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CENTRAL ANGIOTENSIN II INCREASES URINARY FREQUENCY BY ACTING ON BRAIN AT1 RECEPTORS IN RATS

Hypothesis / aims of study

It is known that stress or strain induces voiding frequency [1]. There have been only a limited number of reports on the mechanism of voiding frequency under stress. Although angiotensin II (Ang II) is known as a pressor substance, Ang II is known to be one of the neuropeptides involved in the stress reaction. Previous reports revealed that Ang II is involved in activation in a sympatho-adrenomedullary system as a central neurotransmitter [2]. The aim of the present study was to investigate the relationship with the voiding reflex and the role of central Ang II as a neurotransmitter.

Study design, materials and methods

Thirty-two male Wistar rats (12-week-old) were anesthetized with urethane (1.0 g/kg, i.p.) and catheterized into the bladder dome, and then the catheter was connected to a pump for saline infusion (12 mL/h) and a pressure transducer. A catheter into a femoral artery was connected to a pressure transducer, and a catheter into a femoral vein was connected for saline infusion (1.2 mL/h). Cystometry (CMG) was performed after undergoing stereotaxis and burr hole opening (0.8 mm posterior, 1.5 mm right from the bregma; 4.0 mm below the surface of the brain; the position of the right lateral ventricle) in the prone position (Figure 1). Three hours after the catheterization, the rats were distributed as follows: 1) vehicle (deionized water) intracerebroventricular administration (i.c.v.); 2) Ang II i.c.v.; 3) valsartan (selective AT1R blocker) 10 nmol (3 µL) i.c.v. before Ang II i.c.v.; 4) PD123319 (selective AT2R blocker) 100 nmol (5 µL) i.c.v. before Ang II i.c.v.; 5) valsartan 100 nmol (200 µL) intravenous administration (i.v.) before Ang II i.c.v.; 6) PD123319 100 nmol (200 µL) i.v. before Ang II i.c.v.; and 7) bilateral adrenalectomy (ADX) with hydrocortisone (5 mg/kg per animal) supply before starting CMG and Ang II i.c.v. Ang II (0.01 nmol/µL) and vehicle were administered at 3 doses, 1 µL, 2 µL, and 7 µL, at an interval of 1 hour. Valsartan or PD123319 was administered 30 minutes before the initial Ang II administration. In the CMG, the intercontraction interval (ICI) and maximum detrusor pressure (Pdet) were evaluated. Arterial blood was sampled before blocker administration and initial Ang II i.c.v. and 5 minutes after each Ang II i.c.v. for measurements of peripheral plasma adrenaline (Ad) and noradrenaline (NA) by HPLC.

Results

In comparison with the vehicle-treated group, Ang II administration significantly decreased ICI dose-dependently without alteration of Pdet. Central valsartan administration abolished the Ang II-mediated decrease in ICI. On the other hand, central PD123319 administration did not affect ICI (Figure 2). In our preliminary study, both central administration of valsartan and of PD123319 failed to decrease ICI. Ang II decreased ICI even with intravenous administration of valsartan or PD123319. There was no significant difference in plasma Ad and NA between the vehicle-treated group and the Ang II-treated group. Although ADX was performed, Ang II administration significantly decreased ICI. There was no significant difference in Pdet among the groups.

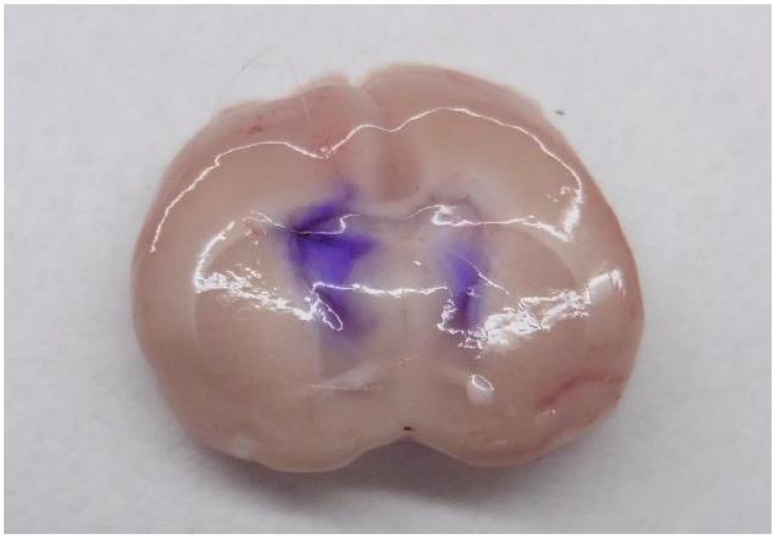

Figure 1: Experimental rat brain section
Crystal violet was administered after the all experiments to comfirm the accuracy of the i.c.v. injection site.

