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Serotonin modulation of catalepsy induced by N^G-nitro-L-arginine in mice

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Abstract

N^G-Nitro-L-arginine (L-NOARG), an inhibitor of nitric oxide synthase, induces catalepsy in mice. The objective of the present work was to investigate if serotonergic drugs are able to modulate this effect. Results showed that the cataleptogenic effect of L-NOARG (40 mg/kg) in male albino–Swiss mice was enhanced by pre-treatment with (+)-*N*-*tert*-butyl-3-(4-[2-methoxyphenyl]piperazin-1-yl)-2-phenylpropanamide ((+)-WAY-100135, 5 or 10 mg/kg), a 5-HT_{1A}-selective receptor antagonist, and by ketanserin (5 or 10 mg/kg), a 5-HT_{2A} receptor and α_1-adrenoceptor antagonist. Prazosin (3 or 5 mg/kg), an α_1-adrenoceptor antagonist, and endo-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl (BRL-46470A, 0.05 or 0.5 mg/kg), a 5-HT_3 receptor antagonist, did not interfere with L-NOARG-induced catalepsy. Ritanserin (3 or 10 mg/kg), a 5-HT_{2A} and 5-HT_{2C} receptor antagonist, tended to enhance the effect of L-NOARG. These results confirm that interference with the formation of nitric oxide induces catalepsy in mice, and suggest that this effect is modulated by 5-HT_{1A} and 5-HT_{2A} receptors.

Keywords: Nitric oxide (NO) synthase inhibitor; Catalepsy; 5-HT receptor; Dopamine receptor; (Mouse)

1. Introduction

Nitric oxide (NO) is a short-lived, highly liposoluble molecule that is generated from the amino acid L-arginine by a family of enzymes called NO synthases (Moncada and Higgs, 1993). In the central nervous system a constitutive, calmodulim-dependent NO synthase has been found in many discrete brain regions (Vicent and Kimura, 1992). Several studies suggest that NO may act as a neurotransmitter or neuromodulator, participating in physiological or pathological conditions such as epilepsy, anxiety, neurotoxicity and learning (Choi, 1993; Kawabata et al., 1993; Guimarães et al., 1994).

NO synthase positive cells are found in the striatum (Vicent and Kimura, 1992), and antagonism of NO formation has been shown to decrease dopamine release in this structure (Sandor et al., 1995). This raises the possibility that NO may play a role in the control of motor behaviour. In agreement with such a possibility, we have recently found that systemic administration of N^G-nitro-L-arginine (L-NOARG), N^G-nitro-L-arginine methylester (L-NAME), or N^G-monomethyl-L-arginine (L-NMMA), inhibitors of NO synthase, induces catalepsy in mice (Marras et al., 1995). We have also shown that this effect is attenuated by previous treatment with L-arginine and that tolerance develops after four days of chronic (twice a day) administration (Del Bel et al., 1998).

The mechanisms for the catalepsy induced by NO synthase inhibitors are not known, but the effect of NO on central neurotransmitters, particularly on dopamine in the basal ganglia, could be important. Along with dopamine, other neurotransmitters such as noradrenaline, acetylcholine, γ-aminobutiric acid, glutamate and serotonin have been implicated in the regulation of locomotor activity (Sanberg et al., 1988).

The influence of serotonin on dopaminergic neurotransmission has aroused great interest as a therapeutic target in schizophrenia (Kapur and Remington, 1996). There is a functional relationship between serotonergic and dopamin-

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ergic striatal neurons (Kapur and Remington, 1996). Catalepsy induced by neuroleptics may be enhanced by imipramine (Waldmeier and Delini-Sutula, 1979) and 5-HT_2 receptor antagonists have been reported to reduce haloperidol-induced catalepsy depending on the haloperidol dose (Bligh-Glover et al., 1995). Inconsistent results, however, have been reported for ritanserin, a mixed 5-$HT_{2A/2C}$ receptor antagonist. Results vary between inhibition (Hicks, 1990; Bligh-Glover et al., 1995; Lucas et al., 1997), no effect (Wadenberg, 1992; Bligh-Glover et al., 1995) or potentiation (Elliott et al., 1990a) of neuroleptic-induced catalepsy. The 5-HT_{1A} receptor antagonist (+)-WAY-100635 has been reported to enhance haloperidol-induced catalepsy (Kalkman et al., 1998). Results concerning the modulation of neuroleptic-induced catalepsy by 5-HT_3 receptors are also contradictory (Elliott et al., 1990b; Silva et al., 1995b).

