Psychopharmacologia (Berl.) 38, 219–230 (1974)

The Relative Attenuation of Self-Stimulation, Eating and Drinking Produced by Dopamine-Receptor Blockade

E. T. Rolls, B. J. Rolls, P. H. Kelly, S. G. Shaw, R. J. Wood, and R. Dale

University of Oxford, Department of Experimental Psychology, Oxford, England

Received December 12, 1973; Final Version April 19, 1974

Abstract. Spiroperidol, which blocks dopamine (DA) receptors, attenuated self-stimulation of the nucleus accumbens, septal area, hippocampus, anterior hypothalamus and ventral tegmental area. Dopamine is thus involved in self-stimulation of many sites (in addition to the lateral hypothalamus). The attenuation was not a simple motor impairment of the speed of bar-pressing in that the nucleus accumbens and septal self-stimulation rates were lower than those in treated animals self-stimulating at other sites (Experiment 1). Feeding was partly attenuated, and drinking was much less attenuated by the spiroperidol. Since the rats bar-pressed for brain-stimulation reward, chewed pellets to eat, and licked a tube to drink, dopamine-receptor blockade may attenuate complex motor responses most. Alternatively, the blockade could affect brain-stimulation reward more than the controls of eating, and these latter more than the controls of drinking (Experiment 2). In Experiment 3, feeding and drinking were equally and severely attenuated when rats had to bar-press to obtain food or water. The attenuation was to a level similar to that found for self-stimulation. These experiments suggest that dopamine receptor blockade impairs eating, drinking and self-stimulation by interfering with complex motor responses.

Key words: Self-Stimulation — Eating — Drinking — Dopamine — Spiroperidol.

Introduction

There is evidence that dopamine receptors are involved in brain-stimulation reward. Self-stimulation of the hypothalamus through implanted electrodes is attenuated by the administration of agents which block dopamine (DA) receptors, for example, haloperidol (Stein, 1967), and the more specific pimozide (Wauquier and Niemegeers, 1972) and spiroperidol (Kelly, Rolls, and Shaw, 1973). Chlorpromazine, which blocks noradrenaline (NA) and DA receptors about equally (Andén, Butcher, Corrodi, Fuxe, and Ungerstedt, 1970) also reduces hypothalamic self-stimulation rate (Stein and Ray, 1960; Stark, Turk, Redman, and Henderson, 1969). Self-stimulation can be obtained in the A9 and A10

areas of Fuxe and Dahlström (1965), that is, in the region of the substantia nigra and intrapeduncular nucleus (Crow, 1972; Anzelark, Arbuthnott, Christie, and Crow, 1973), where dopamine-containing cell bodies are found.

There is also evidence that the attenuation of self-stimulation produced by dopamine-receptor blockade is relatively specific, at least with respect to arousal. Thus spiroperidol (which blocks DA receptors) produces complete attenuation of lateral hypothalamic self-stimulation in doses which have only small effects on arousal measured by locomotor activity and rearing. This is in contrast to the effects of NA-receptor blockade or the depletion of brain NA by disulfiram, which produce a much more marked attenuation of arousal than of self-stimulation (Kelly *et al.*, 1973; Rolls, Kelly, and Shaw, 1974). This evidence indicates that dopamine receptors are involved in self-stimulation of at least some sites, in particular in self-stimulation of the lateral hypothalamus and of the region of DA-containing neurones near the substantia nigra (see also Rolls, 1974).

The purpose of Experiment 1 is to determine whether dopamine receptors are involved in self-stimulation of sites other than the lateral hypothalamus and region of the substantia nigra. In Experiment 1 dose-response curves of the effects of spiroperidol which produces specific dopamine-receptor blockade (Andén *et al.*, 1970), on self-stimulation of the nucleus accumbens, septal region, anterior hypothalamus, hippocampus and ventral midbrain tegmentum were performed. These experiments also give some evidence on whether DA-receptor blockade attenuates self-stimulation by producing an impairment in the ability of the animals to bar-press, that is, in motor ability.

