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Action of a New Psychotropic Drug (Sulpiride) on Avoidance Behavior in Rats

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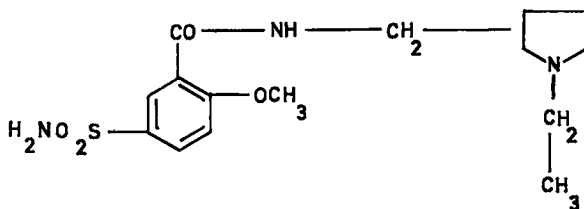
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Received October 29, 1973; Final Version June 11, 1974

Abstract. Sulpiride, a new psychotropic drug with neuroleptic activity, was administered to rats in a Sidman avoidance schedule. Doses ranging from 1 to 80 mg/kg resulted in the animal receiving fewer shocks. This effect was not correlated with an increase of responding and seemed unrelated to the suppressing action abruptly observed at high doses (i. e. 150 to 200 mg/kg). These results differ from those classically obtained with other neuroleptics.

Key words: Avoidance — Drug — Psychotropic — Rat — Sidman Schedule — Sulpiride.

The N (1-ethyl 2-pyrrolidinyl) methyl 2-methoxy 5-sulfamoyl benzamide or sulpiride¹ is an original psychotropic drug acting on the hypothalamic nuclei (S. Takaori *et al.*, 1969).



Like neuroleptics, sulpiride has a very strong antiemetic action (Laville, Cl. and Margarit, J., 1968), but at normal doses, it has only a slight cataleptic effect (Takaori *et al.*, 1969). It is of extremely low toxicity in acute or chronic administration (Kumada, 1968).

In clinical practice, Sulpiride in large doses has an antipsychotic effect without impairing vigilance (Borenstein *et al.*, 1969). It is also used as an antidepressive drug, different from the M.A.O.I. or imipramine (J. Collard, 1969). Moreover, positive results are consistently reported in the treatment of diseases of the gastrointestinal tract, primarily gastroduodenal ulcer (Cornet and Grivaux, 1968).

¹ International generic name of the drug, synthesized by Justin Besançon *et al.*, 1967, Laboratoires Delagrangé, Paris, France.

Until now, no study has been published on the effects of Sulpiride on operant behavior in animals. In the present paper, we have studied the effect of Sulpiride under a Sidman avoidance schedule.

Methods

Subjects. Five adult albino rats, male and female of the Wistar Strain, were used. They were 10 months old at the beginning of the experiment and their weight ranged from 250 to 350 g. They lived in individual cages in the animal room.

Apparatus. The experimental cage was a standard conditioning box for rats. It was equipped with a response lever and a grid floor and was enclosed in an isolating compartment. The aversive stimulus was a brief shock of 0.3 mA; the shock-shock interval was 5 sec, the response-shock interval was 20 sec. The experimental operations were automatically controlled in another room. The experimental events were recorded on a Gerbrands cumulative recorder.

Procedure. Subjects were put in the experimental cage for 60 min daily, from Monday to Friday. The baseline was obtained after 4 to 6 weeks and the results averaged from the last 10 sessions were used as control values. The drug was then given intraperitoneally 1 hr before the session and the different doses (1, 2, 4, 6, 8, 10, 20, 40, 80, 100, 120, 150 mg/kg) were administered randomly. After examination of these doses, the rats were submitted to a chronic treatment extending over 17 days with a daily dose of 150 mg/kg. Experimental sessions were run seven days a week throughout this treatment.

Results

1. Dose-Effect Relationship

Results are summarized in Fig. 1. The control performance before drug-tests was stable in all subjects, with the number of shocks received varying from 20 to 100 depending on the individual (the total number of shocks due in the absence of responding during the whole session was 720).

In all subjects (except in rat 1065 for 1 mg/kg) the number of shocks received decreased with the smallest doses of sulpiride. This effect was not correlated to an increase in response rate. On the contrary, response rate was significantly reduced, except for one subject. Thus, in terms of response-shock ratio, the performance was improved. This effect of Sulpiride was obtained for doses ranging from 1 mg/kg up to 80 mg/kg depending on the individual. The reduction of response rate and number of shocks under the drug depended on the predrug level. It was important in animals with a high control rate, but it was slight in animals with a low control level, resulting in both cases in a better adjustment to the avoidance contingencies.

It must be noted that after the first injection, the subjects never returned to the baseline level.

