The gut microbiota and the brain—kidney axis in hypertension and CKD

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GUMS

Hypertension is an important risk factor for CKD, and approximately 85–90% of patients with stage 3–5 CKD have hypertension .

Current management of early stage CKD focuses;

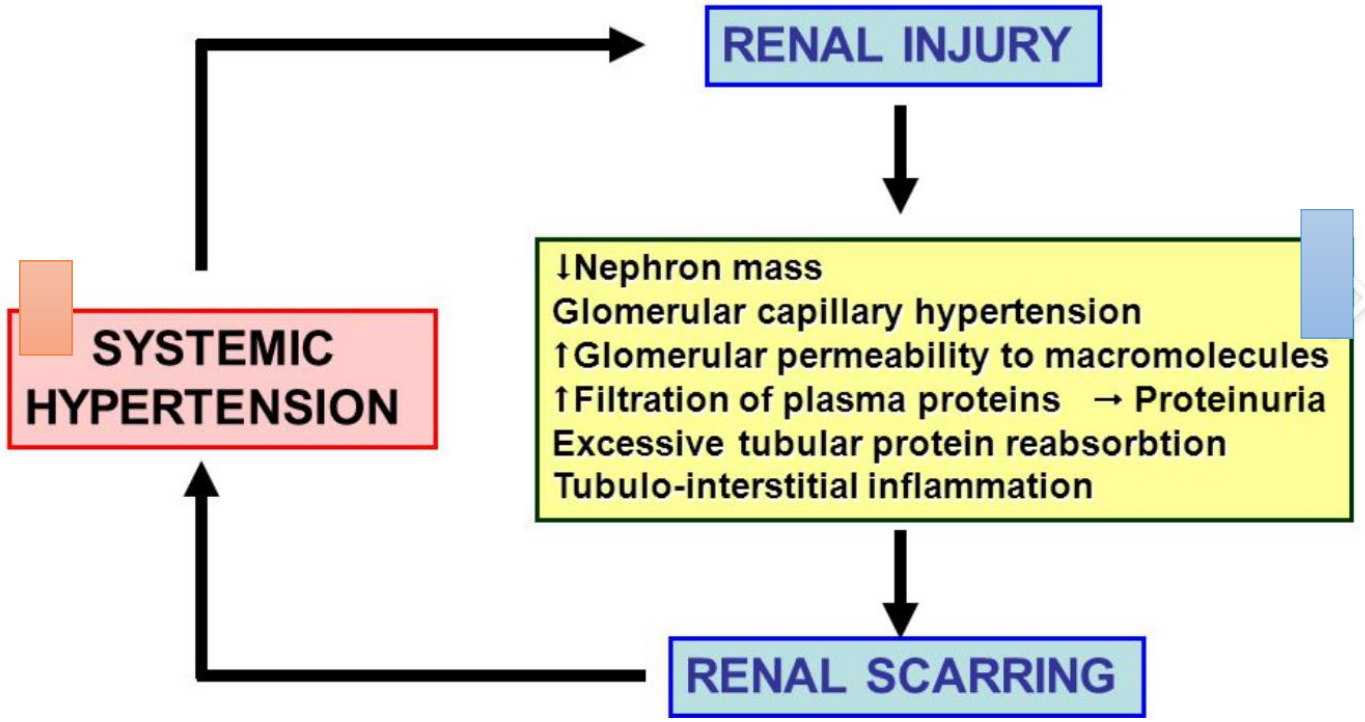
on blood pressure,

reduction of protein and salt intake,

prevention of acute kidney injury and

glycaemic control.

No cure or strategy for prevention of CKD exists,



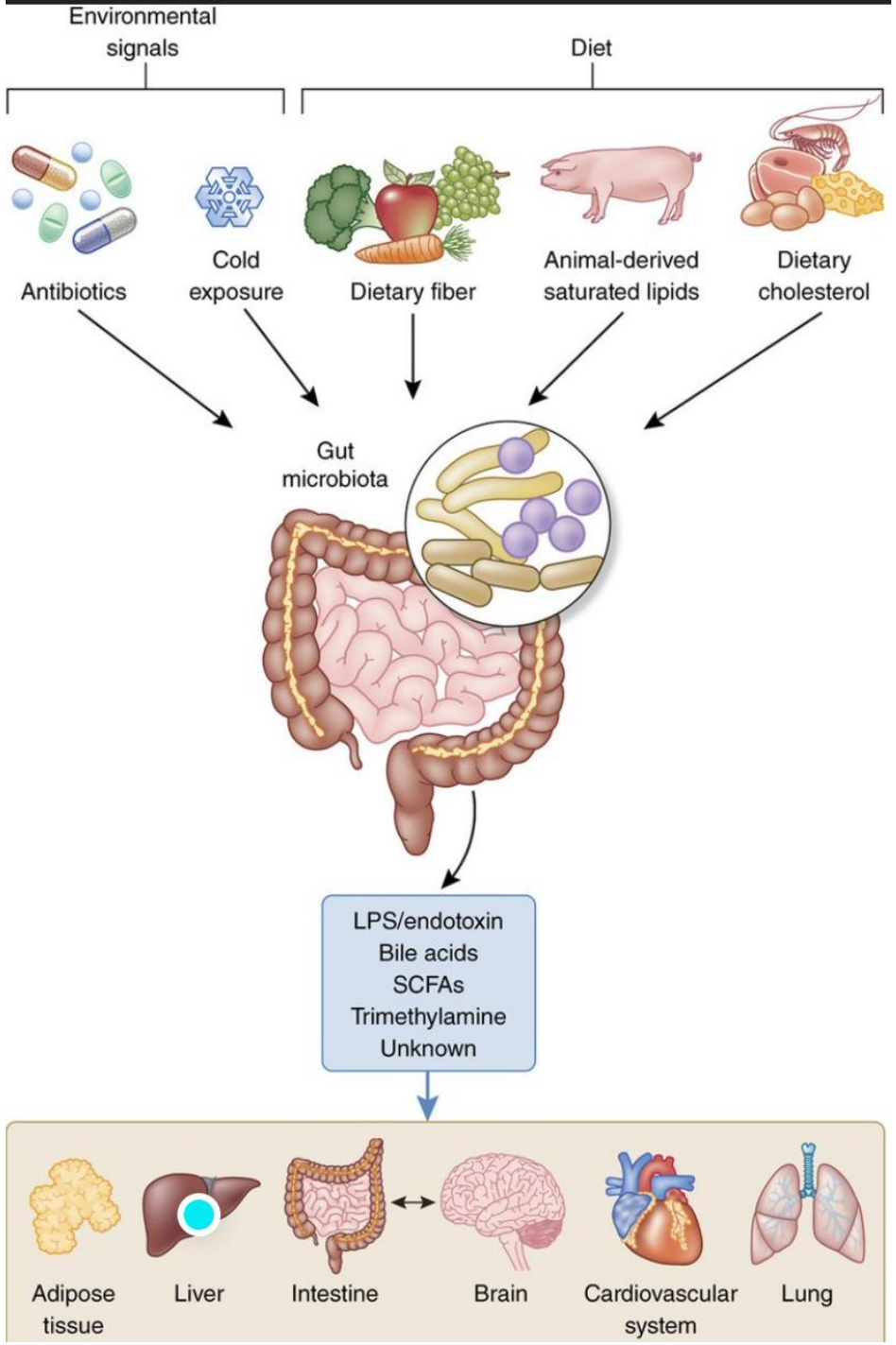
Thus, paradigm-shifting concepts and innovative approaches are needed to detect, manage, control and ultimately cure these diseases.

