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Short communication

Bosentan improves renal regional blood flow in rats with experimental congestive heart failure

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Abstract

The effects of the mixed endothelin receptor antagonist bosentan on renal regional haemodynamics were investigated in rats with aorto-caval fistula, an experimental model of congestive heart failure. A matched group of normal rats served as control. Injection of bosentan (10 mg/kg i.v.) to the rats with decompensated congestive heart failure produced an increase in cortical (+20%) and medullary (+12%) blood flow, and a decrease in vascular resistance in the cortex (−30%) and medulla (−23%), while reducing mean arterial pressure by approximately 10 mm Hg. In rats with compensated congestive heart failure and in normal animals, infusion of bosentan did not affect blood pressure and cortical perfusion. These findings indicate that 1) endothelin receptor blockade produces beneficial effects on renal haemodynamics in rats with experimental congestive heart failure and 2) endothelin-1 may be involved in the pathogenesis of renal hypoperfusion only in decompensated congestive heart failure.

Keywords: Bosentan; Renal hemodynamics; Congestive heart failure; Aorto-caval fistula

1. Introduction

Endothelin-1 is a potent vasoconstrictor peptide with prominent effects on renal haemodynamics. Administration of endothelin-1 is associated with an increase in renal vascular resistance, a decrease in total renal blood flow, and a decrease in cortical blood flow (King et al., 1989; Rubinstein et al., 1995). Increased plasma levels of endothelin-1 and a blunted renal response to endothelin-1 have been found in clinical and experimental congestive heart failure, suggesting an important role of the peptide in the pathogenesis of renal dysfunction in this condition (Cavero et al., 1990; Wei et al., 1994). Indeed, administration of a mixed endothelin receptor antagonist, bosentan, has been shown to produce hypotensive (Teerlink et al., 1994) and vasodilatator (Kiowsky et al., 1995) effects in congestive heart failure. Because of its vasoconstrictor properties, endothelin-1 could potentially contribute to the decrease in renal perfusion and sodium retention in congestive heart failure. However, there are no data about the effects of endothelin receptor blockade on renal haemodynamics in this condition. Thus, the aim of the present study was to investigate the effects of bosentan, a mixed endothelin ET_A/ET_B receptor antagonist (Clozel et al., 1994), on cortical and medullary blood flow in rats with aorto-caval fistula, an experimental model of congestive heart failure (Hoffman et al., 1988; Winaver et al., 1988).

2. Materials and methods

Experiments were performed on male Wistar rats (280–350 g) of local strain. An aorto-caval fistula was surgically created under halothane anaesthesia between the abdominal aorta and the inferior vena cava (side-to-side 1–1.2 mm), as previously reported (Winaver et al., 1988). After the operation, rats were placed in individual metabolic cages for daily measurement of the absolute rate of sodium excretion (UNaV). Based on this parameter, rats with aorto-caval fistula were further divided into two sub-

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groups: compensated (UNaV > 1500 μeq/24 h) and decompensated (UNaV < 200 μeq/24 h). Previously, we demonstrated that decompensated animals have a more advanced stage of congestive heart failure, based on the findings that these rats have an increased activity of the renin-angiotensin system, severe symptoms of systemic and pulmonary congestion, and usually die within 1 week after placement of the fistula (Winaver et al., 1988). A matched group of normal rats served as controls. Five to seven days after the operation, rats were anaesthetized with Inactin (thiobutabarbital sodium salt; RBI, Natick, MA, USA; 100 mg/kg i.p.) and prepared for the measurements of cortical and medullary blood flow by laser-Doppler flowmeter (model 4001, dual-channel; Master Perimed, Sweden) using two needle probes (Periflux 411). For measurement of cortical blood flow, the probe was placed perpendicular to the surface of the cortex, and medullary blood flow was measured by a probe inserted into the outer medulla (at a depth of 4–5 mm). The blood flow was calculated in perfusion units by multiplying the velocity by the concentration of moving blood cells. Mean arterial pressure was measured constantly by a standard pressure transducer connected to the carotid artery line. Cortical and medullary vascular resistances were calculated as mean arterial pressure/cortical blood flow and mean arterial pressure/medullary blood flow, respectively, and expressed as resistance units. An i.v. infusion of normal saline was started at the beginning of the equilibration period and continued throughout experiment at a rate of 1.5% body weight.

Three experimental groups were studied: group 1 (n = 5) consisted of normal rats in which, after a 30 min baseline period, bosentan (10 mg/kg i.v., bolus) was administered. Cortical and medullary blood flow were then recorded on a PC 486, using original software. The rats of group 2 (compensated congestive heart failure, $n = 6$) and group 3 (decompensated congestive heart failure, $n = 5$) underwent an identical protocol to group 1. For comparison of treatment values with baseline value within each group, analysis of variance was used, followed by a Dunnett test. $P < 0.05$ was considered significant.

