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Catalepsy induced by intra-striatal administration of nitric oxide synthase inhibitors in rats

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Abstract

Systemic administration of nitric oxide synthase (NOS) inhibitors induces catalepsy in a dose-dependent manner in male Albino-Swiss mice. The objective of the present work was to investigate if similar effects occur in rats and if these effects are centrally mediated. The results showed that systemic administration of N^G-nitro-L-arginine (L-NOARG, 40–160 mg/kg, i.p.), a non-selective NOS inhibitor, induced catalepsy in rats. Similar effects were found after intracerebroventricular (i.c.v.) injection of L-NOARG (50–200 nmol) or N^G-nitro-L-arginine methylester (L-NAME, 100–200 nmol). The dose–response curve of the former compound, however, had an inverted U shape. The effect of L-NOARG (100 nmol, i.c.v.) was completely prevented by pre-treatment with L-arginine (300 nmol, i.c.v.) but not by D-arginine (300 nmol, i.c.v.). Intra-striatal injection of N^G-monomethyl-L-arginine (L-NMMA, 100 nmol), 7-nitroindazole (7-NIO, 100 nmol), L-NOARG (25–100 nmol) or L-NAME (50–200 nmol) also induced catalepsy. Similar to i.c.v. administration, the latter two compounds produced bell-shaped dose–response curves. The cataleptic effect of intra-striatal administration of L-NAME (100 nmol) was reversed by local treatment with L-arginine (100 nmol). These results suggest that interference with the striatal formation of nitric oxide may induce significant motor effects in rats.

Keywords: Striatum; Motor control; Glutamate; Dopamine

1. Introduction

Nitric oxide (NO) is a short-lived, highly liposoluble molecule, produced from the amino acid L-arginine by a family of enzymes called NO synthases (NOS; Moncada and Higgs, 1993). It acts as a signalling molecule in the central nervous system and has been related to several physiological or pathological conditions (for review, see Bredt, 1999; Esplugues, 2002).

NO seems to play a role in the control of motor behaviour. Mice mutant for the neuronal NOS isoform have altered locomotor abilities (Kriegsfeld et al., 1999) and rats and mice treated with various NOS inhibitors show problems with fine motor control (Star and Star, 1995; Dzoljic et al., 1997; Araki et al., 2001; Uzbay, 2001; Dall'Igna et al., 2001; Del Bel et al., 2002). Systemic administration of N^G-nitro-L-arginine (L-NOARG), an inhibitor of NOS, induces catalepsy in mice (Marras et al., 1995; Navarro et al., 1997; Cavas and Navarro, 2002; Del Bel et al., 2002). This effect is attenuated by previous treatment with L-arginine and suffers tolerance after four days of subchronic (twice a day, 4 days) administration (Marras et al., 1995; Navarro et al., 1997).

The cataleptic effect of NOS inhibitors may involve the striatum. NOS positive neurons are located throughout this structure (Vincent and Kimura, 1992) and NO is proposed to regulate dopamine neurotransmission in the striatum (West et al., 2002). Although there are contradictory results (Silva et al., 1995) most studies suggest that, under physiological conditions, NO increases striatal dopamine by facilitating its release (Hanbauer et al., 1992; Black et al., 1994; Stewart et al., 1996; West and Galloway, 1998; Iravani et al., 1998; West et al., 2002) and/or by decreasing its reuptake (Gue-

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vara-Guzman et al., 1994; Kiss and Vizi, 2001). However, the possible participation of the striatum on the cataleptic effects of NOS inhibition has not yet been directly tested nor has the presence of these effects in other rodent species such as the rat.

The objective of the present study, therefore, was to verify if NOS inhibition can also induce catalepsy in rats and if this effect involves inhibition of NO formation in the central nervous system, particularly in the striatum.

