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OLFACTORY BULB ABLATION IN THE RAT: BEHAVIOURAL CHANGES AND THEIR REVERSAL BY ANTIDEPRESSANT DRUGS

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1 The effects of bilateral olfactory bulbectomy, sham-operation and inducement of peripheral anosmia were studied on locomotor activity, passive avoidance acquisition and irritability.

2 Bulbectomized rats were hyperactive, deficient at learning a step-down passive avoidance response and hyperirritable. Peripheral anosmia, induced by intranasal infusion of $ZnSO_4$ solution resulted in no behavioural changes.

3 Chronic pretreatment with amitriptyline (3 and 10 mg/kg) and a tetracyclic antidepressant mianserin (Org GB 94, 5 and 15 mg/kg) reversed the hyperactivity and reduced the learning deficit of bulbectomized rats. These drugs had no significant effects on sham-operated animals.

4 Neither amitriptyline nor mianserin reduced the exaggerated responses of bulbectomized rats to external stimuli.

5 (+)-Amphetamine (1 and 3 mg/kg) accelerated the acquisition of the passive avoidance response, greatly enhanced the locomotor activity and slightly increased the irritability score of both sham-operated and bulbectomized rats.

6 Chlorpromazine (1 and 3 mg/kg) and chlordiazepoxide (10 mg/kg) significantly reduced the acquisition, locomotor activity and irritability of experimental and control rats.

7 Lithium sulphate (1 and 3 mg/kg) had no effect on activity or irritability but produced a small impairment in acquisition of bulbectomized rats.

8 It is concluded that the reversal by antidepressant drugs of the behavioural syndrome seen after olfactory bulb ablation could constitute a new model for the detection of this group of centrally acting compounds.

Introduction

Established tests for the prediction of antidepressant activity often give either false positives (Zetler, 1963; Barnett, Taber & Roth, 1969) or false negatives (van Riezen, Behagel & Chafik, 1975). Mianserin (Org GB 94) is an example of a drug which was not classified as having antidepressant activity by the usual tests (van Riezen, 1972). However, period analysis of alert electroencephalograms in human volunteers revealed activity similar to that of amitriptyline (Itil, Polvan & Hsu, 1972) and subsequent clinical experience has shown mianserin to be an effective antidepressant (Murphy, 1975; Wheatley, 1975).

In 1971 Cairncross & King reported that behavioural deficits resulting from bilateral ablation of the olfactory bulbs of rats were reversed by chronic treatment with amitriptyline. This suggested that removal of the olfactory bulbs may produce a suitable model for the screening of antidepressant drugs. We have recently reported that both amitriptyline and mianserin reversed the deficit in conditioned behaviour and reduced the hyperactivity of bulbectomized rats (van Riezen, Schnieden & Wren, 1976). We have now enlarged the battery of tests in order to characterize further the 'syndrome' seen after olfactory bulbectomy, and challenged the model with other psychotropic agents.

Methods

Animals and operations

Male Sprague-Dawley rats weighing between 175–215 g were used throughout the experiments. The rats were anaesthetized with sodium pentobarbitone (40 mg/kg, i.p.). A longitudinal

incision was made in the midline, 2 cm long and caudal to the rim of the orbit. Burr holes 2 mm in diameter were drilled through both frontal bones, 2 mm lateral to the frontal suture at a point level with the posterior rim of the orbit. The underlying olfactory bulbs were aspirated using a round ended needle 1.5 mm in diameter. Care was taken to avoid damaging the frontal cortex. The holes were plugged with gel foam (Spongostan Film, 200 × 70 × 0.5 mm; Ferrosan, Denmark) and the wound sutured.

Sham-operated rats were subjected to a procedure identical to that described above, except that immediately after exposure of the olfactory bulbs, the burr holes were plugged and the skin incision sutured.

Upon recovery the rats were housed 5 to a cage, each cage containing both bulbectomized and sham-operated rats. Drug pre-treatment began on the fourteenth day after surgery and behavioural testing on day 21.

