Effect of Intracerebroventricular Captopril on Vasopressin and Blood Pressure in Spontaneously Hypertensive Rats

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SUMMARY In conscious, unrestrained spontaneously hypertensive rats (SHR), mean arterial blood pressure (MAP) increased from a pretreatment value of 150 ± 4 to 179 ± 7 mm Hg within 10 min (p < 0.01) following an intracerebroventricular (l.c.v.) injection of captopril (2 mg/kg body weight), and the plasma vasopressin concentration was increased eightfold (p < 0.01). MAP then fell to 131 ± 5 mm Hg at 120 minutes (p < 0.01), and plasma vasopressin concentration returned to pretreatment levels. The initial increase in MAP was due in large part to increased plasma vasopressin levels since this increase was reduced 50% by pretreatment with a specific antagonist of the pressor action of vasopressin. The reduction in MAP at 120 minutes in captopril-treated rats may have been nonspecific, since a similar effect was observed in SHR given an i.c.v. injection of a control solution. In (Wistar-Kyoto) WKY rats, i.c.v. captopril was without a statistically significant effect on MAP, but the plasma vasopressin concentration increased three-fold (p < 0.01). These findings may reflect an increased sensitivity of the control system for vasopressin release in the SHR.

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KEY WORDS • vasopressin • antidiuretic hormone • captopril • spontaneously hypertensive rat • vasopressin blocker

VASOPRESSIN secretion is elevated in the spontaneously hypertensive rat (SHR) of the Okamoto-Aoki strain, and may be partially responsible for the elevated blood pressure in these animals. Chronic treatment of young SHR with captopril prevented development of the hypertension, decreased vasopressin secretion, and increased water turnover. However, it could not be determined if the prevention of the hypertension was related to reduced vasopressin secretion and whether the reduction in vasopressin secretion was the consequence of increased water intake or a direct action of captopril at sites in the brain that may control vasopressin secretion and where the blood-brain barrier is absent, e.g., the circumventricular organs. Support for a central hypotensive action for captopril is provided by the observation by Hutchinson et al. that the intracerebroventricular (i.c.v.) administration of captopril acutely lowered blood pressure in the SHR. This action could have been due to inhibition of vasopressin secretion, since a brain renin-angiotensin system may be involved in the control of vasopressin secretion. We have therefore investigated the central actions of captopril on vasopressin secretion and blood pressure, by giving this drug i.c.v. in SHR and normotensive WKY rats.

Methods

Five- to 6-week-old male SHR of the Okamoto-Aoki strain and normotensive WKY rats, obtained from Taconic Farms, were housed four to a cage and given Purina Laboratory Chow and tap water ad libitum. When the animals were 6 to 7 weeks old, a stainless steel guide cannula (23 g) was placed stereotaxically into the lateral ventricle and was secured to the skull with dental cement. The rats were than individually housed in "home cages," and allowed to recover for a minimum of 5 days. At 24 hours prior to an experiment, polyethylene catheters (PE 50) were placed into a femoral artery and vein; the
were removed from the cages, the arterial catheter was connected to a Statham P23 Gb transducer, and MAP was recorded on a Brush recorder. The animals remained unrestrained in their individual "home cages" throughout the experiment.

In the first set of experiments, the effect of i.c.v. captopril on blood pressure and plasma vasopressin concentration was tested in 12 SHR and 6 WKY rats. The captopril was made fresh daily in double-distilled water. The osmolality of this solution ranged from 305 to 315 mOsm/kg H₂O, and the pH was 2. Control SHR (n = 9) and WKY (n = 4) were given i.c.v. injections of a control solution containing mannitol at a concentration of approximately 6%, adjusted to equal the osmolality of the captopril solution used that day; the pH was brought to 2 with 1 N HCl. Following an equilibration period of 30 to 60 minutes, each rat's arterial catheter was disconnected from the transducer and 2.2 ml of blood was withdrawn into a chilled heparinized syringe, over a period of 1.5 minutes, while a warm (37°C) 3% polyvinylpyrrolidone solution in an artificial extracellular fluid was injected i.v. The arterial catheter was again connected to the transducer, and 10 minutes later either captopril (2 mg/kg) or the mannitol solution was injected i.c.v. over 30 seconds at a volume of 10 μl. Additional blood samples were taken 10 and 120 minutes after the i.c.v. injection; the sampled blood was replaced with equal volumes of the polyvinylpyrrolidone solution. At the end of the experiment, angiotensin I (A1) (100 ng) was given i.c.v. and i.v. and angiotensin II (A11) (100 ng) was given i.v.

