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The Role of the Nitric Oxide (NO) Pathway in the Discriminative Stimuli of Amphetamine and Cocaine

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FILIP, M. AND E. PRZEGALIŃSKI. *The role of the nitric oxide (NO) pathway in the discriminative stimuli of amphetamine and cocaine.* PHARMACOL BIOCHEM BEHAV **59**(3) 703–708, 1998.—To examine the role of the nitric oxide (NO) pathway in the stimulus effects induced by some psychostimulants, separate groups of rats were trained to discriminate between amphetamine (AMPH; 0.5 mg/kg) and saline, or cocaine (COC; 5 mg/kg) and saline using a standard two-lever operant procedure. Substitution studies showed that AMPH and COC generalized for the training drugs in a dose-dependent manner, their ED_{50} values being 0.1 mg/kg and 1.2 mg/kg, respectively. The dose–response function of both those psychostimulants did not change in the course of the experiment. Moreover, AMPH and COC induced crosssubstitution effects towards each other. Successive combination tests demonstrated that injection of a fixed dose of the NO synthase (NOS) inhibitor 7-nitro indazole (7-NI; 25 mg/kg) plus different doses of AMPH or COC resulted in a leftward shift in the dose–response curves of those psychostimulants and a decrease in their ED_{50} values. On the other hand, pretreatment with the NO donor molsidomine (MOL), injected in a fixed dose of 100 mg/kg before AMPH and COC, shifted the dose–response curves of the psychostimulants to the right and increased their ED_{50} values. Our results indicate that NO plays an inhibitory role in the dopamine (DA)-evoked discrimination effects of AMPH and COC in rats. © 1998 Elsevier Science Inc.

Nitric oxide pathway Amphetamine Cocaine Drug Discrimination Rats

IT has recently been recognized that nitric oxide (NO) may play a role of a neuronal messenger in the central nervous system (6,39). It is formed from L-arginine by NO synthase (NOS) which is a Ca^{2+}-calmodulin–dependent enzyme whose activation may result from stimulation of the *N*-methyl-D-aspartate receptor complex (21).

A growing body of evidence indicates NO involvement in various centrally mediated physiological and pharmacological effects. Among others, it has recently been found that NOS inhibitors attenuate the locomotor hyperactivity induced by the psychostimulants amphetamine (AMPH), cocaine (COC), and methamphetamine (1,44,47), as well as the stereotypy induced by methamphetamine (1), both these effects being mediated by activation of the dopamine (DA) system. Moreover, NOS inhibitors have also been reported to reduce the locomotor responses to D_1 or D_2 DA receptor agonists in reserpine-pretreated animals (46), as well as the yawning behavior evoked by a D_3 DA receptor agonist (7). Finally, it has been found that development of sensitization to the locomotor-stimulating effects of COC and methamphetamine is diminished in animals with an inhibited NOS activity (42,44); however, such an effect has not been observed in the case of sensitization to AMPH (47). Some reports have also indicated that NOS inhibitors are able to protect against the toxicity induced by methamphetamine (16,29) and COC (28).

At the same time, neurochemical data show that NO plays some role in DA release, although the reported results remain inconclusive. In fact, both an increase (48,55) and a decrease (5,32) in basal monoamine efflux after pretreatment with NO precursors or donors have been reported.

In search of further arguments for the role of the NO pathway in the psychostimulant-evoked effects, we examined the influence of the NOS inhibitor 7-nitro indazole (7-NI) and the NO donor molsidomine (MOL) on the stimuli induced by AMPH and COC in rats in a drug discrimination model.

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METHOD

Animals

Male Wistar rats ($n = 20$), weighing 250 ± 10 g at the beginning of the experiment, were obtained from a licenced breeder (Górzkowska, Warsaw, Poland). They were individually housed in cages (40 × 27 × 15 cm) on a 12 L:12 D cycle (the light period between 0600 and 1800 h) at a room temperature of 20 ± 1°C. Tap water was freely available in the home cages. The rats maintained approximately 80–85% of their expected free-feeding body weight having been provided with a daily food ration (15–20 g, Bacutil pellets) after each experimental session. Food was freely available from Friday afternoon to Sunday morning.

Apparatus

Four animal test chambers (Coulbourn Instruments, Model E10-10), contained in larger, light- and sound-proof boxes, were lit with the house-light and equipped with an exhaust fan. In each chamber there were two levers, mounted on either side of a dipper that delivered sweetened milk (0.1 ml). A computer was used to program and record all the experimental events.

