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The Effect of Psychotropic Drugs on Food Reinforced Behaviour and on Food Consumption

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Introduction

Food reinforced behaviour i.e. behaviour conditioned by a reward of food in animals can be suppressed by fear, and there is evidence that some psychotropic drugs can overcome fear and restore the food reinforced behaviour (BRADY, 1956; NAESS and RASMUSSEN, 1958; GELLER and SEIFTER, 1960; GROSSMAN, 1961). The experiments to be described here were part of a programme devoted to investigating the properties of psychotropic drugs. The Skinner box test used was evolved from BRADY's (1956) conditioned suppression technique and the food confict test was a modification of NAESS and RASMUSSEN's (1958) water conflict method. As some drugs were found to enhance food rewarded behaviour in these tests a check was made to see if they would also influence food consumption in the rats' home cages where fear should be minimal.

Methods

1. The Skinner Box Test

The apparatus consisted of a conventional Skinner box 22×24×20 cm (high) having as usual a floor of electrifiable metal bars, two rat manipulanda (levers), and a drinking device to deliver 0.1 ml fluid. A shock generator could deliver alternating current to the bars via a scrambler. Shocks, when used, were of 250 μA intensity and 2 seconds duration.

The experimental subjects were SPF female hooded rats, bred in these laboratories (Alderley Park Strain II). They were received for experimental use at weaning age (3 weeks) and were handled by the experimenter and familiarized with the Skinner box during their growing phase. When they reached 100—120 g (approx 10 weeks old) they were trained in the Skinner box to press either lever for a reward of diluted (1:10) sweetened condensed milk. When they had achieved a satisfactory rate of performance (about 60 presses in 20 minutes), they were divided into groups of six and regular weekly sessions were commenced, twenty minutes long, in which every fourth press was rewarded.

The rats were fasted for 24 hours before use. Thirty minutes before the session they were dosed orally either with saline or the drug to be tested. Drug sessions alternated with saline sessions.

Sedative and neuroleptic drugs were given at the maximum dose possible without causing ataxia or other visible side effect.

In the case of anti-depressants the dose was fixed by reference to other tests believed to indicate anti-depressant activity, the aim being to use doses corresponding to those used clinically.

Lever pressing activity was recorded graphically and the number of presses was also counted electronically.

The effect of drugs was calculated as follows:

$$\left(\frac{2d}{Sb + Sa} - 1\right) \times 100$$

where d is the mean number of presses in the drug session
Sa is the mean number of presses in the Saline Session after
Sb is the mean number of presses in the Saline Session before

i.e. The formula gives the percentage increase (or decrease) over the mean control value. The significance of the results was determined by means of students "T" Test.

In one group of these rats (No. I) the effect on drug responses of aversive stimulation was examined. The procedure was as follows:

Three sequences of warning-shock were presented to the animal at 6 minute intervals during the 20 minute session. The warning consisted of a clicking noise continuing for 2 minutes, at the end of which the shock occurred. The effect of this was to reduce the total number of lever presses during the session in which shocks occurred. The magnitude of the effect was calculated by reference to control sessions before and after. The effect of the drug alone was measured in a sequence of three sessions, as described above and likewise the effect of drug combined with warning and shock was measured by a further 2 sessions thus: control, drug, control, drug + shock, control. The sessions took place at weekly intervals.

Thus it was possible to compare the effects of:

i) Shocks.
ii) Drug.
iii) Shocks + drug.

2. Food Conflict Test

Twenty female SPF albino rats (Alderley Park Strain I) 100—150 g were starved overnight and the next day were placed one at a time in the experimental box. This was made of Perspex 20×20×40 cm and the

floor was an electrifiable grid. Attached to the front wall of the box, nearest the observer, was a food trough. Into this were placed 6 units of breakfast cereal before admitting the rat.

When the rat was introduced a clock was started and the observer noted the time elapsing before the rat took the first unit of cereal. This period is the "feeding latency" referred to in the tables). After the rat had eaten 2 units of breakfast cereal every approach to the food trough was punished with a brief electric shock of duration 0.6 sec. The total number of units eaten within 10 minutes (by the clock) was recorded. Animals not starting within this period were discarded. The starters were earmarked for identification and kept for the second part of the experiment. They were divided into two balanced groups according to their latencies of feeding. Sometimes it was necessary to select from a further 20 to get an adequate group size for the next part of the experiment.

A week later these animals were again starved overnight and again the feeding latency and food eaten were measured in the same way.

This time, however, 30 minutes before admitting the rat into the experimental box it was dosed either with saline (control group) or the drug to be tested (test group). No shocks were given on this occasion. The data from the control groups show that untreated rats were inhibited as a result of their experience in the first session. We also confirmed that when shocks were omitted in the first part of the experiment there was no inhibition of feeding behaviour in the second.