There is also some evidence that dopamine—containing pathways are involved in feeding and drinking. Ungerstedt (1971b) reported that if the nigro-striatal DA system (see Ungerstedt, 1971a) was selectively destroyed by local injections of 6-hydroxydopamine (6-OHDA) rats became aphagic and adipsic (and also hypokinetic but not cataleptic). Oltmans and Harvey (1972) showed that lesions of the nigrostriatal pathway produced aphagia and adipsia which were correlated with the depletion of DA. In a further demonstration that DA pathways are involved in eating, Ungerstedt (1971b) showed that the i.p. injection of pimozide, which blocks DA receptors, attenuates eating. A critical question raised by this work is whether dopamine is equally involved in eating, drinking, and self-stimulation. To examine this, dose-response curves of the effect of spiroperidol (which blocks DA receptors) on food and water intake were made in Experiments 2 and 3. These can be compared with the dose-response curves of the effect of spiroperidol on self-stimulation obtained in Experiment 1.

Experiment 1

Method

Seven male Sprague-Dawley rats weighing 260—350 g at the start of the experiment were implanted with arrays of up to 5 electrodes for self-stimulation. The electrodes were aimed at the ventral tegmental area (VT), the hippocampus (HIPP), the anterior hypothalamus (AH), the septal area (SEPT) and the nucleus accumbens using the coordinates shown in Fig. 1. At the termination of the experiments histological analysis (50 μ thionin-stained sections) showed that the electrodes had been well placed for the different sites (Fig. 1). The electrodes were made of size 00 stainless steel insect pins insulated to within 0.2 mm of the tip, and were implanted under Equi-thesin (Jensen-Salsbury) (3.0 ml/kg) anaesthesia. The animals were tested for self-stimulation in a box 26 cm × 16 cm × 38 cm. Depression of a bar at one end of the box switched on capacitively coupled 0.1 msec constant current stimulus pulses recurring at a frequency of 100 Hz for 0.3 sec. Current return was via screws implanted in the skull.

The animals were tested every second day, once in the morning after a placebo injection and once in the afternoon after a drug or a placebo injection. The morning tests were used only to check that the baseline rate of self-stimulation was constant over days for the different self-stimulation sites. The afternoon tests were used to construct a dose-response curve of the effect of spiroperidol on self-stimulation. The order of drug and placebo injections was completely counterbalanced for subgroups of the rats, and was partially balanced overall. Each testing session was as follows. First, there was a 3-min period of anterior hypothalamic self-stimulation. Then self-stimulation rate was measured at each site for five minutes, with one-minute change-over periods between each site to allow the self-stimulation rate to stabilize at each site. The number of self-stimulations at each site were measured over the five-minute periods. The sites were always tested in the same order. The current at each site was chosen so that regular self-stimulation without pauses occurred, and so that any change in current altered the self-stimulation rate. Thus the rate of self-stimulation at each site was a measure of the potency of the stimulation. The currents for the different sites were approximately $1^1/_2$ times threshold. The currents were held constant for each site for the duration of the experiment. With this procedure self-stimulation at each site had its own characteristic rate (see Fig. 2).

The dopamine-receptor blocking agent used was spiroperidol (generously supplied by Janssen Pharmaceutica, Beerse, Belgium) in doses of 0.02, 0.05 and 0.1 mg/kg. The drug was prepared for intraperitoneal injection by dissolving 2.5 mg of spiroperidol and 7.5 mg of tartaric acid in 50 ml of water. For the dose of 0.1 mg/kg of spiroperidol, 2 ml/kg of this solution was injected. For the smaller doses the solution was diluted so that the final amount of solution injected was still 2 ml/kg. The placebo injection was 2 ml/kg of 7.5 mg of tartaric acid dissolved in 50 ml of water.

Results

Dose-response curves for the effect of spiroperidol on self-stimulation at different sites are shown in Fig. 2. For all the sites a dose-dependent decrease in self-stimulation rate was produced by spiroperidol. This was true for individual rats as well as for the grouped data. (In Fig. 2 the number of rats tested at the different doses varies first, because some of the rats pulled out their implants in the course of the experiment; second, because some rats did not self-stimulate on every electrode, and