The gut microbiota constantly communicates with vital organ systems of the host, such as the brain , bone marrow , vasculature , kidney , immune system and autonomic nervous system (ANS).

Bone-marrow-derived immune cells are activated by the gut microbiota, leading to low-grade inflammation that affects the brain, ANS and the kidney via the circulation.

In addition, immune and gut microbiota-derived products affect renal function and have important effects on CKD.

Gut dysbiosis has an important role in many chronic diseases, and amelioration of this dysbiosis could be a potential strategy for the prevention and management of these diseases.



- The gut harbours trillions of microorganisms.

- Initial microbial colonization …. trans vertically during birth and to continuously evolve to a fairly stable, adult-like composition within the **first 3–5 years** of life.

- In adults, microbial metabolic pathways in the gut are fairly stable, although, as mentioned above, environmental factors, especially diet, profoundly modify the gut microbiota .

Gut physiology:

goblet cells are enriched in the proximal colon, **whereas Peyer's patches** are primarily found in the small intestine.

Approximately 70% of the immune cells in the body reside in the gut;

The **gut is also the second-most innervated organ in the body**

The ***complex vascular bed of the gut enables efficient absorption***

The gut is one of the first major organs to encounter environmental factors

Gut microbial metabolites, including SCFAs that are generated

the SCFA propionate stimulated release of **glucagon-like peptide 1 (GLP1) and the gut hormone peptide YY (PYY)** .

SCFAs also have multiple roles in the maintenance of intestinal homeostasis:

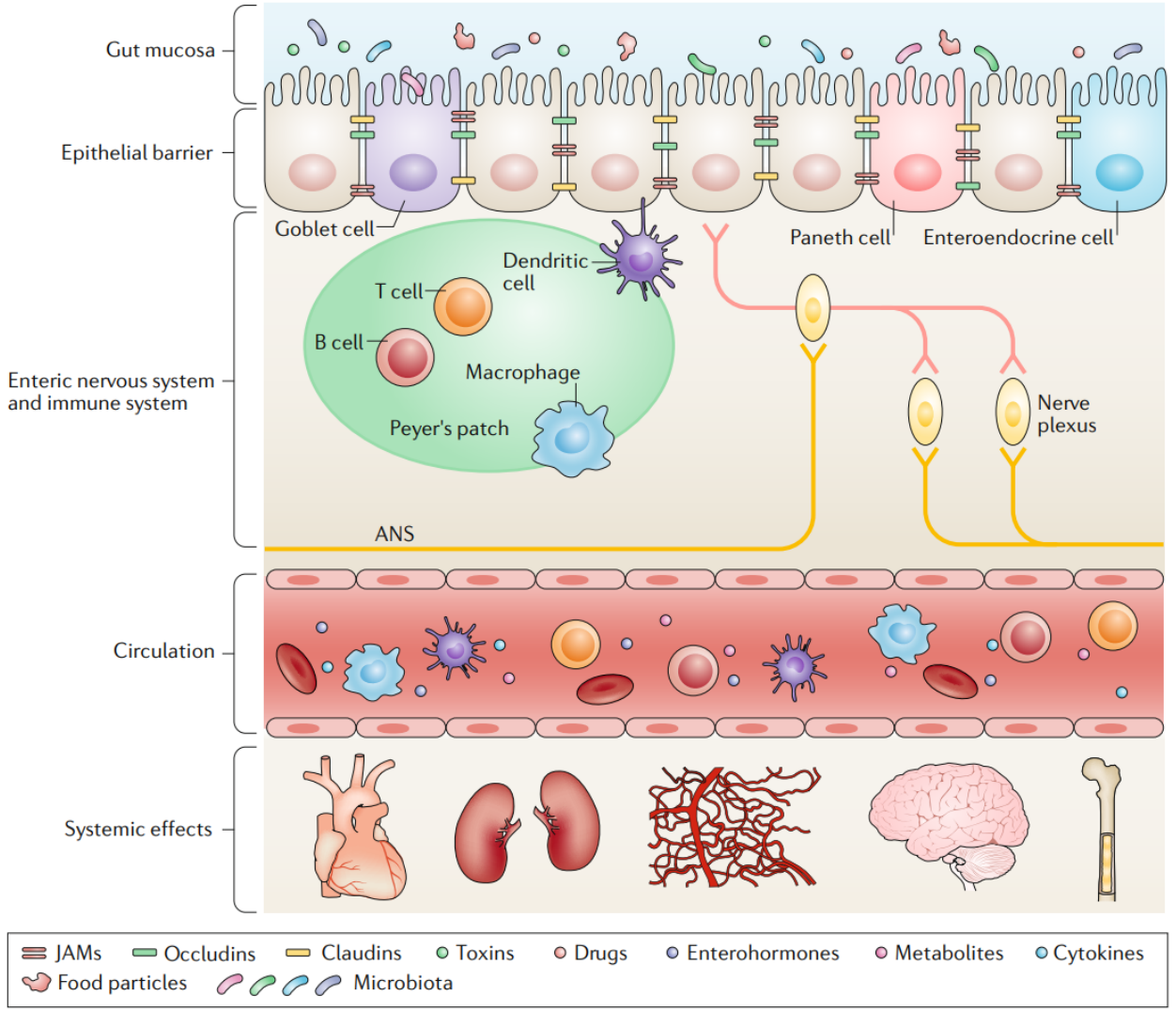


Fig. 1 | **The anatomy of the gut and its interactions with multiple systems.** The epithelial barrier, which is mainly composed of epithelial cells, goblet cells, Paneth cells and enteroendocrine cells, physically separates the gut mucosa from the submucosa. The gut mucosa is the most dynamic reservoir of the gut microbiota, which is constantly influenced and modified by factors including diet, toxins, pathogens and drugs. Tight junction proteins seal the epithelial layer and prevent translocation of pathogenic gut microorganisms across the epithelial barrier. Immune cells residing inside lymph nodes monitor the intestinal environment and maintain gut homeostasis. The enteric nervous system, which is composed of numerous nerve plexuses, perceives mechanical and chemical changes within the gut and communicates with the autonomic nervous system (ANS). Enterohormones, metabolites, immune cells and cytokines derived from this complex mucosal and submucosal network have systemic impacts on other organs such as the kidney, cardiovascular system, bone marrow and brain via the circulation. JAMs, junctional adhesion molecules.

- Role of the gut in the immune system:

The gut is the largest immune organ in the body.

