Pharmacology Biochemistry & Behavior, Vol. 37, pp. 607–611. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Effects of Low Doses of Neuroleptics on Temporal Regulation in a Differential Reinforcement of Response Duration (DRRD) Schedule in the Dog

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Received 3 January 1990

BRUHWYLER, J., E. CHLEIDE AND M. MERCIER. *Effects of low doses of neuroleptics on temporal regulation in a differential reinforcement of response duration (DRRD) schedule in the dog.* PHARMACOL BIOCHEM BEHAV **37**(4) 607–611, 1990.—It has been shown that low doses of neuroleptics could disinhibit behaviour in animals as well as in man. This study aims to measure the effects of low doses of haloperidol (0.01, 0.05, 0.1 mg/kg) and sulpiride (5, 10, 15 mg/kg) in the dog using a differential reinforcement of response duration (DRRD) schedule with positive and negative external stimuli. Together with a decrease in response rate, a leftward shift in the temporal distribution of response duration is measured. These results are discussed in terms of a deregulation of the internal clock, a lessening in the ability to wait for the reward, a reduction in the frustration of not obtaining reinforcements when errors are made and an increase in the sensibility to reinforcement through appetite stimulation or decrease in the satiety level.

Neuroleptics Low doses Temporal regulation Differential reinforcement of response duration schedule Dog Sulpiride Haloperidol Presynaptic DA2 receptors Dopamine

WHILE the depressant action of high doses of neuroleptics is clearly established, it has been difficult to do so with a stimulation at low doses, the response usually being irregular and/or non-dose-related (24). In rats, low doses of sulpiride (SULP, 2.5 and 10 mg/kg IP) and haloperidol (HALO, 0.04 and 0.16 mg/kg IP) have been shown to enhance treadwheel activity but not the locomotion detected by the use of photocell cages (9). Anxiolytic activity was detected using the same species in a two-compartment test and in a conflict procedure of punished responding when low doses of HALO (0.025 to 0.1 mg/kg) and SULP (0.5 and 1 mg/kg) were administered (23).

The clinical use of SULP in psychiatry has consistently shown that a proportion of schizophrenic patients respond with 'disinhibition' or an alerting response which is frequently observed in withdrawn patients (who display reduced locomotor activity) (13). Moreover, it has been reported that low doses of neuroleptics relieve anxiety-related symptoms in psychoneurotic (11), demented (29), borderline (2) and chronically anxious patients (30). These behavioural manifestations are consistent with the hypothesis that low doses of neuroleptics exert specific effects on presynaptic rather than postsynaptic dopaminergic (DA) receptors (10, 17, 23). In particular, SULP at doses from 1 to 10 mg/kg showed a clear preference for the presynaptic DA2 sites (8).

The effects of low doses of neuroleptics have rarely been investigated in temporal regulation schedules. However, in a DRL 20 s in the rat, HALO (0.02 mg/kg) has been shown to shorten the mean interresponse time significantly (1). This study aims to measure the behavioural effects of low doses of HALO and SULP in the dog using a DRRD (differential reinforcement of response duration) schedule. The DRRD is more restraining than DRL because it requires the inhibition of all the behavioural patterns incompatible with holding the operant response (3, 18, 22, 27).

METHOD

Subjects

Five male dogs (2 to 6 years old) of Beagle breed weighing from 11 to 14 kg were used in these experiments. They were housed in separate cages. They were fed at the end of the day with Cervo Expan diet (250 g).

Test Room

The size of the test room was 5.6 × 3.5 m. At the entrance, in

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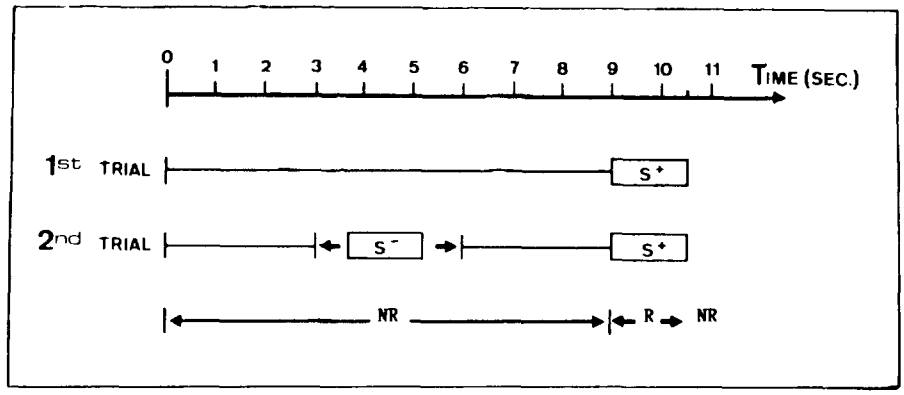