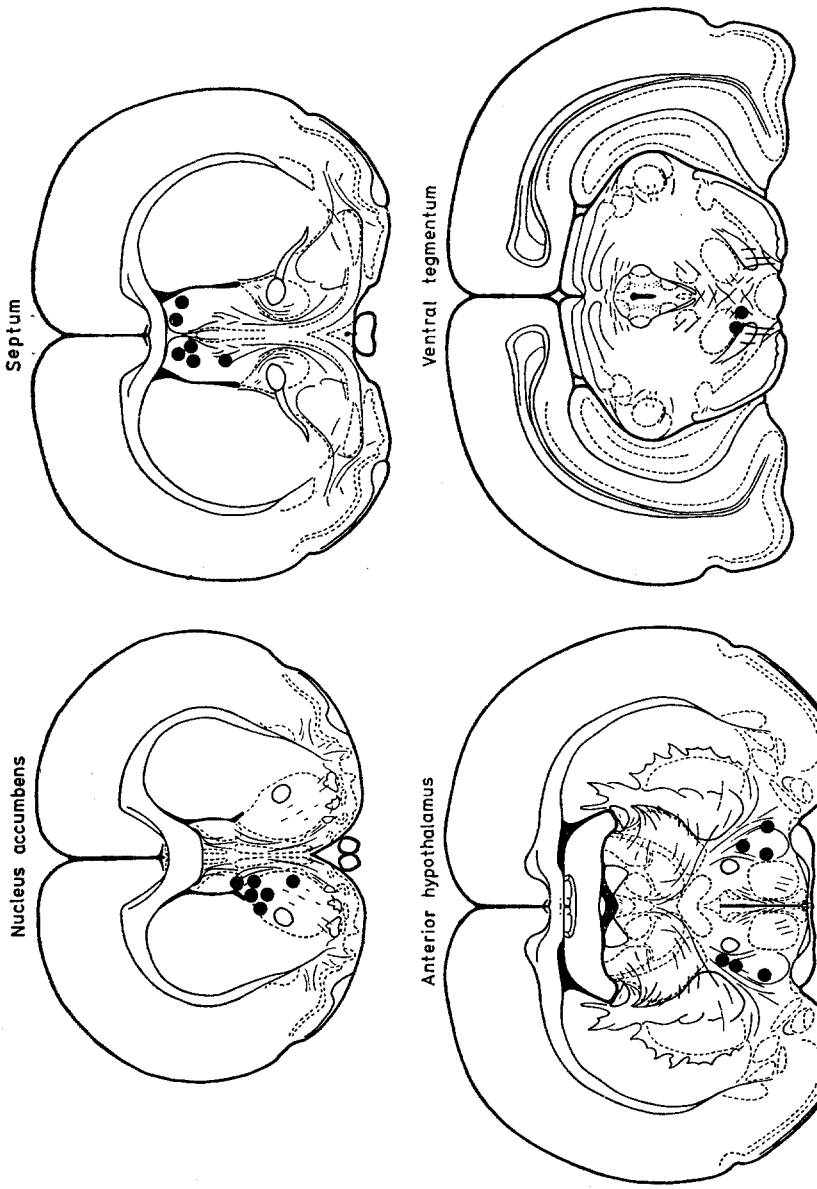

Fig. 1. Examples of the stimulation sites are shown by the black dots. The level-head implantation co-ordinates are: nucleus accumbens: 1.6 mm anterior to bregma, 0.8 mm lateral to the midline and 5.0 mm beneath the dura (+ 1.6, 0.8, 5.0 mm); septum: 0.0, 0.5, 4.4 mm; anterior hypothalamus: − 1.2, 1.4, 7.3 mm; ventral tegmental area: − 6.0, 0.8, 7.8 mm. The hippocampal electrodes were implanted at −4.5; 3.0, 3.0 mm (not illustrated). The

third, because at the nucleus accumbens and AH sites at 0.1 mg/kg two rats were tested twice as part of a balanced subgroup design). For comparison, dose-response curves for lateral hypothalamic self-stimulation are also shown in Fig. 2 (data from Rolls *et al.*, 1974; see Rolls, 1974).

