

REVIEW

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Brain inflammation and hypertension: the chicken or the egg?

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Abstract

Inflammation of forebrain and hindbrain nuclei controlling the sympathetic nervous system (SNS) outflow from the brain to the periphery represents an emerging concept of the pathogenesis of neurogenic hypertension. Angiotensin II (Ang-II) and prorenin were shown to increase production of reactive oxygen species and pro-inflammatory cytokines (interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α)) while simultaneously decreasing production of interleukin-10 (IL-10) in the paraventricular nucleus of the hypothalamus and the rostral ventral lateral medulla. Peripheral chronic inflammation and Ang-II activity seem to share a common central mechanism contributing to an increase in sympathetic neurogenic vasomotor tone and entailing neurogenic hypertension. Both hypertension and obesity facilitate the penetration of peripheral immune cells in the brain parenchyma. We suggest that renin-angiotensin-driven hypertension encompasses feedback and feedforward mechanisms in the development of neurogenic hypertension while low-intensity, chronic peripheral inflammation of any origin may serve as a model of a feedforward mechanism in this condition.

Keywords: Brain inflammation, Neurogenic hypertension, Angiotensin II, Prorenin, Reactive oxygen species, Chronic inflammation, Obesity

Introduction

Hypertension is an epidemic health challenge, a proven major risk factor of the development of cardiovascular disease and the leading cause of morbidity and mortality worldwide [1]. Despite the availability of several classes of antihypertensive drugs, the treatment of hypertension often remains suboptimal. In addition, the prevalence of uncontrolled hypertension continues to rise globally [2].

It is well established that inflammation is involved in the pathogenesis of hypertension [3]. In animals with experimental hypertension, T cells and macrophages accumulate in the kidneys and peripheral vasculature and most likely contribute to the *end organ* damage associated with this disease [4]. Mice lacking lymphocytes (Rag1^{-/-} mice) develop blunted hypertension and are protected from vascular dysfunction and vascular oxidative stress in response to various stimuli, including angiotensin II (Ang-II), norepinephrine (NE) and deoxycorticosterone acetate plus sodium chloride (DOCA-salt). The adoptive

transfer of T cells, but not B cells, restores hypertension in these animals [5]. Dendritic cells from hypertensive mice exhibit increased expression of the B7 ligands CD80 and CD86 indicating dendritic cell maturation and activation. The blocking of these co-stimulatory molecules prevents hypertension and T cell activation during both Ang-II- and DOCA-salt-induced hypertension [6].

It is generally accepted that uncontrolled, resistant hypertension is primarily of neurogenic origin - driven by chronic hyperactivity of the sympathetic nervous system (SNS) [7-9]. Clearly, the SNS stimulation of the heart, vasculature and kidneys increases blood pressure (BP) by augmenting cardiac output, vascular resistance and fluid retention [8]. However, the SNS also acts as an integrative interface between the brain and the immune system [10-12]. Primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs are abundantly innervated by autonomic, mostly sympathetic efferent fibres. NE, the SNS primary neurotransmitter, is released into the lymphoid tissue and modulates the function of immune cells. Most of them express receptors for glucocorticoids, the end product of the hypothalamic

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pituitary adrenal axis. Thus, the SNS and hypothalamic pituitary adrenal axis can regulate the magnitude of innate and adaptive immune responses in multiple ways [12-14]. Additionally, adipose tissue is directly innervated by the SNS and this innervation plays an important role in metabolic and endocrine function [15]. Interestingly, perivascular adipose tissue components can release NE independently from the SNS, possibly exerting co-stimulatory local control of arterial function [16].

