



Brain perivascular macrophages: connecting inflammation to autonomic activity in hypertension

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The contribution of the immune system to the pathogenesis of essential hypertension has been documented in many experimental and clinical studies as extensively reviewed elsewhere [1]. In particular, macrophage infiltration into the vascular walls has been shown to be involved in the development of hypertension via the promotion of vascular inflammation and endothelial dysfunction [2, 3]. In a study by Iyonaga et al. [4], the authors described the role of brain perivascular macrophages (PVMs) in the development of hypertension via enhanced sympathetic activation, thereby linking the immune and autonomic systems.

Brain PVMs, located in the perivascular space surrounding large cerebral arterioles [5], differ from vessel-associated microglia, which are juxtaposed to all cerebral vessels but located beyond the glia limitans [6]. Brain PVMs have been scrutinized in recent years, as their particular location position them as key players in the initiation of cerebrovascular dysfunction, as shown in hypertensive mice and Alzheimer's disease mouse models [7, 8]. In their study, the authors demonstrated that IL-1 β leads to the overexpression of prostaglandin E2 (PGE2), a known trigger of increased sympathetic outflow in cardiovascular centers, in PVMs [9] (Fig. 1). Furthermore, PVM depletion induced by clodronate liposomes was able to limit the blood pressure increase in stroke-prone spontaneously hypertensive rats. While increased PGE2 expression was observed in PVMs, the potential impact of PGE2 in other brain cells, such as

endothelial cells and microglia, cannot be excluded (Fig. 1, routes 1 and 3).

The contribution of the central immune system to sympathetic activity is not completely new, as previous studies have shown that the release of proinflammatory cytokines by activated microglia in the paraventricular nucleus (PVN) contributes to neurogenic hypertension [10]. In this study, hypertension was mimicked by the infusion of Angiotensin II (Ang II) for 4 weeks, and the infusion of minocycline (icv, an anti-inflammatory antibiotic) in Ang II-infused rats was able to decrease the number of activated microglia and the expression of proinflammatory cytokines and attenuate the blood pressure elevation [10]. The contribution of PVMs in the later study cannot be excluded, as the detection and quantification methods were not able to distinguish microglia from macrophages. The possible contribution of Ang II was not studied in the study by Iyonaga et al. [4], but Ang II may also be involved in the activation of PVMs and subsequent sympathetic activity, as the Ang II plasma level is known to be elevated in spontaneously hypertensive rats (SHRs) [11, 12]. Ang II-mediated microglial and PVM activation results from the activation of Angiotensin II type 1 receptor (AT₁R) [7, 13]. The blockade of AT₁R and the stimulation of the counteracting AT₂R [14] are known to promote an anti-inflammatory microglial phenotype [15–17]. Angiotensin receptor antagonists may therefore be of potential importance beyond their blood pressure lowering effects and their beneficial impact on the structure and function of cerebral vessels [18, 19]. Although blood-brain barrier (BBB) permeability was not assessed in the present study, previous studies have indicated increased BBB permeability in the PVN, rostral ventrolateral medulla and nucleus tractus solitarius in SHRs and other hypertensive models, which allows the leakage of Ang II in these key sympathoexcitatory brain areas [20] (as illustrated in Fig. 1, routes 2 and 4).

While the depletion of PVMs by centrally administered clodronate liposomes has proven to be effective in

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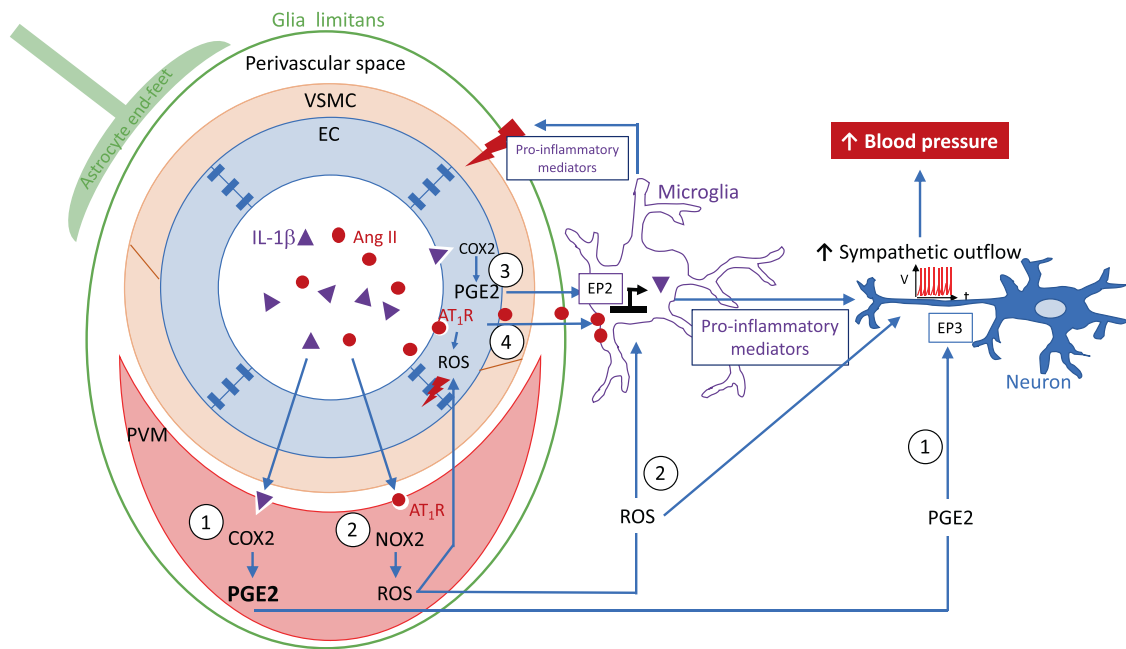


Fig. 1 A schematic overview illustrating the involvement of brain resident immune cells in sympathoexcitation-mediated hypertension. Past and present studies converge on four mechanistic routes involving COX2/PGE2 signaling (route 1 via perivascular macrophages; route 3 via endothelial cells) and AT₁R/NOX2/ROS signaling (route 2 via

PVMs; route 4 via endothelial cells). Ang II Angiotensin II, AT₁R Angiotensin II type 1 receptor, COX2 cyclooxygenase-2, EC endothelial cell, EP2-3 prostaglandin receptor, PGE2 prostaglandin E₂, PVM perivascular macrophage; ROS reactive oxygen species, VSMC vascular smooth muscle cell

preventing neurovascular dysfunction in both acute Ang II-treated and BPH/2J hypertensive mice [7], it had no effect on blood pressure in SHR, contrary to the present study. This differential effect suggests a variable contribution of PVMs to hypertension depending on the extent of neurogenic contribution in the chosen model as well as on the timing of hypertension development and/or the timing of depletion.

In summary, the work by Iyonaga et al. strengthens the crucial link between the immune system and the autonomic system. The clinical translation of this work would be very valuable for identifying new therapeutic strategies for patients with an immune-neurogenic type of essential hypertension. This work highlights the importance of gaining more insights into the pleiotropic roles played by microglia and macrophages in health and diseases. Their interaction with the CNS vasculature [6, 21, 22] position them as key players in the development of hypertension and its subsequent consequences.

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Compliance with ethical standards

Conflict of interest SF has no conflict of interest to report.

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