HHS Public Access

Author manuscript

Curr Opin Nephrol Hypertens. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

Curr Opin Nephrol Hypertens. 2021 March 01; 30(2): 159–165. doi:10.1097/MNH.0000000000000678.

GUT-BRAIN-BONE MARROW AXIS IN HYPERTENSION

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Abstract

Purpose of review—Rapidly emerging evidence implicates an important role of gut-brain-bone marrow axis involving gut microbiota (GM), gut epithelial wall permeability, increased production of proinflammatory bone marrow (BM) cells and neuroinflammation in hypertension (HTN). However, the precise sequence of events involving these organs remains to be established. Furthermore, whether an impaired gut-brain-BM axis is a cause or consequence of HTN is actively under investigation. This will be extremely important for translation of this fundamental knowledge to novel, innovative approaches for the control and management of HTN. Therefore, our objectives are to summarize the latest hypothesis, provide evidence for and against the impaired gut, BM and brain interactions in HTN and discuss perspectives and future directions.

Recent findings—Hypertensive stimuli activate autonomic neural pathways resulting in increased sympathetic and decreased parasympathetic cardiovascular modulation. This directly affects the functions of cardiovascular-relevant organs to increase blood pressure (BP). Increases in sympathetic drive to the gut and BM also trigger sequences of signaling events that ultimately contribute to altered GM, increased gut permeability, enhanced gut- and brain-targeted proinflammatory cells from the BM in perpetuation and establishment of HTN.

Summary—In this review, we present the mechanisms involving the brain, gut, and BM, whose dysfunctional interactions may be critical in persistent neuroinflammation and key in the development and establishment of HTN.

Keywords

Neuroinflammation; Gut Microbiota; Bone Marrow; Autonomic Nervous System; Microglia

Introduction

HTN is the most preventable modifiable risk factor for cardiovascular disease, stroke and chronic kidney disease. American Heart Association/American College of Cardiology estimates that ~48% of Americans have high BP and importantly, ~17% of these hypertensive patients are resistant to all interventions [1]. These numbers are even greater in the African American population who have earlier onset, higher prevalence and more severe

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Conflicts of interest

None.

pathophysiology than non-Hispanic White Americans. Despite extensive research and development of innovative treatment strategies in the last several decades, HTN-related mortality is increasing. Therefore, there is a crucial need to discover novel and innovative mechanism-based therapies for controlling HTN. This need has added urgency during the current novel coronavirus pandemic because HTN is one of the most common comorbidities with unfavorable outcomes accounting for ~30% of all hospitalized COVID-19 patients [2].

Overwhelming evidence of the last decade has implicated dysregulated commensal microbiota in a variety of chronic diseases including diabetes, obesity, chronic kidney disease, heart failure, cardiovascular diseases, etc. Interestingly, all these diseases impact BP regulation and are risk factors for HTN. Therefore, it is reasonable to infer that GM and functions could have a major impact on BP control and cardiovascular homeostasis. Evidence supporting this view was first provided by our group in 2015 [3■]. The study demonstrated gut microbial dysbiosis in both spontaneously hypertensive rats (SHR) and patients with high BP. Selective decreases in butyrate-producing bacterial communities were observed. This basic finding has been validated by other investigators using both multiple animal models of HTN and patients with HTN [4]. Together, these studies led us to propose the hypothesis of impaired gut-brain-BM communication in HTN.

Hypothesis

We propose that hypertensive stimuli, like stress, salt, diet, impact the brain and the gut. In the brain, particularly autonomic brain regions such as the paraventricular nucleus of the hypothalamus (PVN), microglia become activated, altering their interactions with neurons and neuroinflammation results (Fig. 1). Neuroinflammation increases sympathetic and decreases parasympathetic activity to organs such as the gastrointestinal (GI) tract and BM, and raises BP.