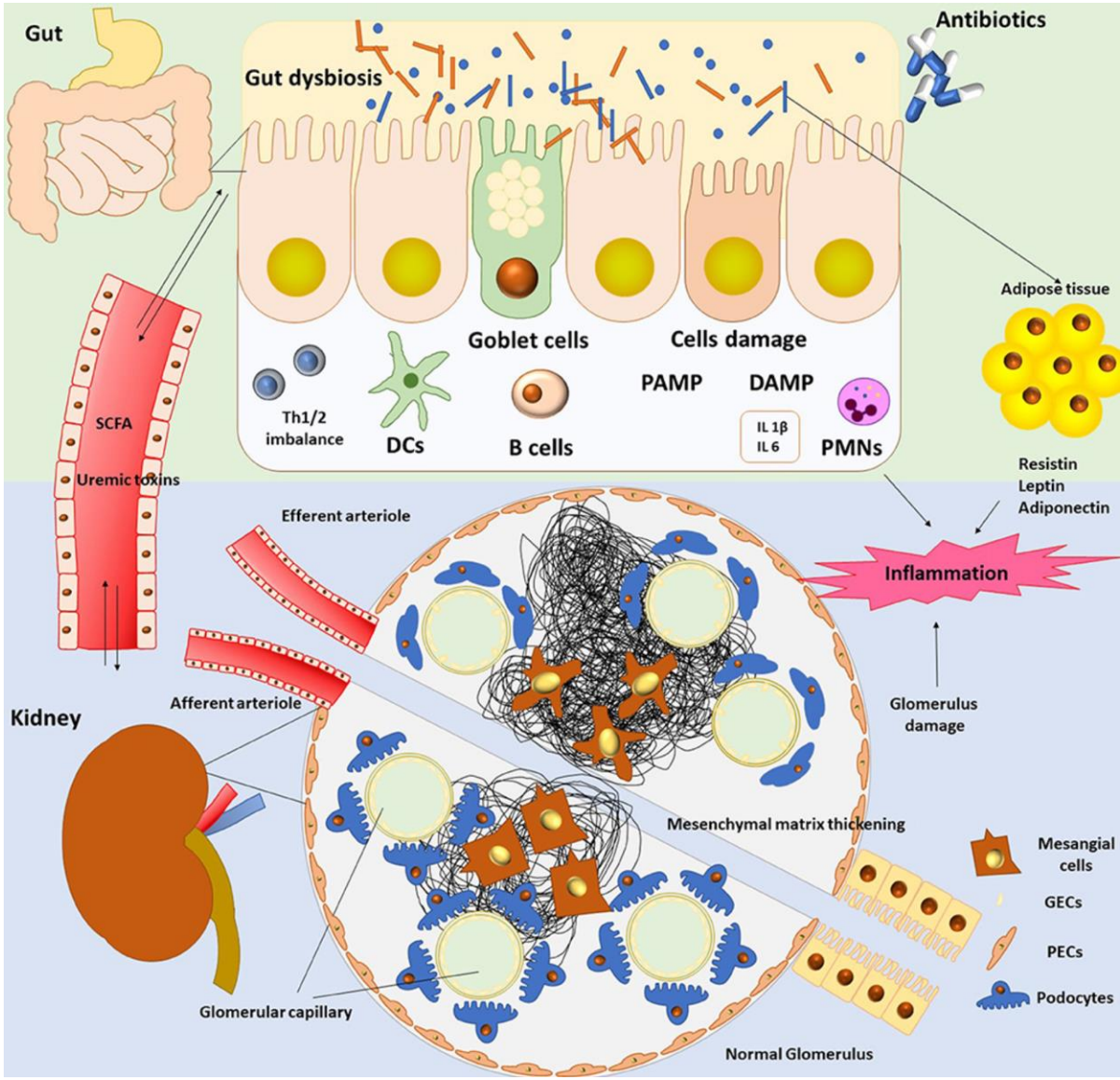
- Mucosal immunity is characterized by individually compartmentalized gut-associated lymphoid tissues (GALTs).

- critical role not only in determining local immune outcomes but also in maintaining systemic physiology.

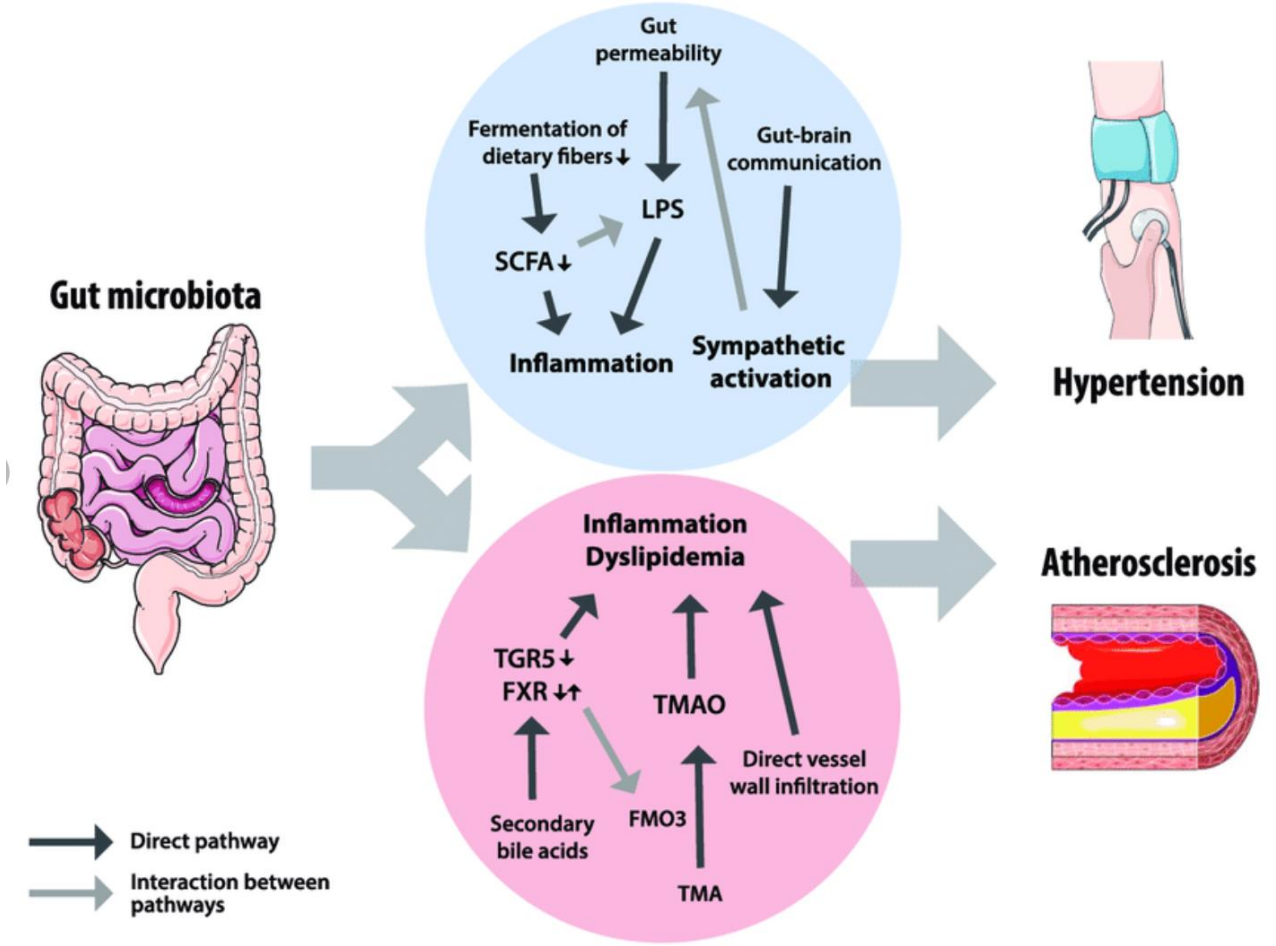
A lack of gut microbiota leads to deficient development of the GALT and abnormal systemic and central immunity.