2. Materials and methods

2.1. Animals

Male Albino Wistar rats (200–250 g) were housed in groups of five or eight per cage in a temperature-controlled room (24 ± 1 °C) under standard laboratory conditions. They had free access to food and water and remained on a 12 h light/12 h dark cycle (lights on at 06:30 a.m.). Procedures were conducted in conformity with the Brazilian Society of Neuroscience and Behaviour guidelines for the care and use of laboratory animals, which are in compliance with international laws and politics. All efforts were made to minimize animal suffering.

2.2. Drugs

N^G-nitro-L-arginine (L-NOARG, Sigma), N^G-nitro-L-arginine methylester (L-NAME, Sigma), N^G-monomethyl-L-arginine (L-NMMA, Sigma), L-arginine and D-arginine (Sigma) were dissolved in saline for i.p. or intracerebroventricular (i.c.v.) administration. For intra-striatal injection L-NOARG was dissolved in a 0.01 N HCl solution. 7-Nitroindazole (7-NIO, Tocris) was dissolved in dimethyl sulfoxide (DMSO, MERK). Appropriate vehicle controls were used for each drug. Since there was no difference between the different vehicles they were grouped together.

2.3. Stereotaxic surgery and intracerebral injection

Rats were anesthetized with 2,5% 2,2,2-tribromoethanol (10 mg/kg, i.p.) and fixed in a stereotaxic frame. For i.c.v. injection a stainless steel guide cannula (0.7 mm OD) was implanted aimed at the right lateral ventricle (coordinates: AP = − 1.0 mm from bregma, L = 1.6 mm, D = 3.5 mm). For intracerebral injection cannulae were implanted aimed at the right dorsal striatum (coordinates: AP = − 0.4 mm from bregma, L = 3.0 mm, D = 3.0 mm). The cannulae were attached to the bones with stainless steel screws and acrylic cement. A stiletto inside the guide cannulas prevented obstruction.

Five to seven days after the surgery i.c.v. or intra-striatal injections were performed with a thin dental needle (0.3 mm OD) that was introduced through the guide cannula until its tip was 1.5 mm below the cannula end. A volume of 0.5 μl (intra-striatal) or 1 μl (i.c.v.) was injected in 1 min using a microsyringe (Hamilton, USA). A polyethylene catheter (PE 10) was interposed between the upper end of the dental needle and the microsyringe. The movement of an air bubble inside the polyethylene catheter confirmed drug flow.

2.4. Procedure

Catalepsy was evaluated by placing the animal with both forelegs over a horizontal glass bar (diameter: 0.5 cm), elevated 9.0 cm from floor. The time in seconds (s) during which the mouse maintained this position was recorded up to 180 s (Zarindast et al., 1993). All tests began 1 h after the last injection.

The following experiments were performed: *Experiment 1*; Intraperitoneal (i.p.) injection of saline (1 ml/kg) or L-NOARG (40–160 mg/kg). *Experiment 2*; i.c.v. injection of Vehicle, L-NOARG (50–200 nmol) or L-NAME (100–200 nmol). *Experiment 3*; first i.c.v. injection of vehicle, L-arginine (300 nmol) or D-arginine (300 nmol) followed, 5 min later, by a second injection of vehicle or L-NOARG (100 nmol). *Experiment 4*; Intra-striatal injection of vehicle, L-NAME (50–200 nmol), L-NOARG (25–100 nmol), L-NMMA (100 nmol) or 7-NIO (100 nmol). *Experiment 5*; Bilateral intra-striatal injection of L-arginine (100 nmol) or saline followed, 5 min later, by a second injection of saline or L-NAME (100 nmol). The doses were chosen based on results from previous studies (Marras et al., 1995; Del Bel et al., 1998; Guimarães et al., 1994).

2.5. Statistical analysis

Since variances among groups were not homogenous, the raw data were log transformed (with the addition of a constant value of 1). The transformed data were submitted to a repeated measure multivariate analysis of variance (MANOVA) followed, when significant treatment × time interactions were found, by one-way analysis of variance (ANOVA) at each assessment point. The Duncan test was used for multiple comparisons.

