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Evidence that NAN-190-induced hypotension involves vascular α_1-adrenoceptor antagonism in the rat

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Abstract

The effect of NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido]-butyl] piperazine), described as a mixed 5-HT_{1A} receptor agonist/antagonist, on cardiovascular function was studied. The i.v. injection of NAN-190 (1–300 μg/kg) dose-dependently decreased blood pressure ($p < 0.001$), while heart rate was not significantly modified compared to saline-treated, anaesthetized adult rats. WAY 100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide), a highly selective 5-HT_{1A} receptor antagonist, increased NAN-190-induced hypotension ($p < 0.05$). In the pithed rat NAN-190 displaced the phenylephrine dose–pressor response curve to the right; ED_{50} values were: ≈ 14, 20, 40 and 270 μg/kg for saline and NAN-190 (1, 10 and 100 μg/kg, respectively); similar ED_{50} values were obtained with prazosin (≈ 20, 69 and 358 μg/kg for 1, 10 and 100 μg/kg of prazosin, respectively). NAN-190 shifted to the right the concentration–response curves to phenylephrine in rat tail artery (α_{1A}-adrenoceptors), in rabbit aorta (α_{1B}-adrenoceptors) and in rat aorta (α_{1D}-adrenoceptors), with pA_2 values of 9.47, 9.02 and 9.99; while Schild slopes were −0.78, −1.13 and −0.90, respectively (not significantly different from unity). The results show that NAN-190 induced hypotension in the anaesthetized, adult rat and suggest that this effect could be explained by antagonism of vascular α_1-adrenoceptors.

Keywords: NAN-190; Hypotension; Rat, anaesthetized; Rat, pithed; α_1-Adrenoceptor, vascular

1. Introduction

Central serotonergic neurons are importantly involved in cardiovascular function regulation (Kuhn et al., 1980). In this regard, it is known that 5-hydroxytryptamine-1A (5-HT_{1A}) receptors, once stimulated by agonists like 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino) tetralin), 5-methoxy-N,*N*-dimethyltryptamine or MDL 73005EF (8-[2-(2,3-dihydro-1,4-benzodioxin-2-ylmethylamino) ethyl]-8-azaspiro [4,5] decane-7,9-dione methyl sulphonate), cause hypotension and bradycardia in normotensive and spontaneously hypertensive rats (Gradin et al., 1985; Martin and Lis, 1985; Dabire et al., 1987; Fozard et al., 1987; Buisson-Defferier and Van Den Buuse, 1992). The central 8-OH-DPAT-mediated hypotension and bradycardia may occur from diminished central sympathetic outflow (Gradin et al., 1985; Fozard et al., 1987), from activation of postsynaptic receptors in the ventrolateral medulla (Clement and Mccall, 1990; Valenta and Singer, 1990) or from activation of somatodendritic 5-HT_{1A} receptors in the dorsal raphe nucleus (Connor and Higgins, 1990).

In order to evaluate the functional role of central 5-HT_{1A} receptors, a number of compounds have been described, among them are some derivatives of arylpiperazines, such as NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido]-butyl]piperazine) (Glennon et al., 1988a), BMY 7378 (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-8-azaspiro [4.5] decane-7,9 dione) (Yocca et al., 1987) and WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxa-