- Germ-free animals have a substantial reduction in the levels of :
- T helper 17 (TH17) cells,
- B cells,
- immunoglobulin A (IgA) and
- plasma cells,
- an imbalance of TH1 and TH2 responses and
- impaired Treg cell function.

impaired blood–brain barrier integrity,
an exaggerated hypothalamic–pituitary–adrenal response to stress,
increased anxiety-like behaviour76,
altered neurotransmitter levels and a reduced metabolic rate in the liver.



The gut microbiota in hypertension



Summary of hypothesized pathways for the effects of gut microbiota on hypertension and atherosclerosis. Gut microbiota could affect hypertension through inflammatory factors, influenced by short chain fatty acids (SCFAs) and lipopolysaccharides (LPS), and through sympathetic activation by gut-brain interactions. The effects on inflammation and dyslipidemia in atherosclerosis could be mediated by bile acid receptors Takeda G-protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR), trimethylamine-N-oxide (TMAO) and trimethylamine (TMA), and direct vessel infiltration of microbiota. The grey arrows indicate interactions between pathways: FXR regulates the TMAO-converting enzyme flavin mono-oxygenase 3 (FMO3), sympathetic activation increases gut permeability, and short chain fatty acids can attenuate the inflammatory effects of LPS.

- **The gut microbiota in CKD:**

As gut dysbiosis and altered gut pathology are associated with hypertension

a decrease in culturable anaerobic bacteria was observed in the faeces of patients with stage 3–4 CKD.

an increase in culturable aerobic bacteria was reported in the faeces of patients with CKD.

patients with ESRD and healthy individuals had distinct faecal microbial compositions,

Moreover, the levels of CRP and IL-6 were significantly higher.

Table 1 | **Changes in the gut microbial composition in hypertension and CKD**

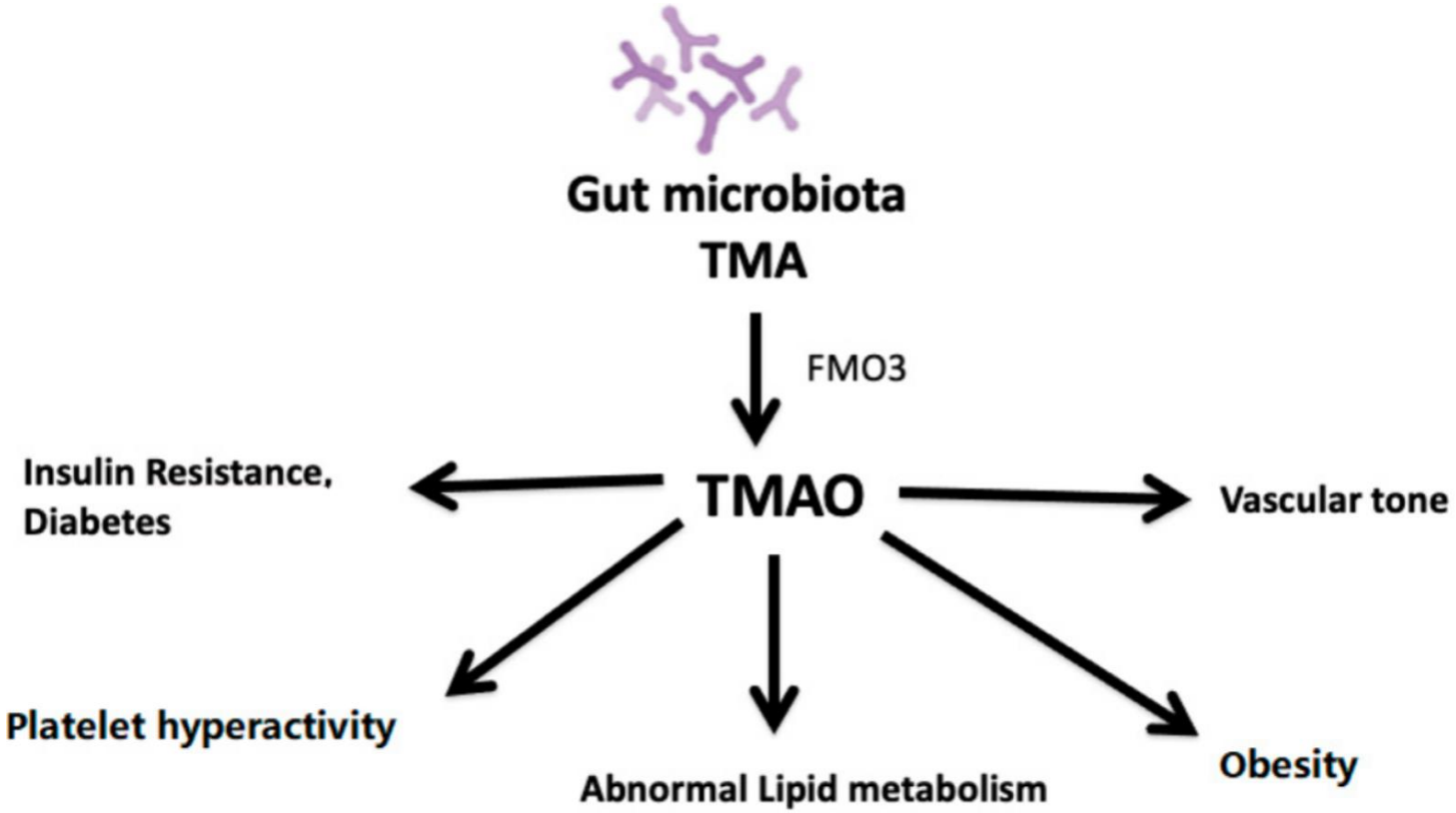
Bacteria	Hypertension		CKD	
	Change (organism)	Refs	Change (organism)	Refs
Actinobacteria				
Bifidobacterium	↓ (rat)	87,89	↓ (human and rat)	103,217
Bacteroidetes				
Bacteroides	↓ (human and rat)	87,89,90,95	↓ (human and rat)	101,104
Prevotella	↑ (human)	90	↓ (human)	107,110
Parabacteroides	↑ (human and rat)	87,90	↑ (human)	110
Firmicutes				
Lactobacillus	↓ (human and mouse)	92	↓ (human and rat)	101,104
Ruminococcaceae	NA	NA	↓ (human)	107
Roseburia	↓ (human)	90	↓ (human)	107
Allobaculum	↓ (rat)	87	NA	NA
Enterococcus	NA	NA	↑ (human)	107
Faecalibacterium	↓ (human)	90	↓ (human)	107
Proteobacteria				
Enterobacteriaceae	NA	NA	↑ (human)	101,105
Klebsiella	↓ (human)	203	↑ (human)	107
Verrucomicrobia				
Akkermansia	↓ (human and rat)	87,90	NA	NA

Changes in microbial composition in comparison with the microbiota of healthy controls. ↑, proportion increased; ↓, proportion decreased; CKD, chronic kidney disease; NA, not available.

