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7-NITROINDAZOLE ENHANCES AMPHETAMINE-EVOKED DOPAMINE RELEASE IN RAT STRIATUM. AN *IN VIVO* MICRODIALYSIS AND VOLTAMMETRIC STUDY

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The intracellular second messenger nitric oxide (NO) is implicated in a variety of physiological functions, including release and uptake of dopamine (DA). In the described study, *in vivo* microdialysis and differential pulse voltammetric techniques were used to determine the involvement of NO in release of DA and its metabolites (dihydroxyphenylalanine, DOPAC; homovanillic acid, HVA) in neostriatum of freely moving rats. While the NO donor molsidomine (30.0 mg/kg; MOLS) and neuronal NO synthase- (nNOS-) inhbitor 7-nitroindazole (10.0 mg/kg; 7-NI) had no effect on the basal *in vivo* microdialysate level of DA, 7-NI specifically enhanced D,L-amphetamine- (1.0 mg/kg i.p.; AMPH) evoked release of DA. Basal or AMPH effects on DOPAC and HVA levels were not influenced by MOLS or 7-NI. Findings indicate that nitrergic systems have an important role in mediating effects of AMPH on dopaminergic systems.

Key words: *molsidomine, 7-nitroindazole, amphetamine, dopamine, DOPAC, HVA, brain microdialysis, in vivo voltammetry, rats.*

INTRODUCTION

Numerous studies have demonstrated that nitric oxide (NO), a potent activator of the guanyl-cyclase-cyclic-GMP enzyme system in the brain and in peripheral tissues, acts as an intracellular messenger of the central nervous system (CNS) (1, 2).

NO is also a neurotransmitter in nitrergic nerves, but is not stored in synaptic vesicles. Also, NO is not inactivated through a reuptake mechanism or via

enzymatic degradation. Rather, in the cell NO is synthesized on demand from L-arginine, by the enzyme nitric-oxide synthase (NOS), then acts locally or diffuses to adjacent cells. The control of NO synthesis is the key to regulating its activity. The neuronal isoform nNOS exists in brain, and nNOS has been localized to midbrain regions in or near the superior colliculus (3, 4). NO has an important role in central regulation of dopaminergic release (5 - 8).

In the mammalian CNS, NO is implicated in a variety of physiological functions, such as memory and learning, regulation of cerebrovascular flow, food and water intake, mediation of nociception, and regulation of release or uptake of several neurotransmitters in brain (9, 10, 11). NO is also involved in the neurotoxicity of Alzheimer's and Huntington's diseases, cerebral ischemia, stroke, and alcohol-induced brain damage (1, 12).

Recently we demonstrated that the NO donors L-arginine and molsidomine (MOLS), and the NO synthase inhibitor L-nitro-L-arginine-methylester (L-NAME), modify dopamine (DA) receptor agonist responses, as manifested by changes in such behaviors as locomotor activity, grooming, stereotyped behavior, oral activity and yawning activity (13 - 16).

The purpose of the present study was to examine the effect of MOLS and the nNOS inhibitor 7-nitroindazole (7-NI) on release of DA and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum of rats, as determined by *in vivo* microdialysis and by *in vivo* pulse voltammetry.

MATERIALS AND METHODS

Animals

Adult 2-3 month old male albino Wistar rats were used in this study. Animals were housed six per cage at 22 ± 1°C, with an alternating light/dark cycle of 12hr/12hr. Rats had free access to standard pelleted food (Murigran, Animal Food Works, Motycz, Poland) and filtered tap water. Animal handling and painless sacrifice (urethane anesthesia overdose and then decapitation by guillotine) was in compliance with the Animal Facility of the Medical University of Silesia. All experiments were approved by the Bioethics Committee for Animals at the Silesian Academy of Medicine; and animal testing was carried out in accordance with NIH regulations, as described in "Principles of laboratory animal care".

