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COMMENT

ATRAP in the paraventricular nucleus of the hypothalamus as another key player in the control of sympathetic outflow

Kenichi Katsurada[1,2]

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Inappropriate activation of the sympathetic nervous system is one of the pathophysiological hallmarks of hypertension. Specific areas in the central nervous system (CNS) including the paraventricular nucleus (PVN) of the hypothalamus and the rostral ventrolateral medulla (RVLM) govern sympathetic outflow to regulate blood pressure [1]. RVLM neurons project to the sympathetic preganglionic nuclei of the spinal cord (intermediolateral cell column: IML) to control sympathetic outflow in peripheral organs, including the heart, kidneys, and blood vessels. PVN neurons project to the IML directly or via the RVLM to modulate sympathetic outflow. The circumventricular organs such as the subfornical organ (SFO), organum vasculosum lamina terminalis (OVLT), and median preoptic nucleus (MnPO) lack a blood–brain barrier and can thus sense the concentrations of angiotensin II (Ang II) in the serum.

In addition, the use of a fluorescent retrograde tracer revealed a neuroanatomical connection among the SFO, MnPO, and PVN in rats [2]. The activation of the MnPO after a microinjection of N-methyl-D-aspartate was shown by extracellular single-unit recording to increase the activity of PVN neurons in rats [2]. Another study demonstrated that the Ang II type 1 receptor (AT1R) is upregulated in the SFO of rats with heart failure, which is another condition with enhanced sympathetic nerve activity. Consistent with this finding, increases in blood pressure, heart rate, and renal sympathetic nerve activity (RSNA) in response to a microinjection of Ang II into the SFO were observed to be enhanced in rats with heart failure. A microinjection of the AT1R antagonist losartan into the SFO decreased the blood pressure, heart rate, and RSNA in rats with heart failure [3]. It is thus apparent that circulating Ang II can act on the SFO and MnPO to convey signals to the PVN, thereby influencing the sympathetic outflow and blood pressure.

The renin-angiotensin system (RAS) in the CNS contributes to the regulation of blood pressure independent of the circulatory RAS. It has been reported that an intracerebroventricular (ICV) infusion of Ang II increased the number of FosB-labeled cells in the PVN of rats, suggesting an activation of the preautonomic neurons. Concurrently, an ICV infusion of Ang II leads to an enhanced basal level of RSNA and an increase in blood pressure [4]. Other studies demonstrated that a microinjection of Ang II into the PVN increases blood pressure, heart rate, and RSNA. These responses to Ang II are augmented in rats with heart failure. In addition, a microinjection of losartan into the PVN decreased the blood pressure, heart rate, and RSNA of rats with heart failure, whereas significant changes in response to losartan were not observed in control rats [5, 6]. These findings suggest that the RAS in the PVN has a critical role in regulating sympathetic outflow and blood pressure.

In a study published in this issue of the *Hypertension Research*, Sotozawa and Kinguchi et al. examined the role of AT1R-associated protein (ATRAP) in the PVN in the regulation of the blood pressure of hypertensive rats induced by a systemic Ang II infusion. ATRAP promotes AT1R internalization and functions as an endogenous inhibitor, selectively suppressing the pathological overactivation of AT1R signaling while preserving physiologically beneficial AT1R signaling [7]. The study is a series of investigations from the same laboratory focusing on ATRAP involved in the tissue RAS [8–10]. The current study is the first to demonstrate the effects of ATRAP in the CNS in which an enhanced expression of ATRAP in the

✉ Kenichi Katsurada
katsurada@jichi.ac.jp

[1] Division of Cardiovascular Medicine, Department of Internal Medicine, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan

[2] Division of Clinical Pharmacology, Department of Pharmacology, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan

PVN achieved by a microinjection of a lentiviral vector into the PVN suppresses Ang II-induced hypertension concomitant with decreased urinary adrenalin.