Procedure

Following initial habituation to the animal chambers, the rats were trained to press levers according to the fixed ratio 10 (FR 10) schedule for reinforcement. Thereafter, separate groups of rats were trained to discriminate between AMPH (0.5 mg/kg) and saline, or COC (5 mg/kg) and saline. Depending on the type of injection (AMPH vs. saline, or COC vs. saline), reinforcement was applied after pressing 10 times only on one of the two levers: the drug (D)- or saline (S)-appropriate. To rule out any position preference, for half of the animals left-lever responses were reinforced after D injections, whereas right-lever responses were reinforced after S injections; those conditions were reversed for the remaining rats. The levers were cleaned between sessions with a 10% ethanol solution to avoid olfactory cues (18). Training was carried out in daily 15-min sessions, from Monday to Friday. Fifteen minutes before the daily sessions, the animals were injected with either D or S according to a 2-week alternate sequence of injections (i.e., SDDSS or DSSDD); half of the rats were trained during the first part of the sequence, the remainder—during the other. Discrimination training was completed when a rat accurately selected the appropriate lever in 10 consecutive sessions (5D and 5S), i.e., the first completed FR 10 must have been achieved with the appropriate lever, with not more than two responses to the inappropriate one. Final phases of the experiment consisted of drug testing, which was performed twice a week (i.e., Wednesdays and Fridays; in substitution experiments), or once a week (i.e., Fridays; in combination experiments). The normal training sequence was used on the remaining days. To be tested on a particular test day, a rat had to meet a criterion (described above) during session(s) preceding the test. Throughout the test sessions, responses to a chosen lever were rewarded according to the FR 10 schedule. Like the training sessions, the test sessions ended after 15 min. Drug doses were given in a mixed sequence to at least six rats. During the test sessions, two pharmacological manipulations were performed. In the substitution tests, rats were tested for lever selection after injections of a dose of the training or a novel drug. In the combination tests, animals were given a fixed dose of 7-NI or MOL, together with different doses of AMPH (0.03–1 mg/kg) or COC (0.3–10 mg/kg). Additionally, various doses of the training drugs were tested twice during a 6-month period of the experiment (i.e., at the beginning of testing and after all the combination trials).

Drugs

The following drugs were used (presession injection times in parantheses): amphetamine sulfate (−15 min; AMPH; Sigma, St. Louis, MO), cocaine hydrochloride (−15 min; COC; Merck, Germany), molsidomine (−20 min; MOL; Polfa, Warsaw, Poland), and 7-nitro indazole (−30 min; 7-NI; RBI, USA). The drugs were dissolved in saline, except for MOL and 7-NI, which were suspensed in a 1% Tween solution. All the drugs were injected IP in a volume of 2 ml/kg of the body weight. Doses of the drugs refer to the weight of the drug forms indicated above.

Data Analysis

Data were scored in a quantal manner, the lever that a rat first pressed 10 times in a test session being labeled as the "selected" lever. The percentage of rats that selected the drug lever for each dose of the test drug was calculated. If after any dose of the tested drug at least 80% of the animals selected the drug-appropriate lever, the stimulus substitution was definied. Then, on the basis of quantal dose–response curves, assessment of the ED_{50} value and 95% confidence limits (95% C.L.), as well as a statistical analysis of data were carried out according to Litchfield and Wilcoxon (33).

Response rates (expressed for individual animals as the total number of their responses on either lever, divided by 15 min) were also calculated as a measure of behavioral disruption of the animals. Those data were analyzed by a one-way analysis of variance. If the overall effect was significant, Student's, *t*-test was used to compare the results after injections of a dose of the tested drugs with those after the preceding saline (substitution experiments) or after the preceding drug training session (combination experiments). The significance was set at $p < 0.05$ in all the cases.

RESULTS

All the rats used in the experiment acquired the ability to discriminate between AMPH and saline or COC and saline in 33 (range 26–42) and 32 (range 28–36) sessions, respectively (data not shown). The stimulus control of both the training drugs and saline injections remained stable throughout the experiment as evidenced by the results of tests in which 0.5 mg/kg of AMPH or 5 mg/kg of COC produced 100 or 90%, respectively, of the drug lever responding, whereas saline induced no substitution effects in either group of the trained animals. Response rates after AMPH or COC were not different from those observed after saline sessions (Tables 1 and 2).