In vivo microdialysis

An *in vivo* microdialysis study was performed on awake and freely moving rats (17, 18). Male 3-month-old Wistar rats were first placed in a stereotaxic frame. Under anesthesia [diazepam (Polfa), 10.0 mg/kg, *ip* and ketamine (Parke-Davis), 80.0 mg/kg *ip*], the dermis overlying the skull was shaved and incised, and a small burr hole was drilled, to allow implantation of the dialysis probe into the right striatum, and coordinates with respect to skull bregma were set according to the stereotaxic atlas of Paxinos and Watson (A, 0.7; L, 3.0 and V, 7.0 mm) (19). Two stainless steel screws were mounted to the cranium and the whole assembly was fixed in place with dental cement (Duracryl Plus, Spofa, Praha). On the following day, the ends of the probe were connected with

teflon tubes and perfused continuously at 2.0 µl/min (Microdialysis pump, Harvard Apparatus Model 22, GB) with artificial cerebrospinal fluid: 145 mM NaCl (Merck), 2.7 mM KCl (Fisher), 1.0 mM $MgCl_2 \times 6H_2O$ (Aldrich), 1.2 mM $CaCl_2 \times 2H_2O$ (Aldrich), 2.0 mM Na_2HPO_4 (Fluka), and phosphoric acid (Fluka) adjustment to pH 7.4. Starting 1 hour later, the microdialysis effluent was collected every 20 min and injected directly onto an MD 150/RP-18 column (150 x 3 mm, 3 µm, ESA, USA) of the HPLC system, ESA Model 5200 A with electrochemical detector (Guard Cell, + 500 mV; electrode E1, + 240 mV at 100 nA/V, electrode E2, - 175 mV at 5 nA/V) and Coluchem II data analysis system, ESA, USA. The original mobile phase, MD-TM Mobile Phase (ESA) was used. After taking three baseline samples at 20 min intervals, rats were injected *ip* with MOLS (30.0 mg/g IP) or 7-NI (10.0 mg/kg IP). Twenty minutes later, immediately after sample collected half the animals were injected with saline (0.9% NaCl, 1.0 ml/kg IP) or D,L-amphetamine (AMPH; 1.0 mg/kg IP), and brain microdialysis samples continued being collected and analyzed every 20 min for the next 180 min. Final results of DA, DOPAC and HVA analysis, in picograms (pg) in 20 µl capacity of loop, were expressed as a percent of the mean of the 3 initial samples prior to MOLS or 7-NI treatment. At the end of the study, the position of the probe in the striatum was verified.

Differential pulse voltammetry

Each rat was anesthetized with chloral hydrate (300 mg/kg IP) (POCH, Gliwice, Poland) and mounted onto a stereotaxic instrument, with the upper incision bar set at 2.4 mm under the interaural line. A carbon fiber electrode was implanted into the striatum (nucleus caudatus) at A = 9.0 and L = 2.2 mm, correlated to the interaural line, and V = 4.5 mm relative to the brain surface according to the stereotaxic atlas of Konig and Klippel (20). The electrodes were prepared, electrochemically pretreated, and calibrated in vitro (21). The Ag/AgCl reference electrode and the auxiliary electrode (a stainless steel wire) were placed in contact with the skull by means of a piece of cotton wool soaked in saline. All electrodes were connected to a polarograph (Biopulse, Tacussel, Lyon, France), and a differential pulse voltammeter was used for monitoring DOPAC peaks. Polarographic parameters used in this study were: potential sweep from -200 mV to +200 mV, scan rate of 10 mV/s, and square pulse modulation of the linear sweep at an amplitude of 50 mV, interval of 0.2 sec and pulse duration of 50 msec. Ascorbic acid peak was recorded at -100 mV, and the DOPAC peak recorded at +60 mV. When implanted in the brain, the carbon-fiber electrode was left to stabilize for 30 minutes, and voltamograms were recorded every 2 minutes. After stabilization of the signal for at least 20 minutes, saline (0.9% NaCl 1.0 ml/kg), MOLS (30.0 mg/kg) or 7-NI (10.0 mg/kg), and 20 minutes later AMPH (1.0 mg/kg), were injected IP; and peaks were recorded every 2 minutes for the next 60 minutes. The mean value of the post-injection peaks, divided by the mean value of the pre-injection peak, times 100, was defined as "DOPAC ratio". At the end of each study, the exact position of the probe in the striatum was verified.

Chemicals

Molsidomine, 7-nitroindazole, D,L-amphetamine and HPLC standards (DA, DOPAC, HVA) were purchased from Sigma Chemical Co., St. Louis, MO, USA.

