Brain angiotensin II stimulates release of pituitary hormones, plasma catecholamines and increases blood pressure in dogs

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Summary

1. The mechanisms of central angiotensin II blood pressure effects in conscious dogs on normal or sodium-deficient diets were examined.
2. The biosynthesis of brain angiotensin II in cerebrospinal fluid from its local precursor angiotensinogen was induced in vivo by injection of 0.5 unit of hog kidney renin through a chronically implanted cannula into the third brain ventricle in conscious dogs.
3. Intracerebroventricular administration of renin induced an increase of arterial blood pressure and a marked drinking response under both dietary regimens. Sodium restriction had no effect on the magnitude of the central angiotensin pressor response.
4. Plasma concentrations of renin and angiotensin II decreased, and plasma antidiuretic hormone, noradrenaline, adrenaline and corticosterone increased, in both groups of dogs.
5. Simultaneous intraventricular administrations of captopril with renin inhibited the central renin effects. Intracerebroventricular injections of [Sar¹, Val⁵, Ala⁹] angiotensin II alone increased plasma renin and angiotensin II concentrations.
6. It is concluded that endogenous brain angiotensin II participates in central mechanisms of blood pressure regulation by the stimulation of the release of antidiuretic hormone, adrenocorticotropic hormone, adrenaline and noradrenaline.

Key words: angiotensin II antagonists, brain, catecholamines, central blood pressure regulation, pituitary hormones, renin-angiotensin system.

Abbreviations: CSF, cerebrospinal fluid; IVT, intracerebroventricular.

Introduction

When angiotensin II (ANG II) is injected into the brain ventricles it produces an increase of arterial blood pressure, release of pituitary hormones, stimulates drinking behaviour and interferes with memory processes (Severs & Daniels-Severs, 1973; Morgan & Routtenberg, 1977; Brosnihan, Berti & Ferrario, 1979; Koller, Krause, Hoffmeister & Ganten, 1979; Simonnet, Rodriguez, Fumoux, Czernichow & Vincent, 1979). Evidence that ANG II can be generated within the brain in connection with a brain renin-angiotensin system has been presented (Ganten & Speck, 1978). The biosynthesis of endogenous brain ANG II from its local precursor angiotensinogen can be induced in vivo by injection of renin into the brain ventricles. Owing to the high concentrations of angiotensinogen in cerebrospinal fluid (CSF) (Printz & Lewicki, 1977) ANG I can be generated from angiotensinogen, if renin is injected intracerebroventricularly. Brain converting enzyme will then convert ANG I into ANG II, which stimulates specific brain ANG II receptors, inducing an increase of arterial blood pressure (Ganten & Speck, 1978).

The present experiments in conscious dogs were carried out to evaluate the mechanisms of blood pressure changes induced by locally formed brain ANG II and to assess whether sodium restriction could influence the mechanisms of central ANG II blood pressure effects.
Methods

Adult male beagles between 14.5 and 19.0 kg with a chronically implanted cannula in the third brain ventricle \((n = 5)\) were kept on a normal control diet (70 mmol of sodium, 205 mmol of potassium/day). Sodium restriction was produced in the same dogs 8-12 weeks later by a low salt diet (C 4036, Altromin GmbH, 4937 Lage, F.R. Germany), which provides 6 mmol of sodium daily and by administration of frusemide (10 mg/kg orally) for 7 days. Tap water was available ad libitum. The dogs were kept in individual metabolic cages during sodium depletion.

All drugs were dissolved in 0.9% sodium chloride solution (saline). Injections of 0.5 unit of hog kidney renin (NBC, Cleveland, Ohio, U.S.A.), the ANG II antagonist \([\text{Sar}^1, \text{Val}^5, \text{Ala}^8]\) ANG II (10 \(\mu\)g/kg), 500 \(\mu\)g of the ANG converting enzyme inhibitor captopril (SQ 14225) and saline (control) were administered intracerebroventricularly in a volume of 25 \(\mu\)L.

Arterial blood pressure was measured directly in the femoral artery via a pressure transducer (Statham P 23 Db).

Blood was taken from a brachial vein at 20 min before and at 15, 60 and 300 min after intracerebroventricular injections. Plasma renin concentration, ANG II, corticosterone and ADH were determined by radioimmunoassay (Mann, Johnson & Ganten, 1980). Noradrenaline and adrenaline in plasma were measured by a radioenzymatic method (Da Prada & Zürcher, 1976).

In separate experiments the volume of water drunk 60 min after the intracerebroventricular injections was recorded.

The dogs were all adapted to the experimental procedure and all experiments were performed in conscious unrestrained dogs.

Values are given as means ± SEM. Results were analysed by Student’s paired and unpaired \(t\)-test if appropriate. The 5% probability level was used as the criterion of significance.

Results

Intracerebroventricular injections of renin in a dose of 0.5 unit induced an increase of arterial blood pressure \((P < 0.001)\) in dogs on a normal and on a low sodium diet. Sodium restriction had no significant effect on the magnitude of the renin-induced pressor response.

Drinking was stimulated in all dogs on both regimens 3–15 min after renin injections into the third brain ventricle \((P < 0.001)\). Between 350 and 1600 ml of water was drunk within 1 h after intracerebroventricular renin. Simultaneous intracerebroventricular injections of renin with captopril completely inhibited the centrally evoked drinking response. Intracerebroventricular \([\text{Sar}^1, \text{Val}^5, \text{Ala}^8]\) ANG II given alone was without influence on water consumption.