Peripheral anosmia was produced by a method similar to that of Alberts & Galef (1971). A hooked catheter was inserted into the mouth of a rat anaesthetized with ether with the bent tip of the catheter facing downwards. It was run back along the hard palate until the rounded apex was felt to enter the oesophagus. The catheter was retracted rostrally so that the tip entered the nasal cavity via the posterior choanae. Five percent (w/v) $ZnSO_4$ solution or saline of similar osmolality (0.5–0.7 ml) was slowly injected until eight drops drained from the external nares. Twenty-four hours following treatment the ability of the rat to detect olfactory cues was tested, before subjecting them to the battery of behavioural experiments.

Test for anosmia

Five small pieces of dried rodent food (Oakes, P.M.D.) sweetened with evaporated milk were placed on the floor of a clean cage, measuring 20 × 40 cm. They were covered with 2.5 cm clean wood shavings. Each rat in turn was placed in the cage and left there for 15 min or until it had located all of the food pellets. The cage was cleaned and fresh shavings and impregnated pellets used for each test.

Locomotor activity test

Locomotor activity was measured with an Animex meter (LKB Farad, Sweden), sensitivity and tuning: 40 μA. Rats were placed individually in a clean perspex cage without bedding material and having a floor area of 1000 cm^2. The rat had access to food and water. The cage was placed on the centre of the meter which was in a darkened room. Activity counts were recorded at 5 min intervals for 30 minutes.

Passive avoidance experiment

The apparatus consisted of an open-topped perspex box 55 cm square with a stainless steel grid floor. The rods were 1.2 cm apart and connected to the terminals of a stimulator (SRI Model 6051) delivering square wave pulses at a constant voltage through a 'scrambler' unit. The shock delivered was constant at 0.85 mA (70 V, 6 ms, 6 Hz).

The rat's paws were wiped with a damp cloth to improve electrical conductivity and it was placed on the central wooden platform, 19 cm square and 4 cm above grid level. The latency time for the rat to step off the platform with all four paws was measured. The rat was immediately removed and the procedure repeated with an intertrial interval of 30 s until the rat remained on the platform for two minutes. The rat was then considered to have learnt to avoid the foot-shock. The number of trials needed by each rat to reach this learning criterion was recorded.

Irritability scoring test

The 'irritability' of a rat was scored by means of an arbitrary numerical system similar to that of King (1958) and Nurimoto, Ogawa & Ueki (1974) (Table 1). The stimuli used were: (a) a puff of air blown sharply on to the back of the rat whilst it was facing away from the experimenter; (b) a loud handclap delivered close to and in front of the rat's nose.

Estimation of pain threshold

Immediately before the passive avoidance experiment each rat was placed on the grid floor of this apparatus and footshock applied for periods of 0.7 s, increasing the intensity by 0.05 mA every 30 s until the animal showed visible signs of discomfort (flinching). The current intensity at this point was used to provide an estimate of pain threshold.

Table 1 Scoring system (after King, 1958) used for irritability scoring test

Score	*Response*
0	No response
1	Slight—rat raises head/ moves away from stimulus
2	Moderate—rat jumps and freezes for 0–2 s
3	Marked—rat jumps and freezes for 2–15 s
4	Extreme—rat jumps and freezes for > 15 s

The maximum score attainable for two stimuli was eight.

Statistics

The results of the locomotor activity and passive avoidance experiments were analysed using a two-tailed Student's t test. Significance values of $P < 0.05$ were used except where otherwise stated. The significance of the results of the irritability scoring test was determined by a Mann Whitney U test.

Results

Verification of lesions

In these studies olfactory bulbectomy was assessed macroscopically. All rats in which less than 70% of the bulbs had been removed or whose frontal cortex had been damaged were omitted from the results. In every successful bulbectomy the accessory olfactory bulbs had also been ablated.

Anosmia testing

All five hypotonic saline-treated rats found and ate the pellets within the 15 min period. The rats receiving an intranasal injection of $ZnSO_4$ solution all failed to find any pellets although they explored the cage thoroughly.

Pain threshold

None of the experimental groups was significantly different from controls with respect to the intensity of footshock required to elicit a pain response (see Table 2).