If we compare the predrug baseline obtained after a long stabilisation of the behavior to the average level obtained in the interinjection sessions we can see that the rate of responding was reduced in three rats and

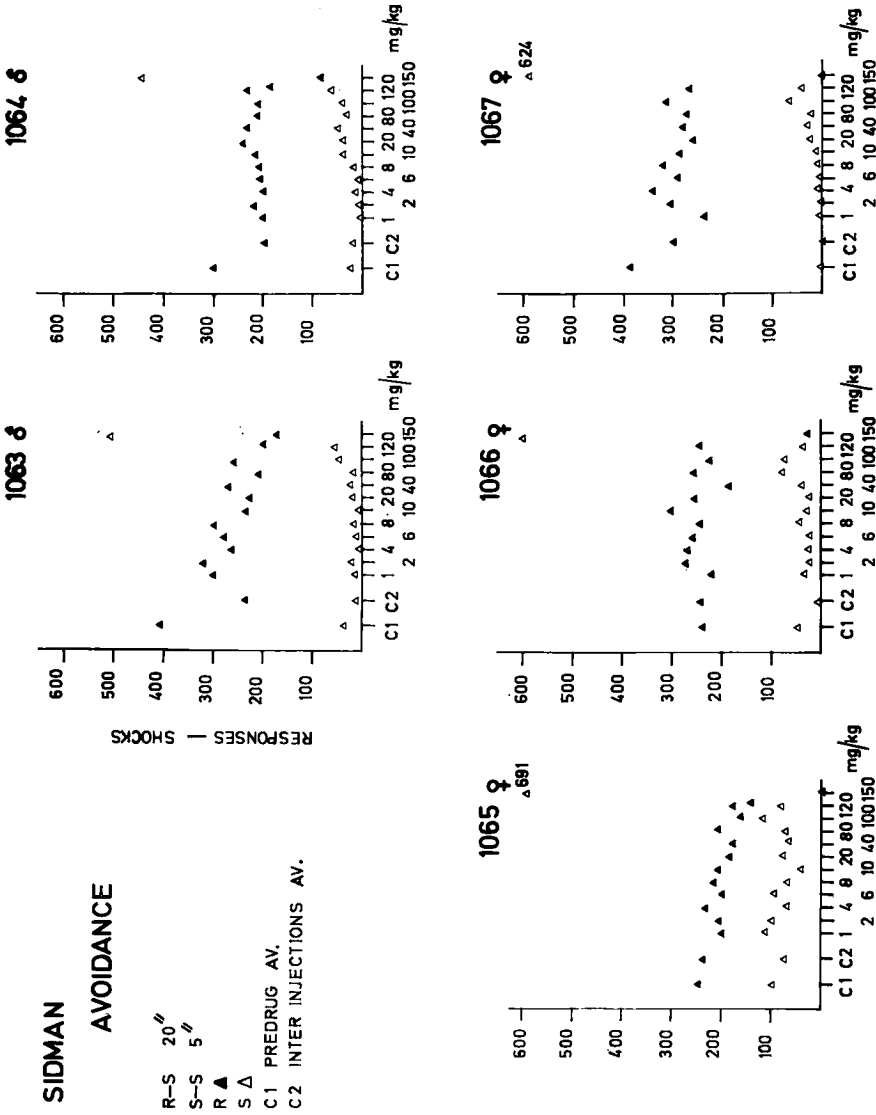


Fig. 1. Sidman Avoidance. Rate of responding and number of shocks received as a function of doses of Sulpiride in five individual rats. (C 1) Control values averaged from the last ten sessions before treatment; (C 2) control values averaged from the sessions without drug interspersed between treatment sessions

remained unchanged in the other two animals characterized by a very good performance in the predrug period. But in all five subjects the number of shocks was reduced.

It seems implausible to interpret these changes occurring in five animals at the same moment after a first injection of the drug as a coincidence. It seems more likely to assign the changes to the drug. For larger