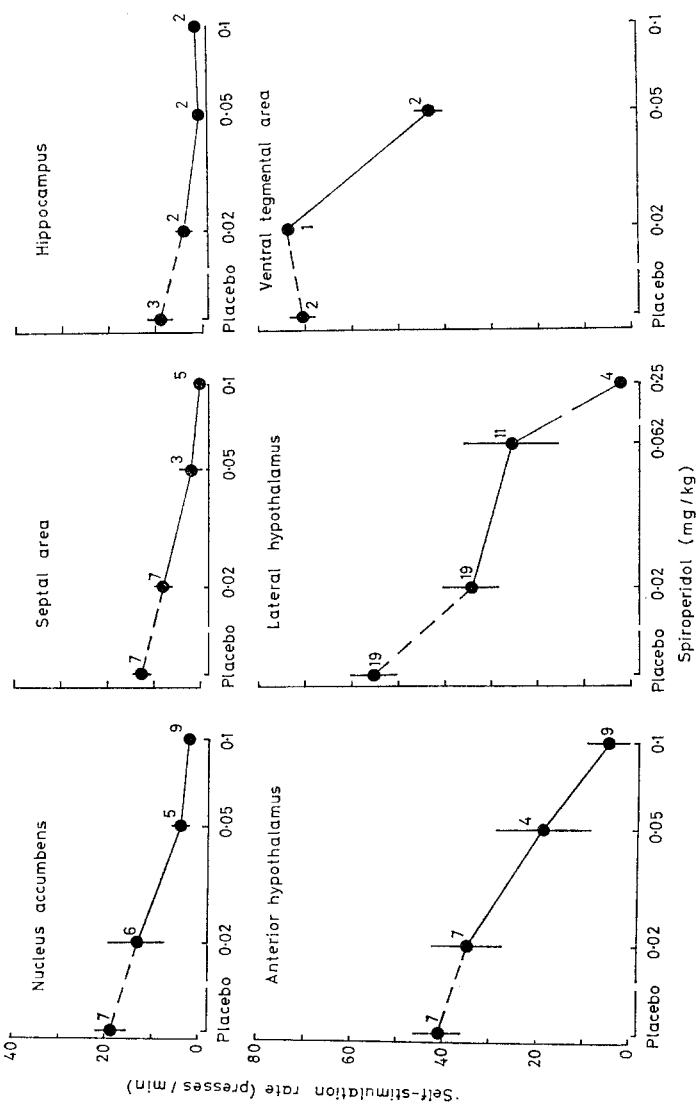

Fig. 2. Dose-response curves of the effect of spiroperidol on self-stimulation rate, expressed as a percentage of the placebo rate. The points represent means ± S.E. The number of rats is indicated beside each point

The baseline self-stimulation rates at the different sites were different. To facilitate comparison between the different self-stimulation sites the results were also expressed as percentages. The self-stimulation rate of each rat after a drug was expressed as a percentage of its own self-stimulation rate after the placebo. The resulting dose-response curves are shown in Fig. 3. It is again clear that a dose-related decrease in self-stimulation rate at the different sites was produced by spiroperidol.

