

Brain Cytokines as Neuromodulators in Cardiovascular Control

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SUMMARY

1. The role of cytokines in cardiovascular control, especially in neurogenic hypertension, has received much attention during the past few years. Brain cytokines have been shown to exert profound effects on neuronal activity. Recently, a number of studies have shown that administration of pro-inflammatory cytokines (PIC) or anti-inflammatory cytokines (AIC) into the central nervous system has a significant impact on sympathetic outflow, arterial pressure and cardiac remodeling in experimental models of hypertension and heart failure.

2. Our objective in this review is to present a succinct account on the effect of cytokines on neuronal activity and their role in cardiovascular disease. Furthermore, we propose a hypothesis of a neuromodulatory role of cytokines in neural control of cardiovascular function.

Keywords: angiotensin, anti-inflammatory cytokine, brain, hypertension, pro-inflammatory cytokine

INTRODUCTION

Numerous clinical reports suggest that patients who have been diagnosed with cardiovascular disease exhibit increased circulating levels of pro-inflammatory cytokines (PIC) such as interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF) α and C-reactive protein.¹⁻³ In fact a number of studies have attempted to determine whether chronically increased levels of PIC in blood can be used as a predictor for the development of hypertension, or are a consequence of this disease.⁴⁻⁹ A correlation between high blood pressure and circulating PIC levels has also been noted in animal models of this disease. PIC and anti-inflammatory cytokines (AIC) interact with renin-angiotensin system (RAS) components in the brain to regulate blood pressure in both normal and disease states such as essential hypertension and heart failure.⁹⁻¹² These interactions likely occur in cardiovascular regulatory sites such as the rostroventrolateral medulla (RVLM), nucleus tractus solitarius (NTS) and the paraventricular nucleus (PVN). In this review we will focus on the role of cytokines in the PVN in cardiovascular control as this hypothalamic nucleus plays a pivotal role in regulating blood pressure in both the normotensive and hypertensive states.

CYTOKINES AND THEIR RECEPTORS IN THE CENTRAL NERVOUS SYSTEM

Inflammatory cytokines are polypeptides whose molecular weights are mostly in excess of 10 kDa. Therefore, cytokines that are produced peripherally are unable to cross the blood brain barrier as their size is above the upper limit (500 Daltons) of passive translocation.¹³⁻¹⁵ Despite this, there are various ways by which peripherally generated cytokines may influence the central nervous system (CNS) to modulate cardiovascular function. For example, one proposed mechanism is that cytokines can penetrate into the brain at the circumventricular organs such as subfornical organ, the organum vasculosum of the lamina terminalis and the area postrema, areas that do not contain a blood brain barrier. Cytokines such as IL-1 β can penetrate the parenchymal membrane at these sites and then be transported via the cerebrospinal fluid as so-called “volume transmission” in the CNS.¹⁶ Another way

in which peripheral cytokines may influence the CNS control of cardiovascular function is via activation of afferent nerves that pass information to sites such as the NTS, which could then relay the information to other cardiovascular control centers in the brain (PVN; RVLM).^{17, 18} A further mechanism was proposed by Waki *et al.*, who suggest that dysfunction of the blood brain barrier produced by up regulation of junctional adhesion molecule (JAM)-1; a leukocyte/platelet adhesion molecule allows the passage of large molecules into the CNS.¹⁹ This mechanism will be discussed further in the following section. Aside from the potential influence of peripheral cytokines on the CNS, it is known that cytokines can be generated within the CNS by activated monocytes, macrophages or activated microglia.²⁰ For example, mRNA and protein for IL-1 β , TNF α and IL-6 have been detected using *in situ* hybridization and autoradiographic techniques in different regions of the brain including the cerebral cortex, hippocampus and the PVN.²¹