The objective of the present study was to investigate the effects of serotonin receptor antagonist agents on nitric oxide synthase inhibitor-induced catalepsy.

2. Materials and methods

2.1. Animals

Male albino–Swiss mice (25–30 g), bred in the local campus animal farm, were housed for 48 h in groups of eight to ten per cage in a sound-attenuated, temperature-controlled (22 ± 1°C) room, with free access to food and water. The experiments were carried out according to the Brazilian Society of Neuroscience and Behaviour guidelines for the care and use of laboratory animals, and all efforts were made to minimise animal suffering.

2.2. Drugs

N^G-Nitro-L-arginine (L-NOARG, Sigma), haloperidol (Janssen), ketanserin tartrate (RBI), (+)-*N*-*tert*-butyl-3-(4-[2-methoxyphenyl]piperazin-1-yl)-2-phenylpropanamide ((+)-WAY-100135, Wyeth Research), prazosin (Wyeth Research), and endo-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl (BRL-46470A, SmithKline Beecham) were dissolved in saline and administered in a volume of 10 ml/kg. Ritanserin (RBI) was dissolved in 0.3 M HCl and the appropriate vehicle was used as control.

2.3. Procedure

Catalepsy was evaluated by placing the animal with both forelegs over a horizontal glass bar (diameter: 0.5 cm), elevated 4.5 cm from floor. The time (s) during which the mouse maintained this position was recorded up to 300 s (Zarrindast et al., 1993). Catalepsy was induced by intraperitoneal (i.p.) administration of L-NOARG (40 mg/kg). Thirty minutes before this injection the animals received one of the following drugs: (+)-WAY-10035 (5 or 10 mg/kg), ketanserin (3 or 10 mg/kg), ritanserin (5 or 10 mg/kg), prazosin (3 or 5 mg/kg), ketanserin (3 or 10 mg/kg) or BRL-46470A (0.05 or 0.5 mg/kg). In another experiment catalepsy was induced by haloperidol (0.3 or 1 mg/kg) and the animals were pre-treated, 30 min before, with ketanserin (3 or 10 mg/kg). Separate control groups were used in each experiment and the animals were used only once. The mice were tested 1, 2 or 4 h after L-NOARG or haloperidol injection.

2.4. Statistical analysis

Since variances among groups were not homogenous, the raw data was 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 by one-way analysis of variance (ANOVA) at each assessment point. The Duncan test was used for multiple comparisons.

3. Results

3.1. Effect of (+)-WAY-100135 on L-NOARG-induced catalepsy

There were significant effects of treatment ($F(5,52) = 16.2$ $P < 0.001$), time ($F(2,104) = 8.42$, $P < 0.001$) and treatment × time ($F(10,104) = 2.39$, $P < 0.05$). L-NOARG induced catalepsy throughout the experiment (Duncan, $P < 0.05$). The highest dose of (+)-WAY-100135 enhanced the cataleptic effect of L-NOARG 1 and 2 h after injection (Duncan, $P < 0.05$, Fig. 1).

