Blood Pressure Responses of Conscious Normotensive and Spontaneously Hypertensive Rats to Intracerebroventricular and Peripheral Administration of Captopril


SUMMARY In conscious spontaneously hypertensive rats, intracerebroventricular injection of captopril (2 mg/kg) resulted in a rapid hypotensive response that lasted several hours. The same dose given by intracerebroventricular injection had no significant effect on blood pressure (BP) of normotensive Wistar-Kyoto (WK) rats over 7 hours. There was no significant change in BP of conscious spontaneously hypertensive rats (SHR) in response to intracerebroventricular injection of vehicle and only a transitory fall in BP in response to intravenous injection of captopril (2 mg/kg). There was no significant differences between plasma renin activity (PRA) of conscious normotensive WKY rats and the PRA of SHR. These results suggest biochemical differences between the brains of SHR and normotensive WKY control rats. These differences could involve the brain renin-angiotensin system or other neuropeptides. (Hypertension 2: 546-550, 1980)

KEY WORDS • spontaneously hypertensive rat • angiotensin converting enzyme • captopril • plasma renin activity • Intracerebroventricular responses

The possible existence of an independent renin-angiotensin system in the brain has been the subject of some controversy. However, all the components of a system necessary for the local formation of angiotensin II have now been demonstrated to be present in brain tissue independently of the circulating renin-angiotensin system. Renin, as distinct from acid protease, has been extracted from brain tissue of rats, dogs, and humans; renin substrate has been extracted from dog brain and partially purified; converting enzyme has been extracted from rat brain, localized and partially purified; angiotensin-like peptides have been demonstrated to be present in cerebrospinal fluid and brain tissue, and specific high affinity binding sites for angiotensin II are present in brain tissue. This system has been suggested to play a role in the maintenance of blood pressure (BP) in the spontaneous hypertensive rat since intracerebroventricular administration of competitive antagonists of angiotensin II lowered BP in six of seven recent reports. In agreement with these observations, the levels of angiotensin II in the cerebrospinal fluid of hypertensive rats have been reported to be higher than those of normotensive rats. We therefore decided to assess the effect of intracerebroventricular injection of the converting enzyme inhibitor, captopril, which blocks the formation of angiotensin II, on the BP of spontaneously hypertensive rats (SHR). Since anesthesia may activate the renin-angiotensin system, we used conscious unrestrained animals previously provided with chronic indwelling cannulae.

Methods

Male SHR of the Okamoto strain and normotensive Wistar Kyoto control rats (NT-WKY) 4-10 months old and weighing 274-380 g were anesthetized with sodium pentobarbitone (20 mg/kg) i.p.,
supplemented with ether. Week’s catheters were made from 1.5 cm PE 10 tubing (Clay-Adams) inserted into 15 cm of PE 50 tubing. The join was sealed using heat-shrink tubing. One end of the catheter was passed through the abdominal muscle and led out subcutaneously to exit through the dorsal skin of the neck. The catheter was connected to a length of PE 50 tubing which was protected by a metal spring and attached to a 1 ml syringe of heparinized saline (20 units/ml). The bevelled PE 10 end of the saline-filled catheter was inserted into the aortic bifurcation and glued into position using cyanoacrylate glue (Loctite, IS495). The same procedure was followed to insert PE 10 tubing into the inferior vena cava at its junction with the femoral veins. Chloramphenicol (100 mg) was injected into the abdominal cavity and the muscle incision sutured. The end of the metal spring protecting the vascular cannulae was sutured to the skin, a plastic skin dressing applied, and the spring taped to a cloth tape harness fitted around the animal’s thorax.

For intracerebroventricular injections, a skin incision was made over the right parietal bone and a 1.5 mm hole was drilled through the parietal bone 5 mm from the anterior suture line of the parietal and 3 mm from the midline suture. A 2 mm tap was threaded into the hole, and a brain injection cannula (Lamon Instrumentation Co. Ltd., Tel-aviv, Israel) was screwed in to a depth of 1 mm. The skin incision was sutured and a plastic skin dressing applied. The animals were returned to their individual home cages; fourteen NT-WKY and 16 SHR were prepared with indwelling arterial cannulae as described above. Blood samples (800 μl) were taken into chilled lithium heparin tubes on ice 2 days after operation for determination of plasma renin activity (PRA). The animals were not disturbed during blood sampling and showed no behavioral changes during the procedure. The PRA was measured by radioimmunoassay of angiotensin I generated after incubating the plasma for 4 hours at 37°C in the presence of the angiotensinase inhibitors, 2, 3 dimercaprol (1.25 mM), Na2 EDTA (10 mM), and phenylmethylsulphonylfluoride (4.6 mM) at pH 6.5. The PRA results are expressed as mean ± one standard error of the mean and significance tested by unpaired t test. At least 48 hours elapsed between blood sampling and assessment of the effects of captopril on blood pressure.