Cytokine receptors have been found in several sites in the brain.²¹ It is interesting to note that their receptors are located on multiple cell types, including glial cells (microglia and astrocytes), as well as neurons, choroid cells and capillary endothelial cells in the brain. In most cases cytokines exert their functions via binding with their corresponding receptors to induce cellular signaling cascades. For example IL-1 β binds onto the IL-1 type 1 receptor to activate the Erk mitogen activated protein kinase pathway.^{22,23} IL-10 activates IL-10 type 1 receptors to increase their tyrosine phosphorylation, thereby activating the transcription factors Jak1 and Stat3.²⁰ However, some cytokines, such as macrophage migration inhibitory factor (MIF), not only have extracellular binding action via CD-74 receptors, but also have intracellular effects.²⁴ Our group has shown that MIF acts intracellularly via its intrinsic thiol protein oxidoreductase (TPOR) to counterregulate angiotensin (Ang) II induced neuronal activation.^{10,}

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CYTOKINES AND NEURONAL ACTIVATION

The actions of cytokines on neuronal activity have been investigated in a number of different fields of study, including epilepsy, neuroinflammation, cerebral ischemia, and heart failure.^{12, 26, 27} For example, the PIC TNF α has significant effects on neuronal activity. One study demonstrated that TNF α increases insertion of the AMPA receptor subunits 1 and 2 into the plasma membrane, consequently increasing Ca²⁺ influx into hippocampal pyramidal neurons.²⁸ Another study indicated that TNF α , acting via its type 1 receptor, activates a protein kinase A (PKA), which subsequently increases neuronal firing frequency in dorsal root ganglion neurons.²⁹ IL-1 β has similar effects on neuronal activity. It increases Ca²⁺ current via phosphorylation of N-methyl-D-aspartic acid receptors, and at the same time decreases outward Ca²⁺-dependent K⁺ current.³⁰ It is interesting to note that both TNF α and IL-1 β bind with their corresponding receptors to activate the transcription factor nuclear factor kappa B (NF κ B) which, in turn, contributes to further production of these two cytokines.³¹ A recently published paper by the same group shows that intracerebroventricular (ICV) infusion of an NF κ B inhibitor significantly attenuates hypertension induced by angiotensin II (Ang II),³² and the relationship between cytokines and hypertension will be discussed in subsequent sections.

Besides the above described intracellular actions on neurons, it has been demonstrated that cytokines can modulate neuronal activity via production of reactive oxygen species (ROS). For example, cytokines increase the generation of ROS by activating NADPH oxidase in microglia, and the released ROS then act in a paracrine fashion to modulate neuronal activity.³³ In addition, cytokines increase inducible nitric oxide synthase production via NF κ B activation,³⁴ and that the resulting nitric oxide that is produced diffuses to adjacent tissues to modulate the activity of gamma-aminobutyric acid neurons.³⁵

CARDIOVASCULAR ACTIONS OF CYTOKINES

During the past few years there have been many reports on the actions/roles of cytokines in cardiovascular diseases such as hypertension and heart failure. To begin with, certain hypertensive rat

models exhibit increased expression of PIC in cardiovascular regulatory regions of the brain such as the PVN and the NTS.^{9, 11, 12, 32} For example, in normal rats made hypertensive via chronic infusion of Ang II, the expression of TNF α , IL-1 β and IL-6 is increased in the PVN, and is accompanied by simultaneously elevated PIC levels in the plasma.³² In another model, the spontaneously hypertensive rat (SHR), the expression of inflammatory markers is significantly increased in the NTS compared to age-matched Wistar Kyoto (WKY) rats.¹⁹ The cause and effect relationship between PIC and hypertension is not fully understood. However, studies by different groups of investigators indicate that ICV infusion of recombinant IL-1 β activates the sympathetic nervous system, and increases resting arterial blood pressure in conscious animals.³⁶⁻³⁸ Moreover, specific microinjection of recombinant IL-1 β into the PVN of the hypothalamus elicits a pressor response in anesthetized rats.³⁹ These studies suggest that PIC may function as modulators of sympathetic neuronal outflow in the CNS, an idea that is reinforced by the fact that cytokines have discrete modulatory actions on neuronal ion channels and discharge, as discussed in the previous section. More evidence for a role of cytokines in cardiovascular regulation comes from studies using TNF α knockout mice. For example, these animals exhibit a reduced Ang II-induced pressor response when compared with wild type mice.⁹ In addition, the reduced pressor effect of Ang II in TNF α knockout mice is associated with a reduction in cardiac hypertrophy. Blockade of a downstream target of TNF α such as NF κ B achieves a similar anti-hypertensive effect to inhibition of TNF α .⁹

