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Effects of endothelin-1 on arterial and venous resistances in anaesthetized rats

Beatriz Palacios, Su Lin Lim, Catherine C.Y. Pang *

Department of Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Mall, Vancouver, B.C., V6T 1Z3, Canada

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Abstract

The effects of endothelin-1 and vehicle (0.9% NaCl) on mean arterial pressure, heart rate, mean circulatory filling pressure, systemic arterial resistance, cardiac output and venous resistance were studied in four groups of pentobarbitone-anaesthetized rats, either in presence or absence of phentolamine. I.v. bolus injections of endothelin-1 at 0.5, 1 and 2 nmol/kg dose dependently increased mean arterial pressure (22, 34 and 40 mmHg), arterial resistance (33, 93 and 122% over baseline), venous resistance (40, 117 and 143% over baseline) and mean circulatory filling pressure (1.0, 1.7 and 1.8 mmHg), but decreased heart rate (−16, −21 and −17 beats/min) and cardiac output (−6, −28 and −35% below baseline). The vehicle did not significantly alter any of these variables. During the continuous infusion of phentolamine (300 μg/kg per min), endothelin-1 caused similar increases in arterial resistance, venous resistance and mean circulatory filling pressure, similar reduction in cardiac output but significantly greater pressor and bradycardic responses, suggesting that the arterial and venous constrictor effects of endothelin-1 are not due to sympathetic activation and the stimulation of α-adrenoceptors. The results show that endothelin-1 raised mean arterial pressure via the increment in systemic arterial resistance, since cardiac output was markedly reduced. This decrease in cardiac output was mediated by increases in arterial as well as venous resistances. The vasoconstrictor and venoconstrictor effects of endothelin-1 were independent of sympathetic tone.

Keywords: Endothelin-1; Circulatory filling pressure, mean; Cardiac output; Arterial resistance, systemic; Venous resistance; Venous tone, body

1. Introduction

Endothelins are a family of 21-amino-acid peptides derived from endothelial cells of the vascular wall. The predominant isoform in the vascular endothelium is endothelin-1 which has initial transient vasodilator followed by sustained vasoconstrictor actions (Yanagisawa et al., 1988). In vivo, endothelin-1 causes marked elevations in arterial pressure and systemic arterial resistance, along with decreases in cardiac output and heart rate (Lerman et al., 1991, 1992; see Rubanyi and Polokoff, 1994). Plasma levels of circulating endothelin-1 are elevated in hypertension (Shichiri et al., 1990), chronic heart failure (Stewart et al., 1992), myocardial ischaemia (Lam et al., 1991), renal failure (Warrens et al., 1990), and haemorrhagic (Chang et al., 1993; Zimmerman et al., 1994), septic (Morel et al., 1989; Sugiura et al., 1989) as well as cardiogenic (Cernacek and Stewart, 1989) shock, raising the possibility that endothelin-1 may participate in cardiovascular regulation. There are few studies on the effects of endothelin-1 on the venous system in vivo.

Endothelin-1 is a potent constrictor of venous smooth muscles in vitro. It constricts perfused mesenteric veins (Warner, 1990; D'Orléans-Juste et al., 1993), saphenous vein in rabbits (Moreland et al., 1992; Auguet et al., 1993) and humans (Yang et al., 1989; White et al., 1994), and human renal (Maguire et al., 1994), coronary (Balligand and Godfraind, 1994; Opgaard et al., 1994), mammary (Yang et al., 1989) as well as omental (Riezebos et al., 1994) veins. Endothelin-1 was reported to have higher efficacy and potency as a constrictor in the human mammary (Yang et al., 1989), renal (Maguire et al., 1994) and coronary (Balligand and Godfraind, 1994; Opgaard et al., 1994) veins than the corresponding arteries. In situ studies show that endothelin-1 contracted veins from the rat mesentery (Fortes et al., 1989), cat gastrocnemius muscle (Ekelund et al., 1993), human forearm (Pernow et al., 1991) and human hand (Haynes et al., 1991, 1994, 1995).

