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Synapses, signals, CDs and cytokines: Interactions of the autonomic nervous system and immunity in hypertension

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In the past several years, there has been increasing interest in the roles of inflammation and immunity in hypertension. Inflammatory cells, including macrophages and T cells are commonly observed in the kidneys of hypertensive animals, and select immunosuppressive agents lower blood pressure and prevent end-organ damage in experimental hypertension.[1, 2] Depending on their phenotype, macrophages can release reactive oxygen species, matrix metalloproteinases and cytokines that promote tissue damage, change gene expression, induce vascular remodeling and lead to vasoconstriction and renal damage. Indeed, mice with reduced monocytes and macrophages develop less vascular remodeling, endothelial dysfunction and vascular oxidative stress as compared to wild type mice in response to either angiotensin II or DOCA-salt challenge.[3] Recently, genetic deletion of macrophages has been shown to blunt virtually all consequences of angiotensin II infusion, including blood pressure elevation, induction of vascular adhesion molecules, vascular dysfunction and superoxide production.[4]

It is fairly easy to imagine that innate immune cells like macrophages are involved in hypertension, but rather surprisingly, it seems that T cells of the adaptive immune system also contribute. Almost 50 years ago, White and Grollman showed that injection of lymph node cells from hypertensive rats could raise blood pressure in normotensive recipient rats.[5] Svendsen and colleagues showed the thymus played a role in the hypertension caused by partial renal infarction and in the sustained phase of DOCA-salt hypertension.[6] When lymphocytes from Lyon rats with genetic hypertension are transferred into Lyon Low pressure rats sustained hypertension develops in the recipients.[7] Our group found that mice lacking lymphocytes are protected against several forms of hypertension, including angiotensin II, norepinephrine and DOCA-salt and that adoptive transfer of T cells can restore hypertension in these models. We have proposed that neo-antigens formed in target tissues such as the kidney and vasculature promote T cell activation, which produce cytokines that lead to vascular and renal dysfunction, promoting hypertension.[8]

In parallel with inflammation, there is unequivocal evidence that the central nervous system plays a critical role in hypertension. Lesions of the forebrain, specifically in the AV3V region, the subfornical organ (SFO) and organum vasculosum of the lateral terminalis

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(OVLT) prevent various forms of experimental hypertension.[9–11] The SFO and OVLT are circumventricular organs that have a poorly formed blood brain barrier, and can be activated by circulating factors such as angiotensin II and salt. Fibers from these extend to the hypothalamus, in particular the paraventricular nucleus (PVN),[12] which in turn relays signals to the rostral ventral lateral medulla (RVLM) and other brainstem centers. These brainstem sites integrate input from the baroreceptors and ultimately modulate sympathetic outflow to the kidney and splanchnic circulation.[13, 14] As tangible evidence of the importance of these pathways, percutaneous renal denervation has recently proven effective in lowering blood pressure in humans with hypertension resistant to conventional therapy.[15]

A major question is how and if these two seemingly very separate systems – the immune and nervous systems –interact to modulate blood pressure. Is there evidence that one can affect the other in promoting blood pressure elevation or alterations of vascular or renal function? It turns out that there is enormous interplay between the autonomic and immune systems. Cells of the immune system possess adrenergic and cholinergic receptors that significantly affect their function. $Alpha_2$-adrenergic receptor stimulation enhances antigen uptake by dendritic cells,[16] while beta adrenergic stimulation inhibits dendritic cell function.[17] T cells possess both alpha and beta adrenergic receptors that have been variously reported to modify polarization, alter proliferation and change surface markers. Monocytes and macrophages also possess α1 and β1 adrenergic receptors that modulate pro-inflammatory cytokine production in response to toll-like receptor (TLR) agonists.[18, 19] Likewise monocyte/macrophages possess α7 nicotinic receptors which suppress cytokine production.[20, 21] Interestingly, it has recently been shown that a subset of $CD4^+$ cells with a memory phenotype contain choline acetyltransferase and produce acetylcholine upon sympathetic nerve stimulation.[22] Tracey and colleagues have described an inflammatory reflex, in which “danger’ signals, such as locally released cytokines and prostaglandins activate vagal afferent nerves that transmit information to the brainstem, the hypothalamus and higher centers. This orchestrates behavioral changes, reduces heart rate variability, increases vagal efferent activity and increases sympathetic outflow.[23] Increased vagal and sympathetic stimulation of secondary lymphoid organs promotes acetylcholine release from the aforementioned T cells, which in turn decreases cytokine production by nearby macrophages and therefore dampens the inflammatory response (Figure). Thus, this represents a reflex circuit that is active in myriad illnesses including sepsis, myocardial infarction and multisystem organ failure.

