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Microglia, the Missing Link in the Brain-Gut-Hypertension Axis

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This article is a commentary on the following: Microglial Cells Impact Gut Microbiota and Gut Pathology in Angiotensin II-Induced Hypertension

The pathophysiological mechanisms of hypertension are complex and involve multiple interacting systems (cardiac, vascular, renal, endocrine, neural, and immune) functioning on a genetic background influenced by environmental factors (epigenetics and epistasis). The complexity was highlighted over 70 years ago in the Mosaic Theory of hypertension by Irvine Page. More recently, this theory has been revisited by David Harrison where molecular and cellular processes, specifically oxidative stress and inflammation, have been identified as common key events underlying the perturbed systems of the Mosaic Theory of hypertension. In the brain, oxidative stress and inflammatory processes increase neuronal firing in the cardioregulatory centers (neuroinflammation) and stimulate sympathetic nervous system activity, leading to vascular dysfunction and renal sodium retention, processes that cause blood pressure elevation. The importance of neuroinflammation in the pathogenesis of hypertension is based on increased cerebral levels of inflammatory mediators and cytokines produced by neurons and microglial cells in experimental models of hypertension, processes driven by activation of the renin-angiotensin-aldosterone system and other prohypertensive factors such as salt.

To add to the complexity and multisystem network of the Mosaic Theory of hypertension, emerging experimental evidence indicates that the gut microbiota plays an important role in blood pressure regulation and metabolism. This was first demonstrated in the 1980s when modification of bacterial flora with antibiotics in rats was associated with steroid-related hypertension. Many studies have now shown that short-chain fatty acids (SCFAs), which are end products of fermentation by the gut microbiota, modulate blood pressure in mice. SCFAs are absorbed into the bloodstream where they exert effects on target tissues, including vessels, kidney, heart, and brain. In mice exposed to an acute bolus of SCFAs, blood pressure decreased rapidly through effects mediated primarily via the G-protein–coupled receptor, Gpr41, localized in endothelial cells. Alterations in SCFA receptors in the small intestine have also been associated with elevated blood pressure in experimental models. Further demonstrating a role for gut microbiota in cardiovascular disease, propionate, an SCFA, significantly attenuated cardiac hypertrophy, fibrosis, vascular dysfunction, and blood pressure elevation in models of hypertension and atherosclerosis. Using new research strategies including metagenomics, which provides high resolution and culture-independent sequencing of bacterial DNA, bioinformatics analysis for microbial identification and taxonomy, fecal transplantation approaches as well as antibiotic-induced microbial depletion in experimental models, have further supported the pathophysiological role of gut microbial dysbiosis in hypertension. In experimental models of hypertension, administration of gastrointestinal-cleansing antibiotics caused a transient reduction in blood pressure and fecal transfer from hypertensive rats to normotensive rats caused hypertension in the recipient animals. Antibiotics, especially tetracyclines, such as minocycline, reduced blood pressure in spontaneously hypertensive rats and in Ang II-induced hypertension. In a case report,
an antibiotic cocktail (vancomycin, rifampin, and ciprofloxacin) given for postsurgical infection, significantly altered the gut microbiota and reduced blood pressure in a patient with resistant hypertension. Together, these studies strongly suggest that the intestinal microbiome influences pathophysiological processes that regulate blood pressure.

Specific mechanisms triggering gut dysbiosis–induced hypertension are unclear, but the gut enteric nervous system and extrinsic and central neural inputs seem to be important. This notion of neural-gut communication was further developed by the Raizada group and more recently was found to be driven by the brain and sympathetic nerves and accordingly has been termed the brain-gut axis in hypertension as highlighted in the current issue. A comprehensive transcriptomic biomarker analysis in experimental hypertensive models using the Comparative Toxicogenomics Database demonstrated that transcriptomic data in the rodent central nervous system converge on processes associated with gastrointestinal function (transit, motility, and inflammation) supporting interplay between the brain and gut in neurogenic hypertension. However, the central elements driving the system remain elusive.

