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Brain inflammation in neurogenic hypertension

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Abstract

One likely mechanism of essential hypertension (EH) is increased sympathoexcitation due to abnormal functions in the cardiovascular center of the brain. Recent findings obtained using experimental animal models of EH have shown that abnormal inflammation in the cardiovascular center may contribute to the onset of hypertension. Inflammatory molecules such as cytokines and reactive oxygen species released from the inflamed vasculature and glial cells in the medulla oblongata and hypothalamus might directly or indirectly affect neuronal functions. This in turn could increase sympathetic nerve activity and consequently arterial pressure. Abnormal inflammatory responses in the brain could also be central mechanisms underlying angiotensin Ⅱ-related EH. In this review, we present the current understanding of EH mechanisms with regard to inflammatory responses in the cardiovascular center.

Key words: Hypertension; Cytokines; Chemokines; Inflammation; Brain; Nucleus tractus solitarius; Angiotensin Ⅱ

Core tip: One likely mechanism of essential hypertension (EH) is increased sympathoexcitation due to abnormal functions in the cardiovascular center of the brain. Recent findings obtained using experimental animal models of EH have shown that abnormal inflammation in the cardiovascular center may contribute to the onset of hypertension. Angiotensin Ⅱ-related EH is no exception to this idea. In this review, we present the current understanding of EH mechanisms with regard to inflammatory responses in the cardiovascular center.

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INTRODUCTION

Essential hypertension (EH) is a polygenic trait with as yet unknown underlying genetic components. However, EH is reported to be strongly associated with increased sympathetic nerve activity[1-3], suggesting the involvement of central mechanisms in the development and maintenance of EH. EH is also known to exhibit increased plasma levels of inflammatory markers such as C-reactive protein, tumor necrosis factor-α (TNFα), interleukin (IL)-6 and intercellular adhesion molecule-1[4,5]. We postulated that one of the mechanisms underlying the onset of EH is abnormal inflammatory responses in the cardiovascular center and accumulating evidence obtained using experimental animal models of hypertension supports this hypothesis[6-9]. In this review, we present the current understanding of EH mechanisms, with a focus on brain inflammation.

HYPERTENSION AND THE CARDIOVASCULAR CENTER

EH and some hypertensive animal models, such as spontaneously hypertensive rats (SHR), Dahl salt-sensitive

