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European Journal of Pharmacology 369 (1999) 195–203

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Acute hemodynamic and renal effects of adrenomedullin in rats with aortocaval shunt

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Received 13 January 1999; accepted 19 January 1999

Abstract

Heart failure is characterized by increased vascular resistance and water retention. Adrenomedullin is a peptide hormone with vasodilating and diuretic properties whose efficacy in heart failure has not been well established. We used an aortocaval shunt model of moderate heart failure in rats and infused increasing doses of adrenomedullin, both as bolus injections and 20-min infusions. In controls, a clear dose-dependent 4.8 ± 1.0 to 13.6 ± 2.3 mm Hg decrease in arterial blood pressure was observed after injection of 1 μg to 30 μg of adrenomedullin. In rats with aortocaval shunt, the hypotensive responses were significantly diminished. The urine flow rate, which was diminished at baseline in rats with aortocaval shunt, was increased and normalized by adrenomedullin administration. The glomerular filtration rate increased after infusion of adrenomedullin (0.5 $\mu g/kg\ min^{-1}$) from 2.37 ± 0.25 to 3.47 ± 0.43 ml/min ($P < 0.01$) in controls and from 1.79 ± 0.33 to 2.58 ± 0.49 ($P < 0.05$) in rats with aortocaval shunt. Similarly, renal blood flow was significantly increased by adrenomedullin in both groups. Our results indicate a beneficial effect of adrenomedullin on renal function in rats with aortocaval shunt. These data suggest that adrenomedullin might be of potential therapeutic value in heart failure, without inordinately decreasing blood pressure.

Keywords: Adrenomedullin; Aortocaval shunt; Glomerular filtration rate; Diuresis; (Rat)

1. Introduction

Increased peripheral resistance, water and sodium retention are predominant features of heart failure. These characteristics have been attributed to activated renin-angiotensin and vasopressin systems and to an elevated sympathetic tone. The cardiac natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide), which are increased in heart failure, represent the major counter-regulating system. However, the efficacy of natriuretic peptides is attenuated in heart failure (Hoffman et al., 1988; Kohzuki et al., 1989). Another vasodilating and diuretic peptide, adrenomedullin, which was first isolated from human pheochromocytoma (Kitamura et al., 1993), is elevated in the plasma of heart failure patients (Jougasaki et al., 1995b; Nishikimi et al., 1995; Jougasaki et al., 1996). Recently, salubrious effects of adrenomedullin were reported in heart failure patients (Nakamura et al., 1997) and its usefulness as therapeutic agent was proposed for this condition (Rademaker et al., 1997). However, adrenomedullin's effects on the circulation and on renal function are imperfectly defined in heart failure.

Although the genetic and biochemical structures of adrenomedullin are now well known, the physiological and pathophysiological importance of this peptide hormone is still unclear (for review see Edwards et al., 1997; Kitamura and Eto, 1997). Intravenous application of human and rat adrenomedullin induced a hypotensive response and increased renal, mesenteric and hindquarter blood flow (Ishiyama et al., 1993; Kitamura et al., 1993; Gardiner et al., 1995). The mechanism of action of adrenomedullin is not entirely clear and different pathways seem to be involved. These pathways include calcitonin gene related peptide receptors (Eguchi et al., 1994; Zhao et al., 1996), nitric oxide (Hirata et al., 1995; Majid et al., 1996), cGMP (Gumusel et al., 1998) and cAMP (Kitamura et al., 1993; Edwards et al., 1996). Other effects of adrenomedullin include the inhibition of endothelin (Kohno et al., 1995) and aldosterone (Yamaguchi et al., 1996) release.

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0014-2999/99/$ - see front matter
PII: S0014-2999(99)00040-0

When administered by an intrarenal infusion, adrenomedullin induced an increase in diuresis, natriuresis, renal blood flow (Majid et al., 1996) and glomerular filtration rate (Ebara et al., 1994; Jougasaki et al., 1995a). However, when given intravenously, adrenomedullin had either no renal effect (Charles et al., 1997) or induced a diuretic response, which was accompanied by increased renal blood flow (Vari et al., 1996). Due to its biological profile, adrenomedullin might contribute to the regulation of cardiovascular tone and electrolyte homeostasis in heart failure. Whether or not the hypotensive and renal effects of adrenomedullin are preserved or diminished in heart failure is unknown. We infused increasing doses of adrenomedullin (both as bolus injections and 20-min infusions) in a rat model of shunt-induced moderate heart failure and measured the effect of adrenomedullin on blood pressure and on renal function.

2. Materials and methods

2.1. Animals

Male Wistar rats, 230–250 g, (Moellegaard Animal Farms, Schoenwalde, Germany) were fed normal rat chow and allowed free access to tap water. The animals were kept on a 12-h light–dark cycle. All experiments were performed between 7 and 12 A.M. The studies were approved by the local authorities and were performed according to the Guiding Principles in the Care and Use of Animals corresponding to American Physiological Society guidelines. The studies were performed with 10–14 animals in each group.

