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Pharmacology Biochemistry and Behavior, Vol. 53, No. 3, pp. 525–530, 1996

0091-3057/96 $15.00 + .00

0091-3057(95)02045-B

Influence of Eticlopride on Cocaine- and DA D_2 Agonist-Induced Behavioral Effects in Rats

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Received 26 January 1995

FERRARI, F. AND D. GIULIANI. *Influence of eticlopride on cocaine- and DA D_2 agonist-induced behavioral effects in rats.* PHARMACOL BIOCHEM BEHAV 53(3) 525–530, 1996.—The influence of the DA D_2 antagonist (−) eticlopride on cocaine- and DA D_2 agonist-induced behavioral effects was investigated by means of two series of experiments, in rats. In the first 10-day series, coadministration of (−) eticlopride (10 and 50 μg/kg, SC) always potently inhibited cocaine (15 mg/kg, IP)-induced hypermotility but did not modify the penile erection (PE)-enhancement produced by the drug at the first injection; it actually counteracted the inhibitory effect of subchronic cocaine on PE. In the second series, (−) eticlopride, at the same doses, antagonized PE elicited by various DA D_2 agonists at nonstereotyping doses; when, along with PE, stereotyped behavior was induced, only the latter was inhibited by (−) eticlopride, which even increased PE.

Cocaine (−) Eticlopride Penile erection Sexual behavior Stereotyped behavior Motility DA D_2 receptors

AMONG the factors contributing to the increase in cocaine addiction in western culture (1,30) is the belief that the drug, unlike others, is a relatively harmless means of increasing physical strength, mental capacity and, last but not least, sexual arousal and potency (21,23,25,40). However, acute and chronic cocaine has been found to result in a number of neurobehavioral abnormalities in animals and humans (8,28,33,36). Certain cocaine-induced effects become progressively more intense after repeated administration (11,28,34), and this phenomenon, which is referred to as "sensitization," has been extensively investigated in animals with regard to locomotor hyperactivity and stereotypy (7,9,34,37,44), because these signs are reputed to reproduce experimentally the psycotomimetic effects observable in humans (35,40). They have been mainly attributed to the ability of the drug to influence central dopaminergic transmission, and both dopamine (DA) D_1 and D_2 receptors seem to be involved (3,6,10,31,42,44,45). The effects of cocaine on sexual behavior are less well documented.

Various authors regard DA as the key neurotransmitter regulating sensations of pleasure (38,40). All drugs that produce gratification, and hence are subject to abuse, activate the dopaminergic system (40). As already mentioned, there is ample documentation on the role of the DA D_2 receptors in modulating the effects of cocaine; also, it is well known that the DA D_2 agonists and antagonists can exert a potent and opposite effect, respectively potentiating and inhibiting sexual behavior (2,18,19,32,43).

Our initial aim was to investigate the modifications produced by cocaine in a certain aspect of animal sexual behavior; namely, the occurrence of penile erections (PE) in the absence of females in oestrus (12,14,16,17). The work is in two parts: in the first series of experiments the pharmacological tools used were cocaine and (−) eticlopride, a selective D_2 antagonist belonging to the class of the benzamides (26); in the second series of experiments we used the D_2 antagonist in question and different DA agonists considered to be selective for the DA D_2 receptors on the basis of in vivo and in vitro studies. These compounds were SND 919 (46), B-HT 958 (24,27), B-HT 920 (4,46), CQ 32-084, and CQP 201-403 (22) and all are known to share, over a certain dose range, the capacity to bring about a marked PE syndrome in the rat (12,13,15,19). Together with PE, we evaluated cocaine-induced hypermotility and stereotyped behavior (SB) induced by some of the DA agonists used.

METHODS

Animals

The subjects were male Long Evans rats (Morini, S. Polo d'Enza, Reggio Emilia, Italy) weighing 230–250 g at the out-

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set. They were housed in groups of six with food and water ad lib and kept on a 12-h light cycle, from 7 a.m. to 7 p.m., for at least 1 week prior to the start of the experiments.

Evaluation of Motor Activity

The rats were intraperitoneally (IP) injected with saline, cocaine, or B-HT 920 and immediately placed in pairs (with the same treatment) in special motility cages (Cibertec, Spain) where their motor activity was automatically recorded for 30 min. The apparatus records any movement made by the animals in the cage and provides the data in the form of a printout, each movement corresponding to a single count. During the 30-min period, two observers, unware of the animal treatments, evaluated their motility, observing each animal every 5 min for 30 s, and rating on a scale of 0–2, where 0 = absent, 1 = normal exploratory behavior for no more than 15 s, and 2 = uninterrupted locomotor movements for at least 25 s. Each motility value was represented by the sum of all the scores attributed to the two animals grouped together in the Cibertec cage, during the 30-min test period.