It is well known that AIC exert inhibitory effects on PIC in the peripheral immune system, and it has become apparent that they may serve a similar role in the CNS.⁴⁰ For example, IL-10 is a multi-potent AIC that exerts anti-hypertensive effects. Viral-mediated systemic delivery of IL-10 significantly ameliorates hypertension and the associated organ damage in both Dahl salt-sensitive hypertensive rats and stroke-prone SHR.^{6, 7} A study by Yu *et. al.* indicates that over expression of IL-10 in the CNS following ICV administration decreases TNF α , IL-1 β , PEG2 and cyclooxygenase-2 (COX-2) expression in the PVN and also ameliorates sympathoexcitation in heart failure rats.¹² MIF is another

cytokine that exerts anti-hypertensive effects when administered into the CNS. In the peripheral immune system, MIF has well known pro-inflammatory actions.^{24, 41} However, in the CNS we have demonstrated that MIF acts intracellularly to increase neuronal delayed rectified K⁺ current via its TPOR motif.^{10, 25} Although the overall expression of MIF levels in PVN tissues obtained from SHR and WKY rats are the same, differential cellular locations seem to play a critical role in regulating neuronal activity.⁴² Increased MIF expression in PVN neurons via viral transduction reduces the development of high blood pressure in SHR.⁴² Thus, although MIF and IL-10 have different mechanisms they can function as anti-hypertensive modulators in the CNS.

Cytokines can be synthesized *de novo* in the CNS. While it is well accepted that cytokines are produced and released by microglia in the brain,⁴³ it has also been shown that cytokines are located in neurons.⁴⁴⁻⁴⁸ In most cases cytokines are synthesized as precursors, which are further converted to their mature forms via enzymatic cleavage. Such is the case with TNF α and IL-1 β .⁴⁹ Therefore, inhibition of PIC production in the CNS is another strategy to remove their neuronal actions. One study by Kang *et. al.* indicates that ICV infusion of a cytokine synthesis inhibitor significantly reduced expression of TNF α , COX-2 and Fra-like immunoreactivity in the PVN, effects that were accompanied by improved cardiac function in heart failure rats.³² Unpublished data by our group has shown that ICV infusion of minocycline, a microglia inhibitor, almost completely abolished the pressor response induced by Ang II infusion. We have also demonstrated that minocycline decreases PIC expression in PVN tissue. Studies by Paton *et. al.* have led to the novel idea that cytokines or other big molecules gain access to the CNS from the peripheral circulation.¹⁹ They demonstrate that there is increased JAM-1 expression in the microvasculature in the NTS of the SHR. The function of JAM-1, as indicated by its name, forms the tight gap junctions between adjacent endothelial cells in the microvasculature. It also attracts leukocytes and platelets adhesion via its leukocyte function-associated antigen and promotes cytokine production in those cells. Accumulated leukocytes and increased cytokines may contribute to the damage of the blood brain barrier, which allows the penetration of large molecules such as cytokines

into the brain. Therefore they hypothesize the idea that neurogenic hypertension is related to vascular inflammation.⁵⁰

