ESC European Society of Cardiology

Cardiovascular Research (2021) **117**, e70–e72
doi:10.1093/cvr/cvab089

EXPERT OPINION

CARDIOVASCULAR RESEARCH Onlife

The neurology of hypertension: merging academic specialties to connect heart and brain pathophysiology

Giuseppe Lembo [1,2]* **and Marialuisa Perrotta**[1]

[1]Department of Molecular Medicine, "Sapienza" University of Rome, Viale Regina Elena, 00161 Rome, Italy; and [2]Department of Angiocardioneurology and Translational Medicine, Via dell'Elettronica, IRCCS Neuromed, 86077 Pozzilli, IS, Italy

Keywords Hypertension • Brain • Autonomic nervous system • Immunity • Dementia

Online publish-ahead-of-print 5 April 2021

The brain is the main regulator of blood pressure (BP) homeostasis, yet it is a target organ of the injury induced by acute and chronic BP alterations, like hypertension and hypotension. As such, medical school textbooks for cardiologists and neurologists deal with the role of BP in influencing the heart and brain connection. On this notice, the advancements in clinical and basic research knowledge, we have assisted in the last decades highlighted the emerging need of professionals with a combined expertise of 'cardio-neurologists' and 'cardio-neuroscientists'.

While neuroscientists with a 'classical' training are well familiar with the neurocentric knowledge of the brain as a target organ of acute and chronic BP variations, they might be less familiar with the basic mechanisms regulating haemodynamic forces—like cardiac and vascular reactivity—which represent the fundamental machinery to develop and regulate BP. On the other hand, cardiologists might lack a deep knowledge of the brain structures more susceptible to target organ damage induced by BP fluctuations or involved in BP regulation. Clinical and basic science environments that routinely combine these two fields of specialization helped in increasing the awareness of how important the heart and brain connection in hypertension is. More recently, the scenario has been enriched by the increasing insights into the previously unrecognized role of the immune system, which interplays with both the cardiovascular and the nervous system to finely tune the steady-state homeostasis as well as pathophysiological conditions.[1] Here, we will comment on recent publications that offer interesting perspectives on the new topics of the neurology of hypertension that inspire and deserve future investigations.

The brain is connected to visceral organs with the autonomic nervous system (ANS)—a combination of afferent/efferent sympathetic and parasympathetic neurons. An imbalance in the ANS is a typical neurogenic cause of hypertension and often accompanies many cardiovascular diseases (CVD).[1] Observations showing that the ANS interacts with the renin–angiotensin–aldosterone system—another master regulator of cardiovascular function—prompted studies investigating how the brain establishes this interplay. Receptors for angiotensin II (AngII) are densely enriched in the brain, particularly in those areas that lack a tight blood–brain barrier (BBB) and are exposed to circulating substances (like AngII itself)—the circumventricular organs (CVOs). Hence, the role of brain AngII receptors was examined to unravel how the brain sets the balance of ANS and regulates cardiovascular function (see reference 1 for review). On another notice, the emerging role of the immune system in hypertension fuelled the search for neuroimmune interactions involved in the ANS control of cardiovascular function. While ANS control of classical organs involved in BP regulation—vasculature, kidney, heart—has been demonstrated in experimental models and humans from decades, the role in modulating the immune response involved in hypertension has been recently discovered.[2] By using peripheral nerves microneurography—a technique that over the past decades allowed to understand the complex reflex regulation of cardiovascular function—it was shown that hypertensive stimuli enhance the sympathetic outflow of the splenic nerve to prime the immune response in the spleen.[2] Selective denervation of the upstream ganglionic station—obtained by coeliac ganglionectomy—inhibited the BP increase to AngII.[2] This observation has been successively confirmed also in genetically hypertensive mice,[3] further indicating a critical role of this neural reflex in hypertension. In a translational perspective, a recent application of bioelectronic medicine tools to hypertension showed that it is indeed possible modulating the immune response by eliciting a splenic neural reflex through the efferent vagus nerve,[4] opening the field to novel therapeutic strategies for CVD.