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mide) (Fletcher et al., 1994; Forster et al., 1995). These compounds have been tested in different behavioral and in vitro models, where NAN-190 has been described as a high affinity 5-HT_{1A} receptor antagonist and as a partial agonist at autoreceptors and postsynaptic sites (Glennon et al., 1988a,b, 1989; Greuel and Glaser, 1992; Peglion et al., 1995; Sharp et al., 1996; Testa et al., 1999), showing also high affinity for α_1-adrenoceptors (Glennon et al., 1988a; Peglion et al., 1995; Orjales et al., 1995; Sharp et al., 1996; Testa et al., 1999; Yoshio et al., 2001). BMY 7378 behaves as a full/partial agonist or as antagonist at 5-HT_{1A} receptors (Yocca et al., 1987; Chaput and De Montigny, 1988; Greuel et al., 1991; Greuel and Glaser, 1992; Villalobos-Molina et al., 2001) and as a highly selective antagonist of α_{1D}-adrenoceptors (Goetz et al., 1995; Testa et al., 1999), while WAY 100635 has been described as a highly selective, neutral 5-HT_{1A} receptor antagonist (Fletcher et al., 1994; Forster et al., 1995; Fornal et al., 1996; Trillat et al., 1998; Testa et al., 1999) and as an inverse agonist at human 5-HT_{1A} receptor-transfected cells (Cosi and Koek, 2000); however, it is also an antagonist of α_1-adrenoceptors (Testa et al., 1999; Villalobos-Molina et al., in press). These results indicate a high degree of recognition between 5-HT_{1A} receptor agonists and antagonists and α_1-adrenoceptors and suggest that cardiovascular effects of 5-HT_{1A} receptor ligands could be partially mediated by α_1-adrenoceptors. We focused our attention in NAN-190 since we have found that i.v. injection of this compound produced hypotension in the anaesthetized rat. This observation, along with two recent reports showing that NAN-190 has a high affinity for recombinant and native α_1-adrenoceptors (Testa et al., 1999; Yoshio et al., 2001), prompted us to characterize NAN-190-induced hypotension in anaesthetized rats and to examine the possibility that this effect is due to its interaction with vascular α_1-adrenoceptors.

2. Methods

2.1. Animals

Male Wistar rats, 6–7 months old ($n = 55$), and adult rabbits ($n = 3$) fed ad libitum were used. All procedures were conducted in accordance with our Federal Regulations for Animal Experimentation and Care (NOM-062-ZOO-1999, Ministry of Agriculture, Mexico) and approved by the Institutional Animal Care and Use Committee.

2.2. Anaesthetized rat protocol

To characterize the NAN-190-induced hypotensive effect, anaesthetized rats (sodium pentobarbital, 50 mg/kg, i.p.) were used. Catheters (PE 10) were placed in the left carotid artery for continuous recording of diastolic blood pressure and heart rate and in the right femoral vein for drug injection; the cannula placed in the carotid artery was connected to a TSD-104A pressure transducer (Biopac, Santa Barbara, CA, USA). Diastolic blood pressure was recorded by a MP100 analyzer (Biopac), while the animals were maintained at 37 °C. The data were analyzed by the Acqknowledge software (Biopac). Once the animals had stabilized for at least 15 min, cumulative vehicle (saline, 1 ml/kg) or increasing doses of NAN-190 (1–300 μg/kg), at intervals that varied between 5 and 15 min depending on the dose, were administered. Blood pressure was allowed to return to basal values after each dose before the next was administered. In some experiments, WAY 100635 (100 μg/kg, i.v., a dose that blocks the hypotensive effect of 8-OH-DPAT, Villalobos-Molina et al., 2001), was administered 15 min before NAN-190 in order to antagonize 5-HT_{1A} receptors.

2.3. Pithed rat protocol

To characterize NAN-190 interaction with vascular α_1-adrenoceptors, rats were anaesthetized and the trachea were cannulated, animals were pithed by inserting a stainless steel rod through the eye orbit and foramen magnum (Gillespie and Muir, 1967) and artificially respired with room air by means of a Harvard pump (56 cycles/min; volume: 20 ml/kg). The vagi were then cut and rats were cannulated as described above. Once the animals had stabilized for at least 15 min, basal diastolic blood pressure was determined; after collection of these data, rats received either physiological saline (1 ml/kg, i.v.) or a single dose of NAN-190 (1, 10 and 100 μg/kg, i.v.) 15 min prior to increasing doses of the α_1-adrenoceptor agonist, phenylephrine (1–3000 μg/kg, spaced by a factor of $10^{1/2}$); prazosin was also used in the same doses to compare α_1-adrenoceptors blockade. One agonist dose–response curve was obtained per animal, in this case the maximal doses that could be tolerated by the rats were used. ED_{50} values were obtained by nonlinear regression and represent the means with 95% confidence intervals.