A systemic infusion of Ang II acts on the SFO and MnPO to activate the PVN. It is well known that Ang II is produced in the PVN in the intrinsic brain RAS [1]. Activation of the RAS in the PVN leads to the sympathoexcitation described above. Enhanced ATRAP thus suppresses the activation of AT1R followed by the RAS in the PVN, thereby decreasing blood pressure concomitant with sympathoinhibition.

Sotozawa and Kinguchi et al. also demonstrated that an enhanced expression of ATRAP in the PVN suppresses cardiac hypertrophy in rats with Ang II-induced hypertension [7]. One possible underlying mechanism is that increased ATRAP/AT1R expression leads to a suppression of the RAS in the PVN, decreasing the sympathetic outflow to the heart. Indeed, this hypothesis is supported by an earlier study that demonstrated that ICV infusion of losartan, leading to a suppression of RAS in the brain, inhibited Ang II-induced hypertension as well as cardiac hypertrophy whereas the vasodilator hydralazine did not change the cardiac hypertrophy despite the blood pressure being decreased to a level lower than that observed in the Ang II-induced rats treated with ICV losartan [11].

These are important findings that suggest a mechanism for the action of ATRAP in the PVN during hypertension. However, there are limitations of this study, some of which are acknowledged by the authors. Urinary noradrenalin levels, as an established marker of systemic sympathetic nerve activity, were not increased by the systemic Ang II infusion and were not significantly decreased by enhanced ATRAP in the PVN. These results may have been due to adjustments of the dose and period of Ang II infusion and the small number of experimental samples. Multiple mechanisms in the PVN underlie the modulation of the sympathetic outflow to regulate blood pressure, including the involvement of the glutamatergic and GABAergic system, the nitric oxide and reactive oxygen species system, inflammation and immune systems, and more [1]. Further studies are needed to test the effects of ATRAP and address the interaction between ATRAP/AT1R and these various mechanisms in the CNS (Fig. 1).

Overall, the study by Sotozawa and Kinguchi et al. focuses on ATRAP in the PVN as another key player in the control of sympathetic outflow; it could be a target for neuromodulation therapies for cardiometabolic diseases with sympathoexcitation such as hypertension, heart failure, chronic kidney disease, diabetes, and obesity. Some of the issues that should be addressed are the changes in the baseline expression of ATRAP in the CNS of these disease conditions and the changes in that expression after intervention with neuromodulation therapies including renal denervation and medications (e.g., angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, etc.) [12].

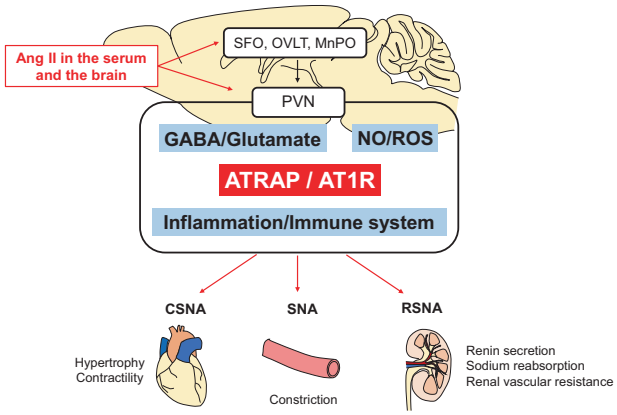

Fig. 1 Proposed model for the integration of angiotensin II (Ang II) in the serum and the brain to the PVN and the subsequent sympathetic outflow regulating the heart, peripheral arterioles, and kidneys. AT1R angiotensin type 1 receptor, ATRAP angiotensin type 1 receptor-associated protein, CSNA cardiac sympathetic nerve activity, GABA gamma-aminobutyric acid, MnPO median preoptic nucleus, NO nitric oxide, OVLT organum vasculosum lamina terminalis, PVN paraventricular nucleus, ROS reactive oxygen species, RSNA renal sympathetic nerve activity, SFO subfornical organ, SNA sympathetic nerve activity

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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