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Angiotensin II-activated Apoptosis in the RVLM Contributes to Sympathoexcitation through the Activation of Ras/MAPK/ERK Pathway

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Background: The rostral ventrolateral medulla (RVLM) regulates sympathetic outflow. Angiotensin II-derived superoxide anion in the RVLM induces the production of reactive oxygen species, which activates mitogen-activated protein kinase (p38 MAPK) and extracellular signal-regulated kinase (ERK). Ras mediates caspase 3-dependent apoptosis through the activation of p38 MAPK and ERK. We hypothesized that angiotensin II-activated caspase 3-dependent apoptosis in the RVLM contributes to sympathoexcitation through the activation of Ras/p38 MAPK/ERK pathway in stroke-prone spontaneously hypertensive rats (SHRSP). **Methods and Results:** Telemetrically measured mean blood pressure (MBP) and heart rate (HR) under a conscious state, and SNA assessed by urinary norepinephrine excretion, were significantly higher in SHRSP than in Wistar-Kyoto (WKY) rats. Activities of Ras, p38 MAPK, ERK, and caspase 3 in the RVLM were significantly higher in SHRSP than in WKY (Ras; 1.7 ± 0.2 U vs 1.3 ± 0.2 U, p38 MAPK; 1.8 ± 0.1 U vs 1.2 ± 0.3 U, ERK; 2.1 ± 0.3 U vs 1.4 ± 0.3 U, caspase 3; 1.7 ± 0.1 U vs 1.1 ± 0.2 U, $n=5$ for each, $P<0.01$). Mitochondrial apoptotic proteins Bax and Bad in the RVLM were also significantly increased in SHRSP. In SHRSP, intracerebroventricular (ICV) infusion of Ras inhibitor, Z-DEVD-FMK, significantly reduced MBP, HR, and SNA (MBP; -38 ± 4 mmHg, HR; -44 ± 18 bpm, SNA; -0.8 ± 0.2 μ g/day, $n=5$ for each, $P<0.01$) (Figure 1) and inhibited activities of Ras/p38 MAPK/ERK, Bax, Bad, and caspase 3 in the RVLM. ICV of caspase 3 inhibitor also decreased MBP, HR, and SNA in SHRSP. ICV of angiotensin II type 1 receptor blocker in SHRSP decreased MBP, HR, and SNA (MBP; -34 ± 5 mmHg, HR; -52 ± 14 bpm, SNA; -0.9 ± 0.2 μ g/day, $n=5$ for each, $P<0.01$) and reduced activities of Ras/p38 MAPK/ERK, Bax, Bad, and caspase 3 in the RVLM. **Conclusion:** Angiotensin II/AT1 receptor-activated caspase 3-dependent apoptosis in the RVLM increases SNA through the activation of Ras/p38 MAPK/ERK pathway in SHRSP. This mechanism of sympathoexcitation may play a crucial role in the pathogenesis of hypertension.

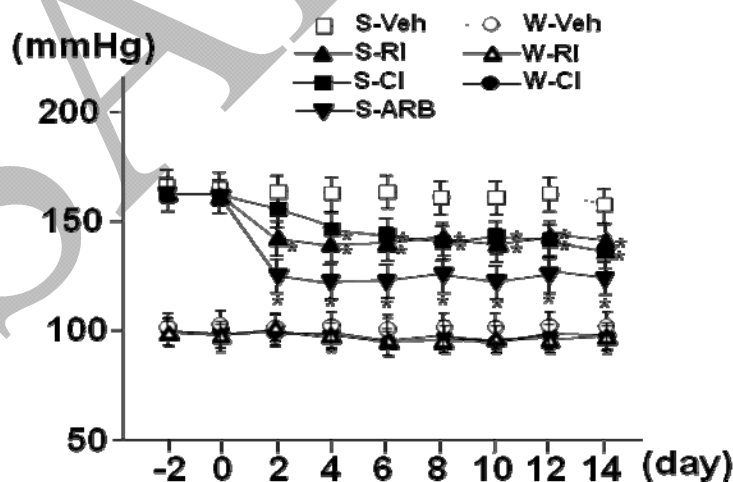


Figure 1. Time courses of mean blood pressure

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