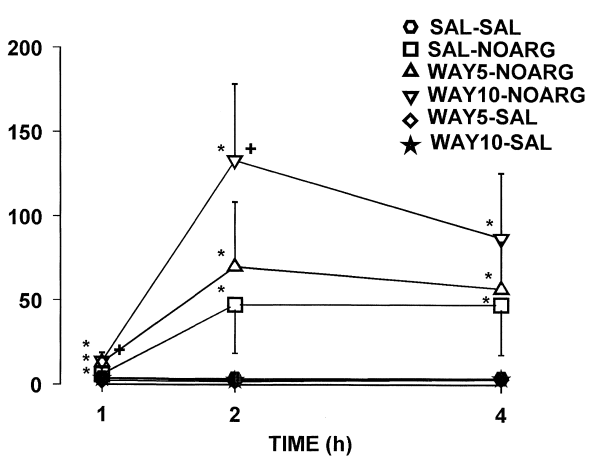

Fig. 1. Effect of (+)-WAY-100135 ($n = 10$, 5 or 10 mg/kg i.p.) or saline ($n = 9$, 10 ml/kg) on catalepsy (in seconds) induced by L-NOARG (40 mg/kg). Points represent the means ± S.E.M. *Significant differences from the control group (SAL–SAL). +Significant differences from (SAL–NOARG) group. (ANOVA followed by the Duncan test, $P < 0.05$).

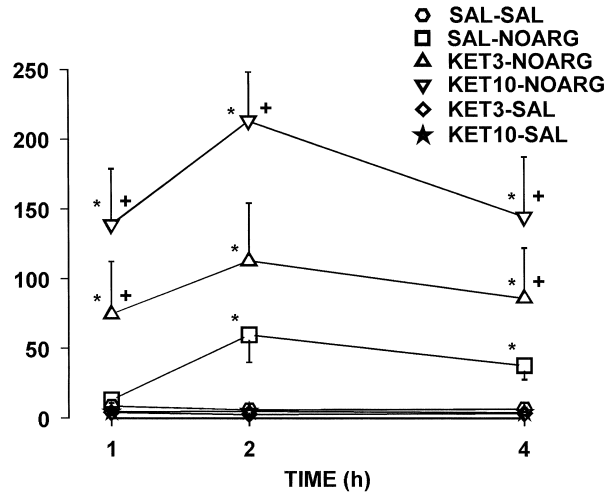

Fig. 2. Effect of ketanserin ($n = 9$, 3 or 10 mg/kg i.p.) or saline ($n = 10$, 10 ml/kg) on catalepsy (in seconds) induced by L-NOARG (40 mg/kg). Points represent the means ± S.E.M. * Significant differences from the control group (SAL–SAL). + Significant differences from (SAL–NOARG) group. (ANOVA followed by the Duncan test, $P < 0.05$).

3.2. Effect of ketanserin on L-NOARG-induced catalepsy

There were significant effects of treatment ($F(5,63) = 21.93$, $P < 0.001$), time ($F(2,126) = 5.24$, $P < 0.01$) and treatment × time ($F(10,126) = 2.55$, $P < 0.01$). L-NOARG induced catalepsy 2 and 4 h after injection. Both doses of ketanserin increased the L-NOARG effect (Duncan, $P < 0.05$, Fig. 2).

3.3. Effect of ritanserin on L-NOARG-induced catalepsy

There were significant effects of treatment ($F(5,40) = 8.90$, $P < 0.001$) and time ($F(2,80) = 4.25$, $P < 0.05$). L-NOARG induced catalepsy throughout the experiment (Duncan, $P < 0.05$). Although a trend in the graphic, ritanserin was not able to enhance the effect of L-NOARG (Duncan, $P > 0.05$, Fig. 3).