2.2. Shunt operation

The aortocaval shunt was induced under ether anesthesia by a modified method developed by Garcia and Diebold (1990). Briefly, a laparotomy was performed and the aorta was punctured with a 1.2 mm disposable needle (Braun Melsungen, Melsungen, Germany) distal to the renal arteries. The needle was advanced into the adjacent inferior vena cava. After temporarily clamping the vessels, the needle was withdrawn and the aortic puncture site was sealed with a drop of cyanoacrylate glue (Instant Krazy Glue, Borden, Willowdale, Ontario, Canada). Sham-operated control animals were treated identically, except that no puncture of the vessels was performed.

2.3. Hemodynamic and renal measurements

All experiments were performed under chloral hydrate anesthesia (400 mg/kg) 30 days after shunt production. A PE-50 tubing catheter was inserted via the left jugular vein into the superior vena cava for assessment of central venous pressures. Arterial blood pressure was measured by cannulating the right carotid artery and registered with a Statham P23XL transducer and a Gould AMP 4600 amplifier. Heart rate was derived from the blood pressure signal. For measurements of urine volume, sodium excretion, glomerular filtration rate and renal blood flow, a PE-50 polyethylene catheter was inserted into the bladder and urine was collected in 20-min periods. Sodium chloride (0.9%) was infused at a flow rate of 2 ml/h throughout the whole experiment. Previous experiments with a flow rate of 2 ml/h had shown that renal excretory function as well as hemodynamic parameters remained unchanged throughout the duration of the experiment. Surgery was followed by a 40-min equilibration period before baseline values were obtained during the following 20 min. Urine was collected in 20-min periods and hemodynamic parameters were registered continuously. Urinary sodium concentration was measured by flame photometry.

2.4. Measurement of glomerular filtration rate and renal blood flow

The right femoral artery was cannulated for infusion of 8% inulin and 1% para-aminohippurate in isotonic saline at a rate of 2 ml/h as described previously (Zhang et al., 1994). Blood samples necessary for determination of inulin and para-aminohippurate were taken from the femoral artery at the midpoint of each collection period. Inulin and para-aminohippurate were analyzed by spectrophotometry for calculation of glomerular filtration rate and renal blood flow. Renal vascular resistance was calculated as mean arterial pressure divided by renal blood flow.

2.5. Determination of cAMP and cGMP excretion

Urinary cAMP was measured by protein binding assay using binding protein isolated from bovine adrenal glands (Gilman, 1970). cGMP was determined by a specific radioimmunoassay (Richman et al., 1980) with antibodies kindly donated by Dr. P. Hamet, Montreal, Canada.

2.6. Administration of adrenomedullin: bolus injections

After baseline values had been obtained, synthetic human adrenomedullin (BioTez, Berlin, Germany) was injected intravenously as a bolus in cumulative doses of 1 μg, 3 μg, 10 μg and 30 μg (dissolved in 200 μl NaCl 0.9%) in 20-min intervals in sham- and shunt-operated rats ($n = 10–12$ in each group). The arterial blood pressure had returned to baseline values before the following bolus injection of adrenomedullin.

2.7. Administration of adrenomedullin: continuous infusions

In a separate protocol in another set of rats with aortocaval shunt or sham-operation ($n = 10–14$ in each group),

the effect of continuous infusion of adrenomedullin was assessed. After baseline values had been obtained, synthetic human adrenomedullin (0.05, 0.1, 0.5 and 1 μg/kg min^{-1}) was infused intravenously for consecutive 20-min periods in sham- and shunt-operated rats.

2.8. Statistical analysis

Differences between groups were evaluated with the unpaired or paired Student's *t*-test or the two-way analysis of variance (ANOVA) for repeated measurements with a posteriori comparison (Bonferroni), whenever appropriate. The significance level was set at $P < 0.05$. All data are expressed as means ± S.E.M. (standard error of the mean).

3. Results

3.1. Effect of shunt on heart weight and hemodynamic parameters

Heart weight increased significantly after 30 days of aortocaval shunt (Table 1) while the total body weight was unchanged. Central venous pressure was elevated in rats with aortocaval shunt (5.5 ± 0.8 vs. 2.2 ± 0.8 mm Hg, $P < 0.05$). No significant differences in arterial blood pressure and heart rate were determined at baseline measurements.

3.2. Effect of bolus injection of adrenomedullin

3.2.1. Hypotensive effect of bolus injection of adrenomedullin

In control rats, bolus injections of adrenomedullin (1 μg–10 μg) decreased arterial blood pressure in a dose-dependent manner (Fig. 1a). A maximal hypotensive effect of 14.0 ± 3.0 mm Hg was reached with a dose of 10 μg of adrenomedullin while a higher dose (30 μg) did not induce a stronger hypotensive effect. When the area under

Table 1
Heart weight and hemodynamic parameters

	Control	Shunt
Heart weight (g)	1.1 ± 0.1	1.5 ± 0.1[a]
Body weight (g)	316 ± 8	319 ± 8
Systolic blood pressure (mm Hg)	105 ± 3	99 ± 4
Diastolic blood pressure (mm Hg)	64 ± 3	57 ± 2
Mean arterial pressure (mm Hg)	78 ± 3	71 ± 2
Central venous pressure (mm Hg)	2.2 ± 0.8	5.5 ± 0.8[a]
Heart rate (bpm)	406 ± 15	393 ± 14

Heart and body weights as well as hemodynamic parameters of sham- and shunt-operated rats are shown.
Data are presented as means ± S.E.M., $n = 10–12$.
[a] $P < 0.05$.

