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D-Cycloserine Decreases Both D_1 and D_2 Dopamine Receptors Number and Their Function in Rat Brain

OTTAVIO GANDOLFI,[1] ROBERTO RIMONDINI AND ROSSELLA DALL'OLIO

Department of Pharmacology, University of Bologna, Via Irnerio 48, I-40126, Bologna, Italy

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GANDOLFI, O., R. RIMONDINI AND R. DALL'OLIO. *D-Cycloserine decreases both D_1 and D_2 dopamine receptors number and their function in rat brain.* PHARMACOL BIOCHEM BEHAV **48**(2) 351-356, 1994.—Twenty-four hours after the implantation of the transstriatal probe D-cycloserine (3 mg/kg IP), a partial agonist of the strychnine-insensitive NMDA-associated glycine recognition site failed to change DA and DOPAC extracellular output in rat striatal dialysates. In extensively washed synaptic plasma membranes prepared both from cortices or striata of rats treated with D-cycloserine [^{3}H]-MK 801 specific binding was increased. In contrast, in striatal membranes the B_{max} values of both [^{3}H]-SCH 23390 and [^{3}H]-spiroperidol bindings to D_1 and D_2 dopamine receptors were decreased. Parallel decreases both of grooming behavior induced by the D_1 agonist SKF 38393 (10 mg/kg IP) and of the hyperactivity elicited by the D_2 agonist LY 171555 (0.3 mg/kg IP) in rat were observed.

D-Cycloserine Dopamine extracellular output [^{3}H]-MK 801 [^{3}H]-SCH 23390
[^{3}H]-spiroperidol binding studies Dopamine-mediated behaviors Rat

PHYSIOLOGICAL variations in the activity of dopaminergic neurons in rat brain have been observed after the administration of drugs that, through different mechanisms, modify the NMDA-sensitive glutamate receptor. Consequently, an increase of dopaminergic tone, which causes the clinical symptoms of schizophrenia, could be strictly related to the deficiency in central glutamatergic transmission (12,20,22). According to this view, it has been suggested that glutamatergic agonists may be useful therapeutic tools in the treatment of schizophrenia, and glutamatergic antagonists could be used in the treatment of Parkinson's disease (6). However, the exact mechanisms underlying the functional interaction between glutamatergic and dopaminergic neurons are at present poorly understood.

Modulatory effects of NMDA-sensitive glutamate receptors on the release of dopamine (DA) have been observed in tissue slices (1,5,13,19,25,29,31,32,34) and in dissociated cell cultures of rat mesencephalon (3,28). However, while in vitro techniques have provided many informations about the effects of glutamatergic drugs on dopaminergic transmission, such data may not correspond with extracellular levels of this transmitters in the intact animal. In vivo microdialysis techniques, did not generate univocal results; intrastriatal infusions with NMDA increased (24,27) or did not influence (18) extracellular levels of DA, while IP injections with PCP increased DA (7) or DOPAC (36) in rat striatum.

In rat anterior striatum, MK-801 transiently decreased extracellular dopamine (39). The potentiation of NMDA-induced release of DA in rat striatum by glycine is debated.

The present work describes biochemical and behavioral investigations that examined the effect of D-cycloserine (DCS), a partial agonist of the strychnine insensitive NMDA-associated glycine site (16), upon dopaminergic transmission in rat striatum. Previous studies from our laboratory have shown that DCS greatly potentiated the neuroleptic activity induced either by D_1 or D_2 dopamine receptor blockers (11); therefore, in this study we examined whether a dose of DCS that per se failed to affect animal spontaneous behavior (15), could modify a) DA outflow in striatal dialysates, b) the kinetic characteristic of D_1 or D_2 dopamine receptors in rat striatal membranes, and c) the dopamine-mediated behaviors induced in rats by specific D_1 (SKF 38393) or D_2 (LY 171555) dopamine receptor agonists.

[1] To whom requests for reprints should be addressed.

METHOD

Animals

Male Sprague-Dawley rats (175–200 g) from Charles River Italia were used in all experiments. They were housed in individual cages (if implanted with transstriatal dialysis probe) or four per cage under standard laboratory conditions with automatic control of light (from 0700–1900 h), temperature (22 ± 2°C) and relative humidity (60%).

