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BRIEF COMMUNICATION

Neuroleptic-Induced Reduction of Quipazine-Elicited Head-Twitches in Rats: Possible Involvement of Striatal Dopaminergic Supersensitivity

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DALL'OLIO, R., A. VACCHERI, O. GANDOLFI, P. RONCADA AND N. MONTANARO. *Neuroleptic-induced reduction of quipazine-elicited head-twitches in rats: Possible involvement of striatal dopaminergic supersensitivity.* PHARMACOL BIOCHEM BEHAV 31(4) 941–944, 1988.—Rats were treated with a single large dose of various neuroleptic compounds and, 5–7 days after, they were assayed for either behavioral sensitivity to apomorphine (hypermotility and stereotyped behavior) or head-twitch response to the mixed serotonin-dopamine agonist quipazine. The animals withdrawn from chlorpromazine, fluphenazine, haloperidol, metoclopramide and the D1 selective blocker SCH 23390, showed enhanced hypermotility and/or stereotyped responses to apomorphine and reduced head-twitch response to quipazine. The rats withdrawn from thioridazine, (−)-sulpiride and sultopride responded to apomorphine only with enhanced hypermotility while their response to quipazine was either unchanged or even increased. The results are discussed in terms of dopaminergic brain areas and/or receptor subtypes involved in the modulation of the head-twitch response to quipazine. We concluded that an enhancement of dopaminergic tone at the striatal level could be related to the reduced head-twitch response to quipazine.

Head-twitches Rats Quipazine Apomorphine Stereotyped behavior Hypermotility Neuroleptics Dopaminergic supersensitivity

BEHAVIORAL evidence indicates that the administration of a single large dose of neuroleptic compounds induces behavioral dopamine supersensitivity (2, 6, 13). Previous work (5) has shown that rats treated with a large dose of haloperidol exhibited increased stereotyped response to apomorphine and reduced head-twitch response to the serotonergic agonist quipazine when they were assayed 5–7 days after the administration of the neuroleptic compound. This finding suggests that quipazine, which also possesses dopaminergic properties (10), stimulated brain dopamine receptors of haloperidol-withdrawn rats to a greater extent with respect to control rats and that such an enhancement of the dopaminergic activity disfavored the magnitude of the serotonergic response.

The present investigation was addressed to understand if the observed correlation between reduced response to quipazine and the increased dopamine-mediated behavior is related to brain areas and/or dopamine receptor subtypes. For this purpose, rats were treated with a large dose of various neuroleptics having different affinities for the D1 and D2 receptors or different abilities to preferentially act on mesolimbic versus striatal areas. After five days the locomotor activity and stereotyped behavior induced by different doses of apomorphine, including the head-twitch response to quipazine, were evaluated.

METHOD

Animals

Male Sprague-Dawley rats (Nossan, Correzzana, Italy) weighing 250–300 g were used. They were housed in groups of four under controlled conditions of light (from 7:00 a.m. to 7:00 p.m.), temperature (22±2°C) and humidity (60%). The animals were allowed free access to a standard laboratory diet and tap water.

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TABLE 1

LA AND SB INDUCED BY THRESHOLD DOSES OF APOMORPHINE IN RATS TREATED 5–7 DAYS BEFORE WITH SINGLE LARGE DOSES OF VARIOUS NEUROLEPTIC COMPOUNDS

Pretreatment (5–7 Days Before)	Dose (mg/kg)		APO-Induced LA		APO-Induced SB
Saline	—	(16)	123.43 ± 11.15	(16)	0.93 ± 0.07
Chlorpromazine	30	(8)	242.37 ± 33.52*	(8)	1.53 ± 0.03*
Fluphenazine	10	(8)	209.86 ± 26.63*	(8)	1.94 ± 0.17*
Haloperidol	10	(8)	212.00 ± 26.46*	(8)	1.57 ± 0.15*
Metoclopramide	100	(8)	194.20 ± 12.13*	(8)	1.44 ± 0.07*
SCH 23390	5	(8)	110.30 ± 20.48	(8)	1.47 ± 0.28*
(−)-Sulpiride	100	(8)	192.94 ± 17.61*	(8)	1.00 ± 0.12
Thioridazine	30	(8)	246.57 ± 39.69*	(8)	1.03 ± 0.07
Sultopride	30	(8)	257.52 ± 57.05*	(8)	1.27 ± 0.13

Rats were pretreated IP with the neuroleptic compounds 5 or 7 days before the trials. In parentheses the number of the animals.

