Pharmacology Biochemistry & Behavior, Vol. 32, pp. 585–587. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Serotonin Receptor Blocking Effect of SCH 23390

MARIA BIJAK AND ANTONI ŚMIAŁOWSKI[1]

Polish Academy of Sciences, Institute of Pharmacology, 31-343 Kraków, Poland

Received 8 September 1987

BIJAK, M. AND A. ŚMIALOWSKI. *Serotonin receptor blocking effect of SCH 23390.* PHARMACOL BIOCHEM BEHAV 32(3) 585–587, 1989.—The effect of SCH 23390 administration on the serotonin system-dependent head twitch behavior was studied in the rat. A small dose of SCH 23390 (1.25 μg/kg), injected 20 min before the test, decreased the number of quipazine-induced head twitches. Repeated treatment with SCH 23390 (0.5 mg/kg, SC), once a day for 18 days, increased the number of spontaneously occurring and quipazine-induced head twitches. The enhancing effect of repeated administration of SCH 23390 was blocked by cyproheptadine (0.4 mg/kg). The results indicate that acute injection of SCH 23390 blocks central serotonin receptors, whereas repeated treatment induces their functional supersensitivity.

Head twitch behavior SCH 23390 Serotonin Supersensitivity Quipazine Cyproheptadine Stress

ALTHOUGH SCH 23390 is regarded as a selective D1 dopamine receptor antagonist, it also binds with high affinity to 5-HT_2 receptors in the brain (3). In biochemical tests SCH 23390 inhibited with nanomolar affinity the 5-HT_2-sensitive spiperone binding in the cerebral cortex of the rat (3, 5, 11). On the basis of above-mentioned biochemical determination, 5-HT_2 receptor-blocking properties of SCH 23390 were proposed.

Up to the present the influence of SCH 23390 on the serotonin system in the brain was studied by biochemical methods, but behavioral investigation into serotonin-blocking properties of this compound has not been undertaken as yet. The aim of the present study was to determine the effect of single and repeated SCH 23390 administration on a behavioral response of rats which is induced by activation of 5-HT receptors and called the head twitch syndrome (7,20).

The head twitch behavior evoked by stimulation of serotonin receptors in rodents is thought to be mediated by 5-HT_2 serotonin receptor (1, 13, 17) and has been widely used to study the influence of drugs on the serotonin function. By using this behavioral model we hope to investigate the blocking effect of SCH 23390 on the central serotonin receptor in two experimental procedures. At first the influence of SCH 23390 on head twitches, evoked by the direct central 5-HT agonist quipazine (10, 14, 21), was studied; the following procedure investigated the effect of quipazine after repeated injection of SCH 23390. As was found in other receptor systems, the latter procedure induced supersensitivity of the blocked receptors (8, 18, 19) which was also shown by behavioral tests (2). Unfortunately, in the serotonin system the problem of receptor supersensitivity is still controversial due to different types of 5-HT receptors and the lack of pharmacological characteristics in some of them (4, 6, 10).

METHOD

Subjects

Male Wistar rats, weighing 230–250 g at the time of the behavioral test, were used. The rats were housed in groups of eight on a natural light-dark cycle; food and water were available ad lib.

Treatment

The animals were treated with SCH 23390 (0.5 mg/kg SC) daily for 18 days, control animals were injected with saline (2 ml/kg). The SCH 23390-treated rats were tested for head twitches 24 hr, or two weeks after the last injection. The testing was done between 11.00 and 15.00 hours. Quipazine (0.6 mg/kg SC) was injected immediately before the experiment. The effect of chronic treatment with SCH 23390 on spontaneous or quipazine-evoked head twitches was compared with that of chronic treatment with saline or single injection of SCH 23390, which the animals received instead of the last injection of saline. The effect of a low dose of SCH 23390 (1.25 μg/kg SC) on quipazine-evoked and spontaneous head twitches was investigated in nontreated rats 20 min after the drug injection. Cyproheptadine (0.4 mg/kg) was injected 30 min before the behavioral test. Each drug solution was prepared directly before use.