Drugs

LY 171555 [Trans-(−)-4a R-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-2H-pyrazolo-(3,4)-quinoline HCl] (Eli Lilly Co., Indianapolis, IN) and D-cycloserine (Aldrich) were dissolved in saline; SKF 38393 (2,3,4,5,-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine) and dizocilpine (MK 801) (RBI, Wayland, MA) were dissolved in distilled water.

In radioligand binding studies [^{3}H]-MK 801, [^{3}H]-SCH 23390, and [^{3}H]-spiroperidol (NEN, Boston, MA), cold SCH 23390 [(R)-(+)-8-chloro-2,3,4,5,-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-maleate] (Schering Corp., Bloomfield, NJ), (+)-butaclamol (Sigma, St. Louis, MO) were employed.

For the analysis of dialysates, 3-hydroxytyramine (DA), and 3,4-dihydroxyphenylacetic acid (DOPAC) (Sigma, St. Louis, MO) were dissolved in perchloric acid (0.1 M).

Transstriatal Dialysis

Extracellular concentrations of DA and DOPAC were studied in groups of rats implanted stereotaxically with a horizontal dialysis probe passing through both dorsal striata (17). In brief, one hole was drilled on each side of the temporal bone at the level of the head of the caudate nucleus according to the stereotaxic atlas (21). A dialysis tube bearing a tungsten wire was fastened in a transverse position to a stereotaxic holder mounted on a stereotaxic apparatus. The dialysis tube (AN.69 Hospal 0.045 mm i.d., active length 6 mm artificial kidney for human) had a the molecular weight cutoff of the membrane 45,000. The probes were implanted during Equitensin anesthesia. The perfusion experiments were carried out 24 h after implantation of the cannula. The striatum was perfused using a microinfusion pump (Carnegie CMA 100) with a Ringer solution at 2 μl/min. Following a 2 h period of equilibration, a minimum of six samples were collected before DCS administration and the collection of samples was continued for 2 h.

The dialysate was collected over 20 min intervals into microcentrifuge tubes containing $HClO_4$ 0.1 M. Upon completion of the microdialysis experiment, each rat was sacrificed and the brain was dissected for the verification of the probe location. DA and DOPAC contained in dialysate were determined by reverse-phase and HPLC-ED coupled system.

The mobile phase, consisting of Na-acetate 0.04 M, SOS 0.6 mM, EDTA 0.004%, MeOH 15%, acetic acid pH 4.1, was delivered (Waters N-509) at 0.8 ml/min and the chromatographic separation was performed on Chrompack 5-C_{18} reverse-phase column (150 × 4.6 mm). The oxidation potential was 0.62 V vs. a Ag/AgCl reference electrode. Recovery of samples exceeded 35% and the detection limit of the assays was about 15 fmol/injection for DA.

High Affinity Radioligand Binding Studies

The binding assays for [^{3}H]-spiroperidol and [^{3}H]-SCH 23390 to D_1 and D_2 dopamine receptors, respectively, were carried out according to (2,9).

Briefly, 30 min following DCS (3 mg/kg IP) or saline administration the animals were killed by cervical dislocation. The brain was rapidly extracted from the skull and striata (or frontal cerebral cortices) were dissected on ice and kept frozen at −70°C until crude synaptic membranes (SPM) were prepared. On the day of the assay, the striata were homogenized with polytron in ice-cold 50 mM Tris-HCl buffer pH 7.4 and the homogenate was resuspended in the same buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$. Aliquots of membrane suspensions were incubated at 37°C for 30 min with different concentrations of [^{3}H]-SCH 23390 (ranging from 0.05 to 5 nM) or [^{3}H]-spiroperidol (from 0.025 to 1.5 nM). The specific binding was determined between the total binding and the binding remaining in the presence of a specific displacer; 1 μM cold SCH 23390 or 1 μM (+)-butaclamol respectively for [^{3}H]-SCH 23390 and [^{3}H]-spiroperidol. In some experiments, striatal membranes were incubated in the presence of ketanserin (200 nM) to exclude the [^{3}H]-spiroperidol binding to striatal 5-HT_2 receptors. In in vitro [^{3}H]-spiroperidol displacement studies, 18 different concentrations of DCS (ranging from 10^{-10} to 10^{-4} M) were added to the incubation mixture containing a saturating concentration of [^{3}H]-spiroperidol (0.5 nM).

