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Effect of nociceptin/orphanin FQ on venous tone in conscious rats

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Abstract

Nociceptin (orphanin FQ) is an endogenous agonist for the opioid receptor-like1 (ORL1) receptor. We investigated the effects of nociceptin on mean circulatory filling pressure, an index of venous tone. The effects of nociceptin (10, 30 nmol/kg, i.v.) and the vehicle (0.9% NaCl) on mean arterial pressure, heart rate and mean circulatory filling pressure were examined in two groups each of conscious rats: rats with, or without, ganglionic blockade through pretreatment with mecamylamine (1 mg/kg, i.v.) and noradrenaline (2 μg/kg min, i.v.). In the unblocked rats, both doses of nociceptin decreased mean arterial pressure and heart rate, and the high dose also decreased mean circulatory filling pressure. In the ganglionic-blocked rats, nociceptin did not alter heart rate but caused greater reductions of mean arterial pressure and mean circulatory filling pressure. The vehicle had no effects in any group. Therefore, nociceptin is a depressor agent with prominent direct venodilator and bradycardic action.

Keywords: Nociceptin; ORL1 receptor; Arterial pressure, mean; Circulatory filling pressure, mean; Venous tone; Capacitance vessel; Ganglionic blockade

1. Introduction

Nociceptin (orphanin FQ) is a heptadecapeptide that has been shown to be the endogenous ligand for the opioid receptor-like1 (ORL1) receptor (Meunier et al., 1995; Reinscheid et al., 1995). The ORL1 is a G-protein-coupled receptor which shares a high degree of sequence homology with the μ-, δ- and κ-opioid receptors (Bunzow et al., 1994; Chen et al., 1994). Nociceptin reduced blood pressure and heart rate in anesthetized (Champion and Kadowitz, 1997; Guiliani et al., 1997) and conscious rats (Kapusta et al., 1997), as well as unanesthetized mice (Madeddu et al., 1999), but increased blood pressure and heart rate in conscious sheep (Arndt et al., 1999). The vasodepressor response of nociceptin was not antagonized by the opioid receptor antagonist, naloxone (Czapla et al., 1998), but was antagonized by the selective nociceptin receptor antagonists, [Nphe[1]]nociceptin(1–13)-NH_2 (Chen et al., 2002) and [F/G]nociceptin(1–13)-NH_2 (Bigoni et al., 1999). Furthermore, guanethidine inhibited the depressor effect of nociceptin while bilateral vagotomy markedly inhibited its bradycardic effect (Guiliani et al., 1997). These results suggest that nociceptin causes vasodepression and bradycardia partially via the inhibition of sympathetic vasomotor tone and activation of vagal outflow to the heart. Nociceptin dilated the constant flow-perfused hindquarter (Czapla et al., 1997) and the pulmonary vascular beds (Nossaman et al., 1998). It also decreased vascular resistance in the hairless skin of the rat hindlimb (Häbler et al., 1999) and dilated the porcine pial arterial vessels (Armstead, 1999). Our recent study has shown that nociceptin causes generalized vasodilatation in anesthetized rats with prominent dilator action in the skeletal muscle, lungs, heart, liver, stomach, kidneys, skin, testes and brain (Abdelrahman and Pang, in 2002).

The venous system plays a crucial role in regulating cardiac output. Drugs which interfere with sympathetic venomotor tone (e.g., α-adrenoceptor antagonists) or have direct venodilator action (e.g., nitrovasodilators) can cause considerable reduction of cardiac output and orthostatic hypotension. To our knowledge, there are no published reports on the action of nociceptin on isolated veins or capacitance vessels in vivo. The aim of the present study was to determine the effect of nociceptin on mean circulatory filling pressure in conscious rats. Mean circulatory

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filling pressure is the pressure which would occur throughout the circulation if all pressures were brought to an equilibrium (Guyton, 1955). In the absence of a change in blood volume, a decrease in mean circulatory filling pressure denotes a reduction in body venous tone (Pang, 2001). The effect of nociceptin on venous tone was also examined in rats devoid of autonomic activity through pretreatment with mecamylamine followed by the restoration of vasomotor tone via the continuous infusion of noradrenaline. Noradrenaline was used because vasodilator drugs have been shown to have greater influence on mean circulatory filling pressure after the elevation of venous tone (Abdelrahman and Pang, 1990, 1992).