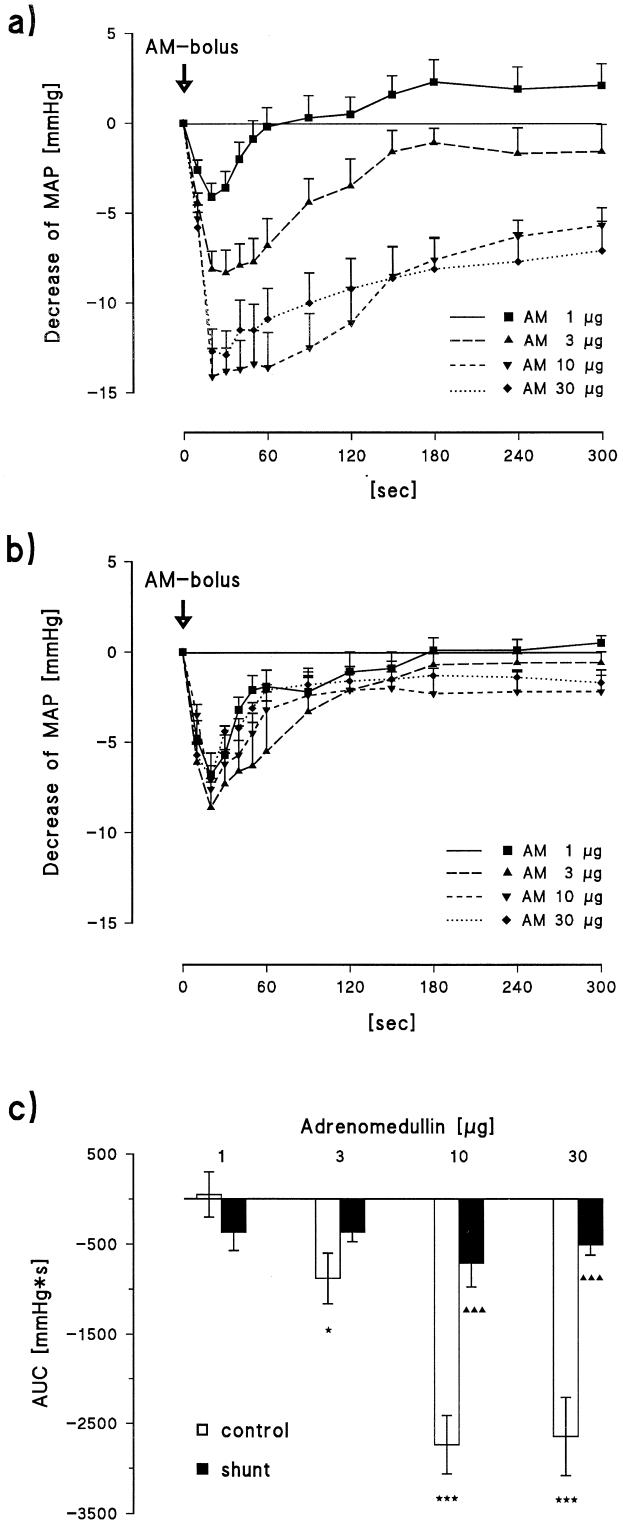


Fig. 1. The time course of the hypotensive response to increasing doses of bolus injections of adrenomedullin is shown for controls (a) and shunt-operated rats (b). In (c), the area under the curve (AUC) for the decrease in mean arterial blood pressure is indicated for sham-operated controls and rats with aortocaval shunt. Data are presented as means ± S.E.M., $n =$ 10–12, ▲▲▲ $P < 0.001$ (vs. control rats), * $P < 0.05$, *** $P < 0.001$ (vs. 1 μg).

the curve of the blood pressure response was evaluated (Fig. 1c), similar results were obtained. In rats with aortocaval shunt, the effect of low doses (1 μg and 3 μg) of adrenomedullin on blood pressure was not different, compared to sham-operated controls (Fig. 1b and c). However, the hypotensive effect of 10 μg and 30 μg of adrenomedullin was significantly blunted in rats with aortocaval shunt, compared to control rats. The maximal blood pressure decrease induced by 30 μg was 8.5 ± 2.0 mm Hg in shunt-operated rats and 13.6 ± 2.3 mm Hg in control rats ($P < 0.01$). In both sham- and shunt-operated rats, the maximal hypotensive effect of adrenomedullin was observed 20 s after intravenous administration. However, the hypotensive effects of high doses of adrenomedullin (10 μg and 30 μg) were of shorter duration in rats with aortocaval shunt than in control rats (Fig. 1b). The calculation of the area under the curve (AUC) of the blood pressure response (Fig. 1c) confirmed the blunted hypotensive response in shunt-operated rats to adrenomedullin (AUC after 30 μg: 509 ± 108 vs. 2639 ± 435 mm Hg s in control rats, $P < 0.001$).