The SNS efferent transmission from the brain to the peripheral tissues is controlled by several forebrain and hindbrain nuclei. Particularly important are the paraventricular nucleus of the hypothalamus (PVN), the circumventricular organs (CVOs), the rostral ventral lateral medulla (RVLM), the anteroventral third ventricle (AV3V) and the nucleus of the solitary tract (NTS) [17,18]. All of these structures demonstrate high expression of Ang-II type 1 receptors (AT1R) [19]. In mammals, CVOs include the median eminence and adjacent neurohypophysis, the organum vasculosum lamina terminalis (OVLT), the subfornical organ (SFO) and the area postrema (AP). CVOs are characterized by their small size, high permeability and fenestrated capillaries, which enable polypeptide hypothalamic hormones to leave the brain without disrupting the blood-brain barrier (BBB) and permit substances that do not cross the BBB to trigger changes in the brain function (that is Ang-II or cytokines) [20].

Pro-inflammatory cytokines produced in the periphery can feed back to the brain, passing through the BBB at points of increased permeability in CVOs and/or disrupted BBB. PVN stimulation with tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) results in augmented adrenocorticotrophic hormone release, increased sympathetic outflow and enhanced cardiac sympathetic afferent reflex with subsequent BP elevation [21-23]. However, pro-inflammatory cytokines are also produced by glia and neurons and the recently identified brain inflammatory response to peripheral inflammation may further contribute to the development of hypertension [11,24-26]. Interestingly, circulating Ang-II can signal NTS neuronal networks across the BBB [27] and contributes to BBB disruption [28-30], enabling its own access to brain areas that are normally protected by the BBB, including the PVN, RVLM, and NTS [31]. Also, pro-inflammatory cytokines (IL-1 β , interleukin-6 (IL-6) and TNF- α) may cause dysregulation of adherens and tight junctions leading to BBB permeabilisation [32,33]. Therefore, the question of whether the feedback or feedforward mechanism prevails and consequently whether neuroinflammation is a cause or rather the effect of hypertension remains open.

Renin-Ang-II system and neuroinflammation

Ang-II acting via its AT1R within the PVN is a major contributor to chronic sympathoexcitation [34]. A slow-

pressor Ang-II model of hypertension has been validated in mice and rats, and it mimics the essential hypertension in humans as reviewed by Reckelhoff and Romero [35]. Anti-inflammatory cytokine interleukin-10 (IL-10) or minocycline, a tetracycline antibiotic, inhibits the activation of microglia and reduces BP in this model [36]. Furthermore, minocycline treatment eradicates the Ang-II-induced increase in mRNAs for pro-inflammatory cytokines (IL-1 β ; IL-6; TNF- α) and the decrease in IL-10 mRNA [36-38]. Ang-II-induced hypertension is dependent upon the activation of the inflammatory nuclear factor kappa B (NF κ B) in the PVN [39], and direct injection of IL-1 β into the PVN or via the intracerebroventricular (ICV) route increases mean BP [23,38,39]. Interestingly, low-intensity exercise normalizes nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) and reactive oxygen species (ROS) content, suppresses TNF- α and IL-6 mRNA expression within the PVN and improves baroreflex control of the heart rate, decreases BP and reduces the low-frequency component of BP variability [40].

Protracted infusion of Ang-II using osmotic minipumps in mice at the rate of 400 ng/kg/min is a slow-pressor dose which raises the systolic BP by 20 to 40 mm Hg [28]. In such a model, a significant increase in leukocyte adhesion on brain venules is observed on day 4 and this effect is maintained on day 14 of Ang-II infusion. Additionally, since the day 14, the leukocyte adhesion is further accompanied by a significant increase in leukocyte rolling [41]. Importantly, BP increases on day 6 in this model [41], while oxidative stress peaks on day 4 [42] of Ang-II infusion. Therefore, it is likely that the increased leukocyte adhesion precedes the onset of hypertension but coincides with the development of oxidative stress. Furthermore, increased leukocyte adhesion in Ang-II-infused mice is associated with increased BBB permeability while the reversal of cerebrovascular inflammation (leukocyte rolling and adhesion) through tempol (superoxide dismutase mimetic) treatment is also associated with restoration of the BBB function [28]. It was observed that Ang-II affects BBB permeability in the tissue culture environment [29,30]. Importantly, the increased BBB permeability facilitates leakage of circulating Ang-II into PVN, NTS and RVLM [31].

