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Effects of a synthetic rat adrenomedullin on regional hemodynamics in rats

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Abstract

The effects of rat adrenomedullin, a novel vasorelaxant peptide, on systemic and regional hemodynamics were examined in conscious Sprague Dawley (SD) rats and spontaneously hypertensive rats (SHR). The intravenous infusion of adrenomedullin at rates of 1.67 and 5 μg/kg per min decreased the mean arterial pressure in a dose-dependent fashion in both types of rats. Adrenomedullin at a rate of 5 μg/kg per min increased the heart rate and cardiac output. As a result, the total peripheral resistance significantly decreased. With regards to the regional hemodynamics, adrenomedullin significantly increased the flow rates in the lungs, heart, spleen, kidneys, adrenal glands and small intestine of SHR. The flow rates in the brain and skin did not change and the flow rates in the skeletal muscle and testis were decreased. These regional hemodynamic changes were also observed in SD rats and there was no qualitative difference in the regional responses to adrenomedullin between SHR and SD rats. Thus, adrenomedullin predominantly increased the flow rates in organs in which adrenomedullin gene was highly expressed. It therefore seems that adrenomedullin may act as a local vasodilatory hormone rather than as a circulatory hormone.

Keywords: Adrenomedullin; Hemodynamics, regional; Spontaneously hypertensive rat (SHR); Microsphere

1. Introduction

Adrenomedullin is a novel vasorelaxant peptide recently isolated from the acid extract of human pheochromocytoma (Kitamura et al., 1993a). The peptide, a 52-amino-acid residues, has one intramolecular disulfide bond and shows a slight homology with the calcitonin gene related peptide (CGRP) and amylin (Kitamura et al., 1993a,b). Adrenomedullin is also identified in the normal adrenal medulla and circulates in healthy human plasma (Kitamura et al., 1994a). In addition, it has been reported that human adrenomedullin mRNA was found to be highly expressed in several tissues including the adrenal medulla, ventricle, lung and kidney, but mRNA expression in brain was very slight (Kitamura et al., 1993b). Adrenomedullin has been shown to possess marked cardiovascular activity. In vivo studies have demonstrated that adrenomedullin is a potent vasodilator and a hypotensive peptide (Ishiyama et al., 1993; Nuki et al., 1993). Recently, the amino acid sequences of rat and porcine adrenomedullins were determined. The rat adrenomedullin as well as human adrenomedullin has been shown to possess marked vasodilatory activity (Kitamura et al., 1994a; Sakata et al., 1993). Thus, it can be considered that adrenomedullin plays an important role in the regulation of systemic and regional hemodynamics. However, no information is available yet about the hemodynamic action of adrenomedullin except its hypotensive action. Therefore, this study was undertaken to determine the hemodynamic effects of adrenomedullin in conscious, unrestrained normotensive and hypertensive rats.

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2. Materials and methods

2.1. General procedure

20–22-week-old spontaneously hypertensive rats (SHR; Charles River, Japan) and 8-week-old Sprague Dawley (SD) rats were used in the present investigation. They were placed on a normal chow until the time of the experiment. Under light sodium pentobarbital anesthesia, polyethylene catheters (PE-50) were placed in the femoral artery for the sampling of reference blood and measurement of systemic arterial pressure and in the femoral vein for the infusion of adrenomedullin. Another catheter was also placed in the left ventricle via the right carotid artery for the injection of microspheres. These catheters were filled with heparinized saline (100 IU/ml) and exteriorized through a cutaneous tunnel at the back of the neck after confirmation of their tip locations by pressure tracings. Animals were allowed to recover for 24 h before initiation of the experimental procedures. Experiments were performed in a temperature controlled room at 23°C.

2.2. Effects of the intravenous infusion of adrenomedullin on mean arterial pressure in SD rats and SHR

The catheterized SD rat or SHR was placed in a small plastic chamber. The femoral arterial catheter was connected to the pressure transducer, and systemic arterial pressure was continuously recorded on a multichannel polygraph (Nihondenki-Sanei, Japan). Adrenomedullin was then infused intravenously at a rate of 1.67 or 5 μg/kg per min and systemic arterial pressure was recorded over the following 30 min period.

