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Differential Up-Regulation of D-1 and D-2 Dopamine Receptor Function in Mesostriatal Areas but not in Cortical-Limbic Brain Regions of Rats Chronically Treated With (−)Sulpiride and SCH 23390

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ABSTRACT

Memo, M., M. Pizzi, E. Nisoli, C. Missale, M.O. Carruba, and P. Spano: Differential up-regulation of D-1 and D-2 dopamine receptor function in mesostriatal areas but not in cortical-limbic brain regions of rats chronically treated with (−)sulpiride and SCH 23390. Drug Dev. Res. **11**:243–249, 1987.

In the present study, the possible functional modifications of both D-1 and D-2 dopamine (DA) receptor subtypes have been studied following chronic treatment with DA antagonists that selectively act on a single class of DA receptors. Particularly, the functional state of D-1 and D-2 receptors has been evaluated by measuring SKF 82526–stimulated and bromocriptine–inhibited adenylate cyclase activity in different brain regions of rats treated with saline, SCH 23390, or (−)sulpiride for 35 days.

The results indicate that in striatum, nucleus accumbens, and substantia nigra, chronic blockade of D-1 DA receptors by SCH 23390 induces up-regulation of D-1 receptors without changing the functional activity of D-2 receptors. Likewise, chronic blockade of D-2 DA receptors by (−)sulpiride causes an up-regulation of D-2 but not D-1 DA receptors in striatum, nucleus accumbens, and substantia nigra. SCH 23390 or (−)sulpiride did not modify the functional activity of either D-1 or D-2 DA receptors located in frontal cortex and hippocampus. In conclusion, these results indicate that treatment with selective D-1 or D-2 DA receptor blockade for 5 weeks induces a receptor-specific up-regulation

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which involves the DA receptors located in the nigrostriatal system but not those present in the limbic-cortical areas.

Key words: D-1 dopamine receptors, D-2 dopamine receptors, adenylate cyclase

INTRODUCTION

Repeated administration of neuroleptic drugs has been shown to reduce the frequency of psychotic episodes [Davis, 1980]. The use of these agents is limited, however, by the development of both early and tardive movement disorders. The former is a Parkinson-like syndrome which is reversed by reducing the dosage of the drug. The latter is an irreversible *side* effect which is characterized by abnormal involuntary movements, especially of the mouth and face [Baldessarini and Tarsy, 1980].

Numerous studies suggest that the clinical efficacy of neuroleptics is mediated by their blocking action at dopamine (DA) receptors [Creese et al., 1976; Seeman et al., 1976], presumably in cortical and limbic regions. Furthermore, it is generally accepted that the Parkinson-like syndrome results from blockade of the DA receptors in basal ganglia. However, how neuroleptics promote tardive dyskinesia is still under discussion. One possibility is that chronic blockade of DA receptors in the extrapyramidal areas induces an elevation in receptor number [Owen et al., 1978; Seeman et al., 1984] and function [Memo et al., 1983], and the resulting increase in dopaminergic transmission may mediate the onset of the syndrome [Klawans et al., 1981].

According to anatomical, biochemical, and pharmacological data, DA receptors can be classified into D-1 and D-2 subtypes. Both subtypes are present in those brain regions where neuroleptics are presumed to act in causing either the antipsychotic effects or the side effects [Spano et al., 1978; Stoof and Kebabian, 1981; Onali et al., 1985; Plantjé et al., 1985; Martres et al., 1985; Dawson et al., 1986; Memo et al., 1987].

We previously found that chronic treatment with haloperidol induces supersensitivity of both D-1 and D-2 receptor function in rat striatum and nucleus accumbens [Memo et al., 1987]. Since haloperidol interacts in vivo with both subtypes of DA receptors, it was of interest to evaluate the possible functional modifications of either D-1 or D-2 DA receptor subtypes induced by repeated administrations of DA antagonists which selectively act on a single class of DA receptor. This approach is now greatly facilitated by the availability of a novel benzazepine, SCH 23390, which is a selective D-1 receptor antagonist [Hyttel, 1983; Iorio et al., 1983].

In the present study, we have investigated the functional state of D-1 and D-2 DA receptors in the mesostriatal and cortical-limbic brain regions of rats treated with saline, SCH 23390, or (−)sulpiride for 35 days by measuring adenylate cyclase (AC) activity. Indeed, it has been shown that D-1 receptors mediate the stimulation of AC [Spano et al., 1978; Kebabian and Calne, 1979] whereas D-2 receptors are associated with inhibition of the cyclic AMP generating system [Onali et al., 1985].

