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Effect of chronic amphetamine administration on the behaviour of rats in the open field apparatus: reversal of post-withdrawal depression by two antidepressants

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The chronic administration of low doses ($<1{\cdot}0$ mg kg^{-1}) of (+)-amphetamine to rats results in hyperactivity. Higher doses of the drug ($>1{\cdot}5$ mg kg^{-1}) lead to marked behavioural stereotypy (Randrup, Munkvad & Udsen, 1963; Ellinwood, Sudilovsky & Nelson, 1973; Ellinwood & Balster, 1974). However, apart from the observations of Tonge (1974) the changes in behaviour of rats following the withdrawal of amphetamine have received scant attention. We have investigated the changes in four behavioural parameters measured in the 'open field' apparatus of groups of rats chronically treated with amphetamine for 21 days and then at 2, 4 and 6 days after drug withdrawal. As the ambulation and rearing activity of the rats was markedly decreased following amphetamine withdrawal we then investigated the effects of three types of antidepressant drugs, which had been administered for several days, on the behaviour of the depressed animals. Such a study, though preliminary, may lead to the development of a model for the evaluation of potential antidepressant drugs.

Mature male Wistar rats were housed in groups of 5 to a cage and had free access to food and drink for the duration of the experiment. 4 experimental groups were treated with (+)-amphetamine, administered in their drinking water, for 21 days. The drug doses increased from 50 mg litre^{-1} after the third day to 100 mg litre^{-1} until day 14 and finally to 200 mg litre^{-1} for the third week. An equal weight of ascorbic acid was added to serve as an antioxidant. The control groups received ascorbic acid only in their drinking water. The water bottles were covered with dark paper and the freshly-prepared drug solution was replaced every two days.

On day 21 the animals were withdrawn and on day 22 the first of 6 daily treatments of an antidepressant agent was administered intraperitoneally. Each group received one of three antidepressants amitriptyline (10 mg kg^{-1}), mianserine (15 mg kg^{-1}) or pargyline (25 mg kg^{-1}). The control groups received an equal volume of vehicle (0·9% w/v NaCl).

During the experimental period the animals' behavioural patterns were assessed at regular intervals using the 'open field' apparatus of the type described by Gray, Levine & Broadhurst (1965) and Gray & Lalljee (1974). Behavioural observations were made at the same time each day. Each animal was tested only once to prevent habituation. This was essential as habituation to the 'open field' leads to the animals showing almost complete inactivity. The walls and base of the apparatus were cleaned with distilled water after each 3-min 'open field' test. Four behavioural parameters were measured: ambulation, rearing grooming and defaecation. The Student's *t*-test was used to evaluate the data. The alpha level was chosen as 0·05.

The results of this study are shown in Tables 1 and 2.

Both amitriptyline and mianserine when given alone significantly reduced the ambulation and defaecation scores (Table 1). Mianserin and pargyline alone also reduced the rearing scores. In those animals which had been treated with amphetamine for 3 weeks before withdrawal, the fluid intake did not differ significantly from that of the control group (control 30 ± 4 ml day^{-1}, experimental 28 ± 3 ml day^{-1}). Nevertheless, the weight of the test group was significantly lower than that of the controls ($P<0{\cdot}05$) (controls 290 ± 15 g, experimental $250^{*} \pm 10$ g) at the end of the amphetamine treatment. The ambulation scores increased throughout the period of amphetamine administration reaching a peak on the day the drug was withdrawn. Neither the rearing nor the grooming scores were significantly different from the control value at the end of the treatment. On withdrawal of the drug, a

* Correspondence.

Table 1. *Effects of three antidepressant drugs on the behaviour of rats in the 'open field' apparatus.*

	Control	Mianserine (4 days)† 15 mg kg^{-1}	Pargyline (6 days) 25 mg kg^{-1}	Amitriptyline (6 days) 10 mg kg^{-1}
Ambulation[1]	115 ± 7	*62 ± 5	125 ± 28	*80 ± 4
Rearing[2]	22 ± 2	*14 ± 4	*8 ± 2	25 ± 5
Grooming[3]	1·5 ± 1	3·5 ± 1·0	2·0 ± 2·0	1·5 ± 0·7
Defaecation[4]	5·0 ± 1	*1·0 ± 0	5·0 ± 1	*2·0 ± 0

1. Number of squares crossed/3 min.
2. Number of times animal removed fore-paws from floor/3 min.
3. Time (s) animal groomed/3 min.
4. Number of faecal boli excreted/3 min.

* Significance from control $P<0.05$.

† Only sufficient of this drug for 4 days treatment was available, however, it had an effect in that time whereas the other depressants required 6 days.

drawal was unaffected. From this study it would therefore appear that mianserin differs from amitriptyline in that it can reverse at least some of the behavioural parameters which are depressed following amphetamine withdrawal. Mianserin also differs from amitriptyline and other tricyclic antidepressants with respect to its actions on brain biogenic amine metabolism. Thus it has been shown to increase noradrenaline turnover, and unlike most dibenzazepine antidepressants, does not affect the monoamine reuptake mechanisms *in vivo* (Leonard, 1974; Kafoe & Leonard, 1976). The grooming behaviour of the rats markedly increased 6 days after withdrawal (Table 2) and this effect was potentiated by pargyline but re-

Table 2. *Effect of amphetamine administration (Amph) on 'open field' behaviour and the effect of pargyline (Parg), amitriptyline (Ami) mianserine (Mian)*, Scores are ± s.e.m.

	Control	21 days on Amph	2 days withdraw + saline	2 days withdraw + saline	4 days withdraw + 4× Mian	6 days withdraw + NaCl	6 days withdraw + 6× Parg	6 days withdraw + 6× Ami
Ambulation	115 ± 7	172 ± 12*	33 ● 6*	23 ± 4*	82 ± 10*†	62 ± 6*	170 ± 29†	76 ± 13
Rearing	22 ± 2	17 ± 2	5 ± 2*	5 ± 2*	13 ± 2*†	7 ± 1*	14 ± 3*†	8 ± 3*
Grooming	1·5 ± 1	1 ± 1	9 ± 3*	2·5 ± 2	2 ± 1	14 ± 7	44 ± 3*†	10·5 ± 3
Defaecation	5 ± 1	1 *	4 ± 1	6 ± 1	1 *†	3 ± 1	3 ± 1	0

* Drug-treated animal significantly different from control ($P<0.05$).

† Animals treated with antidepressant significantly different from corresponding group treated only with saline.

marked decrease in the ambulation and rearing scores was recorded throughout the 6 day observation period; grooming behaviour was initially increased. When mianserin was administered for 4 days to a group of rats that had been withdrawn from amphetamine, the depression of the ambulation and rearing behaviour was partially reversed. Pargyline pretreatment for 6 days after amphetamine withdrawal significantly elevated the ambulation and grooming scores above those of non-drug treated animals; the depression of the rearing behaviour was also partially reversed. By contrast, the behaviour of a group of rats treated with amitriptyline for 6 days after amphetamine withduced by amitriptyline. This behavioural change remains unexplained.

The possibility remains that if the amphetamine-withdrawn rats had been treated with amitriptyline for longer the depressed behaviour would also have been reversed. It would appear that this post-amphetamine withdrawal model of depression may be useful for selecting potential antidepressants that have a different mechanism of action from the conventional tricyclic antidepressants.

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