Influence of Captopril Treatment on Angiotensin II Receptors and Angiotensinogen in the Brain of Spontaneously Hypertensive Rats

PIERRE SCHELLING, PH.D. AND DOMINIK FELIX, PH.D.

SUMMARY The brain renin-angiotensin system (RAS) has been suggested as contributing to the pathogenesis of spontaneous hypertension in rats. Brain angiotensinogen- and angiotensin II (All)-sensitive neurons were therefore investigated in stroke-prone spontaneously hypertensive rats (SHR-sp) and in Wistar-Kyoto (WKY) rats with and without treatment by captopril (CAP). Angiotensinogen was decreased in the anterior hypothalamus but increased in the cortex, the hippocampus, and cerebellum of SHR-sp. There were no differences between SHR-sp and WKY rats concerning the angiotensinogen content of posterior hypothalamus, brain stem, and septum. The sensitivity of the septal neurons to microiontophoretically applied All was elevated, however, in SHR-sp as compared to WKY rats with regard to threshold and maximal response for All-evoked neuronal discharges. The excitation characteristics did not change with the age of animals in both WKY rats and SHR-sp. The treatment of SHR-sp with CAP (50 mg/kg/day per os) starting in weanlings kept animals normotensive and reduced the high sensitivity of septal neurons to All. Simultaneously angiotensinogen content was increased in the anterior hypothalamus and suppressed in the hippocampus. The same treatment of WKY rats reduced blood pressure somewhat and increased the angiotensinogen content in the anterior hypothalamus without affecting the neuronal sensitivity to All. Thus, malfunction of the brain RAS may participate in the hypertension of SHR-sp, since converting enzyme blockade with CAP inhibited the blood pressure rise, augmented the angiotensinogen content of the anterior hypothalamus, and decreased the sensitivity of All receptors in the brains of these rats.

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KEY WORDS • brain renin angiotensin system • chronic captopril treatment • microiontophoresis • septal area • stroke-prone spontaneously hypertensive rats • Wistar-Kyoto rats

THE spontaneously hypertensive rat (SHR)1 has been used as a model for human essential hypertension, and several hypotheses have been formulated about the pathogenesis of the high blood pressure in these rats. Recently, Ganten and colleagues2 have applied the term "peptidergic stimulation syndrome" to the observation that rats of the stroke-prone substrain of SHR (SHR-sp)3 demonstrate an exaggerated response, e.g., of blood pressure, to several peptide hormones after their intracerebral application. Much interest was addressed to the brain renin-angiotensin system (RAS) in this respect, since all components needed for a functional system, including the effector peptide angiotensin II (All) and its receptors have been discovered in the brain (for review see ref. 4).

We have recently demonstrated by means of an electrophysiological and microiontophoretical approach that septal neurons in the brain of 20-week-old SHR-sp with established hypertension exhibited a significantly higher sensitivity to All compared to age-matched normotensive Wistar-Kyoto (WKY) rats.5 These results are consistent with those of others, which have shown a strengthened blood pressure response to All in SHR and SHR-sp when the peptide was applied into the brain ventricles (i.v.t.):2,6

Central All receptor blockade or the inhibition of All synthesis in the brain, e.g., by captopril (CAP):7 are best suited to evaluate the link between the brain RAS and blood pressure control. They have been shown to lower blood pressure in SHR, SHR-sp, and in the New Zealand strain8 of SHR but not in appropriate normotensive controls.9-15 Peripheral administration of CAP either by gavage or with tap drinking water was also reported to attenuate high blood pressure in SHR and SHR-sp and to prevent the develop-
ment of hypertension when the treatment was started in weanlings, 16-18 although the plasma RAS appears to be suppressed rather than to be stimulated in SHR and SHR-sp. 19-21 It was therefore suggested that an interference with extrarenal tissue RAS in blood vessels 22 and in brain 23, 16 could account for the depressor effect of CAP given by mouth.

The present study was carried out to learn about the possible relationship between blood pressure regulation and brain RAS in SHR-sp with regard to the intracerebral distribution of angiotensinogen and the AI receptor properties of septal neurons. Experiments were performed either in SHR-sp during the development of high blood pressure at an age of 9 weeks or in animals with established hypertension at an age of 20 weeks with and without long-term converting enzyme blockade by CAP.

Materials and Methods

Subjects

Male SHR-sp derived from the Kyoto strain 3 (and bred in our institution) were used at ages of 9 weeks and 20 weeks respectively. Age-matched WKY rats served as controls.