Plasma was separated from blood by centrifugation at 4°C. On the same day, plasma osmolality was measured by freezing point depression (Osmette A osmometer), and plasma sodium and potassium concentrations were measured by flame photometry (II 343 flame photometer). The remainder of the plasma was stored at -40°C until vasopressin was extracted with Sep-Pak C₁₈ cartridges, and measured by radioimmunoassay. The standard was the U.S.P. Posterior Pituitary Reference Standard. Average recovery of vasopressin from rat plasma was 78% ± 2% (SE, n = 10). No correction was made for incomplete recovery.

In a second group of experiments, we determined the effect of a specific vasopressin antagonist ([1-(β-mercaptopropyl)-β-cyclopentamethylenepropionic acid],2-(O-methyl)tyrosinearginine-vasopressin; 30 μg/kg i.v.) on blood pressure was tested in SHR given either captopril (n = 7) or the control mannitol solution i.c.v. (n = 5). A third group of SHR was given the vehicle (0.9% NaCl) for the blocker i.v. and captopril i.c.v. (n = 7). All of the animals were surgically prepared as described above. After blood pressure had stabilized for at least 30 minutes, a test dose of 2.5 mU of vasopressin was given i.v. When blood pressure returned to basal levels, the vasopressin antagonist or the vehicle was given in a volume of 0.1 ml, followed by 0.15 ml of 0.9% saline. Ten minutes later, i.c.v. captopril or mannitol was given. Thirty minutes after the i.c.v. injection, i.v. injections of vasopressin (2.5 mU), A1 (100 ng), and A11 (100 ng) and an i.c.v. injection of A1 (100 ng) were given to test the efficacy of the vasopressin antagonist and the captopril.

One- and two-way analyses of variance for repeated measures and, when appropriate, the Newman-Keuls a posteriori tests were performed to identify statistically significant differences within and between groups. Means and the standard error of the means are given in the text, tables, and figures.

Results

In SHR and WKY rats, the i.c.v. injection of captopril completely abolished the pressor response to i.c.v. A1 (100 ng) and reduced the response to i.v. A1 (100 ng) by 40% to 50%.

When SHR were given captopril i.c.v., MAP increased approximately 30 mm Hg within 10 minutes (p < 0.01) and then fell to a level 12% below the zero time value at 120 minutes (p < 0.01; fig. 1, upper panel). In SHR given i.c.v. injections of the control mannitol solution, there was no pressor response. Instead, MAP fell to a level 8% below the initial value at 120 minutes (p < 0.05). In WKY rats, the i.c.v. injection of captopril and the mannitol solution were without statistically significant effects on MAP (fig. 1, upper panel). Although initially MAP in both groups of SHR was higher (p < 0.01) than in both groups of WKY rats, within 120 minutes after i.c.v. injection of captopril or mannitol, MAP in both groups of SHR had fallen to levels that were not significantly different from those in the WKY rats.

Captopril treatment resulted in an eightfold increase (p < 0.01) in the plasma vasopressin concentration in the SHR and a threefold increase (p < 0.01) in the WKY rats (fig. 1, lower panel). The plasma vasopressin concentration returned to control levels at 120 minutes in the SHR, but remained elevated in the WKY rats.

