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Impaired Autonomic Nervous System-Microbiome Circuit in Hypertension: A Premise for Hypertension Therapy

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Abstract

Hypertension affects an estimated 103 million Americans yet gaps in knowledge continue to limit its successful management. Rapidly emerging evidence is linking gut dysbiosis to many disorders and diseases including hypertension. The evolution of the –omics techniques has allowed determination of the abundance and potential function of gut bacterial species by next generation bacterial sequencing, while metabolomics techniques report shifts in bacterial metabolites in the systemic circulation of hypertensive patients and rodent models of hypertension. The gut microbiome and host have evolved to exist in balance and cooperation, and there is extensive crosstalk between the two to maintain this balance, including during regulation of blood pressure. However, an understanding of the mechanisms of dysfunctional host-microbiome interactions in hypertension is still lacking. Here, we synthesize some of our recent data with published reports and present concepts and a rationale for our emerging hypothesis of a dysfunctional gut-brain axis in hypertension. Hopefully, this new information will improve the understanding of hypertension and help to address some of these knowledge gaps.

Keywords

Hypertension; Microbiome; Metabolomics; Autonomic Nervous System

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Introduction

The 2017 Hypertension Guidelines reported that almost half of the US adult population currently has high blood pressure or hypertension, substantially higher than stated in the previous Guideline. Additionally, approximately 15% of adult Americans are diagnosed with treatment resistant hypertension since they do not achieve controlled blood pressure despite lifestyle modifications and 3–4 antihypertensive medications[1–3]. This presents a tremendous socio-economic and health care resource burden, further complicated by racial and sex-related disparities and the increasingly recognized problem of "masked hypertension"[4]. Moreover, the new Guidelines indicate a lowered threshold for pharmacologic treatment of >130/80 mmHg, for persons with or without known cardiovascular disease[1]. Despite these huge problems, the mechanisms that are responsible for this disease are not well understood. This is especially relevant for treatment resistant hypertension, where a dysfunctional autonomic nervous system, immune system, and more recently gut dysbiosis appear to greatly contribute to the hypertensive phenotype[5–7]. Indeed, imbalance and dysregulation of the autonomic nervous system precede and are coincident with the development of hypertension[8–12]. Evidence from animal models describes a change in gut microbiota secondary to the dysfunction of the autonomic nervous system[6]. Gut dysbiosis has been found in some pre-hypertensive populations[13], a condition also characterized by dysfunctional autonomic nervous system[8–11] Despite the breadth of emerging knowledge, current control and treatment of hypertension is not targeting these dysfunctional mechanisms.

The gut microbiome and host have evolved to exist in balance and cooperation, and there is extensive crosstalk between the two systems to maintain this homeostasis, including during regulation of blood pressure. Problems within one system are reflected in the other as the crosstalk is disrupted by the ensuing gut dysbiosis and raised blood pressure. The *overarching objective* of this review is to summarize and update the involvement of the gut and its microbiota in the control of blood pressure. This review will also specifically address the interaction of the gastrointestinal tract with the autonomic nervous system and the gut microbiota as it pertains to blood pressure regulation. Finally, we discuss mechanisms of host-microbiome crosstalk dysregulation within these systems in hypertension. The call for more extensive research in this area is the major focus of this review.

Gut dysbiosis in hypertension: evidence for and against

The gastrointestinal tract presents a vast interface between the external environment and symbiotic and/or pathogenic factors such as food and microbes that interact with the human host. It is the initial point of entry for many deleterious environmental risk factors for hypertension. Moreover, endogenous factors in the gastrointestinal tract, such as its epithelium, metabolism, immune-, endocrine- and nervous systems[14–17] have the potential to play a pivotal role in hypertension. Epidemiological studies have long linked the gut with regulation of blood pressure and hypertension. Early studies suggested environmental factors that affect the gut such as diet and alcohol intake are risk factors for hypertension[18,19]. More recently evidence has been presented indicating that probiotics, antibiotics and dietary supplements can rebalance gut dysbiosis and improve overall gut homeostasis[20,21], as well

as decrease high blood pressure[7, 22–28]. One such supplementation is with the short chain fatty acids, which are the end products of bacterial metabolism generally considered to be beneficial to the host. Despite a plethora of epidemiological studies, the interest in gut dysbiosis and host-microbiota interactions in hypertension only began to rise in the last decade with the evolution of next generation bacterial genome sequencing and metabolomics. There is now persuasive evidence of gut dysbiosis in several forms of hypertension, from hypertension associated with metabolic syndrome, pulmonary hypertension, hypertension in obese pregnancies as well as treatment resistant hypertension and pre-hypertension[13, 29–32].

Recent findings from a cohort study question the enthusiasm for a role of gut dysbiosis in hypertension[33]. However, as pointed out by the Marques group[34], the considerable overlap between diseases, medications, and microbes could account for the lack of strong correlation between the gut and hypertension in that study. Thus, it is important to characterize the microbiome of different phenotypes of hypertension as well as include other confounding factors in microbiome analyses. These may be broken down into three categories: (i) patient choices, which include medication compliance, exercise, alcohol consumption, diet including salt intake and lifestyle; (ii) patient characteristics, such as age, gender, and race; and (iii) patient conditions like hyperlipidemia, diabetes and circulating hormone levels. In addition, employment of metagenomic vs 16S sequencing would elucidate the function of the bacteria in the gut microbiome. Shotgun metagenomics sequencing can reveal the presence of other organisms such as archaea, viruses and fungi in the microbiome and suggest their relevance in various forms of hypertension. This information coupled with metabolomics analyses is beginning to yield a much more complete and rather complex picture of the role of gut dysbiosis in hypertension[35–37].