Experiment 1. Fifty-eight rats were randomly divided into five groups which were treated, once daily, for 10 consecutive days, as follows: (a) saline subcutaneously (SC) + saline IP (S + S group); (b) saline SC + cocaine 15 mg/kg IP (S + C group); (c) (−) eticlopride 50 μg/kg SC + saline IP (E2 + S group); (d) (−) eticlopride 10 μg/kg SC + cocaine 15 mg/kg IP (E1 + C group); and (e) (−) eticlopride 50 μg/kg SC + cocaine 15 mg/kg IP (E2 + C group). Treatments with (−) eticlopride or saline SC were performed 25 min before treatments with cocaine or saline IP. After the 10th day, the treatments were discontinued; 7 days later all rats were injected with cocaine at 15 mg/kg IP.

The behavior of each group was assessed for 30 min on days 1, 5, 10, and 17 of this schedule, the tests being performed between 9 a.m. and 1 p.m. in a soundproof, air-conditioned room (20 ± 2°C), where the animals were monitored by trained observers unaware of the experimental design. Immediately after the pretreatments, the animals were transferred, in groups of four, identical as regards treatment, to glass observation cages (40 × 30 × 34 cm) and allowed to accustom themselves to this environment for 25 min (pretreatment time). Observation started immediately after the treatments, and the following aspects of behavior were considered: PE and motility. PE episodes were counted for each animal exhibiting them; motility was evaluated using the above-described rating scale of 0–2, for, although simple, it gives data in line with those obtained from actimeters (see Table 1) and enabled the observers to record PE and motility simultaneously.

Experiment 2. Another large number of rats was randomly assigned to various groups (the exact number of animals/group is reported in Table 1), which, after pretreatment with saline or (−) eticlopride at 10 and 50 μg/kg SC, were transferred, in groups of three or four, to glass observation cages (40 × 30 × 34 cm) and allowed to accustom themselves to this environment for 25 min. They were then treated with saline or different DA agonists (SND 919, CQP 201-403, CQ 32-084, B-HT 920, and B-HT 958) and immediately observed for 30 min for their PE and SB. PE was evaluated as in Experiment 1; SB was graded as elsewhere (16). In brief, every 5 min, each animal was observed for 30 s and rated on a scale of 0–2, where 0 = absent; 1 = low stereotyped behavior as intermittent or continuous sniffing; 2 = high stereotyped behavior as continuous, compulsive sniffing and/or intermittent or continuous licking, gnawing, and biting. Each SB value was represented by the sum of all the scores attributed to each animal during the 30-min observation period.

TABLE 1

EFFECT OF B-HT 920 AND COCAINE ON MOTOR ACTIVITY IN MALE RATS

Treatment (mg/kg, IP)	Motor Activity (Counts)	Motor Activity (Scores)
Saline	6947 ± 194	5.2 ± 0.7
B-HT 920, 0.1	2317 ± 217*	2.0 ± 0.3†
Cocaine, 15	14373 ± 383*	12.3 ± 0.9†

Saline, B-HT 920 or cocaine were injected immediately before the experiments. For details see methods. Each value is the mean ± SEM of three experiments.

*Significantly different from saline (ANOVA followed by SNK-test).

†Significantly different from saline (Kruskal Wallis followed by Mann-Whitney *U*-test).

Drugs and Treatments

The following drugs were used: SND 919, B-HT 958, and B-HT 920 (Boehringer Ingelheim, Ingelheim am Rhein, Germany); CQ 32-084 and CQP 201-403 (Sandoz, Basel, Switzerland); cocaine hydrochloride (Salars, Como, Italy); (−) eticlopride (RBI, USA). All the drug solutions were freshly prepared, the substances being dissolved in saline at a concentration that allowed the administration of 1 ml/kg. The doses used for the DA agonists, (which are reported in Table 2), for (−) eticlopride (10 and 50 μg/kg) and for cocaine (15 mg/kg) were chosen on the basis of previous experiments. In Experiment 1 only the highest dose of (−) eticlopride plus saline was used, because no statistical difference was obtained in preliminary experiments with the lower dose plus saline.