When calculating the mean feeding latency for the tables of results, latencies of more than 10 minutes are counted as equal to 10 minutes.

3. Food Consumption Experiments

a) Grouped Rats. Female albino rats 100—150 g weight were caged in groups of four and put on a schedule of 22 hours food deprivation and 2 hours feeding. Food consumption was recorded daily. After allowing a week for the rats to become accustomed to this regime the experiments were carried out as follows. Two groups of four rats were used for each drug. One was treated orally with saline on two consecutive days half an hour before feeding and the other with the drug to be tested. On the next two consecutive days the groups were crossed over. Food consumption after drug was compared with that after saline.

b) Isolated Rats. Female albino rats 100—150 g were caged singly and fed for only two hours daily on four consecutive days each week. The remaining three days each week they were grouped and fed ad.lib. Continued isolation and restriction of feeding time have been found to cause loss of condition in rats; but on the above regime they remained in apparent good health throughout the experiments. The animals were treated orally with the drug to be tested, half an hour before feeding time.

Results

1. Skinner Box

The drugs chosen for study represent three pharmacological types used in the treatment of mental disorders.

a) Sedatives (minor tranquillizers)
chlordiazepoxide
meprobamate
phenobarbitone
thalidomide

b) Neuroleptics (major tranquillizers)
chlorpromazine
haloperidol

c) Antidepressants
amitriptyline
imipramine

As will be seen from Table 1 three Sedative drugs, chlordiazepoxide, meprobamate and phenobarbitone, clearly enhance food rewarded lever pressing. One of the neuroleptics, haloperidol, clearly decreases it. Antidepressants have smaller effects but surprisingly amitriptyline tends to increase lever pressing and imipramine tends to decrease it. The variability of control figures in Table 1 is due (a) to different groups of rats and (b) the gradual increase of performance as the rats got older. This is not apparent in the table because the results are not arranged chronologically.

When electric shocks are given, food rewarded lever pressing is reduced by about 70% (see Table 2). Shocks given concurrently with drug treatment still reduce food rewarded lever pressing. Phenobarbitone for instance showed a 206% increase in lever pressing when no shocks were given but only 24% increase when shocks were given. Meprobamate was exceptional in that it appeared to nullify the effect of the shocks.

2. Food Conflict Test

The results obtained in the food conflict test with the same psychotropic drugs are shown in Table 3. Again one can see that phenobarbitone, meprobamate and chlordiazepoxide enhance food seeking behaviour, reducing the number of non-starters and reducing feeding latency. Again haloperidol reduces food seeking behaviour and chlorpromazine has little effect. Imipramine has a tendency to reduce food rewarded behaviour in this test as in the Skinner box.

Statistical tests (Fishers exact test) applied to the numbers of non-starters show significant (p 5%) differences only in the case of chlordiazepoxide and amitriptyline. However, because of the concord between

Table 1. *Effect of drugs on lever pressing*

Drug	Dose mg/kg	Group	No. of rats	Mean no. presses in: Control session before	Drug session	Control session after	Change due to drug %	Significance at 5% level
Sedatives								
Chlordiazepoxide	4	IV	6	157	175	194	nil	N.S.
	8	I	6	37	137	46	+234	Sig.
Meprobamate	10	IV	6	96	100	127	−10	N.S.
	25	III	5	146	280	195	+133	Sig.
	50	IV	6	127	325	157	+130	Sig.
Phenobarbitone	2	III	4	162	138	111	+1	N.S.
	5	II	5	242	409	170	+94	Sig.
	10	II	6	85	195	132	+80	Sig.
	10	II	6	64	191	61	+206	Sig.
Thalidomide	200	I	6	80	112	78	+42	N.S.
Neuroleptics								
Chlorpromazine	1	II	5	170	247	249	+18	N.S.
	4	I	6	46	36	54	−28	N.S.
	8	IV	6	319	86	432	−77	Sig.
Haloperidol	1	I	6	105	1	156	−100	Sig.
	1	VI	6	131	32	208	−81	Sig.
Antidepressants								
Amitriptyline	2	II	6	248	275	242	+12	N.S.
	5	I	6	156	171	122	+23	N.S.
	5	II	6	270	328	292	+21	N.S.
Imipramine	2	II	5	127	71	142	−42	N.S.
	2	IV	6	208	13	183	−93	Sig.
Saline		IV	6	326	366	345	+9	N.S.
Feeding night before test		IV	6	413	282	352	−26	Sig.