In addition to the Ang-II/AT1R mechanism, it has been proven that another member of the renin-angiotensin system (RAS), prorenin, and the prorenin receptor (PRR) plays a role in the central control of neurogenic hypertension [43]. Prorenin, like Ang-II, increases pro-inflammatory cytokine expression (TNF- α and IL-1 β) in the NTS via the NF κ B complex [39,44]. Furthermore, prorenin can elicit a stronger response in cytokine production in Ang-II-pretreated microglia than in non-pretreated microglia. Prorenin-induced increases in cytokine expression are eradicated by the microglial activation inhibitor minocycline

[45]. Down-regulation of PRR in the supraoptic nucleus attenuates BP development in spontaneously hypertensive rats (SHR) [46], another animal model of human hypertension [47,48]. PRR levels are higher in the PVN of human renin-angiotensinogen double transgenic hypertensive mice. Knockdown of PRR in the brains of these animals significantly decreases BP and sympathetic vasomotor tone [49]. Neuron-specific knockdown of PRR also can reduce Ang-II formation and BP in the DOCA-salt mouse model of hypertension [50,51]. Down-regulation of PRR mediated by viral transfection in the supraoptic nucleus decreases BP and the expression of inflammatory mediators [46].

The inflammatory mechanisms associated with neurogenic hypertension are not restricted to the PVN in the brain as studies indicate that the NTS exhibits an inflammatory state in SHR [52]. The theory of vascular inflammation of the brainstem has been presented elsewhere [52] and is not discussed in the current review.

SNS activity and hypertensive responses are associated with the levels of cytokines and oxidative stress markers in the RVLM. Chronic inhibition of the angiotensin-converting enzyme in the PVN attenuates both sympathoexcitation and ROS and modulates expression of cytokines (decreasing TNF- α , IL-1 β , IL-6 and MCP-1 while increasing IL-10) in the RVLM in renovascular hypertension [51]. This effect is due to the high number of PVN neurons projecting to the RVLM (PVN-RVLM neurons). The number of PVN-RVLM neurons is as much as seven times the number of PVN neurons projecting to the spinal cord [53,54], and the PVN-RVLM pathway contributes to the change in SNS activity observed after activation of the PVN. Interestingly, the infusion of tempol (superoxide dismutase mimetic) in the PVN not only reduces the ROS response but also decreases BP and SNS activity in hypertension [55].

In conclusion, Ang-II and prorenin increase the production of ROS and mRNAs for pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), whereas they decrease expression of IL-10 mRNA in the PVN and RVLM [36-38]. Both prorenin and Ang-II act via the NF κ B complex [39,44]. Ang-II also augments BBB permeability in the tissue culture environment and Ang-II-induced hypertension [28-30]. Inflammatory response and ROS formation in the PVN and RVLM results in elevated SNS activity and hypertension. It seems that RAS-induced hypertension represents a combination of feedforward (direct Ang-II and prorenin effects on the PVN and RVLM) and feedback (systemic Ang-II and cytokines signalling via CVOs) mechanisms that may ultimately promote the development of the neurogenic form of hypertension.

Lipopolysaccharide-induced neuroinflammation

Lipopolysaccharide (LPS), both in microglial culture and after ICV injection, elicits an inflammatory response via