Statistical Evaluation

Data, which are presented as means ± SEM, were analyzed using ANOVA followed by Student-Newman-Keuls test (SNK test), Kruskal-Wallis (K-W) test, followed by Mann-Whitney *U*-test and Student's *t*-test, where appropriate, with the level of significance set at $p < 0.05$.

RESULTS

Evaluation of Motor Activity

Table 1 reports the motility counts automatically recorded after treatment with saline, cocaine (15 mg/kg) or the DA D_2 autoreceptor agonist B-HT 920 (0.1 mg/kg) and, comparatively, the motility scores attributed to the same groups of animals in the same test period. In both types of evaluation, and in accordance with data already known (4,8,27), rat motor activity was enhanced by cocaine and depressed by B-HT 920.

Experiment 1. As seen in Fig. 1a, on the 1st treatment day the various treatment groups differed markedly as regards PE [$F(4, 53) = 9.3, p = 0.00$]. In particular, while PE were only sporadically observed in S + S and E2 + S groups, their occurrence was significantly more frequent in the S + C, E1 + C, and E2 + C groups. On the 5th and 10th treatment days

the behavioral pattern changed, although differences between the groups remained marked in both cases [$F(4, 53) = 9.1$; $p = 0.00$ and $F(4, 53) = 12.3$; $p = 0.00$, respectively]. From the 5th treatment onwards only the E2 + C group exhibited a higher number of PE with respect to the S + S group, while the PE of the S + C group were quite similar to those of the S + S group, thus appearing significantly lower than those induced by the first cocaine treatment [$F(2, 35) = 9.1$; $p = 0.00$].

Figure 1b reports the motility recorded in the same animals. At the first treatment motility was enhanced in cocaine-injected rats (S + C group) with respect to S + S rats, and inhibited in the E2 + C group with respect to the S + S and S + C groups. On the 5th and 10th days motility was further enhanced in the S + C group with respect to controls, thus significantly differing from the 1st treatment (K-W; H = 15.3, $p = 0.000$), while (−) eticlopride pretreatments antagonized cocaine-induced effects.

When, after 7 days of suspension of treatment, that is on the 17th day, cocaine was injected into all the groups, the effects observed on PE and motility, compared with those obtained in the same groups on the first treatment day, (Fig. 2a and 2b) were as follows: PE (Fig. 2a) were significantly increased in the S + S group, and, albeit to a lesser extent, in the E2 + S group, while they were significantly inhibited in the S + C and E2 + C groups. Motility (Fig. 2b) was increased by cocaine in all the treatment groups and particularly in the E2 + C group, which differed significantly from all the others (K-W; H = 26.6, $p = 0.000$).