3. Results

3.1. Experiment 1

Results are in Fig. 1. There were significant general effects of treatment ($F_{(3,40)} = 57.47$, $P < 0.001$), time ($F_{(2,39)} = 13.96$, $P < 0.001$) and treatment × time ($F_{(6,76)} = 3.04$, $P = 0.01$). All doses of L-NOARG increased catalepsy time along the whole experiment as compared to saline group (Duncan test, $P < 0.05$). The dose of 160 mg/kg, in

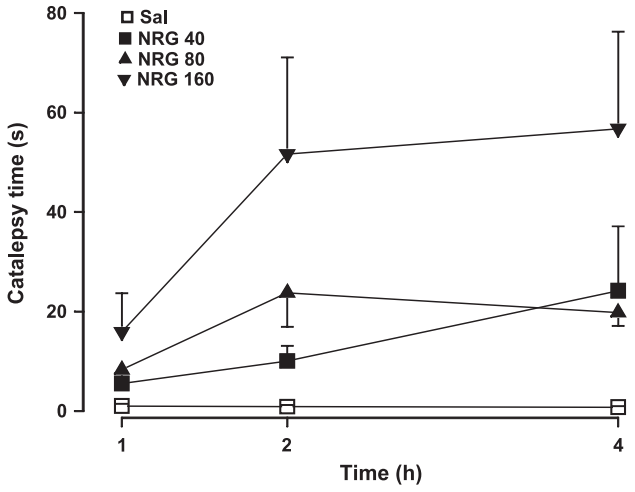

Fig. 1. Catalepsy induced by L-NOARG (NRG, 40–160 mg/kg, $n=6–13$) administered i.p. 1 h before the test. Points represent the means ± S.E.M. All doses of L-NOARG were significantly different from saline ($n=17$, Duncan test, $P<0.05$). * indicates significant difference from L-NOARG 40 and 80 mg/kg (Duncan test, $P<0.05$).

addition, produced greater catalepsy than the 40 and 80 mg/kg doses 2 and 4 h after injection (Duncan, $P<0.05$).

3.2. Experiment 2

All doses of L-NAME and L-NOARG increased catalepsy time (treatment factor, $F_{(5,46)}=52.56$, $P<0.0001$, treatment X time, $F_{(10,88)}=5.8$, $P<0.001$, Fig. 2). The dose–response curve of the latter drug, however, had an inverted U-shape, with the higher dose (200 nmol) producing smaller effects than the 100 nmol dose, 2 h after injection (Duncan, $P<0.05$).

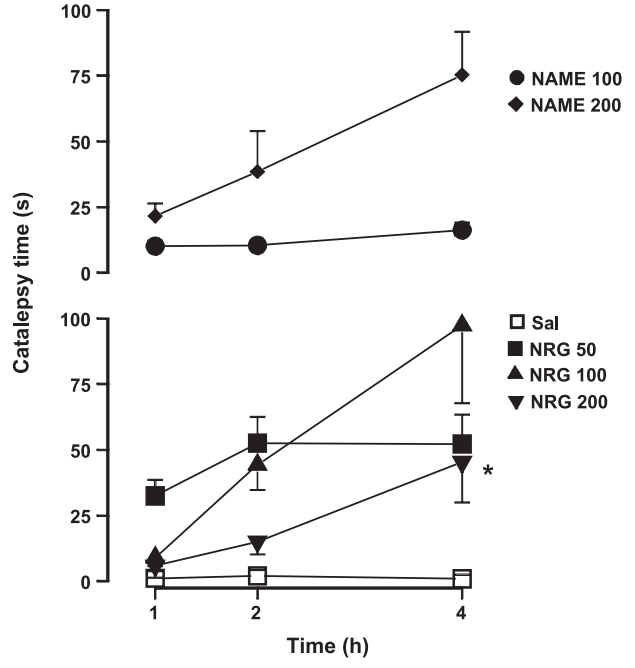

Fig. 2. Catalepsy induced by L-NOARG (50–200 nmol, $n=7$) or L-NAME (100–200 nmol, $n=9–8$) administered i.c.v. 1 h before the test. Points represent the means ± S.E.M. All doses of L-NOARG and L-NAME were significantly different from saline ($n=14$, Duncan test, $P<0.05$). * indicates significant difference from L-NOARG 100 nmol (Duncan test, $P<0.05$).