3. Results

Baseline parameters of the normal rats and rats with compensated and decompensated congestive heart failure are shown in Table 1. Congestive heart failure rats, both compensated and decompensated, displayed a significant decrease in mean arterial pressure and cortical blood flow. In contrast, medullary blood flow in the two congestive heart failure subgroups did not differ from that of normal animals. Rats with decompensated congestive heart failure also displayed a marked diminution in daily sodium excretion.

Administration of bosentan to the decompensated rats produced a sustained and significant hypotensive response (from 76.8 ± 5.8 to 65.4 ± 4.6 mm Hg after 30 min). However, no significant changes in mean arterial pressure were observed after injection of bosentan into the normal

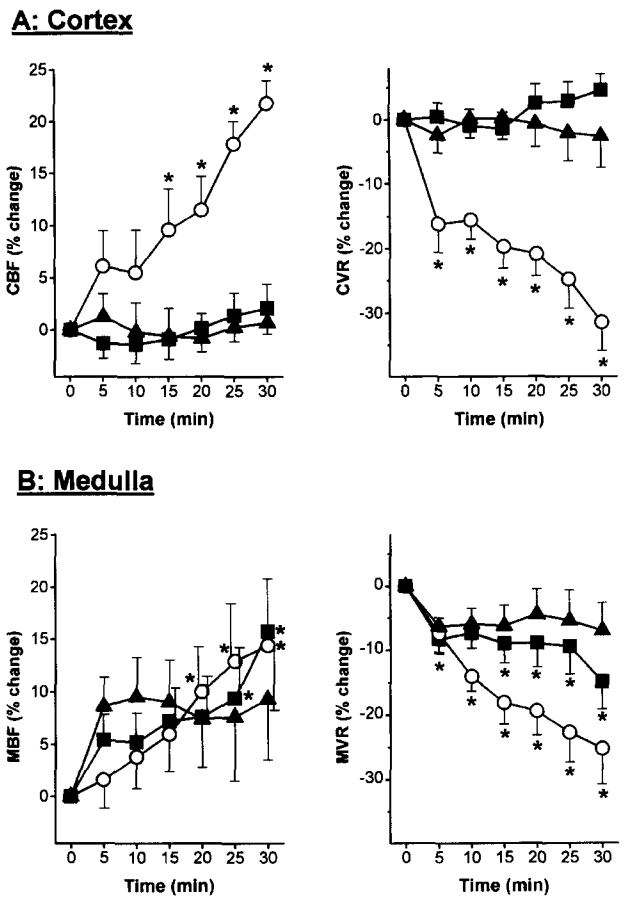

Fig. 1. Effects of bosentan on cortical and medullary haemodynamics of normal rats (solid triangle) and rats with compensated (solid square) and decompensated (open circle) congestive heart failure. Bosentan was injected at $t = 0$. * $P < 0.05$ compared to baseline value in the same group.

Table 1
Baseline parameters in normal rats and in rats with experimental congestive heart failure

	Normal	Compensated congestive heart failure	Decompensated congestive heart failure
Mean arterial pressure (mm Hg)	127.0 ± 3.3	116.5 ± 2.9 [a]	76.8 ± 5.8 [a]
Cortical blood flow (perfusion units)	332.2 ± 20.1	197.6 ± 5.8 [a]	169.6 ± 20.1 [a]
Medullary blood flow (perfusion units)	84.6 ± 4.1	77.0 ± 5.3	90.0 ± 5.4
Absolute rate of sodium excretion (μeq/24 h)	1542.0 ± 35	1788.0 ± 166	44.0 ± 17 [a]

[a] $P < 0.05$ as compared to corresponding value in normal animals.

(from 127 ± 3.3 to 123.6 ± 4.5 mm Hg after 30 min) and compensated congestive heart failure (116.5 ± 2.9 to 113.5 ± 3.2 mm Hg after 30 min) rats.

Fig. 1A depicts the influence of bosentan on cortical blood flow and cortical vascular resistance. Similar to the changes in mean arterial pressure, significant effects were observed only in the group of decompensated animals in which the endothelin receptor antagonist increased cortical blood flow and decreased cortical vascular resistance. No changes in cortical perfusion after bosentan injection were observed in normal and compensated congestive heart failure rats.

Bosentan improved medullary haemodynamics in decompensated and compensated animals, but not in normal rats (Fig. 1B). The decrease in medullary vascular resistance following bosentan administration was more prominent in the decompensated group.

4. Discussion

To our knowledge, the present study is the first demonstration of renal vasodilatator properties of bosentan in experimental congestive heart failure. The fact that bosentan infusion did not produce haemodynamic changes in normal rats is commensurate with reported data suggesting that the endothelin system is activated in advanced congestive heart failure (Wei et al., 1994).