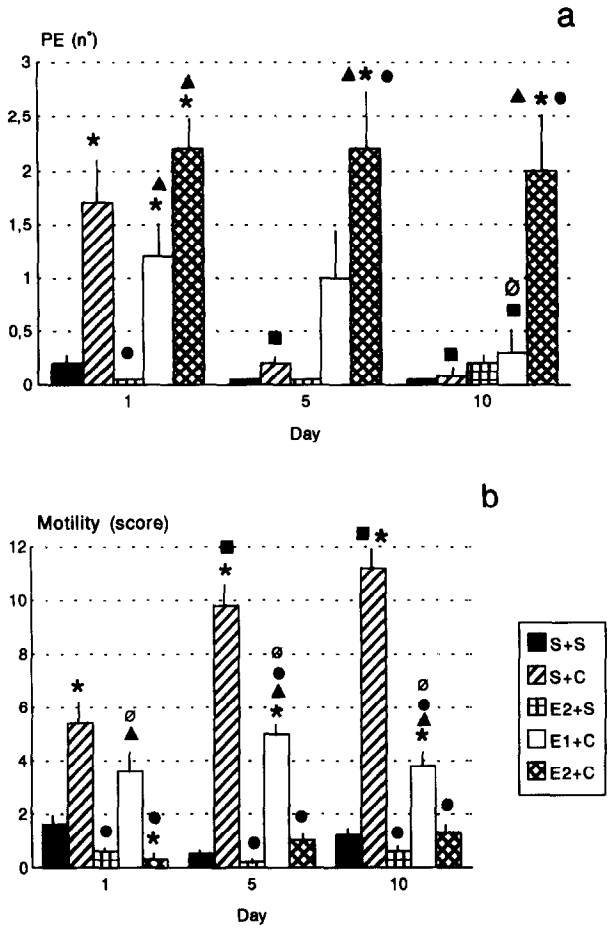

FIG. 1. Effect of (−) eticlopride and cocaine on penile erection (PE) and motility of male rats. Rats were treated once daily for 10 consecutive days; saline (S), (−) eticlopride 10 μg/kg (E1) and 50 μg/kg (E2) were SC injected 25 min before saline (S) or cocaine (C) at 15 mg/kg IP. For details see methods. Each histogram is the mean ± SEM of PE and motility values for rat, during the observation period (30 min). (*) with respect to S + S; (●) with respect to S + C; (▲) with respect to E2 + S; (Ø) with respect to E2 + C; (■) with respect to the same group at the first treatment; all $p < 0.05$, at least (ANOVA followed by SNK-test for PE and Kruskal-Wallis followed by Mann-Whitney U-test for motility).

TABLE 2

EFFECT OF THE SELECTIVE DA D_2 ANTAGONIST (−) ETICLOPRIDE ON DA AGONIST-INDUCED PENILE ERECTION (PE) AND STEREOTYPED BEHAVIOUR (SB) IN MALE RATS

Rats (n°)	Pretreatment (μg/kg, SC)	Treatment (mg/kg, IP)	PE (n°)	SB (score)
6	Sal.	Sal.	0	0.2 ± 0.1
6	Sal.	SND, 0.1	1.5 ± 0.4*	0
6	Eti, 10	SND, 0.1	0.3 ± 0.2**	0
6	Eti, 50	SND, 0.1	0**	0
12	Sal.	SND, 10	1.1 ± 0.2*	6.4 ± 0.5†
6	Eti, 10	SND, 10	0	5.8 ± 1.5
9	Eti, 50	SND, 10	2.6 ± 0.9**	0.4 ± 0.2‡
8	Sal.	CQP, 0.005	1 ± 0*	0
8	Eti, 10	CQP, 0.005	0.7 ± 0.3	0
6	Eti, 50	CQP, 0.005	0**	0
16	Sal.	CQP, 0.5	1.3 ± 0.3*	7.4 ± 0.7†
8	Eti, 10	CQP, 0.5	2.7 ± 0.3**	4.5 ± 0.6‡
7	Eti, 50	CQP, 0.5	2.4 ± 0.5**	1.7 ± 0.6‡
7	Sal.	CQ, 0.5	1.5 ± 0.3*	0
8	Eti, 10	CQ, 0.5	0.5 ± 0.1**	0
6	Eti, 50	CQ, 0.5	0.3 ± 0.2**	0
6	Sal.	B-920, 0.1	3.3 ± 0.2*	0
8	Eti, 10	B-920, 0.1	0.5 ± 0.2**	0
6	Eti,50	B-920, 0.1	0**	0
8	Sal.	B-958, 10	2.5 ± 0.4*	0.2 ± 0.1
8	Eti, 10	B-958, 10	0.5 ± 0.2**	0
6	Eti, 50	B-958, 10	0**	0

(−) Eticlopride (Eti) was injected 25 min before the DA agonists (SND 919 = SND; CQP 201 − 403 = CQP; CQ 32 − 084 = CQ; B-HT 920 = B-920; B-HT 958 = B-958). Assessement of PE and SB started immediately after the last treatment. Each value is the mean ± SEM of PE and SB for the rats in each treatment group during the observation period (30 min).

*Significantly different from Saline + Saline (Sal. + Sal.); **significantly different from respective controls: ANOVA followed by SNK-test.

†Significantly different from Saline + Saline (Sal. + Sal.); ‡significantly different from respective controls: Kruskal-Wallis followed by Mann-Whitney U-test.

Experiment 2

Table 2 reports the results obtained on PE and SB when rats were injected with various DA D_2 agonists alone or in the

