Journal Club

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Cross-Talk between TNF-α and Angiotensin II in the Neural Control of Hypertension

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Review of Woods et al.

Blood pressure is precisely controlled by various sensors around the body. The paraventricular nucleus (PVN) is one of the most important regions in the brain for regulating blood pressure. Briefly, PVN magnocellular neurons project to the neurohypophysis and induce the secretion of vasopressin, which increases water absorption by the kidney and favors blood pressure elevation. In contrast, PVN parvocellular neurons project to the rostral ventrolateral medulla (rVLM) and spinal cord intermediolateral nucleus to activate the sympathetic nervous system, causing norepinephrine release from sympathetic postganglionic terminals. This increases the rate of cardiac pacemaker activity, promotes vasoconstriction, and enhances cardiac contractility to increase blood pressure (Shafton et al., 1998).

Decreases in blood pressure are detected by barosensory receptors located in the carotid sinus and in the aortic arch. Neurons from baroreceptors have afferent projections to the nucleus of the solitary tract, which conveys information to the PVN. Decreases in blood pressure are also detected by afferent arterioles of the kidney, which in response release renin into the blood. Renin cleaves circulating angiotensinogen into angiotensin I, which is physiologically inactive, but becomes active when converted to angiotensin II (AngII) by an enzyme called angiotensin converting enzyme. AngII promotes sodium retention by the kidneys, constriction of blood vessels, and sympathetic activation in the brain, all which serve to increase blood pressure (Benicky et al., 2009; Biancardi et al., 2017).

Chronic elevation of blood pressure can result from positive feedback between AngII and sympathetic activation. AngII receptor 1 (AT1R) is expressed in the cerebral vasculature, circumventricular organs (CVOs), brain regions that lack blood–brain barrier, and neurons (Allen et al., 1998). Under normal physiological conditions, AngII does not enter the brain parenchyma, so AT1R from the vessels and CVO are the main sources of AngII signaling. However, in hypertensive situations in which the blood–brain barrier in the PVN is dysfunctional, AngII can activate neuronal AT1R, which induces proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6. These inflammatory cytokines contribute to neuron excitation in an AngII-induced hypertension model (Kang et al., 2009). Moreover, microinjection of TNF-α into the PVN increased mean arterial blood pressure and renal sympathetic nerve activity in both normotensive and hypertensive rats (Shi et al., 2011).

In a recent study in *The Journal of Neuroscience*, Woods et al. (2021) investigated how AngII-induced release of TNF-α in the PVN may lead to the development of hypertension (Woods et al., 2021). In a model of hypertension resulting from subcutaneous injection of AngII, ISH revealed that AngII induces an increase of TNFR1 in the caudal (parvocellular) PVN, but not the rostral (magnocellular) PVN. Furthermore, knocking down TNFR1 selectively in the PVN was sufficient to abolish AngII-induced hypertension. In addition, using retrograde neuronal tracing, the authors showed that TNFR1-expressing neurons from the PVN project to the spinal cord. Together, these results suggest that AngII-induced activation of the hypothalamic TNF pathway induces hypertension by activating the sympathetic arm of the PVN.

Considering that PVN neurons project to the spinal cord and rVLM and most of them produce and secrete the neurotransmitter glutamate, Woods et al. (2021) investigated the importance of TNF-α signaling to the glutamate ion-channel NMDA receptors in the PVN neurons projecting to the spinal cord. Using retrogradely labeled intermediolateral nucleus-projecting PVN neurons, they performed whole-cell current-clamp in PVN slices. The application of TNF-α increased the firing of neurons and NMDA currents in PVN neurons. Furthermore, hypertensive rats had elevated NMDA currents, which were abolished by pretreatment with a TNFR1 inhibitor. Together, the data suggest that, under hypertension, neuron activation by

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TNF-α and AngII induces PVN glutamatergic excitatory currents to spinal cord regions, resulting in increased sympathetic output, which favors the maintenance of higher blood pressure.

Although CNS AngII actions are mainly thought to be in CVO or PVN neurons, recent data suggest that AT1R-expressing astrocytes promote the accumulation of glutamate in the presynaptic area of PVN presympathetic neurons, indirectly increasing neuron activity (Stern et al., 2016). Also, microglia have been shown to recognize AngII in the CVO-PVN-rVLM pathway that activates the sympathetic nervous system (Biancardi et al., 2017). AngII activation of AT1R in astrocytes and microglia might modulate the amount of proinflammatory cytokines and glutamate in the CVO-PVN-rVLM axis, promoting sympathoexcitatory stimulation.

In conclusion, the work by Woods et al. (2021) suggests that in hypertension the increased AngII levels induce a CNS inflammation that favors the elevated sympathetic activity found in hypertensive subjects. Their findings reinforce the importance of understanding the link between inflammatory and neurohumoral signaling in health and disease. They also suggest a new therapeutic avenue for the treatment of hypertension and cardiovascular diseases associated with hypertension.

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