Difference in Hypotensive Effect of Apelin-12 between Spontaneously Hypertensive Rat and Normotensive Wistar Kyoto Rat

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Abstract : We examined differences in depressor response to apelin-12 (AP12) between spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto (WKY) rats. Intravenous administration of AP12 in SHR and WKY rats elicited depressor response, with little change in heart rate. The decrease in mean arterial pressure was significantly greater in SHR than in WKY rats. This result suggests that AP12 has much greater effects on nitric oxide synthase activity in SHR than in WKY rats.

Key words : Apelin-12, Arterial pressure, Nitric oxide synthase, Spontaneously hypertensive rat, Wistar Kyoto rat.

INTRODUCTION

Obesity is one of our primary concerns, because it is associated with an increased incidence of hypertension and cardiovascular diseases[1,2]. Recent research indicated that adipocytes secrete a number of biologically active substances to regulate body functions[3,4]. Leptin, which is secreted from adipocytes, has been shown to suppress food intake and to regulate body weight in mammals[3]. Recently, apelin, a peptide originally isolated from the stomach, was found to be produced in adipocytes[4]. We found that intravenous administration of apelin-12 (AP12, one of apelin homologues) in Wistar rats elicited depressor response without any changes in heart rate and suggested that nitric oxide might be involved in the depressor response[5]. Here, we examined differences in the effects of intravenous administration of AP12 on arterial blood pressure between spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto rats (WKY).

MATERIALS AND METHODS

Experiments were performed using 10- to 12-week-old, weighing 280-300 g male SHR and WKY rats (n = 5, respectively, Charles River Co. Ltd., Yokohama, Japan). Anesthesia was induced and maintained with ethyl carbamate (Wako Pure Chemicals; 720 mg/kg intraperitoneally (i.p.)) and pentobarbital sodium (Abbott; 35 mg/kg i.p.). The trachea was cannulated with vinyl tubing (2 mm in internal diameter). Femoral artery and vein were cannulated with polyethylene catheters (0.58 mm, internal diameter). Systemic arterial pressure (SAP) and mean arterial pressure (MAP) were measured with a pressure transducer (TP-400T, Nihon Kohden, Japan) connected to carrier amplifier (AP60G, Nihon Kohden, Japan), and heart rate (HR) computed from pulse pressure by a cardiotachometer (AT-601G, Nihon Kohden, Japan). SAP, MAP and HR were recorded on a thermal array recorder (RTA-1100M, Nihon Kohden, Japan). AP12 was administered into the femoral vein. Rectal temperature was maintained at

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37℃ with an infrared heat lamp.

RESULTS AND DISCUSSION

The genealogical differences in hemodynamics between SHR and WKY rats were confirmed. MAP and HR in SHR before the administration of AP12 was 120 ± 6 mmHg and 388 ± 12 bpm (n = 5), while those in WKY rats were 61 ± 3 mmHg and 291 ± 7 bpm (n=5). The hemodynamic values of the MAP and HR were significantly higher in SHR than in WKY rats ($P<0.0001$ in each).

We reported that intravenous administration of apelin-12 (AP12, one of apelin homologues) in Wistar rats elicited depressor response without any changes in heart rate, and that the hypotensive effects of AP12 was dose-dependent in a range of 1-10 nmol/kg[5]. In this report differences in the effects of administration of AP12 between SHR and WKY rats were examined at the dose of 5 nmol/kg. Typical records of depressor responses to AP12 in SHR and WKY rats were shown in Fig 1. Systemic arterial blood pressure decreased to nadir around 0.5 min after the administration of AP12, and recovered within 5min to the previous level before the administration. Slight increase in HR was observed

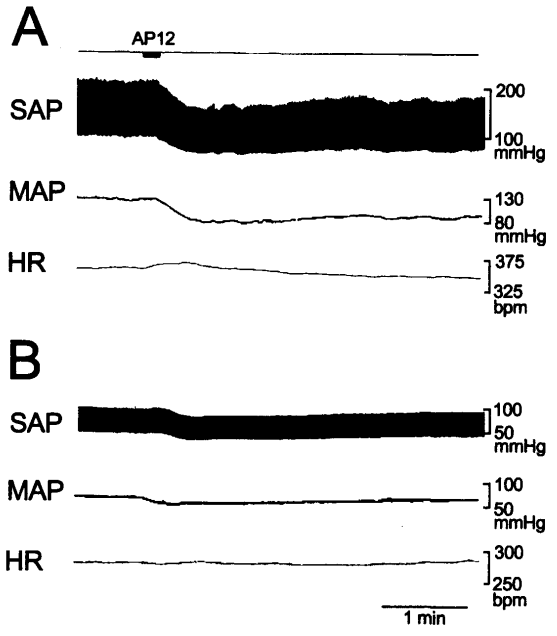

Fig. 1

Typical recordings of the depressor responses to intravenous administration of AP12 (5 nmol/kg) in SHR (A) and WKY rats (B). Abbreviations: bpm, beats per minutes; HR, heart rate; MAP, mean arterial pressure, SAP, systemic arterial blood pressure.

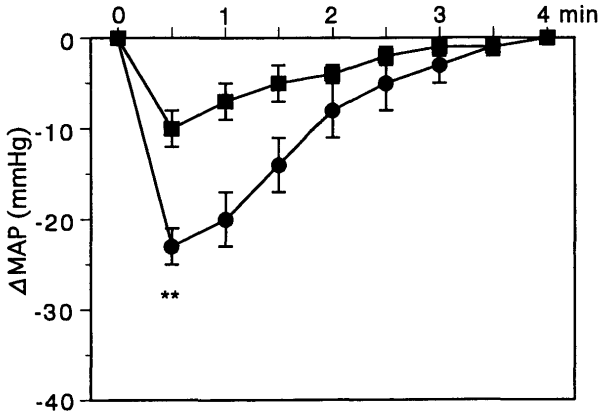

Fig. 2

Decreases in MAP after intravenous administration of AP12 in SHR (-●-●-) and WKY rats (-■-■-). Dose of AP12 was 5 nmol/kg. ** $P<0.01$.

in SHR in Fig. 1A, but little change in HR was elicited in other SHR and all WKY rats (Fig. 1B). In every experiment, rats were also intravenously injected with 0.1 mL of saline solution to confirm that no cardiovascular response was induced. The time courses of depressor response to AP12 in SHR and WKY were shown in Fig. 2. The maximal decrease in MAP in SHR was 23 ± 2 mmHg, (n = 5), while that in WKY rats was 11 ± 2 mmHg. The former was statistically significantly larger than the latter ($P<0.01$).

The depressor response to AP12 was suggested to be elicited via nitric oxide produced by the activation of nitric oxide synthase (NOS) by the AP12[5]. Here, we studied effects on arterial pressure of intravenous administration of AP12 using SHR and WKY rats, and found that the decrease in MAP by AP12 administration was much greater in SHR than in WKY, indicating that AP12 activate NOS much more effectively in SHR than in WKY rats. It was reported that the NOS activity in blood vessels of SHR was significantly lower than that of WKY rats[6]. Thus, our results suggest that AP12 might have an overwhelming greater effect on NOS to produce nitric oxide in SHR than in WKY rats. Further studies are needed to know the followings: (1) how AP12 acts to NOS much more effectively in SHR than in WKY rats; (2) whether a deficiency of apelin homologues is involved in the development of hypertension in SHR; (3) whether apelin homologues are involved in the pathogenesis of obesity.

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