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Anxiolytic Potential of Sulpiride, Clozapine and Derivatives in the Open-Field Test

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BRUHWYLER, J., E. CHLEIDE, J-F. LIÉGEOIS, J. DELARGE AND M. MERCIER. *Anxiolytic potential of sulpiride, clozapine and derivatives in the open-field test.* PHARMACOL BIOCHEM BEHAV **36**(1) 57–61, 1990.—Recently acquired data question the sharp dichotomy between anxiolytics and neuroleptics, since disinhibitory effects have been measured in the rat with very low doses of haloperidol and higher doses of atypical neuroleptics in FI and DRL schedules, but also in the open-field test. That the DA transmission in certain brain regions is involved in some aspects of anxiety has recently been suggested. The present study confirms this hypothesis particularly with high doses of sulpiride (80 mg/kg) and clozapine (24 mg/kg) when tested in the open-field test. Moreover, the results show how a slight chemical modification of clozapine can give a direction to pharmacological activity with one derivative still resembling clozapine and the second one resembling haloperidol. As neuroleptics do not seem to influence the synthesis and utilization of GABA, the higher entry score observed with them would seem to depend above all on DA antagonism in the mesolimbic system.

Anxiolytic Neuroleptic Haloperidol Chlordiazepoxide Sulpiride Clozapine DA2 antagonism
Defecation Open-field Rat

THE open-field test aims to measure the antagonism between the instinctive tendency to explore a new environment and the tendency to shun this new experience (3, 15, 59, 61).

Most of the time, this opposition is evaluated on the basis of the overall ambulation score and the rate of entry into the innermost areas of the open-field (19, 20, 35, 61). The number of times the subject defecates or urinates allows, moreover, its emotional reactivity to be estimated (28, 49, 62). An increase in open-field activity is interpreted in terms of general activation of behavior, anxiolytic effect or specific action on exploratory components of the ethogram. This third explanation could itself result of a decrease in fear and anxiety (4, 5, 16, 53, 61). The authors acknowledge that an increase in the locomotion and particularly in the rate of entry into the innermost areas of the environment reflects an anxiolytic effect. This interpretation is reinforced when there is a decrease in defecation (4, 16, 28, 53, 54, 61).

Numerous tests show that anxiolytics and neuroleptics behave differently when the open-field test is employed. Thus, the effect of anxiolytics is generally biphasic with an increase in ambulation and entry scores for a low dose and a decrease in these same scores when a high dose is administered, accompanied by muscular relaxation, ataxia and sedation (15, 16, 26, 53, 59).

Neuroleptics only exert depressant effects in proportion to the dose administered and these are habitually accompanied by catalepsy (4, 5, 34, 43, 56). It has been observed (51) that cataleptic subjects tend to defecate more often. This effect is obtained (4) with a 10 mg/kg dose of haloperidol (HALO, Haldol®) in the open-field from the second day of administration. In an attempt to elucidate the contribution of peripheral DA mechanisms in the HALO-induced defecation response, fecal measures were recorded from animals that received the peripheral DA receptor antagonist domperidone. Because of domperidone's inability to penetrate the blood-brain barrier at low doses, central mechanisms were not activated. The results demonstrated that domperidone did not influence fecal elimination (49). Since peripheral receptors are not implicated, high doses of HALO could exert a central anxiogenic effect through locomotor restriction leading to an increase in alertness and "emotional defecation" (49). "Emotional defecation" is recognized as a manifestation of a series of behavioural and peripheral changes which are thought to accompany elevated sympathetic nervous system activity (1,28).

Recently acquired data question this sharp dichotomy between classes of psychotropic agents. Thus, it has been possible to measure (13) inhibitory effects which are highly specific to the coarse activity measured automatically in the rat, with a dose of 100 μg/kg of diazepam (DZP, Valium®). Conversely, disinhibitory effects have been recorded (39), accompanied by an increase in locomotor activity, for neuroleptics when they are administered

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in very low doses (0.025 to 0.1 mg/kg HALO and 0.5 to 10 mg/kg sulpiride) (SULP, Dogmatil®). It has been suggested (15) that low doses of neuroleptics, such as HALO and SULP, showed a clear preference for the presynaptic DA2 sites and exerted their antagonism predominantly on these sites. This suggests that DA is implicated in the etiology and expression of anxiety (57, 58, 63). This same disinhibitory effect has been noted (54) with 40 mg/kg of SULP in the rat, translating into a nonsignificant increase in the number of internal areas covered and into a significant decrease in the number of times the rat defecates. On the other hand, with 80 mg/kg, activity is significantly reduced without defecation occurring. This depression cannot, therefore, be related to an anxiogenic effect of SULP, as it was the case for higher doses of HALO.