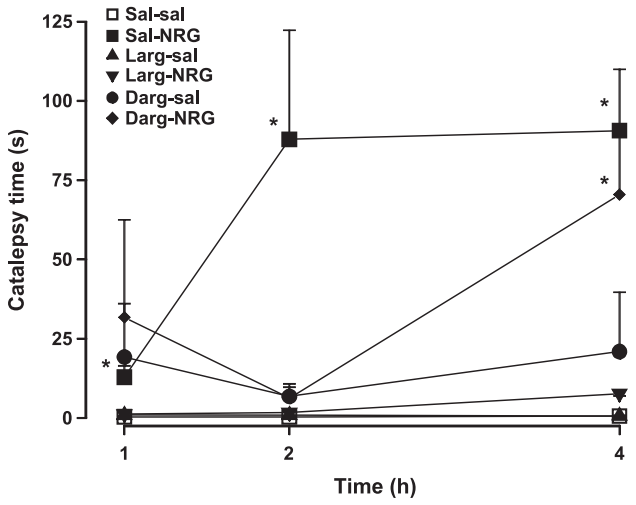

Fig. 3. Catalepsy induced by L-NOARG (NRG, 100 nmol) administered i.c.v. 1 h before the test. Immediately before the drug or saline (Sal, 0.5 μl) administration animals were pretreated with either saline, L-arginine (Larg, 300 nmol) or D-arginine (Darg, 300 nmol). Points represent the means ± S.E.M. of 7–8 rats. * indicates significant difference from saline–saline group (Duncan test, $P<0.05$).

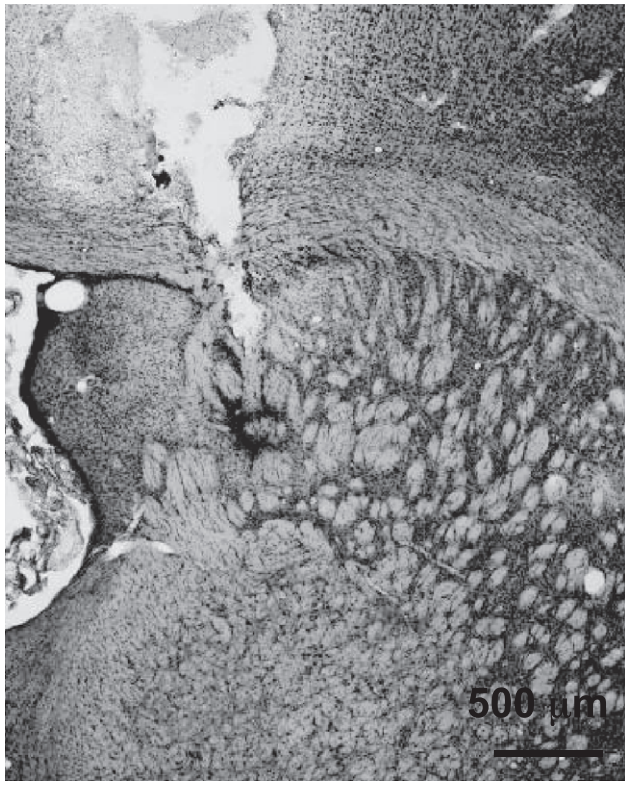

Fig. 4. Photomicrography showing an injection site in the rat dorsal striatum.