In substitution tests, AMPH and COC produced a dose-dependent increase in drug-appropriate responses (Tables 1 and 2). The calculated ED_{50} values (95% C.L.) were 0.1 (0.07–0.15) mg/kg for AMPH and 1.2 (0.99–1.34) mg/kg for COC. Redetermination of the AMPH and COC effects after all combination experiments showed no significant changes in their dose–response curves and in their ED_{50} values compared with the results obtained in the initial testing experiments (e.g., the ED_{50} values: 0.126 (0.06–0.23) mg/kg for AMPH and 1.45 (0.68–3.08) mg/kg, for COC; results not shown).

A crosssubstitution was observed between the psychostimulants studied. COC evoked a dose-related substitution for

TABLE 1

RESULTS OF SUBSTITUTION STUDIES WITH AMPH AND COC IN RATS TRAINED TO DISCRIMINATE BETWEEN AMPH (0.5 mg/kg) AND SALINE

Treatment	Dose mg/kg	% of DL Selection*	Responses/min (±SEM)†
Saline	—	0	59.5 ± 8.5
AMPH	0.03	12.5	58.1 ± 6.7
	0.06	28.6	67.6 ± 10.1
	0.13	50.0	72.3 ± 7.3
	0.25	75.0	66.0 ± 6.3
	0.5	100.0	61.0 ± 8.0
COC	2.5	40.0	65.5 ± 9.5
	5.0	80.0	54.9 ± 14.3
	10.0	100.0	48.0 ± 11.3

*Percentage of rats selecting the drug-appropriate lever (DL).
†Average number of responses during a session.
The number of animals tested for each dose: n = 7–10.
For further details see the Method section.

AMPH (Table 1), and the dose of COC predicted to elicit 50% of the AMPH-lever responses was 2.97 (1.56–5.64) mg/kg. AMPH dose dependently subsituted for COC (Table 2), the ED_{50} value being 0.28 (0.12–0.64) mg/kg.

In combination tests, pretreatment with a fixed dose of 7-NI (25 mg/kg) potentiated the AMPH effects and shifted its dose–response curve to the left. In contrast, administration of a constant dose of MOL (100 mg/kg) before different doses of AMPH resulted in a rightward shift in the AMPH dose–response curve (Fig. 1). The ED_{50} values calculated for AMPH in the rats pretreated with saline, 7-NI or MOL were 0.103 (0.07–0.15), 0.04 (0.03–0.06) or 0.28 (0.17–0.47) mg/kg, respectively, and were statistically significant ($p < 0.05$). Response rates of the animals were reduced after administration of 7-NI and MOL, although statistically significant results were obtained only after a combination of 7-NI with 0.06 or 0.5 mg/kg of AMPH, $F(1, 10) = 12.346, p < 0.01$, and, $F(1, 10) = 10.249, p < 0.001$, respectively (Fig. 1).