Measurement of Blood Pressure

Systolic blood pressure was measured routinely in conscious restrained and warmed rats twice a week with the tail cuff method. In some cases, rats were equipped under ether anesthesia with an indwelling femoral artery catheter, which was exteriorized in the neck. After recovery from the operation, mean blood pressure was recorded directly in the conscious unrestrained rat by a strain gauge transducer.

Converting Enzyme Blockade

Sixteen-week-old SHR-sp (n = 14) received the converting enzyme inhibitor CAP 3 with tap water for 4 weeks (50 mg/kg/day); captopril was a kind gift of Dr. Z.P. Horovitz, Squibb Research Institute, Princeton, New Jersey). Electrophysiological experiments were performed when these rats were 20 weeks old. The results were compared with those from age-matched untreated SHR-sp and WKY rats.

In another experiment, SHR-sp and WKY rats were treated with CAP during their whole lifespan, starting in utero. Nine-week-old animals were used together with untreated SHR-sp and WKY rats of the same age either for the electrophysiological (n ≥ 10, each group) or for the biochemical (n ≥ 17, each group) studies.

Electrophysiological Experiments

Anesthetized animals (45 mg nembutal/kg body wt, given intraperitoneally) were tracheotomized and fixed in a stereotaxic instrument. The left septal area of the brain was exposed, and a multibarreled glass electrode, which allowed the extracellular recording of single unit discharges and the iontophoretic application of substances, was lowered by means of a micro-manipulator into the lateral septal area under microscopic control. The barrels of the compound glass micropipettes (tip diameter = 3-5 μm) contained acetylcholine chloride (ACH), 0.5 M, pH 3.0–3.5 (Fluka), All, 10−3 M, pH 4.5 (Calbiochem), and All receptor antagonist [Sar1, Ala8] All (saralasin, 10−3 M, pH 4.5; Norwich Pharmacal) for iontophoretic application, and 165 mM sodium chloride for control of current effects. Recordings were made with 2 M sodium chloride. The exposed brain surface was moistened with Ringers solution, and the temperature of the animals was kept constant at 37° C during the experiment. The neuronal activity was amplified and displayed on an oscilloscope and plotted directly on an ultraviolet oscillograph.

Biochemical Experiments

Angiotensinogen estimation in cerebral tissue requires that the brain be rinsed free from blood. For this, the abdominal cavity was opened under ether anesthesia and the aorta descendens was ligated above the kidneys. Then the thorax was opened and 10 ml of 1.5% ethylenediaminetetraacetic acid (EDTA) of 37° C was slowly infused into the left heart ventricle. At the same time, the right atrium was incised for bleeding. The brain was quickly removed after perfusion, and the regions were dissected out on ice under microscopic inspection, weighed, and deep-frozen until assayed. Nine of 52 brains had to be discarded, since they were not completely free from blood contamination. The brain tissue (10 to 60 mg wet wt) was homogenized in ice-cold 0.9% sodium chloride solution (500 μl) by sonication for 15 seconds (Branson B12 sonifier, microtip) and centrifuged in the cold at 10,000 g for 20 minutes. The supernatant was mixed with ice-cold 4 M ammonium sulfate in such a manner as to obtain a 2.3 M ammonium sulfate solution, and was incubated for 2 hours at 4° C. After centrifugation at 5000 g and 4° C, the supernatant was discarded. This procedure described before by others allows the precipitable angiotensinogen separation from the nonprecipitable angiotensinases. 23 The angiotensigen-containing proteins were resolubilized in ice-cold bidistilled water (200 μl for 10 mg of initial tissue weight) and were distributed into incubation vials (100 μl for angiotensigen and 50 μl for protein measurement respectively).

