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Effect of clozapine upon schedule-induced polydipsia (SIP) resembles neither the actions of dopamine D1 nor D2 blockade

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Abstract. The effects of clozapine (CLOZ) upon acquired schedule-induced polydipsia in rats were compared to the effects of the dopamine (DA) D_1 antagonist SCH 23390 (SCH) and the DA D_2 antagonist raclopride (RAC). All three compounds suppressed water consumption, but only SCH and RAC decreased drinking efficiency. SCH was the only compound with an effect on panel pressing (PP), causing suppression even at a dose without effect upon water intake. SCH also affected the temporal pattern of licking (TPL) at all doses, while clozapine, 10 mg/kg, only affected the pattern acutely, and raclopride was without effect. In conclusion, PP and the TPL are more sensitive to D_1 than D_2 blockade. While PP and the TPL are more sensitive than water intake to D_1 blockade, the opposite is true for D_2 blockade. It is possible to differentiate between DA D_1/D_2 antagonists and CLOZ in this model, focusing upon reduction in water consumption, with and without reduction in drinking efficiency. Furthermore, it is possible to differentiate between D_1 and D_2 blockade by analyzing water consumption, PP and the TPL.

Key words: Schedule-induced polydipsia – SIP – Clozapine – Raclopride – SCH 23390 – Dopamine D_1 antagonist – Dopamine D_2 antagonist – Major tranquilizers – Rat

Food-deprived rats exposed to an intermittent food schedule exhibit excessive drinking (schedule-induced drinking, SIP) (Falk 1961). The drinking occurs shortly after food delivery. SIP cannot be explained by means of a fluid deficit or homeostatic imbalance (Falk 1971). Evidence for the involvement of the dopamine (DA) system in the development of SIP is substantial. The development of SIP is facilitated by pre-exposure to amphetamine (Mittleman and Valenstein 1985). Bilateral 6-hydroxydopamine lesions of DA neurons in the nucleus accumbens and olfactory tubercle inhibit the development (Robbins and Koob 1980; Wallace et al. 1983), though not the performance (Robbins et al. 1983) of SIP. Lesions of the nucleus accumbens, hippocampus, or parietal cortex (limbic structures) reduce SIP, while lesions of the caudate-putamen (striatum) only reduce drinking efficiency (Mittleman et al. 1990). Furthermore, DA antagonists attenuate SIP (Porter et al. 1984; Ljungberg 1989a; Todd et al. 1992).

The therapeutic effects of antipsychotic compounds have been proposed to be primarily related to their actions upon central DA mechanisms (Carlsson 1978), mediated via the mesolimbic DA system (for review see Chiodo and Bunney 1983; White and Wang 1983; Delini-Stula 1986).

The atypical neuroleptic clozapine (CLOZ) is effective in the treatment of both positive and negative symptoms, without inducing extrapyramidal side-effects (EPS) (Lindström 1988; Fitton and Heel 1990; Meltzer et al. 1991). Clozapine is thought to mediate its effect via the mesolimbic system (Chiodo and Bunney 1983; White and Wang 1983; Skarsfeldt 1988; for review see Fitton and Heel 1990). However, the precise reason for CLOZ's antipsychotic effect and low incidence of EPS still remains elusive. A balanced occupancy of DA D_1 and D_2 receptors (Farde et al. 1989) as well as high affinity for the $5HT_2$ receptor have been hypothesized to be the explanation for the lack of induction of EPS by CLOZ (Gerlach 1991; for review see Meltzer 1991). Furthermore, the anticholinergic (for review see Seeman 1990) and antiadrenergic (Baldessarini et al. 1992) effects of CLOZ have also been hypothesized to be responsible for the valuable properties of the compound.

The purpose of the present investigation was to elucidate whether the effect of CLOZ upon acquired SIP is due to its D_1 or D_2 effect. To this intent, a comparison was made with the effect of the D_1 blocker SCH 23390 (SCH) (Hyttel 1983; Hyttel and Arnt 1987) and the D_2 blocker raclopride (RAC) (Ljungberg 1989a).