Most if not all studies to date, however, remain associative and explorative rather than addressing the causal mechanisms, which undoubtedly presents the biggest challenge in clinical research. An increasing body of work in animal models of hypertension offers indications of mechanism, however vague they may be. Many questions remain unanswered, including: (i) is gut dysbiosis a cause or a consequence of hypertension? (ii) what are the mechanisms that lead to development of gut dysbiosis in hypertension? (iii) what is the role of gut epithelium in altered host-microbiome communication in hypertension? The potential role of hypertensive risk factors such as salt, nutrients, hormones, and obesity, that initiate epithelial epigenetic mechanisms must be considered in this regard; (iv) what effect does gut dysbiosis have on development and/or maintenance of hypertension? Several studies report imbalances in short chain fatty acid levels in rodent models of hypertension and conversely beneficial effects of supplementation of these gut microbiota metabolites in reducing blood pressure in hypertensive animals[7, 25–28]. A clearer mechanistic link is presented in animal fecal matter transplant studies, where significant increases in blood pressure have been reported in rodents receiving fecal matter transplant from their hypertensive counterparts[38, 39]. Conversely, fecal matter transplant from normotensive donor rats to hypertensive recipients significantly decreased blood pressure[39]. The mechanisms for these changes are not yet determined.

Our group has recently linked hypothalamic neuroinflammation and increased sympathetic drive with changes in gut physiology and microbiota associated with angiotensin II-induced hypertension. This suggests a role for a dysfunctional autonomic nervous system in gut dysbiosis, although we were not able to discount a direct effect of hypertension and/or angiotensin II on the gut[40]. This, along with our evidence of decreased proteins that mediate cell-cell connections in gut epithelium of prehypertensive spontaneously hypertensive rats, as well as of gut dysbiosis in prehypertensive and hypertensive populations[13, 24, 28, 35, 38, 41–45]), led us to propose a *dysfunctional autonomic nervous system-gut hypothesis that contributes to development and maintenance of hypertension* (Figure 2). Potential mechanisms utilized by the gut-brain axis for blood pressure control and their failure in hypertension, are discussed below.

Gut as a cardio-regulatory organ: role of the sympathetic nervous system

Sympathetic innervation of the gastrointestinal tract has been extensively studied and characterized. The noradrenergic fibers within the gut wall originate in the prevertebral sympathetic ganglia (celiac-mesenteric ganglia, inferior mesenteric ganglia, and pelvic ganglia) and innervate the stomach, small intestine, large intestine, and rectum. Tyrosine hydroxylase-positive fibers innervate the myenteric and submucosal plexi and gastrointestinal blood vessels. These sympathetic fibers affect gastrointestinal functions such as peristalsis, secretion, absorption, fluid and electrolyte transport across the epithelium, as well as vessel smooth muscle contraction and hence the blood flow to the gastrointestinal tract[46, 47]. Indeed, our recent study highlighted a drastic difference in both the gastrointestinal blood flow and gut stiffness in hypertensive rats, perhaps owing to the increased gastrointestinal sympathetic nerve activity in these rats[6, 48]. Moreover, increased sympathetic nerve activity has been linked with elevated inflammation both systemically and in the gut[5, 49–51], which could contribute to the vascular gastrointestinal leakage[52]. Lastly activation of adrenergic receptors on enteroendocrine cells modifies release of gastrointestinal hormones such as serotonin[53]. Considering the close proximity of gastrointestinal vagal innervation to the same cells[49, 54], this may be the point of convergence of the two arms of the autonomic nervous system (see below paragraphs for relevance of the vagal innervation).

Early investigations highlighted the importance of the splanchnic vascular bed and sympathetic nerve activity in blood pressure regulation in humans and animals[55]. Splanchnic sympathetic nerve activity is essential in the development of high blood pressure in the deoxycorticosterone acetate-salt and angiotensin II rodent models of hypertension[56–58]; conversely, experimental splanchnic denervation lowers blood pressure in hypertensive animals[59, 60]. Splanchnic sympathetic nerve activity regulates the capacitance of the vast mesenteric blood vessel network such that any changes in mesenteric vascular capacitance result in significant modulation of blood pressure[58]. A study also demonstrated that the antihypertensive effects of bariatric surgery are related to reduced sympathetic nerve activity in both hypertensive patients and rats[50]. This is similar to the reduction of renal sympathetic nerve activity by percutaneous catheter-based renal nerve ablation, a novel surgical approach to the treatment of resistant hypertension. In another study in mice, decreases in blood pressure following vertical sleeve gastrectomy are associated with body mass-independent

decreases in hypothalamic endoplasmic reticulum stress, hypothalamic inflammation, sympathetic nerve activity, and significant shifts in the gut microbiota[61]. Thus, even though the effects of bariatric surgery may be multifactorial, part of the antihypertensive mechanism appears related to changes in gut microbiota as well as sympathetic tone in the gut.

Our group recently demonstrated links between enhanced hypothalamus-driven gut sympathetic tone, gut pathology, dysbiosis, and inflammation that play key roles in rodent models of hypertension[6, 40, 48]. The elevated splanchnic sympathetic nerve activity and mild gut pathology in juvenile pre-hypertensive rodents precede hypertension-related gut dysbiosis[6], suggesting that elevated gut sympathetic nerve activity modulates the gastrointestinal environment prior to the development of hypertension[6,8]. Elevated sympathetic tone to the gut in hypertension increases stiffness and hypertrophy of the muscle layer. The increased sympathetic tone promotes gut leakiness by direct effects on epithelial cells, affects the activity of the immune system and specific gut bacteria[6, 62–64]. This elevated sympathetic tone to the gut may contribute to gut dysbiosis. Conversely, diminished beta adrenergic signaling, indicative of reduced overall sympathetic tone, is associated with beneficial effects in the gastrointestinal tract. These effects include increased abundance of the largely beneficial bacteria, *Bacilli Lactobacillales*, increased colonic production of the short chain fatty acids, butyrate, acetate and propionate, and dampened systemic and gut immune responses[65].

