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ATP-MEDIATED SIGNALLING IN THE PRE-SYMPATHETIC AREA OF THE BRAINSTEM IS CRITICAL FOR THE DEVELOPMENT OF HYPERTENSION IN SPONTANEOUSLY HYPERTENSIVE RATS

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Introduction Increased sympathetic drive is associated with the development and progression of essential hypertension. Pharmacological studies have shown a direct stimulatory effect of ATP on bulbospinal sympathoexcitatory (pre-sympathetic) neurones of the rostral ventrolateral medulla oblongata (RVLM), leading to marked increases in sympathetic nerve activity and arterial blood pressure (BP). The aim of this study was to determine whether ATP actions within the RVLM contribute to the control of arterial BP in normotensive and hypertensive rats.

Methods We developed a lentiviral vector (LVV) to drive the expression of a potent membrane-bound ectonucleotidase "transmembrane prostatic acid phosphatase (TMPAP) for facilitated breakdown of extracellular ATP. LVV-TMPAP or control LVV-GFP were injected stereotaxically into the RVLM of pre-hypertensive (8-weeks-old) spontaneously hypertensive rats (SHRs) and age-matched Wistar rats. BP measurements were performed by occlusive tail cuff method. Measurements were commenced 1 week after the injections and repeated weekly for 4 weeks.

Results Expression of TMPAP in the RVLM of SHRs resulted in a significant reduction in arterial BP. Three weeks after the injections, SHRs transduced to express TMPAP in the RVLM had mean arterial BP of 115.6±8.8 mmHg (n=7), which was significantly (p=0.009) lower than that in SHRs transduced to express GFP (152.9 ±8.4 mmHg, n=9). In comparison, TMPAP expression in the RVLM had no significant effect on the mean arterial BP of control Wistar rats (91.4±4.5 vs 92.6±3.5 mmHg, p=0.836, n=8 in both groups).

Conclusion Increased breakdown of extracellular ATP in the brainstem area where the key sympathoexcitatory neurones reside reduces the degree of hypertension in the SHR. These data suggest that ATP-mediated signalling has a significant impact on brain pre-sympathetic circuits and appears to be critical for the development of essential hypertension.