In the gut, hypertensive stimuli cause gut microbial dysbiosis, gut barrier weakening and inflammation. Gut dysbiosis results in an imbalanced GI milieu, causing inflammation. Weakened barrier function allows previously excluded gut contents, such as bacteria and bacterial metabolites, to contact the immune system generating inflammation. This exacerbates leakiness and inflammation and recruits pro-inflammatory BM cell progenitors to the gut, that further increase gut inflammation. The factors crossing the weakened gut barrier, and inflammatory mediators generated in the gut, reach the brain via the circulation and contribute to neuroinflammation and mild systemic inflammation (Fig. 1).

Increased sympathetic drive to BM stimulates release of pro-inflammatory progenitors that enter brain and gut to promote inflammation. Decreased release of progenitors capable of vascular repair also results from increased sympathetic stimulation. The interactions of these three organs reinforce their individual responses resulting in a vicious cycle that sustains and increases HTN (Fig. 1).

1. Microglia and Neuroinflammation

Microglia are resident immune cells of the brain arising from the yolk sac [5–7]. They are self-renewing, long-lived cells with a low replication rate [8]. Microglia are extremely

dynamic cells. In the adult brain, one of their roles is to surveil the brain parenchyma. During brain development they remove unneeded synapses, promote formation of new synapses and myelination [9–11]. In adulthood, contact between a synapse and microglia process increases activity of the synapse and reinforces the circuit, but this is disrupted during inflammation [12]. Microglia are important in the neuronal stem cell niche [13,14] and blood brain barrier (BBB) [15]. Finally, their development is compromised in germ-free mice [16], being spaced further apart, bearing shortened and less branched projections and surveilling smaller areas, suggesting exposure to microbes or microbial products is important for their proper function. The microglial effects of GM are sex-specific during development and adulthood [17].

Neuroinflammation is observed in animal models of HTN in areas controlling the autonomic nervous system. We hypothesize that hypertensive stimuli impact the brain to cause neuroinflammation, either directly or secondarily following transmission from peripheral tissues e.g. Gl tract (Fig. 1). Neuroinflammation is particularly evident in the PVN [18], but also occurs in brainstem nuclei such as nucleus tractus solitarius and rostroventrolateral medulla during HTN, that is associated with increased sympathetic drive controlled through these brain regions [19].

When rodents are hypertensive, the PVN contains numerous activated microglia producing pro-inflammatory cytokines [18], that with the astrogliosis of established HTN produces a pro-inflammatory milieu [20,21]. BM-derived monocytes are recruited by Ccl2 released from microglia [22], differentiating into cells anatomically indistinguishable from activated microglia [23■■], and contribute to the pro-inflammatory environment [23■■]. Reactive oxygen species (ROS) are generated by pro-inflammatory cytokines binding to their receptors on immune cells, by angiotensin signaling in neurons [24] and the cerebrovasculature via activation of the NADPH-oxidase pathway. ROS increases neuronal firing rate in the PVN [24,25] further increasing ROS. If sustained, this overcomes antioxidant capacity. All these factors can stimulate neuronal firing rates in the PVN, neuroinflammation and increase sympathetic outflow.

PVN neuroinflammation promotes closer interaction of microglia with neurons. The phenotypes of PVN neurons impacted by microglial activation is unclear at present, but worthwhile candidates, but not the only ones, for investigation include pre-autonomic, vasopressinergic, oxytocinergic and corticosterone releasing hormone containing neurons, which all modulate BP [26–28]. These are influenced by activity of interneurons whose responses to pro-inflammatory mediators, and ultimate effect on BP, are becoming better understood [19].

Neuroinflammation changes interactions between microglia and cerebral blood vessels to affect BBB integrity. Astrocytic end feet wrap around capillary endothelial cells sealing them. Upon inflammation resident microglia support the BBB by secreting the tight junction protein, claudin 5, but with prolonged inflammation microglia phagocytose astrocyte end feet, increasing permeability [29]. This allows blood borne substances into the brain; some, like lipopolysaccharides (LPS), stimulate further microglial activation. BBB permeability is affected by the gut microbiome. Germ-free mice have a leaky BBB due to poor production

of tight junction proteins, a defect corrected by populating their gut with pathogen-free microbiota [30]. This defect does not result in hypertension because there are no circulating gut microbial products such as LPS to stimulate neuroinflammation and the immune system is less inflammatory in germ-free mice. But in conventionally-raised mice this may be a mechanism connecting GM and HTN, see section 3. Cerebral autoregulation and vascular regulation of brain blood flow are mediated by sympathetic and parasympathetic inputs known to be dysfunctional in essential HTN [31]. This is likely another mechanism by which neuroinflammation, via increased sympathetic outflow, contributes to HTN.