Statistical Analysis

Data from each behavioral and biochemical study were analyzed by one-way ANOVA, and the post-ANOVA test of Neuman-Keuls. Differences between groups were considered to be significant at a p value < 0.05.

RESULTS

Effects of MOLS and 7-NI on in vivo microdialysate DA, DOPAC, HVA levels

The NO-donor MOLS (30.0 mg/kg IP) and neuronal NOS-inhibitor 7-NI (10.0 mg/kg) had no effect on basal *in vivo* microdialysate levels of DA, DOPAC, and HVA; and accordingly, did not influence DA, DOPAC and HVA release in the striatum of freely moving rats (*Figs. 1-6*).

Effects of AMPH on in vivo microdialysate DA, DOPAC, HVA levels

AMPH (1.0 mg/kg IP) evoked DA release in the striatum of control rats, as the *in vivo* microdialysate DA level was increased by as much as 285% over an 80 minute period (*Figs. 1 and 4*). The microdialysate level of DA gradually returned to control values during the subsequent 120 min (*Figs. 1 and 4*). The range for AMPH-induced DA release is a reflection of the variation in basal levels of DA, prior to AMPH administration.

AMPH reduced DOPAC release in the striatum by approximately 45% between 40 and 80 minutes of observation (*Figs. 2 and 5*). AMPH also reduced HVA release in the striatum to a similar extend, with the maximum between 60 to 100 minutes of observation (*Figs. 3 and 6*).

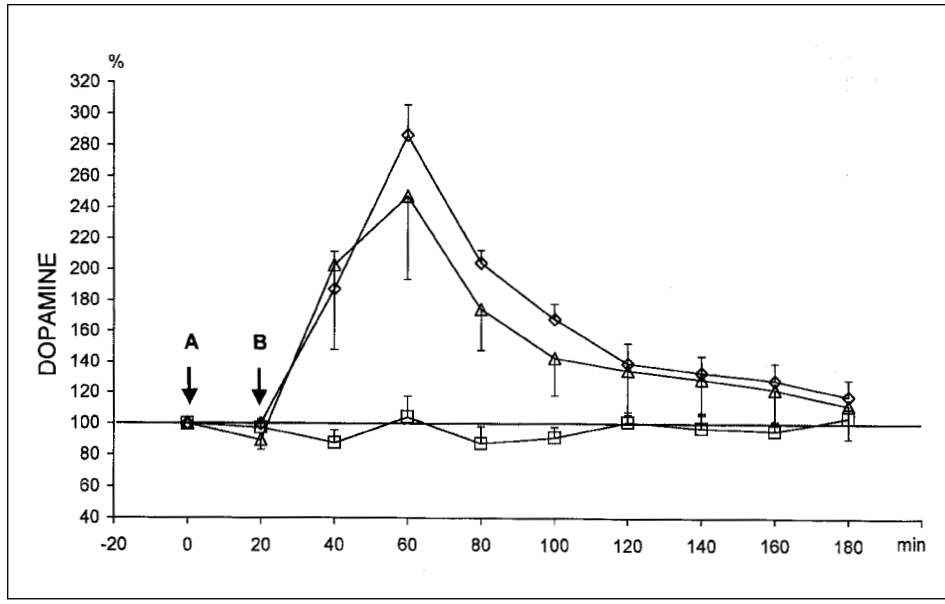

Fig. 1. Amphetamine (1.0 mg/kg IP) - induced release of dopamine into the microdialysate of the striatum in molsidomine (30.0 mg/kg IP) pretreated rats. * — * Molsidomine 30.0 mg/kg IP; o — o Amphetamine 1.0 mg/kg IP; Δ — Δ Molsidomine 30.0 mg/kg IP + Amphetamine 1.0 mg/kg IP. Results for each group are presented in the percent of initial value taken as 100%, and ± SEM of 5-6 male rats. ↓A - Molsidomine injection; ↓B - Saline or Amphetamine injection..