The angiotensinogen-containing aqueous extract (100 μl) was incubated at 37° C in 250 μl of 0.1 M tris-maleate buffer, pH 7.0, containing 2.5 mU hog kidney renin (Sigma Chemical Company, St. Louis, Missouri) together with 25 μl of an angiotensinase inhibitor cocktail. The following inhibitors were present in the incubation mixture: diisopropylphosphofluoride (DFP, 5.7 mMol/liter), dimercaptpropanol (BAL, 3.3 mMol/liter), 8-hydroxyquinoline sulfate (8-OHQ, 4.0 mMol/liter), and EDTA (6.7 mMol/liter). Aliquots of 100 μl were taken from the incubation at different times, the reaction was stopped, and the generated AI was measured by a specific radioimmunoassay. 24 The results are expressed as pmoles AI equivalents per milligram of precipitable protein.
For renin and angiotensinogen measurements in rat plasma, 500 µl of blood was withdrawn from the abdominal aorta under ether anesthesia into a syringe containing 5% (v/v) of angiotensinase inhibitors (25 mM o-phenanthroline and 71 mM EDTA). The blood was centrifuged immediately at 4° C. Plasma was decanted and distributed into incubation vials (50 µl) and kept frozen at −30° C until assayed. Renin substrate and renin in the plasma were estimated as indicated for brain angiotensinogen with the following exceptions: 50 µl of plasma was incubated with 650 µl of buffer containing either 5.0 mU hog kidney renin (JLI) or 50 µl of the angiotensinase inhibitor cocktail with 50 µl of the angiotensinase inhibitor cocktail. Results are given as pmol AI equivalents per milliliter of plasma and as pmol AI per milliliter per hour of incubation respectively.

The protein determination in the brain extract was performed as indicated by Lowry et al. using bovine serum albumin as a standard.

**Results**

The excitation characteristics of septal neurons that respond to All and ACh respectively are featured in table 1, which also includes some previously published results concerning untreated 20-week-old SHR-sp and WKY rats, for better comparison. The threshold and maximal response for All-evoked neuronal discharges occurred at a lower extrusion current, and the postactivity period was increased in the septal area, of 9-week-old SHR-sp compared with age-matched normotensive WKY rats. These results were identical with those from 20-week-old animals. The latency period of All-related neuronal discharges did not differ between strain and age, respectively.

The 4-week converting enzyme inhibition with CAP reduced systolic blood pressure in 20-week-old SHR-sp by 50 mm Hg to 190 mm Hg and influenced the sensitivity of neurons to All. There was an intermediate state between untreated SHR-sp and WKY rats with regard to the neuronal sensitivity (table 1).

The blockade of converting enzyme during the whole lifespan kept 9-week-old SHR-sp normotensive, and reduced the high sensitivity of septal neurons to All, as demonstrated by the significant elevation of threshold and maximal response (fig. 1 and table 1). Furthermore, the postactivity period was shortened in CAP-treated young SHR-sp. No such differences existed between treated and untreated 9-week-old WKY rats (fig. 1 and table 1).

The discharge characteristics of septal neurons due to the application of ACh were equal for both strains and both stages of age and were not affected by CAP-treatment (table 1). The maximal response for the ACh-related neuronal activity was not measured, since too high currents (exceeding 150 µA) used for drug extrusion caused unspecific effects themselves.

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**TABLE 1. Response of Septal Neurons to Iontophoretic Application of Angiotensin II and Acetylcholine in Stroke-Prone Spontaneously Hypertensive Rats and Wistar-Kyoto Rats of Different Ages (9 weeks old and 20 weeks old) With and Without Chronic Converting Enzyme Inhibition by Captopril (CAP)**

<table>
<thead>
<tr>
<th>Angiotensin II</th>
<th>9 weeks old</th>
<th>9 weeks old + CAP*</th>
<th>20 weeks old</th>
<th>20 weeks old + CAP†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (nA)</td>
<td>73 ± 16</td>
<td>68 ± 12</td>
<td>69 ± 10</td>
<td>15 ± 5²</td>
</tr>
<tr>
<td>Max. response (nA)</td>
<td>106 ± 30</td>
<td>88 ± 28</td>
<td>100 ± 31</td>
<td>31 ± 4²</td>
</tr>
<tr>
<td>Latency (sec)</td>
<td>22 ± 28</td>
<td>13 ± 19</td>
<td>39 ± 22</td>
<td>25 ± 20</td>
</tr>
<tr>
<td>Postactivity (sec)</td>
<td>20 ± 19</td>
<td>13 ± 18</td>
<td>33 ± 15</td>
<td>82 ± 174²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acetylcholine</th>
<th>9 weeks old</th>
<th>9 weeks old + CAP*</th>
<th>20 weeks old</th>
<th>20 weeks old + CAP†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (nA)</td>
<td>68 ± 19</td>
<td>75 ± 21</td>
<td>64 ± 33</td>
<td>72 ± 16</td>
</tr>
<tr>
<td>Latency (sec)</td>
<td>26 ± 16</td>
<td>13 ± 15</td>
<td>25 ± 18</td>
<td>22 ± 20</td>
</tr>
<tr>
<td>Postactivity (sec)</td>
<td>20 ± 15</td>
<td>14 ± 15</td>
<td>20 ± 11</td>
<td>10 ± 11</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>83 ± 1.9</td>
<td>70 ± 2.5²</td>
<td>150 ± 1.64*</td>
<td>95 ± 2.24*</td>
</tr>
</tbody>
</table>