Table 2 Effects of bulbectomy (OB), $ZnSO_4$ application and drugs on pain threshold

Treatment	n	*Mean threshold footshock intensity (mA ± s.e.)*
Controls*	31	0.45 ± 0.02
OB	26	0.44 ± 0.02
$ZnSO_4$	5	0.47 ± 0.01
OB + Ami (10 mg/kg)	5	0.45 ± 0.02
OB + M (15 mg/kg)	5	0.48 ± 0.02

n = number of rats per group
* This group includes both sham-operated rats and those treated with intranasal infusion of hypotonic saline. OB rats were pretreated with either amitriptyline (Ami) or mianserin (M) for seven days before testing.

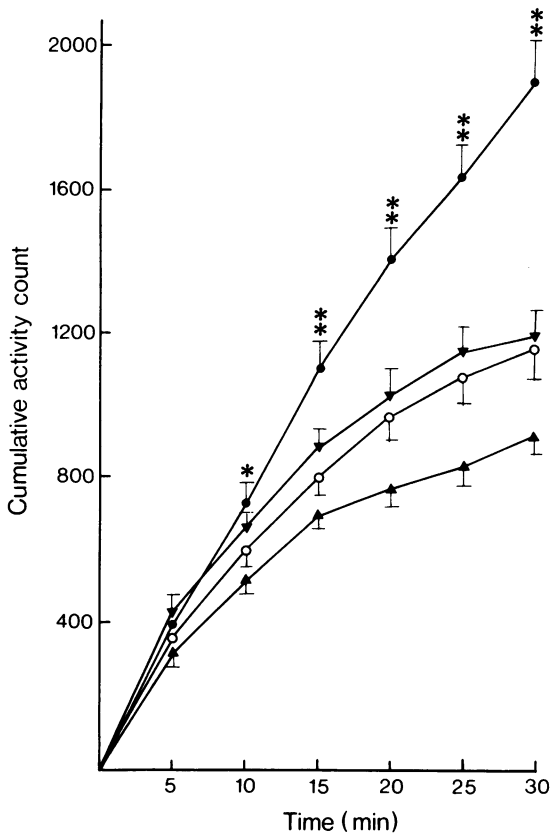

Figure 1 The effects of centrally or peripherally induced anosmia on the locomotor activity of rats. Fourteen days after surgery or 24 h after $ZnSO_4$ or hypotonic saline infusion, rats were placed on an Animex meter for a single 30 min session. (○) Sham-operation, $n = 26$; (▲) hypotonic saline infusion, $n = 5$; (▼) $ZnSO_4$ infusion, $n = 5$; (●) bulbectomy, $n = 26$. Points represent mean activity and the vertical bars indicate s.e. mean.
* Significantly different from sham-operated controls $P < 0.05$; ** $P < 0.001$ as determined by Student's t test (two-tailed).

Spontaneous locomotor activity

Bulbectomized rats had a significantly higher activity throughout the 30 min recording period than sham-operated animals (Figure 1). There were no significant differences between the activity of the control rats and those treated with $ZnSO_4$. Both amitriptyline and mianserin brought about a dose-dependent decrease in the activity of the bulbectomized rats, the decrease due to the higher dose being significantly different ($P < 0.05$) from that of the lower dose as well as from placebo-treated control activity ($P < 0.001$, Figure 2a, b), but had no significant effect on the sham-operated animals (Figure 2c, d).