3.2.2. Renal effects of bolus injection of adrenomedullin

Intravenous infusion of adrenomedullin in sham-operated rats induced an increase in urine volume (from 396 ± 39 μl/20 min at baseline to 575 ± 44 μl/20 min, $P < 0.01$) already at the lowest dose (1 μg, Fig. 2a). At higher doses, no further increase in urine flow was observed in control rats. In rats with aortocaval shunt, baseline urine flow rate was less than in control rats. The lowest dose of adrenomedullin did not significantly change the urine flow rate. At higher doses (3 μg and more), adrenomedullin induced a significant increase in urine flow, which reached levels that were not different from those measured in control rats. Thus, adrenomedullin was able to normalize the urine flow rate in rats with aortocaval shunt. The basal sodium excretion was lower in rats with aortocaval shunt, compared to sham-operated controls ($P < 0.05$, Fig. 2b). Intravenous bolus administration of adrenomedullin did not significantly change the sodium excretion in either group.

To further elucidate the mechanism by which adrenomedullin exerts its diuretic effects in rats with aortocaval shunt, we measured glomerular filtration rate and renal blood flow. The glomerular filtration rate did not significantly change after bolus injections of adrenomedullin (Fig. 3a). The renal blood flow was lower in rats with aortocaval shunt than in controls (2.9 ± 0.6 vs. 4.9 ± 0.6 ml/min, $P < 0.05$, Fig. 3b). Bolus administration of adrenomedullin did not influence the renal blood flow in sham-operated rats. In contrast, in rats with aortocaval shunt, renal blood flow showed a dose-dependent increase (from 2.9 ± 0.6 to 5.1 ± 0.5 ml/min after 10 μg, $P < 0.05$). Thus, the renal blood flow was normalized in rats with aortocaval shunt by bolus administration of adrenomedullin. The renal vascular resistance decreased

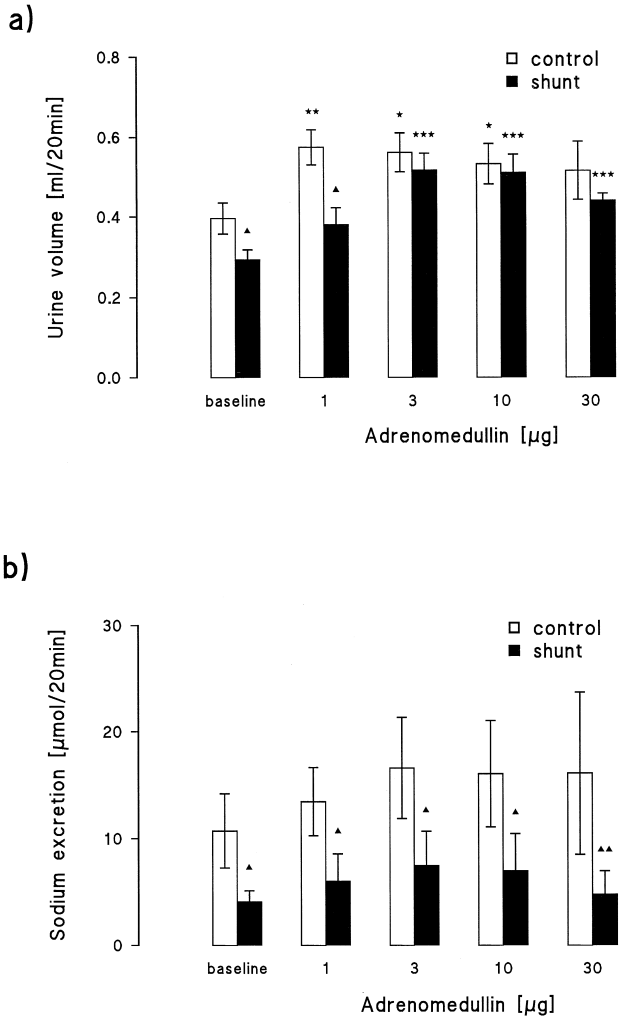


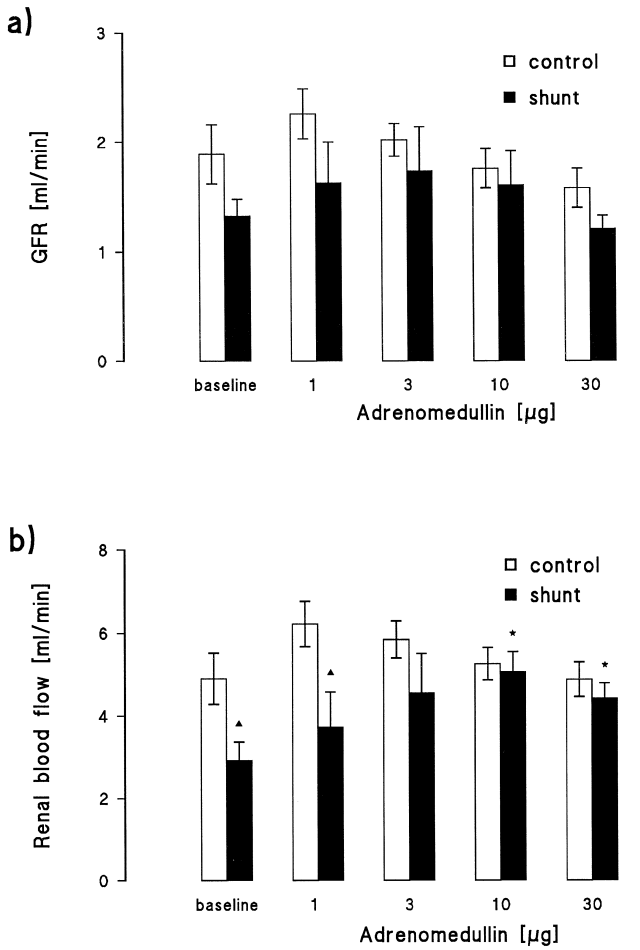
Fig. 2. The diuretic (a) and the natriuretic (b) responses to cumulative doses of bolus injections of adrenomedullin are shown for sham-operated controls and rats with aortocaval shunt. Data are presented as means ± S.E.M., $n = 10–12$, ▲ $P < 0.05$, ▲▲ $P < 0.01$ (vs. control rats); * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (vs. baseline).