The respective contributions of resident microglia and recruited BM-derived “microglia” to neuroinflammation need clarification. It is likely that initial responses to hypertensive stimuli are mediated by resident microglia, but their fate following BM-derived precursor recruitment is unclear. Another unanswered question is whether BM-derived “microglia” attempt the role of homeostatic microglia but are corrupted by the pro-inflammatory environment or immediately secrete pro-inflammatory cytokines and contribute to neuroinflammation.

In two animal models of HTN, sympathetic drive is increased to the gut and BM before BP increases [32■■–34]. This is discussed in the next sections.

2. Bone marrow.

BM is richly innervated by the sympathetic nervous system [35], but receives no direct parasympathetic input. Sympathetic activity contributes to proliferation, differentiation, maturation, exit and intake of BM cells to the compartment. Norepinephrine (NE) is found in sympathetic fibers [36] that run along the vasculature [37], site of the stem cell niche, and BM cells [38]. The immune BM compartment expresses α- and β-adrenergic receptors. α1-adrenergic receptors affect circadian rhythms of cell proliferation rate [39]; daily rhythm of BM cell release is mediated by β2- or β3-adrenergic receptors via endothelial nitric oxide synthase [40,41]. Sympathetic neurons in BM promote neutrophil egress into circulation by stimulating endothelial cells to produce C-X-C motif chemokine ligand 1 (Cxcl1), inflammation, e.g. by LPS enhance Cxcl1 production and egress; denervation or beta receptor blockade inhibits both processes [42]. Neutrophils interact with microglia to promote neuroinflammation in various brain disorders [43,44] but their role in HTN is unclear.

In animal models of HTN, we observed decreased circulating immune cells capable of vascular repair, but increased BM derived pro-inflammatory cells in the gut and autonomic regions of brain [23■■,33,45]. Likewise, in hypertensive patients, there are increased gut–homing pro-inflammatory immune cells compared to normotensive subjects [46■]. Finally, in mice, HTN stimuli-responsive enhanced memory T-cells are found in BM and are enhanced by sympathetic activity [47].

3.1 Gastrointestinal Tract—

Our studies have demonstrated gut pathology and dysbiosis in animal models of HTN. This includes decreased blood flow, increased norepinephrine synthesizing enzyme in small intestine[32■■, 48] thickening and fibrosis of

gut muscle layers[32■■], increased gut stiffness [49], shorter villi in small intestine and fewer mucus-producing goblet cells [32■■], increased gut barrier leakiness[32■■,46■] (corrected by butyrate treatment), lower expression of intestinal alkaline phosphatase [50] (an enzyme that by dephosphorylating a variety of substrates including LPS and extracellular ATP, renders them less inflammatory [51]), altered gut immune system [50–52], increased GALT (gastrointestinal associated-lymphoid tissue) activation [50] and increased BM-derived pro-inflammatory cells in the gut [23■■] and most significantly gut microbial dysbiosis[3■,46■]. These are all affected by increased sympathetic drive, and serve to reinforce the interlinked gut pathologies and increase neuroinflammation in a self-perpetuating fashion. Gut dysbiosis and its association with HTN is discussed in more detail below.

Epidemiological studies have consistently implicated the gut in BP regulation. This includes studies documenting the influence of diet, dietary supplements, probiotics and antibiotics on BP. Our studies were among the first to provide experimental evidence supporting this link in animal models of HTN [3■]. They demonstrated dysbiosis, altered alpha diversity and decreased butyrate-producing bacteria in the SHR, an animal model of human HTN. A plethora of publications followed, essentially confirming gut dysbiosis in animal models of HTN including DOCA-salt, Dahl-salt, stroke-prone SHR, chronic angiotensin II-infusion (rats and mice), obstructive sleep apnea (OSA) on high fat diet, and the L-NAME model although differing characteristics of gut dysbiosis were reported among the models [53]. The importance of GM in HTN is supported by studies of Karbach et. al. who demonstrated attenuated vascular dysfunction due to reduced inflammatory immune cell recruitment to the vessels and lower BP in the hypertensive response to chronic angiotensin II-infusion in germ-free mice [54]. Unequivocally, these studies associate gut dysbiosis and HTN. However, they do not address whether it causes an increased BP and establishes HTN.