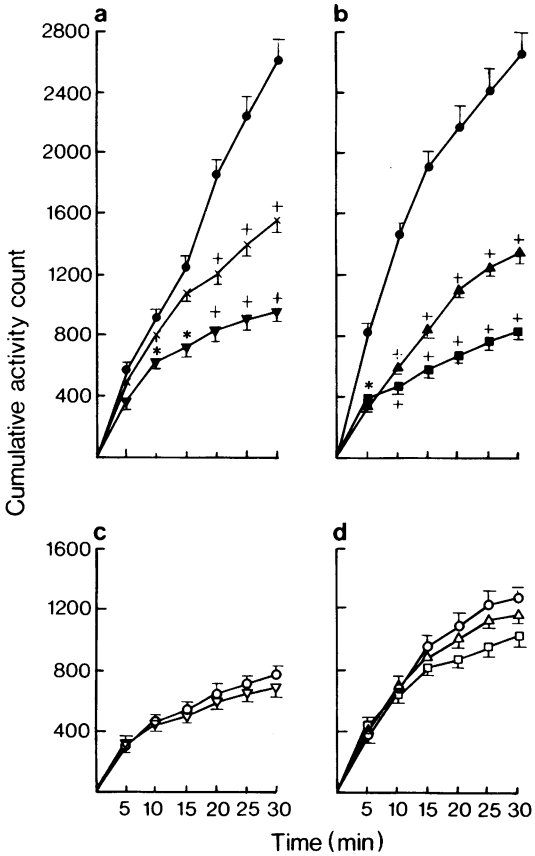

Figure 2 Locomotor activity *v* time curves for (a) bulbectomized rats pretreated with amitriptyline; (b) bulbectomized rats pretreated with mianserin; (c) sham-operated rats pretreated with amitriptyline; (d) sham-operated rats pretreated with mianserin. Chronic drug pretreatment began 14 days after surgery and locomotor activity using an Animex meter was measured on day 21. Closed symbols represent mean values for bulbectomized rats, open symbols for sham-operated rats. (●, ○) Saline pretreatment, $n=8$; (×) amitriptyline 3 mg/kg, $n=5$; (▼,▽) amitriptyline 10 mg/kg, $n=5$; (▲, △) mianserin 5 mg/kg, $n=5$; (■, □) mianserin 15 mg/kg, $n=5$. Vertical bars indicate s.e. mean.
* and + Significantly different from respective saline-pretreated controls ($P<0.05$ and $P<0.001$) as determined by Student's *t* test (two-tailed).

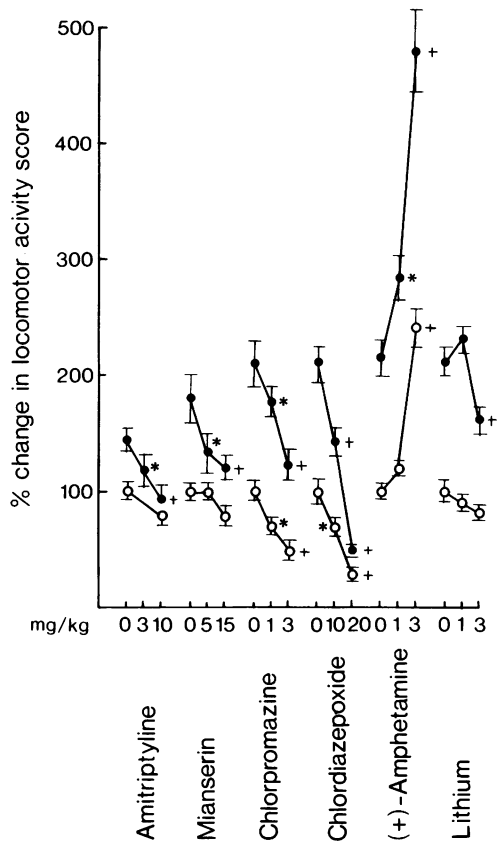

Figure 3 Percentage change in locomotor activity scores (locomotor activity score of placebo-pretreated sham-operated rats = 100%) for bulbectomized (●) and sham-operated (○) rats after pretreatment with psychotropic drugs.

Chronic drug pretreatment began 14 days after surgery and locomotor activity was measured, using an Animex meter, on day 21. Points represent the mean values of between 5 and 8 rats. Vertical bars indicate s.e. mean.
* and + Significant differences ($P<0.05$ and $P<0.001$; two-tailed Student's *t* test) from respective saline-pretreated controls.

Amphetamine produced a significant dose-dependent increase in the acitivity of both bulbectomized and sham-operated groups whereas chlorpromazine and chlordiazepoxide brought about a similarly significant reduction in locomotor activity. Pretreatment with lithium sulphate resulted in no significant changes (see Figure 3).

Passive avoidance acquisition

The results of this experiment are shown in Figure 4. Bulbectomized rats required a significantly greater number of trials to acquire the response than either sham-operated or $ZnSO_4$-treated rats. The performance of bulbectomized rats pretreated with either amitriptyline or mianserin was significantly improved in a dose-dependent manner but similarly treated sham-operated rats showed no greater tendency to avoid the footshock.