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Materials and methods

Drugs. Clozapine [8-chloro-11(4-methyl-1-piperazinyl)-5H-dibenzo [1, 4] diazepine] (Sandoz Pharmaceuticals) was dissolved in 0.1 N HCl, titrated with NaOH to pH 6–7 and diluted with distilled water. SCH 23390 [(R)-(+)-8-chloro-2, 3, 4, 5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol] hemimaleate (Schering, USA), raclopride [(-)-(S)-3, 5-dichloro-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-o-anisam ide] tartrate (Astra, Sweden) and amphetamine (AMPH) [d-α-methylphenethylamine, $^1/_2$sulphate] were dissolved in distilled water and diluted with saline. The solutions were prepared to produce a total injection volume of 1.0 ml/kg. All compounds were administered daily by means of subcutaneous injection (including weekends). On test days, the compounds were administered 30 min before the test session. The control groups received an equivalent volume of vehicle.

Animals. One hundred and fifty two male Wistar rats (Mollegaard, Denmark) weighing 200 ± 10 g at arrival were familiarised to the laboratory for 1 week. The rats were food deprived until they reached 80% of their free feeding weight by adjusting their daily intake of laboratory chow. The rats were fed 10 g Altromin per day. The animals were housed in pairs in a colony room at a constant temperature (20°C) and humidity (60–70%) with a 6:00 A.M. light/6:00 P.M. dark cycle. Water was available ad libitum.

Apparatus. Eight Skinner boxes (Campden Instruments Ltd) were used. The sound-attenuated boxes (64 × 38 × 38 cm) were constructed with two dark, one-way observation windows (d = 16.5 cm). An electric fan ventilated the boxes and provided a constant background noise.

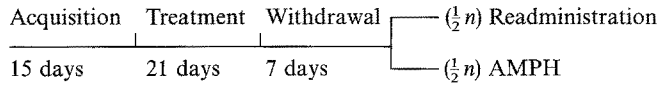
One operant chamber (24 × 24 × 20 cm) was placed in each box. The chambers were constructed of aluminium and Plexiglas, with grid floors. Each operant chamber contained a food dispenser delivering food pellets, Noyes 45 mg, to a recessed food tray covered by a hinged Plexiglas flap. The rats had to push up the flap to obtain access to the pellets. Tray entries were recorded automatically as panel pushes (PP). On the wall next to the food tray, a stainless steel spout protruded into the chamber 4 cm above the floor level and 10 cm to the left of the food tray. The spout was connected to a graduated burette filled with 100 ml water, allowing measurement of water intake to the nearest 0.1 ml. Licks (LK) on the drinking spout were recorded automatically via an interface (Paul Fray Ltd) to an IBM computer (PS/2 30–021).

Procedure. A 45-mg food pellet was dispensed at each minute of the 20-min test session (60-s fixed time, FT). The FT was divided into ten equal 6-s bins. The number of LK in each bin was summarized for the 20-min session. This division is referred to as the temporal pattern of licking (TPL). The total number of LK and PP in the session were also recorded.

Pre-experimental training. The rats were trained for 15 days in one session per day. On day 12, the rats reached a stable level of LK, measured as the total mean of all animals. A stable level was defined as 3 consecutive days (12–14) which were not statistically different. All animals received saline on days 13, 14 and 15 of the training period.

Animals which did not reach 1000 LK, calculated as a mean of the last three days in the training period, were excluded as non-drinkers. Both in our experience and that of others (for review see Mittleman et al. 1988), some animals never develop the SIP behaviour.

Test. The remaining animals were divided into three matched drug groups. Each drug group was further divided into three dose groups and one saline group. The drug groups received treatment for 21 days. The compounds were then withdrawn, and all animals received saline for 7 days. After the withdrawal period, the highest dose of the compounds was readministered to half of the animals in each group, the other half receiving 0.50 mg/kg AMPH. The animals were tested once daily, excluding weekends. The experimental design is shown below.