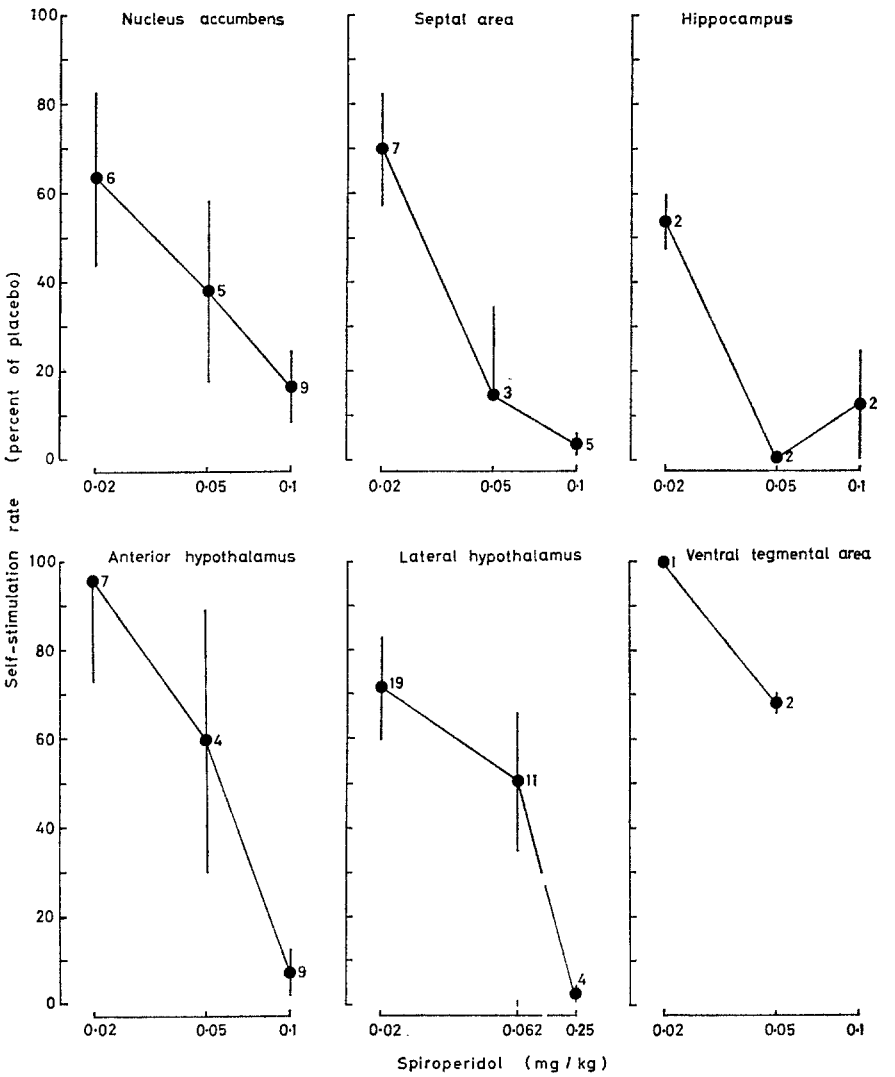

Fig. 3. Dose-response curves of the effect of spiroperidol on absolute self-stimulation rate. Conventions as Fig. 2

Discussion

These results show that in addition to self-stimulation of the lateral hypothalamus, self-stimulation of the nucleus accumbens, septal area, hippocampus, anterior hypothalamus and ventral tegmental area is attenuated in a dose-related manner by the administration of spiroperi-

dol. Spiroperidol produces significant dopamine-receptor blockade in doses between 0.01 and 0.1 mg/kg, and does not block NA receptors until higher doses (e.g. 5 mg/kg) are used (Andén *et al.*, 1970). Thus the attenuation of self-stimulation at these different sites is probably related to the dopamine-receptor blockade produced by spiroperidol. (Other agents which block dopamine receptors, e.g. pimozide, haloperidol and chlorpromazine, produce a similar attentuation of hypothalamic self-stimulation—see Introduction). The dopamine receptors appear to be involved in self-stimulation of a number of different brain regions.

The form of the spiroperidol dose-response curves also allows a conclusion about how the self-stimulation is attenuated. A given dose of spiroperidol (e.g. 0.05 mg/kg) appears to decrease self-stimulation rate relative to the baseline at all the sites tested (see Fig. 2). Yet at this drug dose self-stimulation of the nucleus accumbens and septal area occurred slowly (at approximately 5 bar presses/min), and self-stimulation of the anterior hypothalamus and tegmental area was much faster (at 20—50 bar presses/min). Thus the effect of the spiroperidol was not to attenuate self-stimulation of the nucleus accumbens and septal area by limiting how fast the animals could bar-press. An impairment of the ability of the animals to bar-press rapidly thus cannot explain the effects of dopamine-receptor blockade on self-stimulation.

Experiment 2

The purpose of the experiment was to obtain dose-response curves for the effect of spiroperidol on eating and drinking.

Method

The subjects were 12 male hooded (Lister) rats. The rats were food or water deprived at 12 noon on the day before a test, and injected with spiroperidol the following morning. Doses of 0.016, 0.1, 0.316 and 1.0 mg/kg of spiroperidol dissolved in 0.01 M tartaric acid were injected i.p. in a volume of 1 ml/kg. For eight rats the order of the drug doses and of the placebo (1 ml/kg of 0.01 M tartaric acid) was counterbalanced, and each rat was tested every fourth day. These rats were tested at every drug dose, and on both the feeding and the drinking tests. To investigate the lowest dose condition (0.016 mg/kg) further, the remaining four rats were tested with this dose and with the placebo. The feeding tests and the drinking tests started 2 h 15 min after the injection. For as test of eating a measured amount of food (laboratory chow in pellet form) was placed in the home cage, and was reweighed, together with spillage, after 15 min, 30 min, 45 min, 1 h, 2 h, 3 h and 4 h. Intake was expressed as a percentage of the group mean under the placebo condition. For a test of drinking a burette of water was placed on the cage and readings were taken every minute for ten minutes, and then at the same times as for feeding.

