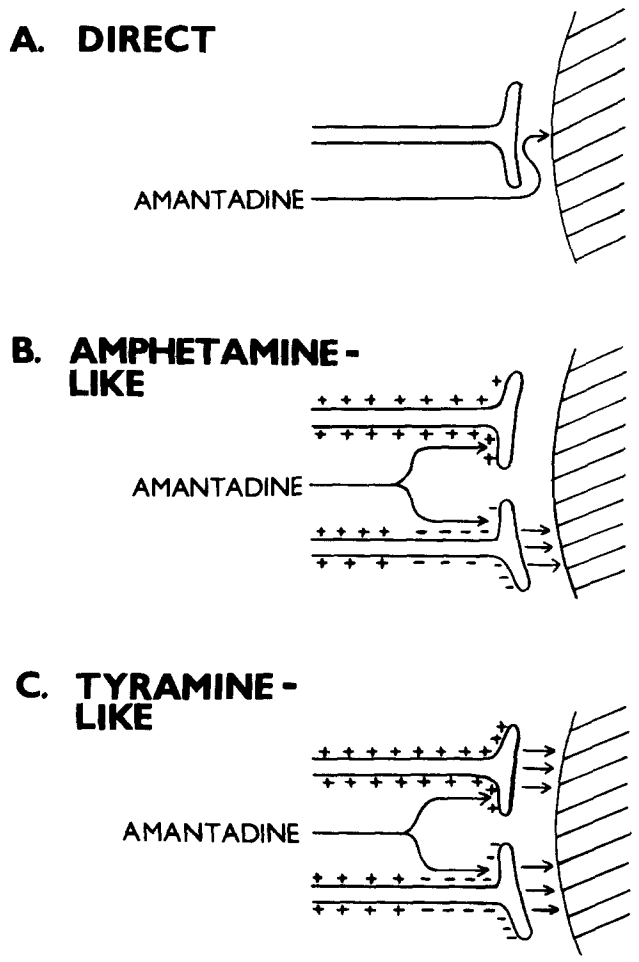

FIG.. 5. Three ways in which amantadine could act on the post-synaptic receptor: (A) Directly; (B) Indirectly, by facilitating the release of transmitter by nerve impulses; (C) Indirectly, by releasing transmitter independently of nerve impulses.

stimulant actions of amantadine would appear to depend on functionally separate pools, the content of the stimulant pool being resistant to depletion, and released only by nerve impulses – so as to facilitate performance instead of disrupting it.

Interaction with Amphetamine

To the extent that the stimulant action of amphetamine and the depressant action of amantadine depend on different intraneuronal pools there would be less likelihood of the two drugs tending to inhibit each other by competing for the same limited supply of transmitter. The outcome of Experiment 2 was consistent with this view: when the two drugs were given together the net effect was an algebraic summation of their separate effects and there was no sign of mutual inhibition or true synergism. Amantadine reduced the rate of responding after amphetamine only in the initial postinjection period during which the amantadine would have been inhibitory even if given alone. This result seems at variance with reports that in mice prior treatment with amantadine either blocks [20] or has no effect [31] on the action of amphetamine. But in addition to procedural and species differences, the dosage of amantadine reported to inhibit amphetamine was considerably higher (150 mg/kg) than the doses used in the present experiment (and exceeded the lethal level for adult Wistar rats in this laboratory). Doses as high as this would have intensified and prolonged the initial depression and maximised the likelihood of finding only an inhibition of amphetamine. Protection against amphetamine overdosage has been reported by Menon and colleagues [20], but on the present evidence the proposed therapeutic use of amantadine for this purpose would require a critical combination of timing and dosage if the excitatory effects of the amphetamine were to be relieved rather than increased.

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