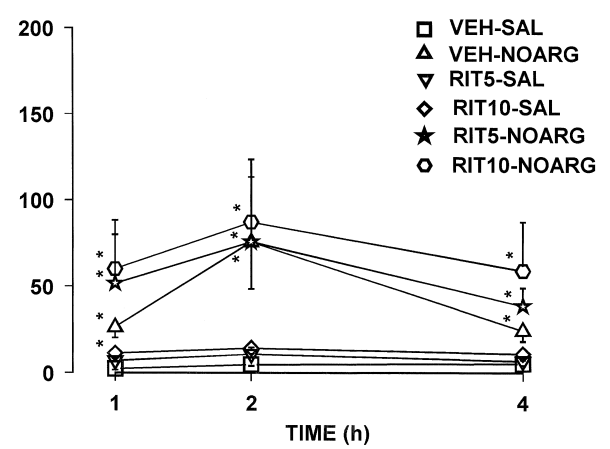

Fig. 3. Effect of ritanserin ($n = 9$, 5 or 10 mg/kg i.p.) or vehicle ($n = 10$, 10 ml/kg) on catalepsy (in seconds) induced by L-NOARG (40 mg/kg). Points represent the means ± S.E.M. * Significant differences from the control group (VEH–SAL, ANOVA followed by the Duncan test, $P < 0.05$).

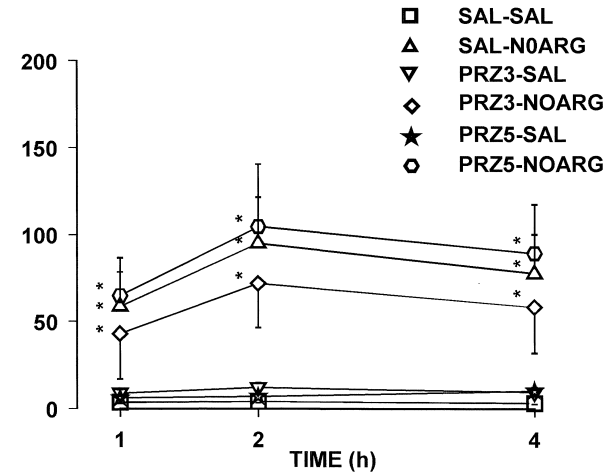

Fig. 4. Effect of prazosin ($n = 9$, 3 or 5 mg/kg i.p.) or saline ($n = 10$, 10 ml/kg) on catalepsy (in seconds) induced by L-NOARG (40 mg/kg). Points represent the means ± S.E.M. * Significant differences from the control group (SAL–SAL, ANOVA followed by the Duncan test, $P < 0.05$).

3.4. Effect of prazosin on L-NOARG-induced catalepsy

There were significant effects of treatment ($F(5,62) = 16.07$, $P < 0.001$) and time ($F(2,124) = 6.27$, $P < 0.01$). L-NOARG induced catalepsy throughout the experiment (Duncan, $P < 0.05$), and this effect was not enhanced by prazosin (Duncan, $P > 0.05$, Fig. 4).

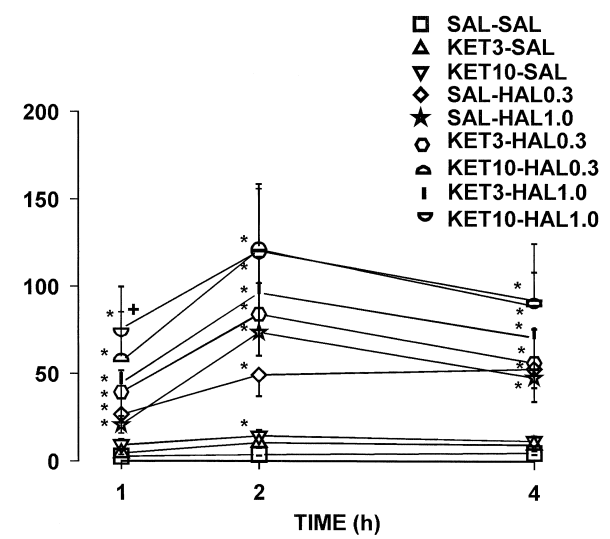

Fig. 5. Effect of ketanserin ($n = 9$, 3 or 10 mg/kg i.p.) or saline (10 ml/kg) on catalepsy (in seconds) induced by haloperidol (0.3 or 1 mg/kg). Points represent the means ± S.E.M. * Significant differences from the control group. + Significant differences from (SAL–HAL) group. (ANOVA followed by the Duncan test, $P < 0.05$).