The [^{3}H]-MK 801 binding assays were carried out according to (35). On the day of the experiment, cerebral cortices and striata, dissected as previously described, were homogenized in 10 vol ice-cold 0.32 M sucrose. The homogenate was centrifuged at 1,000 × g, the pellet resuspended in 0.32 M sucrose, and centrifuged again at 1,000 × g. The supernatants were pooled, centrifuged at 45,000 × g to yield P_2 pellets. These were resuspended in 20 vol Tris-HCl pH 7.7 at 4°C and centrifuged at 45,000 × g. Pellets were suspended in ice-cold water and centrifuged again. This procedure was repeated three times and the pellets were frozen at −80°C for at least 18 h. On the day of the assay, pellets were thawed, suspended in 5 mM Tris-HCl pH 7.7 at 4°C, and centrifuged at 30,000 × g, then the pellets were washed four times in 100 vol 5 mM Tris-HCl pH 7.7 and incubated at room temperature for 20 min prior to centrifugation at 30,000 × g. The final pellet was resuspended in Tris-HCl to give a protein concentration of 0.8–1 mg/ml. Aliquots of membrane suspensions were incubated for 2 h at 25°C with [^{3}H]-MK 801 (5 nM, striata) or with different concentrations of [^{3}H]-MK 801 (ranging from 0.5 to 25 nM, cortices). In some experiments, extensively washed membranes were incubated in the presence of different concentrations of DCS (ranging from 10^{-8} to 10^{-4} M) and a saturating concentration (5 nM) of [^{3}H]-MK 801. The specific binding was determined between the total binding and the binding left in the presence of 1 μM cold MK 801.

At the end of incubation period, the mixtures for [^{3}H]-MK 801, [^{3}H]-SCH 23390 and [^{3}H]-spiroperidol binding assays were rapidly filtered through Watman GF/C filters and the radioactivity remaining on the filters was counted by liquid scintillation spectrometry using ATOMLIGHT (NEN, Boston, MA).

The kinetic characteristics of the specific bindings were analyzed as described (33): proteins were measured using BSA as standard (23).

LY 171555-Induced Hyperactivity

Rat locomotor activity was evaluated by means of actometric cages consisting of 38 × 30 × 25 cm plastic cages with stainless steel grid floor previously described (10). DC current (65 V, 25 μA) was continuously delivered to the grid floor and

every closure of the circuit by a rat's paw was recorded. The animals, after a 1 h habituation to the cage, received saline or DCS (3 mg/kg IP) followed by the specific D_2 agonist LY 171555 (0.3 mg/kg IP), and their activity counts were taken every 10 min for 2 h.

SKF 38393-Induced Grooming Behavior

This response is considered a specific nonstereotyped behavior mediated by D_1 receptors consisting of "episodes of grooming with the snout being directed rigorously towards the body" (26). The rats were placed into the actometric cages and were allowed to explore for 60 min before receiving DCS (3 mg/kg IP) or saline followed by the selective D_1 agonist SKF 38393 (10 mg/kg IP). Observers unaware of the treatments recorded the total grooming time (min) starting after SKF 38393 administration for 60 min. To characterize the behavioral effects induced by DCS, groups of rats were treated with saline or DCS (3 mg/kg IP) followed 30 min later by IP injections with MK 801 (0.25 mg/kg IP) following 1 h habituation period to the experimental environment. Locomotor activity was recorded for 120 min.

Statistical Analysis

Behavioral results were analyzed by means of ANOVA followed by single comparisons of the means (Dunnet's t-test); radioligand binding data were analyzed by Student's t-test, and extracellular concentrations of DA and DOPAC were analyzed by means of two-way analysis of variance.

RESULTS

Biochemical Studies

Twenty-four hours after the implantation of the transstriatal probe a steady-state extracellular output of DA (203 ± 2.9 fmol/sample) and DOPAC (19.3 ± 0.3 pmol/sample) was found.

In Fig. 1, the average basal values in the last three samples of the stabilized output were considered as 100% and values obtained after saline or DCS treatment were expressed as percentage of control. While saline administration failed to change the basal values of DA and DOPAC, DCS induced a slight but nonsignificant increase in DA (that parallel with a decrease in DOPAC concentrations) in striatal dialyzates.