Toll-like receptor 4 [56,57]. An early and essential step in this process is the NADPH oxidase-dependent production of ROS, which in turn stimulates mitogen-activated protein kinase (MAPK) pathways. While LPS activates all three of the major MAPK pathways, the p38 MAPK pathway seems to be most closely associated with LPS-induced up-regulation of inflammatory mediators [58], including TNF- α , IL-1 β and cyclooxygenase 2 (COX-2), the inducible form of cyclooxygenase regulating synthesis of prostaglandin E2 (PGE2) [56,57,59,60]. COX-2 and PGE2 are known to activate the SNS [21,22,61]. ICV LPS also stimulates the hypothalamic expression of AT1R mRNA, but not the angiotensin-converting enzyme mRNA, via an NADPH oxidase-dependent pathway that does not require p38 MAPK [60]. Therefore, Zhang *et al.*'s [60] study suggests that Ang-II and the pro-inflammatory cytokines may share a common mechanism for up-regulation of the AT1R. Ang-II activates NADPH oxidase-dependent superoxide production [62] and MAPK signalling pathways [63-66]. NADPH oxidase-dependent superoxide production up-regulates AT1R, which contributes to the increased sympathetic drive [67]. NADPH oxidase-dependent superoxide generation can be reduced either by blocking NADPH oxidase activity [62] or by destroying ROS [62,68]. The downstream effects of Ang-II- and LPS ROS-generating systems seem to be differentially regulated as the p38 inhibitor has no effect on LPS-induced AT1R activity but substantially reduces mRNA for TNF- α and COX-2 [60].

Intraperitoneal LPS infusion is a well-characterized rodent model of systemic inflammation. In contrast to high-dose endotoxin triggering a robust yet transient inflammatory response, low-dose endotoxin causes low-grade persistent inflammatory reactions from the host. This reaction is comparable to low-grade systemic inflammation elicited by periodontal bacteria or a hyperlipidic diet [69-72]. LPS-induced chronic systemic inflammation augments levels of TNF- α , IL-1 β , IL-6 and inducible nitric oxide synthase (iNOS) in the RVLM. The expression of pro-inflammatory factors in this study [25] was comparable to that found in the brain of other animal models of hypertension with neurogenic components, including chronic infusion of Ang-II and SHR [24,73]. Oxidative stress resulting from inflammation in the RVLM is downstream to microglial activation via a COX-2-dependent mechanism. COX-2 augments expression of the pro-inflammatory cytokines and iNOS in the RVLM. The increase of protein expression and enzyme activity of COX-2 is reversible by inhibiting microglial activation. Interestingly, COX-2 activation seems to be downstream to the loss of endothelial integrity in the RVLM [25]. Microglial activation and the presence of COX-2 and cytokines ameliorate redox-sensitive expression of the Kv4.3 channel protein [25]. Kv4.3 contributes to the transient