FIG. 1. Final procedure (NR = nonreinforced response, R = reinforced response, S^+ = positive stimulus, S^- = negative stimulus).

the right-hand corner there was a board (60 × 50 × 2 cm) fastened to the ground. In the opposite corner, at the end of the room, the food dispenser (50 × 76 × 52 cm) was situated. The auditory signals for the test were emitted from two loud-speakers incorporated in the ceiling. Water was available throughout the session. During the experimental sessions, the experimenter stood in an observation booth fitted with two-way mirrors. The booth contained all the controls of the external stimuli, the distribution of reinforcements as well as the material for observing and recording the sessions. The observation and recording material consisted of two cameras, one giving an overall view of the room, the other filming the dog on the board. These pictures were later recorded on video tape and analyzed.

Shaping

A free exploration phase (3 sessions) was followed by 10 sessions during which the dog was conditioned to remain on the board for 1 sec, to move in response to an auditory stimulus (click) and to jump on to the food dispenser in order to get the reinforcement. During the next 20 sessions, the waiting time required on the board was progressively raised to 9 s. Each trial ended with the auditory signal being given for 1.5 s. A more detailed description of this shaping is given elsewhere (3,22).

Final Procedure (Fig. 1)

The final procedure was a schedule of differential reinforcement of response duration (DRRD) with limited hold (LH) and positive and negative external cues (3, 5, 22). It consisted in the random alternation of 2 kinds of trials. In the first type of trial, a maintenance response lasting 9 seconds on the board was required for reinforcement to be obtained. At the end of this time delay an auditory discriminative stimulus of 1.5 s was given to the animal. Every time it left the board between 9 and 10.5 s and then jumped on the food dispenser, it received a piece of meat (5 g). The second type of trial differed from the first by the random addition of the same auditory stimulus, presented between the 3rd and the 6th s of the time delay. Both auditory stimuli, presented between 3 and 6 s and at 9 s were identical from a physical point of view and had the same duration (1.5 s); the animal could only discriminate between them according to their location in time. Both kinds of trials were distributed randomly during the session. Thus, the added stimulus was doubly random, first, because it was not given on each trial and, secondly, because it was given at random between 3 and 6 s. In every case, the only reinforced response was the response to the stimulus at 9 s, any premature (<9 s) or late (>10.5 s) response not being reinforced. Every correct (R = reinforced) or wrong (NR = nonreinforced) response restarted the trial. Experimental sessions were limited by the subject obtaining 8 reinforcements and/or by a maximum time of 900 s. Performance was considered stabilized when 70% of responses were correct (after 30 sessions).

Drug Administration

HALO (Haldol®: 0.01, 0.05 and 0.1 mg/kg) and SULP (Dogmatil®: 5, 10 and 15 mg/kg) were administered orally in capsule form in random order, with each dose being given every two weeks in a random order. The experimental sessions took place 4 hours following drug administration. On the day before drug administration, the subjects received a placebo, which was administered in the same way, and took part in a control session 4 hours following the administration.

Data Analysis

The statistical analysis of the effects on total response rate (responses per minute) was obtained from an analysis of variance, with the factor 'dose' as classification criterion, followed by post hoc *t*-tests for comparing control values with a given dose. Temporal distribution of response duration was used to describe the performance more qualitatively.

RESULTS

The effect of the pharmacological treatment on response rate

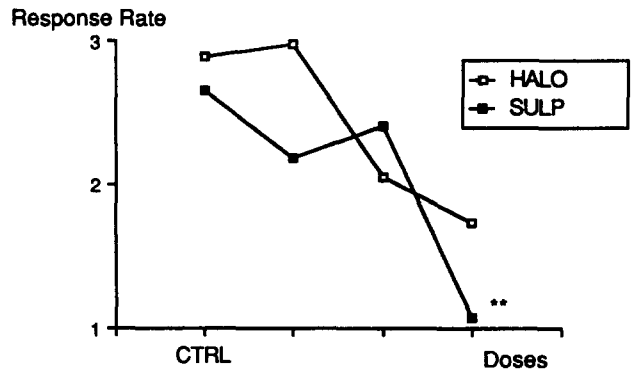

FIG. 2. Effects of haloperidol (HALO: 0.01, 0.05, 0.1 mg/kg) and sulpiride (SULP: 5, 10, 15 mg/kg) on response rate (number of responses per minute) compared with control sessions (CTRL) (**$p<0.01$).