APO-induced LA=60-min locomotor activity counts (mean values ± SEM) following the administration of 150 μg/kg SC apomorphine.

APO-induced SB=stereotyped behavior (mean values ± SEM of individual mean scores obtained from 6 observations taken at intervals of 10 min for 1 hour) following the administration of 250 μg/kg apomorphine.

*$p<0.05$ when compared to the respective saline-apomorphine mean value (one-tailed Dunnett t-test after ANOVA in apomorphine-induced LA groups; Mann-Whitney U-test in apomorphine-induced SB groups).

Drugs

Haloperidol (10 mg/kg) (Serenase, Lusofarmaco, Milan), (−)-sulpiride (100 mg/kg) (Ravizza, Milan), and sultopride (30 mg/kg) (Barnotil, Vita Farmaceutici, Turin) were injected as commercial solution. The following drugs were dissolved in saline: chlorpromazine HCl (30 mg/kg) (Carlo Erba, Milan), fluphenazine HCl (10 mg/kg) (Recordati, Milan), metoclopramide HCl (100 mg/kg) (Recordati, Milan), SCH 23390 maleate (5 mg/kg) (Schering-Plough, Bloomfield, NJ), thioridazine HCl (30 mg/kg) (Sandoz, Basle), quipazine maleate (1 and 2 mg/kg) (Miles Laboratories, Elkhart, IN) and apomorphine HCl (150 and 250 μg/kg) (Sigma Chem., St. Louis, MO).

Procedure

The rats were injected intraperitoneally with the neuroleptics 5 days before the behavioral trials. The D1 antagonist SCH 23390 (7) was administered IP 7 days before, in view of its prolonged occupation of D1 receptors (11). Control groups received 5 ml/kg IP of saline. Each animal was used only once.

Quipazine-induced head-twitch (HTW). The animals were injected IP with 1 or 2 mg/kg of quipazine and placed into transparent Plexiglas cylinders (20 cm diameter; 25 cm height). Immediately after, the number of HTW was counted for 60 min. The appearance of other unusual behaviors was also noted.

Apomorphine-induced locomotor activity (LA). After 3 hr habituation to the actometric cages (9), the rats were injected with 150 μg/kg SC apomorphine and their LA was evaluated for the following 60 min.

Apomorphine-induced stereotyped behavior (SB). The rats received apomorphine at the threshold dose of 250 μg/kg SC and were immediately placed into 18 cm diameter Plexiglas cages with corrugated paper covering the floor. SB was scored every 10 min for 1 hour according to the 0 to 4 rating scale described by Costall and Naylor (3). The individual data were the mean scores of the 6 observations from each rat.

Statistical Analysis

LA data were analyzed by means of ANOVAs followed by single comparisons of the means (Dunnet t-test). SB and HTW values were statistically evaluated by employing the Mann-Whitney U-test.

RESULTS

Table 1 shows the LA and SB induced by apomorphine, 150 and 250 μg/kg respectively, in rats treated 5–7 days before with a large dose of neuroleptics; the HTW responses to 1 and 2 mg/kg of quipazine of parallely pretreated rats are given in Table 2.

The animals withdrawn from chlorpromazine, fluphenazine, haloperidol and metoclopramide showed increased values of both LA and SB and exhibited reduced counts of HTW to both doses of quipazine.

Rats withdrawn from SCH 23390 did not change their LA response to the lower dose of apomorphine whereas they showed increased apomorphine-induced SB and reduced quipazine-elicited HTW. Rats previously treated with thioridazine and sultopride showed augmented LA and no change in both SB and HTW.