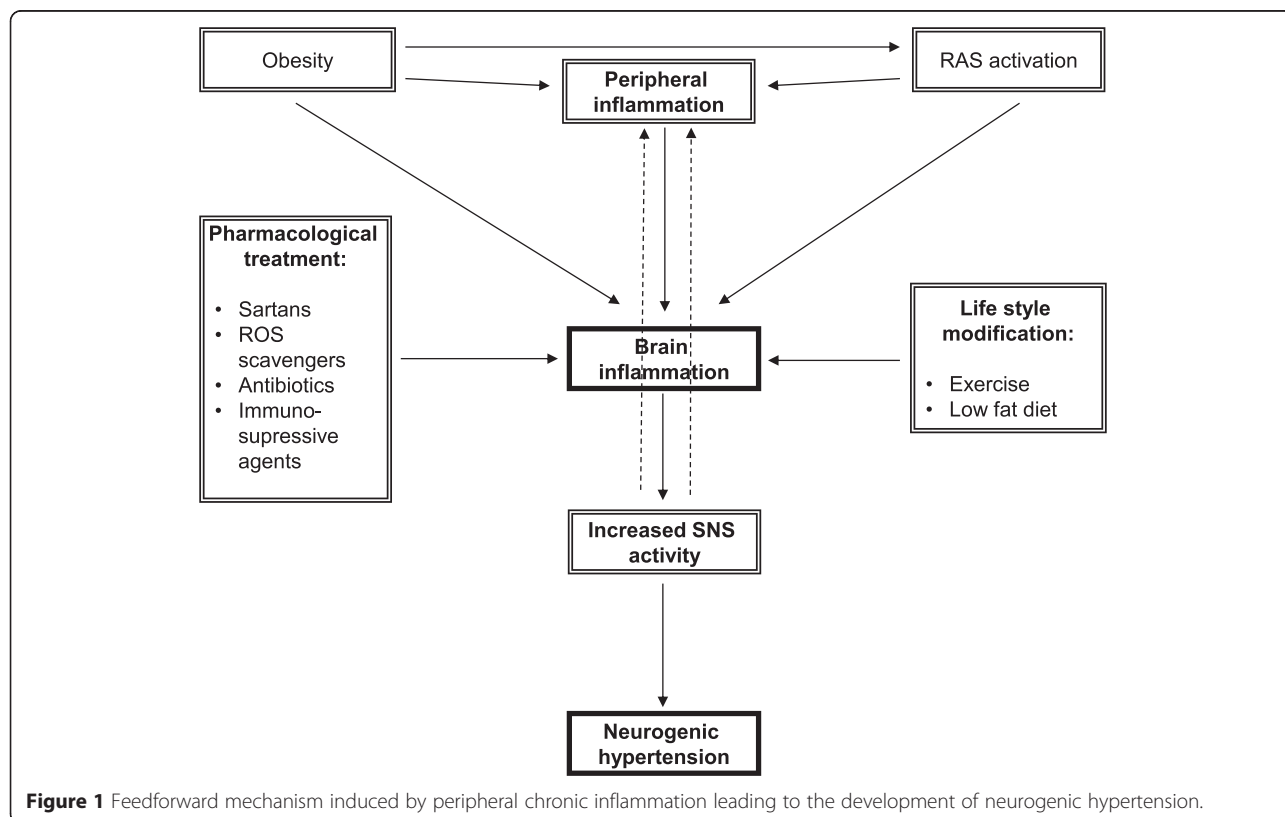
outward potassium current, and its activation diminishes neuronal excitability by increasing the duration of action potential [74]. By reducing Kv4.3 channel protein expression, neuroinflammation in the RVLM promotes hypertension via SNS activation that may result from a redox-sensitive increase in neuronal excitability. It is unlikely that the observed neuroinflammation in the RVLM resulted from direct entry of blood-borne inflammatory cytokines as the LPS-promoted long-term pressor response and the reduction in expression of the voltage-gated potassium channel Kv4.3 in the RVLM were antagonized by minocycline (an inhibitor of microglial activation), the COX-2 inhibitor, pentoxifylline (a cytokine synthesis inhibitor) or tempol (superoxide dismutase mimetic), either infused into the cisterna magna or microinjected bilaterally into the RVLM. The same treatments were ineffective against LPS-induced systemic inflammation [25].

To summarize, LPS in microglial culture or provided either centrally via ICV injection or peripherally via intraperitoneal infusion causes endothelial dysfunction and activates microglia in the brain nuclei controlling SNS efferent transmission to induce COX-2-dependent neuroinflammation and a subsequent increase in ROS production. LPS and Ang-II seem to share a common mechanism contributing to an increase in sympathetic neurogenic vasomotor tone and neurogenic hypertension

[25,56,57,59,60]. Therefore, peripheral chronic inflammation may potentially lead to neurogenic hypertension without a pre-existing hypertensive condition, suggesting a feedforward brain-originated mechanism of peripheral cardiovascular pressor responses.

Obesity-induced neuroinflammation

Obesity is proven to be a mild inflammatory condition often accompanied by increased RAS activity [26,75]. A high-fat diet (HFD) and obesity are associated with the activation of microglia [76,77] and astrocytes [76,78,79], suggesting an inflammatory state in the CNS. In rodents, HFD feeding also initiates an inflammatory cascade in both the PVN and the SFO, two brain regions that are critical for the regulation of BP and energy balance. An increased number of glial cells are Ang-II dependent, and they are localized specifically within the parvocellular portion of the PVN and the SFO [80]. Diet-induced obesity and leptin increase AT1aR expression in the SFO [80,81]. The silencing of AT1aR in mice or the pharmacological blocking of brain AT1R in rats attenuates leptin-induced SNS activity in renal and brown adipose tissue, while not attenuating leptin-induced decreases in food intake or body weight. ICV administration of captopril reverses the effects of leptin on renal and brown adipose tissue SNS activity in rats, suggesting that the production of Ang-II within the brain contributes to the



interaction between the brain RAS and leptin [81]. There is a mounting evidence for a distributed brain network of leptin action, encompassing the NTS [82–84], the SFO [85,86] and the ventromedial and dorsomedial hypothalamic nuclei [87], all of which are involved in neurohumoral control of the circulation and Ang-II action.