- Interestingly, in the 5/6 nephrectomy CKD model, the levels of uraemic toxins in serum correlated with the abundance of Clostridia-affiliated and Bacteroidia affiliated species in the indigenous gut microbiota106.

- To date, more than 80 uraemic toxins have been reported to accumulate in patients with CKD.

- Most of these toxins are widely considered to contribute to uraemic syndromes.



expression of three genes involved in the production of TMA was also significantly increased in the gut microbiota of patients with CKD .

- **The gut–kidney axis**

- metabolism dependent
- and
- immune pathways .

- In the immune for example, lymphocytes, monocytes and cytokines have a critical role in communication between the gut and the kidney.

- Crosstalk between the metabolism dependent and immune pathway also has an important role in maintaining the balance of the gut–kidney axis.

- **Metabolism-dependent pathway.**

- Patients on haemodialysis who had intact colons had significantly higher levels of p-cresyl sulfate and indoxyl sulfate than those who did not have colons, indicating an important contribution of colonic microorganisms to the production of uraemic toxins.

- Colonic transit time…to the production of uraemic toxins.

In addition, as renal function declines, the colon replaces the kidney as the primary site of excretion of urea and uric acid.

- Constant exposure of colonic epithelial cells to urea reduces their viability and decreases epithelial barrier function in vitro and disrupts colonic tight junction proteins (for example, claudin 1, occludin and zonula occludens 1) both in vitro and in vivo.

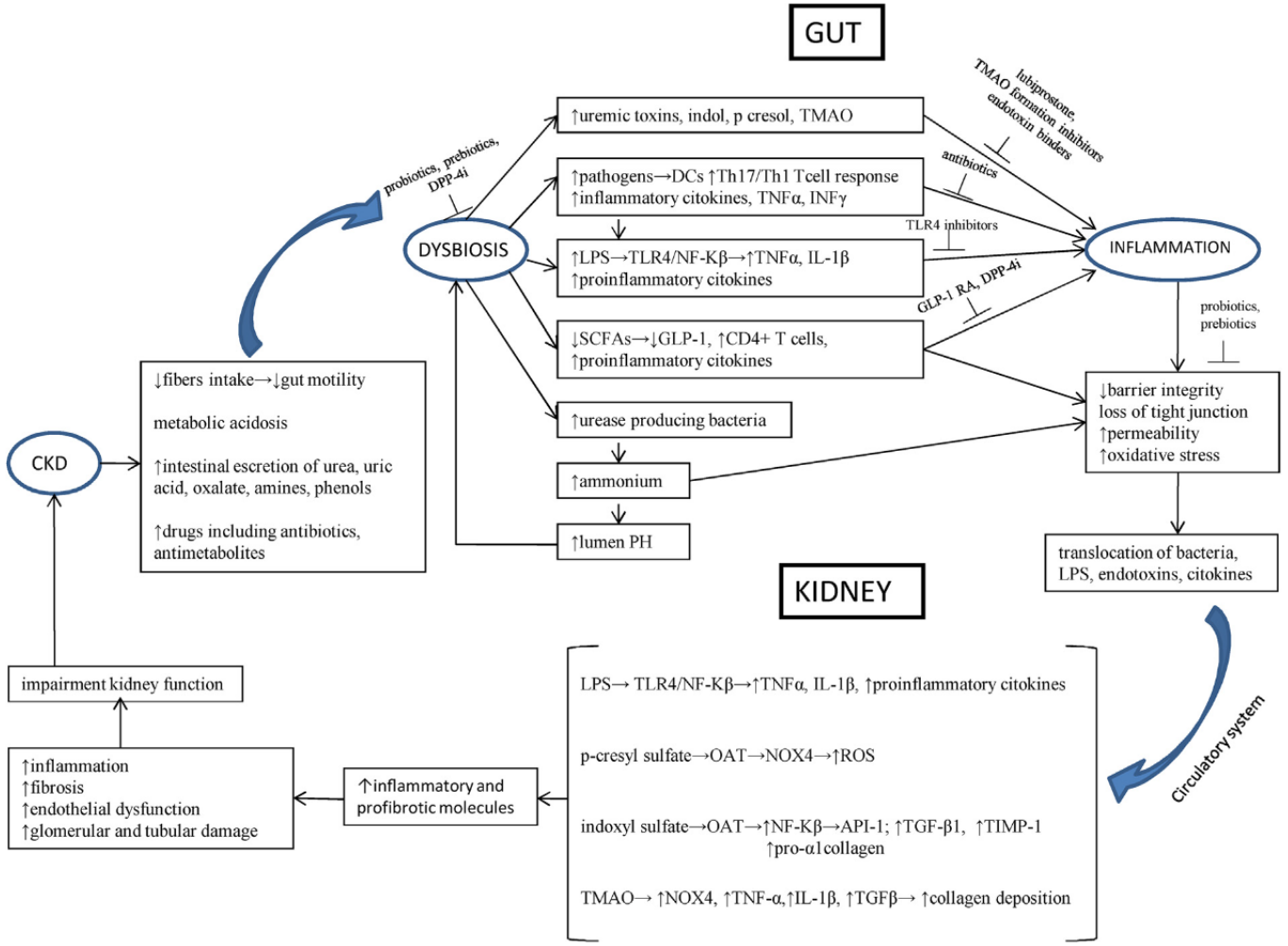


Fig. 1. Bidirectional relationship between altered gut microbiota and chronic kidney disease.
CKD favors pathobiont overgrowth and symbionts abundance reduction. This causes on the one hand an increase in urease-producing bacteria with increased production of endotoxins and on the other hand a reduction of short-chain fatty acids (SCFAs)-producing bacteria which have beneficial effects. The consequences are activation of the immune system, inflammation and damage of the intestinal barrier. The "leaky gut" allows the translocation of bacteria, lipopolysaccharides (LPS), toxins and cytokines into the systemic circulation. In the kidney, inflammatory cytokines and pro-fibrotic factors induce inflammation, nephrotoxicity, cell injury and impairment of renal function. In the figure the potential therapeutic targets are illustrated.
API-1: plasminogen activator inhibitor type 1, DCs: dendritic cells, LPS: lipopolysaccharides, NF-kb: nuclear factor kappa beta, OAT: organic anion transporter, ROS: reactive oxygen species, TLR4: toll-like receptor 4, TMA: trimethylamine, TMAO: trimethylamine-N-oxide, INF-γ, interferon γ; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor- β; TIMP-1, tissue inhibitor of metalloproteinases-1; NOX4, NADpH oxidase-4; GLP-1, Glucagon-Like Peptide-1; GLP-1 RA, GLP-1 Receptor Agonists; DPP-4i, Dipeptidyl Peptidase-4 inhibitors.

- immune pathway.

- Another pathway that links the gut microbiota and the kidney is mediated by the immune system.