Results

Dose-response curves of the effect of spiroperidol on eating or drinking after 1 h are shown in Fig. 4. It is clear that spiroperidol produces a

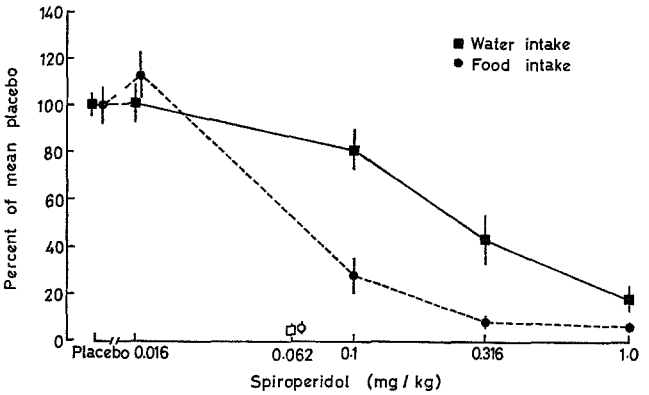

Fig. 4. Dose-response curves of the effect of spiroperidol on eating and drinking in the rat (Experiment 2). The points represent the mean ± S.E. of the intake of each rat expressed as a percentage of the mean intake after placebo (see text). The open symbols show the response in Experiment 3 of rats which bar-pressed to obtain food (circle) or water (square) in a Skinner bix

greater reduction in eating than in drinking. The time courses of the eating and drinking were very similar. Eating and drinking gradually stopped over the first 45 min, and were very low for the next 3 h.

Discussion

Spiroperidol reduces self-stimulation rate more than feeding, and feeding more than drinking. This may be seen by comparing Fig. 4 with Fig. 3 (and also with Fig. 33 of Rolls, 1974). For example, a dose of 0.1 mg/kg of spiroperidol reduced self-stimulation rate to between 5 and 20% at different sites, eating to 28.0 ± 7.8, and drinking to 81.5 ± 8.9% (mean ± S.E.). One possible conclusion is that dopamine receptors are closely involved in brain-stimulation reward, and less so in the controls of eating and drinking in that order. Another possibility is that spiroperidol impairs motor behaviour, and therefore produces a large attenuation of the complex response of bar-pressing, less attenuation of the motor behaviour of picking up and chewing food, and least attenuation of the motor response of licking water from a tube. To test which of these possibilities is correct, in Experiment 3 rats pressed a bar to obtain food or water, so that a complex motor response was involved in both feeding and drinking. If the dopamine receptor blockade produced by spiroperidol acts by impairing motor behaviour, then the feeding and drinking should be affected equally by the spiroperidol. On this hypothesis, the impairment should be similar to that found with self-stimulation, which

was tested with a similar response. If in contrast the spiroperidol impairs the control system involved in drinking least specifically, then drinking should be least severely attenuated in this experiment.

Experiment 3

The purpose of this experiment was to determine whether the differential effect of spiroperidol on feeding and drinking was due to differences in the complexity of the motor response in the two situations. In this experiment the response required to obtain food or water is the same, i.e. the rats must press a lever in a Skinner box.

Method

The subjects were 12 male hooded (Lister) rats. The method was the same as in Experiment 2 except that the doses of spiroperidol used were 0.016 and 0.062 mg/kg. These doses and the placebo were injected in counterbalanced order. Each rat was tested 6 times, in each drug condition with both food and water deprivation. Before the experiment began the rats had been trained to work for food and water in Skinner boxes. Rewards of 0.1 ml tap water or 45 mg Noyes food pellets were delivered for each bar press. No rat could obtain rewards of both food and water during a single test session. Two hours and 15 min after the injection the rats were placed in the Skinner boxes for 4 h. During this time the responses were monitored by electromagnetic counters.

Results

The effect of spiroperidol on eating and drinking after one hour in the Skinner box is shown in Fig. 5. When the response required to obtain food or water is the same, no difference is found in the effect of spiroperidol on feeding and drinking. When required to work for food or water the rats are much more sensitive to spiroperidol than in the ad lib situation (see the response to 0.062 mg/kg shown in Fig. 4). Most of the bar-pressing ceased within 15 min of the injection.