Neuroimmune interactions are also established in the brain and participate in the modulation of neural mechanisms and reflexes. The lack of a BBB in CVOs allows free transit of circulating substances other than AngII—like cytokines, which are induced by hypertensive stimuli—permitting the direct activation of neurons and microglial cells. On this notice, the evidence that CVOs also express cytokines' receptors supports the existence of central neuroimmune mechanisms modulating the direct effect of AngII. ANS control of the cardiovascular system depends on the precise coordination between neurons in central autonomic brain nuclei—the subfornical organ, the paraventricular nucleus of the hypothalamus, the nucleus of the solitary tract (NTS), and the rostral ventrolateral medulla (RVLM)—that integrate baroreceptor reflex and efferent sympathetic tone. However, the elucidation of central and peripheral neuroimmune mechanisms involved in the development of hypertension is just at the beginning. A recent observation highlighted a role of the

* Corresponding author. Tel: 39.0865915225, E-mail: lembo@neuromed.it

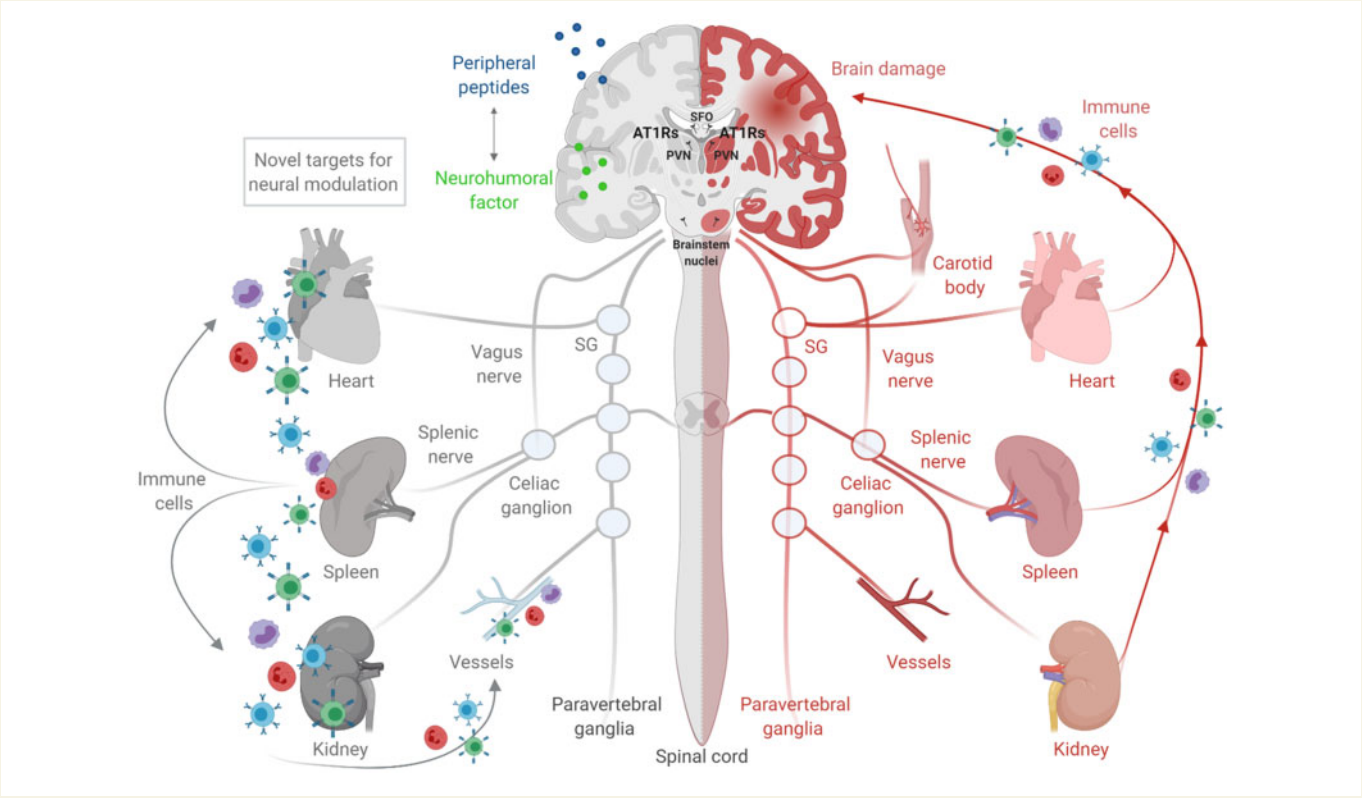


Figure 1 Schematic representation of the heart and brain connection. The left side of the figure represents the routes through which the brain influences pathways involved in blood pressure regulation. The right side of the figure shows how hypertension may induce brain damage. Figure created with Biorender.com.

TNF-α type-1 receptor (TNFR1) expressing neurons of the area postrema (AP)—located dorsally to the NTS—in the hypertensive response and enhanced renal sympathetic outflow in rats.[5] Interesting to notice, the AP represents an important autonomic structure that communicates with both the NTS (the first station of the baroreceptor reflex) and RVLM (a crucial generator of sympathetic tone), thus suggesting that neuroimmune mechanisms might be involved in setting ANS balance in hypertension. Future studies will be necessary to elucidate the complex interactions established among the nervous, immune, and cardiovascular systems.

While we have summarized some key nodes of the brain-to-periphery connection, where neuroimmune interactions emerge as relevant and indispensable regulators of BP, the other way around is crucial as well. Signals collected at peripheral districts are conveyed to the brain where they contribute to the multitude of information integrated by central autonomic brain nuclei and transduced into reflex responses. One of the most intensely studied peripheral relay stations that modulates signals that are transmitted to the brain is the carotid body, a highly vascularized ensemble of nerve fibres that finely tunes brain-to-periphery connections (see reference 6 for review). Investigating whether neuroimmune interactions take place in this organ would be worthy.