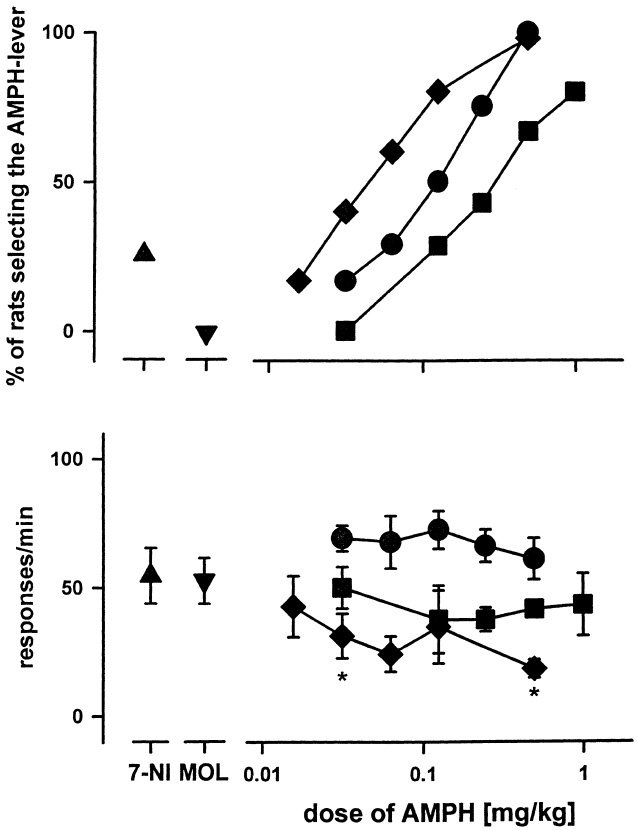

FIG. 1. Results of combination tests with 7-NI or MOL plus AMPH, obtained in rats trained to discriminate between AMPH (0.5 mg/kg) and saline. Symbols denote the performance of rats injected with AMPH (0.03–0.5 mg/kg; circles), or treated with 7-NI (25 mg/kg; diamonds) or MOL (100 mg/kg; squares) plus different doses of AMPH. For comparison, performance after 7-NI (25 mg/kg; triangles) or MOL (100 mg/kg; inverse triangles) given alone is shown. Asterisks denote a significant difference in response rates between a particular dose of the tested drugs and the preceding amphetamine training session (Student's t-test). The number of animals tested for each dose: n = 6–8. For further details see the Method section.

TABLE 2

RESULTS OF SUBSTITUTION STUDIES WITH COC AND AMPH IN RATS TRAINED TO DISCRIMINATE BETWEEN COC (5 mg/kg) AND SALINE

Treatment	Dose mg/kg	% of DL Selection*	Responses/min (±SEM)†
Saline	—	0	70.0 ± 7.6
COC	0.3	14.3	60.4 ± 11.4
	0.6	33.3	52.7 ± 10.2
	1.3	50.0	68.9 ± 5.0
	2.5	62.5	58.0 ± 8.9
	5.0	90.0	80.4 ± 10.0
AMPH	0.25	40.0	68.9 ± 2.8
	0.5	80.0	60.1 ± 10.1
	1.0	83.3	40.2 ± 9.1

*Percentage of rats selecting the drug-appropriate lever (DL).
†Average number of responses during a session.
The number of animals tested for each dose: n = 6–10.
For further details see the Method section.

Administration of 7-NI, 25 mg/kg, in combination with different doses of COC also produced a leftward shift in the COC dose–response curve. On the other hand, the discriminative ability of COC was reduced after MOL (100 mg/kg), the injections of which shifted the dose–response curve for COC to the right (Fig. 2). The ED_{50} values calculated for COC in animals pretreated with saline, 7-NI or MOL were 1.15 (0.99–1.34), 0.59 (0.36–1.01), or 6.19 (3.3–11.8) mg/kg, respectively, and differed significantly ($p < 0.001$). Response rates of the animals were significantly reduced after administration of 7-NI in combination with 1.3 mg/kg, $F(1, 10) = 8.108, p < 0.05$, or 5 mg/kg, $F(1, 10) = 46.196, p < 0.001$, of COC (Fig. 2).

When given alone, 7-NI or MOL produced 30 or 0% of the AMPH- and 25 or 0% of the COC-appropriate responses, respectively. Moreover, neither 7-NI nor MOL administered alone changed the response rates of rats in either of the training group of animals (Figs. 1 and 2).