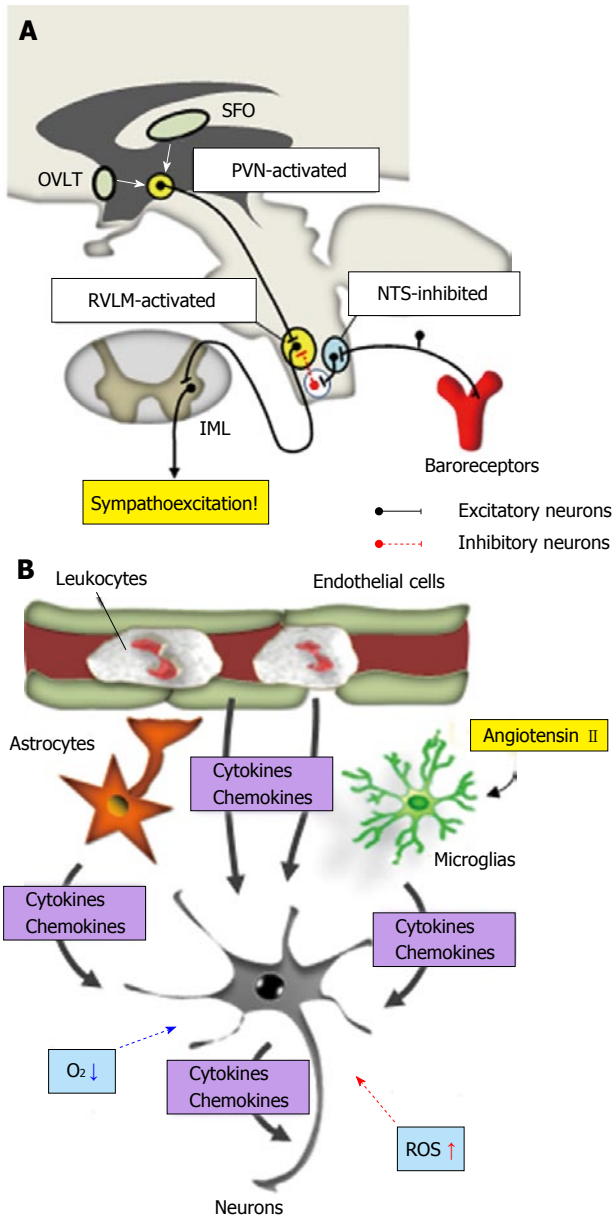

Figure 1 Abnormal inflammatory responses in the cardiovascular center and neurogenic hypertension. A: Sympathetic pre-motor neurons controlling vasomotor sympathetic nerve activity are located primarily in the rostral ventrolateral medulla (RVLM). These neurons receive numerous excitatory and inhibitory inputs from other areas of the brain, such as the hypothalamus and parts of the medulla oblongata. Over-activation of hypothalamic paraventricular nucleus (PVN) and RVLM neurons and/or attenuated nucleus tractus solitarius (NTS) responses to baroreceptor inputs are probable mechanisms of neurogenic hypertension (see text). Abnormal inflammatory responses may contribute to altered neuronal functions in the cardiovascular center; B: Inflammatory molecules released from vascular endothelial cells, leukocytes, astrocytes, microglial cells and neurons may affect neuronal functions in the cardiovascular center and induce sympathoexcitation. Hypoxia and ROS production induced by abnormal inflammatory responses may also affect neuronal functions (See text). OVLT: Organum vasculosum of the lamina terminalis; SFO: Subfornical organ; IML: Intermediolateral cell column; ROS: Reactive oxygen species.

rats and angiotensin Ⅱ (ANG Ⅱ)-induced hypertensive animals, are known or suggested to have increased basal activity in the sympathetic nervous system[1-3,10-13]. This indicates that one of the mechanisms underlying hypertension is neurogenic. Increased sympathetic nerve activity results in hypertension *via* several means, including increased peripheral resistance due to vasoconstriction.

Sympathetic pre-motor neurons controlling vasomotor sympathetic nerve activity are located primarily in the rostral ventrolateral medulla (RVLM). It has been reported that RVLM neurons in SHR are overexcited[14], in part due to increased levels of reactive oxygen species (ROS) within the RVLM[15,16]. These neurons receive numerous excitatory and inhibitory inputs from other areas of the brain, such as the hypothalamus and parts of the medulla oblongata, and the neuronal activities in the RVLM are responses to a variety of physiological conditions. One of the most important regulatory mechanisms in cardiovascular homeostasis is the baroreceptor reflex. The nucleus tractus solitarius (NTS) is the primary termination site of the baroreceptor afferents. Second (or higher) order NTS neurons excite gamma-aminobutyric acid (GABA)-ergic inhibitory neurons in the caudal ventrolateral medulla that project into and inhibit RVLM neurons, thereby decreasing sympathetic preganglionic neuronal outflow[17]. Given that the baroreceptor reflex was found to be altered in neurogenic hypertension (*e.g.*, upward resetting)[18], the abnormal functions in the central arc of the reflex may contribute to neurogenic hypertension. In fact, we previously reported that microinjection of $CoCl_2$, a non-selective neurotransmission blocker, into the NTS dramatically increased arterial pressure in both normotensive rats (Wistar Kyoto: WKY rats) and SHR; however, the response was highly attenuated in the latter (Waki *et al*[6], unpublished data). Thus, attenuation of NTS functions could contribute in part to neurogenic hypertension in SHR. Moreover, it has been suggested that the altered NTS functions in SHR may be due to increased GABAergic responses within the NTS[19].

The hypothalamic paraventricular nucleus (PVN) is another area of the brain that controls arterial pressure by modulating RVLM neurons. The PVN receives excitatory inputs from the organum vasculosum of the lamina terminalis and the subfornical organ (SFO), which lie outside of the blood brain barrier (BBB) and can detect plasma osmolarity and the presence of ANG Ⅱ in the blood. In salt-sensitive and ANG Ⅱ-induced hypertension, excitation of these pathways is a probable mechanism of neurogenic hypertension[9,10,20,21] and such alterations of the cardiovascular center in neurogenic hypertension could be explained in part by abnormal inflammatory responses (Figure 1A).

INFLAMMATION IN THE CARDIOVASCULAR CENTER

Chronic inflammation is now known to be related to not only allergic disease and autoimmune disease, but also other diseases such as lifestyle-related diseases and cancer. In neurological disorders, demyelinating disease and Alzheimer's disease are generally considered to be chronic inflammatory diseases of the brain[22,23]. These intractable diseases exhibit degenerative morphology of

the nervous system, whereas the brain in EH and SHR does not show this type of morphological abnormality. It is clear then that neurogenic hypertension in EH cannot be categorized as a neurodegenerative disease with severe brain inflammation. However, since some cytokines/chemokines act as neuromodulators *via* paracrine or autocrine signaling, it has been suggested that even minor inflammatory responses in the brain could affect neuronal homeostasis[24-27]. Moreover, some cytokines/chemokines are constitutively synthesized and released within the brain and play a crucial role in the brain development. Based on these views, we hypothesized that abnormal inflammation in the cardiovascular center contributes to neurogenic hypertension. This hypothesis was supported by our findings that the gene expression patterns of inflammatory molecules in the cardiovascular center differ between SHR and WKY rats[28,29], although SHR neurons did not show degenerative morphological features.