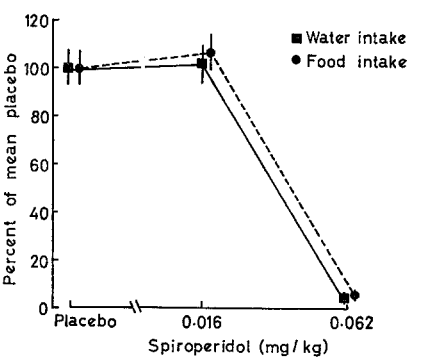

Fig. 5. Dose-response curve of the effect of spiroperidol on bar-pressing for food or water in a Skinner box. Conventions as Fig. 4

Discussion

The finding that self-stimulation of the septal area, nucleus accumbens, anterior hypothalamus, hippocampus and ventral tegmental area is attenuated by spiroperidol provides an indication that dopamine is involved in self-stimulation of many different brain sites. It has previously been shown that dopamine is involved in self-stimulation of the lateral hypothalamus and substantia nigra, in that self-stimulation of the lateral hypothalamus is attenuated by the dopamine-receptor blocking agents pimozide (Wauquier and Niemegeers, 1972) and spiroperidol (Kelly, Rolls, and Shaw, 1973; Rolls, Kelly, and Shaw, 1974) and self-stimulation of the substantia nigra is equally facilitated by *d*- and *l*-amphetamine which have an equipotent effect on dopamine (Phillips and Fibiger, 1973). In addition we have observed that self-stimulation with electrodes in the region of the locus coeruleus is attenuated by pimozide and spiroperidol.

The role of motor disturbance in the attenuation of self-stimulation produced by dopamine-receptor blocking agents is at present unclear. It is clear that a simple motor incapacitation cannot account for the attenuation of self-stimulation at some sites (e.g., the septal area and nucleus accumbens), in that the absolute rate of self-stimulation after spiroperidol is higher at other sites (e.g., the lateral hypothalamus and midbrain tegmentum). (At these latter sites spiroperidol does attenuate self-stimulation, but the base-line self-stimulation rate is higher). Thus the self-stimulation is not limited by the rate at which the animals can press the bar. A similar conclusion seems probable for the squirrel monkey, in that intracranial injections of 4—8 μg of spiroperidol can abolish self-stimulation, yet the animal can perform the motor response of touching the bar (personal observation with M. J. Burton and S. G. Shaw). In both the rat and the monkey the degree of catalepsy associated with the abolition of self-stimulation is small (Kelly *et al.*, 1974). Thus catalepsy may not account for the effect of dopamine-receptor blockade on self-stimulation, and reward may be directly affected. However, it remains to be clearly shown that some disturbance of motor behaviour does not account for the effect of spiroperidol on self-stimulation.

It was observed that, in Experiment 1, after treatment with intraperitoneal spiroperidol rats often self-stimulated for 1—2 min when first tested for self-stimulation before a total abolition of self-stimulation became apparent. (This was despite the long injection-test interval). At this time the rats usually faced the self-stimulation bar. The effect did not recur when subsequent sites were tested on a particular day. A sudden cessation of relatively fast bar-pressing also occurred when rats worked for food or water (Experiment 3).

When a complex response, bar-pressing, was required to obtain either food or water, then the feeding and drinking were equally and severely affected by spiroperidol (Experiment 3). The impairment was comparable to that found for self-stimulation, in which bar-pressing was also the response required (Rolls, 1974; Rolls *et al.*, 1974). Thus it appears that the main effect of dopamine-receptor blockade on feeding, drinking and self-stimulation is accounted for by an effect on motor behaviour. In Experiment 2, it appears that drinking was relatively little affected by spiroperidol due to the relatively simple nature of the licking required to obtain water. There is no evidence that dopamine-receptor blockade interferes specifically with the controls of drinking. Such evidence would require careful elimination of effects on motor behaviour produced by the dopamine-receptor blockade.

The impairment in bar-pressing for food or water (Experiment 3) was at least as great as the impairment in bar-pressing for brain-stimulation reward (Experiment 1, Rolls, 1974; and Rolls *et al.*, 1974). (The impairment may appear to be greater, due perhaps to the shorter test period used in the self-stimulation experiments.) This finding suggests that impairment of motor function accounts for the effects of dopamine-receptor blockade on self-stimulation. The motor impairment appears to be at a relatively central level, in that absolute bar-pressing rate was not primarily affected by the treatment (see Experiment 1).

The conclusion that dopamine-receptor blockade attenuates drinking, eating and self-stimulation by an impairment of central motor systems is consistent with other findings. Wauquier and Niemegeers (1972) show that many types of avoidance behaviour, as well as rewarded behaviour, are equally impaired by pimozide. This interpretation of the effect of dopamine-receptor blockade on eating, drinking and self-stimulation in animals is consistent with the view that in man disturbances of dopamine function in the extra-pyramidal motor system lead to the lack of voluntary behaviour seen in Parkinsonism (Hornykiewicz, 1973; Sacks, 1973).