significantly in controls (after 10 μg) and in rats with aortocaval shunt at the highest doses of adrenomedullin ($P < 0.05$, Fig. 3c), compared to baseline values.

3.2.3. Effect of adrenomedullin on urinary cGMP and cAMP

We tested whether or not the renal effects of adrenomedullin were reflected by an increased excretion of cAMP or cGMP. In shunt-operated rats, basal cGMP excretion was higher than in control rats (5240 ± 1050 vs. 1890 ± 300 pmol/20 min, $P < 0.05$, Fig. 4a). Adrenomedullin did not significantly influence cGMP excretion in either group. In contrast, cAMP excretion increased after bolus injections of 10 μg and 30 μg of adrenomedullin in control rats ($P < 0.05$, Fig. 4b), whereas the cAMP increase in rats with aortocaval shunt failed to

reach significance ($P = 0.06$). The cAMP excretion was not different between sham- and shunt-operated rats.



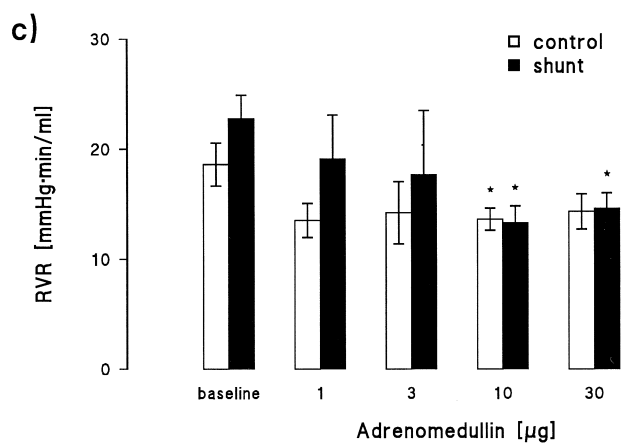


Fig. 3. The effect of cumulative doses of bolus injections of adrenomedullin on glomerular filtration rate (GFR) (a) and renal blood flow (b) are shown for sham-operated controls and rats with aortocaval shunt. The renal vascular resistance (RVR) is shown in (c). Data are presented as means ± S.E.M., $n = 10–12$, ▲ $P < 0.05$ (vs. control rats), * $P < 0.05$ (vs. baseline).

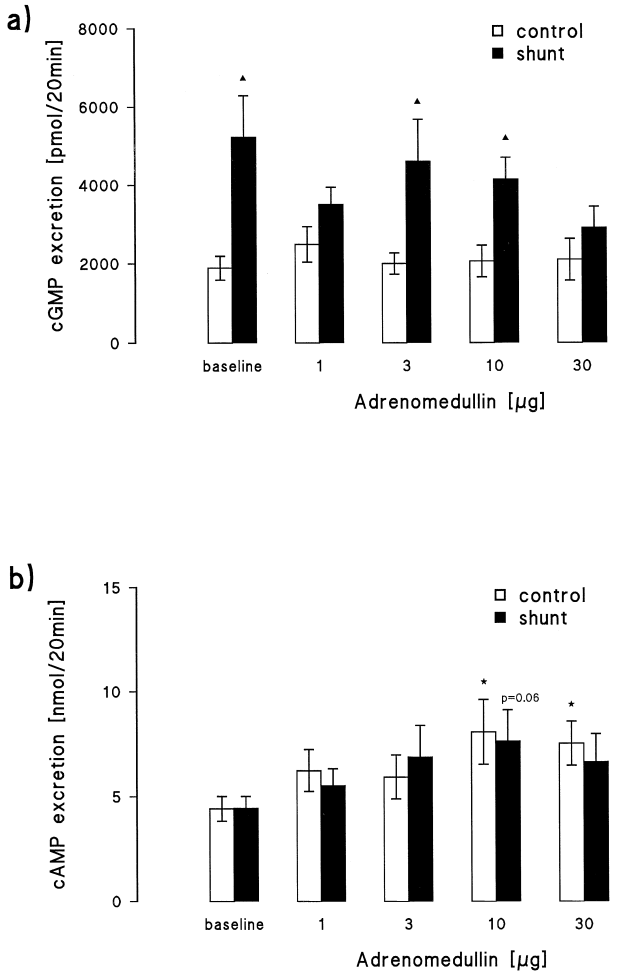


Fig. 4. The excretion of cGMP (a) and cAMP (b) is shown at baseline and after cumulative doses of adrenomedullin for shunt- and sham-operated rats. Data are presented as means ± S.E.M., $n = 10–12$, ▲ $P < 0.05$ (vs. control rats), * $P < 0.05$ (vs. baseline).