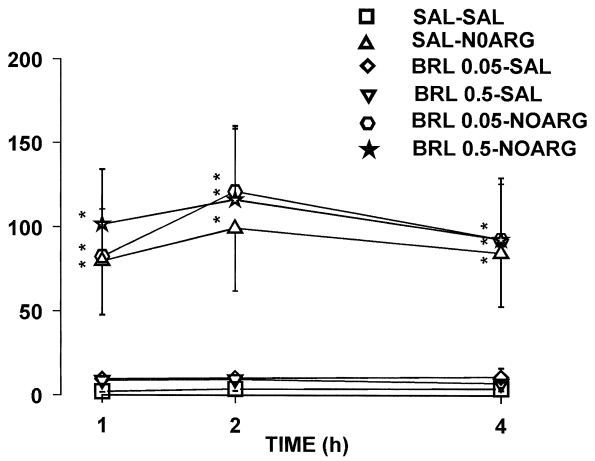

Fig. 6. Effect of BRL-46470A ($n = 10$, 0.05 or 0.5 mg/kg i.p.) or saline ($n = 5$, 10 ml/kg) on catalepsy (in seconds) induced by L-NOARG (40 mg/kg). Points represent the means ± S.E.M. *Significant differences from the control group (SAL–SAL, ANOVA followed by the Duncan test, $P < 0.05$).

3.5. Effect of ketanserin on haloperidol-induced catalepsy

There were significant effects of treatment ($F(8,81) = 14.94$, $P < 0.001$) and time ($F(2,162) = 30.51$, $P < 0.001$). Both doses of haloperidol induced catalepsy throughout the experiment (Duncan, $P < 0.05$), and this effect was enhanced by ketanserin (10 mg/kg) 1 h after injection (Duncan, $P < 0.05$, Fig. 5).

3.6. Effect of BRL-46470A on L-NOARG-induced catalepsy

There was a significant treatment effect ($F(5,39) = 4.7$, $P < 0.01$). L-NOARG induced catalepsy throughout the experiment (Duncan, $P < 0.05$), and this effect was not enhanced by BRL-46470A (Duncan, $P > 0.05$, Fig. 6).

4. Discussion

Confirming previous reports (Marras et al., 1995; Del Bel et al., 1998), L-NOARG was found to induce catalepsy in mice. This effect was increased by (+)-WAY-100135 and ketanserin, but not by ritanserin, prazosin or BRL-46470A. Ketanserin was also able to enhance haloperidol-induced catalepsy.

Catalepsy has been defined as a failure to correct an externally imposed posture. It has been widely used to evaluate the motor effects of drugs, particularly those related to the extrapyramidal system (Sanberg et al., 1988). Drugs that decrease dopaminergic neurotransmission in the striatum, such as neuroleptics, induce catalepsy in rodents and Parkinson symptoms in humans (Sanberg et al., 1988).

The mechanisms involved in the catalepsy induced by L-NOARG are not yet understood. Although peripheral mechanisms could be involved, the active dose used in the present study was equal to or greater than those recently shown to significantly inhibit cerebral NO synthase in rats after systemic administration (Salter et al., 1995).

It is possible that NO synthase inhibitors induce catalepsy by interfering with striatal dopamine. NO facilitates striatal dopamine efflux (West and Galloway, 1998). Although some contradictory reports exist (Silva et al., 1995a), antagonism of NO formation attenuates dopamine release in the striatum (Bowyer et al., 1995; Sandor et al., 1995) and inhibits the increased locomotor activity found after dopamine agonist administration (Abekawa et al., 1994; Starr and Starr, 1995).

Serotonergic mechanisms have been proposed to modulate the extrapyramidal side effects induced by antipsychotic agents. Therefore, we tested the hypothesis that serotonergic mechanisms may also play a role in L-NOARG-induced catalepsy. The general findings of the study favour this hypothesis.