According to this paradigm, the function of each class of DA receptors has been determined in vitro by measuring the ability of the selective D-1 agonist SKF 82526 [Silbey et al., 1982] and the selective D-2 agonist bromocriptine [Trabucchi et al., 1976; Kebabian and Calne, 1979] to respectively stimulate or inhibit AC activity.

The results obtained indicate that repeated administrations of (−)sulpiride and SCH 23390 differentially up-regulate D-1 and D-2 receptor function in mesostriatal but not in cortical-limbic brain regions.

MATERIALS AND METHODS

Sixty-three male Sprague-Dawley rats (Charles River, Italy) weighing 170–200 g each were used. They were divided into three groups and injected daily with saline, SCH 23390 (30

μg/kg s.c. three times) or (−)sulpiride (10 mg/kg i.p.) for 35 consecutive days. One week after the last injection, animals were killed by decapitation, and cerebral nuclei were dissected out and stored at −20°C.

Adenylate cyclase was measured in homogenates according to Memo et al. [1987]. Cyclic AMP content was determined by radioimmunoassay from NEN-DuPont.

For statistical evaluation, analysis of variance followed by two tailed Student's t-test was used. Statistical analysis was applied to the points corresponding to individual agonist concentrations.

RESULTS

In Figure 1 are shown the dose-response curves for SKF 82526–induced stimulation and bromocriptine-induced inhibition of AC activity in the striatum of rats chronically treated with saline, SCH 23390, or (−)sulpiride. SKF 82526 stimulated AC activity to the same extent and with the same potency in homogenates of striatum obtained from controls and (−)sulpiride-treated rats (panel A). However, SCH 23390 treatment produced a significant enhancement in the ability of SKF 82526 to stimulate striatal AC activity (panel A). These effects appeared to be due to an increase of the Vmax, rather than to a change in the affinity for the enzyme, as shown by the fact that the EC-50 value for SKF 82526 stimulation of AC in SCH 23390-treated rats was similar to that in saline-treated rats.

Data reported in panel B indicate that chronic blockade of D-2 receptors by (−)sulpiride induced an increased responsiveness of AC to bromocriptine. Indeed, bromocriptine decreased AC activity by about 30% in the striatum from either saline- or SCH 23390-treated rats while it inhibited the enzyme activity by about 50% in the same brain areas of rats treated with (−)sulpiride.

The same pattern of results was obtained in two other mesostriatal brain areas—nucleus accumbens and substantia nigra (Figs. 2, 3).

On the contrary, chronic treatment with SCH 23390 or (−)sulpiride affected neither the ability of SKF 82526 to stimulate AC activity nor that of bromocriptine to inhibit the cyclic AMP generating system in both frontal cortex and hippocampus (Figs. 4, 5).

As shown in panels A, SKF 82526 stimulated AC activity to the same extent and with the same potency in frontal cortex and hippocampus independently of the drug treatment. Likewise, data in panels B indicate that bromocriptine inhibited AC activity in both frontal cortex and hippocampus to the same extent and with the same potency in the three experimental groups.

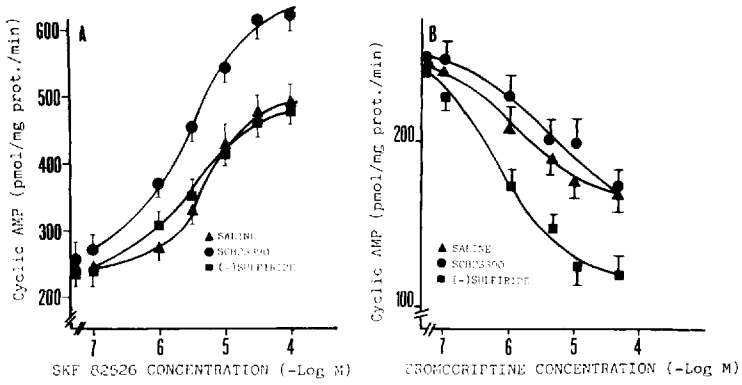

Fig. 1. SKF 82526–stimulated (**A**) and bromocriptine-inhibited (**B**) adenylate cyclase (AC) activity in homogenates of striatum from rats chronically treated with saline (▲), SCH 23390 (●), or (−)sulpiride (■). Each value is the mean ± S.E. of at least three separate experiments.