Measures and statistical analysis. The total number of LK, PP and amount of water consumed were analyzed in relation to four phases, acute and chronic administration, the withdrawal period and readministration. Acute delivery (day 1) and readministration (day 29) were analyzed by means of a one-way analysis of variance (ANOVA), with dose groups treated as between-subject factors. Chronic administration (day 2–21) and the withdrawal period (day 22–28) were analyzed by means of a two-way ANOVA with a repeated measures design, dose groups again being treated as between-subject factors. To show how soon the drug groups returned to the control level, the withdrawal period was also analyzed using a one-way ANOVA, with dose groups treated as between-subject factors.

If the ANOVAs were significant, further comparisons were made using Dunnett's *t*-test (comparison with the control mean).

The drinking efficiency was calculated on the last day of chronic treatment (day 21) as the number of LKs divided by the amount of water consumed (LK/ml). A one-way ANOVA was performed, with treatment as a between-subject factor, and further comparisons made using Dunnett's *t*-test.

The TPLs were analyzed by calculating the time when the subjects reached one quarter of their total number of LKs between two consecutive pellets (quarter life, QL). QL was analyzed by means of the Mann-Whitney rank test. If the QL for the treatments was higher or lower than the QL for the saline group, the TPL was considered to have moved to the right or left, respectively.

Results

Effect of clozapine upon water consumption

Acute CLOZ induced a reduction in water intake [$F(3,39) = 13.59$, $P < 0.001$] (Fig. 1). Post-hoc comparison revealed that this occurred at 2.5 and 10 mg/kg, with the suppressing effect of 10.0 mg/kg being significantly higher than that of 2.5 mg/kg. CLOZ also induced suppression in the chronic phase [$F(3,39) = 6.43$, $P < 0.01$], again at 2.5 and 10.0 mg/kg. The effect induced by 10 mg/kg administered chronically was not as pronounced as when administered acutely, and there was no significant difference between the 10.0 mg/kg and 2.5 mg/kg dose groups. A Groups × Time interaction effect [$F(39,507) = 1.82$, $P < 0.01$] was seen, suggesting a changed relationship between groups with respect to water intake over time. Immediately after withdrawal, all dose groups returned to control levels [$F(3,39) = 1.57$, $P > 0.05$] and no significant interaction was found [$F(117,9) = 2.00$, $P > 0.05$]. When CLOZ, 10.0 mg/kg, was readministered after the withdrawal period, there was no significant difference in the reduction of water intake between the control group, which on this day received CLOZ, 10 mg/kg, for the first time, and the previous 10 mg/kg dose group [$F(1,10) = 2.37$, $P > 0.05$]. The reduction was comparable to the reduction induced by chronic treatment [$F(1,15) = 2.91$, $P > 0.05$] (Table 1). The effect of 0.50 mg/kg AMPH on the 10.0 mg/kg

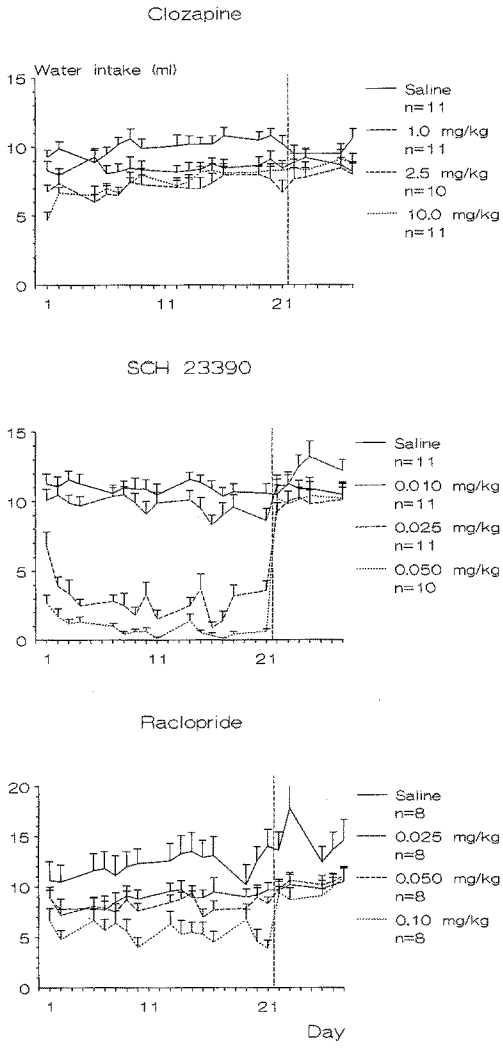


Fig. 1. Water consumption ± SEM as a function of days. The vertical dotted line indicates withdrawal