3.3. Experiment 3

There were significant effects of treatment ($F_{(5,39)}$= 13.84, $P<0.001$), time ($F_{(2,38)}=4.25$, $P=0.021$) and treatment × time ($F_{(10,74)}=2.23$, $P=0.024$, Fig. 3). L-NOARG increased catalepsy time along the whole session (Duncan, $P<0.05$). This effect was prevented when the animals were pretreated with L-arginine (Duncan, $P>0.05$). However, pre-treatment with D-arginine failed to prevent the cataleptic effect of L-NOARG 4 h after injection (Duncan, $P<0.05$).

3.4. Experiment 4

A representative intra-striatal injection site can be seen in Fig. 4. Significant effects of treatment ($F_{(8,61)}=19.76$, $P<0.001$), time ($F_{(2,60)}=15.18$, $P<0.001$) and treatment × time ($F_{(16,118)}=5.17$, $P<0.001$) were found (Fig. 5). Catalepsy was induced by all treatments, as compared to saline (Duncan, $P<0.05$). The dose–response curve of L-NOARG had an inverted U-shape, with the higher dose (100 nmol) producing smaller effects than the two other doses (Duncan, $P<0.05$). A similar trend was observed with the higher dose of L-NAME (200 nmol), as compared to the 100 nmol dose, 4 h after injection.

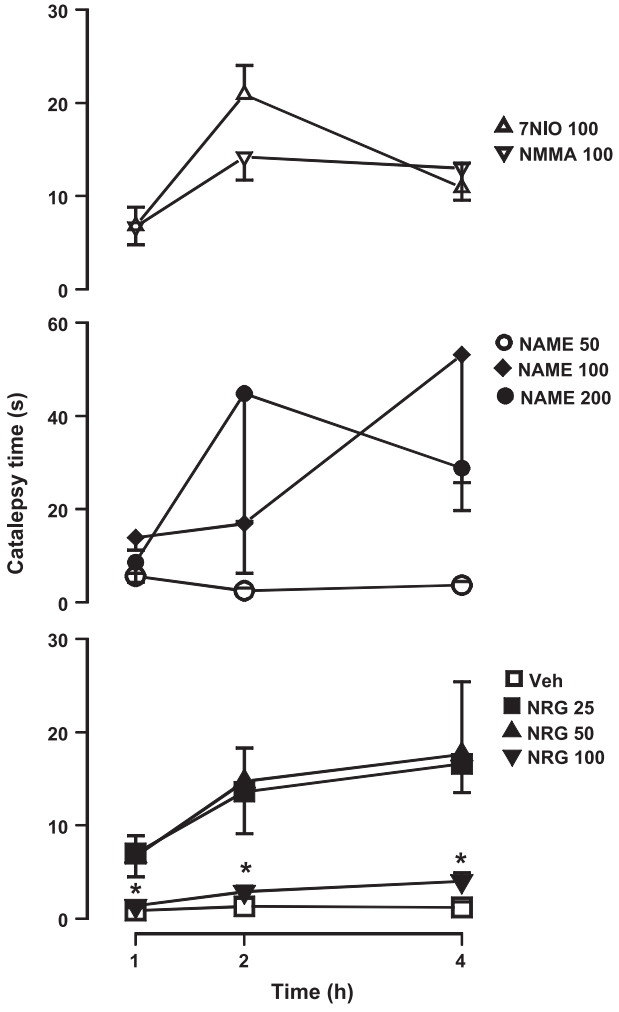

Fig. 5. Catalepsy induced by intra-striatal administration of L-NOARG (NRG 25–100 nmol, $n=6–7$), L-NAME (50–200 nmol, $n=6–7$), 7-nitroindazole (7NIO 100 nmol, $n=8$) or N^G-monomethyl-L-arginine (NMMA, 100 nmol, $n=8$) 1 h before the test. Points represent the means ± S.E.M. All treatments were significantly different from vehicle (Veh, $n=16$, Duncan test, $P<0.05$). * indicates significant difference from L-NOARG 25 and 50 nmol (Duncan test, $P<0.05$).