2. Materials and methods

2.1. Animal preparation

Male Sprague–Dawley rats (350–450 g) were anesthetized with halothane (4% in air for induction and 1.5% for maintenance). A polyethylene (PE50) catheter was introduced into the left iliac artery to record mean arterial pressure by a pressure transducer (PD23DB, Gould Statham, CA, USA). Heart rate was derived electronically from the upstroke of the arterial pulse pressure by a Grass 7P4G tachograph. The vehicle or drugs were administered through a catheter inserted into the right iliac vein. The left iliac vein was also cannulated to allow the insertion of a catheter into the inferior vena cava for the measurement of central venous pressure by another pressure transducer (P23DB, Gould Statham). A saline-filled, balloon-tipped catheter was advanced into the right atrium through the right external jugular vein. The proper positioning of the balloon was tested by transiently inflating the balloon, which when correctly placed, resulted in a simultaneous decrease in mean arterial pressure to 20–25 mm Hg and an increase in central venous pressure within 5 s of circulatory arrest. All cannulae were filled with heparinized saline (25 IU/ml) and tunneled to the back of the neck, exteriorized and secured. The rats were allowed 6 h to recover from the effects of surgery and anesthesia before further use.

2.2. Measurements of mean circulatory filling pressure

The method for determining mean circulatory filling pressure has been described in detail elsewhere (Pang, 2001). Briefly, steady-state readings of mean arterial pressure and central venous pressure were noted at 4–5 s after temporarily stopping the circulation by inflation of the atrial balloon. To correct for the incomplete equilibration of arterial and venous pressures during circulatory arrest, mean circulatory filling pressure was calculated by the following equation: mean circulatory filling pressure = VPP + 1/60(FAP − VPP), where FAP and VPP denote the final arterial pressure and venous plateau pressure, respectively, and 1/60 represents the ratio of arterial to venous compliance.

2.3. Experimental protocol

The rats were divided into four groups ($n = 6–7$ each). Mean arterial pressure, heart rate and central venous pressure were continuously monitored and displayed on a Grass Polygraph (Model RPS 7C8). The rats were given 30 min to stabilize before baseline values of mean arterial pressure, heart rate and mean circulatory filling pressure were obtained. Afterwards, two groups of rats were given i.v. injections of nociceptin (10 and 30 nmol/kg) or an equivalent volume of the vehicle (0.9% NaCl) at dose intervals of 8 min. Pressure and heart rate measurements were taken at the plateau phase of depressor response to nociceptin (between 1–2 and 2–3 min for the low and high dose, respectively), and at the same time points in the vehicle-treated rats. Two other groups of rats were pretreated with mecamylamine (1 mg/kg, i.v. bolus), and measurements were taken at 10 min later. Afterwards, noradrenaline was infused continuously (2 μg/kg min), and measurements were again taken at 10 min after the initiation of infusion. This was followed by injections of nociceptin or vehicle as described for groups I and II.

2.4. Statistical analysis

All data are presented as mean ± S.E.M. The data were analyzed by one-way (between groups of rats) or two-way (within the same group) repeated measures analysis of variance followed by multiple comparison of group data using Tukey test (SigmaStat statistical software), with $P < 0.05$ selected as the criterion for statistical significance.

Table 1
Baseline values (mean ± S.E.M.) of mean arterial pressure, heart rate and mean circulatory filling pressure in conscious rats ($n = 6–7$ per group)

	Mean arterial pressure (mm Hg)	Heart rate (beats/min)	Mean circulatory filling pressure (mm Hg)
Group I—nociceptin	101 ± 3	410 ± 14	6.5 ± 0.3
Group II—saline	108 ± 3	422 ± 11	6.1 ± 0.3
Group III—nociceptin baseline	108 ± 2	399 ± 19	5.9 ± 0.3
After mecamylamine	82 ± 3[a]	436 ± 19	4.5 ± 0.3[a]
After noradrenaline	132 ± 4[a,b]	417 ± 23	7.5 ± 0.3[a,b]
Group IV—saline baseline	103 ± 2	385 ± 20	6.8 ± 0.5
After mecamylamine	77 ± 3[a]	403 ± 22	5.6 ± 0.6
After noradrenaline	136 ± 2[a,b]	382 ± 28	9.5 ± 1.1[a,b]

The rats received mecamylamine (1 mg/kg, i.v. bolus) and noradrenaline (2 μg/kg min, i.v. infusion).
[a] Significantly different ($P < 0.05$) from the baseline value.
[b] Significantly different from mecamylamine treatment.