The latest concepts regarding brain inflammation and hypertension can be summarized as follows. First, the peripheral vascular inflammation found in EH and experimental animal models likely occurs in cardiovascular control regions of the brain, and inflammatory molecules released from vascular endothelial cells and leukocytes can penetrate the brain parenchyma through the damaged BBB. Then, transported cytokines/chemokines could directly or indirectly affect neuronal functions[6,8,30-32]. Vascular inflammation in the brain might also disturb local blood supply and cause localized hypoxia[6,33]. These reactions may subsequently affect neuronal functions in the cardiovascular center. Second, cytokines/chemokines released from astrocytes, microglial cells or macrophages in the cardiovascular center may affect neuronal functions and induce sympathoexcitation[8,20]. Further details on brain inflammation in SHR and ANG Ⅱ-induced hypertension are introduced in the following sections.

SHR AND BRAIN INFLAMMATION

We have identified several genetic profiles in the NTS of SHR to understand the potential mechanisms of NTS dysfunction in this animal model. Compared with the NTS of WKY rats, the NTS of SHR exhibits altered gene expression patterns of junctional adhesion molecule-A (JAM-A) and leukotriene B4 (LTB4)-related molecules (enzymes), such as LTB4-12-hydroxydehydrogenase and 5-lipoxygenase[34,35]. LTB4 (a fatty acid) and JAM-A protein are also overexpressed in the NTS of SHR. Both molecules are known to exert pro-inflammatory functions by facilitating leukocyte adhesion to the endothelial cells[36-39]. Indeed, we have identified vascular inflammation in the NTS of SHR characterized by leukocyte accumulation[34,35]. Moreover, LTB4 microinjection into the NTS of WKY rats or adenoviral overexpression of JAM-A in the NTS of WKY rats induces sympathoexcitation, hypertension and leukocyte adhesion to the endothelial cells in the NTS[34,35]. Although it is not known how high levels of LTB4 and JAM-A in the NTS can contribute to neurogenic hypertension, we speculate that vascular inflammation in the NTS may induce NTS dysfunction. This hypothesis is supported by the following findings: (1) inflamed vasculature in SHR increased gene expression of TNF, IL-6, IL-1β and the downstream transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); (2) IL-6 within the NTS attenuated the baroreceptor reflex function[40]; and (3) IL-1β in the brain increased sympathetic nerve activity[41]. Therefore, these pro-inflammatory cytokines produced in response to vascular inflammation in the NTS may penetrate the brain parenchyma through the damaged BBB, thereby affecting neuronal functions (presumably GABAergic interneuron functions) in the NTS. Further research is needed to test this hypothesis.

Vascular inflammation is also known to induce focal ischemic and hypoxic conditions. It has been reported that SHR exhibit increased brainstem vascular resistance relative to WKY rats and that blood flow in the SHR brainstem at normal arterial pressure could fall below the flow in the WKY brainstem[42]. We recently reported that NTS ischemia can increase arterial pressure *via* activation of O_2-sensing molecules such as heme oxygenase, which depends on O_2 to catalyze heme into carbon monoxide, biliverdin and iron, all of which can modulate membrane ion channel functions[33,43,44]. Taken together, ischemia/hypoxia in the NTS caused by vascular inflammation may produce neurogenic hypertension. In addition, it is known that hypoxia stimulates endothelial nitric oxide synthase (eNOS) as a compensatory mechanism to enhance perfusion[45]. Indeed, we found that gene expression of eNOS in the NTS was higher in SHR than in WKY rats[46]. Abnormal production of eNOS may facilitate an uncoupled state that increases the amount of peroxynitrite[47,48]. This is supported by the high superoxide levels observed in the vasculature of SHR compared with WKY rats[49]. Thus, increased ROS levels might also affect NTS neuronal functions[6].

We have also investigated the expression profiles of chemokines in the NTS of SHR. Gene expression of chemokine (C-C motif) ligand 5 (Ccl5) and related molecules such as the Ccl5 receptor were downregulated in SHR compared with WKY rats[28]. With the exception of common chemokine functions such as leukocyte activation, some chemokines including Ccl5 are constitutively expressed within the central nervous system and are crucial for neuronal homeostasis[24]. In the case of Ccl5, glial cells are a likely source of Ccl5 in the central nervous system[50]. Most importantly, Ccl5 can modulate glutamate transmission by activating the Ccl5 receptors Ccr1, Ccr3 and Ccr5[51]. We previously demonstrated that Ccl5 within the NTS decreases arterial pressure, suggesting that Ccl5 facilitates barosensitive neuronal activities in the NTS[28]. These observations indicate that the downregulation of Ccl5 and the expression of its receptors in the NTS may contribute to the hypertension phenotype in SHR. Our idea that the downregulation of pro-inflammatory chemokines may mediate the mechanisms underlying neurogenic hypertension contradicts the concept that brain inflammation is a causative factor of hypertension. How-

ever, our supposition is that the downregulation of Ccl5 and the network of related molecules may be secondary to specific vascular inflammation to protect against both further inflammatory reactions and BBB dysfunction at the expense of altered glial-neuronal homeostasis in the NTS[28].