After intracerebroventricular renin plasma renin concentration decreased by 25\% \((P < 0.05)\) in dogs on a normal diet and by 58\% from 24.7 ± 6.5 to 10.4 ± 4.6 pmol of ANG I h\(^{-1}\) ml\(^{-1}\) \((P < 0.01)\) in sodium-depleted dogs. In the same animals ANG II decreased by 55\% from 227 ± 37 to 102 ± 26 fmol/ml \((P < 0.01)\). Intracerebroventricular injection of the ANG II antagonist saralasin alone caused the opposite effect: an increase of plasma renin \((P < 0.01)\) and of ANG II concentrations \((P < 0.05)\); the same changes were also seen after simultaneous injection of captopril in combination with renin.

Intracerebroventricular administration of renin increased ADH, noradrenaline, adrenaline and corticosterone in dogs on both dietary regimens. In dogs on a normal diet ADH increased threefold \((P < 0.05)\), noradrenaline by 58\% \((P < 0.02)\), adrenaline by 81\% \((P < 0.05)\) and corticosterone by 86\%. In dogs on a low sodium diet ADH increased by 159\% from 3.6 ± 0.4 to 9.4 ± 3.4 pg/ml, noradrenaline by 76\% from 0.21 ± 0.05 to 0.37 ± 0.07 ng/ml, adrenaline by 27\% from 0.24 ± 0.06 to 0.30 ± 0.03 ng/ml and corticosterone by 157\% from 0.7 ± 0.1 to 1.8 ± 0.1 \(\mu\)g/100 ml \((P < 0.001)\). These central renin

![Fig. 1. Effects of intracerebroventricular administration of renin on plasma concentrations of renin, ADH, noradrenaline, adrenaline, corticosterone, on arterial blood pressure and on water consumption in conscious dogs on a normal diet \((n = 5)\). Results are given as means ± SEM. Open columns, control; striped columns, after intracerebroventricular injection of 0.5 unit of renin. *\(P < 0.05\); **\(P < 0.02\); ***\(P < 0.01\); ****\(P < 0.001\).](image-url)
effects were inhibited by simultaneous intracerebroventricular injections of captopril. Intracerebroventricular saralasin alone was without significant effect on plasma catecholamines, ADH or corticosterone.

**Discussion**

Intracerebroventricular administration of renin leads to the local formation of brain ANG II, which in turn increases arterial blood pressure (Reid & Ramsay, 1975; Schölken, Steinbach & Ganten, 1979; Schelling, Ganten, Sponer, Unger & Ganten, 1980). The magnitude of this central pressor response to endogenously formed brain ANG II or to exogenously administered ANG II (Brosnihan et al., 1979) in dogs is not influenced by sodium restriction, whereas peripheral intravenous pressor responses to ANG II were attenuated by sodium depletion (Liang, Gavras & Hood, 1978), suggesting different mechanisms in the brain and periphery. In all dogs on both regimens copious drinking was induced by intracerebroventricular renin (Reid & Ramsay, 1975). This drinking behaviour in response to central ANG II during various states of sodium balance was also seen in rats (Kapsha, Keil, Klase & Severs, 1979). The ANG converting enzyme inhibitor captopril completely inhibited the centrally evoked drinking responses in dogs and the pressor responses in rats (Schölken, 1979). Plasma renin and plasma ANG II concentrations decreased in all dogs. However, the suppression was more prominent after sodium restriction with an activated plasma renin–angiotensin system. This is in agreement with results in rats maintained on a low sodium intake where plasma renin activity was suppressed after intracerebroventricular injection of ANG II (Kapsha et al., 1979). In contrast, intracerebroventricular injection of saralasin caused the opposite effect: an increase of plasma renin and ANG II. Thus there appears to be a coupling between the brain renin–angiotensin system and the circulating plasma renin–angiotensin system (Reid & Day, 1977; Ganten & Stock, 1978; Kapsha et al., 1979), which may be mediated by blood pressure changes or by humoral and/or neural pathways (Ganten & Speck, 1978).

Stimulation of brain ANG II biosynthesis increased plasma ADH in conscious dogs as it was seen with intracerebroventricular injections of ANG II in monkeys (Simonnet et al., 1979) and rats (Haack & Möhring, 1978). Apart from its volume-retaining effect, ADH has been proposed to be also a pressor hormone (Möhring, 1978) and to potentiate vascular effects of various vasoconstrictor agents (Karmazyn, Manku & Horrobin, 1978). The dependence of pressor responses elicited by intracerebroventricular injection of ANG II on the release of ADH has been demonstrated (Hutchinson, Schelling, Möhring & Ganten, 1976). The parallel increase of noradrenaline and adrenaline after intraventricular ANG II generation indicates that both the sympatho-neuronal and the sympatho-adrenal axis may be stimulated (Ganten, Unger, Rockhold, Schaz & Speck, 1979). After injections of renin into the brain ventricles, plasma corticosterone, probably mediated by adrenocorticotropic hormone release, was in greatly raised concentration. This confirms previous reports (Reid & Day, 1977), and is of particular interest because corticosterone increases the sensitivity of vascular smooth muscle to vasopressor agents (Dietz, Schömig, Haebara, Mann, Rascher, Lüth, Grünherz & Gross, 1978). Furthermore, corticosterone increases brain angiotensinogen content, which could in turn increase the central ANG II biosynthesis (Wallis & Printz, 1980). The concomitant increase of catecholamines, corticosterone and ADH after stimulation of brain ANG II biosynthesis may thus represent a self-potentiating mechanism to increase blood pressure. Previous work has shown that this humoral pattern is characteristic for central peptidergic stimulation (Ganten et al., 1979).

**References**