In this issue of Circulation Research, Harwani et al[24] provide evidence that the effector limb of this reflex is profoundly disturbed in the setting of pre-hypertension. These investigators examined how angiotensin II and nicotine modulate TLR induced cytokine release from isolated splenocytes of young normotensive Wistar Kyoto (WKY) and SHR prior to the development of hypertension. As expected from the circuit shown in the Figure, nicotine pre-exposure suppressed TLR9-mediated interleukin-6 (IL-6) secretion in splenocytes of normal WKY rats, while angiotensin II had no effect. In contrast, pre-exposure to either nicotine or angiotensin II paradoxically increased IL-6 release in response to TLR7/8 and TLR9 stimulation in SHR splenocytes. Nicotine’s anti-inflammatory effect in WKY and pro-inflammatory response in SHR were also observed in vivo. Using flow cytometry, the investigators identified a population of activated macrophages ($CD161a^+$) that seems responsible for production of IL-6 in SHR.

The differential effect of nicotine on IL-6 production could have significant implications for other aspects of inflammation in hypertension. Mice lacking IL-6 are protected against the development of hypertension.[25] IL-6 synergizes with TGFβ to promote polarization of T cells to produce IL-17, while TGFβ promotes skewing of T cells to a regulatory phenotype in the absence of IL-6.[26] Prior studies from our group have shown that T cells producing

IL-17 are critical in the development of hypertension.[27] These cells likely infiltrate the perivascular space and the kidney, and the secreted IL-17 promotes superoxide production and accumulation of other inflammatory cells. Thus, the increase in IL-6 in SHR macrophages might have a critical role in skewing responses of T cells that are pro-hypertensive.

It is of interest that SHR demonstrate abnormal macrophage responses prior to the onset of hypertension. This temporal relationship indicates that altered nicotinic responses might be a cause, rather than a consequence of hypertension. There is ample evidence that early life events in SHR affect blood pressure. Classic studies by McCarty and colleagues more than 20 years ago showed that cross fostering SHR pups to normal WKY dams led to a permanent decline in blood pressure and sympathetic outflow as the SHR aged.[28, 29] This might be related to epigenetic events that occur early in life.[30] Alterations in DNA methylation and histone modifications have recently been identified in several relevant genes in the SHR, including the sodium potassium chloride cotransporter 1, the angiotensin converting enzyme and the β-1 adrenergic receptor in SHR. [31 32, 33] In their current work, Harwani et al found that the α7 nAchR signaling is altered in the SHR, as the splenocyte responses were not blocked by its known inhibitor α-bungarotoxin. Future studies examining epigenetic modification of genes encoding signals downstream of the α7 nAchR might be quite revealing in this regard.

The studies by Harwani et al largely focused on splenocytes, and one can question how important this organ is in the genesis of hypertension. Studies often focus on the spleen, because it is a ready source of leukocytes in small animals. Antigen presentation by macrophages and dendritic cells occurs in secondary lymphoid organs, including the spleen and lymph nodes, which receive both vagal and sympathetic innervation. Thus, the interplay between T cells and macrophages shown in the Figure could also occur in lymph nodes. Of interest, removal of the celiac ganglion, which provides splenic innervation, prevents both angiotensin II and DOCA-salt hypertension.[34, 35] This has been attributed to hemodynamic factors, however it is conceivable that an anti-inflammatory effect of denervation might also play a role.

Given these interactions, it is interesting to note that similarities exist between the immune and autonomic nervous systems.[36] Both have synapses, develop memory and share a variety of signaling molecules. In both systems, signals from upstream cells (pre-ganglionic neurons and antigen presenting cells) markedly alter function of downstream cells (post-ganglionic neurons and T cells). Plasticity is a feature common to both, and DNA rearrangement, needed for T cell diversification, has been reported in the central nervous system. Chemokines, known to play critical roles in inflammatory cell homing, also contribute to development of the central nervous system.[37]

In summary, the study by Harwani et al further emphasizes that perturbations of the immune system and the resultant inflammation contribute to hypertension. It should be noted that despite intensive study for the past century, the etiology of most cases of human hypertension remains unknown. This study offers a new understanding of how the interplay between neural signaling and innate immune cells contributes to hypertension, and perhaps provides novel therapeutic directions for this common and devastating disease.