Behavioral Testing

For the measurement the rats were placed in pairs in observation cages and their head twitches were counted manually (immediately after their placing in the cages) for every 5 minutes during 20-minute sessions. The total number of head twitch episodes was assessed for each rat; after completing

[1]Requests for reprints should be addressed to Dr. Antoni Śmiałowski, Institute of Pharmacology, 31-343 Kraków Poland, Smętna 12.

the data, the mean value was calculated for each group and estimated statistically using the ANOVA and the t-test for a specific comparison.

The following drugs were used: cyproheptadine HCl (Serva), quipazine maleate (Miles Lab. Inc.), and SCH 23390 maleate (Schering Corporation).

RESULTS

Quipazine injected in a dose of 0.625 mg/kg induced approximately 50 head twitch episodes during a 20-min experimental session (Fig. 1B). The placing of noninjected rats in the observation cage induced a smaller number of head twitches (Fig. 1A). Injection of a low dose of SCH 23390 (1.25 μg/kg) 20 min before the experimental session significantly inhibited the quipazine-induced head twitches, but had no effect on spontaneous head twitches (Fig. 1).

Repeated treatment with SCH 23390 enhanced the number of spontaneous head twitches; a significantly larger number of head twitch episodes was observed one day after an 11- and a 17-day treatment with SCH 23390 (Fig. 2); the latter effect was significantly diminished (−49%) by pretreatment with cyproheptadine, 0.4 mg/kg, applied 30 min before the behavioral test. In rats tested on day 14 after the last repeated injection of SCH 23390, the number of head twitch episodes was similar to that in saline-treated group (Fig. 2).

To determine changes in the sensitivity to the serotonergic agonist after repeated SCH 23390 administration, quipazine (0.6 mg/kg) was given to rats pretreated with SCH 23390 for 18 days, as well as to the control group. Both groups were tested 24 hr after the last treatment. The rats treated repeatedly with SCH 23390 showed a significantly higher incidence of head twitches after quipazine administration than the control group (Table 1). Fourteen days after the last SCH 23390 administration the number of quipazine-induced head twitches significantly diminished in comparison with saline-treated animals.

DISCUSSION

The obtained results demonstrate that SCH 23390 applied acutely significantly decreases the number of quipazine-induced head twitches, whereas when applied repeatedly it enhances the quipazine effect in this behavioral model. The dose of SCH 23390 used to block the quipazine effect was low (1.25 μg/kg) and did not influence the motility of control rats. Our results show that SCH 23390 given acutely behaves like other receptor-affecting antagonistic compounds which block the receptor, and develops its supersensitivity when administered for a longer time (2, 15, 18). The supersensitivity of serotonin receptor after repeated treatment with SCH 23390 was shown in our study as an increase in the incidence of spontaneous and quipazine-induced head twitches. That effect developed during SCH 23390 administration: it was not found after 4 days of treatment, but appeared after 11 days. A subsequent administration of SCH 23390 did not significantly potentiate that effect. The supersensitivity is followed by the subsensitivity of 5-HT_2 receptors to quipazine on day 14 after the last treatment with SCH 23390 manifested as reduced sensitivity to quipazine.

Interestingly, changes in the sensitivity of the 5-HT receptor are also visible in the spontaneous behavior. Rats treated repeatedly with SCH 23390, which received no other treatment, revealed a higher head-twitch frequency one day after the last treatment. The placing of rats in a new environment (observation cage) induced a mild stress reaction. It has been demonstrated that various forms of stress affect serotonin neurons in the brain, this effect being manifested by an increased level of both serotonin and its metabolite (5-HIAA) (9, 12, 16). The stress-induced release of 5-HT may be responsible for enhancement of the head twitch reaction observed in rats placed in a new environment; SCH 23390 administration potentiated that effect. Since the increase in the spontaneous head twitch syndrome after repeated SCH 23390 administration was diminished by cyproheptadine, a specific 5-HT_2 receptor antagonist, the sensitization of this receptor is probably responsible for the latter effect.