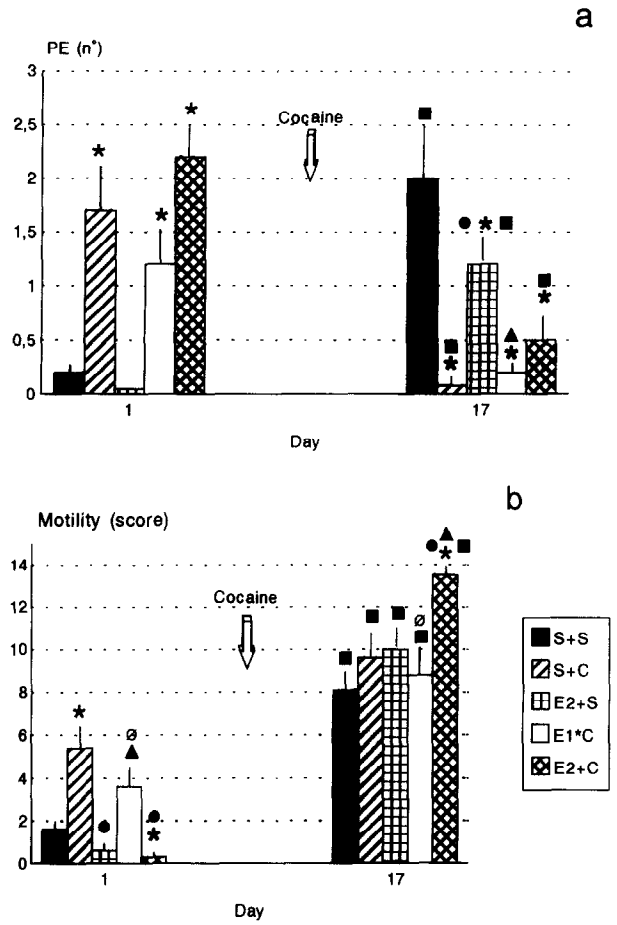

FIG. 2. Effect of (−) eticlopride and cocaine on penile erection (PE) and motility of male rats. Following 10 daily treatments (see Fig. 1 and methods), at 7th day after drug abstinence, each group received cocaine (15 mg/kg, IP) and was immediately observed for 30 min. Each histogram is the mean ± SEM of PE and motility values for rat, during the observation period (30 min). (*) with respect to S + S; (●) with respect to S + C; (▲) with respect to E2 + S; (Ø) with respect to E2 + C; all $p < 0.05$, at least (ANOVA followed by SNK-test for PE and Kruskal-Wallis followed by Mann-Whitney U-test for motility); (■) with respect to the same group at the first treatment, $p < 0.05$, at least (Student's t-test for PE and Mann-Whitney U-test for motility).

presence of the DA D_2 antagonist, (−) eticlopride. All the DA agonists potently elicited PE with respect to controls [ANOVA, $F(7, 63) = 9.8$; $p = 0.000$]. The phenomenon induced by SND 919 and CQP 201-403 at low doses (0.1 and 0.005 mg/kg, respectively) incapable of inducing SB, was significantly counteracted by (−) eticlopride at 10 and 50 μg/kg. When the two DA agonists were administered at a high dose (10 and 0.5 mg/kg, respectively), they induced SB, which was dose-dependently antagonized by (−) eticlopride; however, not only did (−) eticlopride fail to antagonize DA agonist induced-PE, it actually increased them. CQ 32-084 (0.5 mg/kg), B- HT 920 (0.1 mg/kg), and B-HT 958 (10 mg/kg), all described as selective for DA D_2 autoreceptors and therefore unable to induce SB (4,14,24,27) at any dose, stimulated a high number of PE that were dose-dependently antagonized by (−) eticlopride at 10 and 50 μg/kg.

DISCUSSION

Most of the effects produced by cocaine in humans, such as euphoria, anorexia, hyperactivity, and psychosis (33) are duplicated in the laboratory animal subjected to specific experimental tests (45). First of all, our work shows that an animal model is also able to confirm the reported sexual stimulant properties of acute cocaine. Although a number of neurotransmission systems have been found to be involved in cocaine activity (8), there is general agreement that the dopaminergic systems, particularly the DA D_2 receptors, play a key role in eliciting the phenomena observed (44,45). Cocaine enhancement of PE in rats is not surprising, because (a) one of the main actions of the drug is the blockade of DA reuptake, leading to an increase in synaptic availability of this catecholamine; and (b) the DA agonists share the ability to induce PE in rat, over a certain dose range. However, the stimulant effect of cocaine on PE was seen to disappear after five daily injections, nor was interruption of the treatment for a week able to restore it. In fact, the results obtained when (after a week of suspension of treatment) cocaine was readministered to the animals confirmed that cocaine-induced behavioral modifications last for a long time after the ingestion of the drug; sensitization for hypermotility remains, as already reported, as does tolerance for PE. Although many people consider cocaine to be one of the best aphrodisiacs, reliable human and experimental evidence in support of this claim is scanty (25). On the contrary, it appears that, whereas cocaine, like other stimulants, often heightens sexual power in the short run, its long-term use may lead to loss of sexual desire and virility, possibly for neurogenic reasons (23,25). Insofar as that is so, there would appear to be points of similarity between laboratory findings for animals and documented human behavior.