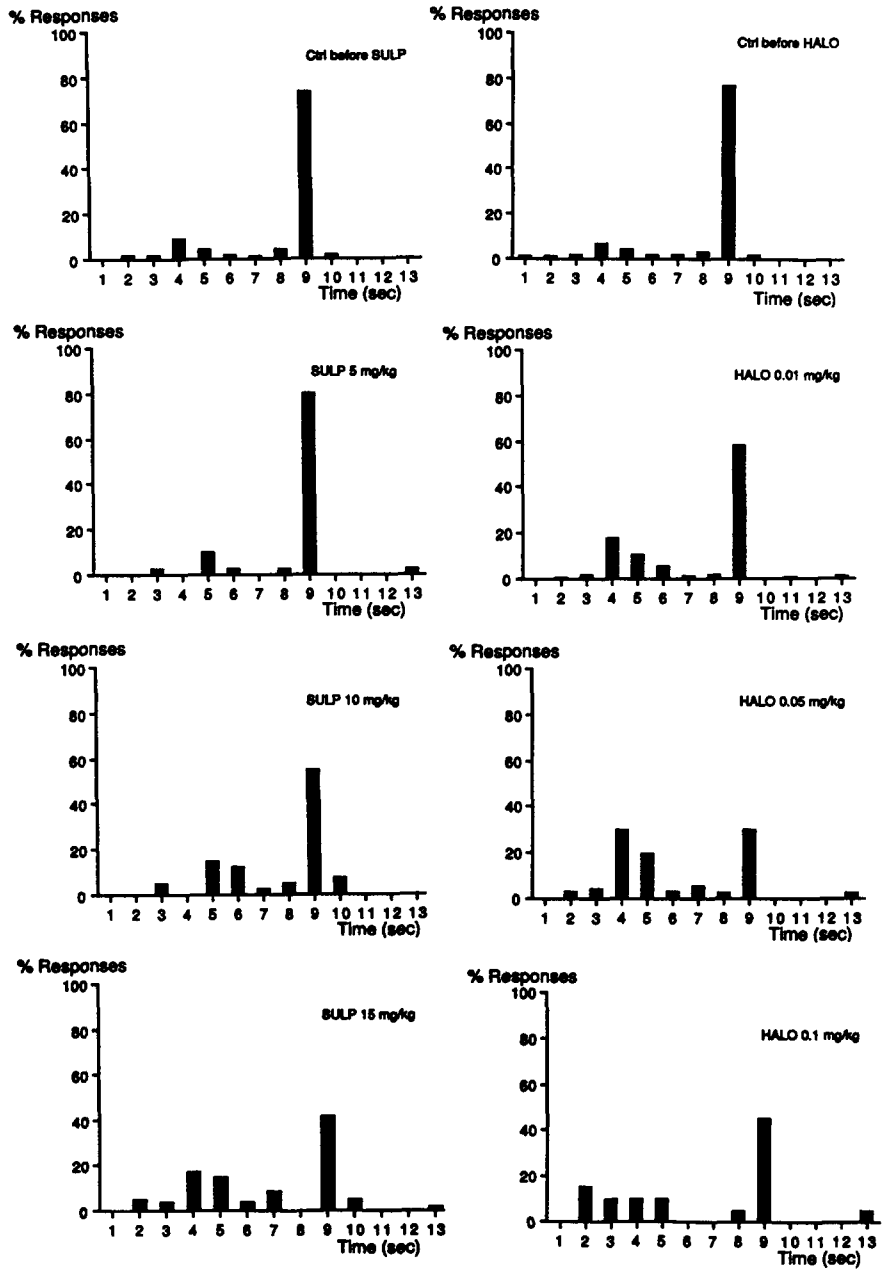

FIG. 3. Effects of haloperidol (HALO: 0.01, 0.05, 0.1 mg/kg) and sulpiride (SULP: 5, 10, 15 mg/kg) on the temporal distribution of response duration compared with control sessions (CTRL).

was significant ($p<0.01$) for SULP, $F(3,13)=7.88$, but not significant ($p>0.05$) for HALO. SULP decreased the response rate significantly for the higher dose (15 mg/kg, $t=4.58$, $p<0.01$) (Fig. 2).

Figure 3 shows the temporal distribution of response duration for the 2 drugs compared to the control sessions. For the controls, temporal distribution was typically bimodal with the principal mode (75%), centered on 9 s, corresponding to the correct responses, with the secondary mode (15%) situated between 3 and 6 s, being the moment at which the negative stimulus was presented. With HALO, the mode corresponding to the correct responses decreased sharply. The greatest decrease was obtained with 0.05 mg/kg (30% in place of 75%). The greatest proportion of incorrect responses was produced between 3 and 6 s, the moment at which the negative stimulus was presented. This proportion was 15% for the control and rose 57% with a dose of 0.05 mg/kg. The same description applies for SULP from 10 mg/kg, with a decrease in the mode corresponding to the correct responses from 76% to 62% for 10 mg/kg then to 47% for 15 mg/kg, whilst the secondary mode corresponding to the responses produced when the negative stimulus was applied rose from 17% to 31% for 10 mg/kg and to 39% for 15 mg/kg. With the lowest dose (5 mg/kg) a slight improvement in performance was noted with 80% of the responses correct.

