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Blockade by Neuroleptics of Water Intake and Operant Responding for Water in the Rat: Anhedonia, Motor Deficit, or Both?

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LJUNGBERG, T. *Blockade by neuroleptics of water intake and operant responding for water in the rat: Anhedonia, motor deficit, or both?* PHARMACOL BIOCHEM BEHAV 27(2) 341–350, 1987.—Four different neuroleptic drugs, haloperidol, metoclopramide, sulpiride and cis-flupenthixol, were tested for their ability to attenuate an operant lever-pressing response with water as reward and the corresponding consummatory act, i.e., the non-conditioned water intake. All four neuroleptic drugs tested more potently attenuated the operant lever-pressing response than the consummatory water intake, just as the conditioned avoidance response previously has been found to be more potently attenuated than the non-conditioned escape reaction. The results suggest that a certain class of learned behaviors, labelled operant or instrumental behaviors, are more susceptible to the attenuating effects of neuroleptic drugs than the class of behaviors labelled non-conditioned consummatory acts. It was further concluded that the attenuation of the lever-pressing response could be explained by a decreased ability of the animals to initiate or perform the required operant response (i.e., a motor deficit) while the attenuated water intake caused by higher doses of the neuroleptics could be interpreted as a motivational effect (e.g., "anhedonia"). When studying the effects of the neuroleptic drugs it is therefore of great importance to know whether the behavior measured in the particular experimental design used is operant or consummatory. The implications of the findings are discussed.

Dopamine Neuroleptics Consummatory behaviors Operant behaviors Basal ganglia

NEUROLEPTIC drugs in low doses have been widely recognized to attenuate positively reinforced operant behaviors in experimental animals, in which, for example, food, water or intracranial self-stimulation are used as reinforcers. The exact mechanism(s) behind this effect is(are) however not known and several theories have been put forward. These include "motor-incapacitation" theories, stating that neuroleptic drugs interfere with the ability of the animals to perform the required motor responses (see e.g., [9, 11, 17, 19, 21, 26, 29, 31, 35, 39, 40]), the "anhedonia" hypothesis stating that neuroleptic drugs block the ability of reinforcers to sustain responding while the ability of the animals to perform the responses is largely spared [15, 30, 41] and the "incentive-motivational learning" theory stating that neuroleptic drugs interfere with the incentive-motivational learning capacity but not with stimulus-stimulus associative learning (see e.g., [3,4]). Several excellent reviews have been written, covering the extensive literature in this field [3, 12, 41].

It is also well known that the dopamine system is critically involved in consummatory behaviors, and decreased dopaminergic transmission by, e.g., neuroleptic drugs or lesions of the dopamine system, has been found to drastically reduce both food and water intake [8, 14, 29, 38].

One difficulty in interpreting the published reports on the effects of neuroleptic drugs on operant responding is that effects of a full range of doses have not been tested separately, but in directly comparable experimental conditions, on the operant (instrumental) behavior and the relevant consumatory act. Furthermore, the results have not been fully compared with manipulations of the experimental parameters used in the design.

In order to overcome this, we have in the present study investigated the effects of four neuroleptic drugs on two different groups of rats, both kept under the same water restriction schedule. One of the groups was trained to perform an operant response to gain water as reward, the other group only needed to lick water from a nipple in the test cage. Dose-response curves were constructed for both groups and the results were compared with manipulations of the experimental parameters, i.e., degree of water deprivation ("motivation"), response effort and amount of reward delivered. The four neuroleptics tested were haloperidol (a D-2 antagonist, used as an antipsychotic and known to induce extra-pyramidal side-effects), metoclopramide (a D-2 antagonist, not used as an antipsychotic but known to induce extra-pyramidal side-effects), sulpiride (an atypical neuroleptic which acts as a D-2 antagonist, used as an antipsychotic and considered to induce less extra-pyramidal side-effects than, e.g., haloperidol) and cis-flupenthixol (a mixed D-1/D-2 antagonist used as an antipsychotic) (see e.g., review [33] and references in [24,25]).

METHOD

Animals

The experiments were performed on 118 male Sprague

Dawley rats (ALAB, Sollentuna) which arrived at the animal colony at least one week prior to the start of the experiments. During the experiments, the animals were housed singly under conditions of controlled temperature and humidity on a 12 hour light/12 hour dark schedule (light on 7 a.m.–7 p.m.) with ordinarily lab chow ad lib. The rats weighed 200 grams at the start of the experiments.

Except for getting water (as reward) during the 45 minutes-long experimental session, the animals also had access to water for 15 minutes in their homecage, 60 minutes after the end of their experimental session. During weekends the animals had free access to water.

Apparatus

All experiments were performed in slightly modified Skinner boxes (length=30 cm, width=20 cm, height=20 cm) with Plexiglas fronts, backs and tops. The floor consisted of stainless steel bars 5 mm in diameter, placed 20 mm apart. All Skinner boxes were placed inside sound-protecting boxes equipped with one-way observation windows. Electric fans ventilated the boxes and provided a constant background noise in the boxes.