* Corresponding author. Tel.: (1-604) 822-2039; Fax: (1-604) 822-6012.

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In vivo studies performed in our laboratory using conscious rats showed that high doses of endothelin-1 only slightly increased mean circulatory filling pressure, the driving force of venous return (Waite and Pang, 1990). Mean circulatory filling pressure is the mean vascular pressure that exists after the circulation stops and all pressure in the circulation is made to equilibrate (Guyton, 1955). An elevation of mean circulatory filling pressure results from a reduction of unstressed vascular volume or a reduction in venous compliance from stimulation of the venous smooth muscle. The effect of endothelin-1 on mean circulatory filling pressure was enhanced by hypotension-induced sympathetic activation and blocked by phentolamine (Waite and Pang, 1992). To our knowledge, there are no reported in vivo studies on the effect of endothelin-1 on venous resistance. Venous resistance, though lower in magnitude than arterial resistance, is a major determinant of cardiac output due to low pressure in the venous circulation (Rothe, 1993; Pang, 1994). An increase in venous resistance reduces flow, venous return and cardiac output and increases upstream distending pressure causing the accumulation of blood in the venous system, the magnitude of the pooling depends on the upstream compliance (Rothe, 1993).

The aim of this study was to examine the effects of endothelin-1 on venous and arterial resistances using pentobarbitone-anaesthetized rats and to assess the involvement of sympathetic tone on the effects of endothelin-1 via the administration of phentolamine.

2. Materials and methods

2.1. Animal preparation

Male Sprague-Dawley rats (420–500 g) were anaesthetized with pentobarbitone (60 mg/kg). Body temperature was maintained at 36–37°C by means of a rectal probe and a heat lamp connected to a Thermistemp Temperature Controller (Model 71; Yellow Springs Instrument, OH, USA). A catheter (PE50) filled with heparinized saline (0.9% NaCl, 25 I.U./ml) was implanted into the left iliac artery and connected to a pressure transducer (P23DB, Gould Statham, CA, USA) for the continuous measurement of mean arterial pressure which was displayed on a Grass polygraph recorder (Model RPS, 7C8). The heart rate was determined electronically from the systemic blood pressure trace by a cardiotachograph (Grass, Model 7P4G). PE50 cannulae were also inserted into the right iliac vein for the administration of drugs, and the inferior vena cava through the left iliac vein for the recording of central venous pressure by another pressure transducer (P23DB, Gould Statham). A saline-filled, balloon-tipped catheter was inserted into the right atrium via the right external jugular vein. The positioning of the balloon was guided by transient inflation of the balloon, which when correctly placed, stopped the circulation within 5 s of balloon inflation. This led to a simultaneous increase in central venous pressure to a plateau value and a decrease in mean arterial pressure to less than 25 mmHg. Additional catheters were inserted into the left ventricle via the right carotid artery, for the injection of radioactively labelled microspheres, and into the right iliac artery for the withdrawal of a reference blood sample, as described in Wang et al. (1995) and Waite et al. (1995). The position of the ventricular catheter was verified by appearance of the ventricular pulse pressure.

The method for determining mean circulatory filling pressure (MCFP) has been described in detail elsewhere (see Tabrizchi and Pang, 1992; Wang et al., 1995). At 4–5 s after inflation of the atrial balloon, plateau readings of mean arterial pressure and central venous pressure were measured. To avoid the need to equilibrate arterial and venous blood pressures during circulatory arrest, the arterial pressure contributed by the small amount of trapped arterial blood was corrected by the following formula: $MCFP = VPP + 1/60\ (FAP - VPP)$, where FAP represents the final arterial pressure and VPP the venous plateau pressure obtained within 5 s of circulatory arrest, and $1/60$ represents the arterial-to-venous compliance ratio.