2.4. Contraction of rat aortic and tail arterial rings and rabbit aortic rings

In another set of experiments, isolated arteries were used in order to test the affinity of NAN-190 for α_1-adrenoceptors present in rat tail artery (α_{1A}-adrenoceptors), in rabbit aorta (α_{1B}-adrenoceptors) and in rat aorta (α_{1D}-adrenoceptors). Rats were anaesthetized with ether and rabbits with pentobarbital (60 mg/kg, i.p.) and the arteries were dissected. Aortae and tail arterial rings (3–5 mm in length) were placed in Krebs solution and cleaned of surrounding fat and connective tissues. We used endothelium-denuded arterial rings incubated in 10-ml chambers, filled with Krebs solution (in mM): NaCl,

118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; EDTA, 0.026; and glucose, 11.1 at 37 °C and pH 7.4 with constant oxygenation (95% O_2/5% CO_2), attached to the bottom of the chamber and to an isometric Grass FT03 force displacement transducer (Astro-Med, West Warwick, RI, USA), coupled to a MP100 analyzer and processed by Acqknowledge software. Arteries were subjected to an initial optimal tension of 4 g (rabbit aorta), 3 g (rat aorta) and 2 g (rat tail artery), as evaluated in preliminary experiments using increments in initial tension up to reach the optimal. Rat aorta was exposed to 1×10^{-7} M, while rat tail artery and rabbit aorta were exposed to 3×10^{-6} M noradrenaline and washed every 30 min for 2 h (Ibarra et al., 2000). In the last stimulation by noradrenaline, the arterial rings were exposed to carbachol (1×10^{-6} M) to verify the functionality of endothelium. The absence of endothelium was confirmed by the lack of a relaxing response to carbachol (Furchgott and Zawadski, 1980).

Cumulative concentration–response curves to phenylephrine (1×10^{-9} to 1×10^{-4} M) were obtained for each artery in the presence of rauwolscine and propranolol (1×10^{-7} M, each) to block α_2- and β-adrenoceptors, respectively. Following the first phenylephrine curve, arteries were incubated with increasing concentrations of NAN-190 (1×10^{-10} to 1×10^{-8} M, spaced by a factor of $10^{1/2}$, one concentration of the antagonist was used in each arterial ring in every experiment) for 30 min before and during phenylephrine addition. In order to avoid fatigue of the arterial preparation, a 60-min recovery period was allowed between phenylephrine curves, and to rule out any change in tissue sensitivity to the agonist, due to the long duration these experiments parallel assays were carried out, i.e., arteries in the presence of phenylephrine (control) and arteries in the presence of the agonist plus the antagonist. For rabbit aorta two control phenylephrine curves were obtained for each ring as a result of an increase in the response. Following the second curve, the rabbit aortae were incubated with NAN-190 as described for rat arteries.

Contraction is given in percentage of maximal phenylephrine effect for an easy comparison among experiments. Data are the means ± S.E.M. of arterial rings from three (rabbits) and four (rats) different animals per group. The pA_2 and slope were obtained by Schild plots (Arunlakshana and Schild, 1959).

2.5. Drugs

NAN-190 hydrobromide, phenylephrine hydrochloride, WAY 100635 hydrochloride, (−)-noradrenaline hydrochloride, rauwolscine hydrochloride and (±)-propranolol hydrochloride, were purchased from Research Biochemicals Int. (Natick, MA, USA); carbachol hydrochloride was obtained from Sigma (St. Louis, MO, USA); all reagents were dissolved in physiological saline. Fresh solutions were prepared for each experiment and the doses refer to the free base of substances. Other reagents were analytical grade from local sources.

2.6. Statistics

Two-way analysis of variance followed by Student–Newman–Keuls test were performed for anaesthetized rats; significance was considered when $p < 0.05$.