Lever Pressing Responding

To test the ability to perform a lever-pressing response a specially developed lever was used which was fitted to one of the end walls, next to the centrally positioned dipper cup. The lever resembled a millwheel. The four wings were 4 cm long and 3 cm wide and made out of 5 mm black plastic. One quarter of a turn, which was signalled to the animal as a distinct click and as a sudden and transient drop in resistance, was defined as one lever press, and unless otherwise stated, it gave the animal one "reward." The weight necessary to turn the lever could be varied. Unless otherwise stated, it was set to 20 g. The lever is described in more detail in [23].

A dipper of standard type, operated by a solenoid, delivered 0.05 ml water every time it was activated. The water cup was present in the test box at all times except for a short period of time directly after a lever-press, when it was refilled with water. In one of the experiments, the amount of water delivered as reward was decreased. This was achieved by fitting another cup on the dipper arm.

Water Intake

In the boxes where water intake was tested, the levers and the dipper mechanisms were removed and water nipples, connected to a small water container placed outside the Skinner box, were mounted in place of the dipper cups. The animal thus only needed to lick the nipple to obtain the water, not to perform or learn any operant response.

Both water intake and number of lever-presses were monitored every 5 minutes during the experimental session.

Experimental Procedure

The animals were trained for the lever-pressing response using manual shaping, and mastered the task within the first session. The animals lever-pressing for water under standard conditions (i.e., continuous reinforcement and the weight necessary to turn the lever set to 20 g; n=49) and the animals simply drinking the water (n=54) all showed stable responding by the fourth day. The animals trained to operate the lever with increased effort (n=8; see Fig. 9) and with fixed ratio 10 (FR 10; n=7; see Fig. 9) required longer training to reach a stable baseline response (5–7 days).

The animals were their own controls. Whey they had reached a stable baseline response, they were injected with the drug vehicle alone for 1 to 2 days and then on the following day tested with the drug. No animal was tested with drug on more than three occasions, nor with more than one drug, nor with the same dose more than once, and at least one week elapsed between each drug test. The different doses (see below) were given in a random order.

Three parameters known to affect the responding were experimentally manipulated: the duration of water deprivation; the effort required to perform the lever-presses and the amount of water delivered at each reward.

The effect of duration of water deprivation on the lever-pressing response and water intake was tested on the first day after removal of the water. All the animals tested had had free access to water for at least 48 hours before it was removed. Those animals which were required to press the lever with increased effort were allowed two days of training under the new condition before the test day where records were taken. The force necessary to turn the lever was increased in a stepwise manner until the animals could no longer perform the response. Experiments in which the effects of decreased reward-volume were tested were interspersed randomly with the tests of drug effects. The group of animals tested for extinction (n=6) was given the same amount of training as the other animals tested.

Drug Treatments

Haloperidol (Leo, Sweden) was dissolved in 1% lactic acid, and cis-flupenthixol (H. Lundbeck AB, Denmark) was dissolved in saline. Racemic sulpiride (Delagrange, France) was dissolved in a minimal quantity of glacial acetic acid, made up to volume with 5% glucose and adjusted to pH 7 with 1 M NaOH. Metoclopramide (Primperan, 5 mg/ml; H. Lundbeck AB, Sweden) was diluted from ampoules for injection with isotonic saline. All doses refer to the above mentioned forms. The injections were given subcutaneously in a volume of 1 ml/kg (except for the two highest doses of metoclopramide; 10 and 20 mg/kg which were given in a volume of 2 and 4 ml/kg respectively).

The following range of doses (in mg/kg) were tested in the lever-pressing (lp) and water intake (wi) experiments: Haloperidol: lp (0.01–0.1); wi (0.02–0.5). Cis-flupenthixol: lp (0.02–0.5); wi (0.02–0.5). Metoclopramide: lp (1–10); (2–20). Sulpiride: lp (100–200); wi (200).

Statistics

The group response was expressed using the median and the degree of significance was calculated using the Mann-Whitney U test, the Kruskall Wallis one-way analysis of variance (KRUWA), the Friedman two-way analysis of variance [34] or the Student's t-test for paired samples. In the cases where the Student's t-test was used for multiple comparisons (see Figs. 2–6, 8–9) the Bonferoni method for adjustment of p level was used [43]. By this method the p value of the Student's t-test is adjusted according to the formula $p^*=p/m$, where p^* is adjusted p value, p is the p level set by the researcher (in this case 0.05, two-tailed), and m is the number of comparisons.