2.3. Measurements of systemic and regional hemodynamics

Radioactive microspheres were used to measure the cardiac output and regional blood flow, according to the method of Tsuchiya et al. (1978) and Ishise et al. (1980). Two different radionucleide-labelled microspheres (^{141}Ce and ^{85}Sr, New England Nuclear, USA), 15 ± 3 μm in diameter, were used. Following a 60 min stabilization period for the rat to adapt to the chamber, 0.25 ml of saline solution containing 75 000 microspheres was injected into the left ventricle. The injection procedure was carried out over a 15 s period. Arterial blood samples for reference blood were obtained using a withdrawal pump at a rate of 0.55 ml/min starting immediately before the injection of the microspheres and ending 60 s after. 10 min after the first injection of microspheres, adrenomedullin was infused intravenously at a rate of 5 μg/kg per min. Systemic arterial pressure and heart rate were stabilized about 10 min after the start of adrenomedullin infusion and a second injection of microspheres was performed. After termination of the second injection of microspheres, the animal was killed by the injection of pentobarbital sodium. The brain, lungs, heart, liver, spleen, adrenal glands, kidneys, stomach, intestines (small and large), mesenterial fat, skin, hindlimb skeletal muscles and testis were removed and weighed. Due to the relatively low blood flow to the skin and skeletal muscles, at least 5 g of these tissues were removed. Skin and skeletal muscle samples contained 300–400 microspheres from each microsphere injection and all other tissues contained over 500 microspheres, except for the adrenal glands. Adequate mixing and distribution of the microspheres was confirmed by another series of experiments in which renal blood flow of the right kidney was similar to that of the left kidney. The activities of each batch of microspheres in stock solution, reference blood and tissue samples were analyzed using a gamma scintillation counter.

The cardiac output was calculated as follows: cardiac output (ml/min) = (injected isotope counts (cpm) / reference blood counts (cpm)) $\times$ 0.55 (ml/min). Total injected radioactivity was obtained by subtracting the residual radioactivity from the radioactivity before injection. Absolute organ flow was calculated as follows: organ blood flow (ml/min) = (organ isotope counts (cpm)/reference blood counts (cpm)) $\times$ 0.55 (ml/min). In the present paper the organ blood flow is expressed as ml/g of organ/min.

2.4. Statistical analysis

Results are expressed as means $\pm$ S.E.M. The data were evaluated using paired or nonpaired Student's t-test, where P values less than 0.05 were regarded as significant.

2.5. Chemicals

In the present study we used a synthetic rat adrenomedullin which was purchased from Protein Research Foundation (Osaka, Japan).

3. Results

3.1. Effects of adrenomedullin on mean arterial pressure in SD rats and SHR

The mean arterial pressure of SD rats and SHR at the start of the study was 118 ± 5 and 176 ± 7 mmHg, respectively. Fig. 1 shows the time course of mean arterial pressure. Neither mean arterial pressure was changed by the vehicle, but the intravenous infusion of adrenomedullin at rates of 1.67 and 5 μg/kg per min

Table 1
Effects of adrenomedullin on systemic hemodynamics in Sprague Dawley (SD) rats and spontaneously hypertensive rats (SHR)

	SD rat ($n = 7$)		SHR ($n = 9$)	
	Control	Adrenomedullin (5 μg/kg per min, i.v.)	Control	Adrenomedullin (5 μg/kg per min, i.v.)
Mean arterial pressure (mmHg)	121 ± 4	107 ± 3 [b]	175 ± 5 [a]	137 ± 3 [b]
Cardiac output (ml/min)	127 ± 11	160 ± 12 [b]	114 ± 3	156 ± 6 [b]
Heart rate (beats/min)	379 ± 18	444 ± 10 [b]	413 ± 14 [a]	486 ± 7 [b]
Total peripheral resistance (mmHg · min/ml)	0.97 ± 0.08	0.71 ± 0.05 [b]	1.54 ± 0.05 [a]	0.89 ± 0.05 [b]