3. Results

3.1. Hypotensive effect of NAN-190

Basal diastolic blood pressure were 113 ± 3 mm Hg in saline-treated, 111 ± 2 mm Hg in NAN-190-treated and 110 ± 2 mm Hg in WAY 100635-treated rats ($n = 5$ rats per group). NAN-190 induced a dose-dependent decrease in diastolic blood pressure up to a maximal of ≈ −42 ± 3 mm Hg, while repeated doses of saline did not modify it ($p < 0.001$ saline vs. NAN-190 and saline vs. NAN-190 plus WAY 100635, Fig. 1). Heart rate (basal value, 368 ± 16 beats/min) was not significantly modified by NAN-190 (Δ, −9 ± 7 beats/min) compared to controls (Δ, −3 ± 7 beats/min). Interestingly, prior administration of WAY 100635 (100 μg/kg, i.v.) produced a transient decrease in blood pressure (−27.5 ± 2 mm Hg, $n = 5$) and did not block NAN-190-induced hypotension but rather increased it ($p < 0.05$, Fig. 1).

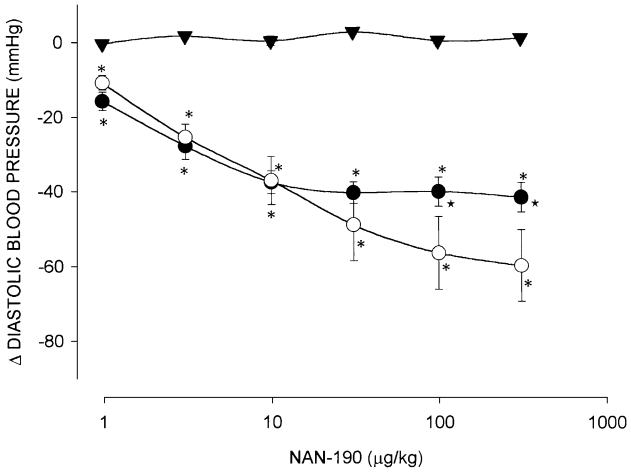

Fig. 1. Effect of NAN-190 on the diastolic blood pressure of the adult rat. Anaesthetized rats of 6–7 months of age were subjected to cumulative injection of saline (▼, 1 ml/kg), or to increasing i.v. doses of NAN-190 in the absence (●) and in the presence of WAY 100635 (○, 100 μg/kg). Points represent the means ± S.E.M. of five rats per group. *$p < 0.001$ saline vs. NAN-190 and saline vs. NAN-190 plus WAY 100635; ★$p < 0.05$ NAN-190 vs. NAN-190 plus WAY 100635.

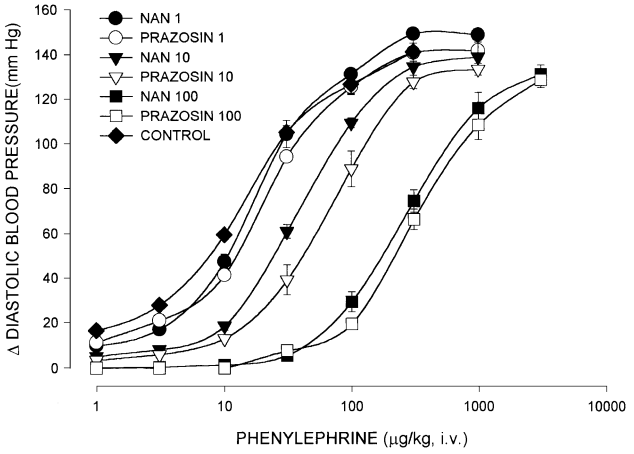

Fig. 2. Antagonist action of NAN-190 and prazosin in the pressor response to phenylephrine in the adult rat. Pithed rats of 6–7 months of age were subjected to increasing i.v. doses of phenylephrine in the presence of 1, 10, and 100 μg/kg NAN-190 or prazosin. Points represent the mean of three (control) and five rats per group.