RESULTS

Normal Water Intake

Control animals, individually housed under standard laboratory conditions with food and water ad lib, were found to

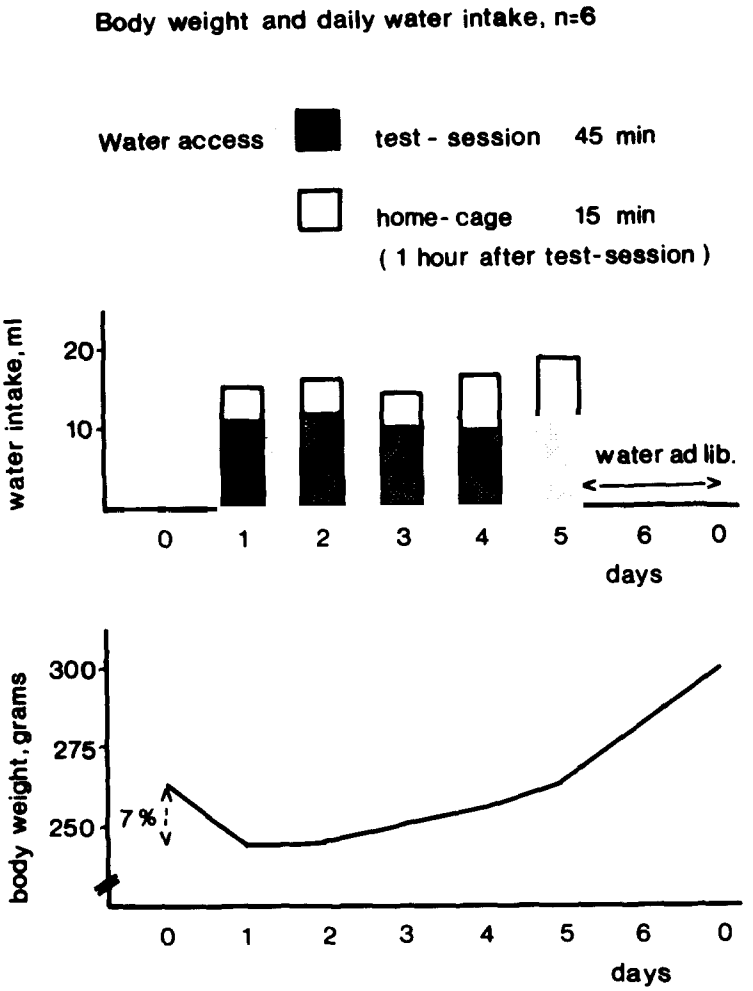

FIG. 1. The top part of the figure shows median daily water intake during the 45 minutes-long experimental sessions and during the 15 minutes with access to water in the homecage, 60 minutes after the experimental session in animals tested according to the water intake paradigm. The lower part of the figure shows median body weight in the same animals.

consume 10.4 ml of water/100 g of bodyweight day (i.e., 10.4%; n=15) (cf. [5,7]). Kept under the water restriction schedule described above, the animals were found to consume 6.4% water per day (i.e., 4.4% during the experimental session and an additional 2% during the 15 extra minutes in their homecage; n=6, see Fig. 1). Despite the reduced total water intake the animals were found to gain weight and to be in very good condition (see Fig. 1 and cf. [7]).

It was further found that the total water intake during the experimental sessions was stable over a whole week of experiments (Friedman two-way analysis of variance, n.s., n=6; see Fig. 1).

Calculation of the Results

It was found that injection with vehicle only did not alter the stable baseline responding (except for the very first injection, when occasionally a decreased response could be seen). Despite this, only sessions where control injections were given were used for calculations of the baseline response (see below).

A reference value (called "control end value") was calculated for each animal by taking the median value (amount of water consumed or number of lever-pressing responses) on each day of control conditions (except for the first control injection, as mentioned above).

To get a measure of the effect of an experimental treatment, we calculated the total responding after that treatment as a percentage of the "control end value" for that animal. The group median of these percentage values for a given treatment was then calculated and used as a measure of the effect of that treatment. The group medians for the drug treatments could be calculated in this way since the drugs were given in a random order and as no effects could be found as a result of the previous injections. The degree of significance for a given treatment was calculated using the Student's *t*-test for paired samples as described in the statistics section above.

The accumulated data, for both the lever-pressing and the water intake, was calculated for each period of 5-minute. The results obtained were expressed as a percentage of the control end value and the median for each 5-minute period was calculated for the whole group. The results are shown in Figs. 2–9.

There was no statistical significant variation in the lever-pressing and water intake baselines (i.e., in the "control end