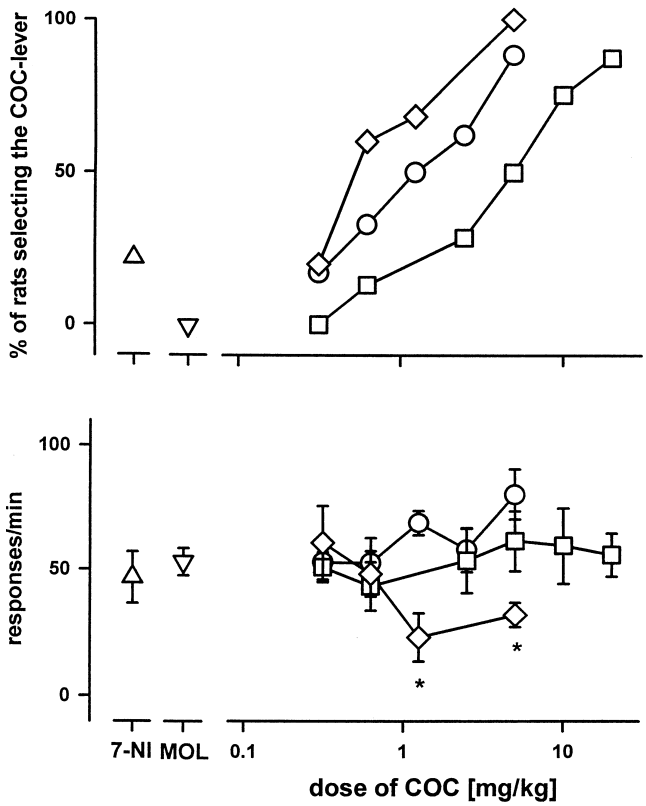

FIG. 2. Results of combination tests with 7-NI or MOL plus COC, obtained in rats trained to discriminate between COC (5 mg/kg) and saline. Symbols denote the performance of rats injected with COC (0.3–5 mg/kg; circles), or treated with 7-NI (25 mg/kg; diamonds) or MOL (100 mg/kg; squares) plus different doses of COC. For comparison, performance after 7-NI (25 mg/kg; triangles) or MOL (100 mg/kg; inverse triangles) given alone is shown. Asterisks denote a significant difference in response rates between a particular dose of the tested drugs and the preceding cocaine training session (Student's *t*-test). The number of animals tested for each dose: n = 6–8. For further details see the Method section.

DISCUSSION

In line with the findings presented by a number of authors, the results of the present article also indicate that AMPH and COC may be used as effective discriminative stimuli in rats. In fact, we observed that separate groups of rats injected with 0.5 mg/kg of AMPH or 5 mg/kg of COC, i.e., with doses similar to those used in other studies (12,13,20)—discriminated between AMPH and saline, or COC and saline.

In the light of the results presented in a considerable body of literature, it is assumed that discriminative effects of the abovementioned psychostimulants are centrally mediated, and that the DA neurotransmitter system plays a primary role in these effects. Conclusive evidence for this suggestion is provided by studies with several direct or indirect DA agonists, DA reuptake inhibitors and releasers that substitute for AMPH and COC, as well as by some other reports on DA antagonists that attenuate the psychostimulant-evoked discrimination (3,4,14,15,19,52). Furthermore, drugs that affect other neuronal systems do not completely mimic (9,14,41,52) or antagonize (2,10,26,38,43), the AMPH or COC cues. The central origin of the AMPH and COC cues was demonstrated in substitution studies after local injections of those drugs to the nucleus accumbens (11,41,53), as well as in combination experiments with locally administered DA antagonists that prevented the effects of systemic or intra-accumbens injections of psychostimulants (11,41).

A great number of reports indicate that AMPH and COC can symmetrically substitute for each other (4,9,14,1,52), this observation suggesting that both these cues are very similar. Our present findings are in agreement with the above results. In fact, we observed substitution effects of COC in rats trained with AMPH, and those of AMPH in animals treated with COC. Interestingly, the ED_{50} values for AMPH and COC were twice as high as the values obtained when either drug was tested in rats trained to discriminate the same drug from saline. These results are contrary to the findings of Huang and Wilson (27), according to which no differences in the ED_{50} values of AMPH and COC in crosssubstitution tests were observed. On the other hand, our data are supported by the results of D'Mello and Stolerman (17). In fact, like ourselves, the latter authors demonstrated decreases in the potencies of action of AMPH and COC. A possible explanation of these results may be based on a supposition that development of tolerance to the discriminative effects of AMPH and COC takes place during the long duration of the experiment. However, such a possibility seems to be hardly probable, because we found that the dose–response curves of either AMPH or COC under conventional training conditions were not shifted to the right over a 6-month period of our experiment.