More studies are required to directly confirm these ideas, but the currently available data from animal models of hypertension as well as the human prehypertensive population suggest two possible scenarios. One is that gut dysbiosis may be a consequence of the progressively hypertensive gut environment resulting from elevated sympathetic drive to the gut[6,13]. Alternatively, altered gut-microbiota crosstalk elicited by prolonged hypertensive stimuli results in elevated sympathetic drive to the gut (Figure 1)[6,13]. Support for this latter scenario is evidenced by studies demonstrating that fecal matter transplant from spontaneously hypertensive rats into normotensive Wistar Kyoto rats enhances sympathetic activity, neuroinflammation and increases blood pressure[39]. Consistent with this are studies that demonstrate that fecal matter transplant from normotensive animals to animal models of hypertension reduce blood pressure[38,39]. To resolve this a study needs to be performed determining whether gut dysbiosis precedes increased sympathetic nervous system activity to the gut or vice versa. Thus, it appears that our understanding of the complex and interconnected nature of microbial-host interactions is still incomplete and more effort is needed to fully understand the mechanisms and role of gut dysbiosis in hypertension.

Role of the vagus nerve: is the vagal afferent feedback from the gut to the brain cardio-regulatory regions perturbed in hypertension?

Role of vagal afferent input from the gut

The vagal nerve is part of the pivotal neural circuitry connecting the heart, lungs, and structures in the neck and abdomen to the brain. In the gastrointestinal tract, a rich network of vagal connections extends from the brain and nodose ganglia to interpenetrate layers of the gastrointestinal tract. This circuitry welds the central nervous system and gastrointestinal

tract together in a bidirectional neural network in which outflow from the central nervous system has pervasive effects on gastrointestinal function, and the gastrointestinal tract influences the central nervous system via extensive vagal afferent nerves. Unmyelinated vagal afferent nerves with cell bodies in the nodose ganglion innervate the mucosa or the muscularis layer of the gastrointestinal tract. The nerves innervating the mucosa predominately express neurotensin receptor 1 and G-protein coupled receptor 35 (Gpr35). The vagal afferent nerves in the muscularis layer are a more mixed population but predominantly express glucagon-like peptide 1 receptor and neuropeptide Y receptor Y2[66]. Vagal regulation of gastrointestinal physiology involves sensory stimulation of these afferent vagal fibers that receive information about the internal milieu of the gastrointestinal tract. This information may be sensed directly by the afferent nerve fibers that have receptors for gut microbiota metabolites such as short chain fatty acids (FFAR3 or Gpr41), aromatic acidic metabolites, the tryptophan metabolite kynurenic acid (Gpr35), many lipid receptors, e.g. Lpar3, and peptide hormones released from enteroendocrine cells such as cholecystokinin and NPY. They may receive information mechanically, for example by distension (stretch) of the gastrointestinal wall, and immunologic stimulation (i.e. proinflammatory cytokines).

The afferent fibers also receive input from the gut enterochromaffin cells via serotonin type 3 receptors in “synapse like”[67] or very close connections[66]. Enterochromaffin cells have receptors for various gut microbiota metabolites, e.g. Gpr41, and Gpbar1 for secondary bile acids, etc. and for glucagon-like peptide 1. This peptide is released from a subtype of enteroendocrine cells which have many receptors that respond to substances in food, for example, proteins and lipids, reviewed in[68], and acts in a paracrine fashion on enterochromaffin cells. Upon adequate stimulation of these receptors, enterochromaffin cells release serotonin in a calcium dependent fashion. The released serotonin increases activity in the vagal afferents. There is also a newly described enteroendocrine cell function in the small intestine and colon. The new function lead to the suggestion of neuropod as an alternative name for the cell. Neuropods form glutamate synapses with vagal afferents[54]. These cells responded to glucose to increase vagal afferent firing rates. It will be interesting to discover if there are other neuropod responses to substances such as alcohol and salt, ingestion of which are known risk factors for hypertension, to alter gut afferent input to the brain and autonomic system regulation.

This sensory information is transmitted to the nucleus of the solitary tract to initiate an appropriate efferent response through autonomic nerves from the dorsal motor nucleus of the vagus. These efferent pathways innervate the enteric nervous system, the gut immune system, the enteroendocrine cells and the gut epithelium, regulating secretion of neuroendocrine hormones, variations in gastrointestinal motility, barrier function, and the intestinal immune response. Thus, perturbations within any or all of these variables may lead to dysfunction of the gut-brain axis, as documented in several disease states. Most notably, work by Cryan et al highlights the role of the gut vagal projections in mental and neurological disorders such as anxiety, depression, and some neurodevelopmental and neurodegenerative disorders[69–71]. Interestingly, both anxiety and depression are comorbid with cardiovascular disease[72–75] suggesting that some of the etiology may overlap. Moreover, electrical stimulation of the vagus nerve has been proposed recently as a

treatment for inflammatory disorders of the gastrointestinal tract such as inflammatory bowel disease (IBD, e.g. Crohn's disease, ulcerative colitis, etc.)[76,77], while potentially producing changes in the gut microbiota via decreases in intestinal permeability[78–80]. Again, considering the presence of inflammation and increased intestinal permeability in rodent models of hypertension as well as in human hypertension[6, 7, 28, 40, 48, 81], the presence of reduced vagal influence on the gut in hypertension is highly probable.