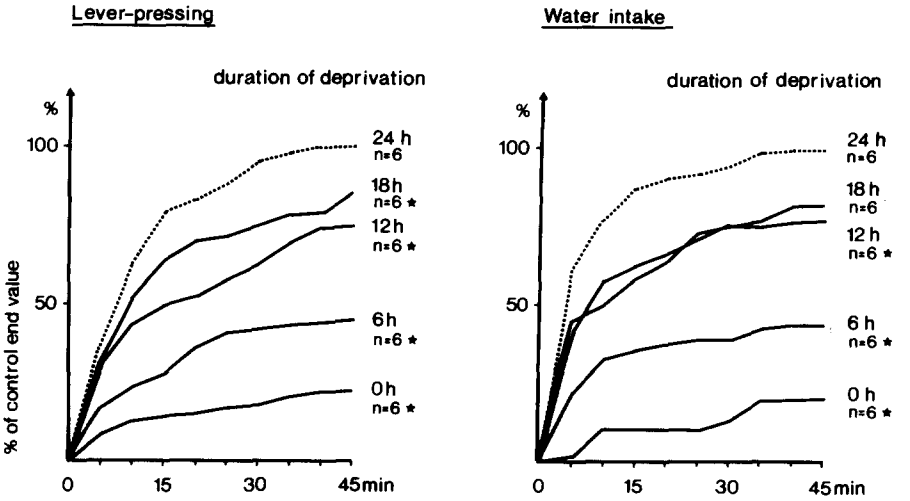

FIG. 2. Effects of duration of water deprivation on lever-pressing (left part of the figure) and on water intake (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (★ signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method).

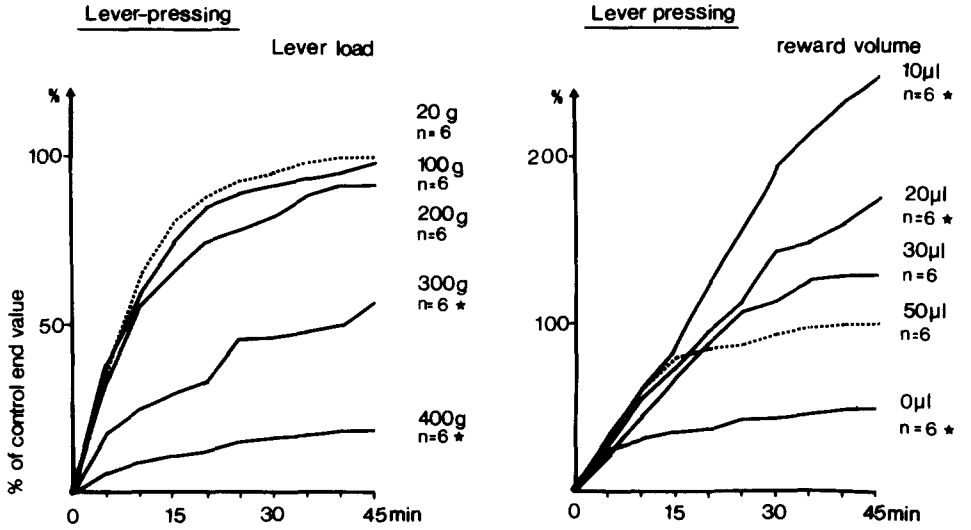

FIG. 3. Effects of increasing the force necessary to turn the lever (left part of the figure) and of decreasing the amount of water delivered as rewards (right part of the figure) on the lever-pressing response. The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (★ signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method).

values") between groups (KRUWA). For control injections (i.e., the "control end values") the median total number of lever-presses performed during a session was 286 (n=49) and the median total amount water consumed during a session was 12.6 ml (n=54). The control end values for animals tested under FR 10 was 251 (n=7; n.s.) and for animals tested under conditions with increased effort (200 g) it was 154 (n=8; $p<0.001$, both compared to the animals tested on haloperidol under standard conditions using KRUWA followed by the Mann-Whitney U test).

Experimental Results

Manipulation of the parameters. Three parameters known to affect the responding were experimentally manipulated: the duration of water deprivation, the effort required to perform the lever-presses and the amount of water delivered at each reward.

When the duration of water deprivation was decreased both the total number of lever-presses performed during a session and the total amount of water consumed were decreased to a similar degree (see Fig. 2).

It was found that with up to 10 times the standard force, the animals could still master the response. If the force was increased even further they had great difficulties and the total number of responses was drastically decreased (see Fig. 3).

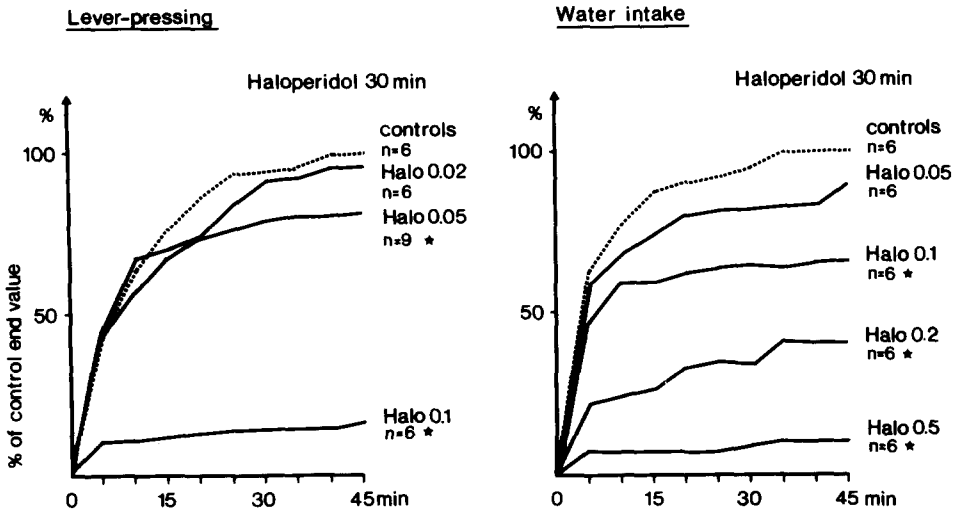

FIG. 4. Effects of haloperidol on lever-pressing (left part of the figure) and on water intake (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (* signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method). Number of animals are given for each dose and the doses are expressed as mg/kg. Haloperidol was given 30 minutes before the start of the test session.