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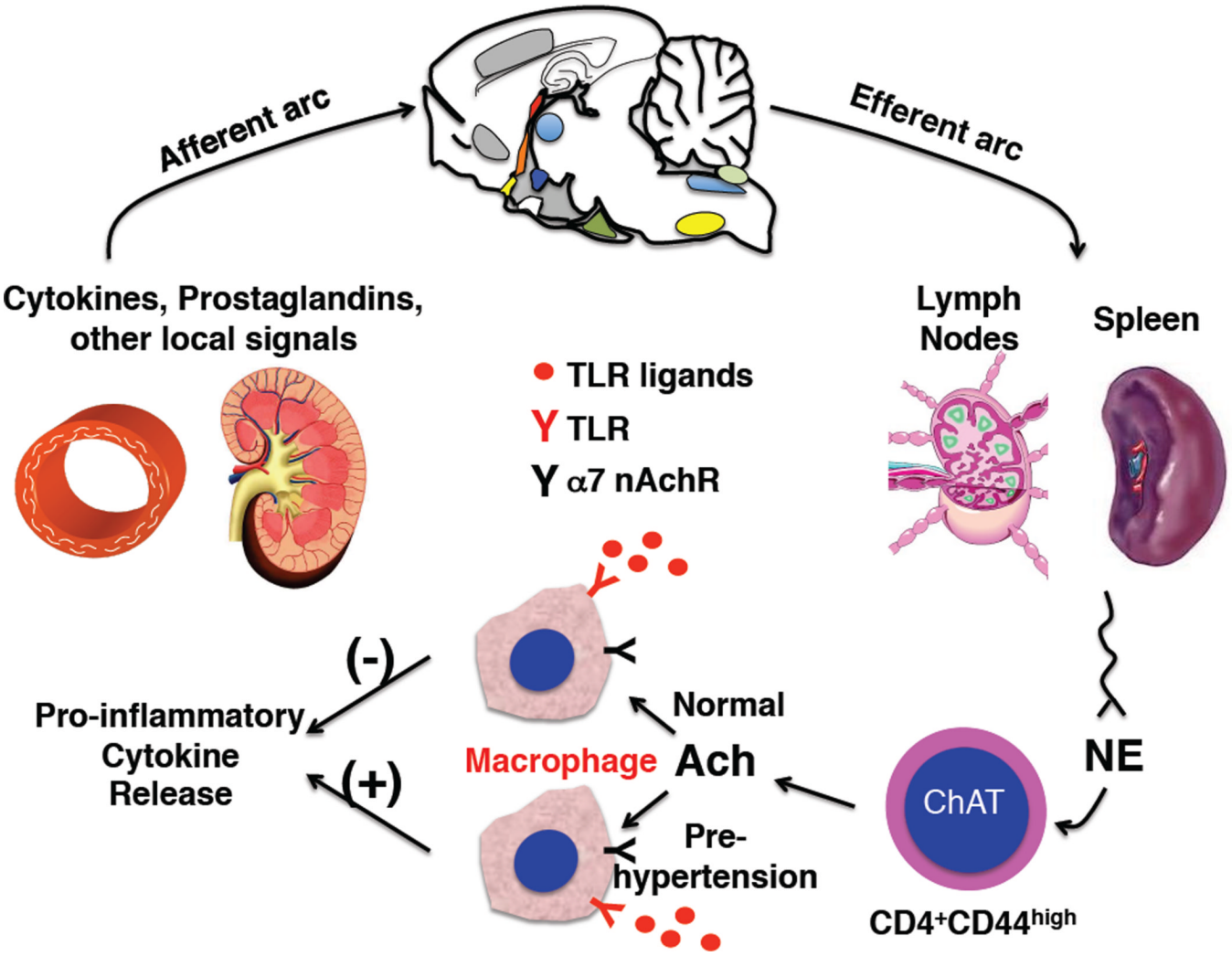

Figure.

Abnormal cytokine release in pre-hypertension. Shown is the “inflammatory reflex” in which local signals in tissues such as vessels and the kidney activate vagal afferent signals to the brain. These ultimately increase vagal and sympathetic outflow. In secondary lymphoid organs, increased norepinephrine (NE) release acts on a subset of memory ($CD44^{high}$) $CD4^{+}$ T cells that contain choline acetyltransferase and produce acetylcholine (Ach). The released ach acts on a7 nicotinic receptors of adjacent splenocytes, including macrophages. In normal circumstances, this has an inhibitory effect on pro-inflammatory cytokine release in response to various stimuli such as toll-like receptor (TLR) activation. In the paper by Harwani et al, this effect of nicotinic stimulation is markedly altered in SHR prior to the development of hypertension, such that cytokine release is paradoxically increased. (Illustration: Ben Smith)