Clozapine (CLOZ), another atypical neuroleptic, which very rarely causes extrapyramidal side effects in man, has revealed certain disinhibitory effects with low doses in temporal cue schedules of the FI and DRL type (8,9). Since CLOZ displays agranulocytosis as a serious toxic effect (27), an investigation was undertaken to find potential antipsychotic agents free of extrapyramidal and other toxic side effects (17). Two derivatives of CLOZ (Der A and Der B), recently obtained by the Pharmaceutical Institute of Liège by modulating the structure of the tricyclic nucleus, have revealed a stimulating effect on the DA discharge from the ventral tegmental area in the rat using an extensively described technique (18) or apomorphine antagonist action, for Der A and Der B respectively (unpublished results).

This study has two purposes, namely to confirm or invalidate the view put forward by several authors (8,54) in respect of the anxiolytic action of CLOZ and SULP and to see how a slight modification of the structure of CLOZ, in respect of parameters such as the bioisoteric replacement of one of the benzenic nuclei by a heterocycle, the suppression of the halogenated substituent or the replacement of the central heteroatom by another, can give a direction to pharmacological activity.

METHOD

Animals

Two hundred and ten Wistar rats, 100 to 120 days old, weighing from 350 to 400 g were used for this experiment. When they were 50 days old, the subjects had been put together in cages in groups of 10 and placed in an L/D:12/12 cycle (dark period from 7 a.m. to 7 p.m.). The temperature was held constant at 21°C. Food and water were available ad lib. All experiments took place between 10 a.m. and 3 p.m.

Apparatus

It consisted of a square surface of wood, the sides of which measuring 96 cm, surrounded by a 28 cm high wooden partition. The base, painted in white, was divided into 36 squares the sides of which were 16 cm long. The open-field was placed in a ventilated, sound-proof room lighted by a 40-W bulb.

Procedure

Thirty minutes before the test, each group consisting of 10 rats received an IP injection containing either HALO (0.2, 1, 5 mg/kg), chlordiazepoxide (CDP, Librium®, 5, 10, 20 mg/kg), SULP (20, 40, 80 mg/kg), CLOZ (Sandoz Ltd, 8, 16, 24 mg/kg), Der A (8, 16, 24 mg/kg), Der B (8, 16, 24 mg/kg) or an NaCl solution (9/1000). HALO and SULP were obtained directly in injectable form. CDP was dissolved in a physiological solution (NaCl 9/1000). CLOZ, Der A and Der B were dissolved in a physiological solution (NaCl 9/1000) acidified with acetic acid buffered with NaOH at pH 6. The placebo was injected into 3 groups of 10 subjects. Four subjects were removed from the experiments, two from the placebo groups due to thyroid goitres, one from the 1 mg/kg HALO group for hyperaggressivity and one from the 24 mg/kg Der A group as it died 10 minutes after drug administration.

Thirty minutes after drug administration, the rat was carefully placed in a particular compartment next to the partition and left in the open-field for 10 minutes. During this period, the total number of compartments entered, the total number of interior compartments entered, separated into class 2 (median) and class 3 (central) compartments and the number of fecal boluses were measured.

The averages obtained for the different parameters and the different groups were statistically compared with the help of the analysis of variance, with the "dose" as classification criterion, followed by post hoc Student's *t*-tests.

RESULTS

Ambulation Score

The pharmacological treatment is significant ($p<0.01$) for HALO, $F(3,53)=5.21$, CDP, $F(3,54)=10.48$, and SULP, $F(3,54)=9.41$, but nonsignificant ($p>0.05$) for CLOZ and its two derivatives. Only a medium dose of CDP and a high dose of SULP increase ambulation in significant fashion ($p<0.01$). In contrast, HALO reduces the score for all doses (significantly).

Entry Score

The effect of the pharmacological treatment on the number of class 2 areas entered is significant for CDP, $F(3,54)=6.03$, SULP, $F(3,54)=3.49$ ($p<0.01$), CLOZ, $F(3,54)=2.85$, and Der A, $F(3,53)=3.18$ ($p<0.05$) but not significant for HALO and Der B. CDP and CLOZ increase this score significantly ($p<0.01$) for the medium dose and the higher dose ($p<0.05$) respectively. SULP and Der A increase this score significantly with the higher doses.

The effect of the pharmacological treatment on the number of class 3 areas entered is significant only for CDP, $F(3,54)=6.35$, $p<0.01$, and nonsignificant with the other drugs. CDP increases this parameter significantly ($p<0.01$) with a medium dose and the highest dose. With HALO, SULP and Der B subjects never enter class 3 areas.