The main objective of the present study was to examine the role of the NO pathway in the AMPH- and COC-evoked discrimination. Our results seem to indicate that NO plays the role of an inhibitory endogenous substance in discriminative effects of the psychostimulants in rats, because inhibition of NOS enhances the effects of both AMPH and COC, while an increased NO level attenuates them. In fact, we found that pretreatment with 7-NI, a selective short-acting inhibitor of the brain neuronal NOS in vivo (36,40), decreased the ED_{50} values of AMPH and COC and shifted their dose–response curves to the left. Importantly, the dose of 7-NI used in our experiment (25 mg/kg, IP) was very close to that (30 mg/kg, IP) reported to reduce the NOS activity by about 80–85% in several brain structures at 30–120 min after single administration of the inhibitor (36). It cannot be excluded, however, that the 7-NI–induced shifts of the AMPH and COC dose–response curves to the left may be additive effects, because the NOS inhibitor—when given alone—produced 30 and 25% drug-lever responding in the AMPH and COC discriminations, respectively. In contrast to the results obtained with 7-NI, in animals pretreated with MOL, an opposite effect, i.e., an increase in the ED_{50} values of AMPH and COC and a shift of their dose–response curves to the right was observed. In vivo, MOL is metabolized to 3-morpholinosydnonimine (SIN-1), which spontaneously releases NO (31,50). Although both MOL and SIN-1, used as tools to modify the NO pathway in the brain, are commonly injected ICV (23,25,30), an early study of Tanayama et al. (49) clearly demonstrated that MOL administered peripherally (PO) was rapidly and evenly distributed in many tissues, including the brain. In other words, enhancement and particularly attenuation of the AMPH and COC discriminative effects by 7-NI and MOL, respectively, seems to be connected with manipulation of the brain levels of NO.

Our results have been supported by some immunohistochemical and biochemical studies. In fact, the presence of

NOS in the sites of origin of DA cells and in their terminal regions has been demonstrated (51). Moreover, microdialysis data have shown that NO has an inhibitory influence on the DA release in the striatum (24), and that NO donors reduce the methamphetamine-stimulated DA overflow in this structure (5). In line with the above-cited studies, also findings of Silva et al. (45) revealed an increased DA release in vivo following intrastriatal administration of 7-NI, the later effect being antagonized by coperfusion with L-arginine. However, in contrast to the above in vivo studies, the results of in vitro experiments indicate that NO increases the DA release; such an effect was observed after NO donors or precursors in striatal slices (34,35,55).

The above considerations do not permit an unequivocal conclusion about the mechanism responsible for the involvement of NO in the discriminative effects of AMPH and COC. However, on the basis of our experiments, at least three potential mechanisms may be excluded. Because 7-NI is a neuronal NOS inhibitor only, its selectivity rules out a possible pharmacokinetic interaction between this drug and the psychostimulants studied. At the same time, in contrast to other arginine-based NOS inhibitors (8), 7-NI is devoid of a cholinolytic activity (40), which excludes involvement of this mechanism in the effects of AMPH or COC. This seems particularly important, because a muscarinic receptor antagonist has been shown to enhance some behavioral effects of AMPH (37). We also found that attenuation by MOL of the dose-related discriminative effect of COC was not accompanied with a reduction in the response rate, though a certain nonsignificant decrease in the rate-responding was observed when MOL was given in combination with AMPH. Furthermore, 7-NI reduced the rate of responding when it was administered jointly with some (particularly the highest) doses of the training drugs, having simultaneously increased their stimulus effects. Thus, the above observation concerning MOL combined with COC and 7-NI combined with either of these psychostimulants seems to exclude the occurrence of a "perceptual masking" phenomenon (22) in the stimulus effects studied.

Apart from our discrimination study, a great number of behavioral experiments demonstrated the influence of the NO system on different effects of psychostimulants. However, in contrast to our results, the other findings showed that the inhibition of NOS activity in rodents attenuated rather than increased the acute effects of psychostimulants. In fact, N^G-nitro-L-arginine methyl ester was demonstrated to prevent the locomotor hyperactivity evoked by single injection of AMPH (47) or COC (44), as well as the hyperactivity and stereotypy induced by methamphetamine (1). Furthermore, 7-NI and N^G-nitro-L-arginine, another NOS inhibitor, were able to abolish 3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride (SKF 38393; a D_1 DA receptor agonist)- and N-n-propyl-N-phenylethyl-p-(3-hydroxyethyl)ethyl-amine hydrochloride (RU 24213; a D_2 DA receptor agonist)-induced motor activities in monoamine-depleted mice (46).

In other words, on the basis of our results and the literature data presented above, it may be postulated that the role of NO in the psychostimulant-evoked conditional (discrimination effects) and unconditional (locomotor effects and stereotypy) behavior may not be the same, because these effects probably stem from different brain structures or from different parts of a particular structure [see (54)] where NO may show an opposite action.

In conclusion, our results show that 7-NI, a selective NOS inhibitor, enhances, while MOL, an NO donor, attenuates the stimulus effects of AMPH and COC in the drug discrimination model, which may indicate that NO plays an inhibitory role in the above-mentioned effects of the psychostimulants studied.

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