Brain perivascular macrophages

Hypertension Research (2020) 43:148–150
https://doi.org/10.1038/s41440-019-0359-7

COMMENT

Brain perivascular macrophages: connecting inflammation to autonomic activity in hypertension

Sébastien Foulquier[1,2,3]

Received: 11 October 2019 / Revised: 16 October 2019 / Accepted: 17 October 2019 / Published online: 19 November 2019

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-1β 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 (AT_1R) [7, 13]. The blockade of AT_1R and the stimulation of the counteracting AT_2R [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

✉ Sébastien Foulquier
s.foulquier@maastrichtuniversity.nl

[1] Department of Pharmacology-Toxicology, Maastricht University, Maastricht, The Netherlands

[2] CARIM, School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands

[3] MHeNs, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands

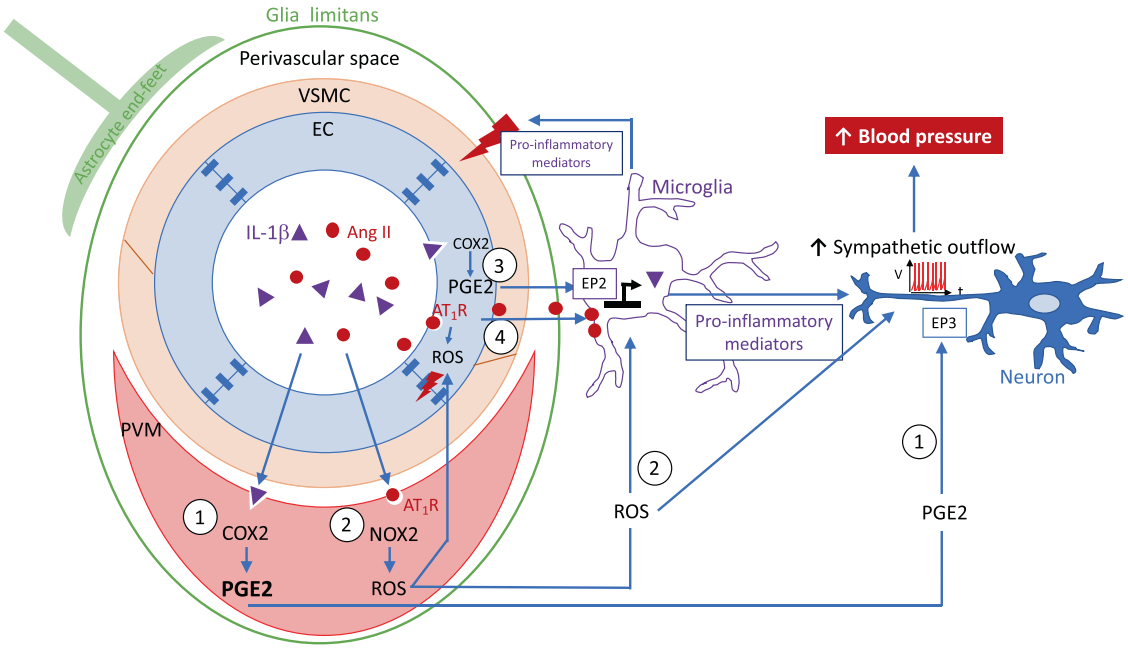

Fig. 1 A schematic overview illustrating the involvement of brain resident immune cells in sympathoexcitation-mediated hypertension. Past and present studies converge on four mechanistic routes involving COX2/PGE2 signaling (route 1 via perivascular macrophages; route 3 via endothelial cells) and AT_1R/NOX2/ROS signaling (route 2 via PVMs; route 4 via endothelial cells). Ang II Angiotensin II, AT_1R 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 SHRs, 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.

Funding SF has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 666881 SVDs@target and from the Netherlands CardioVascular Research Initiative (CVON 2012-06 Heart Brain Connection).

