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12-Hydroxyeicosatetraenoic acid potentiates angiotensin II-induced pressor response in rats

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Abstract

We studied whether 12-hydroxyeicosatetraenoic acid (HETE) affected the angiotensin II-induced pressor response in rats. After intravenous administration of 1 and 3 μg/kg 12-HETE, the angiotensin II-induced pressor response was not potentiated. However, 10, 20 and 30 min after the administration of 10 μg/kg 12-HETE, the angiotensin II-induced pressor responses were increased by 7.5, 6.8 and 4.8 mm Hg, respectively. The significant pressor response was observed at 10 and 20 min after the administration. In this study, we clearly demonstrated that 12-HETE potentiated the angiotensin II-induced pressor response. © 2001 Published by Elsevier Science B.V.

Keywords: 12-Hydroxyeicosatetraenoic acid; Angiotensin II; Hypertension

It has been reported that 12-hydroxyeicosatetraenoic acid (HETE), which is generated from arachidonic acid via the 12-lipoxygenase pathway, was increased in spontaneously hypertensive rats (SHR) and two-kidney, one clip (2K1C) rats, and that lipoxygenase inhibitors lowered the blood pressure in SHR and 2K1C rats (Nozawa et al., 1990; Stern et al., 1993). Recently, we reported that 12-HETE potentiates the angiotensin II-induced vascular contraction in isolated hamster aorta (Takai et al., 1998). However, it was unclear whether 12-HETE potentiates the angiotensin II-induced pressor response. We now examined whether 12-HETE would affect the angiotensin II-induced pressor response.

Eighteen male rats weighing 250–300 g were purchased from Japan SLC (Shizuoka, Japan). For study of pressor responses, the rat was anesthetized with sodium pentobarbital (35 mg/kg, i.p.). The intravenous administration of 1 μg/kg angiotensin II was repeated until constant pressor responses were obtained. To study the effects of 12-HETE, 1, 3 or 10 μg/kg 12-HETE was administered 10 min before angiotensin II, and the pressor responses were measured. All results are presented as means ± S.E.M. Differences were considered significant when the P values were less than 0.05 with Fisher's multiple range test.

The pressor response induced by intravenous administration of 1 μg/kg angiotensin II was 38 ± 2 mm Hg, and this control response was regarded as 100%. The angiotensin II-induced pressor responses were not affected after 1 and 3 μg/kg 12-HETE, while the response was potentiated after 10 μg/kg 12-HETE (Fig. 1). The angiotensin II-induced pressor responses were increased by 7.5 ± 0.8, 6.8 ± 1.2 and 4.3 ± 2.1 mm Hg, respectively, 10, 20 and 30 min after intravenous administration of 10 μg/kg 12-HETE, and the increase was significant 10 and 20 min after the administration.

In the present study, we demonstrated for the first time that 12-HETE potentiates the angiotensin II-induced pressor response in rats. The effect of 12-HETE was observed up to 20 min after its intravenous administration, while the effect disappeared after 30 min. 12-HETE is one of the products of arachidonic acid and it is well known that these products are unstable. Therefore, 12-HETE may be metabolized to inactive compounds. Although 12-HETE has no effect on the baseline response, it potentiated the angiotensin II-induced pressor response. Furthermore, 12-HETE did not affect the norepinephrine-induced pressor response (data not shown). Previously, Saito et al. (1992) reported that the addition of 12-HETE increased intra-

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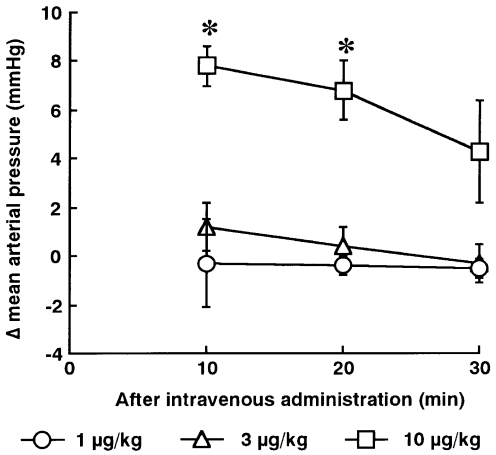

Fig. 1. Effects of 1, 3 and 10 μg/kg 12-HETE on the pressor response to 1 μg/kg angiotensin II in the rat.

cellular calcium levels induced by angiotensin II but not by norepinephrine in cultured vascular smooth muscle cells in rat. We also reported that, whereas 12-HETE did not directly induce vascular contraction in isolated hamster aorta, it significantly potentiated the vascular contraction induced by angiotensin II but not by norepinephrine (Takai et al., 1998). Therefore, 12-HETE may potentiate the pressor response via an increase of the vascular contraction by angiotensin II.

The plasma 12-HETE concentration in SHR is significantly increased compared with that in Wistar Kyoto (WKY) rats (Sasaki et al., 1997). Inhibition of lipoxygenase decreases the blood pressure in SHR (Stern et al., 1993; Sasaki et al., 1997). In 2K1C renovascular hypertensive rats, lipoxygenase inhibitors prevent the development of hypertension (Nozawa et al., 1990). However, these compounds used for lipoxygenase inhibition are non-specific 12-lipoxygenase inhibitors and may reduce various metabolites from unsaturated fatty acids, including arachidonic acid. In any case, the hypotensive mechanism of lipoxygenase inhibitors has not as yet been clarified. Our present results clearly suggest that the 12-HETE level may be involved in the regulation of blood pressure.

In conclusion, the present study showed that 12-HETE potentiates the angiotensin II-induced pressor response, and the increase of 12-HETE may be involved in the pathogenesis of hypertension.

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