- Colonization of commensal microbiota in germ-free mice induced changes in the inflammatory cytokine profile in the bone marrow, which is the primary site of origin of immune cells.

- Cytokines have important effects in haematopoiesis, and
- antibiotic mediated depletion of the intestinal microbiota in mice led to the suppression of multipotent progenitors in the bone marrow .

- Therefore, the gut microbiota modulates not only the activation of intestinal immune cells but also the profile of immune progenitor cells in the bone marrow.

- Following bone marrow ablation, reconstitution of WKY rats with bone marrow from SHRs led to an elevation in blood pressure and inflammation, whereas reconstitution of SHRs with WKY bone marrow had the opposite effect15.

- In a clinical setting, renal dysfunction has been found in recipients of bone marrow transplants122, suggesting a contributory role of the bone marrow in the initiation of kidney inflammation.

- In addition, immature myeloid cells derived from the bone marrow have been reported to be responsible for elevation in the circulating levels of soluble urokinase plasminogen activator surface receptor (suPAR)124, which has been implicated in the onset and progression of CKD125.

- **Communication between the pathways**.

- The gut microbial metabolite p-cresyl sulfate and indoxyl sulfate bind albumin in the circulation and are rapidly released from albumin immediately before being eliminated by tubular secretion.

- The levels of p-cresyl and indoxyl sulfates increase concomitantly with CKD progression, and this increase has been attributed to decreased renal clearance and increased production due to gut dysbiosis.

- Gut-microbiota-derived uraemic toxins induce inflammation in the gastrointestinal tract, as evidenced by increased intestinal permeability in patients and animals with uraemia, increased penetration of bacteria across the intestinal wall in uraemic rats,the detection of endotoxaemia in patients with ESRD and histological evidence of chronic enterocolitis in patients on dialysis.

- Pathological accumulation of p-cresyl and indoxyl sulfates in the circulation results in systemic inflammation in blood vessels, endothelial dysfunction, insulin resistance and activation of the renin–angiotensin–aldosterone system, which are all common features of hypertension and CKD.

- The resulting dysbiosis and deregulation of local gut immune responses perpetuate loss of renal function, accumulation of metabolic wastes and changes in metabolic state in a positive feedback loop.

- In addition to expansion of indole-forming and pcresol-forming bacteria, contraction of families of SCFA producing bacteria has been reported in patients with ESRD compared with healthy individuals.
- These changes included reductions in the Lactobacillaceae and Prevotellaceae families, which express genes that encode butyrate-forming enzymes (phosphotransbutyrylase and butyrate kinase), and in the butyrateproducing bacteria Roseburia spp. and Faecalibacterium prausnitzii. Beneficial effects of butyrate on colonic inflammation have been reported.

- In the deoxycorticosterone acetate (DOCA) hypertension model, a highfibre diet that promoted the growth of acetate-producing bacteria and acetate supplementation attenuated renal fibrosis. These findings indicate that SCFAs regulate immune responses and attenuate kidney pathology.

- **The brain–gut–kidney axis**
- Our research group was the first to demonstrate a contribution of the brain–gut–bone-marrow axis to blood pressure elevation.
- Emerging evidence has led to expansion of this concept to that of the brain–gut– kidney axis (Table 2).
- The brain has considerable involvement in the gut–kidney axis through communication with metabolism-dependent and immune pathways via the sympathetic nervous system (SNS).

Table 2 | **Evidence for a gut–kidney axis and a brain–gut–kidney axis**

Evidence	Species	Refs
Gut–kidney axis		
• Gut dysbiosis in hypertension and CKD	Human and rat	87,89,90,101,103–106
• Altered gut metabolite profile in hypertension • Increased levels of gut-microbiota-derived uraemic toxins in CKD	Human and mouse	106,118,203,233
• Intestinal pathology and inflammation in hypertension • Intestinal and renal inflammation in CKD	Human and rat	234,235
• Proteinuria, renal failure and uraemia in intestinal inflammatory bowel disease	Human	236
• Angiotensin-II-induced hypertension is attenuated in germ-free mice • Rodent models of spontaneous renal diseases do not develop severe disease in germ-free conditions	Mouse and rat	8,79,100,106
Brain–gut–kidney axis		
• Altered autonomic nervous system in hypertension and CKD	Human and rat	156,162,164,170,237
• Increased microglial activation and neuroinflammation in hypertension • Increased neuroinflammation and cognitive impairment in CKD	Human, rat and mouse	175,177,178,205

CKD, chronic kidney disease.

Sympathetic nervous system and brain.

- The occurrence of increased SNS activity in hypertension and CKD is well established. **Efferent fibers of the SNS innervate the renal vasculature and juxtaglomerular cells, and afferent fibers convey mechanical and chemical information from the kidney.**
- Rapid turnover of noradrenaline in autonomic brain centers has been shown in rats with 5/6-nephrectomy-induced CKD .
- In addition, the sympathetic dampening agent moxonidine lowers urinary albumin excretion and reduces glomerulosclerosis in subtotally nephrectomized rats165.
- **These data indicate altered bidirectional autonomic communication between the brain and the kidney in CKD.**
- **Uraemic toxins do not have a direct effect on renal afferents, as evidenced by a study that showed similar levels of muscle sympathetic nerve activity in patients with uraemia on haemodialysis and in nonuraemic kidney transplant recipients with diseased native kidneys.**
- **The SNS directly innervates both primary (bone marrow) and secondary (spleen) immune organs.**
- Expression of adrenergic receptors on immune cells residing in immune organs indicates regulatory effects of sympathetic catecholamines on the immune system.
- Both anti-inflammatory and pro-inflammatory effects of adrenergic signalling have been demonstrated, depending upon the subtype of adrenergic receptors expressed, the level of activation of specific cell types and the stage of disease progression.
- However, persistent activation of the SNS results in changes in signalling within immune organs and cells towards pro-inflammatory pathways168, as observed in hypertension and CKD169,170.
-

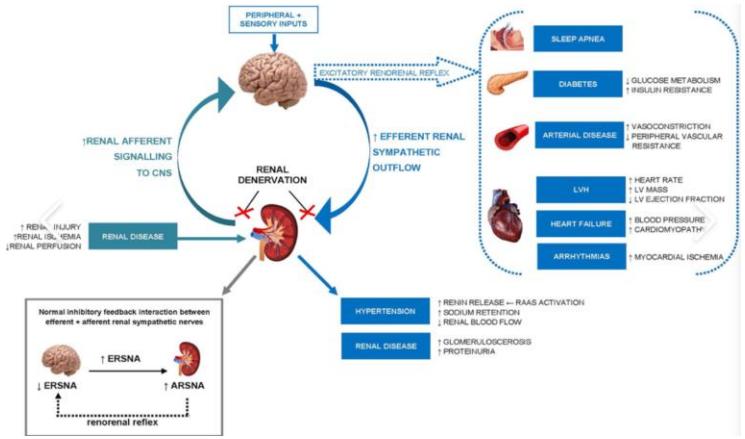
- In addition to peripheral blood vessel control, the SNS regulates water and sodium balance through direct innervation of the nephron, the renal vasculature and juxtaglomerular cells.