**Systolic BP (mm Hg)**

<table>
<thead>
<tr>
<th>9 weeks old</th>
<th>128 ± 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 weeks old</td>
<td>244 ± 2.44*</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Number of cells or animals investigated is indicated in parentheses. *CAP treatment (50 mg/kg body wt/day) during whole life span. †Treatment with CAP for 4 weeks previous to the experiments. \( p < 0.001; \ p < 0.01; \ |p| < 0.05 \) (Student’s t test). •SHR-sp vs WKY; •CAP-treated rats vs untreated animals of the same strain.
The angiotensinogen concentrations in different brain regions of 9-week-old SHR-sp and WKY rats are presented in figure 2. The values varied from 0.37 pmol A1 equivalents/mg precipitable protein in the parietal cortex to 2.96 pmol A1/mg protein in the anterior hypothalamus. Elevated angiotensinogen levels were measured in the parietal cortex, the hippocampus, and the cerebellar cortex of SHR-sp as compared to WKY rats. An inverse relationship was found in the anterior hypothalamus, where angiotensinogen was decreased in the hypertensive rats. There was no difference in the angiotensinogen content between SHR-sp and WKY rats as to posterior hypothalamus, septal area, and brain stem.

Chronic inhibition of converting enzyme induced an increase of angiotensinogen content in the anterior hypothalamus of 9-week-old SHR-sp and WKY rats (fig. 2). In the hippocampus of hypertensive rats and in the brainstem of normotensive controls, CAP treatment attenuated the angiotensinogen concentrations, while no changes occurred in the other areas investigated (fig. 2).

Plasma renin concentrations were equal in SHR-sp and WKY rats, but plasma angiotensinogen was higher in SHR-sp (table 2). The chronic converting enzyme blockade stimulated renin and suppressed angiotensinogen in both strains (table 2).

**Discussion**

The existence of specific AII receptors in the septal area of the rat brain has been demonstrated in vitro and in vivo. In the present study, we report about several differences between SHR-sp and WKY rats with regard to the AII-evoked discharges of septal neurons. The increased sensitivity of septal neurons to AII in SHR-sp, which confirmed our earlier findings, does not seem to be dependent on the stage of hypertension, since the same results were obtained during development of high blood pressure at an age of 9 weeks as well as in 20-week-old SHR-sp with established hypertension. Converting enzyme blockade with CAP for 4 weeks slightly decreased blood pressure and attenuated the high sensitivity of septal neurons to AII in 20-week-old SHR-sp. Moreover, CAP treatment throughout lifespan kept 9-week-old SHR-sp normotensive, and restored the AII-related neuronal sensitivity to that found in WKY rats. This effect of converting enzyme blockade was related to SHR-sp only, since apparently no changes occurred in treated WKY rats, although the animals became slightly hypertensive. The specificity of the AII-related neuronal activation and its strain-related difference are underlined by the fact that ACh-induced discharges revealed no sensitivity changes, and that AII-evoked activities could be blocked by the AII receptor antagonist, saralasin.

Brain angiotensinogen was determined in whole tissue extract; thus, intra- and extracellular renin sub-

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**Figure 1.** Threshold for angiotensin II evoked excitation of septal neurons in 9-week-old stroke-prone spontaneously hypertensive rats (SHR-sp) (upper panel) and in age-matched Wistar-Kyoto (WKY) rats (lower panel) with and without chronic converting enzyme inhibition by captopril (CAP). N = number of neurons; each square corresponds to a single unit; applied current in nanoamperes (nA) for drug ejection at threshold level. For significance of difference, see table 1.