3.3. Effect of continuous infusion of adrenomedullin

3.3.1. Hemodynamic effects of continuous infusion of adrenomedullin

In order to test whether the beneficial effect of acute bolus injections of adrenomedullin in rats with aortocaval shunt could be confirmed by longer application and thus be of more potential clinical relevance, 20-min infusions of adrenomedullin were performed. Adrenomedullin elicited a dose-dependent hypotensive effect in controls and in rats with aortocaval shunt (Fig. 5a). The decrease in mean arterial blood pressure was blunted in rats with shunt (maximal decrease: 13.8 ± 1.9 mm Hg), compared to controls (21.6 ± 3.2 mm Hg, ANOVA: $P < 0.001$). The renal blood flow, which was lower in rats with aortocaval shunt, increased in both groups with infusion of adrenomedullin (Fig. 5b, $P < 0.001$). The renal vascular resistance after infusion of adrenomedullin was significantly reduced in both, controls and rats with aortocaval shunt (Fig. 5c).

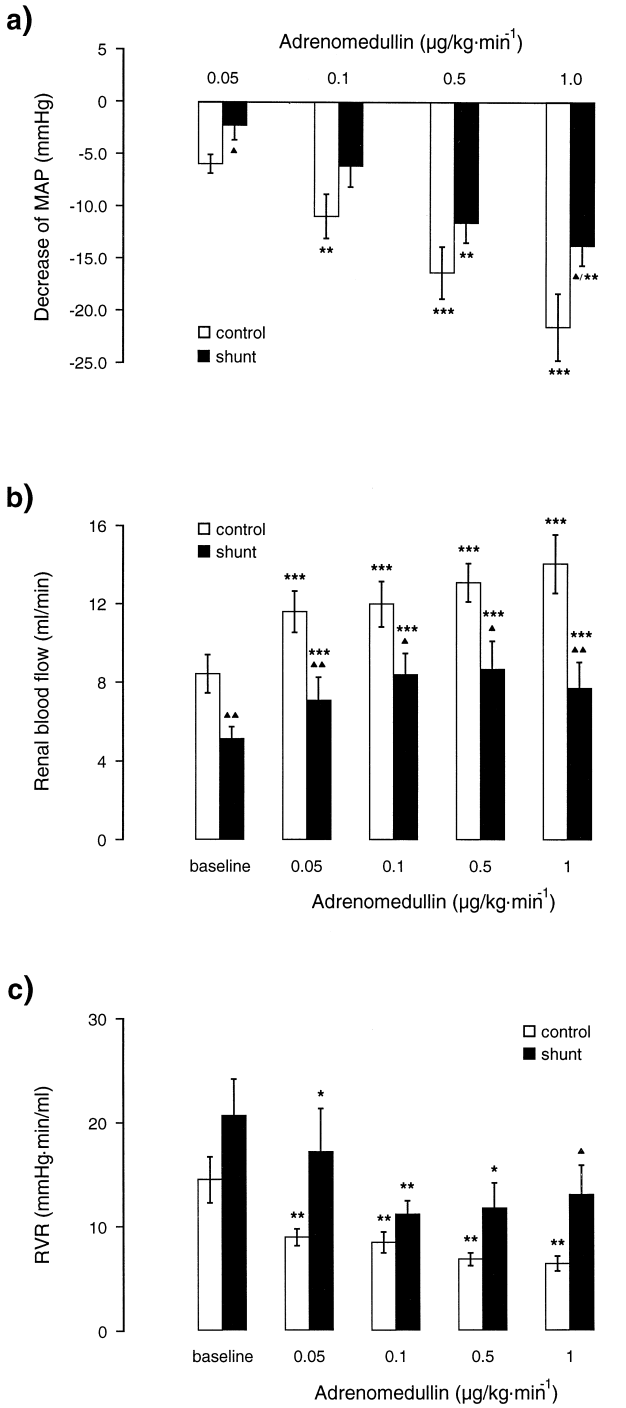


Fig. 5. The influence of increasing doses of adrenomedullin infusion on mean arterial pressure (MAP) (a), renal blood flow (b) and on the renal vascular resistance (RVR) are shown for controls and shunt-operated rats. Data are presented as means ± S.E.M., $n = 10–14$, $^{\blacktriangle}P < 0.05$, $^{\blacktriangle\blacktriangle}P < 0.01$ (vs. control rats), $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (vs. baseline).

3.3.2. Renal effects of continuous infusion of adrenomedullin

Similar to bolus injections of adrenomedullin, a continuous infusion increased the urine flow in sham- and shunt-operated rats (Fig. 6a). In control rats, no dose-dependency could be observed with the maximal increase in urine volume occurring already at the dose of 0.05 µg/kg min^{-1}. The urine flow rate, which was lower in rats with aortocaval shunt, was normalized (to baseline levels of controls) with adrenomedullin. Sodium excretion (Fig. 6b) was significantly enhanced by about 50% in controls and