Defecation

The pharmacological treatment is significant for all the drugs: HALO, $F(3,53)=3.11$, CDP, $F(3,54)=3.22$, SULP, $F(3,54)=3.38$ ($p<0.05$), CLOZ, $F(3,54)=8.18$, Der A, $F(3,53)=6.98$, and Der B, $F(3,54)=5.20$ ($p<0.01$). CLOZ and its derivatives reduce the number of fecal boluses for all doses (significantly). CDP and HALO reduce defecation significantly when higher doses are administered. With SULP, a significant reduction in the number of times the animal defecates can be noted for a medium dose (see Table 1).

DISCUSSION

As numerous studies have shown, CDP increases the ambulatory activity for low doses while this effect disappears for high doses (15, 16, 20, 53). The absence of effects on locomotion with high doses cannot be related to increased anxiety since defecation doesn't increase significantly and since entry into the innermost areas remains at a significant level. Sedation, ataxia and/or muscular relaxation could be responsible of this low activity whilst the anxiolytic effect continues to act on the antagonism between exploration and fear in favour of the former tendency.

TABLE 1

EFFECTS OF DRUGS ON THE BEHAVIOURAL PARAMETERS IN THE OPEN-FIELD TEST

Drugs (mg/kg)		Total Ambulation Mean (SD)	Entry Score Area 2 Mean (SD)	Area 3 Mean (SD)	Defecation Mean (SD)
Control		15.1 (17.7)	0.1 (0.3)	0.0 (0.0)	3.2 (3.4)
HALO	(0.2)	0.9 (0.6)†	0.0 (0.0)	0.0 (0.0)	3.3 (2.4)
	(1)	4.2 (3.4)*	0.1 (0.5)	0.0 (0.0)	1.8 (2.4)
	(5)	1.0 (1.2)†	0.1 (0.3)	0.0 (0.0)	0.3 (0.7)*
CDP	(5)	17.4 (32.0)	0.9 (2.2)	0.1 (0.3)	3.4 (1.0)
	(10)	73.9 (57.9)†	3.4 (4.6)†	0.7 (0.9)†	3.0 (3.3)
	(20)	14.1 (10.1)	0.7 (1.0)	0.4 (0.8)*	0.2 (0.4)*
SULP	(20)	10.2 (8.2)	0.0 (0.0)	0.0 (0.0)	1.8 (2.8)
	(40)	19.1 (13.5)	0.1 (0.3)	0.0 (0.0)	0.2 (0.4)*
	(80)	44.5 (20.8)†	0.5 (0.8)†	0.0 (0.0)	3.8 (3.1)
CLOZ	(8)	17.4 (16.7)	0.3 (0.0)	0.6 (1.9)	0.0 (0.0)†
	(16)	8.9 (8.2)	0.2 (0.4)	0.0 (0.0)	0.2 (0.4)†
	(24)	11.0 (25.7)	0.5 (0.0)*	0.0 (0.0)	0.0 (0.0)†
Der A	(8)	15.9 (27.5)	0.0 (0.0)	0.0 (0.0)	0.5 (1.6)†
	(16)	4.7 (4.7)	0.3 (0.9)	0.0 (0.0)	0.0 (0.0)†
	(24)	15.1 (29.2)	1.3 (2.6)*	0.3 (1.0)	0.0 (0.0)†
Der B	(8)	4.5 (5.1)	0.0 (0.0)	0.0 (0.0)	2.1 (1.8)
	(16)	12.6 (19.1)	0.1 (0.3)	0.0 (0.0)	0.3 (0.9)†
	(24)	1.6 (1.3)	0.0 (0.0)	0.0 (0.0)	0.2 (0.6)†

M = mean; SD = standard deviation; *$p<0.05$; †$p<0.01$.

According to some (24), it is the GABAergic potentiation which is responsible for the anxiolytic effect, while for others (25, 36, 37), reduction in 5-HT turnover is the main causal factor. It is possible that GABAergic action on the raphe exerts control over the ascendant 5-HT neurons and thus reduces 5-HT turnover (12). The anxioselective action of buspirone and the fact that it does not interact directly with the benzodiazepine/GABA system but well with DA receptors as agonist or antagonist (32,44) have led some authors (57) to propose a role for DA in the pathology and treatment of anxiety. According to them (57), some of the modulatory influences of benzodiazepines on GABA neurotransmission would be expressed via DA pathways which mediate a variety of functions such as ataxia, conflict-reward interactions and anxiolysis. Particularly, it seems that the mesocortical and mesolimbic DA systems play a role in the cerebral circuitry of emotionality and that the benzodiazepines modulate this in some manner (57).