CLOZ group did not differ significantly from that on the saline group [$F(1,9) = 1.25$, $P > 0.05$] (Table 1).

Effect of SCH 23390 upon water consumption

The reduction in water intake (Fig. 1) induced by acute SCH [$F(3,39) = 23.77$, $P < 0.001$], was seen at both 0.025 and 0.050 mg/kg, with the suppressing effect of 0.050 mg/kg being significantly higher than that of 0.025 mg/kg. The suppression continued throughout chronic treatment [$F(3,39) = 101.36$, $P < 0.001$] and an interaction effect was seen [$F(39,507) = 1.53$, $P < 0.05$]. After withdrawal, all groups returned to the control level [$F(3,39) = 1.55$, $P > 0.05$] and there was no interaction effect [$F(12,156) = 1.19$, $P > 0.05$]. When 0.050 mg/kg was readministered, the reduction in water intake was more pronounced than when administered to the saline group [$F(1,8) = 8.16$, $P < 0.001$] (Table 1). The reduction was not significantly different from the reduction induced by chronic treatment [$F(1,13) = 2.76$, $P > 0.05$] (Table 1). AMPH 0.50 mg/kg induced the same suppression when given to the pretreated 0.050 mg/kg group of SCH as when given to the saline group [$F(1,8) = 1.56$, $P > 0.05$] (Table 1).

The effect of raclopride upon water consumption

Acute RAC did not suppress water intake [$F(3,28) = 1.53$, $P > 0.05$] (Fig. 1). In the chronic phase, RAC induced suppression of water intake [$F(3,28) = 7.31$, $P < 0.001$], at both 0.05 mg/kg and 0.10 mg/kg. The relationship between groups changed over time suggested by the interaction [$F(38,364) = 1.88$, $P < 0.01$]. After withdrawal, all animals immediately returned to the control level [$F(3,28) = 2.75$, $P > 0.05$] and no interaction was seen [$F(12,112) = 1.29$, $P > 0.05$]. When RAC, 0.10 mg/kg, was readministered (Table 1), the reduction of water intake was not different from the effect upon the saline group [$F(1,6) = 0.20$, $P > 0.05$]. The reduction was comparable to the reduction induced by chronic treatment [$F(1,10) = 0.97$, $P > 0.05$]. When AMPH 0.50 mg/kg was administered to the pretreated RAC group there was a distinct trend towards an increased suppression of the water intake as compared to the saline pretreated group [$F(1,6) = 1.18$, $P > 0.05$] (Table 1).

Effect of clozapine on panel pressing

CLOZ (Fig. 2) at the doses tested did not affect the PP [acute: $F(3,39) = 0.80$, $P > 0.05$; chronic: $F(3,39) = 0.65$, $P > 0.05$; withdrawal: $F(3,39) = 0.44$, $P > 0.05$].

Table 1. Water consumption. Effect of the compounds when readministered. Saline (SAL); compound (COMP); amphetamine 0.050 mg/kg (AMPH); $^*P<0.05$ compared to SAL on day 21; $^+P<0.05$ compared to SAL/COMP. The following comparisons were also made but no significance found: COMP/COMP = COMP; SAL/AMPH = COMP/AMPH; SAL/AMPH = SAL

Treatment Compound mg/kg	Chronic		Readministration			
	SAL	COMP	SAL/ COMP	COMP/ COMP	SAL/ AMP	COMP/ AMP
Clozapine 10.0	10.2±0.6	8.3±0.5*	4.5±1.1	6.7±0.9	8.4±0.5	7.4±0.7
SCH 23390 0.050	10.6±0.7	0.6±0.2*	3.8±0.7	1.3±0.5$^+$	10.2±0.7	8.5±1.2
Raclopride 0.10	14.0±1.7	3.9±0.8*	7.1±3.6	5.4±1.4	11.4±4.3	6.4±1.5