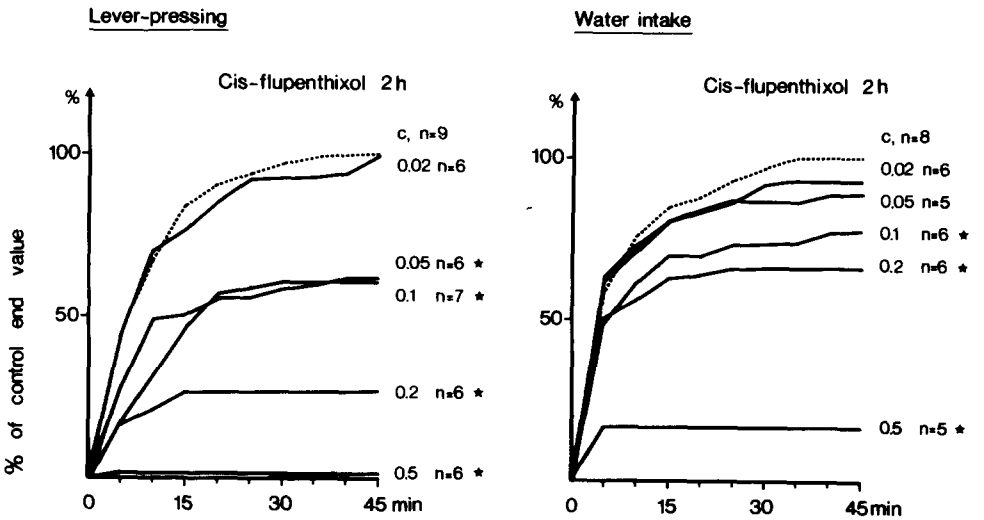

FIG. 5. Effects of cis-flupenthixol on lever-pressing (left part of the figure) and on water intake (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (* signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method). Number of animals are given for each dose and the doses are expressed as mg/kg. Cis-flupenthixol was given 2 hours before the start of the test session.

When the amount of water delivered at each reward was decreased the animals compensated for this by increasing the number of lever-presses performed during the session. When no water was delivered, extinction was seen (see Fig. 3).

Effects of drugs on responding under standard condition. In preliminary experiments doses of haloperidol, cis-flupenthixol and metoclopramide were found that inhibited the response to more than 75%. The blockade observed was very similar for all three drugs in that the lever-pressing response was more potently blocked than the water intake (see Figs. 4–6). Apart from the doses shown in the figures the following doses were also tested and found to produce non-significant effects: haloperidol 0.01 mg/kg on the lever pressing response (91%, n=5) and 0.02 mg/kg on the water intake (110%, n=5) and metoclopramide 1 mg/kg on the lever-pressing response (84%, n=6).

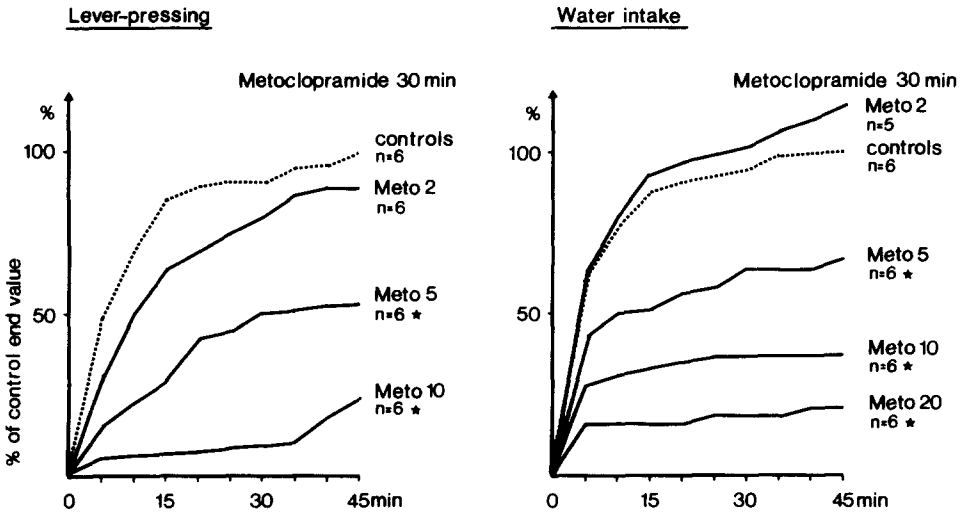

FIG. 6. Effects of metoclopramide on lever pressing (left part of the figure) and on water intake (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (* signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method). Number of animals are given for each dose and the doses are expressed as mg/kg. Metoclopramide was given 30 minutes before the start of the test session.