3.2. NAN-190 blockade of the pressor response to phenylephrine

In pithed rats phenylephrine elicited a dose-dependent increase in diastolic blood pressure (basal value was, 44 ± 2 mm Hg), which was displaced to the right by increasing doses of NAN-190 or prazosin (Fig. 2). Agonist ED_{50} values were: 14.52 (11.8–17.2, confidence interval, 95%), 19.73 (12.3–27.2), 40.37 (30.2–50.5) and 270.37 (166.3–320.6) μg/kg in the absence and in the presence of 1, 10 and 100 μg/kg NAN-190, respectively; while ED_{50} values for prazosin were: 13.96 (11.99–15.93), 20.03 (17.27–22.79), 68.93 (43.14–94.71) and 357.87 (268.40–447.34) μg/kg in the absence and in the presence of 1, 10 and 100 μg/kg prazosin, respectively (Fig. 2). Heart rate was increased in a dose-dependent manner by phenylephrine up to 107 ± 9 beats/min above basal (311 ± 13 beats/min), and was not significantly modified by NAN-190 (120 ± 8 beats/min).

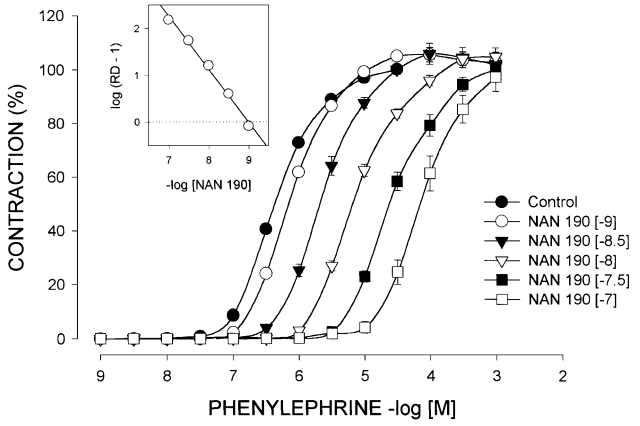

Fig. 4. Effect of NAN-190 on the concentration–response curve to phenylephrine in rabbit aorta. Arterial rings were incubated with increasing concentrations of NAN-190 (inset, Schild plot). Points represent the means ± S.E.M. of three animals.

3.3. α_1-Adrenoceptor antagonism by NAN-190

The effect of NAN-190 on phenylephrine response was measured in tail arteries and aorta from adult Wistar rats and in rabbit aorta. NAN-190 concentration-dependently shifted the phenylephrine response to the right in the three arteries (pA_2 values of 9.47 ± 0.22, 9.02 ± 0.06 and 9.99 ± 0.12 with Schild slopes of −0.78 ± 0.13, −1.13 ± 0.06 and −0.90 ± 0.09 not significantly different from unity, were obtained in rat tail artery, rabbit aorta and rat aorta, respectively), indicating a competitive interaction of the antagonist with the α_1-adrenoceptors present in these vessels (Figs. 3–5).

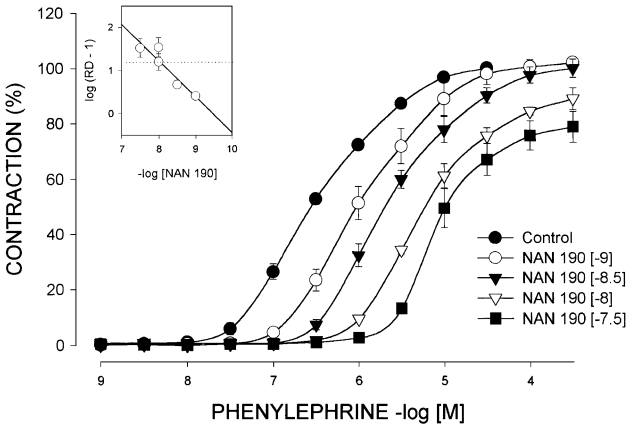

Fig. 3. Effect of NAN-190 on the concentration–response curve to phenylephrine in tail arteries of adult Wistar rats. Arterial rings were incubated with increasing concentrations of NAN-190 (inset, Schild plot). Points represent the means ± S.E.M. of four animals.