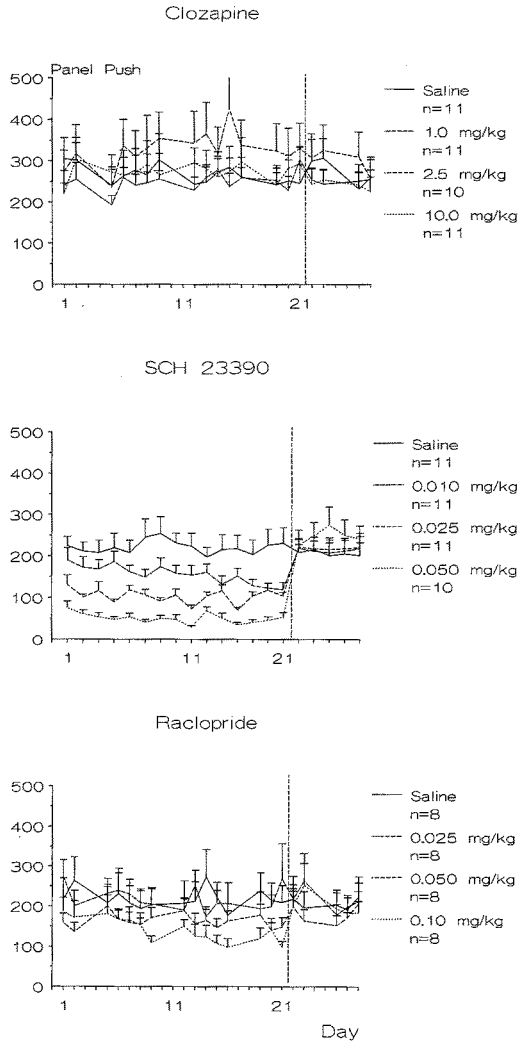


Fig. 2. Panel pressing ± SEM as a function of days. The vertical dotted line indicates withdrawal

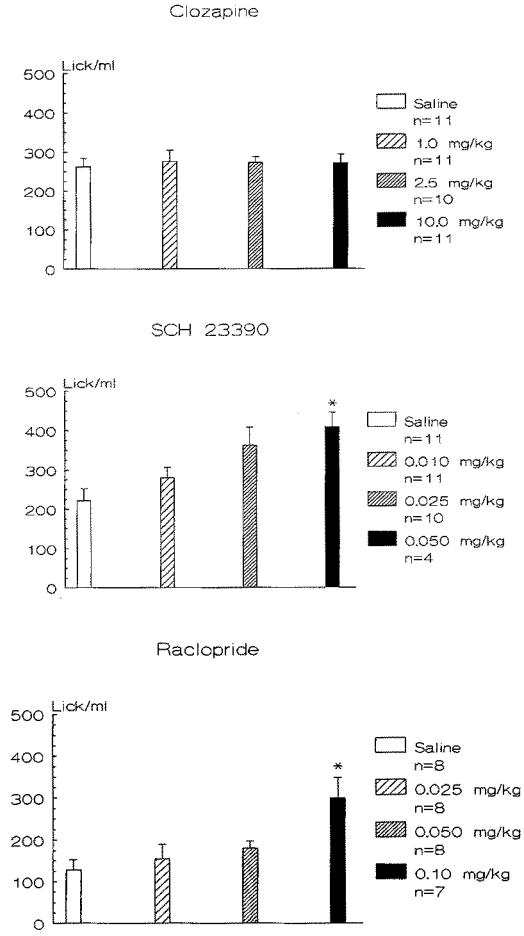


Fig. 3. Drinking efficiency ± SEM. The graphs represent the last day of chronic treatment (day 21). An increased number of LK/ml indicates a decreased drinking efficiency. * $P < 0.05$ compared to saline

Effect of SCH 23390 on panel pressing

SCH (Fig. 2) 0.025 and 0.050 mg/kg induced suppression in the acute phase [$F(3,39) = 7.45$, $P < 0.001$], while all doses induced suppression in the chronic phase [$F(3,39) = 17.65$, $P < 0.001$]. An interaction effect was seen [$F(39,507) = 1.63$, $P < 0.05$]. After withdrawal, all dose groups returned to the control level [$F(3,39) = 0.48$, $P > 0.05$] and no interaction was seen [$F(12,156) = 0.41$, $P > 0.05$].

