Angiotensin II, a stress-related neuropeptide facilitates micturition reflex in rats

Shogo Shimizu, Takahiro Shimizu, Kumiko Nakamura, Youichirou Higashi, Takaaki Aratake, Suo Zou, Motoaki Saito

Pharmacology, Kochi University, Japan

Introduction: Psychological stress is involved in the development of the lower urinary tract symptoms. We investigated the effects of centrally administered angiotensin II (Ang II), a stress-related neuropeptide on the micturition reflex, and the downstream signaling mechanisms.

Methods: Study (1): Male Wistar rats (330-430 g) were anesthetized with urethane, and cystometry was performed. Ang II (10, 20, and 70 pmol/rat, icv) was serially administered. The effects of pretreatment with icv- or iv-administered Ang II type 1 (AT1) or type 2 (AT2) receptor antagonist [valsartan (10 nmol icv or 100 nmol/rat, iv) or PD123319 (100 nmol/rat, icv or iv)] on the Ang II-induced responses were evaluated.

Study (2): In anesthetized male Wistar rats, Ang II [(0 or 30 pmol/rat, icv) or (100 or 300 pmol/rat, iv)] was administered. Muscimol (a GABA_A receptor agonist; 100 or 300 pmol/rat) or baclofen (a GABA_B receptor agonist; 30 or 100 pmol/rat) was icv administered 30 min before or 15 min after icv administration of Ang II. Moreover, U-73122 (a PLC inhibitor; 300 or 1000 pmol/rat), chelerythrine (a PKC inhibitor; 300 or 1000 pmol/rat), apocynin [a NADPH oxidase (NOX) inhibitor; 20 or 200 nmol/rat], or tempol (an anti-oxidant; 2 or 20 nmol/rat) was icv administered 30 min before icv Ang II administration.

Results: Study (1): Central administration of Ang II rapidly and dose-dependently decreased the urinary bladder intercontraction interval (ICI) without altering maximum voiding pressure, blood pressure, or plasma concentration of catecholamine. Central pre-treatment with valsartan (but not PD123319) significantly suppressed central Ang II-induced shortening of ICI.

Study (2): Compared to the vehicle-treated group, icv-administered Ang II (but not iv-administered Ang II) significantly decreased threshold pressure, single voided volume, and bladder capacity. Central pre-treatment with muscimol, baclofen, U-73122, chelerythrine, apocynin or tempol significantly and dose-dependently suppressed central Ang II-induced shortening of ICI. Moreover, central post-treatment with muscimol or baclofen ameliorated central Ang II-induced shortening of ICI.

Conclusions: Central Ang II helps facilitate the rat micturition reflex by inhibiting the GABAergic nervous system and activating AT1 receptor/PLC/PKC/NOX/superoxide anion pathways.