[a] Significant difference between SD rats and SHR at basal condition; [b] significant difference between control and experimental periods ($P < 0.05$).

decreased mean arterial pressure in a dose-dependent fashion in both SD rats and SHR (Fig. 1). In both groups of rats, the mean arterial pressure started to decrease immediately after the start of adrenomedullin infusion and reached a steady state within 5 min after the infusion. Percent decreases of mean arterial pressure in SD rats and SHR were 12 ± 4 and 26 ± 5% at a rate of 5 μg/kg per min, respectively. In comparison to changes of mean arterial pressure in SHR, those in SD rats were weaker. Based on these results, adrenomedullin was infused intravenously at a rate of 5 μg/kg per min and the regional hemodynamics were measured 10 min after the start of adrenomedullin infusion.

3.2. Effects of adrenomedullin on systemic hemodynamics

Effects of adrenomedullin on mean arterial pressure, cardiac output, heart rate and total peripheral resistance (TPR) are tabulated in Table 1. In the basal condition, mean arterial pressure was significantly higher in SHR than in SD rats. Since no significant differences in cardiac output were observed between SD rats and SHR, the elevated arterial pressure in SHR could be accounted for by the significantly elevated TPR as compared to SD rats.

After the start of adrenomedullin infusion at a rate of 5 μg/kg per min in both groups of rats, the mean arterial pressure decreased with maximum reduction within 5 min after the start of infusion, and this low level was maintained during the continuous infusion. Cardiac output increased in both groups along with significant increases in heart rate. Percent increases of cardiac output in SD rats and SHR were 23 ± 6 and 36 ± 5%, respectively. Thus, the increase in cardiac output was more evident in SHR. The basal values of TPR in SHR were significantly higher than those in SD rats, however, the infusion of adrenomedullin reduced the TPRs in SHR to the basal values of the TPR in SD rats (Table 1).

Table 2
Effects of adrenomedullin on regional blood flow in Sprague Dawley (SD) rats and spontaneously hypertensive rats (SHR)

	SD rat ($n = 7$)		SHR ($n = 9$)	
	Control	Adrenomedullin (5 μg/kg per min, i.v.)	Control	Adrenomedullin (5 μg/kg per min, i.v.)
Brain	0.81 ± 0.09	0.78 ± 0.06	0.90 ± 0.06	0.91 ± 0.07
Lung	0.69 ± 0.12	1.16 ± 0.18 [b]	0.51 ± 0.06	0.95 ± 0.11 [b]
Heart	4.79 ± 0.24	7.21 ± 0.31 [b]	6.01 ± 0.54 [a]	9.56 ± 0.59 [b]
Liver	1.31 ± 0.03	1.57 ± 0.10 [b]	1.00 ± 0.07 [a]	1.60 ± 0.12 [b]
Liver (hepatic artery)	0.09 ± 0.02	0.26 ± 0.03 [b]	0.07 ± 0.01	0.23 ± 0.03 [b]
Liver (portal vein)	1.22 ± 0.03	1.20 ± 0.07	0.93 ± 0.06 [a]	1.37 ± 0.12 [b]
Spleen	2.70 ± 0.27	5.42 ± 0.33 [b]	1.76 ± 0.20 [a]	4.30 ± 0.57 [b]
Kidney	6.59 ± 0.31	7.90 ± 0.39 [b]	5.53 ± 0.29 [a]	8.52 ± 0.41 [b]
Adrenal gland	4.12 ± 0.61	6.21 ± 0.55 [b]	3.20 ± 0.22	9.95 ± 0.94 [b]
Stomach	1.33 ± 0.09	1.54 ± 0.17	0.81 ± 0.08 [a]	1.39 ± 0.10 [b]
Small intestine	1.16 ± 0.17	1.02 ± 0.13	1.19 ± 0.11	1.71 ± 0.15 [b]
Large intestine	1.39 ± 0.10	1.26 ± 0.14	0.90 ± 0.07	1.09 ± 0.15
Mesenterium	0.69 ± 0.05	0.67 ± 0.02	0.43 ± 0.05	0.49 ± 0.09
Muscle	0.24 ± 0.02	0.07 ± 0.01 [b]	0.19 ± 0.02	0.10 ± 0.02 [b]
Skin	0.13 ± 0.01	0.10 ± 0.01 [b]	0.06 ± 0.01 [a]	0.07 ± 0.01
Testis	0.20 ± 0.01	0.17 ± 0.01 [b]	0.16 ± 0.02	0.14 ± 0.01 [b]