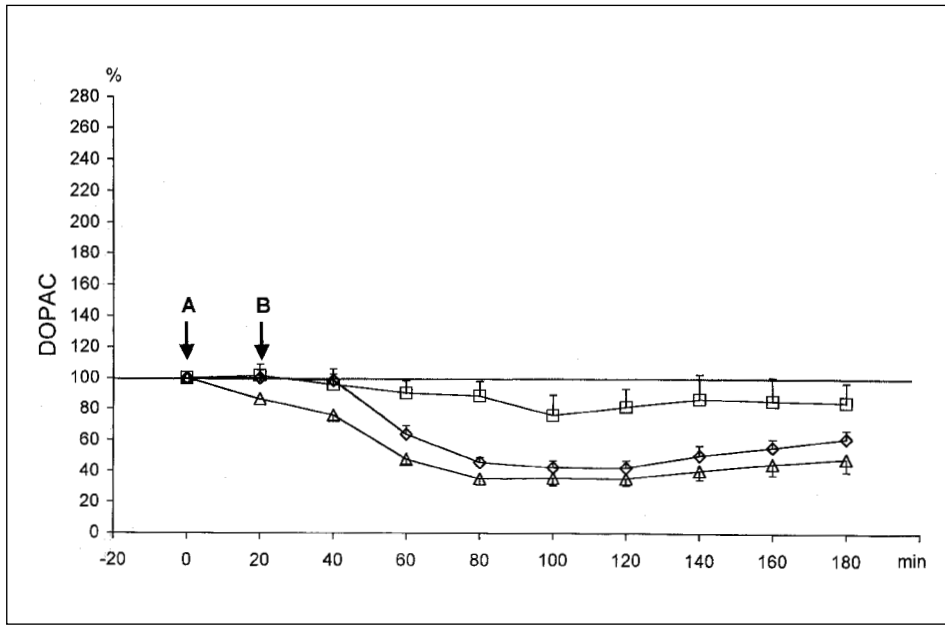

Fig. 2. Amphetamine (1.0 mg/kg IP) - induced release of DOPAC into the microdialisate of the striatum in molsidomine (30.0 mg/kg IP) pretreated rats. Legend as in *Figure 1*.

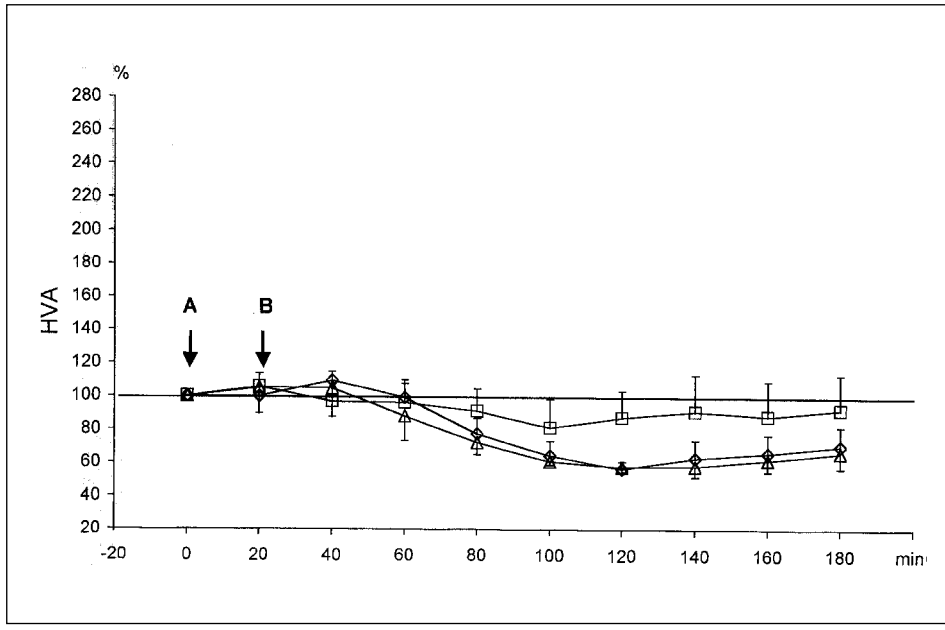

Fig. 3. Amphetamine (1.0 mg/kg IP) - induced release of HVA into the microdialisate of the striatum in molsidomine (30.0 mg/kg IP) pretreated rats. Legend as in *Figure 1*.