2.2. Microsphere technique

A well-stirred suspension (150 μl) of microspheres containing 20 000–25 000 microspheres (15 μm diameter; Du Pont Canada, Ontario, Canada) labelled with ^{57}Co were injected and flushed into the left ventricle over 10 s after 30-min stabilization (baseline measurements) and at 10 min after the start of the infusion of phentolamine as well as at 13 min after i.v. bolus injections of endothelin or the vehicle. Blood was withdrawn for 1 min at 0.35 ml/min from the right iliac artery cannulae into a heparinized syringe (0.9% NaCl, 50 I.U./ml) starting at 10 s before the injection of each set of microspheres using a Harvard infusion/withdrawal pump. The radioactivity contained in the blood samples, syringes used for injection of microspheres and collection of blood and test tubes used for holding the radiolabelled samples was counted using a 1185 Series Dual Channel Automatic Gamma Counter (Nuclear-Chicago, IL, USA) with a 3 inch NaI crystal at energy settings of 80–160 keV. The withdrawn blood was slowly injected back to the animals immediately after the counting of radioactivity.

2.3. Experimental protocol

Rats were randomly divided into four groups with $n = 6$ each. At 12 min after baseline measurements, cumulative doses of endothelin-1 (0.5, 1 and 2 nmol/kg) or equal volumes of saline (0.2, 0.2 and 0.4 ml/kg) were injected as an i.v. bolus into two groups at dose intervals of 15 min. Mean arterial pressure, heart rate and cardiac

output followed by mean circulatory filling pressure measurements were taken at 13 min after injection, at the plateau phase of the response to endothelin-1. In another two groups, phentolamine was continuously infused (300 μg/kg per min, at 0.7 ml/h) starting at 10 min after obtaining the first baseline measurement until the end of the experiment. After another 12 min, dose–response curves to endothelin-1 or saline were constructed as described above. The dose of phentolamine used completely inhibited the pressor effects of the α_1-adrenoceptor agonist methoxamine and the α_2-adrenoceptor agonist B-HT 920 (Tabrizchi and Pang, 1987).

2.4. Drugs

Endothelin-1 (human/porcine, Peninsula Labs., Belmont, CA, USA) and phentolamine HCl (CIBA, Kenilworth, NJ, USA) were dissolved in normal saline. Aliquots of stock endothelin-1 were stored at −20°C until use. Phentolamine was freshly prepared before use.

2.5. Calculations and data analysis

Cardiac output (CO, ml/min), arterial resistance (R_A, mmHg min/ml) and venous resistance (R_V, mmHg min/ml) were calculated according to the formulae:

$$CO = \frac{\text{rate of withdrawal of blood} \times \text{total injected cpm}}{\text{cpm in withdrawn blood}}$$

$$R_A = \frac{MAP}{CO}$$

$$R_V = \frac{MCFP - CVP}{CO}$$

where MAP is mean arterial pressure, MCFP is mean circulatory filling pressure and CVP is central venous pressure.

Due to the technical difficulty of monitoring right atrial pressure in small animals, central venous pressure rather than right atrial pressure was used to calculate pressure gradient to venous return (MCFP-right atrial pressure), as mean central venous pressure is nearly identical to mean right atrial pressure (see Rothe, 1993).

All results were expressed as means ± S.E.M. and analyzed by the analysis of variance, followed by Duncan's multiple range test, with $P < 0.05$ selected as a criterion for statistical significance.

3. Results

Baseline values of mean arterial pressure (range from 101 ± 6 to 107 ± 3 mmHg), heart rate (from 343 ± 10 to 351 ± 9 beats/min), venous resistance (from 0.043 ± 0.003 to 0.050 ± 0.003 mmHg min/ml), systemic arterial resistance (from 1.14 ± 0.08 to 1.21 ± 0.07 mmHg min/ml), cardiac output (from 90 ± 5 to 92 ± 6 ml/min) and mean circulatory filling pressure (from 4.8 ± 0.2 to 5.2 ± 0.1 mmHg) were not significantly different among the four groups of rats ($n = 6$ each). In two groups of rats, the infusion of phentolamine significantly ($P < 0.05$) reduced mean arterial pressure (from 106 ± 2 to 88 ± 3 mmHg, pooled values from two groups, $n = 12$), cardiac output (from 91 ± 3 to 74 ± 4 ml/min, $n = 12$) and mean circulatory filling pressure (from 4.8 ± 0.1 to 4.4 ± 0.2 mmHg, $n = 12$), but did not significantly alter the values of heart rate and arterial and venous resistances.