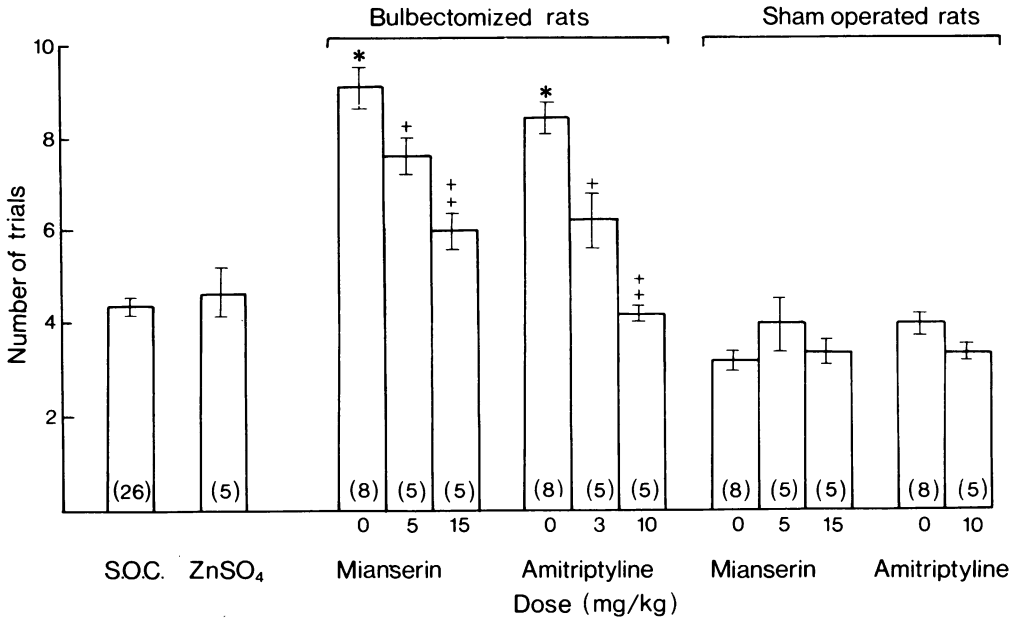

Figure 4 The effects of bulbectomy, $ZnSO_4$ treatment and drug pretreatment on passive avoidance acquisition. Chronic drug pretreatment began 14 days after surgery and the passive avoidance test was carried out on day 21. Each column represents the mean number of trials needed by each group to acquire the response (avoidance of footshock by remaining on platform for at least two minutes). S.O.C. = sham-operated controls. Numbers in parentheses at base of columns show the group size. Vertical bars indicate s.e. mean. * Significantly different from sham-operated controls ($P < 0.001$); + and ‡ significantly different from saline-pretreated bulbectomized rats ($P < 0.05$ and $P < 0.001$ respectively) as determined by Student's t test (two-tailed).

Table 3 Effects of drug pretreatment on passive avoidance and irritability

		Step-down passive avoidance[1]		*Irritability*[2]	
Drug	*mg/kg*	*Bulbectomized rats*	*Sham-operated rats*	*Bulbectomized rats*	*Sham-operated rats*
Amitriptyline	3	−−	/	0	/
	10	−−−	0	−	0
Mianserin	5	−−	0	0	0
	15	−−−	0	−	0
Amphetamine	1	−−−	−−−	0	0
	3	−−−	−−	+	++
Chlorpromazine	1	0	++	−	0
	3	+++	+++	−−−	−
Chlordiazepoxide	10	++	++	−−	−
Lithium	1	0	0	0	0
	3	++	0	0	0

[1] Measured as the number of trials a rat required before acquiring the appropriate response, i.e. remaining on the safety platform for at least 2 minutes.
[2] Measured as the cumulative score obtained by grading the rat's response to two novel stimuli (for further details see text).
Rats were pretreated for 7 days before testing. Symbols represent the mean response of between 5 and 8 rats. (/) no experiment; (0) no effect; (− or +) decrease or increase in the number of trials or irritability score, $P < 0.1$–0.05; (−− or ++) $P < 0.05$–0.01; (−−− or +++) $P < 0.01$–0.001.