**Table 2. Angiotensinogen and Renin Concentrations in Plasma of 9-week-old Stroke-Prone Spontaneously Hypertensive Rats (SHR-sp) and Age-Matched Wistar-Kyoto Rats (WKY) With and Without Converting Enzyme Inhibition by Captopril (CAP)**

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>WKY + CAP</th>
<th>SHR-sp</th>
<th>SHR-sp + CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensinogen (pmol A1/ml)</td>
<td>466.1 ± 9.7</td>
<td>69.6 ± 12.1*</td>
<td>538.6 ± 9.8*</td>
<td>105.7 ± 6.6*</td>
</tr>
<tr>
<td>(9)</td>
<td>(7)</td>
<td>(9)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>Renin (pmol A1/ml/hr)</td>
<td>12.1 ± 1.6</td>
<td>303.7 ± 44.0**</td>
<td>16.4 ± 1.3</td>
<td>325.4 ± 8.2**</td>
</tr>
<tr>
<td>(11)</td>
<td>(7)</td>
<td>(9)</td>
<td>(8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM; number of animals is indicated in parentheses. *p < 0.001 (Student's t test); SHR-sp vs WKY; CAP-treated animals vs untreated rats of the same strain.
EFFECT OF CAPTOPRIL ON BRAIN ALL AND ANGIOTENSINOGEN/Schelling et al. 939

FIGURE 2. Angiotensinogen content (pmol All/mg precipitable protein) in distinct brain regions of 9-week-old stroke-prone spontaneously hypertensive rats (SHR-sp) and age-matched Wistar-Kyoto (WKY) rats with and without chronic converting enzyme inhibition by captopril (CAP). Values are means ± SEM measured from 8 to 10 tissue samples; ** p < 0.01. SHR-sp vs WKY controls; * p < 0.05. CAP-treated animals vs untreated rats (Student's t test).

strate content could not be distinguished. An overall interstitial distribution of angiotensinogen, which may represent an overflow from brain tissue that drained into the cerebrospinal fluid for clearance,24 could veil the more meaningful intraneuronal prohormone content. Contamination of the brain angiotensinogen pool by plasma renin substrate was avoided, however, by the rinsing procedure followed by careful microscopic inspection of the brains and the brain regions of interest, and the discarding of those containing traces of blood. It should be noted, in this respect, that CAP treatment induced a rise of the angiotensinogen content in the anterior hypothalamus of SHR-sp and WKY rats, whereas it strongly suppressed plasma renin substrate. This supports the view that angiotensinogen is synthesized within the central nervous system and does not come from circulating prohormone entering the brain.24, 29 The angiotensinogen concentrations, being lowest in the parietal cortex and highest in the anterior hypothalamus, are in agreement with the values reported by others.23 The angiotensinogen content in the anterior hypothalamus was decreased in the SHR-sp as compared to WKY rats, but tended to be elevated in some other brain regions. Surprisingly, a homogeneous and rather low concentration was measured in the septum of both strains, and neither the high sensitivity of neurons to All in SHR-sp nor its attenuation by CAP found any expression in the tissue levels of angiotensinogen. Angiotensinergic fibers probably originating in another region could reach the septal area where they could influence the neuronal activity by the release of All. The septal angiotensinogen content would be without importance, therefore, in the local activation of those neurons.

Several studies have shown involvement of the brain RAS in the malfunction of cardiovascular control in SHR. The exaggerated responses of centrally applied All on blood pressure and water intake2-8 and the blood pressure lowering effects of intracerebral blockade of either All receptors9, 10, 12 or All synthesis in SHR11, 13-15 merit attention in this respect. The increased sensitivity of septal neurons to All reported here is consistent with these findings, particularly since chronic converting-enzyme blockade prevented the pathogenesis of hypertension and completely normalized the properties of these neurons to All. A possible role for drinking behavior is discussed for the septal area,31, 32 and limbic structures may be implicated in cardiovascular adaptations to emotional stimuli.33 Moreover, the development of DOCA-salt hypertension was recently reported to be prevented in rats with lesions of the lateral septal area.34 Thus, these and our results suggest that brain septum could take part in blood pressure regulation. The properties of septal neurons in SHR-sp may also reflect the qualities of All-sensitive neurons in other brain regions, which
could be related to blood pressure control. For instance, the organum vasculosum of the lamina terminalis (OVLT) has been shown to contain All-sensitive neurons, and to be critical for All-related central effects.

In agreement with our in vivo studies on septal neurons, Stamler and colleagues observed an increased specific binding of All to membranes prepared from OVLT of SHR as compared to WKY rats. Some differences between both strains concerning the in vitro binding of All to brain receptors in relation to age and to sodium have been shown, too. These differences include an elevated receptor capacity in SHR on a low sodium diet and an enhanced receptor sensitivity in young SHR. Comparative investigation of the distribution of several components of the brain RAS in SHR and WKY rats has revealed further differences, e.g., elevated renin concentrations in the brain stem and neurohypophysis of SHR-sp, decreased AI converting enzyme in the brain stem, hypothalamus, and cortex of SHR, and an enhanced All-like immunocytochemical staining of the stria terminalis and of fibers in the frontal hypothalamus of SHR.