The model of congestive heart failure which we used enabled us to distinguish between the rats with compensated and decompensated congestive heart failure. The finding of significantly lower baseline values of mean arterial pressure, cortical blood flow, and UNaV in rats with decompensated congestive heart failure attests to the more severe stage of disease in this subgroup. At the same time, rats with compensated congestive heart failure had nearly normal values of mean arterial pressure and UNaV, albeit with a decrease in cortical blood flow. Our study showed that the most prominent changes in renal and systemic haemodynamics after bosentan administration were observed only in decompensated animals. In this subgroup, administration of the endothelin receptor blocker produced a dramatic increase in cortical blood flow, despite the systemic hypotensive response induced by the drug. In conditions of profound cortical hypoperfusion observed in decompensated rats (baseline cortical blood flow was reduced by approximately 50%), these changes might be regarded as highly beneficial. Bosentan caused an increase in medullary perfusion which was of a larger magnitude in decompensated congestive heart failure. However, baseline medullary blood flow was not compromised in rats with aorto-caval fistula, suggesting that in congestive heart failure preferential perfusion to the medulla might occur (Barger, 1966). Our results indicate that endothelin-1 is involved in the pathogenesis of renal cortical hypoperfusion only in decompensated animals with severe congestive heart failure, since endothelin receptor blockade was effective only in this subgroup of rats. Other vasoconstrictor systems activated in congestive heart failure, such as renin-angiotensin and the sympathetic nervous system, may likewise contribute to the decrease in renal perfusion in congestive heart failure (Riegger and Liebau, 1982; Dzau, 1987; Van Zwieten, 1988). It is therefore possible that the latter systems are activated at an earlier stage of the disease, whereas the endothelin system assumes a significant role in more advanced stages of congestive heart failure.

In conclusion, our results demonstrate that administration of the mixed endothelin receptor antagonist bosentan increases cortical and medullary blood flow in rats with decompensated congestive heart failure. Endothelin receptor blockade could be an effective approach to the treatment of deranged renal haemodynamics in severe congestive heart failure.

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References

Barger, A.C., 1966, Renal hemodynamic factors in congestive heart failure, Ann. N.Y. Acad. Sci. 139, 276.

Cavero, P.G., W.L. Miller, D.M. Heublein, K.B. Margulies and J.C. Burnett, Jr., 1990, Endothelin in experimental congestive heart failure in the anesthetized dog, Am. J. Physiol. 259, F312.

Clozel, M., V. Breu, G.A. Gray, B. Kalina, B.-M. Loffler, K. Burri, J.M. Cassal, G. Hirth, M. Muller, W. Neidhart and H. Ramuz, 1994, Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist, J. Pharmacol. Exp. Ther. 270, 228.

Dzau, V.J., 1987, Renal and circulatory mechanisms in congestive heart failure, Kidney Int. 31, 1402.

Hoffman, A., J.C. Burnett, Jr., A. Haramati and J. Winaver, 1988, Effects of atrial natriuretic factor in rats with experimental high-output heart failure, Kidney Int. 33, 656.

King, A.J., B. Brenner and S. Anderson, 1989, Endothelin: a potent renal and systemic vasoconstrictor peptide, Am. J. Physiol. 256, F1051.

Kiowsky, W., G. Sutsch, P. Hunziker, P. Muller, J. Kim, E. Oechslin, R. Schmitt, R. Jones and O. Bertel, 1995, Evidence for endothelin-1 mediated vasoconstriction in severe chronic heart failure, Lancet 346, 732.

Riegger, A.J.G. and G. Liebau, 1982, The renin-angiotensin-aldosterone system, antidiuretic hormone and sympathetic nerve activity in an experimental model of congestive heart failure in the dog, Clin. Sci. 62, 465

Rubinstein, I., K. Gurbanov, A. Hoffman, O.S. Better and J. Winaver,

1995, Differential effect of endothelin-1 on renal regional blood flow: role of nitric oxide, J. Cardiovasc. Pharmacol. 26 (Suppl. 3), S208.

Teerlink, J.R., B.-M. Loffler, P. Hess, J.-P. Marie, M. Clozel and J.-P. Clozel, 1994, Role of endothelin in the maintenance of blood pressure in conscious rats with chronic heart failure, Circulation 90, 2510.

Wei, C.M., A. Lerman, R.J. Rodeheffer, C.G. MCGregor, R.R. Brandt, S. Wright, D.M. Heublein, P.C. Kao, W.D. Edwards and J.C. Burnett, Jr., 1994, Endothelin in human congestive heart failure, Circulation 89, 1589.

Winaver, J., A. Hoffman, J.C. Burnett, Jr. and A. Haramati, 1988, Hormonal determinants of sodium excretion in rats with experimental high-output heart failure, Am. J. Physiol. 254, R776.

Van Zwieten, P.A., 1988, Compensatory changes of sympathetic tone, the renin-angiotensin-aldosterone system, vasopressin, and ANF as potential therapeutic targets in congestive heart failure, Z. Kardiol. 77 (Suppl. 5), 67.