The role of aberrant vagal afferent inputs from the gut to the brain in hypertension becomes increasingly plausible when considering the overlap in the regions of the nucleus of the solitary tract receiving input from cardiac and gut sensory afferents[82]. Eighty to ninety percent of the vagus nerve consists of afferent sensory fibers[83, 84], and those distributed in the gastrointestinal tract are responsible for sensing changes in mechanical, chemical, endocrine and immune factors. These gut afferents report to a region of the nucleus of the solitary tract that overlaps with the area receiving cardiorespiratory afferent inputs from both baro- and chemoreceptors. Moreover, there appears to be very little viscerotopography of putative second order neurons controlling the cardiorespiratory and gastrointestinal tract[85,86]. Thus, one sub-region of the nucleus of the solitary tract can control multiple functions, and effects of activation of cardiorespiratory reflexes may be indistinguishable from effects of activation of gastrointestinal reflexes - in terms of reflex specificity[82]. Both baroreceptor- and chemoreceptor-mediated afferent feedback to the nucleus of the solitary tract as well as the processing of the cardiorespiratory reflexes by second order neurons in the nucleus, are altered in and contribute to hypertension[86–90]. There is indirect evidence suggesting alterations in afferent vagal feedback from the gut in hypertension. There is decreased vagal afferent excitability in diet-induced experimental obesity[91], a condition often accompanied by hypertension. Considering that gut vagal afferents sense at a minimum, proinflammatory signals, bacterial metabolites, and endocrine factors[78] all of which are dysregulated in the hypertensive gut[6, 7, 28, 37, 40, 48, 51, 92], it is reasonable to propose that aberrant vagal afferent function also exists in hypertension. Activation of the gastrointestinal vagal afferents results in immediate bradycardia and reduction in blood pressure[93]. This confirms that gastrointestinal vagal afferents contribute to regulation of blood pressure. The reflex can become dysregulated to cause both blood pressure and heart rate to decline in vasovagal syncope (the most common cause of fainting). Thus, in hypertension, *dampening of the vago-vagal reflexes originating in the gastrointestinal tract, similar to those regulating cardiac and respiratory function, may contribute, in part, to the hypertensive phenotype*. Further studies are warranted to address this knowledge gap.

The potential role of vagal efferents on the gut in hypertension

Reduced cardiac vagal tone, in addition to increased sympathetic tone, is associated with development and maintenance of high blood pressure in both animal and human hypertension[94–100]. Impaired vagal influence on the heart has been detected from early hypertensive phases throughout established hypertension In humans[101–107]. A reduction in cardiac vagal tone has also been observed in comorbid conditions of cardiovascular disease such as obstructive sleep apnea and diabetes, as well as heart failure[108–112]. To our knowledge, disturbances in vagal efferent modulation of the gastrointestinal tract are yet to be reported in hypertension. Considering the presence of gut pathology and inflammation in

rodent and human hypertension[6, 28, 48], and the reported decrease in vagal tone to the gut in diabetes[113] and inflammatory gastrointestinal disorders such as IBD[114, 115], it is interesting to hypothesize that similar to the heart, decreased vagal efferent tone to the gut is also present in hypertension.

Functional aspects of the gut microbiome in hypertension

Several studies have investigated the functional potential of the gut microbiome in human hypertension[13,28,37,116–122]. This was made possible by newer -omics techniques and made necessary by increased understanding of the importance of functional characterization of microbiota beyond mere sequencing of bacterial content. Not only may metabolic products of the gut bacteria have direct cardio- and neuro-regulatory properties, but gut bacteria can also affect production of hormones and neurotransmitters by the host that are essential for physiological homeostasis. We focus on three pivotal factors to illustrate their importance in hypertension below.

Short chain fatty acids in hypertension

Short chain fatty acids are the products of gut microbial fermentation of complex polysaccharides such as the fiber found in vegetables and fruits. They are almost completely absent in animals lacking gut microbiota, so the host relies on the gut microbiota to supply them[123]. Short chain fatty acids, commonly acetate, butyrate and propionate, are important energy sources for the gut epithelium, and are also absorbed across the epithelium into the circulation. One advance in understanding the host-microbiota interactions in hypertension is confirmation of the presence of specific short chain fatty acid-sensing receptors in the kidney and vasculature[27, 124]. These receptors are traditionally known as odorant receptors since they are expressed on the cell membranes of olfactory receptor neurons to give rise to the sense of smell. The short chain fatty acids act as ligands for Gpr41 and OlfR78, as well as for other receptors, of the host. Stimulation of these two receptors modulates renin secretion and vascular tone, and so these products of gut bacterial metabolism have the ability to regulate blood pressure[27,124]. For example, propionate caused the release of renin from the kidney via Olfr78, while Olfr78 knockout mice had reduced basal blood pressure[124] On the other hand, the vasodilatory response to propionate is mediated via Gpr41[125]. Indeed, the abundance of specific short chain fatty acid-producing gut bacteria as well as circulating short chain fatty acids such as butyrate are reduced in hypertensive rodents and patients[28,30,126–131]. Conversely, supplementation with the short chain fatty acids butyrate and acetate, can alleviate hypertension[25–28, 124], presumably not only via actions on their receptors in the vascular system and kidney[126].

We have recently demonstrated reduced circulating short chain fatty acids in the spontaneously hypertensive rat and human hypertension[28, 128]. Lack of short chain fatty acids in hypertension can potentially affect the nervous system. Indeed, acetate has effects via the central nervous system[126, 127] and alleviates hypertension[26]. Central effects of short chain fatty acids are further supported by our recent data demonstrating reduced short chain fatty acid receptors in the paraventricular nucleus of the hypothalamus, the hub of sympathetic regulation in the forebrain. Intracerebroventricular administration of butyrate

leads to a decrease in blood pressure in normotensive Wistar Kyoto rats. This effect is dampened in the spontaneously hypertensive rat, and is associated with reduced butyrate-sensing receptors. As a consequence there are dampened effects on neural activation in the paraventricular nucleus of the hypothalamus and other cardioregulatory brain regions[128]. Fecal matter transplantation from normotensive animals to hypertensive animals lowers blood pressure. The fecal matter of normotensive animals is rich in short chain fatty acid-producing bacteria and this process also increases expression of the short chain fatty acid receptors, Gpr41 and Gpr43 in the paraventricular nucleus. Activation of these receptors is associated with lowering of blood pressure[39]. Moreover, short chain fatty acids can directly regulate the sympathetic nervous system via receptors expressed on sympathetic ganglia and potentially affect the neural feedback from the gut via the receptors expressed on vagal afferents[78, 132, 133]. Thus, we propose that *gut bacterial metabolites such as short chain fatty acids may be involved in neural regulation of blood pressure via their receptors expressed in cardioregulatory brain regions* (Figure 2) *and sympathetic and vagal ganglia. Therefore, reduction in both the availability of short chain fatty acids in the circulation and short chain fatty acid-sensing receptors may contribute to the pathophysiology of hypertension*.