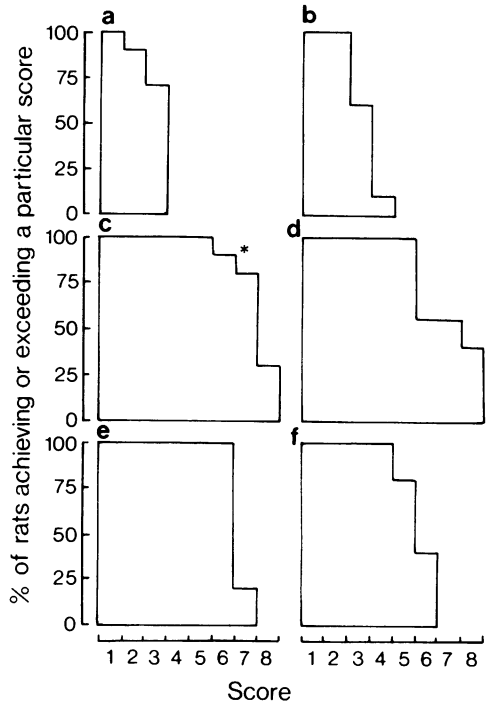

Figure 5 Effects on the irritability score of (a) sham-operation and hypotonic saline infusion; (b) intranasal $ZnSO_4$ infusion; (C) bulbectomy; (d) saline pretreatment of bulbectomized rats; (e) chronic pretreatment of bulbectomized rats with amitriptyline (10 mg/kg); (f) chronic pretreatment of bulbectomized rats with mianserin (15 mg/kg). Numbers in parentheses show group size.
*Significantly different from sham-operated controls ($P < 0.01$) as determined by a Mann Whitney U test. Drug pretreatment produced no significant changes.

Table 3 summarizes the results of this experiment. In comparison to the antidepressants, amphetamine improved the performance of both sham-operated and bulbectomized rats. Chlorpromazine and chlordiazepoxide significantly delayed acquisition in both groups while lithium sulphate slightly increased the deficit exhibited by bulbectomized rats.

Irritability scoring

The results of this experiment are shown in Figure 5. Most of the sham-operated, hypotonic-saline-treated and $ZnSO_4$-treated rats received a cumulative rating of 3 and none more than 4, whereas all bulbectomized animals scored at least 5 and 30% obtained the maximum possible score of 8. In addition to the exaggerated startle and freezing response, the bulbectomized rats would often attack the stimulus source. Both antidepressants slightly but non-significantly reduced the hyperirritability score of the bulbectomized rats. No change in the responses of the sham-operated rats pretreated with either amitriptyline or mianserin was observed.

Amphetamine produced a non-significant increase in the scoring. In contrast, pretreatment with either chlorpromazine or chlordiazepoxide resulted in a signficant reduction in the aggressive response of the bulbectomized rats. These drugs did not change the low scores of the sham-operated animals. Lithium again had no effect (see Table 3).

Discussion

In agreement with Marks, Remley, Seago & Hastings (1971), Sieck (1972) and Cain (1974), we have demonstrated that removal of the olfactory bulbs precipitates a specific behavioural syndrome. One possibility for the behavioural changes was that they could be attributed to loss of olfactory sensibility. However, our experiments have shown that the performance of rats rendered peripherally anosmic was not significantly different from controls. Therefore this adds to the considerable number of reports suggesting that the alterations in behaviour observed after ablation of the olfactory bulbs are not due to anosmia *per se* (Hankins, Garcia & Rusiniak, 1973; Cain & Paxinos, 1974).

Examination of the locomotor activity results showed that the graph of the cumulative activity of the bulbectomized rats followed a straight line whereas that of sham-operated animals levelled off after 15–20 min (see Figure 1). Similar results have been reported (for both increased locomotor activity and passive avoidance deficits) for lesions in various limbic sites, for example, amygdala (Pellegrino, 1968), hippocampus (Douglas & Isaacson, 1966; McCleary, 1966), and septum (Thomas, 1972). These have been explained by a failure in the habituation of exploratory behaviour and a similar argument could be put forward for the bulbectomized rat, especially as the olfactory bulb has been shown to have a wealth of interconnections with the limbic system (Powell, Cowan & Raisman, 1965).