There were no significant changes in mean arterial pressure, heart rate, mean circulatory filling pressure, arterial resistance, venous resistance and cardiac output with injections of the vehicle in the time-control group (Fig. 1). I.v. bolus of each dose of endothelin-1 elicited a biphasic mean arterial pressure response, which was comprised of an initial transient depressor response that lasted ≅ 40 s (results not shown) followed by a dose-dependent and sustained pressor response that reached plateau at 10 min after injection (Fig. 1A). Endothelin-1 significantly reduced heart rate and dose dependently reduced cardiac output. Venous resistance, arterial resistance and mean

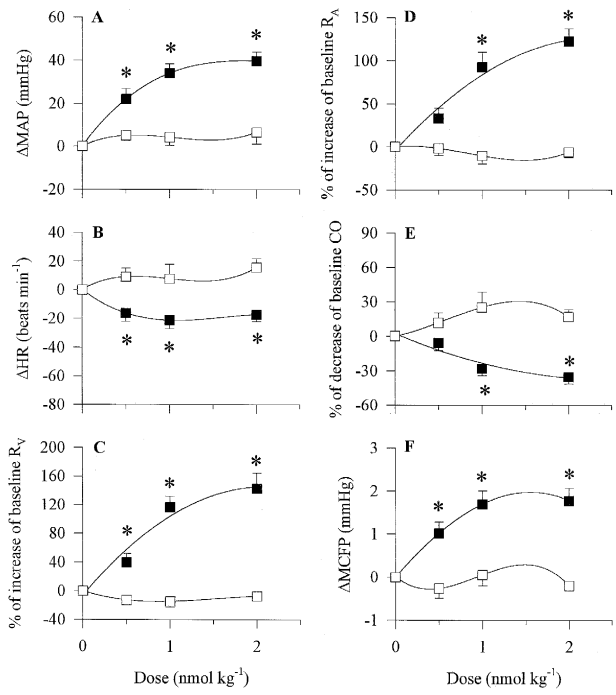

Fig. 1. Changes (mean ± S.E.M.) induced by cumulative i.v. bolus injections of endothelin-1 (■) or equivalent volumes of vehicle (0.9% NaCl, □) on mean arterial pressure (MAP, A), heart rate (HR, B), venous resistance (R_V, C), arterial resistance (R_A, D), cardiac output (CO, E) and mean circulatory filling pressure (MCFP, F) in two groups of pentobarbitone-anaesthetized rats ($n = 6$ each group). The measurements were obtained 13 min after the injection of endothelin-1 or vehicle. * Significantly different ($P < 0.05$) from the corresponding values in the vehicle group.