At the same time, BP variations continuously challenge the brain, making this latter at the centre of a vicious circle (*Figure 1*). Hypertension is well known to modify the structure and function of the cerebral vasculature, yet how the frequently reported cerebrovascular effects of hypertension lead to cognitive decline and boost Alzheimer's disease remain to be elucidated. Considering that a significant proportion of the population in industrialized countries is exposed to a constantly growing risk of dementia and that hypertension is one of the most diffuse vascular risk factors in the adult and aged population, the interactions existing between each other represent a crucial matter of investigation. While basic science studies started to highlight immune-related mechanisms that underlie the potent effects induced by BP in the brain,[7] the possibility to identify patients at risk in early stages is becoming a demanding clinical need. Large community-based population studies clearly associated hypertension with increased risk of dementia.[8] On this notice, a recent analysis conducted on the UK biobank population clarified that while aging is an undoubtable risk factor that contributes to cognitive decline in CVD, mid-life exposure to high BP is strongly associated with clinically manifest brain damage [identified as white matter hyperintensities (WMH)].[8] Significant associations between increased WMH and BP were found, even before the age of 50 and when antihypertensive treatments assured BP values below common thresholds.[8] Thus, the availability of diagnostic tools to identify patients at risk in pre-hypertensive or at early hypertensive stages may help to develop approaches to preserve brain health in hypertensive patients. Recent works conducted in populations of hypertensive subjects characterized by adequate BP control and by the absence of any clinical sign of brain damage—thus in a pre-symptomatic phase—identified a specific pattern of subtle structural and functional brain alterations, through advanced tools of neuroimaging.[9,10] The

application of a neuroimaging-based non-invasive biomarker to hypertensive patients could prove as an invaluable tool to identify patients at risk of developing dementia.

Conflict of interest: none declared.

Funding

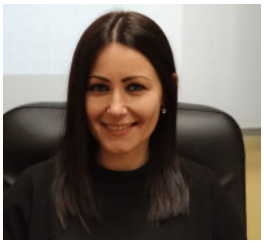
'Ricerca Corrente' from Italian Ministry of Health to G.L.