HALO reduces overall exploratory activity for all doses and induces catalepsy as several authors have shown in their experiments (4, 49, 56). In agreement with results previously obtained in a novel open-field environment in mice (1), the drop in activity is accompanied by a significant reduction in defecation. The motor restriction caused by catalepsy is not therefore sufficient to explain the increase in emotionality as some authors have found in chronic treatment (4) or in well-habituated environments (49–52). In fact, in the open-field, HALO is tested in animals when they are already in a hyperaroused and/or anxious state, thereby creating a possible ceiling effect for obscuring the observation of further changes in the affective state of the animal and particularly in defecation (52).

The results obtained with 40 mg/kg of SULP perfectly corroborate those found in the literature (54). At this dose, SULP doesn't change exploration and entry scores significantly while decreasing defecation significantly. For 80 mg/kg, whereas others (54) observe a significant reduction in ambulatory activity and an absence of defecation, our results confirm the anxiolytic nature of SULP, with a significant increase in overall movement and in the number of internal areas covered without any effect on defecation. This discrepancy might be due to the chronic dosage regimen during 20 days in their experiences while the administration of SULP was acute in ours. The authors (54) noted that seventeen days from the beginning of the SULP injections, the animals began to show physiological disturbances and some animals died. Our results provide confirmation of several studies (22,45) which note a pattern of action specific to SULP in FI 2 min. In addition to neuroleptic properties, certain antidepressant potentialities are attributed to SULP (2,54). The more recent investigations concur in attributing to SULP selective action on DA receptors (33,47) almost exclusively in the mesolimbic system, which would explain the absence of extrapyramidal effects (23,29).

With CLOZ at high dose, we clearly encounter the anxiolytic hypothesis formulated by certain authors (8,9). In fact, whereas overall activity doesn't increase, the number of class 2 areas increases and defecation decreases significantly for a dose of 24 mg/kg. It has, moreover, been possible to show that CLOZ does not induce catalepsy (7), block DA agonist-induced stereotypies (31) or produce DA receptor supersensitivity (55) or a chronic depolarization state in A9 brain regions (11). As with SULP, numerous experimenters (23,29) acknowledge that CLOZ has a DA action which is distinctly more mesolimbic than nigro-striatal.

Regarding the two derivatives of CLOZ, the considerable resemblance they retain in respect of the mother substance is the drop in defecation observed for all doses. This quite excludes the intervention of anxiety in their general action on behavior in the open-field. Der A has no significant effect on the overall locomotor score. On the other hand, when high doses are given, though this score remains unchanged, entry into the class 2 areas increases to a significant extent. Its overall profile retains most of the characteristics of CLOZ. Der B tends to decrease general activity for a high dose but this tendence is nonsignificant. It has no significant effect on the entry score but decreases defecation significantly. Its profile resembles more HALO than CLOZ.

One can conclude from this study that, while CLOZ has anxiolytic tendencies, these are fragile and can easily be modified by focusing, on the one hand, on the presence or not of halogenated substituents in the tricyclic nucleus and, on the other hand, on the replacement of one of the benzenic nuclei by a bioisoteric heterocycle and of the central heteroatom by another. This last-mentioned modification is connected with differences of pharmacological activity between CLOZ, clothiapine and loxapine noted in the literature. Among these dibenzazepine derivatives, CLOZ is classed, in contrast to the other, as an atypical neuroleptic.

Increase in total locomotor activity could be explained for CDP and SULP by the drop in 5-HT turnover (36, 37, 41, 42, 60), which is either direct for SULP or indirect via the GABA for CDP. In contrast, CLOZ, which has revealed an antagonistic LSD action in the raphe, increases 5-HT turnover (21) and would not, as a result, increase ambulatory activity. No 5-HT activity is known for HALO (40). On the other hand, predominantly nigro-striatal DA activity would suffice to inhibit all locomotion through catalepsy (10,29). As neuroleptics do not seem to influence the synthesis and utilization of GABA in the substantia nigra and the corpus striatum (30), the higher entry score, observed with SULP and CLOZ, would seem to depend above all on DA antagonism in the mesolimbic system.

Disinhibitory and anxiolytic potential for neuroleptics had been measured in different tests: two-compartment test (39), conflict

test (39), FI (8), DRL (9) and open-field (54). Clinical studies themselves had reported that neuroleptics could relieve anxiety-related symptoms (46), borderline (6) and chronically anxious patients (38,48). This research is in agreement with the hypothesis according to which the DA transmission in certain brain regions and particularly in the mesolimbic and mesocortical systems could be involved in some aspects of the etiology and expression of anxiety (57).

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