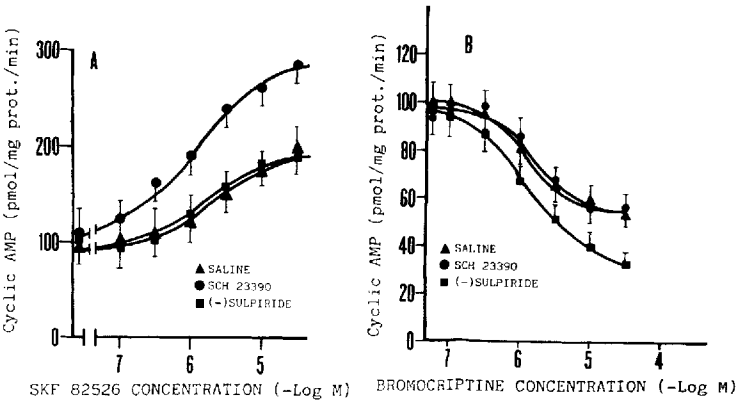

Fig. 2. SKF 82526-stimulated (A) and bromocriptine-inhibited (B) AC activity in homogenates of nucleus accumbens from rats chronically treated with saline (▲), SCH 23390 (●), or (−)sulpiride (■). Each value is the mean ± S.E. of at least three separate experiments.

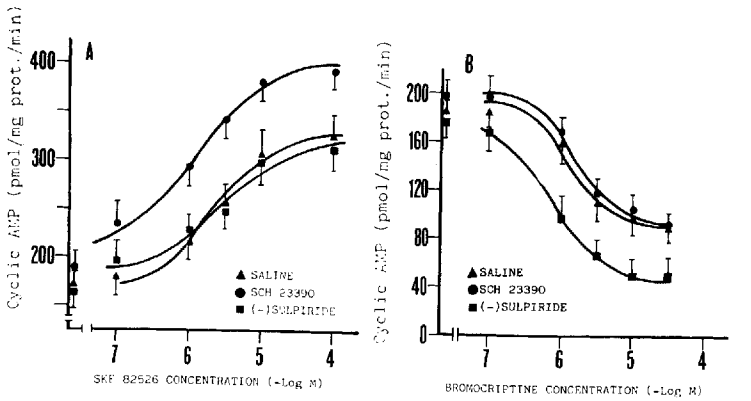

Fig. 3. SKF 82526-stimulated (A) and bromocriptine-inhibited (B) AC activity in homogenates of substantia nigra from rats chronically treated with saline (▲), SCH 23390 (●), or (−)sulpiride (■). Each value is the mean ± S.E. of at least three separate experiments.

DISCUSSION

The present study shows that treatment with the selective D-1 antagonist SCH 23390 for 35 days induced up-regulation of D-1 receptors without changing the functional activity of D-2 receptors whereas treatment with the D-2 antagonist (−)sulpiride for the same period of time caused an up-regulation of D-2 but not D-1 receptors. The development of DA receptor supersensitivity was detectable in the mesostriatal areas but not in the cortical-limbic regions.

Indeed, after repeated administration of SCH 23390, the responsiveness of D-1 receptors, as determined by measuring the ability of SKF 82526 to stimulate AC activity, was greatly increased in the striatum, nucleus accumbens, and substantia nigra, while in the same brain areas the responsiveness of D-2 receptors, determined as bromocriptine-induced inhibition of AC activity, was not modified.

Likewise, repeated administrations of the D-2 receptor antagonist (−)sulpiride caused an increase in the ability of bromocriptine to inhibit AC activity in striatum, nucleus accumbens, and substantia nigra with no changes in the AC-stimulatory effect of SKF 82526. On the contrary, in frontal cortex and hippocampus neither SKF 82526-stimulated nor bromocriptine-inhibited AC activity was modified following repeated administrations of (−)sulpiride or SCH 23390.