[a] Significant difference between SD rats and SHR at basal condition; [b] significant difference between control and experimental periods ($P < 0.05$). Values are given as ml/g · min.

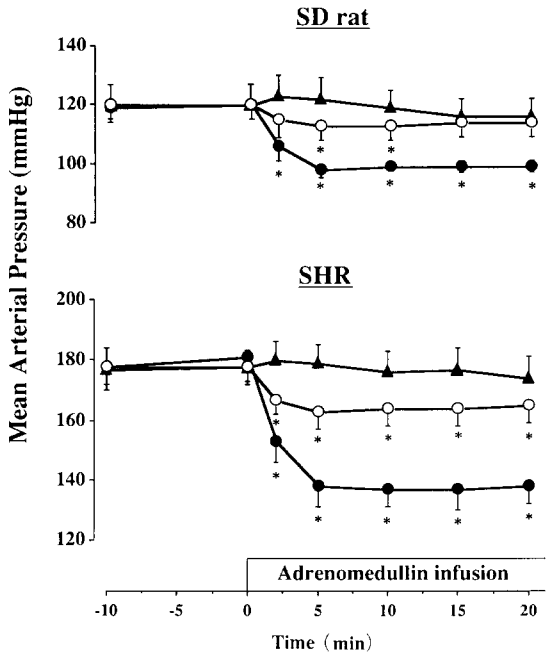

Fig. 1. Time course of the change in mean arterial pressure during the intravenous infusion of adrenomedullin at rates of 1.67 and 5 μg/kg per min in Sprague Dawley (SD) rats and spontaneously hypertensive rats (SHR). Upper panel shows the time course in SD rats and lower panel shows those in SHR. ▲ Vehicle, ○ adrenomedullin 1.67 μg/kg per min, i.v., ● adrenomedullin 5 μg/kg per min. * Significant difference between control and experimental periods ($P < 0.05$).

3.3. Effects of adrenomedullin on regional blood flow

The organ blood flows of SHR differed from those of the normotensive SD rats in several instances (Table 2). The flow rates in the spleen, liver via portal vein, kidneys and skin of SHR were significantly lower than those of SD rats. Conversely, the flow rate in the heart of SHR was higher than that of SD rats. With respect to organ vascular resistance, the organ vascular resistance increased significantly in all organs of SHR, except for the heart (Fig. 2).

Table 3
The percent distribution of cardiac output to each organ in spontaneously hypertensive rats

	Control	Adrenomedullin (5 μg/kg.min, i.v.)
Brain	1.39±0.08	1.03±0.07 [a]
Lung	0.69±0.10	1.05±0.11 [a]
Heart	5.80±0.40	7.14±0.37 [a]
Spleen	0.91±0.10	1.66±0.26 [a]
Kidney	14.1 ±0.73	16.2 ±1.12 [a]
Adrenal gland	0.17±0.01	0.38±0.04 [a]
Small intestine	4.69±0.35	5.06±0.48
Large intestine	2.06±0.18	1.80±0.23

[a] $P < 0.05$ compared with control. $n = 9$. Values are given as percentages.