- The renorenal reflex is an inhibitory feedback loop that constitutes renal afferent nerves that convey signals to the CNS, governing sympathetic outflow .

- An impaired renorenal reflex in hypertension and CKD leads to augmented sympathetic excitation to the blood vessels, heart and kidney161.

- Multiple central neural sites have been implicated in the regulation of sympathetic outflow, including the paraventricular nucleus of hypothalamus (PVN), NTS and rostral ventrolateral medulla (RVLM).

- These regions communicate with each other and integrate diverse inputs to determine the tonicity of sympathetic outflow171.



- *Am J Physiol Regul Integr Comp Physiol 309: R444 – R458, 2015. First published July 8, 2015; doi:10.1152/ajpregu.00078.2015.—*

- **the activity of the RAS and of glial cell-mediated proinflammatory processes have independently been linked to this neural control and are, as a consequence, both attractive targets for the development of antihypertensive therapeutics.**

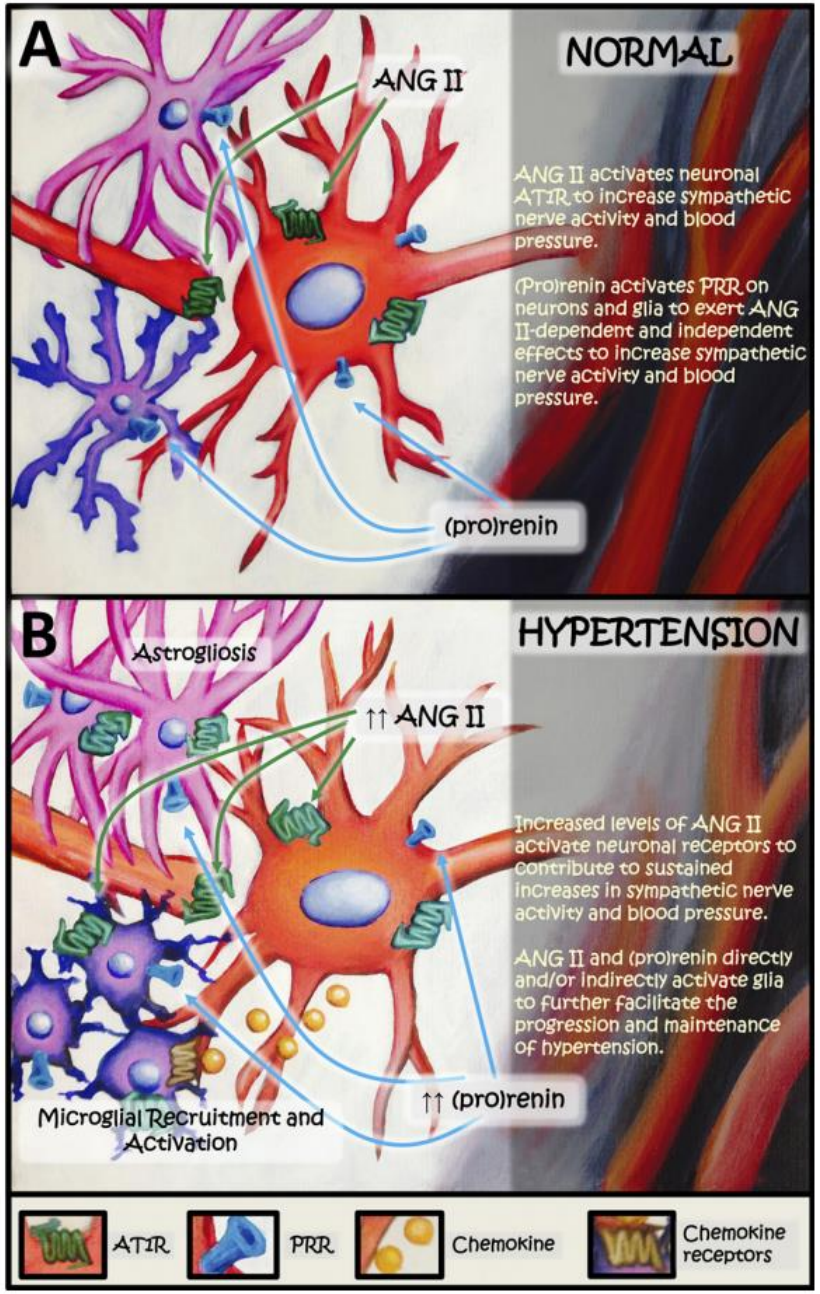


Fig. 2. Hypothetical model for the roles of neurons and glia in the central nervous system's actions of the renin-angiotensin system in normotensive (*A*) and hypertensive (*B*) conditions.

Indoxyl Sulfate Affects Glial Function Increasing Oxidative Stress and Neuroinflammation in Chronic Kidney Disease: Interaction between Astrocytes and Microglia

*Simona Adesso[1,2], Tim Magnus[3], Salvatore Cuzzocrea[4], Michela Campolo[4], Björn Rissiek[3], Orlando Paciello[5], Giuseppina Autore[1], Aldo Pinto[1] and Stefania Marzocco[1]**

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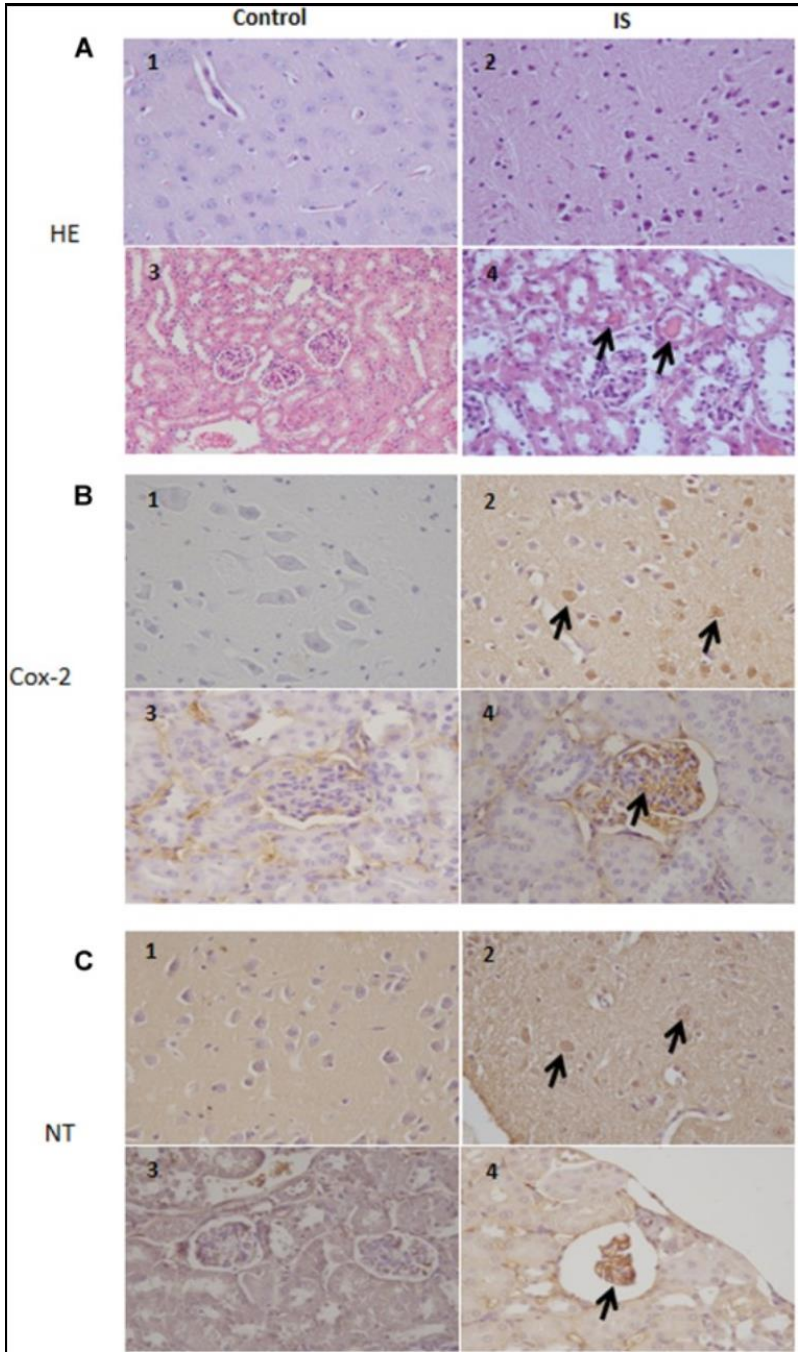