Gut bacterial metabolites promote host health by exerting local protective functions regulating mucosal barriers[134] and immune mechanisms[135]. Short chain fatty acids such as butyrate have potent immunosuppressant activity, both systemically and centrally[127, 128, 136–139]. Centrally, they can produce anti-inflammatory and metabolic effects in microglia and astrocytes[137128], activation of which has been associated with central neuro-modulating/neuroinflammatory effects in hypertension[140, 141]. This view is supported by our finding that butyrate normalizes expression of angiotensin II type1a receptors in astrocytes of the spontaneously hypertensive rat *in vitro*[142]. This is consistent with the role of butyrate in epigenetic modification[127, 128, 136–139, 143], since heightened angiotensin type 1a receptor expression in the spontaneously hypertensive rat is linked to hypomethylation of the promotor region of the gene[144]. Most of the short chain fatty acids are absorbed and utilized by the gut epithelial cells as a crucial source of energy or are transported into the systemic circulation largely via specialized trans-epithelial short chain fatty acid transporters in the colon[128, 145, 146]. Our data indicate that low butyrate in the systemic circulation of hypertensive rodents may be partly due to reduced trans-epithelial transport of this short chain fatty acid across the colon. This would cause accumulation of butyrate in the colon[128] despite presumably lower production due to decreased abundance of butyrate-producing bacteria in the spontaneously hypertensive rat gut microbiota[7]. Thus, butyrate accumulates in the colon to be excreted in the feces, depriving the host of its anti-hypertensive effects. Moreover, accumulation of butyrate in the gut could also directly or indirectly have deleterious effects on the local gut bacterial, epithelial, immune and neural environment, including via epigenetic influences in the spontaneously hypertensive rat gut[128]. Considering the low circulating butyrate in the systemic circulation of hypertensive patients[28], further studies are needed to ascertain whether these mechanisms observed in rodent models of hypertension are translational. Thus, several short chain fatty acid-dependent mechanisms are currently being investigated to test whether using nutritional and bacterial supplements would alleviate gut dysbiosis and attenuate hypertension.

Increased circulating metabolites of hypertensive patients that may contribute to enhanced sympathetic drive.

We have recently undertaken a study of the metabolome of hypertensive patients compared with reference subjects. Our unpublished findings show several metabolites that support increased sympathetic drive in hypertension. There was increased 3 methoxy-4-hydroxymandelate, a byproduct of catabolism of neuronal norepinephrine, in the systemic circulation of hypertensive patients compared to normotensive reference subjects (by 1.5-fold, adjusted p value=0.007). That 3 methoxy-4-hydroxymandelate is increased in the circulation of hypertensive patients aligns with increased sympathetic drive. Also, the circulating concentration of gamma amino butyric acid (GABA), a major inhibitory neurotransmitter, was depleted in hypertensive patients compared to normotensive reference subjects (by 0.7 fold, adjusted p value=0.01). Quinolinic acid, a neurotoxic and gliotoxic metabolite of tryptophan, likely increases sympathetic drive in hypertension by increasing neuroinflammation, although this has not been experimentally proven. Quinolinic acid was increased in the circulation of African Americans with hypertension compared with non-Hispanic Caucasian Americans with hypertension.[37]. African Americans also have a higher prevalence of treatment resistant hypertension, are more salt-sensitive, and develop hypertension earlier and with more severe end organ damage than other American races and ethnic populations. Thus, insights into mechanisms of this hypertension issue in African Americans may advance our understanding and lead to improved control methods to address these high and damaging rates.

Tryptophan metabolism in hypertension

Quinolinic acid is not the only metabolite of tryptophan whose metabolism is altered during hypertension. Our unpublished data from a small cohort of hypertensive patients suggest shifts in serotonin metabolism in hypertension. Tryptophan is a dietary precursor to serotonin, which is synthesized predominantly in gut enterochromaffin cells (80–90% of total body content of serotonin) by tryptophan hydroxylase 1. Tryptophan can be metabolized towards kynurenine and indole pathways. The indole pathway is specifically a gut microbiota-dependent pathway, but the kynurenine pathway is both host and microbiota mediated, albeit via different enzymes. Since serotonin synthesis is substrate dependent, as tryptophan hydroxylase is never fully saturated, its synthesis is dependent upon the supply of tryptophan and the amount of tryptophan directed to the other pathways. Kynurenine can be metabolized to either kynurenic acid, that is considered to be beneficial, or to quinolinic acid, which is neurotoxic and gliotoxic. Interestingly, kynurenic acid is a ligand for Gpr35, a receptor that is activated by aromatic acidic metabolites. Gpr35 is found on enterochromaffin cells in the gut, the cells that produce serotonin, and their stimulation results in release of serotonin. The released serotonin binds to serotonin type-3 receptors on unmyelinated vagal afferents in the gut mucosa to alter vagal afferent input to the nucleus of the solitary tract. The cell bodies of these afferents in the nodose ganglion also express Gpr35, and their activation inhibits N-type calcium channels, reducing neurotransmitter release[147]. This would tend to decrease vagal afferent input to the brain. Clearly, it would be very useful if we understood how kynurenic acid is involved in modulating sympathetic outflow, if at all, and whether the increased kynurenine in hypertensive people affects this. In

these patients we found that circulating kynurenine is increased compared with normotensive reference subjects (by 1.2-fold, adjusted p value=0.04, unpublished).