Summing up the above data, i.e., the inhibition of quipazine-induced head twitches by acute SCH 23390 administration and the enhancement of this syndrome after repeated treatment, confirm our earlier hypothesis about the blocking effect of SCH 23390 on central 5-HT_2 receptors.

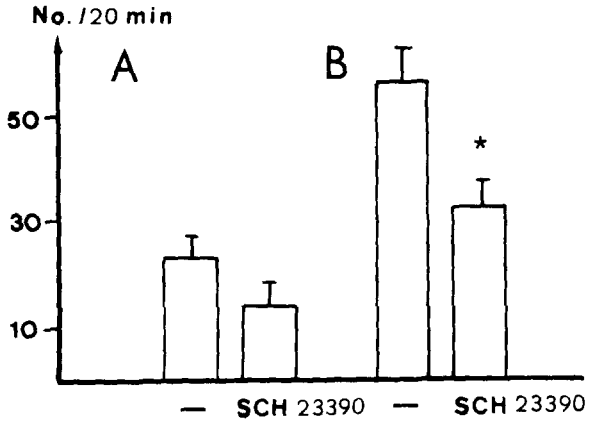

FIG. 1. The effect of SCH 23390 (1.25 μg/kg), injected 20 min before the test, on spontaneous (A) and quipazine-evoked (B) head twitches in the rat. Each bar represents the mean and the standard error of values from 8 animals. *$p<0.05$, t-test.

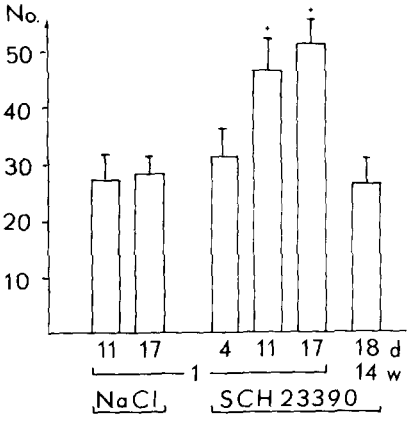

FIG. 2. The effect of chronic treatment with saline (NaCl) and SCH 23390 on the incidence of spontaneous head twitches in the rat. Each bar represents the mean and the standard error of values from 8 animals. $p<0.05$, t-test; d—days of treatment, w—withdrawal (days).

TABLE 1

THE EFFECT OF ACUTE AND REPEATED SCH 23390 ADMINISTRATION ON THE QUIPAZINE-EVOKED HEAD TWITCHES IN THE RAT

Pretreatment			Treatment	Incidence of Head Twitches		
Compound	Days	Days of Withdrawal	Before the Test	Mean	±SEM	$p<$
NaCl	18	1	NaCl	20.25	2.3	
NaCl	18	1	Quipazine	63.25	5.4	0.001*
SCH 23390	1	1	Quipazine	58.50	5.1	ns†
SCH 23390	18	1	NaCl	45.37	4.7	0.001*
SCH 23390	18	1	Quipazine	89.20	8.5	0.05†
SCH 23390	18	14	Quipazine	32.25	3.8	0.01†‡

*Significance vs. group No. 1; †Significance vs. group No. 2, ‡Significance vs. group No. 3, t-test, N=8 per group.

ACKNOWLEDGEMENTS

Thanks are due to the Miles Laboratories Inc. for the generous gift of quipazine and to the Schering Corporation for their kind supply of SCH 23390.