What was for us an unexpected finding was the effect on PE when (−) eticlopride was administered before cocaine. The inability of the DA blocker to antagonize PE induced by cocaine at the first injection, coupled with its ability, at the highest dose, to restore an increase in PE, no longer apparent after cocaine alone, on the 5th and 10th treatment days, seemed to us strange for the following reasons: (a) DA agonist-induced PE in rats have been attributed to DA D_2 receptors (5,14,16); and (b) the selective DA D_2 antagonist, (−) eticlopride, at a dose as low as 10 μg/kg, has been reported as significantly inhibiting PE induction exerted by the selective DA D_2 agonist SND 919 (18). This was why we decided to perform a second series of experiments to investigate, in more detail, the effects of (−) eticlopride on PE induced by various DA D_2 agonists. Because it is known that these drugs produce distinct behavioral effects according to the doses and/or to their affinity for different DA receptor subtypes (16), we chose, as pharmacological tools, two classes of DA agonists. B-HT 920, B-HT 958, and CQ 32-084 have been mainly described as selective DA D_2 autoreceptor agonists (4,13,24,27); they elicit PE and decrease rodent motor activity but are unable to induce SB (12,27). SND 919 and CQP 201-403, like most DA-mimetics, seem, at low doses, to act preferentially at presynaptic level and to stimulate PE but not SB, while at higher doses they induce both signs (13,16,17,22). By and large, the results of Experiment 2 indicate that (−) eticlopride potently counteracts PE induction when it is not accompanied by SB; in the case of a contemporaneous DA agonist-induction of PE and SB, only the latter sign is antagonized by (−) eticlopride, yet which, at the highest dose, surprisingly stimulated the occurrence of PE. An analysis of the data on

the influence of (−) eticlopride on cocaine-induced PE and motility shows several analogies between the results of Experiments 1 and 2. In fact, while (−) eticlopride antagonized cocaine hyperactivity and behavioral sensitization to this sign after repeated treatments, a phenomenon widely described and here confirmed (34,39), it did not inhibit the contemporaneous stimulant effect on PE; indeed it antagonized the inibitory effect of cocaine on this same parameter, observed after repeated treatments with the stimulant. One tentative hypothesis is that induction of PE by DA D_2 agonists at stereotyping doses, as well by chronic cocaine, potentially exists but is masked by the occurrence of marked SB and motility, respectively; (−) eticlopride, by blocking these effects, facilitates PE. An alternative hypothesis is that although (−) eticlopride is able to act on all the DA receptors involved in the observed phenomena, it has a greater affinity for those underlying SB and hypermotility (DA D_2 postsynaptic receptors) rather than for those involved in PE (DA D_2 presynaptic- or DA D_3 receptors) (41). However, in view of our as yet limited understanding of the various DA receptor subtypes and of the specific affinity for them of the DA agonists and antagonists, any suggestion as to the mechanisms underlying the observed phenomena is bound to be purely speculative. The appearance of PE when (−) eticlopride was associated with cocaine indirectly demonstrates that the contemporaneous inhibition of motor hyperactivity is not a simple consequence of a general physiological dampening of cocaine effects due to (−) eticlopride-induced sedation. Although the precise mechanisms of interaction between (−) eticlopride and cocaine are difficult to understand and have yet to be clarified, it has been demonstrated, through electrophysiological experiments, that (−) eticlopride potently antagonizes cocaine-induced excitation, without producing a consistent reversal of cocaine-induced neuronal depression (30). Interestingly, recent studies in our laboratory showed that (−) eticlopride actively antagonizes several DA-mediated behaviors, suggesting its potential therapeutic efficacy in the treatment of human psychoses (20).

In conclusion, if similarities between the cocaine-induced effects in animals and those in humans suggest a certain validity of experimental models in predicting the activity of the drugs in humans, it is reasonable to speculate that chronic cocaine induces not only sensitization for motor activity but also tolerance for sexual stimulation. Moreover, although acute (−) eticlopride at very low doses might antagonize cocaine-induced hyperactivity and, rather than interfering with the sexual stimulant effects, actually restore them once they have waned, continued treatment with the DA D_2 antagonist would not be able to avert the adaptive neurochemical modifications brought about by cocaine abuse.

AKNOWLEDGEMENTS

This work was supported in part by grants from Ministero della Pubblica Istruzione (60%) and by Consiglio Nazionale delle Ricerche (CNR); SND 919, B-HT 920, B-HT 958, and CQ 32-084, CQP 201-403 were kindly donated by Boehringer Ingehleim and Sandoz, respectively.

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