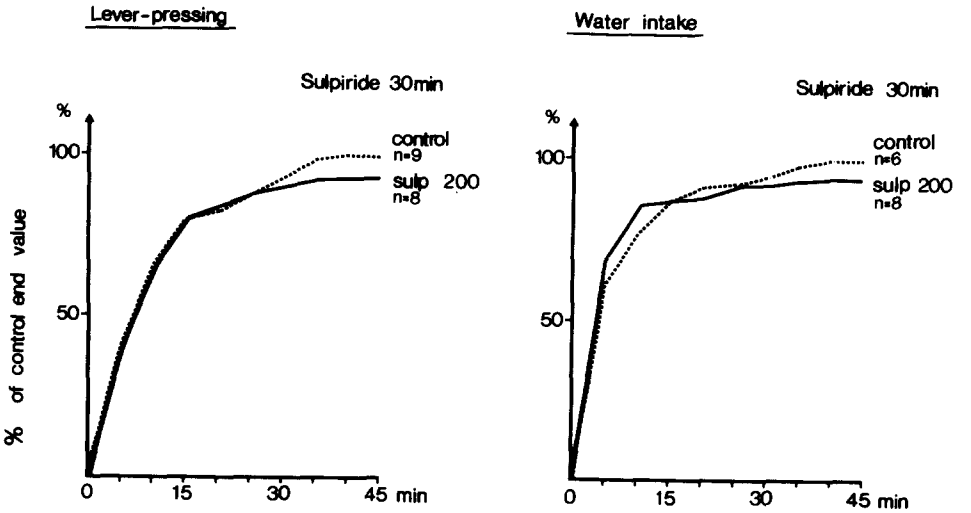

FIG. 7. Effects of sulpiride on lever pressing (left part of the figure) and on water intake (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (n.s. at the 0.05 level). Number of animals are given for each dose and the doses are expressed as mg/kg. Sulpiride was given 30 minutes before the start of the test session.

Despite the fact that very high doses of sulpiride were used, only weak effects were seen. Two hundred mg/kg given 30 minutes before testing showed no significant effects (see Fig. 7). When the same dose was tested 5 hours after administration, a partial blockade of the lever-pressing response was observed. No effects were seen on the water intake (see Fig. 8). When tested 24 hours after administration, no significant effects could be detected (lever pressing=114%, n=8; water intake=93%, n=8).

Effects of haloperidol on responding under conditions with increased effort. Animals were trained on an FR 10 schedule or under conditions where the force necessary to turn the lever was increased to 200 grams. Dose-response curves for haloperidol were constructed as described above. It was found that haloperidol blocked the responding under these two conditions with increased effort as potently as it blocked responding under the standard conditions (see Fig. 9).

DISCUSSION

It was found in the present study that all neuroleptic drugs tested antagonised the lever-pressing response more po-

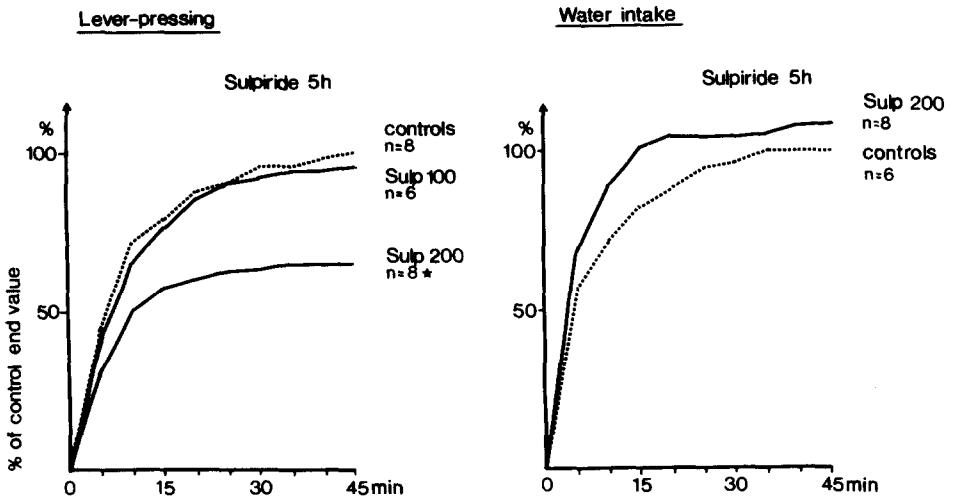

FIG. 8. Effects of sulpiride on lever-pressing (left part of the figure) and on water intake (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (★ signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method). Number of animals are given for each dose and the doses are expressed as mg/kg. Sulpiride was given 5 hours before the start of the test session.