Table 2. *Interaction between drugs and aversive stimulation*

Drug	Dose mg/kg p.o.	Effect on lever pressing: In no-shock session	In shock session
Phenobarbitone	10	206% increase[1]	24% increase[1]
Meprobamate	50	130% increase	176% increase
Chlordiazepoxide	8	234% increase	79% increase
Chlorpromazine	4	28% decrease	73% decrease
Amitriptyline	5	23% increase	80% decrease
Imipramine	2	47% decrease	80% decrease
No treatment		0 (theoretically)	69% decrease

[1] As compared with no-drug-no-shock sessions before and afterwards.

Table 3. *Food conflict test. Second session*

Drug	Dose mg/kg	Mean latency min		Non-starters		Group size
		T	C	T	C	
Meprobamate	50	3.8	7.5	0	0	6
Phenobarbitone	15	7.9	10.0	5	7	7
Chlordiazepoxide	8	3.9	5.5	0	5	12
Thalidomide	100	7.8	7.9	6	6	8
Chlorpromazine	4	6.3	6.9	7	6	13
Chlorpromazine	1	6.9	6.1	4	3	6
Haloperidol	2	10.0	7.3	6	4	6
Amitriptyline	2	3.7	10.0	1	6	6
Imipramine	2	10.0	8.7	7	4	7

T = Drug treated group; C = Saline treated control group.

these food conflict results and the Skinner box results it was considered necessary to test some of these drugs on straightforward food consumption.

3. Home Cage Food Consumption Tests

a) Grouped Rats. The results of this experiment clearly showed that chlordiazepoxide (8 mg/kg) and phenobarbitone (15 mg/kg) had no effect on food consumption. However, the drugs had equally clearly increased food rewarded lever pressing in the Skinner box situation (Table 1) and therefore the following experiments were carried out.

b) Isolated Rats. The results of two experiments on the food consumption of isolated rats are given in Tables 4 and 5. In the first experiment the food consumption of the rats after treatment with drug was compared with their consumption on the preceding and following days when they were dosed with normal saline. In the second experiment half the rats were treated with drug and the rest with saline and on the following day the subgroups were crossed over.

Table 4. *Isolated rats*

Drug	Dose mg/kg p.o.	Total food consumption of 6 rats (grams)			$\frac{2d}{p+f} - 1 \times 100$	
		Preceding day (p)	Under drug (d)	Following day (f)		
Meprobamate	50	47	44	55	−14%	N.S.
	100	46	61	64	+11%	N.S.
	200[1]	39	45	45	+ 7%	N.S.
Chlordiazepoxide	8	34	62	47	+53%	Sig.
	8	41	85	51	+85%	Sig.
Phenobarbitone	10	33	57	59	+24%	Sig.
	20	47	74	55	+47%	Sig.

[1] This dose caused ataxia.

Table 4 shows the results of the first experiment in which the three drugs—chlordiazepoxide, phenobarbitone and meprobamate—that had shown increases of food rewarded lever pressing in the Skinner box were examined. The first two can be seen to have increased food consumption, but surprisingly meprobamate had little effect.

Table 5. *Isolated rats*

Drug	Dose mg/kg	Total food consumption of 10 rats (grams)		Percentage increase due to drug	
		Under drug	Under saline		
Meprobamate	100	104	89	17	Sig.[1]
Chlordiazepoxide	16	146	88	66	Sig.
Chlordiazepoxide	16	161	75	114	Sig.
Phenobarbitone	16	137	109	26	Sig.
Thalidomide	200	79	78	1	N.S.
Chlorpromazine	8	99	88	12	N.S.
Haloperidol	1	29	79	−63	Sig.
Haloperidol	1	13	77	−83	Sig.
Amitriptyline	5	72	81	−11	N.S.
Imipramine	2	90	93	−3	N.S.
Saline	—	77	73	5	N.S.
Saline	—	116	107	9	N.S.

[1] Just significant, probability = 5%.

Table 5 shows again that chlordiazepoxide and phenobarbitone enhance food consumption. Again meprobamate has little effect. On the other hand haloperidol markedly reduces food consumption. This would explain its effect on food rewarded lever pressing. The other drugs—thalidomide, chlorpromazine and the antidepressants—had no significant effect on food consumption. With the possible exception of imipramine they were also ineffective in the Skinner box (Table 1).

Discussion

The results reported above are summarized in Table 6. Four test situations have been used and in three of these the rats are isolated, in the fourth they are grouped with other rats.

As regards sedatives, the conclusion these results point to is that the more powerful sedative drugs are capable of enhancing food consumption or food rewarded behaviour under certain circumstances. One prerequisite for this enhancement seems to be that the animals are isolated.