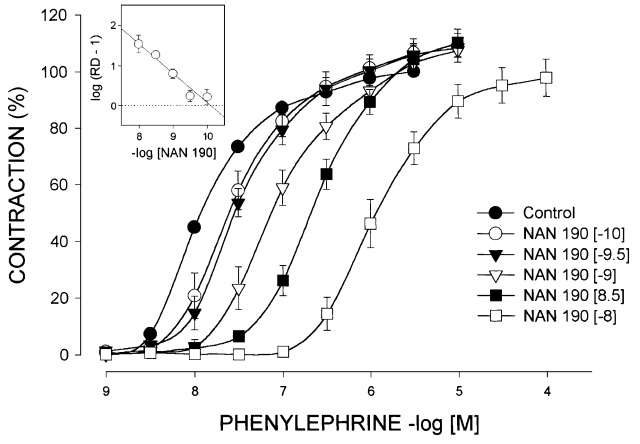

Fig. 5. Effect of NAN-190 on the concentration–response curve to phenylephrine in aorta of adult Wistar rats. Arterial rings were incubated with increasing concentrations of NAN-190 (inset, Schild plot). Points represent the means ± S.E.M. of four animals.

4. Discussion

To our knowledge, this is the first report that shows a dose-dependent hypotensive effect of NAN-190 in the adult anaesthetized rat and its functional interaction with vascular α_1-adrenoceptors; even though, it has been recently shown that NAN-190 binds with high affinity and it is an antagonist at recombinant and native α_1-adrenoceptors (Testa et al., 1999; Yoshio et al., 2001).

NAN-190 has been described as a high affinity 5-HT_{1A} receptor antagonist (Glennon et al., 1988a,b, 1989), at both pre- and postsynaptic sites (Glennon et al., 1988a, 1989; Greuel and Glaser, 1992; Sharp et al., 1996). However, very recent reports showed NAN-190 to have high affinity for recombinant α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors (0.40, 3.2 and 0.37 nM, respectively), transfected in Chinese hamster ovary cells (Testa et al., 1999) and pA_2/pK_i values of 9.18 and 9.09 for α_1-adrenoceptors (Orjales et al., 1995; Peglion et al., 1995) and pA_2 values of 9.0, 8.8 and 9.5 for α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, respectively (Yoshio et al., 2001). These observations, along with our findings that injection of this compound induced hypotension in the anaesthetized rat, suggest that NAN-190 hypotensive effect could be related to vascular α_1-adrenoceptor blockade, as we demonstrated in this study. In support of this contention, we found (a) a clear correlation between NAN-190-induced dose-dependent hypotension in anaesthetized rats and a significant displacement of phenylephrine pressor effect in the pithed rats, and (b) a similar blockade by prazosin on α_1-adrenoceptor stimulation by phenylephrine in the pithed rat model.

Our results show that the 5-HT_{1A} receptor antagonist, NAN-190, displaced phenylephrine effect to the right in isolated arteries with a pA_2 of 9.47 (0.34 nM), which is very close to that reported in rat tail artery (pA_2 of 9.0, Yoshio et al., 2001) and for α_{1A}-adrenoceptors in transfected cells (0.40 nM, Testa et al., 1999); we found a pA_2 of 9.02 in rabbit aorta, close to the pA_2 of 8.8 in dog carotid artery (Yoshio et al., 2001), which is threefold higher than the affinity for cloned α_{1B}-adrenoceptors: 0.95 vs. 3.2 nM (Testa et al., 1999), and a pA_2 of 9.99 was obtained which is very close to 9.5, reported for rat aorta (Yoshio et al., 2001), and is $\approx$ 4-fold higher than the affinity for cloned α_{1D}-adrenoceptors in transfected cells, i.e., 0.10 vs. 0.37 nM (Testa et al., 1999). Furthermore, since the Schild slopes were not different from unity, the data indicate that the antagonism is competitive and a homogeneous population of α_1-adrenoceptors is present in each vessel (Kenakin, 1993), in other words, NAN-190 is a non-subtype-selective α_1-adrenoceptor antagonist, as prazosin is.

From the present data we suggest that the hypotensive action of NAN-190 is related to its interaction, as an antagonist, at vascular α_1-adrenoceptors and points out a word of caution in the interpretation of results when NAN-190 is used as a 5-HT_{1A} receptor agonist/antagonist.

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