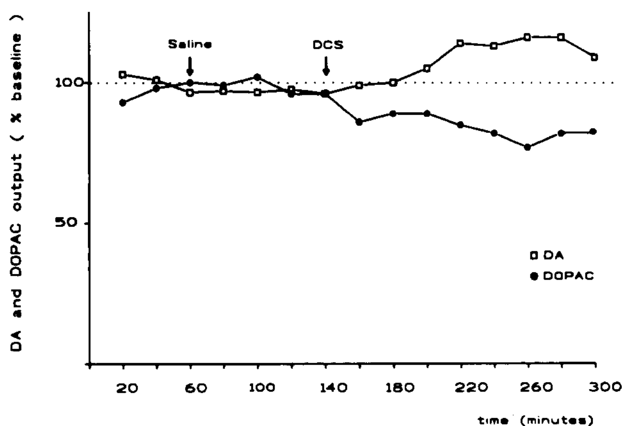

FIG. 1. Effects of DCS (3 mg/kg) on DA and DOPAC output from rat striatum. Each time represents the mean of data from six animals expressed as a percentage of the basal value. Mean (±SEM) baseline values were: DA 203 ± 2.9 fmol/sample $n = 15$; DOPAC 19.3 ± 0.3 pmol/sample $n = 15$.

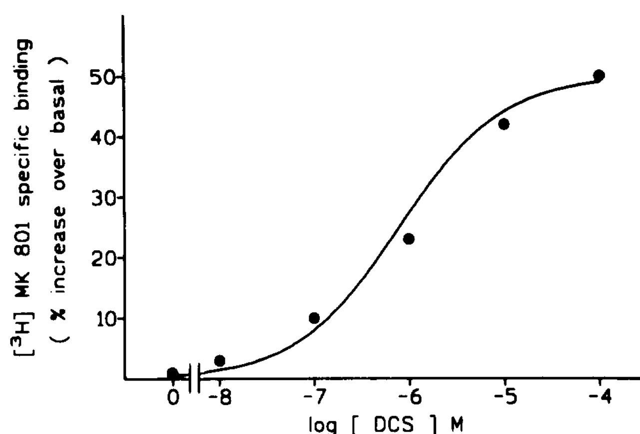

FIG. 2. Stimulation of specific [^{3}H]-MK 801 binding (5 nM) by DCS in extensively washed SPM prepared from rat frontal cortex. The stimulation of binding was measured as an increase over basal specific binding (measured in the absence of DCS; 295 ± 22 fmol/mg) expressed as a percentage.

Figure 2 shows the concentration-dependent increase of [^{3}H]-MK 801 specific binding (5 nM) to extensively washed SPM prepared from rat frontal cortex by the in vitro addition of DCS (10^{-8} – 10^{-4} M). The maximal response was about 50% with the highest DCS concentration. In contrast, the addition of DCS (ranging from 10^{-10} to 10^{-4} M) into the assay tubes failed to modify [^{3}H]-spiroperidol binding (0.5 nM) to SPM prepared from rat striata (not shown). In this experi-

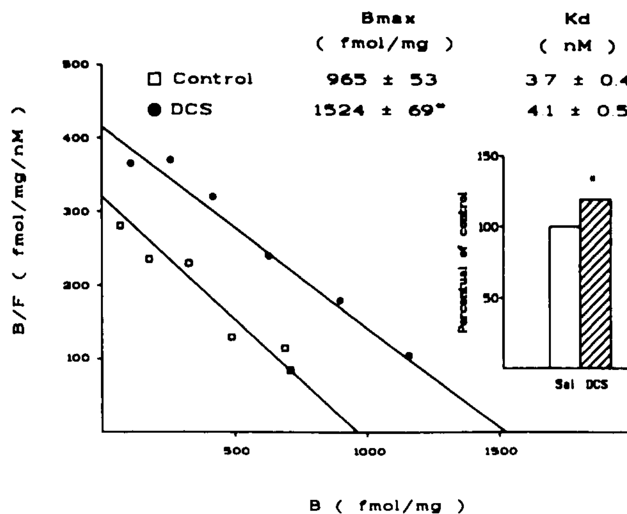

FIG. 3. Scatchard analysis of [^{3}H]-MK 801 specific binding to extensively washed SPM prepared from the frontal cortex of rats treated with DCS (3 mg/kg IP) 30 min before sacrifice. The data result from the transformed data from saturation curves (0.5 – 25 nM) of [^{3}H]-MK 801. Insert: increase of specific [^{3}H]-MK 801 binding (5 nM) to striatal SPM. Specific [^{3}H]-MK 801 binding in saline-treated rats was 123 ± 7 fmol/mg. The nonspecific binding was defined with 10 μM cold MK 801. The results are from a single representative experiment run in triplicate. $^*p < 0.05$ (Student's t-test) significantly different from saline-treated rats.