There is abundant support in the literature for the conclusion that sedative drugs enhance food rewarded lever pressing and some for enhancement of home cage food consumption.

Table 6

	Skinner box	Food conflict	Food consumption	
			Isolated	Grouped
Sedatives				
Meprobamate	E	E	NA	NA
Chlordiazepoxide	E	E	E	NA
Phenobarbitone	E	E	E	NA
Thalidomide	NA	NA	NA	
Neuroleptics				
Chlorpromazine	R	NA	NA	
Haloperidol	R	R	R	
Antidepressants				
Amitriptyline	NA	E	NA	
Imipramine	R	R	NA	

E = enhanced food rewarded behaviour; R = reduced food rewarded behaviour; NA = no action on rewarded behaviour.

In the Skinner box situation RICHELLE *et al.* (1962) showed that in rats 10 mg/kg i.p. of chlordiazepoxide greatly enhanced food rewarded lever pressing on two different schedules of reinforcement. COOK (1964) showed the same for the monkey, both with chlordiazepoxide 20 mg/kg p.o. and meprobamate 50 mg/kg p.o. WEISSMAN (1959) showed that 8 mg/kg of pentobarbital i.p. enhanced food rewarded lever pressing in rats and VERHAVE (1959) showed that secobarbital 30 mg/kg s.c. did the same in the monkey, both on fixed interval and fixed ratio schedules. RICHELLE (1965) showed that food rewarded lever pressing was enhanced in the cat by meprobamate (absolute dose 200 mg; route not stated).

In NAESS and RASMUSSEN's (1958) water conflict test amobarbital 10—20 mg/kg s.c. and meprobamate 50—100 mg/kg s.c. increased the number of shocks tolerated by rats trying to get water.

In the home cage situation, increases of food consumption have been shown to occur in various species with chlordiazepoxide, barbiturates and meprobamate. RANDALL and SCHALLEK (1960) used rats and dogs and found that 12.5—50 mg/kg s.c. of chlordiazepoxide enhanced food consumption. The rats were presumably in groups; no effect was observed with meprobamate 50 mg/kg s.c. JONES (1943) showed that phenobarbitone 80 mg/kg/day p.o. depressed overall food intake but increased consumption of food offered three hours after the daily dose. OPITZ and AKINLAJA using singly caged rats obtained an effect with 8 mg/kg p.o. of phenobarbitone and the same dose of chlordiazepoxide. SPENGLER and WASER (1959) reported increased food consumption in singly housed male rats due to phenobarbitone 60 mg/kg i.p., and meprobamate at 200 mg/kg i.p.

Thus, although we could not show meprobamate to affect appetite appreciably, there is support in the literature for the results now reported on phenobarbitone and chlordiazepoxide. It is of interest to know whether these drugs act by control of anxiety or whether their action is primarily an enhancement of the appetite mediated by a direct action on the hypothalamic feeding centres. If one assumes that the level of anxiety is least in the "home-cage-grouped" situation, in which increased appetite is more difficult to show, it follows that the drugs act by controlling anxiety.

Turning to neuroleptics the literature shows that in all situations they reduce food rewarded behaviour. In the Skinner box lever pressing rate is decreased by neuroleptics (BRADY, 1956; WEISSMAN, 1959; GROSSMAN, 1961; COOK, 1965). Chlorpromazine reduces the number of shocks tolerated to obtain food or water (COOK, 1964; NAESS and RASMUSSEN, 1958). In the home cage situation JANSSEN (1965) has shown that all neuroleptics at small doses reduce food consumption. OPITZ and AKINLAJA (1966) confirm some of JANSSEN's findings. Our findings on neuroleptics are mainly consistent with these although chlorpromazine appears to be relatively feeble. It is therefore essential to interpret Skinner box results with neuroleptics against the background of their basic anorexiant effect.

The two antidepressants tested showed only marginal effects. Amitriptyline had a tendency to increase food rewarded behaviour whereas imipramine tends to decrease it. The effects are not great enough to be apparent in the food consumption tests. Although these two drugs are both antidepressants there are differences between them both clinically and in laboratory tests, amitriptyline having more sedative action than imipramine; thus SARGENT (1964) recommends amitriptyline for patients who cannot sleep and STILLE (1964) finds it three times more potent than imipramine in reducing spontaneous activity in mice.

Conclusions and Summary

1. Various measurements have been made of the change in food rewarded behaviour due to drugs.

2. Some sedatives enhance food rewarded behaviour in solitary rats. The Skinner box is a sensitive method of demonstrating this.

3. The evidence suggests that these sedatives act by controlling fear.

4. It is not possible using the Skinner box to say whether neuroleptics control fear because they have a basic anorexiant effect in laboratory animals.

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