Fecal microbiota transplantation (FMT) strategies have addressed cause or effect. Durgan's group was the first to demonstrate that FMT from OSA-HTN rats into normotensive rats resulted in significantly increased BP and altered microbiota [55]. Similarly, our studies showed that FMT from WKY attenuated high BP in SHR and abolished HTN-related vascular dysfunction [56,57]. Additionally, attenuations of enhanced sympathetic activity and neuroinflammation were observed in SHR recipients of WKY FMT. Conversely, FMT from SHR into WKY impaired vascular function and increased neuroinflammation and BP [56,57]. Recently, Joe et. al. demonstrated that germ-free rats had lower BP and reduced vascular contractility; both were reversed by FMT from conventionally-reared rats [58■]. Cumulatively, these observations provide strong support for the presence and contribution of gut dysbiosis to HTN in animal models.

Is there evidence to support this concept in human HTN? Our study with a small cohort of subjects was the first to demonstrate gut dysbiosis in subjects with high BP [46■]. Multiple later studies essentially supported this and described essentially similar bacterial phylogeny and characteristics [53,59–61]. Shotgun metagenomics analyses demonstrated depletion of butyrate-producing bacteria in patients with high BP and circulating butyrate was decreased in a small cohort [46■]. Increases in biomarkers of gut leakiness (fatty acid binding protein 5, zonulin and LPS) and gut targeting pro-inflammatory T_H17 cells associated gut dysbiosis

with increased permeability and inflammation [46■]. In fact, zonulin tightly correlated with systolic BP (SBP). In addition, a stepwise linear regression model of butyrate-producing bacteria and zonulin predicted SBP with ~55% accuracy and found various bacteria positively and negatively linked to SBP [46■]. Interestingly, some relevant to gut inflammation (*Eubacterium siraeum* and *Alistipes finegoldii*) and gut barrier function (*Bacteroides thetaiotaomicron*) have also been reported elsewhere [62].

Li et. al [63■]. directly addressed cause versus effect of microbiota on BP. First, by demonstrating similar characteristics of microbiota of pre-hypertensive and hypertensive subjects. Further, classifiers based on GM and metabolites discriminated hypertensive and control subjects. Finally, FMT from hypertensive subjects into germ-free mice increased their BP. These data are consistent with animal data and support the conclusion that altered GM, at least in part, is the cause of high BP.

3.2 Dietary sodium, microbiota and hypertension—Sodium consumption is an independent risk factor for HTN. Since the GI tract is among the first organs encountering sodium, it is unsurprising that sodium is increasingly found to influence GM. The first evidence from studies of the Dahl-salt rat model of HTN showed that FMT from salt-resistant rats into salt-sensitive rats exacerbated HTN [64]. Our recent study advanced the concept and demonstrated that a probiotic, *Bifidobacterium breve*, prevented the increase in BP, cardiac and renal pathology, improved colonic integrity, and restored T_H17 and T_{reg} contents in mesenteric lymph nodes and aorta of the DOCA-salt rat model of HTN [65]. Sodium depletes *Lactobacillus sp*ecies, increasing T_H17 cells, intestinal inflammation, and high BP. Mice treated with *Lactobacillus murinus* displayed decreased $T_H17$cells and attenuated high BP. Similarly, challenging a small cohort of humans with moderately high salt reduced GI *Lactobacillus species*, and increased both T_H17 cells and BP [66,67]. These studies suggest the influence of salt on GM-induced inflammation could be the mechanism for salt's hypertensive potential. Additionally, a recent study implicates intestinally-derived corticosterone in HTN by showing that a diet supplemented with 8% sodium significantly shifted the GM and increased BP [68]. This appeared causative since FMT from high salt diet donor rats increased BP in normal rats. The altered microbiota produced more corticosterone and contained decreased inhibitory enzymes of the aldosterone pathway. This suggests that high salt-induced HTN may be initiated by GM and involves immunomodulation and metabolites derived from bacteria.

