Antidepressant versus neuroleptic activities of sulpiride isomers on four animal models of depression

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Abstract. The atypical neuroleptic sulpiride is also prescribed for depression because of its activating effect. However, such an effect does not necessarily imply an action identical to that of classical antidepressants, and a laboratory comparison of the neuroleptic and antidepressant activities of sulpiride may contribute to a better definition of its psychotherapeutic profile. Sulpiride isomers were studied in the rat in four behavioural models of depression which are thought to be influenced by neuroleptics in different ways. Desipramine (imipramine) and haloperidol were employed in each test as a standard antidepressant and neuroleptic, respectively. The four tests were: 1) prevention of apomorphine-induced sedation; 2) antagonism of apomorphine-induced hypothermia; 3) behavioural despair (swim test); 4) learned helplessness (FR2 lever pressing escape). Desipramine ameliorated behaviour in all tests; haloperidol ameliorated the response to test 1, influenced that to test 2 in a neuroleptic-like way and worsened the responses to tests 3 and 4. (-)-Sulpiride worked in a similar way to haloperidol in all tests. (+)-Sulpiride significantly and dose-dependently ameliorated the responses to test 3 and was inactive in the others. No conclusion was drawn from test 1 owing to its lack of specificity; the results of the remaining tests indicated a neuroleptic profile of (-)-sulpiride and suggested a potential “antidepressant” activity of (+)-sulpiride which merits further investigation.

Key words: Sulpiride isomers — Imipramine — Desipramine — Haloperidol — Apomorphine — Hypomotility — Hypothermia — Behavioural despair — Learned helplessness — Rat

Sulpiride is clinically used both as an antipsychotic and antidepressant (for review see Peselow and Stanley 1982). The latter use is probably because of its atypical neuroleptic profile: it does not produce marked catalepsy (Elliott et al. 1977), it does not antagonize dopamine (DA) stimulation of adenylate cyclase in rat striatum (Trabucchi et al. 1975; Keabian and Calne 1979) and it preferentially blocks DA receptors mediating behavioural sedation in the rat (Costall et al. 1980; Montanaro et al. 1983) at doses unable to affect post-synaptic DA receptors. However, the activating effect of sulpiride seen in the treatment of depression as well as in schizophrenia (Jenner and Marsden 1982) does not necessarily mean that the drug is clinically effective as a pure antidepressant agent. Laboratory studies of the effect of sulpiride in animal models of depression are lacking. The present investigation made a behavioural comparison of the neuroleptic versus antidepressant activities of sulpiride by choosing, among the many animal models available for the screening of antidepressants, some having the feature of being influenced by neuroleptics in the opposite direction to that of antidepressants.

Such models were: 1) Prevention of apomorphine-induced sedation; 2) Antagonism of apomorphine-induced hypothermia; 3) Behavioural despair; 4) Learned helplessness.

Although racemic sulpiride is the clinically used form, mounting neurochemical and behavioural evidence indicates (-)-sulpiride as the active enantiomer in the CNS. Nevertheless, (+)-sulpiride seems not to be completely devoid of pharmacological activity: in fact it prevents restraint-induced gastric ulcer in the rat within the same range of doses of (-)-sulpiride (Montanaro et al. 1979) and strongly potentiates methamphetamine-induced hyperactivity (Montanaro et al. 1981). For such reasons both isomers of sulpiride were included in our investigation. Moreover, both a classical neuroleptic and a typical antidepressant were introduced in each study as standard reference compounds for comparison with the effects of sulpiride.

Materials and methods

Animals. Male Sprague-Dawley rats (Nossan, Como, Italy) were used. Their weight was 200—220 g for all the experiments except for the “learned helplessness” one, in which the initial weight was 350—400 g. All the animals were maintained under controlled conditions of illumination (light on from 7:00 a.m. to 7:00 p.m.), temperature (22 ± 2°C) and humidity (60%), and were allowed free access to standard laboratory diet and tap water.

Drugs. Sulpiride isomers were available as vial solutions (100 mg/2 ml) kindly gifted by Ravizza (Muggiò, Italy). Haloperidol (Sernace, Lusofarmacó, Milan, Italy) was always used as the classical neuroleptic; a typical antidepressant was represented in experiment 1 by imipramine (Tofranil, Ciba-Geigy, Basel, Switzerland) whereas desipramine (Nortynil, Chiesi, Parma, Italy) was used in the others. All drugs were available as commercial vials and were diluted with NaCl 0.9% solution. Apomorphine HCl (Sigma Chemical Co., St. Louis, MO, USA), used in experiments 1 and 2, was always freshly dissolved in distilled water just before administration.
**Apparatus.** Motility tests in experiments 1 and 3 were performed in actometric cages similar to those described by Babbini et al. (1973). They consisted of eight plastic boxes, 38 x 30 x 25 cm, containing a stainless steel grid floor. A 65 V, 25 mA DC current was continuously delivered to the grid, the circuit being closed by the rat's feet; every switch of the circuit was recorded as one motility count, and counts were printed at a prefixed interval.

In experiment 2, body temperature was measured by means of a rectal probe connected to a 6-channel digital temperature recorder; small plexiglas cylinders were used in order to restrain the animals during the measurements.