The altered kynurenine in hypertension may also affect serotonin synthesis. Increased kynurenine has been suggested to predict a decrease in serotonin synthesis in the hypertensive gut because of a shift towards synthesis of kynurenine from tryptophan, at the expense of serotonin[148]. Serotonin synthesis may be further compromised in hypertension because tryptophanase A, the gene for the bacterial enzyme that converts tryptophan to indole, is enriched in the gut microbiome of hypertensive patients; nonetheless, tryptophanase A expression can be regulated by the amount of tryptophan present in the gut[149]. However, the major stable breakdown product of serotonin in the host, 5-hydroxyindole acetic acid, suggests an increase in the circulation of hypertensive subjects (unpublished data) and increased serotonin bioavailability in hypertension. In addition, most circulating serotonin is taken up by platelets, unless they are activated[150], such as is the case in hypertension as well as in patients with atherothrombosis[151, 152]. Moreover, short chain fatty acids such as butyrate stimulate production of serotonin in the enterochromaffin cells of the gut[153, 154]. This may be important because despite decreased abundance of butyrate producing bacteria in the gut of hypertensive rodents, there is more butyrate in the proximal colon of these rats than in their normotensive controls. This is due to decreased transport of butyrate across the gut epithelium[128]. The result is low circulating butyrate, but potentially increased serotonin production in the enterochromaffin cells of the gut due to the stimulation by butyrate trapped in the gut. Since we also observed reduced circulating butyrate and decreased butyrate producing bacteria in our hypertensive patient cohort[28], a similar mechanism could be present in human hypertension. These apparently conflicting results deserve further research efforts for resolution.

Gut serotonergic signaling in blood pressure control

The putative link between gut dysbiosis and serotonergic metabolism in hypertension is intriguing, considering the comorbidity of high blood pressure with anxiety and depression, where irregular serotonin neurotransmission is an established part of the pathophysiology[81, 155–157]. As mentioned above, most serotonin is synthesized by the specialized enterochromaffin cells in the gastrointestinal tract. While gut bacteria can also produce serotonin[158], most importantly they exert a powerful influence on the production of serotonin by the host gut[154, 159]. To probe for this possibility in hypertension-induced gut dysbiosis, we compared relative gene expression levels in gut epithelial cells isolated from spontaneously hypertensive rats and their normotensive controls, Wistar Kyoto rats, using RNAseq methods. We observed remarkable differences in the expression of genes associated with the synthesis, metabolism and reuptake of serotonin in the gut epithelium of the hypertensive rats compared to the normotensive rats (Figure 2). More studies are needed to delineate the functional changes associated with these alterations in serotonergic pathways in hypertension-induced gut dysbiosis, especially in humans.

Enterochromaffin cell-derived serotonin has both local gastrointestinal, as well as more widespread systemic effects, on endothelial cells, vascular smooth muscle cells, enteric neurons, vagal afferents, enterocytes, and immune cells[150, 160–165]. Thus, serotonin has the

ability to dramatically change the functions of neural, immune, gut and cardiovascular cells and disrupt homeostasis, including blood pressure regulation[150, 160, 161]. In the systemic circulation, serotonin regulates blood pressure via its action on blood mononuclear cells, the vasculature, heart, adrenal glands, kidney, and brain circumventricular organs[150, 160, 161]. Increased circulating serotonin is known to heighten vascular constriction in hypertension[162–165]. Systemically, it reduces sodium excretion by the kidney which can cause renal failure[166,167] while it can also promote cardiac hypertrophy in the mouse via a direct effect on cardiomyocytes[166, 168, 169]. The effects of serotonin on the heart can also be exerted via actions on both the vagus and sympathetic nerves controlling the heart[169], which are both receptor subtype- and species-dependent. This suggests that serotonin can directly modulate the autonomic nervous system. Indeed, serotonin directly affects the sympathetic ganglia[170] and inhibition of serotonin receptors decreases blood pressure in obese Zucker rats[171]. Serotonin also prevents hypertension caused by psychosocial stress in rats[172]. Thus, long-term activation of neurons in the sympathetic ganglia by serotonin may increase the sympathetic drive in hypertension. Centrally, serotonin influences on blood pressure arise from stimulation of serotonin receptors on neurons within the neural circuits that determine sympathetic and vagal outflows[173–176]. Considering that there are a multitude of central cardioregulatory brain regions as well as serotonin receptor subtypes, this indoleamine could have divergent effects determining the sympathetic and vagal outputs controlling blood pressure. These could potentially be imbalanced in during hypertension.

Serotonin afferent feedback in blood pressure control

As mentioned before, the nucleus of the solitary tract, as a major cardio-regulatory site, is the site of termination of primary sensory neurons, including those from the baroreceptors, chemoreceptors, and cardiopulmonary receptors that participate in reflex regulation of blood pressure[177, 178]. In addition, the nucleus of the solitary tract receives peripheral inputs from the vagal afferent nerve terminals in the gut with cell bodies in the nodose ganglia[86, 179]. The activity of these are modulated by serotonin via the its type 3 receptor[150, 180]. Indeed, activation of serotonin type 3 receptors on the vagal afferents in the gut is involved in several physiological and pathophysiological conditions, including distention- and chemical-evoked vagal reflexes, nausea, and vomiting, as well as visceral hypersensitivity[180]. Moreover, stimulation of serotonin type 3 receptors on the cardiac vagal afferents accounts for the bradycardia elicited by activation of the Bezold-Jarisch reflex[150], potentially by affecting the processing of the arterial chemoreceptor reflex within the nucleus of the solitary tract[181]. In this way, gut serotonin signaling could be converging with or modulating other cardio-regulatory feedback mechanisms within the NTS, which are deregulated in hypertension[89, 182–184]. Thus, *we propose that changes in the availability of serotonin in the gut and systemic circulation, as a result of gut dysbiosis, will modulate vagal sensory afferent feedback to the NTS to promote hypertension* (Figure 2). Both the sensory and synaptic terminals of primary afferents in the nucleus of the solitary tract have serotonin receptors. This suggests that blood pressure control by serotonin at this site could be influenced by the levels of circulating serotonin (largely from gut and platelets) and by serotonin released within the nucleus of the solitary tract from the terminals of raphe neurons. Considering the data suggesting changes in serotonergic metabolism and the presence of gut dysbiosis in hypertension that affects synthesis and transport of serotonin in

the gut, further studies are needed to elucidate the potential role of gut microbial dysbiosis on the serotonergic gut-brain axis in hypertension.