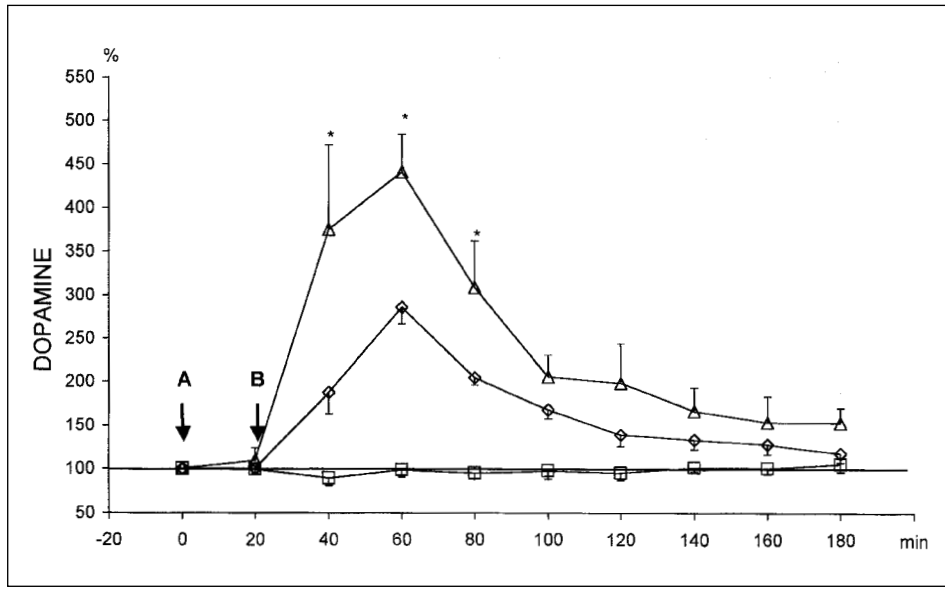

Fig. 4. Amphetamine (1.0 mg/kg IP) - induced release of dopamine into the microdialisate of the striatum in 7-Nitroindazole (10.0 mg/kg IP) pretreated rats. * — * 7-Nitroindazole 10.0 mg/kg IP; o — o Amphetamine 1.0 mg/kg IP; Δ — Δ 7-Nitroindazole 10.0 mg/kg IP + Amphetamine 1.0 mg/kg IP. Results for each group are presented in the percent of initial value taken as 100%, and ± SEM of 5-6 male rats. ↓A - 7-Nitroindazole injection; ↓B - Saline or Amphetamine injection. * $p < 0.05$.

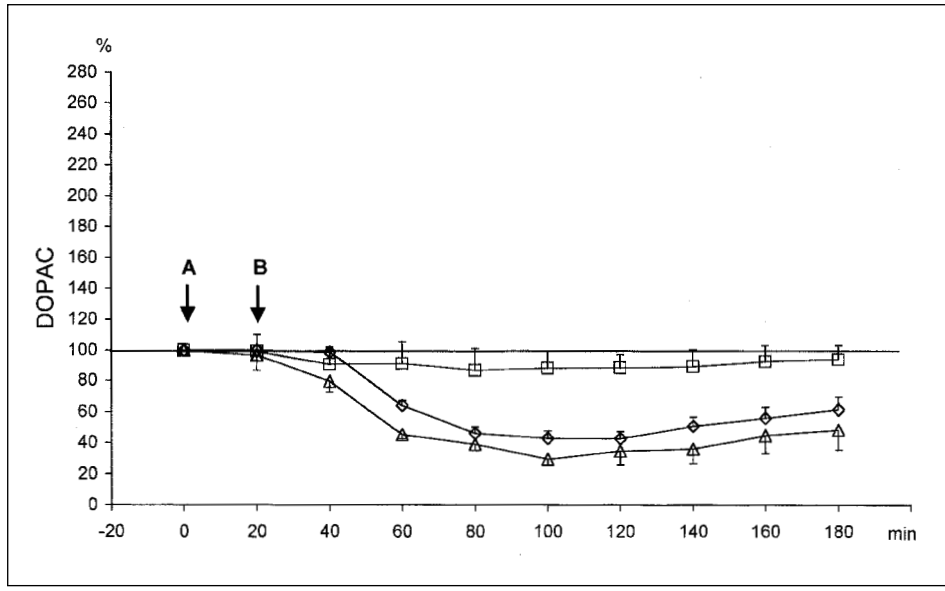

Fig. 5. Amphetamine (1.0 mg/kg IP) - induced release of DOPAC into the microdialisate of the striatum in 7-Nitroindazole (10.0 mg/kg IP) pretreated rats. Legend as in *Figure 4*.