The escape tests in experiment 4 were performed in four operant chambers (28 x 20 x 20 cm) enclosed in wooden soundproof containers; the floor of each box was represented by a stainless steel grid (the bars being 10 mm diameter and 10 mm spaced) connected to a 4-channel shock generator through a scrambler. Centred on the left-hand wall was a lever 6 cm off the floor and a light cue mounted 6 cm along the lever. For the inescapable shock sessions the same operant chambers were modified by substituting for the left-hand white wall, a yellow one without lever and light cue.

**Procedures**

**Test 1. Prevention of apomorphine-induced sedation.** According to Serra et al. (1979, 1981a) long-term administration of antidepressants to rats induces subsensitivity of DA autoreceptors, whereas chronic treatment with neuroleptics induces supersensitivity of the same DA autoreceptors. Both antidepressant and neuroleptic pretreatments prevent the hypomotility induced by a low dose of apomorphine such as 25 mg/kg, but only neuroleptic pretreatment causes a very low dose of apomorphine, such as 6.25 mg/kg, to produce an overt sedative effect.

Groups of 24 animals were pretreated SC with saline (1 ml/kg), (-)-sulpiride and (+)-sulpiride (20 mg/kg), haloperidol (1 mg/kg) and imipramine (20 mg/kg) once daily for 10 days. Four days after the last injection, animals (eight per group) were treated SC with 0, 6.25 and 30 µg/kg apomorphine and 10 min later placed into the actometric cages where their motility response was recorded for 30 min.

**Test 2. Antagonism of apomorphine-induced hypothermia.** The model proposed by Puech et al. (1981) is based on the differential effects of neuroleptics and antidepressants on the hypothermic response induced in mice by moderate or high doses of apomorphine. Neuroleptic drugs antagonize the hypothermia induced by a moderate dose (1 mg/kg) but not that induced by a higher one (16 mg/kg), whereas antidepressants preferentially antagonize the latter. The same approach has been employed by us in rats, the moderate and high doses of apomorphine being 1 and 25 mg/kg respectively.

Immediately after the measurement of their baseline rectal temperature (time 0) rats were randomly divided in 13 groups of 10 animals and pretreated IP with saline (5 ml/kg), desipramine (1, 4, and 16 mg/kg), haloperidol (0.125, 0.25 and 0.5 mg/kg), (-)-sulpiride (2, 4, 8, 16 and 32 mg/kg) and (+)-sulpiride (32 and 64 mg/kg). One hour later the rectal temperature was measured again (time 60) in order to detect possible direct effects of the pretreatments; then the rats received 1 or 25 mg/kg apomorphine and after 30 min their temperature was measured (time 90).

**Test 3. Behavioural despair.** Rats, when forced to swim in a cylinder from which they cannot escape, assume within few minutes a characteristic immobile posture. A variety of therapeutically effective antidepressant treatment (including ECT and REM sleep deprivation) reduce immobility duration, whereas neuroleptics enhance it. Porsolt et al. (1978) suggested that this behaviour reflects a state of lowered mood or "hopelessness", since, after the first attempts to escape the aversive situation, rats find that escape is impossible and resign themselves to the experimental situation.

Groups of 12–14 rats were forced to swim for 15 min in a cylinder (40 cm height, 18 cm diameter) containing 18 cm of water at 25°C. They were allowed to dry, and 15 min, 19 h and 23 h after the trial were treated IP with saline (5 ml/kg), desipramine (20 mg/kg), haloperidol (0.1 mg/kg) and sulpiride isomers at doses of 2.5, 5, 10, 20 and 40 mg/kg. One hour after the last injection the animals were again placed in the cylinder and the total duration of immobility within 5 min was measured by an observer unaware of the treatments.

Parallel groups of naive rats (n = 6) were treated with the drugs mentioned above, at the same doses and according to the same administration schedule. One hour after the last injection the rats were placed into the actometers and their 5-min locomotor activity was recorded in order to assess possible direct effects of the drugs upon rat spontaneous motility.

**Test 4. Learned helplessness.** Prior exposure to an uncontrollable and inescapable stressful situation induces in rats, as well as in dogs and in other mammals, a deficit in the acquisition of a subsequent escape task. This phenomenon, labelled by Seligman as "learned helplessness", has been attributed to motivational and cognitive deficits (Maier and Seligman 1976), since it resembles some features of the human depressive syndrome. Alternatively, Weiss et al. (1975) and Anisman et al. (1979) have proposed that the neurochemical changes induced by inescapable shock result in a motor activation deficit that hinders escape performance. In any case the effect of the inescapable shock on the subsequent escape performance is also detectable after a delay of several days (Seligman et al. 1975) and is selectively reversed by chronic, but not acute (Sherman et al. 1979; Telner and Singhal 1981), administration of treatments effective as antidepressants including ECT, thus appearing a valid model for the study of antidepressants.

On the first day of experiment rats were randomly divided in two subgroups (40 animals each). The animals from the first group (shock group) were submitted to 80 inescapable and unpredictable footshocks (0.4 mA, 15 s) with a random intertrial interval (10–110 s, 60 s mean); the remaining 40 animals (no shock group) spent 100 min in the shock chamber without receiving any footshock. Starting 24 h after the pre-shock session, eight rats from each group were daily treated IP for 7 days with saline (5 ml/kg), desipramine (20 mg/kg), haloperidol (0.2 mg/kg), (-)-sulpiride and (+)-sulpiride (20 mg/kg). Sixty minutes after the last injection all rats were exposed to 20 random (10–110 s; 60 s mean) shocks (0.4 mA) which could be interrupted by pressing twice the lever (FR2 escape task). In case of escape failure the shock terminated after 60 s.