The infusion of adrenomedullin to SHR increased the flow rates in the lungs, heart, liver via hepatic artery and portal vein, spleen, kidneys, adrenal glands and gastrointestinal tract and decreased the flow rates in the skeletal muscle and testis. The flow rate in the brain was not affected by the infusion of adrenomedullin (Table 2). In SD rats, adrenomedullin showed almost the same effects on the organ flow rates, that is, it increased the flow rates in the lungs, heart, liver, spleen, kidneys and adrenal glands and decreased the flow rates in the skin, skeletal muscle and testis (Table 2). The flow rate in the brain was not affected. The

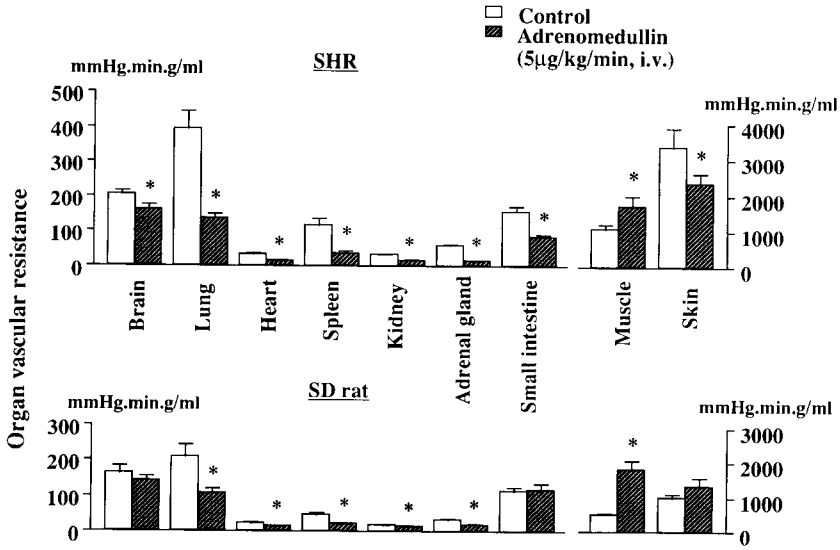

Fig. 2. Organ vascular resistance before and 10 min after the start of adrenomedullin infusion at a rate of 5 μg/kg per min in normotensive Sprague Dawley (SD) rats (lower panel) and spontaneously hypertensive rats (SHR; upper panel). * Significant difference between control and experimental periods ($P < 0.05$).

calculated organ vascular resistance in both groups of rats decreased in all organs except for the skeletal muscle and testis, hence, a significant reduction of systemic arterial pressure was induced by the infusion of adrenomedullin (Fig. 2).

Table 3 shows the percent distribution to each organ in SHR. Adrenomedullin significantly increased the percent distribution of the cardiac output to the lungs, heart, spleen, kidneys and adrenal glands. Adrenomedullin decreased the percent distribution to the brain even though the flow rate was not affected. The percent distribution of cardiac output to the gastrointestinal tract was not changed.

4. Discussion

The effects of rat adrenomedullin on systemic and regional hemodynamics were examined in conscious normotensive and hypertensive rats. Adrenomedullin induced a dose-dependent hypotension, which is consistent with previous reports (Sakata et al., 1993). The onset of pressure reduction occurred within 20–30 s after the start of infusion and the pressure reached a steady-state within 5 min after the start of infusion. There was no difference in the time course of arterial pressure change between SD rats and SHR. However, the hypotensive response of SD rats was less impressive than that of SHR.

An intravenous infusion of adrenomedullin at a rate of 5 μg/kg per min increased the heart rate and cardiac output in both groups of rats. These cardiac responses can be explained by a reduction in cardiac afterload via peripheral vasodilation and reflex sympathetic activation due to hypotension. The direct action of adrenomedullin to the heart is also possible, because Kitamura et al. (1993b) reported that rat adrenomedullin mRNA is highly expressed in the ventricle, and that adrenomedullin increased cAMP levels in rat platelets. In addition, the amino acid sequence of adrenomedullin shows slight homology with CGRP which exerts positive inotropic and chronotropic action along with an increase in cAMP levels (Franco-Cereceda and Lundberg, 1985; Gennari and Fischer, 1985). In the present study, adrenomedullin increased cardiac output and heart rate by 36 and 18% in SHR, respectively. These results show an increase in stroke volume, thus indicating the positive inotropic effect of adrenomedullin.