Several reports indicate that 5-HT_{1A} receptor agonists inhibit neuroleptic-induced catalepsy in rodents (Broekkamp et al., 1988; Bartoszyk et al., 1996; Lucas et al., 1997) and there is a report of catalepsy induced by (+)-WAY-100635 (Kalkman et al., 1998). Similarly, in our study (+)-WAY-100135, a 5-HT_{1A} receptor antagonist (Assié and Koek, 1996), enhanced L-NOARG-produced catalepsy.

5-HT_2 receptor agonists such as (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) or (±)-2,5-dimethoxy-4-bromoamphetamine hydrobromide (DOB) have been consistently reported to inhibit neuroleptic induced catalepsy (Hicks, 1990; Elliott et al., 1990b; Neal-Beliveau et al., 1993; Wadenberg and Ahlenius, 1995). However, responses obtained with 5-HT_2 receptor antagonists are conflicting. Some studies show anti-cataleptic effects of these compounds (Ohno et al., 1994; Lucas et al., 1997) but negative results also exist (Wadenberg, 1992; Pires et al., 1994) and one study found that ketanserin was cataleptogenic (Kalkman et al., 1998). It has been proposed that the effects of 5-HT_2 receptor antagonists depend on the conditions under which catalepsy is induced (Kapur and Remington, 1996).

In our experiment, ketanserin produced a dose-dependent potentiation of L-NOARG-induced catalepsy in mice and ritanserin tended to do the same. Ketanserin also increased haloperidol-induced catalepsy. Ritanserin has a high affinity ($k_i < 10$ nM) for both 5-HT_{2A} and 5-HT_{2C} receptors whereas ketanserin shows high affinity only for the 5-HT_{2A} receptor (Peroutka, 1993). Although ketanserin has also considerable affinity for α_1-adrenoceptors (Saxena, 1995), the classical α_1-adrenoceptor antagonist prazosin did not modify the catalepsy induced by L-NOARG. This seems to rule out a direct influence of α_1-adrenoceptor blockade on the ketanserin-induced potentiation of catalepsy. Taken together, these results suggest that 5-HT_{2A} receptors modulate catalepsy induced by L-NOARG.

A previous report by another group (Kalkman et al., 1998), which used doses similar to those of our study, has already shown a cataleptogenic effect of ketanserin in rats. The onset of cataleptic activity, however, was slower than that induced by a neuroleptic drug, with the maximal effect being seen at the end of the 5-h observation period. This may help to explain why a cataleptic response to the 5-HT_{2A} receptor antagonist administered alone was not seen in this study. Different animal species and drug administration routes, or the presence of active metabolites (Heykants et al., 1988), could also have contributed to this difference.

Contradictory results have been found concerning the effect of 5-HT_3 receptor antagonism on neuroleptic-induced catalepsy. Silva et al. (1995b) reported both inhibition and facilitation, depending on the doses used. No effect of 5-HT_3 receptor agonists was found (Elliott et al., 1990b). The doses of the 5-HT_3 receptor antagonist used in the present work were the same or higher than those showing a significant anxiolytic effect (Blackburn et al., 1993), making it improbable that the lack of effect in our study was due to insufficient dosage.

Manipulation of the central serotonergic system can influence catalepsy induced by antipsychotic agents although the precise mechanism of this effect is unclear (Balsara et al., 1979; Neal-Beliveau et al., 1993; Wadenberg, 1996). Histological evidence suggests that serotonergic neurons from the raphe nuclei make direct synaptic contacts with dopamine-rich areas such as the striatum and nucleus accumbens (Fuxe, 1965). In our study, the effects of the 5-HT drugs on catalepsy induced by L-NOARG were similar to those reported for neuroleptics. Therefore, the results agree with the suggestion that the cataleptic effect observed after L-NOARG may involve changes in striatal dopaminergic neurotransmission.

In conclusion, the present results confirm that systemic administration of L-NOARG produces catalepsy in mice, and indicate that 5-HT_{1A} and 5-HT_{2A} receptors can modulate this effect.

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