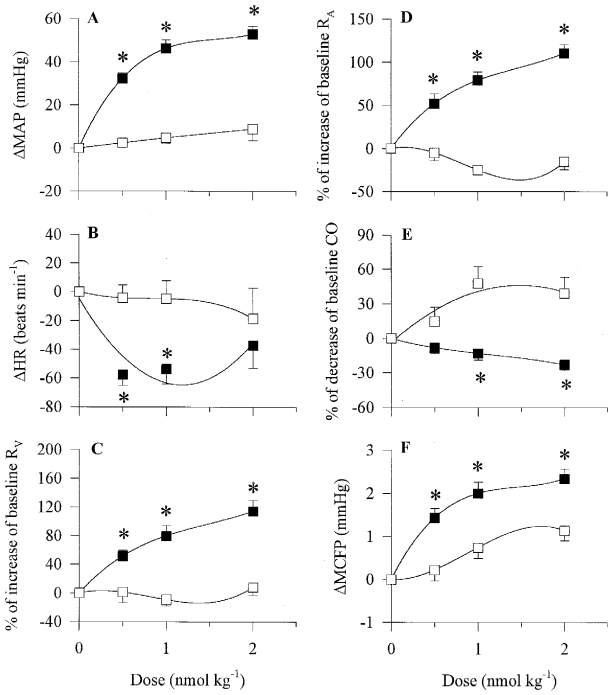

Fig. 2. Changes (mean ± S.E.M.) induced by cumulative i.v. bolus injections of endothelin-1 (■) or equivalent volumes of vehicle (0.9% NaCl, □) on mean arterial pressure (MAP, A), heart rate (HR, B), venous resistance (R_V, C), arterial resistance (R_A, D), cardiac output (CO, E) and mean circulatory filling pressure (MCFP, F) in two groups of pentobarbitone-anaesthetized rats ($n = 6$ each group) continuously infused with phentolamine (300 μg/kg per min). The measurements were obtained 13 min after the injection of endothelin-1 or vehicle. * Significantly different ($P < 0.05$) from the corresponding values in the vehicle group.

circulatory filling pressure were all dose dependently increased by endothelin-1, relative to the corresponding values in the time-control group (Fig. 1B,C,D,E,F).

In phentolamine-treated time-control rats, injections of the vehicle did not cause significant changes in mean arterial pressure, heart rate and venous resistance (Fig. 2A,B,C). The vehicle, however, increased cardiac output and reduced arterial resistance with the two largest doses and increased mean circulatory filling pressure at the last dose, relative to the corresponding baseline values obtained 10 min after the start of phentolamine infusion (Fig. 2D,E,F). These changes were likely secondary to haemodynamic adjustment associated with the continuous infusion of phentolamine. Endothelin-1 significantly and dose dependently ($P < 0.05$) increased mean arterial pressure, venous resistance, arterial resistance and mean circulatory filling pressure and decreased heart rate and cardiac output relative to the corresponding values in the phentolamine-treated time-control group (Fig. 2A,B,C,D,E,F). In the presence of phentolamine, endothelin-1 caused significantly greater pressor and bradycardic responses but similar effects on venous resistance, systemic arterial resistance, mean circulatory filling pressure and cardiac output relative to the responses in intact rats.

4. Discussion

Similar to our previous studies in conscious rats (Waite and Pang, 1990, 1992) i.v. bolus injections of endothelin-1 in anaesthetized rats dose dependently reduced heart rate and increased mean arterial pressure (+22, +34 and +40 mmHg at 0.5, 1 and 2 nmol/kg) as well as mean circulatory filling pressure (+1.0, +1.7 and +1.8 mmHg, respectively). Whereas the magnitudes of the pressor responses to endothelin-1 in the anaesthetized rats were similar to those in conscious rats, the increases in mean circulatory filling pressure were greater than those in previous studies (+0.5 to +0.8 mmHg at 2 nmol/kg) using conscious rats. However, the maximum increase in mean circulatory filling pressure by endothelin-1 was still small relative to those elicited by noradrenaline (+3.3 mmHg), angiotensin II (+4.8) and the α_2-adrenoceptor agonist B-HT 920 (+3.0 mmHg) in conscious rats (Pang and Tabrizchi, 1986). It should be noted that baseline mean circulatory filling pressure (5.0 mmHg) in the pentobarbitone-anaesthetized rats in the present study was lower than mean circulatory filling pressures (between 5.7 to 5.9 mmHg) in conscious rats in the previous two studies (Waite and Pang, 1990, 1992); the baseline values of mean arterial pressures (99–107 mmHg) were, however, similar among the three studies. Pentobarbitone anaesthesia has been shown to reduce basal mean circulatory filling pressure (by 0.9–1.5 mmHg) in rats (Waite et al., 1995; Wang et al., 1995). Vasoconstrictor agents generally elicit greater contractile response at a lower baseline pressure. The greater mean circulatory filling pressure response to endothelin-1 may, therefore, be due to the lower baseline values of mean circulatory filling pressure in the present study.