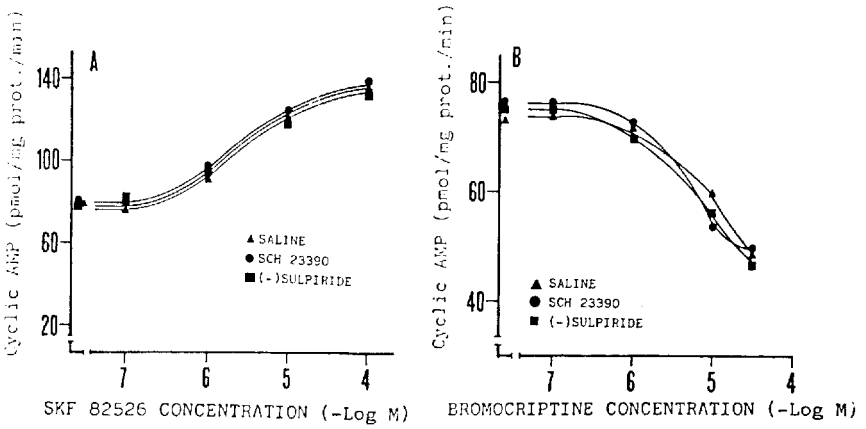

Fig. 4. SKF 82526-stimulated (A) and bromocriptine-inhibited (B) AC activity in homogenates of hippocampus from rats chronically treated with saline (▲), SCH 23390 (●), or (−)sulpiride (■). Each value is the mean of at least three separate experiments with an S.E.M. less than 10%.

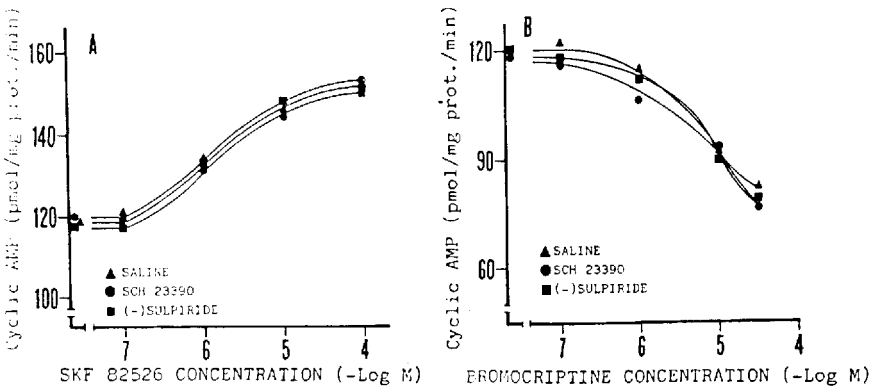

Fig. 5. SKF 82526-stimulated (A) and bromocriptine-inhibited (B) AC activity in homogenates of frontal cortex from rats chronically treated with saline (▲), SCH 23390 (●), or (−)sulpiride (■). Each value is the mean of at least three separate experiments with an S.E.M. less than 10%.

These data support the evidence for the presence of at least two distinct subpopulations of DA receptors that individually react to persistent blockade. Thus, both D-1 and D-2 receptors share ability to plastically adapt to changes in neuronal inputs with other receptors for neurotransmitters in the central nervous system. In line with the present data, it has been previously shown by using the 3H-SCH 23390 binding technique that repeated administrations with SCH 23390 but not with (−)sulpiride increased the number of D-1 receptors in rat striatum and substantia nigra [Porceddu et al., 1985, 1986].

Long-term treatment with either D-1 or D-2 DA receptor blocker does not modify the functional activity of the DA receptors located in frontal cortex and hippocampus. The lack of supersensitivity may be related to the properties of the DAergic pathway innervating the cortical and limbic brain regions. Electrophysiological studies have indeed shown that meso-cortical-limbic DA neurons exhibit faster spontaneous firing rates and higher turnover rates than those DA neurons projecting to the striatum and mesolimbic regions [Brown et al., 1979; Bannon et al., 1981; Chiodo et al., 1984]. Furthermore, the DA receptors present in the nerve terminals of mesocortical DA neurons seem to have a different sensitivity to endogenous DA

than those present in striatal DA neurons [Chiodo et al., 1984; Talmaciu et al., 1986]. These differences may be relevant in determining a differential response to chronic drug treatment.

In conclusion, our results indicate that persistent blockade of D-1 or D-2 receptors induces a selective up-regulation of DA receptors located in the nigrostriatal system but not of those present in the mesolimbic-cortical areas. These experimental data may be of clinical relevance in view of the following observations. During prolonged administration of neuroleptics in man, extrapyramidal side effects show a tendency to diminish [Chase and Tamminga, 1980]. The development of such a tolerance could be very likely related with the up-regulation of the DA receptors located in basal ganglia. On the contrary, the antipsychotic activity of neuroleptics does not decrease during the course of the treatment [Crow et al., 1980]. This observation may be correlated with the data reported in this paper showing that the function of cortical-limbic DA receptors is not modified by the chronic treatment.

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