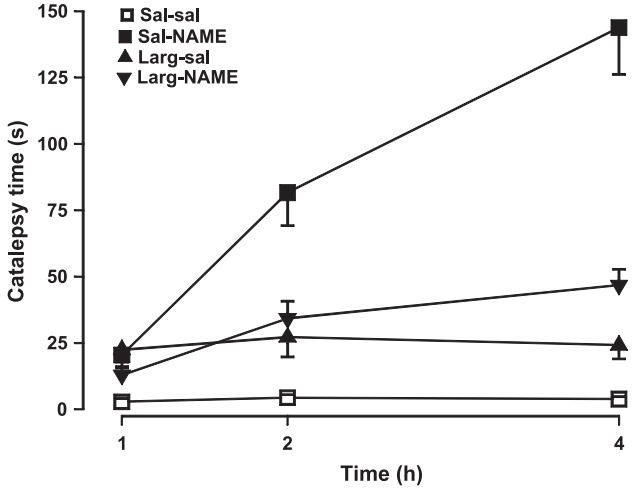

Fig. 6. Catalepsy induced by intra-striatal administration of L-NAME (100 nmol, $n=9$) 1 h before the test. Immediately before the drug or saline (Sal, 0.5 μl) administration animals were pre-treated with either saline or L-arginine (Larg, 100 nmol). Points represent the means ± S.E.M. of 8–9 rats. All treatments were significantly different from saline–saline group. In addition, the saline-L-NAME group was also significantly different from the other groups (Duncan test, $P<0.05$).

3.5. Experiment 5

There were significant effects of treatment ($F_{(8,31)}$= 43.66, $P<0.001$) and time ($F_{(2,62)}=15.18$, $P<0.001$), but no treatment × time interaction ($F_{(6,62)}=2.21$, $P=0.054$, Fig. 6). The cataleptic effect of L-NAME was antagonised by pre-treatment with L-arginine (Duncan, $P<0.05$). Administration of L-arginine, however, produced a small but significant effect (Duncan, $P<0.05$).

4. Discussion

Catalepsy is defined as a failure to correct an externally imposed posture. Drugs that decrease dopaminergic neurotransmission in the striatum, such as neuroleptics, induce catalepsy in rodents and Parkinson symptoms in humans (Koffer et al., 1978; Sanberg et al., 1988). This test is widely used to evaluate motor effects of drugs that act on the extrapyramidal system (Sanberg et al., 1988; Hauber, 1998).

Similar to previous results obtained in mice (Marras et al., 1995; Del Bel and Guimarães, 2000; Del Bel et al., 1998; Nucci-da-Silva et al., 1999), systemic administration of a non-selective NOS inhibitor, L-NOARG, induced

catalepsy in rats. Although peripheral mechanisms could have been involved in such effect, the active doses of L-NOARG used in the present study are equal or greater than those that significantly inhibit cerebral NOS in rats after systemic administration (Salter et al., 1995).

Favouring a centrally mediated action of NOS inhibitors, catalepsy was also observed after i.c.v. administration of L-NOARG and L-NAME. The former drug, infused into the lateral ventricle, did not alter systemic blood pressure and was able to inhibit NOS in regions close to the ventricle for over 4–6 h (Greenberg et al., 1997). The cataleptic effect of i.c.v. injected L-NOARG was prevented by pre-treatment with L-arginine but not by D-arginine, suggesting that inhibition of NO formation was the probable mechanism of the observed effects (Del Bel et al., 1998).

Injection into the striatum of the non-selective NOS inhibitors L-NOARG, L-NAME or L-NMMA, or the selective neuronal NOS inhibitor 7NIO, also induced catalepsy. Similar to L-NOARG i.c.v. administration, the cataleptic effect of L-NAME was antagonised by pre-treatment with L-arginine. This suggests that this structure could be an important site for the motor effects found after systemic injection of these compounds.