In the current issue, Sharma et al provide new insights on how the central nervous system influences hypertension through the gastrointestinal system. In particular, they develop the theory that prohypertensive factors, especially Ang II, enhance sympathetic outflow and neuroinflammation through microglial activation, leading to sympathetic activation of the gut, altered gut microbiota, and increased mucosal permeability, processes promoting release of microbial toxins, proinflammatory mediators, and SCFAs into the circulation to cause systemic inflammation and blood pressure elevation. The concept of the leaky gut characterized by an increase in permeability of the gastrointestinal mucosa allowing bacterial toxins, metabolites, reactive oxygen species, proinflammatory molecules, and cytokines to leak into the bloodstream was originally associated with celiac disease and other inflammatory bowel diseases. However, as evidenced in the study in this issue, these processes are more widespread causing systemic inflammation implicated in a multitude of diseases including diabetes mellitus, chronic kidney disease, aneurysms, stroke, and hypertension. The novelty of the Sharma study is that it clearly identifies microglial activation in the paraventricular nuclear region of the hypothalamus and neuroinflammation as being key drivers for the brain-gut axis in hypertension pathophysiology.

These findings were based on elegant experiments that investigated central effects of a chemically modified tetracycline-3 (CMT-3), which has primarily anti-inflammatory rather than antibiotic actions, on microglia activity, gut microbial communities and gut pathology, and blood pressure in hypertensive rats. CMT-3 administered intracerebroventricularly, but not peripherally, inhibited microglial activation, modified gut microbiota, improved gut integrity and reduced blood pressure, clearly defining a neuroinflammation-gut link. This brain-gut communication is not unidirectional but appears to be bidirectional since gut microbiota and their products are also implicated in sympathetic nerve activity. Bacterial SCFAs have been shown to influence microglia homeostasis and neural control mechanisms in hypertension. Accordingly, the communication between the brain and the gut is circuitous where prohypertensive factors stimulate brain-gut communication and a leaky gut causing hypertension through systemic inflammatory processes and oxidative stress, which in turn promote sympathetic nervous system activation and perpetuation of the damaging processes underlying hypertension (Figure 1).
Targeting the dysfunctional brain-gut connection with antibiotics that have anti-inflammatory properties, such as CMT-3, may be a novel approach in the management of hypertension. However, there are a number of concerns and limitations that need to be addressed when such strategies are considered. First, antibiotics, and especially tetracyclines such as minocycline, have been associated with severe intracranial hypertension in both pediatric and adult patients.\textsuperscript{19,20} Hence, antibiotics may actually increase rather than decrease blood pressure, a phenomenon also observed in salt-sensitive hypertensive rats.\textsuperscript{10} Second, although CMT-3 was described as an anti-inflammatory tetracycline derivative in the article in this issue,\textsuperscript{15} it does have some antibiotic and antifungal actions and therefore the changes observed in the CMT-3–treated rats may not only be because of reduced neuroinflammation. Third, if antibiotics are indeed effective antihypertensive agents, acting in part through modulation of the gut microbiota, epidemiological, and clinical studies would have already shown a relationship between antibiotic use and blood pressure, especially considering the large population of patients who are hypertensive and on antibiotics for unrelated diseases. Finally, while research on experimental models has defined cross-talk between the brain and microbiota/gut in the pathophysiology of hypertension, evidence for such a system in humans still awaits confirmation. Nevertheless, based on preclinical data and from a theoretical viewpoint, the brain-gut axis in

\textit{Figure 1 - Schematic demonstrating the circuitous relationship between prohypertensive factors, microglial activation, sympathetic outflow, and gut microbiota in the pathophysiology of hypertension. Neurogenic inflammation and oxidative stress are key molecular processes driving the brain-gut axis. Ang indicates angiotensin; PVN, paraventricular nucleus; and SNS, sympathetic nervous system.}
hypertension is certainly conceivable and could constitute a new axis to the framework of the Mosaic Theory of hypertension. However, to date, robust clinical evidence for this is still lacking. Before any consideration can be given for microglia-microbiota-gut targeted therapies to treat hypertension, unambiguous proof of clinical efficacy and safety without unwanted secondary effects is needed.

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Disclosures

None.

Footnotes

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References


9. Morris DJ, Brem AS. The role of gut metabolism of adrenal corticosteroids and hypertension - clues gut cleansing antibiotics give us [published online January 25, 2019]. Physiol Genomics. doi: 10.1152/physiolgenomics.00115.2018