3.3 Maternal microbiota and BP control in offspring—Poor maternal diet and disease have been implicated in detrimental fetal programming that permanently alters the physiology of offspring and induces diseases in later life, including HTN. Evidence suggests that GM play an important role in maternal-fetal cross-talk. For example, influencing the GM by maternal administration of probiotics was protective against HTN-associated developmental programming [69]. Similarly, diet-induced maternal influences affect interplay between microbiota and hypertensive programming [70–73]. Our studies investigated a direct involvement of maternal microbiota in HTN by using an antihypertensive drug, captopril, in the SHR model. Captopril treatment altered maternal GM, attenuated gut pathology and neuroinflammation [74]. Their male offspring

demonstrated persistently decreased SBP and neuroinflammation and improvements in gut inflammation and pathology [75■]. These observations demonstrate that lowering maternal high BP rebalances the GM, improves the dysregulated gut-brain axis, and transmits this to their offspring. Thus, targeting the maternal gut-brain axis may be a viable strategy for control of HTN in subsequent generations. One caveat is the use of captopril, that as an ACE (angiotensin converting enzyme) inhibitor, is contraindicated in pregnancy. Therefore, this concept requires validation with other classes of anti-hypertensive drugs and strategies like probiotics and high-fiber diet. The translational and therapeutic implications are profound for breaking transgenerational transmission of HTN.

Conclusion

Experimental and clinical studies strongly implicate altered GM, gut leakiness and gut pathology with HTN. Furthermore, evidence for a dysfunctional gut-brain-BM axis is mounting. Interventional strategies correcting GM have generally lowered high BP and rebalanced the gut-brain axis. However, many questions remain to be answered before establishing full clinical and translational impacts of the GM in HTN. The following deserve consideration for moving this concept towards possible therapeutics.

- Mechanisms of cross-talk between gut epithelium and microbiota must be investigated; organoid cultures from animal models [76] and human subjects would be invaluable here.
- Comprehensive cohort studies with different ethnic groups and both sexes are needed to address environmental influences such as diet, salt sensitivity, genetic background, etc.
- Impacts of antihypertensive drugs, particularly, ACE inhibitors, angiotensin receptor blockers and calcium channel antagonists on GM need to be correlated to their effectiveness in controlling BP, focusing on ethnic and gender disparities.
- Are there unique ethnic/gender gut microbiomes and gut bacterial metabolite signatures in HTN?
- HTN is a risk factor for COVID-19 infection. HTN and COVID-19 both reflect altered GM and inflammation. It would be interesting to investigate whether unique host-GM communication in hypertensive patients renders them more susceptible to COVID-19.

Financial support and sponsorship

This work was supported by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) grants HL033610, HL110170, and HL132448.

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■ of special interest

■■ of outstanding interest

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Key points

- Neuroinflammation is particularly evident during HTN and contributes to HTN via increased sympathetic outflow.
- BM pro-inflammatory progenitors extravasate to the brain, and contribute to neuroinflammation.
- Human studies and animal models strongly support the presence and contribution of gut dysbiosis to HTN.
- Hypertensive stimuli (diet, angiotensin II, salt, stress, and maternal factors) dysregulate the gut-brain-BM axis, leading to high BP.