Conclusions and Future Directions

Despite the myriad of proof that associates gut dysbiosis with hypertension, evidence about the mechanistic role of gut dysbiosis in hypertension is lacking. We propose that the focus of hypertension research should be shifted to address functional aspects of host-microbiome interactions in order to better understand and address the clinical problem of hypertension. This was recently highlighted by a special NIH report calling for mechanistic research into the role of microbiota in blood pressure regulation[185]. Here, *we propose a role for gut dysbiosis-associated neuromodulating factors such as short chain fatty acids and serotonin in promoting autonomic nervous system dysfunction. Thus, this would contribute to the hypertensive phenotype, an effect that may be exerted both locally via modulation of gut vagal afferents feedback to the brain cardioregulatory regions, and centrally, via modulation of efferent sympatho-vagal balance* (Figure 2). In this review, we have presented the concepts and rationale behind our hypothesis. Our approach has been somewhat provocative in order to stimulate critical thinking and further investigation aimed at determining the mechanisms of host gut-microbiome communication in blood pressure control and hypertension.

However, many questions remain unanswered. Some are presented as follows:

- Do hypertensive signals, such as high salt intake, directly influence gut epithelial cells epigenetically to initiate host-microbiome cross-talk? There is a plethora of evidence of microbiome-mediated changes in the gut epithelium[186–188]. However, the epithelium-initiated signaling concept is rapidly evolving and appears to be extremely relevant for hypertension, and its comorbid conditions like atherosclerosis and heart failure.
- How do sympathetic and vagal pathways interact with the gut and coordinate their influences in hypertension? Elucidation of effects of gut-derived serotonin on vagal afferent function in dysbiosis would be valuable for delineating the involvement of the central nervous system.
- Is the central nervous system the site receiving hypertensive signals that initiate hypertensive mechanisms, and which neuronal and glial phenotypes are influenced?
- Topics related to gut-brain axis dysfunction in human hypertension should be addressed in parallel: Can unique metabolomic and microbiome signatures be validated? Do they respond to hypertensive stimuli and are there racial and gender differences in metabolic and microbiome signatures in hypertension? Initial studies have provided tantalizing data. Therefore, a large cohort study should be undertaken.

- Are there metabolomic and microbiome signatures associated with the pre-hypertensive state and can they potentially serve as guides for development of biomarkers for hypertension?

In conclusion, the host-microbiome field in hypertension holds much potential for the development of novel and personalized strategies for environmental, racial and sex-based management of hypertension.

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Abbreviations:

Metabolites Trp	tryptophan
5-HTP	5 hydroxytryptophan
5-HT	serotonin or 5-hydroxytryptamine
5-HIA	5-hydroxyindole acetate, 5-HIAA, 5-hydroxyindole acetate Genes: Tph1, tryptophan hydroxylase 1
Ddc	Dopa decarboxylase
Moa	Monoaminoxidase a
Aldh2	Aldehyde dehydrogenase 2
Lrp5	LDL receptor related protein 5
Slc6a4	solute carrier family 6 member 4 or serotonin transporter
Slc18a	solute carrier family 18 member A1 or vesicular monoamine transporter

Non-Standard Abbreviations and Acronyms:

Gpr35	G protein-coupled receptor 35
Gpr41	G protein-coupled receptor 41

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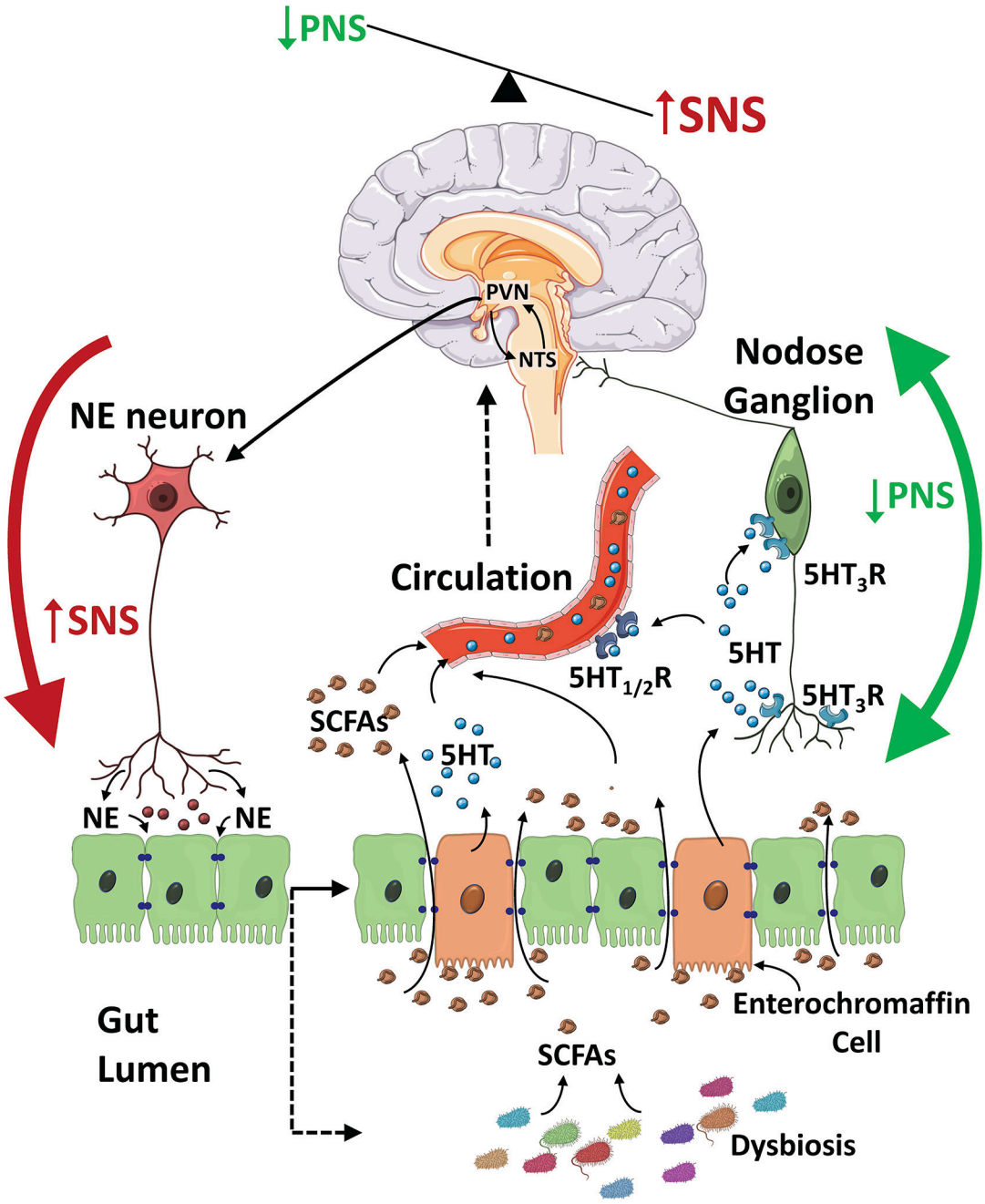