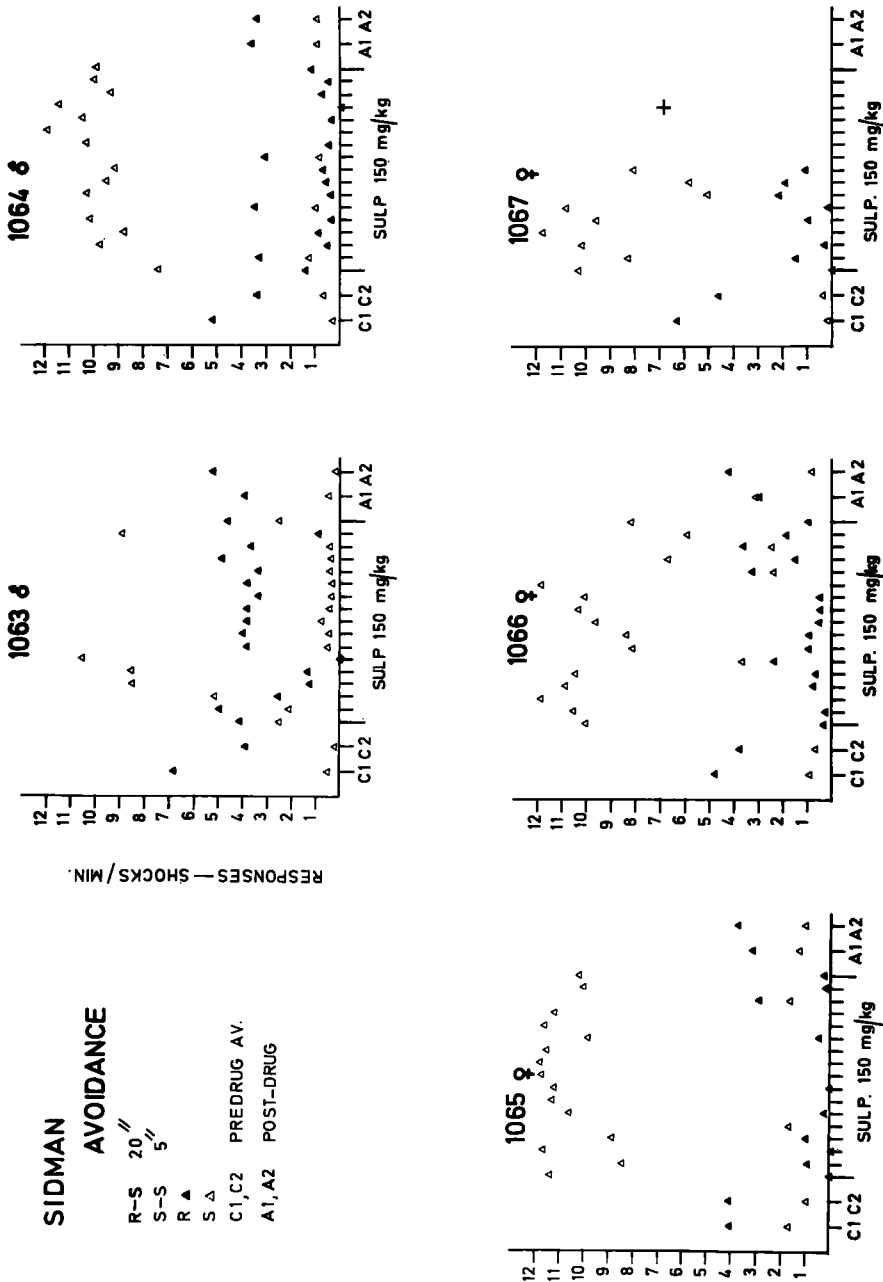


Fig. 2. Sidman Avoidance. Chronic treatment. Rate of responses and shocks per minute in five individual rats. (C1) control level averaged from the last ten sessions before the first administration of drug (C1 in Fig. 1); (C2) control level averaged from the ten sessions preceding the chronic treatment. A1 and A2: sessions without drug just after the end of the chronic treatment

doses, the number of shocks increased, reaching and overpassing the control level. The responses were either less frequent or less regularly distributed through time. Drastic breakdown of avoidance behavior was observed in all animals at the dose of 150 mg/kg.

2. Chronic Treatment

Fig.2 gives day by day individual results in terms of responses per minute and shocks per minute. Chronic administration of 150 mg/kg for 17 consecutive days did not show evidence of tolerance, except in rat 1063. Operant behavior was practically depressed to zero throughout the treatment except for occasional restoration of a normal, or quasi-normal, rate in one to four sessions depending on the individual. These partial or total restorations give no evidence of a tolerance effect because they do not persist: on the day after, the suppressing effect of the drug on response rate was again observed. Operant behavior returned to the baseline level (C 2) on the first day following the last session of chronic treatment.

In one rat (number 1063), operant responding was reinstated from the sixth day of treatment onwards except for a suppression on the 15th day. It must be noted that this was the only subject in which the dose of 150 mg/kg did not produce a complete suppression of operant responding until the third day of treatment.

Conclusion

The effect of Sulpiride on Sidman avoidance in rats does not compare with the effect of psychotropic drugs of widely explored classes, such as major and minor tranquilizers, or psychostimulants. The subjects receive fewer shocks, though the response rate in the Sidman schedule remains unchanged (or is reduced), an effect that seems unrelated to the suppressing action abruptly observed at high doses (150 to 200 mg). Further observation showed that this effect persisted 30 days after the end of the chronic treatment.

From these first results, Sulpiride appears as an original substance that deserves further examination from psychopharmacologists.

Chronic treatment with a high dose (150 mg/kg) did not show evidence of tolerance nor withdrawal reactions.

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