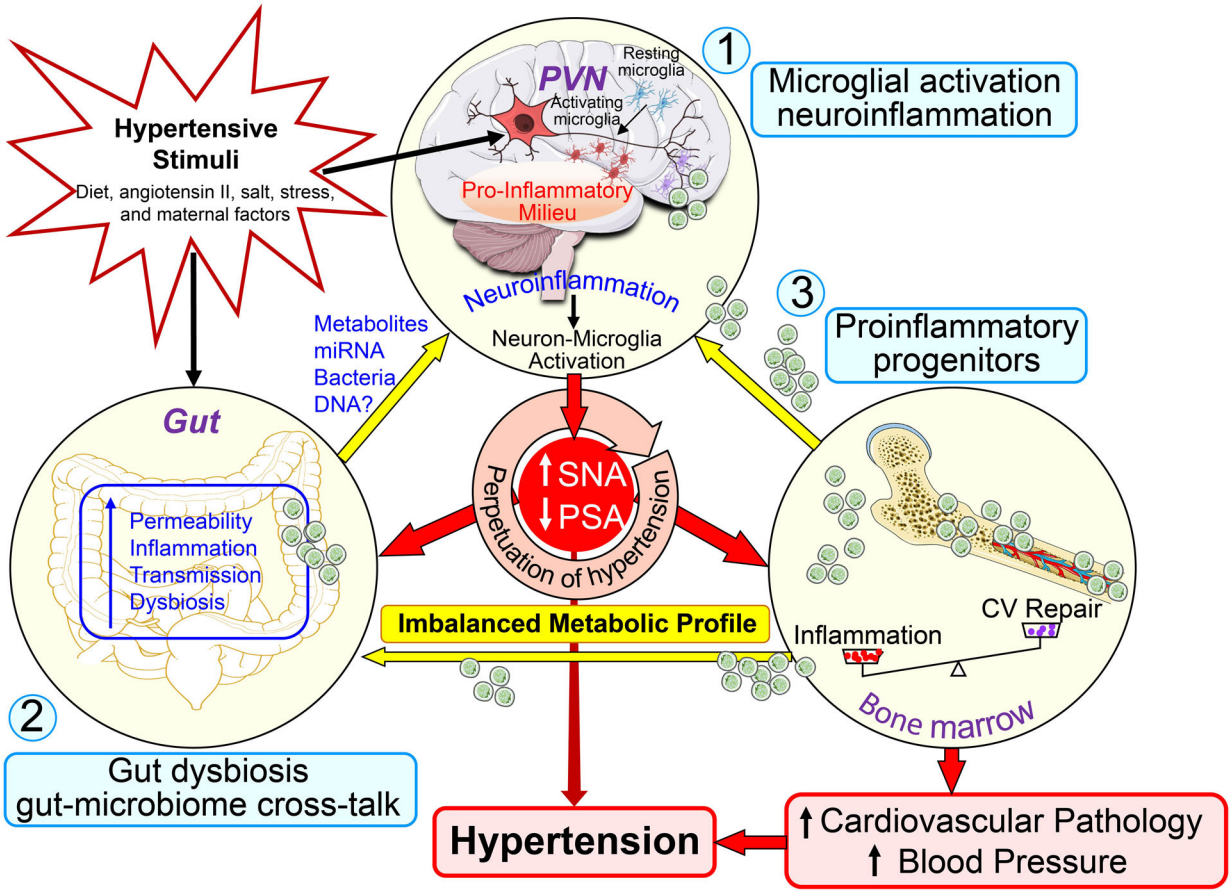

FIGURE 1.

Brain–gut-bone marrow axis. Increases in hypertensive stimuli, such as diet, angiotensin II, salt, stress, and maternal factors, enhance neuronal activity and trigger neuroinflammatory pathways in cardioregulatory brain centers to result in sympathoexcitation. Sympathetic activity to the BM induces mobilization of hematopoietic stem cells, and stimulates their differentiation into inflammatory cells. These cells may then migrate to the brain to become microglia/macrophages and propagate neuroinflammation, as well as to the gut to contribute to intestinal inflammation. Sympathetic activity to the gut may modulate motility and local immune responses. Finally, low-grade inflammation of the gut coupled with alterations in GM may result in bacterial metabolites entering circulation, where they could negatively affect both neuronal activity and immune cells like microglia. This triangular interaction may play an important role in perpetuating the progression of HTN and may be critical in the establishment of HTN. CV, cardiovascular repair; PSA, parasympathetic nerve activity; PVN, paraventricular nucleus; and SNA, sympathetic nerve activity.