In the normal condition, microglia exist primarily in a resting state with low levels of CD45 expression, which increases to high levels upon activation by inflammatory stimuli such as LPS and in various neurologic conditions such as Alzheimer's disease [88–90]. For this reason, it is not possible to differentiate activated microglia and bone marrow-derived cells in the CNS only on the basis of CD45 expression. Such differentiation is feasible using the radiation bone marrow chimaera model [91]. Using this model, Buckman *et al.* showed that less than 10% of the CD11b⁺CD45^{hi} cells were of microglial origin; 93% of the bone marrow-derived cells in the CNS were found in the parenchyma but were not associated with vessels and had a distinct stellate morphology characterized by enlarged somata [92]. The hypothesis that bone marrow-derived monocytes act like macrophages in the CNS was supported by Simard *et al.* [93], who demonstrated that bone marrow-derived monocytes/macrophages enter the CNS and phagocytose and degrade amyloid more effectively than resident microglia in a mouse model of Alzheimer's disease. The physiological significance of immune cell recruitment to the CNS during obesity and whether these cells are recruited as a consequence of obesity-induced neuroinflammation and/or contribute to the neuropathology associated with obesity have yet to be determined. It is not known if forebrain and hindbrain nuclei controlling the SNS outflow from the brain to the peripheral tissues are affected by bone marrow-derived monocytes. Importantly, the number of CNS-infiltrating monocytes is positively correlated with body weight, fat mass and markers of inflammation in adipose tissue (CD68 and CCL2 gene expression) [92].

In conclusion, obesity initiates an inflammatory cascade in both the PVN and the SFO. The increase in the number of glial cells is Ang-II dependent [80]. The inflammatory ability of resident microglial cells might potentially be enhanced by HFD-induced recruitment of bone marrow-derived monocytes to the brain [92]. Therefore, obesity primarily not associated with hypertension may trigger feedforward launching of neurogenic hypertension by a brain-originated mechanism.

Future directions

Inflammation of forebrain and hindbrain nuclei controlling the SNS efferent transmission from the brain to the periphery seems to constitute a key element in the development of neurogenic hypertension. Marvar *et al.* [49] proposed for the first time a feedforward mechanism with

a central role of Ang-II in brain inflammatory response and subsequent SNS activation. We suggest that RAS-driven hypertension encompasses feedback and feedforward mechanisms, while chronic low-intensity peripheral inflammation of any origin may serve as an example of a feedforward mechanism in the development of neurogenic hypertension (Figure 1). Chronic systemic inflammation and Ang-II (or even prorenin) may share the same signalling pathways, ultimately leading to increased production of pro-inflammatory cytokines in brain nuclei controlling cardiovascular function.

Clearly, the results from animal studies discussed above open up enormous potential for translation, both in terms of pharmacological therapy and lifestyle modifications. Sartans (AT1R blockers) are already commonly used for therapy in hypertension, diabetes and stroke but have not been studied in humans in the context of their central anti-inflammatory action. Nevertheless, the safety profile of this group of drugs is relatively well known. Antibiotics, ROS scavengers and immunosuppressive agents are also likely candidates for controlled randomized trials in humans. Finally, low-intensity but repetitive exercise and a low-fat diet represent a safe approach to reducing the risk of brain inflammation and the subsequent development of neurogenic hypertension.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PJW drafted and wrote the manuscript. MR, MWW and UD commented and revised the manuscript. All authors have read and approved the final version of the manuscript.

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