REFERENCES

1. Bedard, P.; Pycock, C. "Wet dog" shake behavior in the rat a possible quantitative model of central 5-hydroxytryptamine activity. Neuropharmacology 16:663–670; 1977.
2. Bernardi, M.; Palermo-Neto, J. Effects of the apomorphine administration on rearing activity of control and experimental rats withdrawn from long-term haloperidol treatment. Gen. Pharmacol. 15:363–365; 1984.
3. Bischoff, S.; Heinrich, M.; Sonntag, J.; Kraus, J. The D-1 dopamine receptor antagonist SCH23390 also interacts potently with brain serotonin (5-HT_2) receptors. Eur. J. Pharmacol. 129:367–370; 1986.
4. Blackeshear, M. A.; Martin, L. L.; Sanders-Bush, E. Adaptive changes in the 5-HT_2 binding site after chronic administration of agonists and antagonists. Neuropharmacology 25:1267–1271; 1986.
5. Christensen, A. V. Classification of neuroleptics: Implications for tardive dyskinesia. Pol. J. Pharmacol. Pharm. 37:295–309; 1985.
6. Conn, P. J.; Sanders-Bush, E. Central serotonin receptors: effector systems, physiological role and regulation. Psychopharmacology (Berlin) 92:267–277; 1987.
7. Corne, S. J.; Pickering, R. W.; Warner, B. A method for assessing the effects of drugs on the central actions of 5-hydroxytryptamine. Br. J. Pharmacol. Chemother. 20:106–120; 1967.
8. Creese, I.; Chen, A. Selective D1 dopamine receptor increase following chronic treatment with SCH 23390. Eur. J. Pharmacol. 109:127–128; 1985.
9. De Souza, E.; Van Loon, G. Brain serotonin and catecholamine responses to repeated stress in rats. Brain Res. 367:77–86; 1986.
10. Green, A. R.; Youdim, M.; Grahame-Smith, D. D. Quipazine: its effects on rat brain 5-hydroxytryptamine metabolism, monoamine oxidase activity and behavior. Neuropharmacology 15:173–179; 1976.
11. Hicks, P. E.; Schoemaker, H.; Langer, S. Z. 5-HT receptor antagonist properties of SCH 23390 in vascular smooth muscle and brain. Eur. J. Pharmacol. 105:339–342; 1984.
12. Joseph, M. H.; Kennet, G. A. Application of in vivo voltammetry to the study of serotonergic function in rat hippocampus in stress. In: Fillenz, J. M.; MacDonald, M.; Marsden, C., eds. Monitoring neurotransmitter release during behaviour. Chichester: Ellis Harwood, Health Sci. Ser.; 1986:261–264.
13. Lucki, J.; Nobler, M. S.; Frazer, A. Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. J. Pharmacol. Exp. Ther. 229:133–139; 1984.
14. Malick, J.; Doren, F.; Barnett, A. Quipazine-induced head-twitch in mice. Pharmacol. Biochem. Behav. 6:325–329; 1977.
15. Muller, P.; Seeman, P. Dopaminergic supersensitivity after neuroleptics: time-course and specificity. Psychopharmacology (Berlin) 60:1–11; 1978.
16. Palkovits, M.; Brownstein, M.; Kizer, J.; Saavedra, J.; Kopin, I. Effect of stress on serotonin concentration and tryptophan hydroxylase activity of brain nuclei. Neuroendocrinology 22:298–304; 1976.
17. Peroutka, S. J.; Lebovitz, R. M.; Snyder, S. H. Two distinct central serotonin receptors with different physiological functions. Science 212:827–829; 1981.
18. Stauntom, D. A.; Magistretti, P. J.; Koob, G. F.; Shoemaker, W. J.; Bloom, F. E. Dopaminergic supersensitivity induced by denervation and chronic receptor blockade is additive. Nature 299:72–74; 1982.
19. Trendelenburg, U. Supersensitivity and subsensitivity to sympathicomimetic amines. Pharmacol. Rev. 15:225–276; 1963.
20. Vetulani, J.; Bednarczyk, B.; Reichenberg, K.; Rokosz, A. Head twitches induced by LSD and quipazine: similarities and differences. Neuropharmacology 19:155–158; 1980.
21. White, F.; Appel, J.; Kuhn, D. Discriminative stimulus properties of quipazine: Direct serotonergic mediation. Neuropharmacology 18:143–151; 1979.