Effect of raclopride on panel pressing

RAC (Fig. 2) at the doses tested did not affect PP [acute: $F(3,28) = 1.53$, $P > 0.05$; chronic: $F(3,28) = 1.58$, $P > 0.05$; withdrawal: $F(3,28) = 0.20$, $P > 0.05$].

Effect of clozapine on drinking efficiency

CLOZ (Fig. 3) at the doses tested did not affect the drinking efficiency [$F(3,39) = 0.06$, $P > 0.05$].

Effect of SCH 23390 on drinking efficiency

SCH reduced drinking efficiency in a dose dependent manner (Fig. 3) [$F(3,32) = 4.33$, $P < 0.05$], but only 0.050 mg/kg significantly increased LK per ml water consumed.

Effect of raclopride on drinking efficiency

RAC only reduced drinking efficiency at 0.10 mg/kg [$F(3,27) = 4.97$, $P < 0.01$] (Fig. 3).

Effect of clozapine upon the temporal pattern of licking

Acute CLOZ, 10 mg/kg, caused an increase in QL from 10 to 12 s ($P < 0.05$) (Table 2). This increase vanished on the last day (day 21) of the chronic period ($P > 0.05$) (Table 2).

Table 2. Effect of different treatments on temporal pattern of licking. The values presented are quarter life ± SEM measured in seconds. Saline (SAL). * $P < 0.05$ compared to SAL (Mann-Whitney rank test). N represents the total of all dose groups for the different compounds. N was approximately equal in the four groups

Compound	Clozapine ($N=43$)			
Dose (mg/kg)	SAL	1.0	2.5	10.0
Acute	10±0.5	12±1.4	11±0.6	12±0.7*
Chronic	13±0.6	15±1.3	13±1.3	15±0.7
Compound	SCH 23390 ($N=36$)			
Dose (mg/kg)	SAL	0.010	0.025	0.050
Acute	13±0.6	12±0.7	15±0.8	13±0.9
Chronic	12±0.6	14±0.9*	18±1.1*	18±1.8*
Compound	Raclopride ($N=32$)			
Dose (mg/kg)	SAL	0.025	0.050	0.10
Acute	14±1.2	12±1.6	12±1.3	14±1.7
Chronic	12±0.9	16±1.7	12±0.7	17±2.1

Effect of SCH 23390 upon the temporal pattern of licking

Acute SCH, at the doses tested, was without effect upon QL (Table 2). However, on day 21 of the chronic period, all three doses increased QL ($P < 0.05$) (Table 2).

Effect of raclopride upon the temporal pattern of licking

RAC, at the doses tested, was without effect upon QL both acutely and chronically (Table 2).

Discussion

The data from the present study indicate that CLOZ, SCH and RAC, at the doses tested, differentially disrupt acquired SIP. That the highest doses of SCH suppressed all of the indices measured might be considered due to induction of akinesia and catalepsia. We therefore tested the animals by placing them upon a vertical grid, and no immobility was found. In a previous study where we tested SCH 0.10 mg/kg, immobility was induced in the rats. Ljungberg (1989b) has tested SCH at doses ranging from 0.010 to 0.50 mg/kg in a water-rewarded operant responding task. He found that the animals were still capable of performing operant responding at 0.050 mg/kg and at that dose the water intake was only slightly reduced. Therefore, the effects of the highest dose of SCH in this experiment are probably not due to the induction of akinesia and catalepsy.