Other brain regions involved in cardiovascular control are also reported to exhibit specific inflammatory conditions in SHR. In the PVN and RVLM, TNFα and IL-1β mRNA/protein levels were increased in SHR compared with WKY rats[52]. These pro-inflammatory cytokines are known to increase neuronal activity *via* activation of the N-methyl-D-aspartate or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, or transcription factor NFκB[8]. Thus, it is possible that the inflammatory responses observed in the PVN and RVLM also contribute to over sympathoexcitation in SHR. Since these inflammatory molecules can induce ROS production, the functional roles of RVLM cytokines and their potential link to the ROS-related hyperactivity of RVLM neurons in SHR[15,16] need to be elucidated. Finally, it will be of interest to assess whether centrally acting antihypertensive agents modulate the inflammatory responses found in the cardiovascular center of SHR (Figure 1B).

ANG II-INDUCED HYPERTENSION AND BRAIN INFLAMMATION

A high level of sympathetic nerve activity has been reported in ANG Ⅱ-related hypertension in EH and its animal model, suggesting that brain mechanisms mediate this type of hypertension[10,11,21]. Increased levels of plasma ANG Ⅱ are known to induce vascular inflammation[53]; this could occur in the brain vasculature because systemic infusion of ANG Ⅱ-induced leukocyte adhesion in the brain vasculature and increased permeability of the BBB have both been reported[54]. Xu *et al*[55] also recently found that JAM-A expression in the NTS was increased by systemic infusion of ANG Ⅱ. These findings suggest that vascular inflammation in the cardiovascular center may also be one of the mechanisms underlying ANG Ⅱ-induced hypertension. Since pressor responses to systemic ANGII infusion are dampened in IL-6 or TNFα knockout animal models, these pro-inflammatory molecules might be involved in the onset of ANG Ⅱ-induced hypertension[8,56]. It is noteworthy that ANG Ⅱ might be a key molecular mediator of the hypertension phenotype in SHR based on the findings that chronic administration of an AT1-receptor antagonist (an ANG Ⅱ receptor blocker) in SHR reduced arterial pressure, leukocyte adhesion in the brain vasculature, and expression of TNFα, IL-1β, NFκB and adhesion molecules in blood vessels[30,31,57].

As mentioned above, SFO neurons might also be excited by plasma ANG Ⅱ, which would likely be mediated through AT1 receptor activation[9,10,20,21]. The signal from the SFO would excite PVN neurons and in turn increase sympathetic outflow. ANG Ⅱ is a potential neurotransmitter in this pathway and might mediate AT1 receptor expression in PVN neurons. However, Raizada and colleagues postulated that activation of the microglia in the PVN is required to establish hypertension in ANG Ⅱ-induced hypertension[7,20]. Importantly, microglial cells also express AT1 receptors. They found that ANG Ⅱ in the PVN activated microglia and facilitated production of pro-inflammatory cytokines such as TNFα, IL-1β and IL-6[20]. They also found that central administration of minocycline, an antibiotic that can cross the BBB and inhibit microglial activation, attenuated ANG Ⅱ-induced pressor responses and specific inflammatory responses (*i.e.* microglial activation and pro-inflammatory cytokine expression)[20]. Moreover, viral vector-mediated overexpression of IL-10, an anti-inflammatory cytokine, in the PVN also decreased microglial activities and demonstrated anti-hypertensive effects[20]. All told, activation of microglial cells in the PVN and the consequent release of pro-inflammatory cytokines mediate ANG Ⅱ-induced hypertension. Although the precise mechanism through which pro-inflammatory molecules increase the neuronal activities in the PVN remains unknown, activation of the N-methyl-D-aspartate or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, or the NFκB transcription factor is a potential candidate[8]. To support this notion, central administration of an NFκB inhibitor was found to decrease pressor responses in an animal model of ANG Ⅱ-induced hypertension[58]. It is also conceivable that, because pro-inflammatory cytokines are known to affect ion channels *via* the production of ROS, there are multiple pathways to excite PVN neurons (Figure 1B).

CONCLUSION

Studies using experimental hypertensive animals have revealed that pro-inflammatory molecules in the cardiovascular control regions of the brain may contribute to neurogenic hypertension. It is important, however, to verify whether this scenario is applicable to EH. Moreover, it will be of interest to assess whether anti-inflammatory drugs have any efficacy or advantages in the treatment of hypertension.

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