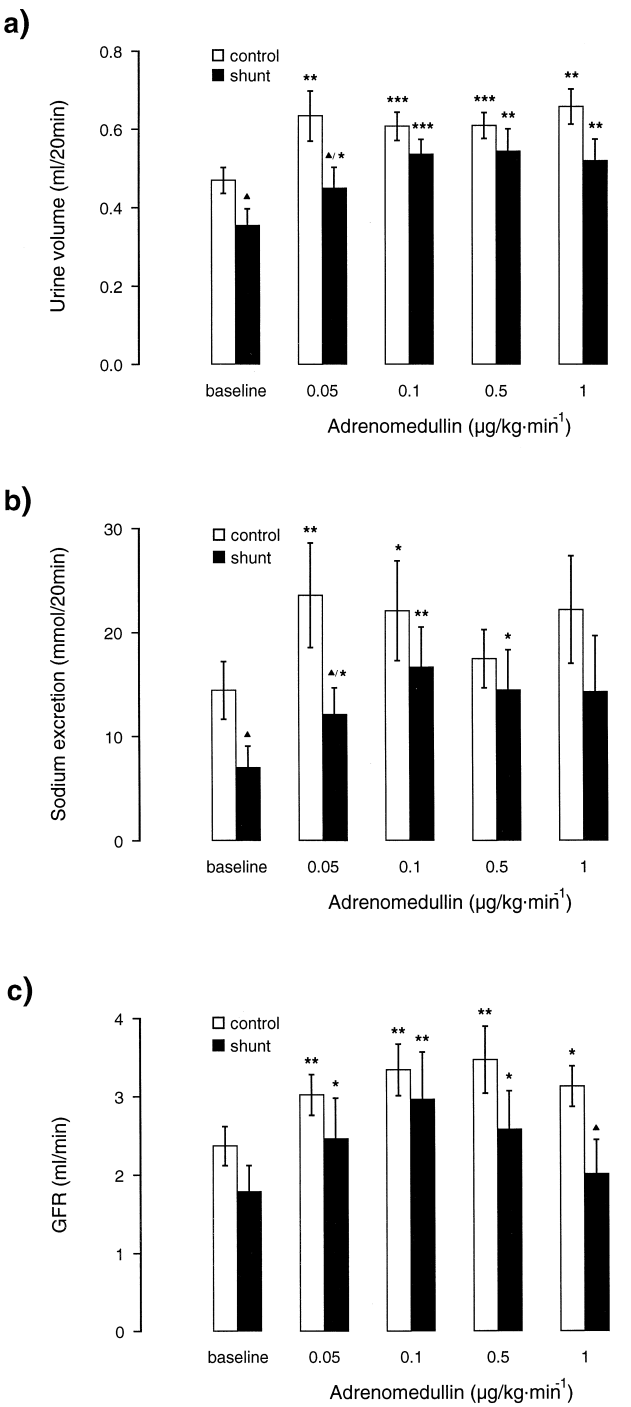


Fig. 6. The effect of increasing doses of adrenomedullin infusion on urine volume (a), sodium excretion (b) and on the glomerular filtration rate (GFR) (c) are shown for sham-operated controls and rats with aortocaval shunt. Data are presented as means ± S.E.M., $n = 10–14$, $^{\blacktriangle}P < 0.05$ (vs. control rats); $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (vs. baseline).

by about 100% in rats with aortocaval shunt by infusion of lower doses of adrenomedullin (0.5 and 1.0 $\mu g/kg\ min^{-1}$) without a further increase at higher doses. Adrenomedullin administered as continuous infusion was able to significantly increase the glomerular filtration rate in both groups (Fig. 6c).

4. Discussion

We showed that intravenous administration of adrenomedullin normalized the decreased renal blood flow and urine flow rate in rats with aortocaval shunt. The decrease in renal vascular resistance by adrenomedullin was accompanied by an attenuated hypotensive response, suggesting that adrenomedullin might be useful in the treatment of water retention in heart failure. The blunted hypotensive response along with preserved renal efficacy in our heart failure model was observed both after short-acting bolus injections and after continuous infusions of adrenomedullin.

The vasorelaxant and hypotensive properties of adrenomedullin have been described previously (Kitamura et al., 1993; Santiago et al., 1995). Similar to our results, the maximal hypotensive response was observed within the first minute after administration of adrenomedullin with a duration of about 5 min. In higher doses, the duration of adrenomedullin's hypotensive effect increased (Kitamura et al., 1993; Santiago et al., 1995).

Our's is the first report to describe an attenuated blood pressure response to adrenomedullin in experimental heart failure, compared to normal rats. The vasodilating effects of adrenomedullin in heart failure have been documented by forearm blood flow measurements in human subjects (Nakamura et al., 1997). In patients with heart failure, the vasodilatory effects were diminished, which is consistent with the responses we observed. The hemodynamic responses to adrenomedullin were previously compared between spontaneously hypertensive rats and Wistar–Kyoto rats. No differences in hypotensive response or regional blood flow were observed (He et al., 1995; Ishiyama et al., 1995). Recently, chronic administration of adrenomedullin in Wistar and two-kidney, one-clip rats did not induce a different hypotensive effect between both groups (Khan et al., 1997). The reason for the attenuated blood pressure response we observed in our model of moderate heart failure is not entirely clear. Differences in basal plasma concentrations of adrenomedullin could have influenced the effect of adrenomedullin. Diminished responsiveness to adrenomedullin could be related to down-regulation of its receptors. However, no such reports are available yet. Alternatively, the predominance of vasoconstricting systems like the renin-angiotensin system or the sympathetic nervous system, which are both activated in this model (Willenbrock et al., 1996, 1997), could limit the extent of the hypotensive response. In addition, differences in basal arterial blood pressures (although not significant in our study) might have affected the extent of the hypotensive response.