Results

As shown in figure 1, intracerebroventricular injection of captopril (2 mg/kg) produced no significant change in MAP of seven conscious NT-WKY over the 7-hour period of observation (F = 0.74; p > 0.05). By contrast, intracerebroventricular injection of the same dose of the drug significantly lowered (F = 4.27, p < 0.005) the MAP of nine conscious SHR over the 7-hour period of observation. This effect was rapid in onset and persisted for the 7 hours of observation. Intracerebroventricular injection of vehicle alone produced no decrease in MAP of six conscious SHR over 7 hours; the BP increase was of borderline significance (F = 1.68, p > 0.05). Intravenous injection of captopril (2 mg/kg) in seven conscious SHR produced a transient fall in BP 15 and 30 minutes after injection. However, the response was not maintained and was not significant when the whole time course was assessed by analysis of variance (F = 1.25, p > 0.05).

Oral administration of captopril at 20 mg/kg lowered (F = 1.46, p > 0.05) the MAP of seven SHR over the 7-hour period of observation. The same dose of the drug had no significant effect on the BP of eight NT-WKY (fig. 2).

The PRA of 16 conscious SHR was 1.42 ± 0.33, and of 14 conscious NT-WKY was 1.94 ± 0.24 ng ml-1 hour-1. These values are not significantly different (p > 0.05).

Discussion

The present results show that the converting enzyme inhibitor captopril causes a rapid, marked, and prolonged fall in BP of SHR when injected into the lateral cerebral ventricle. The BP was not affected by injection of the vehicle alone. Furthermore, the action
of captopril appeared to be restricted to the SHR since no change in BP occurred in normotensive WKY control rats after intracerebroventricular injection of the inhibitor.

The same dose of the drug administered intravenously to SHR caused only a transient drop in BP. This transient effect of intravenous captopril contrasts with the more prolonged effect of the same dose of the drug in anesthetized SHR.\textsuperscript{4} Impairment of homeostatic mechanisms by anesthesia may account for the difference in the duration of the hypotensive response, but possible interaction of captopril with anesthetics may also be involved. The fall in BP of SHR treated with captopril orally was not statistically significant, but this may be due to the dose being lower than those used by other groups.\textsuperscript{26} In the current study, significant falls in BP were produced by a tenfold lower dose into the cerebral ventricles. This finding raises the possibility that captopril given peripherally acts via a central nervous mechanism. Although the drug does not appear to cross the blood-brain barrier of normotensive cats,\textsuperscript{26} this observation may not apply to spontaneously hypertensive rats that may have increased cerebrovascular permeability.\textsuperscript{27} In SHR, Mann et al.,\textsuperscript{27} were unable to antagonize the pressor responses to centrally administered angiotensin I using peripherally administered captopril. They did not observe a fall in BP of SHR after intraventricular infusion of captopril. Their observations could be influenced by their use of chloralose anesthesia, whereas our current results were obtained in conscious animals. However, it is still possible that the drug could act by blocking the formation of endogenous angiotensin II at brain sites where the blood-brain barrier is absent. Examples of such sites are the area postrema, the subfornical organ, and the neurohypophysis. These areas are also known to be involved in volume and BP homeostasis.
Angiotensin converting enzyme is a dipeptidyl carboxypeptidase with wide substrate specificity. Possible actions of the inhibitor on other neuropeptides therefore need to be considered: the hypertensive response to intracerebroventricular captopril is unlikely to be a result of potentiating bradykinin since there was no significant change in MAP of NT-WKY, (F = 1.06, p > 0.05). Control MAP was 189 \pm 8 \text{ mm Hg} for SHR and 116 \pm 2 \text{ mm Hg} for NT-WKY.

Figure 2. Effect of oral administration (p.o.) of 20 mg captopril/kg on mean blood pressure (MAP) of SHR and NT-WKY. The fall in MAP of SHR was not statistically significant \( F = 1.46, p > 0.05 \). There was no significant change in MAP of NT-WKY, (\( F = 1.06, p > 0.05 \)). Control MAP was 189 \pm 8 \text{ mm Hg} for SHR and 116 \pm 2 \text{ mm Hg} for NT-WKY.

The different effects of central captopril in the SHR and NT-WKY suggests that angiotensin or perhaps other neuropeptides are involved in the maintenance of the elevated BP in the conscious spontaneously hypertensive rat.

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References

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