The rats previously administered with (−)-sulpiride exhibited increased LA, no change in SB and augmented HTW response to quipazine.

TABLE 2

HTW RESPONSE INDUCED BY QUIPAZINE IN RATS WITHDRAWN FROM VARIOUS NEUROLEPTIC COMPOUNDS

Pretreatment (5–7 Days Before)	Dose (mg/kg IP)		Quipazine 1 mg/kg IP		Quipazine 2 mg/kg IP
Saline	—	(12)	93.83 ± 8.62	(12)	116.33 ± 9.26
Chlorpromazine	30	(6)	52.83 ± 13.13*	(6)	59.17 ± 9.47*
Fluphenazine	10	(6)	59.00 ± 11.94*	(6)	62.33 ± 16.26*
Haloperidol	10	(6)	55.75 ± 6.50*	(6)	86.17 ± 14.32*
Metoclopramide	100	(6)	24.00 ± 10.70*	(6)	81.29 ± 16.07*
SCH 23390	5	(6)	34.40 ± 8.86*	(6)	53.00 ± 12.11*
(−)-Sulpiride	100	(6)	131.83 ± 12.90*	(6)	196.40 ± 38.67*
Thioridazine	30	(6)	88.17 ± 15.53	(6)	146.50 ± 29.77
Sultopride	30	(6)	99.17 ± 15.60	(6)	115.00 ± 22.25

Mean values ± SEM of the head-twitches (HTW) counted for 60 min starting immediately after quipazine administration. In parentheses the number of the animals.

*Significantly ($p<0.05$) lower and †significantly ($p<0.05$) higher than the respective control group (two-tailed Mann-Whitney U-test).

DISCUSSION

The present investigation has shown that rats withdrawn from a single large dose of various neuroleptics exhibit: a) behavioral dopaminergic supersensitivity (increased LA and/or SB following threshold doses of apomorphine), as already reported by others (2, 6, 13), and b) reduced, unchanged or increased quipazine-induced HTW according to the neuroleptic treatment administered 5 days before. The neuroleptics included in our study are known to have different affinities for D1/D2 receptor subtypes as well as different abilities to preferentially act on limbic or striatal areas. Therefore our results concerning changes in HTW response to quipazine could be interpreted in terms of either receptor subtypes or brain areas affected by the previous neuroleptic treatment. Less elevated HTW response to quipazine was exhibited by animals withdrawn from chlorpromazine, fluphenazine, haloperidol, metoclopramide and SCH 23390. Such drugs block dopamine receptor subtypes with different specificity; in fact, while chlorpromazine, haloperidol and fluphenazine are considered unselective antagonists of both D1 and D2 receptors, metoclopramide and SCH 23390 are selective blocking agents of D2 and D1 receptors respectively (7,12). On the other hand, chlorpromazine, fluphenazine, haloperidol and metoclopramide are known to induce extrapyramidal side effects in the clinical use (1,8). Accordingly, in the present study, withdrawal from all the above mentioned drugs, including SCH 23390, was followed by increased stereotyped response to apomorphine.

On the contrary, withdrawal from thioridazine, sultopride and (−)-sulpiride was followed by unchanged or even augmented HTW response to quipazine. While such neuroleptics differ in their receptor specificity (12) (thioridazine is an unselective dopamine antagonist, (−)-sulpiride and sultopride selectively block D2 receptors), they share the clinical feature of producing few extrapyramidal symptoms (1,8). On the other hand, the data from the present study have shown that rats withdrawn from thioridazine, sultopride and (−)-sulpiride exhibited increased LA to the low dose of apomorphine while they did not respond with SB to the high dose of the dopamine agonist.

In conclusion, the above mentioned results indicate that the common characteristic of the neuroleptics which brought about reduced HTW response to quipazine is their ability to induce enhanced sensitivity to the threshold dose of apomorphine for SB. It is known that SB is prevalently controlled at the striatal level, whereas LA prevalently depends on the mesolimbic function (5). Therefore our results seem to suggest that an increased dopaminergic neurotransmission in the striatum disfavors the expression of a serotonergic behavior as the HTW response to quipazine.

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