2.5. Drugs

Nociceptin (Phoenix Pharmaceuticals, CA, USA) was dissolved in distilled water, and kept in aliquots at −20 °C until the day of the experiment when it was diluted with normal saline (0.9% NaCl). Mecamylamine and noradrenaline (Sigma, St. Louis, MO, USA) were also dissolved in normal saline.

3. Results

3.1. Effect of mecamylamine and noradrenaline on mean arterial pressure, heart rate and mean circulatory filling pressure

There are no significant differences in baseline readings of mean arterial pressure, heart rate and mean circulatory filling pressure among the four groups (Table 1). Mecamylamine significantly decreased mean arterial pressure in groups III and IV, did not alter heart rate in either group, and decreased mean circulatory filling pressure significantly in group III and insignificantly in group IV. The infusion of noradrenaline increased mean arterial pressure and mean circulatory filling pressure in both groups III and IV, but did not significantly alter heart rate.

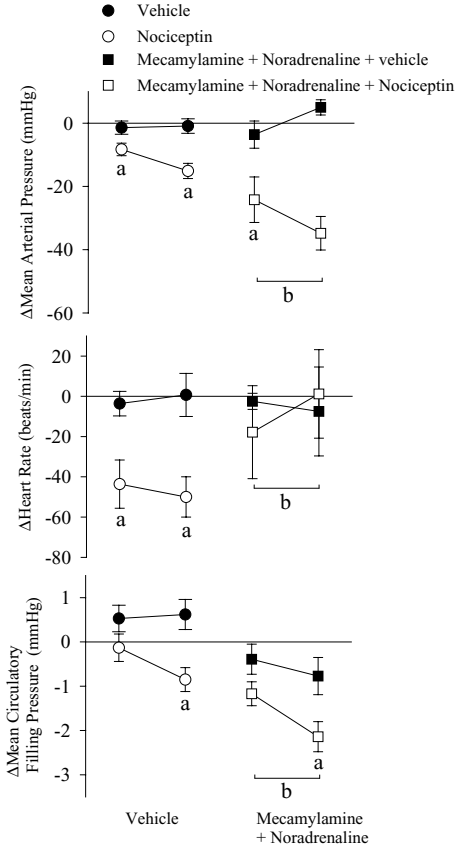

Fig. 1. Effects (mean ± S.E.M., $n = 6–7$ per group) of nociceptin (10 and 30 nmol/kg) or an equal volume of normal saline (0.9% NaCl) on mean arterial pressure, heart rate and mean circulatory filling pressure in conscious, intact rats and rats pretreated with mecamylamine (1 mg/kg i.v.) and noradrenaline (2 μg/kg min i.v.). All points are changes from the baseline value immediately prior to the injection of nociceptin or saline. (a) Significantly different ($P < 0.05$) from the corresponding changes in the saline group. (b) Significantly different from the corresponding changes elicited by both doses of nociceptin in the intact rats.

3.2. Effect of nociceptin on mean arterial pressure, heart rate and mean circulatory filling pressure

Saline did not significantly alter mean arterial pressure, heart rate or mean circulatory filling pressure in either the intact or ganglionic blocked, time-control rats (Fig. 1). Both doses of nociceptin significantly reduced mean arterial pressure and heart rate in the intact rats, relative to the changes in the time-control rats; however, only the high dose of nociceptin significantly decreased mean circulatory filling pressure. In the ganglionic-blocked rats, both doses of nociceptin decreased mean arterial pressure but did not affect heart rate; the high dose of nociceptin also decreased mean circulatory filling pressure significantly. The decreases in mean arterial pressure and mean circulatory filling pressure by both doses of nociceptin were significantly greater, and the changes in heart rate were smaller, in the ganglionic-blocked rats relative to the intact rats.