Because of the changes in affective and exploratory postlesion behaviour, some influence of olfactory bulb lesions on avoidance behaviour would be expected. We have confirmed this for the passive avoidance situation where bulbectomized rats are deficient at acquiring the response (Marks *et al.*, 1971; Sieck, 1972). In contrast, workers investigating the behaviour of such rats in two-way active avoidance experiments have reported faster escape and better avoidance learning (Brown, Harrell & Remley, 1971; Sieck & Gordon, 1972; Sieck, 1972; 1973). Most rats which were slow to reach the passive avoidance

learning criterion were observed to adopt fixed 'escape' tendencies such as leaping for the cage top or jumping on to the grid as soon as they were placed on the platform. This suggests that bulbectomized rats appreciated that they would be shocked but were unable to acquire an appropriate avoidance response or were less able to inhibit the step-down response. The opposite effects on active and passive avoidance tests also argue against an explanation in terms of altered sensitivity to painful stimuli and, more directly, our results show that bulbectomized rats have similar pain thresholds to controls.

Before entering into a full discussion of the specific effects of the antidepressants amitriptyline and mianserin on the olfactory bulbectomy syndrome, it is constructive to consider the actions of the other psychoactive drugs used in this study. It can be seen that the major tranquillizer chlorpromazine and the anxiolytic drug chlordiazepoxide and lithium sulphate (at the higher dose) all exaggerated the learning deficit exhibited by bulbectomized rats in the step-down passive avoidance test. In contrast, amphetamine enhanced their performance in a manner similar to that of the antidepressants. Such an action of amphetamine is not surprising in view of its well-documented central effects. However, the behavioural effects of amphetamine can be differentiated from those of the antidepresants by examination of the locomotor activity results, when a clear difference emerges.

It is suggested therefore that the bulbectomized rat model dissociates the antidepressants from other classes of psychotropic drugs using tests measuring locomotor activity and passive avoidance responding. Amitriptyline and mianserin reversed both the increased activity and poor performance in the passive avoidance test exhibited by the bulbectomized rats, without lessening their irritability, as measured by grading their responses to sudden novel stimuli directed towards them. This suggests that bulbectomy produces two distinct deficits characterized by their sensitivity to antidepressant drugs. However, several workers have reported that bulbectomy facilitates mouse killing (Bugbee & Eichelman, 1972; Ueki, Nurimoto & Ogawa, 1972a). Ueki and co-workers (1972b) have demonstrated that amitriptyline selectively antagonizes this component of the 'hyper-irritability' syndrome. Caution should therefore be exercised when defining 'irritability' in future studies of bulbectomized animals, especially since in our experiments the pain thresholds of bulbectomized rats were not altered.

At the biochemical level Pohorecky, Zigmond, Heimer & Wurtman (1969) and Cairncross & King (1971) showed that bulbectomy results in a significant reduction in telencephalic noradrenaline. Subsequent chronic pretreatment with amitriptyline resulted in an enhancement of learning which was paralleled by an increase in the noradrenaline content of the telencephalon (Cairncross, Schofield & King, 1974). They suggested that the results offer a possible explanation for the mode of action of amitriptyline in the clinical situation. However Leonard (1974) concluded from neurochemical studies that, in contrast to the tricyclic antidepressants, mianserin does not affect the release or uptake of 5-hydroxytryptamine or noradrenaline after acute administration. Given chronically for three weeks this drug does increase the release of noradrenaline, particularly in the midbrain and brainstem regions, since the steady state concentration of normetanephrine was increased. Mianserin therefore has a different neurochemical profile from that of amitriptyline, but like amitriptyline increases the concentration of brain noradrenaline (though by a different mechanism).

As both amitriptyline and mianserin have behaved identically in the tests described in this paper and in others (van Riezen *et al.*, 1976) the model has withstood the challenge of a novel antidepressant which was not predicted using coventional screening methods.

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