Figure 1:

A hypothetical representation of host-microbiota interactions in hypertension. Increased sympathetic nervous system activity (SNS) to the gut contributes to epithelial dysfunction leading to gut dysbiosis. The dysbiosis-related bacterial metabolite imbalance including shifts in short chain fatty acid (SCFA) production and their accumulation in the gut lumen increases production of serotonin (5HT) by the enterochromaffin cells in the gut. The local 5HT is able to modulate the activity of gut vagal afferents via $5HT_3$ receptors ($5HT_3R$) potentially dampening the vagal gut-brain neural axis, while 5HT released into circulation can affect the vasculature and cause vasoconstriction. Moreover, circulating 5HT can reach

the brain cardioregulatory regions via the circulation and across the leaky blood brain barrier that occurs in hypertension. Thus, the combination of increased SNS to the gut and dampened vagal afferent parasympathetic nervous system (PNS) drive from the gut to the brain cardioregulatory regions such as the nucleus of the solitary tract (NTS) contributes to perpetuation of the hypertensive phenotype.

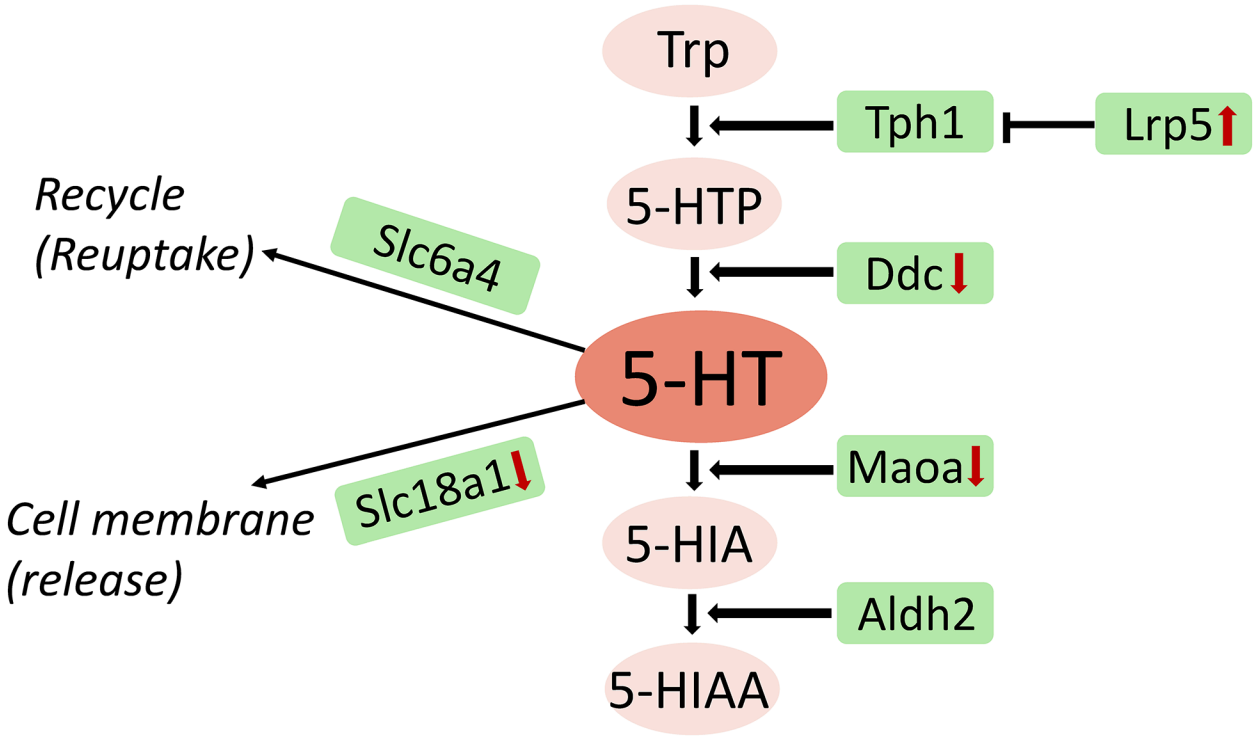

Figure 2:
Relative expression levels of genes associated with gut epithelial serotonergic synthesis, metabolism, release and uptake in spontaneously hypertensive rats (SHR) and their normotensive controls (WKY) from RNAseq analysis. Genes are shown in green boxes, tryptophan metabolites in pink circles. Red arrows indicate significant changes (upwards arrow for increase, downwards arrow for decrease) in SHR compared with WKY.