Blood pressure response to central and peripheral injection of angiotensin II and 8-C-phenylglycine analogue of angiotensin II in rats with experimental hypertension

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Summary

1. We have compared the effect of central and peripheral administration of angiotensin II and (1-succinamoyl-5-valine-8-phenylglycine)angiotensin II on blood pressure of male conscious unrestrained rats with normal blood pressure, and with spontaneous hypertension or chronic renal hypertension.

2. After central and peripheral injection of angiotensin II all rats exhibited a significant dose-related increase in blood pressure.

3. Administration of the analogue was without effect in normotensive rats. Ten-weeks-old rats with spontaneous hypertension showed a significant blood pressure decrease after central injection, but an increase after peripheral injection. This centrally induced decrease could not be observed in spontaneously hypertensive rats 14 weeks old. In these animals the analogue increased the blood pressure. In rats with chronic renal hypertension in contrast to peripheral injection, central administration decreased the pressure significantly.

4. Plasma renin activity was not changed after central injection of the analogue in normotensive rats.

5. These observations suggest the participation of the intrinsic brain isorenin-angiotensin system in central blood pressure regulation in these forms of experimental hypertension.

Key words: angiotensin II, angiotensin II analogue, central blood pressure regulation, experimental hypertension, intrinsic brain isorenin-angiotensin system.

Introduction

The centrally induced pressor activity of angiotensin II in normotensive animals is markedly attenuated by central administration of AII(1) analogues with specific AII receptor-blocking properties (Sweet, Ferrario, Khosla & Bumpus, 1973; Solomon & Buckley, 1974; Schoelkens, 1974, 1975; Vollmer, Buckley, Solomon & Jandhyala, 1974). These blocking agents might act on central receptor sites of the intrinsic brain isorenin–angiotensin system (Fischer-Ferraro, Nahmod, Goldstein & Finkelstein, 1971; Ganten, Marquez-Julio, Granger, Haydak, Karsunky, Boucher & Genest, 1971).

To investigate the possible participation of this intrinsic brain isorenin–angiotensin system in central blood pressure regulation in experimental hypertension, we have compared the effects of central (by injection into the lateral ventricle of the brain) and peripheral (intravenous) administration of a new specific AII antagonist (1-succinamoyl-5-valine-8-phenylglycine)AII (Schoelkens, Wissmann, Lindner & Geiger, 1976), on systemic blood pressure. In addition the central pressor activity of AII in experimental hypertension was tested. Plasma renin activity was determined after central injection of the AII analogue in normotensive rats.

Methods

Three experimental groups were studied: (1) conscious unrestrained normotensive Sprague-Dawley rats (Hoe SPRK SPF71); (2) rats with spontaneous hypertension, of 10 and 14 weeks of age (FH-NIH-Montreal-Ingelheim); (3) Sprague-Dawley rats (Hoe SPRK SPF71) with chronic renal hypertension, induced by applying solid silver clips (0.2 mm diameter) to both renal arteries. Blood pressure was measured directly with a chronically

(1) Abbreviation: AII, angiotensin II.
implanted catheter in the abdominal aorta (Weeks & Jones, 1960). All experiments were performed in male rats, weighing 150-400 g. The AII antagonist (1-succinamoyl-5-valine-8-phenylglycine)AII (Schoelkens et al., 1976), in doses of $3 \times 10^{-11}$ mol/kg (30 ng/kg) and $30 \times 10^{-11}$ mol/kg (300 ng/kg), was given centrally through a permanently implanted catheter in the lateral ventricle of the brain (Hayden, Johnson & Maickel, 1966) and peripherally by a permanently implanted catheter in the jugular vein of the same animal, to compare the central and the peripheral effect of the AII analogue in the same animal. AII was administered in the same way, in the same dose.

To another group of rats AII and the AII analogue were dissolved in sodium chloride solution (9 g/l; saline), which was also used for control injections. The volume of injection was 5 μl. Arterial blood pressure was measured via a Statham pressure transducer (model P23Db); measurement and recording were done with instruments of the Hellige Program 19 (Fritz Hellige and Co., Freiburg, West Germany). Rats with a blood pressure $>150$ mmHg were considered to be hypertensive.

The AII analogue, $300 \times 10^{-11}$ mol/kg (3 μg/kg), was injected into the lateral ventricle of male conscious normotensive Sprague-Dawley rats (Hoe SPRK SPF71). After 5 and 15 min blood was taken for the determination of the plasma renin activity (ng of A1 h$^{-1}$ ml$^{-1}$) by radioimmunoassay (Haber, Koerner, Page, Kliman & Purnode, 1969), a commercially available kit (Isotopendienst West, Frankfurt A.M., West Germany) being used. Results are presented as mean values ± SEM. For statistical analysis Student’s t-test was used. A P value less than 0.05 was used as the criterion of significance.