References

1. Carnevale D, Lembo G. Neuroimmune interactions in cardiovascular diseases. *Cardiovasc Res* 2021;**117**:402–410.
2. Carnevale D, Perrotta M, Pallante F, Fardella V, Iacobucci R, Fardella S, Carnevale L, Carnevale R, De Lucia M, Cifelli G, Lembo G. A cholinergic-sympathetic pathway primes immunity in hypertension and mediates brain-to-spleen communication. *Nat Commun* 2016;**7**:13035.
3. Asirvatham-Jeyaraj N, Gauthier MM, Banek CT, Ramesh A, Garver H, Fink GD, Osborn JW. Renal denervation and celiac ganglionectomy decrease mean arterial pressure similarly in genetically hypertensive Schlager (BPH/2J) mice. *Hypertension* 2021;**77**:519–528.
4. Carnevale L, Pallante F, Perrotta M, Iodice D, Perrotta S, Fardella S, Mastroiacovo F, Carnevale D, Lembo G. Celiac vagus nerve stimulation recapitulates angiotensin ii-induced splenic noradrenergic activation, driving egress of CD8 effector cells. *Cell Rep* 2020;**33**:108494.
5. Korim WS, Elsaafien K, Basser JR, Setiadi A, May CN, Yao ST. In renovascular hypertension, TNF-alpha type-1 receptors in the area postrema mediate increases in cardiac and renal sympathetic nerve activity and blood pressure. *Cardiovasc Res* 2019; **115**:1092–1101.
6. Brognara F, Felippe ISA, Salgado HC, Paton JFR. Autonomic innervation of the carotid body as a determinant of its sensitivity - implications for cardiovascular physiology and pathology. *Cardiovasc Res* 2020.
7. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. *Circ Res* 2019;**124**:1025–1044.
8. Wartolowska KA, Webb AJS. Midlife blood pressure is associated with the severity of white matter hyperintensities: analysis of the UK Biobank cohort study. *Eur Heart J* 2020;**42**:750–757.
9. Carnevale L, D'Angelosante V, Landolfi A, Grillea G, Selvetella G, Storto M, Lembo G, Carnevale D. Brain MRI fiber-tracking reveals white matter alterations in hypertensive patients without damage at conventional neuroimaging. *Cardiovasc Res* 2018; **114**:1536–1546.
10. Carnevale L, Maffei A, Landolfi A, Grillea G, Carnevale D, Lembo G. Brain functional magnetic resonance imaging highlights altered connections and functional networks in patients with hypertension. *Hypertension* 2020;**76**:1480–1490.

Authors

Biography: Prof. Giuseppe Lembo M.D. PhD trained at 'Federico II' University of Naples, Italy and at the University of California at San Diego as research scientist. In 1995, he opened his lab at the Department of Angiocardioneurology and Translational Medicine at IRCCS Neuromed (Pozzilli, Italy) —an excellence centre for neurological and neurovascular diseases—where he is currently based as Professor of Applied Medical Techniques of 'Sapienza' University of Rome and serves as director of the clinical and research units. Member of national and international academic societies, he is advisory scientist for the Italian Ministry of Health. His research activity started by studying the pathophysiological role of autonomic nervous system in hypertensive patients and evolved by investigating molecular mechanisms of hypertension in experimental models. His current work focuses on the heart and brain connection in experimental models and patients. Supported by national and international granting agencies, his research led to the publication of numerous papers on high impact journals.



Biography: Marialuisa Perrotta was trained at Sapienza University of Rome where she graduated in 2013. In 2018 she got a PhD in Clinical and Translational Medicine at IRCCS Neuromed/UNIMOL University. Her PhD work was developed at Prof. Lembo's lab where she focused on the establishment of innovative experimental approaches for evaluating the neuroimmune activity in models of hypertension. With this background, in the last few years, she developed a PostDoc research program in Prof. Lembo's lab, focused on the dissection of specific brain areas controlling the neuroimmune mechanisms of hypertension. Her research work significantly contributed to this area of investigation in Prof. Lembo's research group.