NOS inhibitors may decrease motor activity by interfering with striatal dopamine. For example, antagonism of NO formation attenuates dopamine release in the striatum (Bowyer et al., 1995; Sandor et al., 1995; West et al., 2002) and inhibits the increased locomotor activity found after dopamine agonists administration (Abekawa et al., 1994; Star and Star, 1995).

Glutamate mediated neurotransmission interacts with dopaminergic neurotransmission in the striatum and play an important role in controlling motor behaviour (Calabresi et al., 1997; West et al., 2002). For example, antagonism of NMDA receptors attenuates catalepsy induced by dopamine receptor antagonists such as haloperidol (Moore et al., 1993; Pappa et al., 1993; Yoshida et al., 1994). NOS neurons in the striatum receive glutamate inputs and this enzyme is closely associated with NMDA receptors thought the postsynaptic protein PSD95 (Esplugues, 2002). Those neurons are proposed to act as detectors of glutamatergic activity, signalling glutamate-mediated activity to the environment. NO can inhibit monoamine reuptake, thus increasing the half-live of dopamine in the extracellular space (Kiss and Vizi, 2001). Electrophysiological study also showed that systemic administration of a neuronal NOS inhibitor increases the firing rate of a subpopulation of striatal cells, possibly output neurons (Sardo et al., 2002).

NO has complex interactions with NMDA mediated neurotransmission. It can mediate NMDA-induced increase in cGMP and facilitate glutamate release but can antagonize NMDA receptors (Garthwaite, 1991; Lipton et al., 1993; Hoyt et al., 1992; Manzoni and Bockaert, 1993). It can also facilitate dopamine release via NMDA-receptor dependent and independent mechanisms (West et al., 2002). However, although NO-mediated increase in striatal dopamine efflux is blocked by glutamate antagonists, these latter compounds failed to decrease basal dopamine efflux. This suggests that, although basal dopamine release in the striatum is not under the influence of endogenous glutamate, this neurotransmitter is important for NO-mediated facilitation of dopamine release (Calabresi et al., 1997; West et al., 2002).

Although these evidence suggest that an influence of NO on dopamine and NMDA-mediated neurotransmission may be related to our results, it is not possible to rule out NO-mediated effects on other striatal neurotransmitter systems such as the cholinergic, serotonergic and gabaergic (West et al., 2002).

The dose–response curves of NOS inhibitors after i.c.v. or intra-striatal injection had an inverted U-shape. Similar findings have been reported in other experimental models after systemic (Cappndijk et al., 1995; Leza et al., 1996; Masood et al., 2003) or intra-cerebral (Guimarães et al., 1994) administration of these drugs. The reason for these bell-shaped curves is unknown.

The effects of NO may vary depending on several factors such as the functional state of the target neurons and the instant composition of the extracellular fluid. Small changes in NO local concentration may be a key factor in determining its biological effect (Contestabile, 2000). For example, excessive production of NO may negatively modulate NMDA function (Contestabile, 2000) and a reduction in glutamate release induced by elevation of cGMP levels or administration of a NO donor has been described in rat nerve terminals (Sisitaga et al., 1997). There are suggestions that, at high concentrations, NOS inhibitors may be converted to L-arginine (Hecker et al., 1990) or interfere with endothelial NOS (Esplugues, 2002). Another possibility would be a dual effect of NO on dopamine or glutamate-mediated neurotransmission in the striatum. An inhibitory, rather than facilitatory, role of NO on striatal dopamine release has been suggested by some studies (Silva et al., 1995, 2003). In our study, L-arginine, although reversing the cataleptic effect of intra-striatal L-NAME, produced a small but significant cataleptic effect when administered alone. This result agrees with a recent study showing cataleptic effect of sodium nitroprusside, a NO donor (Dall'Igna et al., 2001). In addition, biphasic effects of L-arginine on striatal dopamine efflux have also been reported (Silva et al., 1997).

Despite these contradictory results, our findings confirm in rats results previously obtained in mice, showing that acute treatment with NOS inhibitors induces catalepsy. They also suggest that this effect involves inhibition of NO formation in the striatum.

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