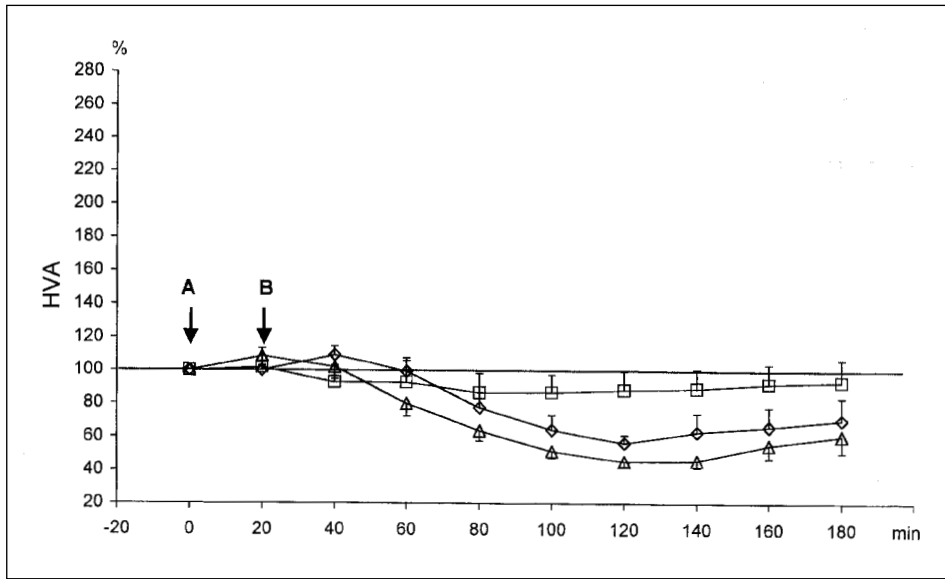

Fig. 6.Amphetamine (1.0 mg/kg IP) - induced release of HVA into the microdialisate of the striatum in 7-Nitroindazole (10.0 mg/kg IP) pretreated rats. Legend as in *Figure 4*.