All three compounds suppressed water consumption, but only RAC and SCH reduced drinking efficiency. These differences may be explained by postulating different anatomical sites of action of the three compounds. Classical antipsychotic compounds have been shown to decrease the number of spontaneously active DA neurons in both the nigrostriatal and the limbic areas of the rat brain, while atypical antipsychotic compounds selectively decrease the number of active neurons in the limbic area (Chiodo and Bunney 1983; White and Wang 1983; Skarsfeldt 1988). Our results, and the different anatomical sites of action of the compounds tested, are in accordance with the findings of Mittleman et al. (1990), who concluded that it is possible to fractionate the components of the SIP behaviour into two distinct neuronal systems, one involving hippocampal-ventral striatal circuitry and the other involving corticodorsal striatal connections. Classical neuroleptics would be expected to reduce water consumption and drinking efficiency in the SIP model via a combination of effects upon the nigrostriatal and the limbic systems, while atypical neuroleptics would be expected to reduce water consumption via effects upon the limbic system alone, without affecting drinking efficiency. According to this explanation SCH and RAC act as typical neuroleptics in the SIP model with respect to water consumption and drinking efficiency. Contradictions exist as to whether SCH should be considered typical or atypical (For review see Delini-Stula 1986; Imperato et al. 1987; Coffin et al. 1989; Christensen 1990; Hietala et al. 1990). RAC is classified as a typical neuroleptic, but shows a large separation between the doses required for blockade of apomorphine-induced hyperactivity and those inducing catalepsy in rats (Ögren et al. 1986)

SCH was the only compound affecting PP, and that even at the lowest dose which did not affect water consumption. RAC and CLOZ, at doses suppressing water consumption, were without effect. Therefore, it seems that PP is more sensitive to DA D_1 than D_2 blockade and that PP is more sensitive than water intake to D_1 blockade, whereas the opposite is suggested for D_2 blockade.

This same sensitivity is seen when analyzing the temporal pattern of licking. SCH, after chronic treatment, moved QL to the right at all doses tested, whereas CLOZ only affected the TPLs at the highest dose given acutely, and RAC was without effect. The temporal pattern of licking is therefore much more sensitive to D_1 than D_2 blockade and the temporal pattern is more sensitive than water intake to the D_1 blockade, whereas the opposite is suggested for D_2 blockade. The closely related effect of the compounds tested upon PP and the TPLs imply a close dependency between food consumption and the temporal pattern of licking.

There was no induction of tolerance after repeated administration of CLOZ or RAC. Christensen et al. (1985) showed that D_2 antagonists lost their ability to antagonize DA-agonist induced stereotyped behaviour, suggesting that tolerance had developed. This discrepancy between the effects of RAC in the two experiments could be explained by suggesting that water consumption in the SIP model is more sensitive to motoric effects (drinking efficiency) than stereotypical behaviour. The potentiation of the effect of SCH when readministered is in accordance with the findings of Christensen et al.

(1985). When readministered, SCH reduced water consumption to the same level as the last day of chronic treatment (day 21) indicating that 1 week after withdrawal, the receptors or neural circuits were still affected by previous treatment with the D_1 blocker. The increased reduction of water intake throughout the period of administration also reflects the potentiation of the effect of SCH (Fig. 1), this potentiation accounting for the significant interaction observed. Administration of AMPH to the previous drug groups and control groups showed that only for RAC was there a trend towards induction of hypersensitivity in this model.

In conclusion, the effects of CLOZ in this model resemble neither the effects of DA D_1 nor D_2 blockade. The effect of CLOZ could be distinguished from the effects of DA D_1 and D_2 antagonists by examining reduction of water consumption, with or without reduction of drinking efficiency. Whether it is the regional distribution of DA receptors with high affinity for CLOZ (Van Tol et al. 1991) or the multiple effects of CLOZ which are responsible for its lack of influence upon drinking efficiency cannot be concluded at present. However, the effects of CLOZ are more closely related to the effects of a D_2 blocker than a D_1 blocker. Furthermore, it is possible to differentiate between D_1 and D_2 blockade by examining water consumption, panel pressing and the temporal pattern of licks.

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