Endothelin-1 reduced cardiac output and increased systemic arterial resistance (+33, +93 and +122% over baseline) as well as venous resistance (+40, +117 and +143% over baseline). Therefore, endothelin-1 has similar efficacy in constricting resistance arteries and veins. Our results show that endothelin-1 reduces cardiac output via the constriction of arterioles and venous vessels. The site whereby endothelin-1 increased venous resistance is not known. An important location of venous resistance is the hepatic bed where there exists a pressure gradient of 4–15 mmHg between the portal vein and the inferior vena cava at the exit junction of the hepatic vein (Tabrizchi et al., 1993; Pang, 1994). Vasoactive drugs such as angiotensin II markedly elevated the gradient between the portal venous pressure and central venous pressure (Tabrizchi et al., 1993). An increase in hepatic venous resistance would be expected to reduce venous return via the accumulation of blood in the venules of the splanchnic bed. The magnitudes of the constrictor effects of endothelin-1 on arterial and venous resistance vessels are similar to those of the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) which, at 7, 15 and 30

μmol/kg, raised arterial resistance by +84, +140, +192% and venous resistance by +62, +72 and +110% over baseline values, respectively (Wang et al., 1995). To our knowledge, this study is the first to quantify the effect of endothelin-1 on venous resistance.

The infusion of phentolamine significantly lowered mean arterial pressure due to the reduction of cardiac output, as systemic arterial resistance was unchanged. These results are similar to previous observations from our laboratory which showed that the infusion of phentolamine reduced mean arterial pressure and cardiac output but not systemic arterial resistance in halothane-anaesthetized rats (Tabrizchi and Pang, 1987). Mean circulatory filling pressure was also reduced by phentolamine indicating the importance of α-adrenoceptors in the maintenance of basal venomotor tone. The maintenance of systemic arterial resistance despite of α-adrenoceptor blockade by phentolamine was likely a result of the release of large amounts of vasoconstrictor agents as a consequence of reduced venous return, cardiac output and mean arterial pressure. Vasopressin and angiotensin II were shown to be released in large amounts following the administration of phentolamine or prazosin in rats (Waeber et al., 1983; Burnier et al., 1983).

Endothelin-1 caused a similar decrease in cardiac output and similar increases in mean circulatory filling pressure, systemic arterial resistance and venous resistance in phentolamine-treated rats as it did in intact rats. Pressor and bradycardic responses to endothelin-1 were significantly enhanced in the presence of phentolamine. In contrast to previous results in conscious rats (Waite and Pang, 1992), the effect of endothelin-1 on mean circulatory filling pressure in pentobarbitone-anaesthetized rats was not abolished by the infusion of phentolamine. The reason for the discrepancy in the response to phentolamine likely involves the applications of anaesthetics and surgery in the present study vs. the use of conscious rats in the previous one. Thus, the venoconstrictor action of endothelin-1 in control as well as phentolamine-treated rats was intensified in the present study due to the attenuation of vasomotor regulation by surgical anaesthesia. In contrast, the venoconstrictor effect of endothelin-1 in control or phentolamine-treated conscious rats in the previous study was suppressed as a result of modulating influence of vasomotor regulation. Technical difficulties preclude the use of conscious animals for the concurrent measurements of mean circulatory filling pressure and arterial and venous resistances.

To summarise, endothelin-1 dose dependently increased mean arterial pressure, mean circulatory filling pressure, systemic arterial resistance and venous resistance and reduced cardiac output and heart rate in pentobarbitone-anaesthetized rats. The results show that endothelin-1 elevated mean arterial pressure by increasing systemic arterial resistance and reduced cardiac output by increasing the resistances of both the systemic arterial and venous vessels.

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