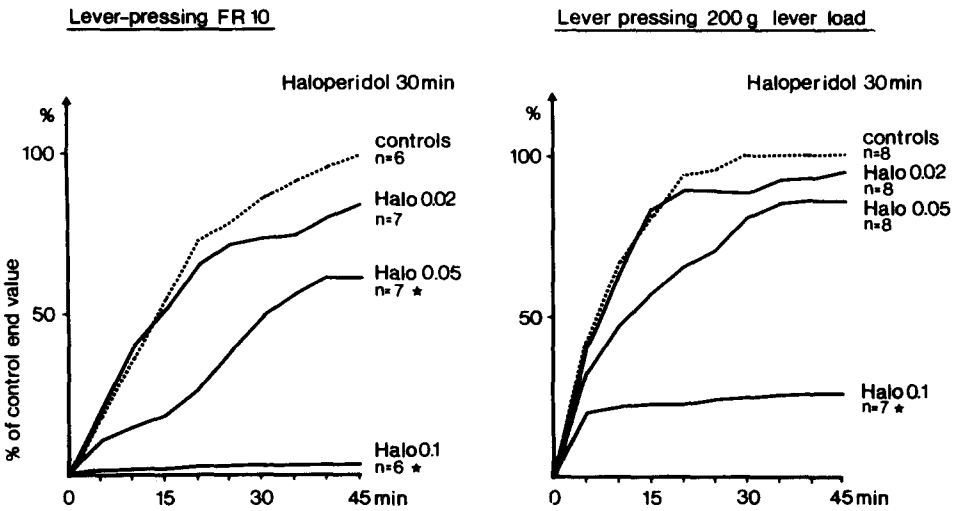

FIG. 9. Effects of haloperidol on lever-pressing responding under conditions where increased effort is required, i.e., FR 10 (left part of the figure) or a force of 200 grams necessary to turn the lever (right part of the figure). The data are group medians, expressed as a percentage of the values during the control sessions, each rat acting as its own control. The end values are tested by the Student's t-test for paired samples (★ signifies $p<0.05$, two-tailed, adjusted for multiple comparisons by the Bonferoni method). Number of animals are given for each dose and the doses are expressed as mg/kg. Haloperidol was given 30 minutes before the start of the test session.

tently than the water intake. Manipulations of the experimental parameters gave a clue for understanding these results. If the animals were made less thirsty, i.e., they were water-deprived for a shorter period of time before testing, they showed a similar decrease in *both* the water intake *and* the lever-pressing response (see Fig. 2). Less thirsty animals thus decreased their lever-pressing response in direct relation to the magnitude of their water deficit, in this case caused by water deprivation (i.e., in direct relation to their "motivation" for water).

The finding that with certain (lower) doses of neuroleptic drugs the lever-pressing response was severely attenuated, while the ability of the rats to regulate their body water simply by drinking the water was not affected, shows that the attenuation of the lever-pressing response induced by the lower doses of neuroleptics cannot be explained by a "blunting" of the reactions of the animals towards the water. The effects of the lower doses of neuroleptics on the lever-pressing response are instead explained by a decreased ability of the animals to perform the required operant response.

This is however not a pure motor phenomenon as the animals were still capable of walking to the nipple and consuming water when tested with low doses of neuroleptics in the water intake experimental set-up. When higher doses of neuroleptics were given, the water intake was also decreased in a dose-dependent manner similar to the pattern seen when the animals were made less thirsty (see Fig. 3 and cf. [42]).

When the amount of water delivered at each reward was decreased, the animals reacted promptly by increasing and prolonging their responding during the session (see Fig. 3). This pattern of reaction could not be mimicked by the administration of the neuroleptic drugs, showing that the estimation of the reward value was not affected in this way by the neuroleptics. When the force necessary to turn the lever was increased, the animals decreased their responding in a force-dependent manner.

It can therefore be concluded that the results obtained in the present study show that the attenuation of operant responding after low doses of neuroleptics cannot be explained by an effect on the ability of the animals to regulate their body weter (i.e., on "motivation" or on "reinforcing properties" of the water). The attenuation of responding is instead explained by a decreased ability to initiate or perform the operant response required to gain access to the water.

It has previously been suggested that complex behavioral patterns, or behaviors that require more effort, are more susceptible to the attenuating effects of neuroleptics (see e.g., [10, 14, 27, 29]). This might be an important factor in explaining our results as the lever-pressing response is both a more complex behavior and requires more effort from the animals than licking the water in the water intake paradigm. In separate experiments, this possibility was therefore investigated. It was found, however, that haloperidol attenuated lever-pressing responding as potently under standard conditions as when the effort required to press the lever was increased or when the response was made even more complex by forcing the animals to press the lever ten times in order to obtain a reward (compare Figs. 4 and 9). This result thus shows that the effort required, or the complexity of the response, were not important factors in explaining the more potent effects of neuroleptics on the lever-pressing response than on the water intake.