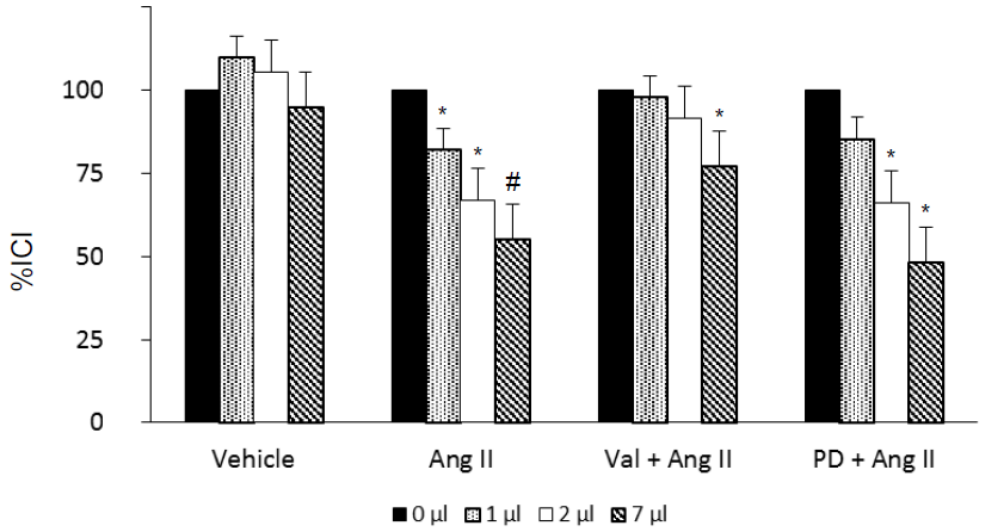

Figure 2: Effects of centrally administered angiotensin II and AT1 or AT2 receptor blocker on ICI
Vehicle and Ang II were serially administered at an interval of 1 hour. CMG was performed every hour after i.c.v. administration. Relative values of ICI calculated as the ratio of the average of those measured for 10 minutes after the administration to the average of those measured for 10 minutes before the initial Ang II administration. Valsartan and PD123319 were administered 30 minutes before the initial Ang II i.c.v. administration.
Ang II: angiotensin II 0.01 nmol/µL i.c.v.; Val: Valsartan 10 nmol/3 µL i.c.v.; PD: PD123319 100 nmol/5 µL i.c.v.
* $p < 0.05$, significantly different from the %ICI before initial Ang II administration.
# $p < 0.05$, significantly different from the %ICI before initial and 1 µL Ang II administration.

Interpretation of results

In the current data, the ICI was measured for 10 minutes after Ang II administration because Ang II is metabolized in the early phase and has a half-life of < 2 minutes at 37 °C [3]. The present data showed that Ang II increased urinary frequency without an effect on Pdet. A centrally administered AT1R blocker, but not an AT2R blocker, abolished the Ang II-induced decrease in ICI. In this study, central administration of a low dose (10 nmol) of valsartan was performed because the high dose (100 nmol) i.c.v. caused severe hypotension in our preliminary study, indicating that central endogenous Ang II was acting as a pressor. Peripheral valsartan or PD123319 administration failed to abolish the Ang II-mediated decrease in ICI. Because the plasma Ad and NA could affect the voiding reflex, ADX was performed to abolish the effects of plasma Ad and NA. The present data showed that there was no significant difference in the ICI between the Ang II group and the ADX pre-treated Ang II group. It could be speculated that there were no relationships between ICI and plasma Ad and NA with central Ang II administration.

Concluding message

Central administration of Ang II decreased ICI without an effect on Pdet by acting on brain AT1 receptors.

References

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Disclosures

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