Compliance with ethical standards

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

References

1. Rodriguez-Iturbe B, Pons H, Johnson RJ. Role of the immune system in hypertension. Physiol Rev. 2017;97:1127–64.
2. Chan CT, Moore JP, Budzyn K, Guida E, Diep H, Vinh A, et al. Reversal of vascular macrophage accumulation and hypertension by a CCR2 antagonist in deoxycorticosterone/salt-treated mice. Hypertension. 2012;60:1207–12.
3. Elmarakby AA, Quigley JE, Olearczyk JJ, Sridhar A, Cook AK, Inscho EW, et al. Chemokine receptor 2b inhibition provides renal protection in angiotensin II—salt hypertension. Hypertension. 2007;50:1069–76.
4. Iyonaga T, Shinohara K, Mastuura T, Hirooka Y, Tsutsui H. Brain perivascular macrophages contribute to the development of hypertension in stroke-prone spontaneously hypertensive rats via sympathetic activation. Hypertens Res. 2019. https://doi.org/10.1038/s41440-019-0333-4. [Epub ahead of print]
5. Faraco G, Park L, Anrather J, Iadecola C. Brain perivascular macrophages: characterization and functional roles in health and disease. J Mol Med. 2017;95:1143–52.
6. Koizumi T, Taguchi K, Mizuta I, Toba H, Ohigashi M, Onishi O, et al. Transiently proliferating perivascular microglia harbor M1 type and precede cerebrovascular changes in a chronic hypertension model. J Neuroinflamm 2019;16:79.
7. Faraco G, Sugiyama Y, Lane D, Garcia-Bonilla L, Chang H, Santisteban MM, et al. Perivascular macrophages mediate the neurovascular and cognitive dysfunction associated with hypertension. J Clin Investig. 2016;126:4674–89.

8. Park L, Uekawa K, Garcia-Bonilla L, Koizumi K, Murphy M, Pistik R, et al. Brain Perivascular macrophages initiate the neurovascular dysfunction of Alzheimer Aβ peptides. Circ Res. 2017;121:258–69.
9. Zhang Z-H, Yu Y, Wei S-G, Nakamura Y, Nakamura K, Felder RB. EP_3 receptors mediate PGE_2-induced hypothalamic paraventricular nucleus excitation and sympathetic activation. Am J Physiol Heart Circ Physiol. 2011;301: H1559–1569.
10. Shi P, Diez-Freire C, Jun JY, Qi Y, Katovich MJ, Li Q, et al. Brain microglial cytokines in neurogenic hypertension. Hypertension. 2010;56:297–303.
11. Hübner N, Kreutz R, Takahashi S, Ganten D, Lindpaintner K. Altered angiotensinogen amino acid sequence and plasma angiotensin II levels in genetically hypertensive rats. A study on cause and effect. Hypertension. 1995;26:279–84.
12. Bolterman RJ, Manriquez MC, Ortiz Ruiz MC, Juncos LA, Romero JC. Effects of captopril on the renin angiotensin system, oxidative stress, and endothelin in normal and hypertensive rats. Hypertension. 2005;46:943–7.
13. Biancardi VC, Stranahan AM, Krause EG, de Kloet AD, Stern JE. Cross talk between AT1 receptors and Toll-like receptor 4 in microglia contributes to angiotensin II-derived ROS production in the hypothalamic paraventricular nucleus. Am J Physiol Heart Circ Physiol. 2016;310:H404–415.
14. Foulquier S, Steckelings UM, Unger T. Perspective: a tale of two receptors. Nature 2013;493:S9.
15. Bhat SA, Sood A, Shukla R, Hanif K. AT2R activation prevents microglia pro-inflammatory activation in a NOX-dependent manner: inhibition of PKC activation and p47phox phosphorylation by PP2A. Mol Neurobiol. 2019;56:3005–23.
16. Valero-Esquitino V, Lucht K, Namsolleck P, Monnet-Tschudi F, Stubbe T, Lucht F, et al. Direct angiotensin AT2-receptor stimulation attenuates T-cell and microglia activation and prevents demyelination in experimental autoimmune encephalomyelitis in mice. Clin Sci. 2015;128:95–109.
17. Benicky J, Sánchez-Lemus E, Honda M, Pang T, Orecna M, Wang J, et al. Angiotensin II AT1 receptor blockade ameliorates brain inflammation. Neuropsychopharmacology. 2011;36:857–70.
18. Foulquier S, Dupuis F, Perrin-Sarrado C, Gatè KM, Leroy P, Liminana P, et al. Differential effects of short-term treatment with two AT(1) receptor blockers on diameter of pial arterioles in SHR. PLoS ONE. 2012;7:e42469.
19. Foulquier S, Lartaud I, Dupuis F. Impact of short-term treatment with telmisartan on cerebral arterial remodeling in SHR. PLoS ONE. 2014;9:e110766.
20. Biancardi VC, Stern JE. Compromised blood-brain barrier permeability: novel mechanism by which circulating angiotensin II signals to sympathoexcitatory centres during hypertension. J Physiol. 2016; 594:1591–600.
21. Foulquier S, Caolo V, Swennen G, Milanova I, Reinhold S, Recarti C, et al. The role of receptor MAS in microglia-driven retinal vascular development. Angiogenesis. 2019. https://doi.org/10.1007/s10456-019-09671-3. [Epub ahead of print]
22. Foulquier S, Namsolleck P, Van Hagen BT, Milanova I, Post MJ, Blankesteijn WM, et al. Hypertension-induced cognitive impairment: insights from prolonged angiotensin II infusion in mice. Hypertens Res. 2018;41:817–27.