The importance of adrenomedullin in regulating vascular tone and water and electrolyte homeostasis is a matter of debate (Edwards et al., 1997; Kitamura and Eto, 1997). Elevated adrenomedullin plasma levels have been described in heart failure (Jougasaki et al., 1995b; Nishikimi et al., 1995; Jougasaki et al., 1996), after myocardial infarction (Kobayashi et al., 1996) and in renal failure (Eto et al., 1996). The increased plasma concentrations of this diuretic and vasodilating peptide do not prevent water retention nor increased peripheral resistance in heart failure, raising the possibility that the efficacy of the adrenomedullin system might be attenuated in volume retaining disorders, similar to the blunted efficacy of the natriuretic peptide system (Hoffman et al., 1988; Kohzuki et al., 1989).

Analysis of the renal mechanisms by intra-arterial renal infusion of adrenomedullin had demonstrated that the renal excretory responses were induced by an increase in glomerular filtration rate and paralleled by an enhanced excretion of cAMP (Ebara et al., 1994; Hirata et al., 1995). When the integrated renal and hemodynamic effects of intravenous administration of adrenomedullin were tested, the glomerular filtration rate was unchanged while renal blood flow increased (Vari et al., 1996; Hjelmquvist et al., 1997). In our study, glomerular filtration rate was not modified by bolus injections, but increased with continuous infusion of adrenomedullin, indicating that a prolonged exposure to adrenomedullin is required to influence glomerular filtration. In contrast, renal blood flow increased with bolus injections of adrenomedullin only in our heart failure model, while a continuous infusion augmented renal blood flow also in control animals. These data indicate that instead of being blunted, the renal effects of adrenomedullin were preserved or even more pronounced in experimental heart failure. The observation that the maximal renal effect was observed already at low doses, when only a minor hypotensive effect was present, suggest that prolonged low-dose infusions of adrenomedullin might be appropriate for potential application in heart failure.

A beneficial effect of adrenomedullin has previously been suggested in sheep with pacing-induced heart failure, but no controls were investigated in that study (Rademaker et al., 1997). Our aim was to analyze whether the renal and hemodynamic effects of adrenomedullin were preserved in rats with aortocaval shunt, a model which is characterized by a lower urine flow rate and a diminished renal blood flow, compared to normal rats. The main observation was the normalization of renal blood flow and the improvement in urine flow rate to normal levels in rats with aortocaval shunt. The renal vascular resistance decreased to the same degree in control and shunt-operated rats. This finding suggests that the response of the renal vasculature is not

blunted, even in the presence of an attenuated systemic hypotensive response. This novel observation could be related to regional differences in the vasodilating effects of adrenomedullin (He et al., 1995), which in turn would improve renal perfusion and thus represent an additional beneficial mechanism for adrenomedullin in heart failure.

The diminished hypotensive response to adrenomedullin in the shunt-induced model of heart failure is not unique for this peptide hormone: a blunted response has been described for nitric oxide mediated vasodilation (Abassi et al., 1997) as well as for atrial natriuretic peptides (Hoffman et al., 1988) and brain natriuretic peptide (Hoffman et al., 1991). However, in contrast to the natriuretic peptides, which lose their renal efficacy in parallel with its blunted hypotensive effects, the renal effects of adrenomedullin were not diminished, indicating a specific effect of adrenomedullin.

Bolus injections of adrenomedullin showed a non-significant tendency on sodium excretion, while continuous infusion increased natriuresis in controls and rats with aortocaval shunt. It should be noticed, however, that this parameter shows a large variation and we do not have any indications that adrenomedullin might induce an increased free water clearance or exert any effect via inhibition of vasopressin.

The renal effect of adrenomedullin is at least partially mediated by cAMP (Kitamura et al., 1993; Edwards et al., 1996). The excretion of cGMP, the second messenger of the atrial natriuretic peptide and nitric oxide, was unchanged after administration of adrenomedullin, indicating that adrenomedullin's effect was not mediated by cGMP. The increased cAMP excretion after adrenomedullin administration supports the notion that cAMP might be involved in the mediation of adrenomedullin's renal effects. Since the cAMP excretion was not different between controls and rats with aortocaval shunt, down-regulation of the renal adrenomedullin receptors seems unlikely.

In summary, intravenous bolus injection and continuous infusion of adrenomedullin in rats with aortocaval shunt normalized the diminished renal blood flow and reversed the attenuated urine flow rate to normal. The combination of increased renal blood flow, in the face of a lesser propensity to reduce blood pressure, is intriguing and of potential interest in the management of heart failure.

Acknowledgements

The authors thank Astrid Schiche, Jeannette Mothes, Rita Günzel and Inge Beyersdörfer for excellent technical assistance and secretarial help. The authors thank Friedrich C. Luft, Berlin, Germany, for critically reviewing and editing the manuscript. This project is supported by a grant from the Deutsche Forschungsgemeinschaft (DFG) to R.W. (Wi 814/7-1).

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