This work was supported by the Medical Research Council.

References

Andén, N. E., Butcher, S. G., Corrodi, H., Fuxe, K., Ungerstedt, U.: Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. Europ. J. Pharmacol. **11**, 303—314 (1970)

Anlezark, G. M., Arbuthnott, G. W., Christie, J. E., Crow, T. J.: Electrical self-stimulation with electrodes in the region of the interpeduncular nucleus. J. Physiol. (Lond.) **234**, 103 P (1973)

Costal, B., Naylor, R. J., Olley, J. E.: Catalepsy and circling behaviour after intracerebral injections of neuroleptic, cholinergic and anticholinergic agents into the caudate-putamen, globus pallidus and substantia nigra of rat brain. Neuropharmacol. **11**, 645—663 (1972)

Crow, T. J.: A map of the rat mesencephalon for electrical self-stimulation. Brain Res. **36**, 265—273 (1972)

Fuxe, K., Hokfelt, T., Ungerstedt, U.: Morphological and functional aspects of central monoamine neurons. Int. Rev. Neurobiol. **13**, 93—126 (1970)

Hornykiewicz, O.: Dopamine in the basal ganglia. Brit. med. Bull. **29**, 172—178 (1973)

Kelly, P. H., Rolls, E. T., Shaw, S. G.: Functions of catecholamines in brain-stimulation reward. Brain Res. **36**, 363—364 (1974)

König, J. F. R., Klippel, R. A.: The Rat Brain. Baltimore: Williams and Wilkins (1963)

Oltmans, G. A., Harvey, J. A.: L. H. syndrome and brain catecholamine levels after lesions of the nigrostriatal bundle. Physiol. Behav. **8**, 69—78 (1972)

Phillips, A. G., Fibiger, H. C.: Dopaminergic and noradrenergic substrates of positive reinforcement. Science **179**, 575—576 (1973)

Rolls, E. T.: The neural basis of brain-stimulation reward. Progr. Neurobiol. **3** (in press, 1974)

Rolls, E. T., Kelly, P. H.: Neural basis of stimulus-bound locomotor activity in the rat. J. comp. physiol. Psychol. **81**, 173—182 (1972)

Rolls, E. T., Kelly, P. H., Shaw, S. G.: Noradrenaline, dopamine, and brain-stimulation reward. Pharmac. Biochem. Behav. **2** (in press, 1974)

Sacks, O.: Awakenings. London: Duckworth 1973

Stark, P., Turk, J. A., Redman, C. E., Henderson, J. K.: Sensitivity and specificity of positive reinforcing areas to neurosedatives, antidepressants and stimulants. J. Pharmacol. exp. Ther. **166**, 163—169 (1969)

Stein, L.: Psychopharmacological substrates of mental depression. In: Antidepressant Drugs. S. Garattini and M. N. G. Dukes, Eds., Int. Congress. Series, **122**, pp. 130—140. Excerpta Med. Found. Amsterdam 1967

Stein, L., Ray, O. S.: Brain stimulation reward "thresholds" self-determined in rat. Psychopharmacologia (Berl.) **1**, 251—256 (1960)

Ungerstedt, U.: Stereotaxic mapping of the monoamine pathways in the rat brain. Acta physiol. scand. Suppl. **367**, 1—48 (1971a)

Ungerstedt, U.: Adipsia and aphagia after 6-Hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta physiol. scand. Suppl. **367**, 95—117 (1971b)

Wauquier, A., Niemegeers, C. J. E.: Intracranial self-stimulation in rats as a function of various stimulus parameters. II. Influence of haloperidol, pimozide and pipamperone on medial forebrain stimulation with monopolar electrodes. Psychopharmacologia (Berl.) **27**, 191—202 (1972)

Note Added in Proof. In a replication of one of the findings of Experiments 2 and 3 it was found that spiroperidol (0.316 mg/kg) produced a greater ($N = 10$, $P < 0.005$, one-tailed t-test) attenuation of bar-pressing for water (7.0% of mean placebo) than of licking to obtain water (25.5% of mean placebo) when the same rats used in both test situations in a fully counter-balanced design.

E. T. Rolls
University of Oxford
Department of Experimental Psychology
South Parks Road
Oxford, UK