TABLE 1

KINETIC CHARACTERISTICS OF [^{3}H]-SCH 23390 AND [^{3}H]-SPIROPERIDOL BINDING TO SUSPENSIONS PREPARED FROM CRUDE STRIATAL MEMBRANES OBTAINED FROM RATS TREATED WITH SALINE OR DCS (3 mg/kg IP)

	Specific Bindings			
	[^{3}H]-SCH 23390		[^{3}H]-spiroperidol	
Treatment	B_{max} (fmol/mg)	K_d (nM)	B_{max} (fmol/mg)	K_d (nM)
Saline	721 ± 55	0.93 ± 0.04	368 ± 24	0.21 ± 0.01
DCS (3 mg/kg IP)	487 ± 32*	0.84 ± 0.04	179 ± 11*	0.17 ± 0.01

The specific bindings of [^{3}H]-SCH 23390 (D_1 receptor) (0.5 to 5 nM) and of [^{3}H]-spiroperidol (D_2 receptor) (0.025 to 0.5 nM) were determined in membranes of rats sacrificed 30 min following drug injection.

*$p < 0.05$ (Student's t-test) significantly different from saline-treated rats.

ment, although the percent of the specific binding over total was more that 70%, we failed to find any displacement of [^{3}H]-spiroperidol specific binding to striatal SPM (0.05 mg/ml).

Scatchard analysis of [^{3}H]-MK 801 binding to extensively washed SPM prepared from cortices of rats treated with a single injection with DCS (3 mg/kg IP) is shown in Fig. 3. In cortices of rats treated 30 min before the sacrifice with DCS, we found an increase (by 57%) in the maximum number (B_{max}) of [^{3}H]-MK 801 recognition sites while the apparent affinity constant (K_d) was unaffected. Consistently, the figure shows also (insert) that this treatment increased by around 20% the [^{3}H]-MK 801 specific binding to extensively washed SPM prepared from rat striata. In contrast, Scatchard analysis (Table 1) of the saturation isotherm curves showed that DCS decreased the B_{max} values of both D_1 (32%) and D_2 (52%) receptors located in rat striatal membranes. No changes in K_d values were observed.

Behavioral Studies

Table 2 reports the actometric activity induced by the NMDA antagonist MK 801 (0.25 mg/kg IP) in rats pretreated (5 min) with saline or DCS (3 mg/kg IP). In our experimental conditions, MK801 increased rat motor activity by about five times. DCS fully antagonized MK 801-induced hypermotility at doses that per se failed to affect animal spontaneous behavior (205 ± 20 vs. 198 ± 21). Stereotyped licking, biting, and ataxia were never observed during casual observations of rat's gross behavior.

TABLE 2

A SINGLE INJECTION WITH DCS (30 MIN BEFORE) ANTAGONIZED THE MK 801 INDUCED HYPERMOTILITY IN RATS

	Rat Actometric Motility	
	Pretreatment	
Treatment	Saline	DCS (3 mg/kg IP)
Saline	205 ± 20	198 ± 21
MK 801 (0.25 mg/kg IP)	1101 ± 189*	267 ± 73

Mean values ± SEM of motility counts recorded from 20 to 120 min after drug administration $n = 8$ per group.

*$p < 0.05$ in comparison to saline-pretreated group (Dunnet's t test after ANOVA).

SKF 38393 (10 mg/kg IP) induced grooming behavior and LY 171555 (0.3 mg/kg IP) elicited hyperactivity in rats pretreated with saline or with DCS (3 mg/kg IP) are shown in Table 3. The D_1 agonist SKF 38393 (10 mg/kg IP) doubled the rat's grooming time while the locomotor activity simultaneously recorded from the same animals over the observation period failed to change (not shown). Similarly, the D_2 agonist LY 171555 (0.3 mg/kg IP) induced a statistically significant increase in animal motor activity. The pretreatment with DCS fully antagonized both the increase of grooming behavior elicited by SKF 38393 and the hyperactivity induced by LY 171555 when administered before the D_1 or the D_2 agent respectively.