4. Discussion

Nociceptin was found to concurrently decrease mean arterial pressure and heart rate in conscious rats. It caused greater reductions in mean arterial pressure in rats pretreated with mecamylamine and noradrenaline, and this was likely due to the higher baseline mean arterial pressure (greater vasoconstrictor tone) secondary to the continuous infusion of noradrenaline. The depressor effect of nociceptin has been reported previously in anesthetized or conscious rats and mice (Champion and Kadowitz, 1997; Guiliani et al., 1997; Kapusta et al., 1997; Madeddu et al., 1999). Guiliani et al. (1997) have shown that the depressor response to nociceptin is markedly attenuated in rats pretreated with guanethidine, and suggested that the hypotensive mechanism of nociceptin involves the inhibition of sympathetic vasomotor tone. Furthermore, Malinowska et al. (2000) have shown in pithed rats that nociceptin inhibits the pressor response elicited by electrical stimulation of the preganglionic sympathetic nerve, and this may be via the stimulation of postganglionic prejunctional ORL1 receptors which leads to the inhibition of sympathetic nerve activity. Nociceptin, however, has been shown to dilate preconstricted arterial preparations (Gumusel et al., 1997; Hughins et al., 2000; Champion et al., 1998) as well as isolated perfused vascular beds (Czapla et al., 1997; Nossaman et al., 1998), which suggest that the peptide may cause vasorelaxation via a direct action.

The nociceptin induced decrease in mean arterial pressure was not accompanied by reflex tachycardia as occurs with other vasodilator peptides, e.g., calcitonin gene-related peptide (Abdelrahman and Pang, 1992), but was accompanied by a decrease in heart rate, as has been reported for endomorphins 1 and 2 (Champion et al., 1997). The mechanism by which nociceptin causes bradycardia is unclear, and can be either a direct cardiac action or an indirect action, through vagal stimulation or a decrease in sympathetic influence. Since nociceptin did not reduce heart rate in the ganglionic-blocked rats, its bradycardic effect is not mediated via a direct action on the heart nor via the modulation of cholinergic or adrenergic activity through action at the postganglionic prejunctional nerve terminal. The bradycardic effect of nociceptin is, therefore, likely preganglionic and/or central. Our findings are in line with the results of Guiliani et al. (1997) which show that either bilateral vagotomy or guanethidine treatment attenuated the bradycardic effect of nociceptin, and that a combination of vagotomy and guanethidine abolished the bradycardia. These findings suggest that nociceptin may cause bradycardia via concurrent withdrawal of sympathetic tone and increase of vagal tone. A possible mechanism by which nociceptin causes bradycardia is via central activation of nociceptin receptors. The i.c.v. injection of nociceptin has been shown to decrease heart rate in anesthetized rats, and the response is inhibited by i.c.v. injection of [Nphe^1]nociceptin(1–13)-NH_2 (Chen et al., 2002). Nociceptin has also been shown to cause bradycardia via central suppression of gamma-aminobutyric acidergic inhibitory inputs to cardiac vagal neurons (Venkatesan et al., 2002). It is, however, unclear if nociceptin, given i.v. as in the present study, can access the medullary cardiovascular center to regulate autonomic outflow to the heart.

The ability of nociceptin to concurrently reduce mean arterial pressure and mean circulatory filling pressure in intact rats show that it has prominent venodilator action in vivo. As expected, the venodilator action of nociceptin is augmented in rats pretreated with noradrenaline, which increases vasomotor tone. In our experience, nociceptin is a more efficacious venodilator than verapamil, flunarizine and nifedipine (Ca^{2+} channel blockers; Waite et al., 1988), hydralazine (D'Oyley et al., 1989), isoprenaline (β-adrenoceptor agonist; Abdelrahman and Pang, 1990), zaprinast (type V phosphodiesterase inhibitor; Ng and Pang, 1998), nitroglycerin (Poon and Pang, 2002), and pinacidil (potassium channel opener; Waite et al., 1995), which all decrease mean arterial pressure but increase mean circulatory filling pressure in rats. Its venodilator efficacy appears to be similar to those of fenoldopam (dopamine D_1-receptor agonist; Ng and Pang, 2000), calcitonin gene-related peptide (Abdelrahman and Pang, 1992), adenosine (Glick et al., 1992; Tabrizchi, 1997) and hexamethonium (ganglionic blocker; D'Oyley and Pang, 1990), which are able to concurrently reduce mean arterial pressure and mean circulatory filling pressure in intact rats. There are no published reports on the venous effect of nociceptin; however, opioids have been shown to have venodilator action in the isolated rings of canine pulmonary, mesenteric and saphenous veins (Greenberg et al., 1994; Muldoon et al., 1983). It is, however, unclear if the arterial or venous dilator action of nociceptin is endothelium-dependent.

In conclusion, nociceptin/orphanin FQ is a vasodilator peptide which decreases both mean arterial pressure and mean circulatory filling pressure in conscious, unrestrained rats. The depressor effect of nociceptin is accompanied by bradycardia which is abolished by ganglion blockade.

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