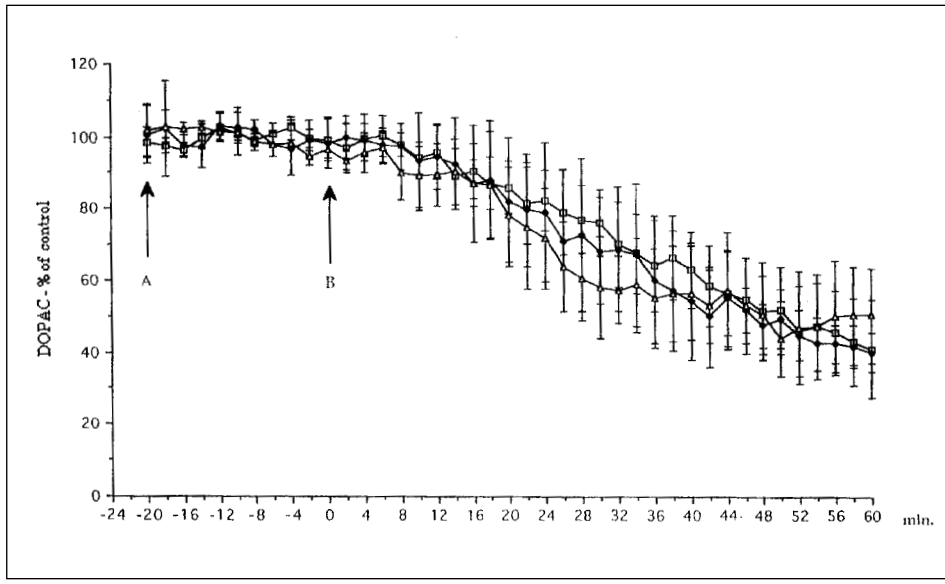

Fig. 7. Effect of amphetamine and 7-Nitroindazole on DOPAC release in the striatum of rats estimated by in vivo differential pulse voltametry (n = 5-6). □ — □ 0.9% NaCl 1.0 ml/kg IP + Amphetamine 1.0 mg/kg IP; ◆ — ◆ 7-Nitroindazole 10.0 mg/kg IP + Amphetamine 1.0 mg/kg IP; Δ — Δ Molsidomine 30.0 mg/kg IP + Amphetamine 1.0 mg/kg IP. Results for each group are presented in the percent of initial value taken as 100%, and ± SEM of 5-6 male rats. ↑A - Saline, 7-Nitroindazole or Molsidomine injection; B - Amphetamine injection.

Effects of MOLS and 7-NI on AMPH-induced alterations in the in vivo microdialysate levels of DA, DOPAC, and HVA

The NO-donor MOLS (30.0 mg/kg IP) had no effect on AMPH-evoked release of DA (*Fig. 1*), DOPAC (*Fig. 2*), or HVA (*Fig. 3*), as indicated from analysis of the striatal *in vivo* microdialysate of so-treated rats. However, the nNOS-inhibitor 7-NI (10.0 mg/kg IP) enhanced the AMPH-evoked release of DA, as indicated by the approximate 50% elevation in the *in vivo* microdialysate level of DA, from as early as the first measurement at 20 min ($F_{1,9} = 19.16$; $p = 0.0018$) through 60 min ($F_{1,9} = 5.67$; $p = 0.04$) (*Fig. 4*). Overall, this represented nearly a doubling of AMPH-evoked DA levels in the microdialysate.

Neither MOLS nor 7-NI modified DOPAC and HVA levels in the striatal microdialysate, alone or after AMPH treatment (*Fig. 2, 3 and 5, 6*).

Effects of MOLS and 7-NI on AMPH-induced alterations in the in vivo voltammetric level of DOPAC in striatum

The level of DOPAC in rat striatum, as assessed by *in vivo* voltammetry, was reduced by approximately 50%, 60 min after administration of AMPH (1.0 mg/kg IP) (*Fig. 7*). Pretreatment with MOLS (30.0 mg/kg) or 7-NI (10.0 mg/kg) did not modify AMPH-induced DOPAC release (*Fig. 7*).

DISCUSSION

The behavioral effects of the psychostimulant AMPH are believed to be mediated primarily by enhancement of dopaminergic neurotransmission, and more specifically on its capacity to increase DA overflow (22). *In vitro* studies have demonstrated that AMPH may facilitate dopaminergic neurotransmission via a number of mechanisms, including direct release of DA from nerve terminals, inhibition of DA uptake, and inhibition of monoamine oxidase - B (MAO-B) activity (22). Both *in vivo* voltametry and brain microdialysis studies demonstrated an increase in DA eflux after AMPH, which attained its maximum response 20-40 minutes after administration, and with concomitant reduction in DOPAC and HVA overflow levels (18, 22 - 25). Our present data are compatible with the above findings. As DA functions as a volume transmitter in the striatum (26), it is this DA overflow that is being assessed by *in vivo* microdialysis. Although microdialysis probes are distant from release sites (i.e., individual nerve endings), the levels of DA in the microdialysate are reflective of DA overflow concentrations - the meaningful index of DA in striatum. Electrodes in *in vivo* voltammetry procedures are located closer to release sites, and provide an opportunity to better assess synaptic and perisynaptic neurotransmitter release and clearance (27). Besides, AMPH appears to release preferentially a newly synthetised pool of DA (8), and the membrane DA carrier may be involved in AMPH-evoked release of DA (22, 28).

Both the *in vivo* microdialysis data and *in vivo* voltammetry data in our study demonstrate that there is no effect of MOLS alone or 7-NI alone on DA release in striatum. MOLS, a donor of NO, is metabolized in mammals to 3-morpholinosyndonimine (SIN-1), which spontaneously releases NO (29, 30). Both MOLS and SIN-1 are used as pharmacological tools, and if administered systemically, are rapidly distributed to virtually all tissues including brain.