In a second series of experiments, we determined the effect of a bolus i.v. injection of a specific antagonist of the pressor action of vasopressin on the blood pressure changes induced by i.c.v. captopril (fig. 2). When SHR were given captopril but not the vasopressin antagonist, MAP increased within 1 minute, and peaked at 10 minutes, with an increase of 35 ± 4 mm Hg, and was still elevated at 30 minutes (p < 0.01). When treatment with the vasopressin antagonist preceded i.c.v. captopril, there were no statistically significant changes in MAP, although MAP was increased 18 ± 5 mm Hg at 10 minutes. The vasopressin antagonist was without effect on MAP in SHR that had been given mannitol i.c.v. Thirty minutes after administration of the vasopressin antagonist, the pressor response to 2.5 mU of vasopressin i.v. was completely blocked; this dose of vasopressin increased MAP 34 ± 3 mm Hg in SHR that were not treated with the vasopressin antagonist.
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Discussion

In the present experiments, we have found that the i.c.v. injection of captopril in SHR resulted in an initial marked increase in MAP, followed by a fall of MAP below control levels. The initial pressor response was largely due to the eightfold increase in the plasma vasopressin concentration, since this response was substantially blocked by i.v. injection of a specific vasopressin pressor antagonist. The residual increase in MAP in the vasopressin-blocked rats may have been due to inhibition of brain kininase activity by the captopril; i.c.v. bradykinin increases blood pressure.9 The subsequent fall in MAP in the captopril-treated SHR may have been non-specific, since a similar reduction was seen in SHR given control i.c.v. injections. I.c.v. captopril had no effect on MAP in WKY rats.

The effects of i.c.v. captopril on blood pressure in SHR are controversial. Our findings are consistent with the report by Schölkens et al.10 However, Mann et al.11 found that i.c.v. captopril had no effect on blood pressure in SHR anesthetized with chloralose; and Hutchinson et al.4 reported a large, prolonged fall in MAP in conscious SHR. These divergent findings may be due, at least in part, to the use of anesthesia in the case of Mann et al.,11 or to the use of an inappropriate solution for control i.c.v. injections in the cases of both Mann et al.11 and Hutchinson et al.4 Captopril in concentrated solution in either saline11 or artificial cerebrospinal fluid4 is markedly hypertonic and acidic. For these reasons, we dissolved captopril in distilled water to provide a solution with an osmolality of approximately 300 mOsm/kg H2O and a pH of 2. The solution that we used for control i.c.v. injections was made isosmotic with mannitol, which is presumed inert, and was brought to pH 2 with HCl.

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In the present experiments, the marked increase in vasopressin secretion in both SHR and WKY rats was due to a specific action of captopril, since i.c.v. injection of the control mannitol solution was without effect on the plasma vasopressin concentration. The stimulation of vasopressin release by captopril was not due to blockade of a brain renin-angiotensin system, since the central administration of AI1 increases vasopressin secretion,8 but may have resulted from potentiation of the actions of brain kinins. There is evidence that bradykinin can act centrally to stimulate
vasopressin release. Alternatively, captopril could have stimulated vasopressin secretion by increasing the release of brain prostaglandins. Prostaglandin E, i.c.v. increases vasopressin secretion, and captopril may stimulate release of prostaglandins. Finally, our observation that acute treatment of SHR with captopril i.c.v. transiently increases vasopressin secretion and blood pressure does not rule out the possibility that prolonged central treatment with captopril will decrease vasopressin secretion and blood pressure. Two hours after i.c.v. captopril, the plasma vasopressin concentration had fallen to control levels and MAP had fallen below control levels.

Captopril i.c.v. increased the plasma vasopressin concentration eightfold in SHR, but only threefold in WKY rats. This difference may reflect an enhanced sensitivity of the system controlling vasopressin release, and may account for the increased secretion of vasopressin that has been observed in SHR. Increased secretion of vasopressin combined with increased pressor responsiveness to vasopressin provides a role for vasopressin in the development and maintenance of hypertension in the SHR.

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