In addition, we report now that the angiotensinogen content was lower in the anterior hypothalamus of SHR-sp but higher in some other brain areas compared to normotensive WKY rats. Moreover, angiotensinogen appears to accumulate in the anterior hypothalamus of both SHR-sp and WKY rats under CAP treatment. The functional significance of the lower prohormone content of this region in SHR-sp is not yet known. It could be interpreted either as a decreased local angiotensinogen synthesis or as an increased turnover of the local brain RAS in the hypertensive animals. In fact, the AI accumulation within the hypothalamus was observed to be more prominent in SHR-sp than in WKY rats after the acute central blockade of AI conversion (Ganten and Hermann, personal communication). An increased turnover of the brain RAS at least in some regions in combination with an enhanced sensitivity of intracerebral receptors to All may contribute, therefore, to the pathogenesis of hypertension in the Japanese strain of SHR. Somewhat controversial results were obtained in the New Zealand strain of genetic hypertensive rats. Sirett and coworkers measured a lower All receptor binding in SHR compared to that of controls. No exaggerated response of centrally applied All either on water intake or on blood pressure was observed in this rat strain. In addition, immunoreactive All-like material was found to be elevated in the cerebrospinal fluid of the New Zealand SHR; this was never seen in SHR-sp compared to controls. In spite of these differences, however, central blockade of All receptors by saralasin applied i.v. also attenuated the high blood pressure in the New Zealand SHR.

Before we discuss the mechanisms of actions by which converting enzyme inhibition influenced the brain RAS, the question should be answered as to whether CAP had passed the blood brain barrier. It is generally assumed that CAP does not permeate into brain tissue after acute i.v. or mouth administration. The drug, however, probably gains access to the brain under the conditions described here (given by mouth over several weeks at a high dose), since brain renin was observed to be increased in comparable experiments. The suppression of All formation could have down-regulated the enhanced neuronal sensitivity for All in the brain of SHR-sp without affecting it under unstimulated conditions in WKY rats. Such a positive regulation between effector and receptor has been reported to exist between plasma All and its adrenal receptors. Studies of vascular smooth muscle have shown that CAP can have membrane effects changing the receptor sensitivity to pressor agents. Although these actions were sometimes ascribed to the inhibition of intravascular All synthesis, they could nevertheless be independent from a RAS. Thus, such changes of membrane properties could also account for the attenuated All sensitivity of neurons in SHR-sp. As for angiotensinogen, a differential regulation is evident. Captopril attenuated brain renin substrate in some regions but augmented it in the anterior hypothalamus. We have shown before that CAP tended to decrease the angiotensinogen levels in cerebrospinal fluid. We suggested that the strong suppression of plasma angiotensinogen under those conditions was due to the increased consumption of substrate by the elevated plasma renin and to the missing stimulatory effects of All. This augmentation may also be applicable to the brain regions where a decrease of renin substrate was observed. As far as the anterior hypothalamus is concerned, the regulatory mechanisms are clearly different from those in plasma. The stimulation of angiotensinogen probably is a compensatory response to the suppression of renin substrate in plasma or to the fall in blood pressure observed in both strains under CAP treatment.

Conclusions

We demonstrated a different activity of the brain RAS in SHR-sp as compared to WKY rats, which was especially shown by the higher sensitivity of septal neurons to All in SHR-sp and the lower angiotensinogen content in the anterior hypothalamus of these rats. The CAP treatment kept SHR-sp normotensive and completely reduced the enhanced receptor sensitivity to All so that it was the same as measured in WKY rats. The angiotensinogen levels were increased in both strains under the CAP treatment, whereas the effect on the receptor sensitivity was confined to the SHR-sp only. The lower angiotensinogen content in the anterior hypothalamus of SHR-sp could be due to an increased consumption of brain substrate. This together with an enhanced sensitivity of brain receptors to All may support the view of a brain RAS being more active in SHR-sp than in WKY rats. Since converting enzyme blockade partly restored parameters of the brain RAS in SHR-sp as compared to WKY rats and, furthermore, lowered blood pressure in the hypertensive animals, a causal link between brain RAS and central blood pressure control may be possible.
Acknowledgments

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