7-NI, an NOS inhibitor, selectively blocks nNOS (31, 32, 33) but not eNOS (34). 7-NI exerts some neuroprotective action in global ischemia in rats (35), and reduces post-ischemia-induced NO release (11, 31, 36 - 38). NOS inhibitors have been shown to either potentiate (6, 7) or attenuate (5) basal DA release *in vivo*, depending on conditions of the experiment. It appears that NO initially induced glutamate release, and extracellular glutamate enhances or inhibits DA release in a concentration-dependent manner (8).

Recently, we reported that the NO donor L-arginine and NO-synthase inhibitor L-NAME modify the response of central DA D1 and D3 receptors to the respective agonists SKF-38393 [(+/-)1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol] and quinpirole, as evaluated by specific behavioral parameters: oral movements and yawning (13, 14). In another study we provided further support for the modulation by NO of central DA receptor reactivity in response to specific agonists (SKF-8393 and quinpirole) and antagonists (haloperidol and SCH-23390 [R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine]). This was evaluated by behavioral methods including locomotor activity, grooming, rearing, locomotor coordination and catalepsy (16) or by cardiovascular effects (39). In yet another study we examined effects of NO donors, L-arginine and MOLS, and NOS inhibitor, L-NAME, on AMPH (4.0 and 10.0 mg/kg IP)- and apomorphine (1.0, 2.0 and 3.0 mg/kg IP)-induced stereotyped behavior in male and female Wistar rats (15). We reported that only L-NAME, not L-arginine or MOLS, reduced the intensity of effect and shortened the duration of AMPH-induced stereotyped behavior. However, both NO donors (arginine, MOLS) and L-NAME did not modify apomorphine-induced stereotyped behavior (15). Others have also found that L-NAME reduced locomotor activity, stereotyped behavior, and methamphetamine-induced DA release in striatum (40, 41).

Przegaliński and Filip (42) found that MOLS (30-100 mg/kg) dose-dependently potentiated hyperactivity of rats induced by AMPH, cocaine, SKF-38393, and bromocriptine. AMPH and cocaine represent indirect agonists, while SKF 38393 and bromocriptine represent direct agonists at DA receptors. Conversely, 7-NI in the dose range 10 to 30 mg/kg inhibited locomotor hyperactivity induced by the above indirect and direct acting DA agonists. It must be added that the nonspecific NOS antagonist L-NAME exerted inhibitory effects on hyperlocomotor activity, similar to that of 7-NI (42). Also, others find that 7-NI attenuates SKF 38393-induced locomotor activity in reserpinized mice (43). The sum of these studies demonstrate that NO potentiates DA-evoked effects, and

that the interaction between NO and DA involves both DA D_1 and D_2 receptors. Other have shown that MOLS significantly attenuated the learning deficit in T-maze induced by 7-NI in rats (44).

The role of NO in modulation of DA release is controversial. Although there are exceptions, NO-generating drugs generally evoke DA release (1, 45, 46, 47, 48) while simultaneously decreasing DOPAC and HVA (49). The stimulatory effect of NO donor on DA release was abolished by pretreatment with 7-NI (8). On the other hand, 7-NI exerted no effect on 1-methyl-4-phenylpyridinum (MPP^+)-induced DA efflux assessed by *in vivo* microdialysis or by *in vitro* superfusion of striatal slices (50). Guevera-Guzman et al. (51) demonstrated an inhibitory role of NO on DA release. Others found that 7-NI provided full protection against the depletion of DA and its metabolites after methamphetamine in mice (52, 53). However, Silva et al. (54) have founded that 7-NI increased DA release after its intrastriatal administration, and potentiated NMDA-induced DA efflux (8). The NOS inhibitor L-NAME and NMDA antagonist MK-801 abolished AMPH-induced NO formation and protected against striatal depletion of DA (55).

The complexity of NO in evoking or inhibiting DA release indicates that other neuronal systems have an important intermediary role in the process, with glutamate being one such identified phenotype. For the experimental conditions of the study described in this paper, 7-NI had a potently enhanced AMPH-evoked DA release (*in vivo* microdialysate level) in the striatum of rats. This neurochemical effect would prominent influence behavioral end-points, and could alter interpretations of receptor sensitization processes.

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