DISCUSSION

In previous studies employing the same procedure and the same species, we showed that benzodiazepines and barbituates, for low and medium doses, increased the response rate and the number of errors when the negative stimulus was applied between 3 and 6 s. On the other hand, with high doses of neuroleptics, a predominant increase was noted in the number of errors produced after the criterion time (>10.5 s) together with a decrease in response rate (4,5).

The great increase in incorrect responses when the negative stimulus was applied that was observed in this invertigation using low doses of neuroleptics is not wholly comparable with that obtained with anxiolytics since here the response rate does not increase and even tends to decrease (significantly for a dose of 15 mg/kg SULP). However, it corroborates the behavioural disinhibition detected in other experimental procedures with low doses of antipsychotic drugs (9,23).

It's difficult to invoke a general increase in activity or excitation to interpret those effects, as it is the case for benzodiazepines (26, 28, 34), since here there are accompanied by a decrease in response rate. However, other hypotheses can be proposed to take into account this marked behavioural disinhibition. It may have its origin in a deregulation of the speed of the internal clock. Its temporal regulation thus being affected, the subject finds itself no longer able to discriminate between the duration of its responses and restricts itself to responding to the first stimulus that appears. It has been shown that neuroleptic drugs affect time estimation by decreasing the rate at which a pacemaker emits pulses and produces rightward shifts of a constant percentage for timing functions obtained across a range of signal durations (12, 20, 21). Among the receptors for biogenic amines for which neuroleptic affinity data were compared with neuroleptic effects on time estimation (D1, D2, D3, NE-α, 5-HT1, 5-HT2), only the affinity for the D2 receptor reliably predicted the dose required to produce a rightward shift (20, 21, 25). Effects on time estimation have been observed for drugs that increase the effective level of brain dopamine (e.g., amphetamine) but as predicted, the observed shifts were in the opposite direction (i.e., leftwards) (19). Amphetamine acts mainly on the presynaptic endings by triggering the release of DA. Consequently, the action of low doses of neuroleptics on the estimation of response duration, observed in this study, could be explained by antagonist action on the DA2 presynaptic receptors (10, 17, 23). In the future, it would also be interesting to examine further the role of the different types of dopamine receptors, using specific D1 antagonist (SCH 23390) and agonist (SKF 38393) or specific D2 antagonist (zetidoline) and agonist (bromocriptine), in temporal integration mechanisms. Moreover, a correlation between binding affinity for the presynaptic receptor and the possibility to produce "paradoxical" effects with low doses of neuroleptic could also be investigated. But as a DRRD schedule with external cues is not wholly comparable to time estimation procedures used in previous studies (12, 20, 21), it is only the direction of the shift in the response function measured in this work that is consistent with literature and not the magnitude of the shift nor the form of the function. Without additional data showing that the temporal placement of the signals at both shorter and longer durations than the criterion time and without variation in the criterion time to look for proportional changes in clock speed, it is not possible actually to reinforce or to exclude this hypothesis.

Like for benzodiazepines (6,31), premature nonrewarded responses have been observed in animals treated with a low dose of haloperidol (1) and subjected to a DRL schedule, in which they were required to let a specified time elapse between successive responses to obtain reward. Like anxiolytics (32,33), low doses of neuroleptics could lessen the ability of dogs to wait for an expected reward, that is reduce impulse control (14). Another possibility exists that they act through a reduction in the frustrating effects of not obtaining reinforcements when errors are made (32), which itself could be regarded as an anxiolytic effect. Finally, they could increase the sensibility to reinforcement through appetite stimulation or decrease of the satiety level such as it is the case for benzodiazepines (7, 15, 16).

Despite the fact that different hypotheses still subsist to interpret the mechanism of action of low doses of neuroleptics, the present findings suggest that DA antagonists may possess disinhibitory properties. Since it has been demonstrated that patients with different types of psychiatric disorders tend to respond with disinhibition to the neuroleptic treatment (11, 13, 25, 29, 30, 35, 36), this investigation reveals that the study of cognitive processes like temporal regulation in the animal can supply neuropharmacology or psychiatric illnesses with useful informations.

ACKNOWLEDGEMENTS

We would like to thank Dr. P. Kelly for the translation of this text, Dr. J. P. Peters for computer processing of the data and G. Houbeau for practical assistance.

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