**Results**

**Blood pressure change after administration of the AII analogue (Fig. 1)**

In normotensive rats ($n = 5$) the analogue caused a small, non-significant pressure increase after either central or peripheral administration. At 5 and 15 min after central injection of the analogue in normotensive rats ($n = 25$) no significant changes of plasma renin activity were seen.

Spontaneously hypertensive rats ($n = 11$), 10 weeks old, showed a significant ($P<0.01$) blood pressure decrease after central injection, but a significant ($P<0.001$) increase after peripheral injection. In rats with spontaneous hypertension at an age of 14 weeks ($n = 14$) this centrally induced depressor response could not be observed: in these rats central injection of the analogue increased the pressure significantly ($P<0.02$). A significant increase $P<0.05$ was also seen after peripheral administration. Central administration of the analogue lowered the blood pressure ($P<0.01$) in all rats with chronic renal hypertension ($n = 6$). In contrast peripheral injection caused only a small non-significant increase of blood pressure.

**Blood pressure change after the administration of AII**

After central and peripheral administration of $2.9 \times 10^{-11}$ mol/kg (30 ng/kg) and $29 \times 10^{-11}$ mol/kg (300 ng/kg) of AII all rats exhibited a significant ($P<0.001$) dose-related blood pressure increase.

In normotensive rats ($n = 8$) blood pressure was increased by 13 ± 2 (SEM) mmHg and 18 ± 2 mmHg respectively after central injection of the two doses,
and 8 ± 1 mmHg and 30 ± 5 mmHg respectively after peripheral injection.

The 14-weeks-old spontaneously hypertensive rats (n = 8) showed an increase of blood pressure after central application by 26 ± 3 mmHg and 37 ± 5 mmHg respectively, and after peripheral application 21 ± 4 mmHg and 40 ± 11 mmHg respectively.

In rats with chronic renal hypertension (n = 10) blood pressure was elevated after central injection by 18 ± 4 mmHg and 28 ± 3 mmHg respectively, and after peripheral injection by 21 ± 4 mmHg and 35 ± 8 mmHg respectively.

In comparison with normotensive rats, animals with spontaneous hypertension and chronic renal hypertension had a significantly increased pressor response after central administration of AII. However, no significant difference between rats with spontaneous hypertension and chronic renal hypertension was found in the pressor response.

Discussion

Animals with spontaneous hypertension and chronic renal hypertension had a significantly increased pressor response compared with the known central pressor effect of AII in conscious normotensive rats (Severs & Daniels-Severs, 1973; Hutchinson, Schelling & Ganten, 1975; Ganten, Hutchinson & Schelling, 1975). However, no difference in the central pressor response could be seen between the two forms of hypertension.

In contrast to normotensive rats, in which central application of the AII analogue caused no significant pressor effect, a significant decrease of blood pressure could be demonstrated in 10-weeks-old rats with developing spontaneous hypertension. Similar results were obtained in animals with chronic renal hypertension, but not in 14-weeks-old rats with spontaneous hypertension. This suggests an AII receptor-blocking effect at central receptor sites with a resulting blood pressure decrease in situations when an activation of the renin-angiotensin system may occur, for instance, the developing phase of spontaneous hypertension (de Jong, Lovenberg & Sjoerdsma, 1972; Sen, Smey & Bumpus, 1972) and in renal hypertension. Ganten et al. (1975) and Hutchinson et al. (1975) showed that AII, produced by the intrinsic brain isorenin-angiotensin system, is secreted into the cerebrospinal fluid. Its concentration is elevated in the cerebrospinal fluid of spontaneously hypertensive rats. §H-labelled AII, injected intravenously into rats, does not cross the blood-cerebrospinal fluid barrier as an intact molecule. Central administration of another AII analogue (21,3,4,8-AI) also caused a decrease of systemic blood pressure in spontaneously hypertensive rats less than 3 months old (Hutchinson et al., 1975; Ganten et al., 1975). Comparing the effect of the AII analogue after central and peripheral administration it seems likely that different mechanisms are responsible for the opposite influences on blood pressure in spontaneous hypertension in 10-weeks-old animals and in renal hypertension.

From these results it can be assumed that the intrinsic brain isorenin-angiotensin system seems to be involved in central blood pressure regulation in experimental hypertension.

References


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