One of the screening methods used to find new antipsychotic drugs is the conditioned avoidance response test (CAR). In this test, the neuroleptic drugs block the avoidance response more potently than the escape reaction (see e.g., [1]). It is interesting to compare the results obtained in the present study with previously published results on inhibition of avoidance and escape reactions (cf. [1]) as the relative blocking effects in the two very different experimental test situations are so similar.

It might therefore by hypothesized that neuroleptic drugs blocking D-2 receptors affect different "classes" of behaviors (i.e., the operant or instrumental phase vs. the consummatory act) with different potencies. Learned behavioral acts, where the animals reach a goal by performing an operant response (e.g., a lever-pressing response or a conditioned avoidance response) are attenuated by lower doses of neuroleptics than the non-conditioned consummatory act (like water intake in the present study or the escape reaction in the CAR). If these two classes of behaviors are looked upon superficially it might be stated that the difference between them is merely the degree of complexity. An alternative view put forward in this paper is that this difference in complexity reflects something more, i.e., that these two classes of behaviors serve different functions in the behavioral repertoire of an animal and are goverened differently by mechanisms in the CNS.

It has previously been discussed whether the shock in the CAR just acts as a stronger stimulus (pain) than the sound or light cue used, and that stronger stimuli can overcome the behavioral blockade caused by the lower doses of neuroleptics (see e.g., [3, 13, 14]). In our two experimental designs the threatening stimulus to all animals, i.e., the water deficit, is the same. The differential effects of the neuroleptics are therefore difficult to explain in terms of stronger stimuli initiating the consummatory act than the operant lever-pressing response.

Furthermore, an important experiment has recently been published by Gramling and Fowler [16]. They tested the effects of neuroleptics in both an operant and a reflexive licking paradigm in rats and found that the neuroleptics more potently attenuated the operant licking than the reflexive licking, even though the licking movements were the same in both paradigms. These results are very much in line with our own results and further emphasise that the complexity of the response or the nature of the stimuli are not the important factors explaining the selective effects of low doses of neuroleptics.

A more reasonable interpretation is, as discussed above, that learned operant behaviours are dependent upon forebrain structures other than those involved in the initiation and regulation of the consummatory acts. The former structures/behaviors might be more directly linked to DA mechanisms and therefore more susceptible to the effects of low doses of the neuroleptics. The consummatory acts might be less dependent on DA mechanisms and can in a more reflex-like manner be activated by appropriate non-conditioned stimuli.

When the effects of neuroleptic drugs on various behavioral paradigms are investigated and the effects discussed in terms of whether the drugs affect the capacity of the animal to perform the response or whether they affect motivation or the reinforcing properties of the reward, it is of great importance to know which of these two "classes" of behaviors is actually measured in the paradigm used. Depending upon the paradigm, and thereby depending upon which type of behavior is investigated, different explanations of the effects of neuroleptics can be given. If a behavioral design is used where the animals perform a learned operant response, the effects of the neuroleptics can be interpreted as a motor deficit (see e.g., [10, 26, 40]). If however a design is used where the animals perform a consummatory act, the effects of the neuroleptics can instead be interpreted as causing a motivational deficit (see e.g., [10, 18, 36, 42]).

The specific effects of sulpiride could further be used as a clue to understand the pharmacological mechanism(s) behind the observed effects. When administered to experimental animals, sulpiride has been described as potently antagonising locomotion induced by various dopamine (DA) agonists like DA itself [6], d-amphetamine [25] and apomorphine [24]. This locomotion-blocking effect of sulpiride has been attributed to an effect of sulpiride on the DA innervation in the nucleus accumbens septi and has been found to occur even after very short time periods (30–60 minutes) after the injection of sulpiride (see [6, 24, 25]).

This is in striking contrast to the anti-stereotypic effects of sulpiride and to the catalepsy induced by sulpiride administration, both of which are very weak and can only be observed several hours after the injection (see e.g., [20,22]).

This has been explained tentatively by a poor penetration of sulpiride into those brain areas important for the DA agonist-induced stereotyped behaviors and for the DA antagonist-induced catalepsy. These areas may be in the basal ganglia, as e.g., intraventricular injections of sulpiride or direct local injections of sulpiride into the basal ganglia can potently antagonise DA agonist-induced stereotyped behaviors and induce catalepsy [2, 20, 32].

The dopaminergic innervation in the nucleus accumbens has previously been shown to be important in incentive-motivational learning [37]. Our results showing that sulpiride was ineffective in our model at a time after injection when pharmacological studies have shown sulpiride to exert potent effects in the nucleus accumbens, together with our demonstration that sulpiride affects the lever-pressing response at the same time that it has a pharmacological effect in the basal ganglia, indicate that the findings in the present study might be better explained by DA-blocking effects of the neuroleptics in these areas of the basal ganglia than in limbic areas. This might be explained by the fact that we only used well-trained animals. The DA system in the nucleus accumbens might be more important when an operant response is actually learned, than when well-trained responses are performed which are more dependent upon basal ganglia mechanisms, as has previously been suggested by, e.g., [3,13].

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