INTERACTIONS BETWEEN CYTOKINES AND ANGIOTENSIN II IN THE BRAIN

There are many hypertensive states associated with activation of the RAS in the CNS, especially neurogenic hypertension. We have reported that Ang II elicits a significantly greater increase in firing frequency in SHR neurons compared with WKY rat neurons.²⁵ However, *intracellular*-administration of MIF normalizes the chronotropic action of Ang II in SHR neurons, which reaches a similar level as seen in WKY rat neurons. We further demonstrated that the intracellular action of MIF depends on the cellular redox TPOR motif, based on the loss-function mutation of cysteine residue 60 to serine [C60S]. Furthermore, viral-mediated increases in expression of wild type MIF in PVN neurons significantly attenuates the development of hypertension in SHR.⁴² However, similar transduction of the mutant [C60S]-MIF, which lacks TPOR activity, does not alter the development of hypertension. Similar to MIF, other cytokines or chemokines have been investigated in angiotensin-related animal models of hypertension. As mentioned earlier, TNF α is involved in Ang II-mediated responses such as salt appetite, cardiac hypertrophy and hypertension.⁹ Although the detailed mechanisms by which PIC work along with or AIC function against the RAS are not been fully understood, it is likely that they share a common intracellular signaling factor, namely ROS. TNF α , classified as a PIC, has been shown to increase ROS production in the endothelium.⁵¹⁻⁵⁴ As mentioned above, MIF can function as an intracellular anti-oxidant reagent to scavenge ROS inside of the cell. With respect to the RAS, it is well known that Ang II induces oxidative stress by increasing ROS production.^{2, 3, 55} Therefore, PIC may influence neuronal activity by facilitating Ang II-induced ROS activation; on the other hand, AIC may dampen neuronal activation induced by Ang II via inhibiting ROS production. It is possible that cytokines regulate neuronal activity via interfering with the action of the RAS in the CNS via direct or indirect mechanisms. Our unpublished data indicate that viral transduction of rat IL-10 in the PVN

attenuates hypertension induced by systemic Ang II infusion. Similar results are obtained with ICV infusion of the inhibitor of microglial activation, minocycline (unpublished data). As mentioned earlier, central administration of IL-1 β increases sympathetic activity and arterial blood pressure.³⁶⁻³⁹

Based on previously published work and our own preliminary studies we propose the following hypothesis (see schematic diagram in Figure 1) for the neuromodulatory actions of cytokines and their interactions with Ang II in controlling neuronal activity within CNS cardiovascular control centers. First we hypothesize that Ang II increases the production and/or release of PIC from glia, either microglia or astroglia. Subsequently, the released PIC increase ROS production via a specific receptor-mediated autocrine action at glia, or a paracrine effect at adjacent neurons. We also propose that Ang II, acting via stimulation of NADPH oxidase, elicits direct (non-cytokine dependent) increases in ROS formation in both neurons and microglia. Finally, we hypothesize that the ROS, produced by cytokine dependent and independent pathways in microglia and neurons, acts to increase neuronal discharge, and consequently sympathetic outflow and arterial blood pressure. Such an organization where ROS is a common downstream mediator would not only mean that Ang II alone would increase neuronal firing, but also that the effects of Ang II could be amplified via generation of cytokines. Lastly, we propose that AIC directly antagonize PIC actions by inhibiting their production and/or release, and will indirectly antagonize Ang II actions via inhibition of PIC.

CONCLUSIONS AND FUTURE DIRECTIONS

As mentioned above PIC and AIC in the CNS function as neuromodulators to directly or indirectly regulate neuronal activity. With respect to neurogenic hypertension PIC such as TNF α and IL-1 β acting on their respective receptors in the CNS increase sympathetic discharge, eventually contributing to hypertension development, although the cellular mechanisms by which they regulate neuronal activity are not fully understood. This review attempts to summarize the most recent discoveries on the role of cytokines, and their interactions with Ang II, in cardiovascular function in particular as they

relate to neurogenic hypertension. We acknowledge that the situation in the CNS is highly complicated, and we hypothesize that the balance of PIC to AIC is a critical factor regulating neuronal activity and ultimately modulation of cardiovascular function. We also believe that the communication between neurons and glial cells in the CNS may play a critical role in ultimately determining neuronal activity, thereby contributing to overall discharge of CNS efferents that control cardiovascular function. Critical issues that require further study include determination of which particular non neuronal cells are important for cytokine and ROS generation, which specific cytokines/receptor combinations are more important in stimulating increased neuronal discharge in hypertension, and establishment of the relative contributions of Ang II and cytokines to the day to day control of sympathetic outflow in normal and hypertensive states.

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Figure legends

Figure 1. Schematic outline of the hypothesis showing the proposed interactions between PIC, Ang II, AIC and ROS in controlling neuronal discharge in cardiovascular control centers such as the PVN.

