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 boved PE 10 end of the saline-filled catheter was inserted into the aortic bifurcation and glued into position using cyanoacrylate glue (Loctite, 15495). 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; the cannulae taken to the top of the cage enclosed in a 1S495). The same procedure was followed to insert PE 10 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, 1S495). 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.

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At 2 to 4 days after surgery, experiments were performed on the conscious rats; their cannulae were connected to Statham, P23Db pressure transducers for continuous recording of pulsatile and mean arterial pressure (MAP) on a Grass model 7C polygraph. The arterial lines were kept patent by infusion of a heparinized (20 units/ml) solution of 5% dextrose in water at 1.2 ml/hour. Intracerebroventricular injections of artificial cerebrospinal fluid alone or containing the converting enzyme inhibitor, captopril, in a volume of up to 5 

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. 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. 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, this observation may not apply to spontaneously hypertensive rats that may have increased cerebrovascular permeability. In SHR, Mann et al., 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 intracerebroventricular 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 hypotensive response to intracerebroventricular captopril is unlikely to be a result of potentiating bradykinin since response to intracerebroventricular captopril is unlikley to be a result of potentiating bradykinin since central administration of this peptide raises BP in the conscious rat.

It is possible that angiotensin converting enzyme inhibitors might impair the degradation of both substance P and met-enkephalin. Both of these peptides appear to be pressor or intracerebroventricular administration. It is therefore unlikely that the hypotensive effect of central captopril is due to potentiation of the actions of substance P or met-enkephalin.

The hypotensive responses to angiotensin II antagonists and the elevated levels of angiotensin II in the cerebrospinal fluid of genetically hypertensive rats suggest that captopril exerts its hypotensive effect in the SHR by blocking the formation of angiotensin II in the brain.

It is possible that the brain angiotensin system merely mirrors the activity of the circulating renin-angiotensin system. The PRA of SHR has been reported to be higher than that of NT-WK by Sen et al. and De Jong et al. However, all of these measurements have involved sampling techniques that subject the animals to various degrees of stress that may elevate PRA. In the current experiments, in which blood was collected from resting, unstressed animals, PRA was similar in both SHR and NT-WK. This finding makes it unlikely that the major hypotensive action of captopril in the SHR is related to actions on the circulating renin-angiotensin system.

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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