The main aim of the present study is to determine whether or not adrenomedullin plays the role of a circulatory hormone or local hormone in the regulation of hemodynamics. Intravenous infusion of adrenomedullin resulted in significant increases of the flow rates in the lungs, heart, spleen, kidneys, adrenal glands and small intestine of SHR. However, the flow rates in the brain, large intestine and skin did not change and the flow rates in the skeletal muscle and testis were decreased. These regional hemodynamic changes were also observed in SD rats and there were no qualitative differences in the regional responses to adrenomedullin between SHR and SD rats. Thus, adrenomedullin-induced vasodilation varies among different organ vascular beds. It is difficult to state clearly the precise significance of the heterogeneous response to adrenomedullin from the present study. The heterogeneous expression of adrenomedullin gene among organs may account for the heterogeneous responses. As tabulated in Table 3, the percent distribution of cardiac output to the lungs, heart, spleen, kidneys and adrenal glands increased significantly with adrenomedullin administration. These results indicate that the vascular beds in the above listed-organs responded more predominantly when compared to the vascular beds in other organs. Sakata et al. (1993) reported that rat adrenomedullin mRNA was expressed in adrenal glands, lungs, kidneys, heart, spleen and duodenum, but it was not detectable in the brain, liver, pancreas and testis. Thus, adrenomedullin predominantly increased the flow rates in organs in which adrenomedullin gene was highly expressed. These findings taken together seem to indicate that adrenomedullin may act as a local hormone rather than as a circulatory hormone.

The vasodilatory mechanism of adrenomedullin is unknown at the present time. However, Eguchi et al. (1994) and Ishizaka et al (1994) recently reported that cultured rat vascular smooth muscle cells possess specific adrenomedullin receptors that are functionally coupled to adenylate cyclase. Thus, it can be considered that adrenomedullin-induced vasodilation may be mediated via the stimulation of cAMP production. Nuki et al. (1993) reported that the vasodilatory action of adrenomedullin on rat mesenteric vascular beds was not affected by the pretreatment of atropine and propranolol, but was inhibited by the presence of CGRP-(8–37), an antagonist for the CGRP receptor. Based on these findings, it can be speculated that adrenomedullin-induced vasodilation is not mediated via the cholinergic and adrenergic receptors, but might be partially mediated via the CGRP receptors. However, the effects of CGRP on regional hemodynamics are different from those of adrenomedullin. Although CGRP significantly decreased mean blood pressure and TPR to the same extent that adrenomedullin did, it increased blood flow to the stomach, liver and skin and decreased it to the brain, kidneys and spleen (Dipette et al., 1987), while adrenomedullin increased blood flow to the kidneys, spleen and stomach and did not affect it to the brain and skin. Thus, we found significant differences between the regional hemodynamic actions of CGRP and adrenomedullin. In addition, We also found the significant difference in the regional hemodynamic action of adrenomedullin when compared with that of

other vasodilators, such as Ca-antagonist and potassium channel opener (Hof, 1983; Kimura et al., 1988; Shoji et al., 1990). These vasodilators did not affect the flow rate of the kidney. Thus, the regional hemodynamic actions of adrenomedullin are unique among those of many vasodilators.

In summary, an intravenous infusion of adrenomedullin at a rate of 5 μg/kg per min to SD rats and SHR resulted in significant increases of the flow rates in the lungs, heart, spleen, kidneys, adrenal glands and small intestine of both strains of rats. The flow rates in the brain and skin did not change and the flow rates in the skeletal muscle and testis were decreased. Thus, adrenomedullin predominantly increased the flow rates in organs in which adrenomedullin gene was highly expressed. It therefore seems that adrenomedullin may act as a local vasodilatory hormone rather than as a circulatory hormone.

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