DISCUSSION

DCS has been shown to be a partial agonist of the strychnine-insensitive NMDA-associated glycine site in vitro (16,38), and the present in vitro data indicate that this drug, over a wide range of doses increased [^{3}H]-MK 801 binding to extensively washed SPM from rat cerebral cortex. This radioligand assay is considered as a biochemical marker of NMDA channel activation in a membrane preparation (4,30); therefore, the enhancements of [^{3}H]-MK 801 specific binding both in cortex and striatum of rats receiving DCS are indicative of the increased frequency of the opening of the NMDA-associated cation channels in both brain areas. Our results are also consistent with other studies that showed a twofold increase of cGMP levels in the cerebellum of mice 30 min after similar doses of DCS (14,40). Therefore, this effect is quite area-unspecific, as although in striatum the number of [^{3}H]-MK 801 recognition sites is lower (40%) than in cortex they are modulated in the same manner but at different extent by DCS. The specificity of this action was further supported by our observation that a low dose of DCS was effective in antagonizing the behavioral response resulting from NMDA blockade (the hypermotility induced in rat by MK 801). Other data showing that ICV injection of D-alanine and D-serine, by acting through the same receptor, inhibit the hyperactivity induced by PCP (37) and block the stereotypy induced by ICV administration of PCP or MK 801 (8), also support this inter-

TABLE 3

A SINGLE INJECTION WITH DCS (30 min) ANTAGONIZED BOTH THE SKF 38393-INDUCED GROOMING BEHAVIOR AND THE LY 171555-INDUCED HYPERMOTILITY IN RATS

Pretreatment	Treatment			
	Grooming Behavior (10 mg/kg IP)		Motility (0.3 mg/kg IP)	
	Saline	SKF 38393	Saline	LY 171555
Saline	8.4 ± 0.9	17.3 ± 0.9*	210 ± 21	1050 ± 113*
DCS 3 mg/kg IP	7.1 ± 1.6	5.1 ± 1.1	200 ± 20	470 ± 75

Mean values ± SEM of LY 171555-induced hypermotility (motility counts in 100 min recording) and SKF 38393-induced grooming time (number of min in 1 h observation).

*$p < 0.05$ significantly different of respective control (Dunnet's t-test after ANOVA).

pretation. The results reported in this paper suggest that the DCS enhancement of [^{3}H]-MK 801 binding ex vivo could represent a meaningful physiological phenomenon regarding dopaminergic function in that the specific bindings of both [^{3}H]-SCH 23390 and [^{3}H]-spiroperidol in striatum were decreased 30 min after DCS administration. In contrast, we failed to find any change in binding paramethers to D_1 or D_2 receptors to cortical membranes (not shown). This difference could be, in part, explained by the low specific binding of [^{3}H]-SCH 23390 in rat cerebral cortex where [^{3}H]-spiroperidol preferentially labels 5-HT_2 receptors.

Because DCS did not directly interact (up to 10^{-4} M) with D_2 receptors in vitro and we did not find any change in apparent affinity constants of [^{3}H]-SCH 23390 and [^{3}H]-spiroperidol bindings ex vivo, we can exclude the possibility that this action is due to a direct effect of the drug still present in the tissue at the time of the D_1 or D_2 radioligand assays. Therefore, we can hypothesize that these rapid changes could be the result of a NMDA receptor-mediated process that could allosterically modulate DA receptors; alternatively a G protein-mediated process can be involved. Parallel decreases both in D_1 or D_2 receptor-mediated function were suggested by behavioral studies showing that a dose of DCS that did not affect rat spontaneous motility (15) decreased both D_1 agonist-induced grooming behavior and the hypermotility elicited by LY 171555 in the rat.

This inference is further strenghtened by our recent observations that similar doses of DCS greatly potentiated the neuroleptic effect induced by D_1 or D_2 dopamine receptor blockers (11).

The possibility that DCS could modify some presynaptic mechanisms in dopaminergic transmission is unlikely because DCS failed to change DA and DOPAC output in dialysates from rat striatum. Further studies of the effect of this drug on the neuroleptic or amphetamine-induced increases in the release of DA with a different (I-shape) cannula, are in progress in our laboratory.

In conclusion, our results suggest the importance of transsynaptic mechanisms in the functional interaction between glutamatergic and dopaminergic neurons in mammalian brain providing that cortico-striatal connections are intact; however, on the base of present data it is difficult to interpret how an increased glutamatergic tone leads to a rapid downregulation of dopaminergic receptors and function. Perhaps indirect effects through G proteins are involved. Improved understanding of such neural mechanisms could represent an attractive target, leading to the discovery of therapeutically useful drugs, particularly in schizophrenia and Parkinson's disease.

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