- Taken together, we can show that the AhR is important for the IS induced activation of NF-kB, ROS and pro-inflammatory cytokine production, and downregulation of cell protective factors such as Nrf2, HO-1 or NQO1 in glial cells.
- Some of these pathways can be specifically blocked.
- Evidences of IS-induced effects on CNS are here supported also by in vivo experiments.
- IS induced histological brain alterations and the expression of oxidative stress and inflammatory markers, such as nitrotyrosine and COX-2.

Figure 6: The putative schematic illustration of the mechanism underlying choline-elicited cardiovascular protection in hypertension.

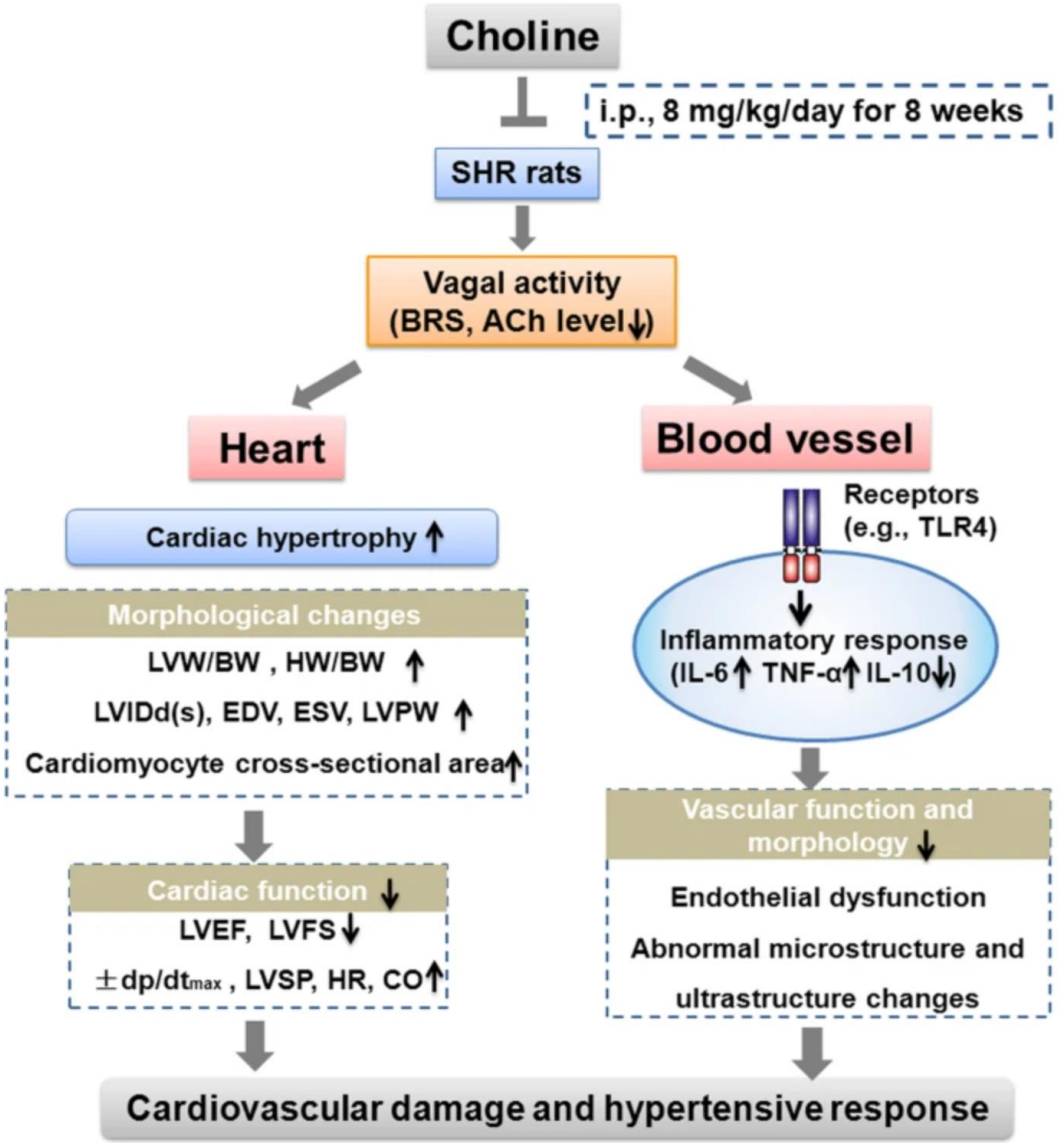
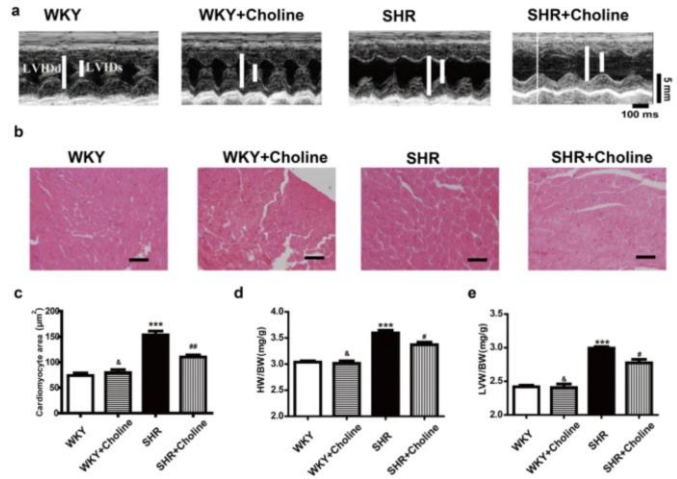


Figure 2: Choline attenuated cardiac hypertrophy in SHRs.



(**a**) Representative H&E staining of cardiac cross-section. (**b**) Quantification of cross-sectional areas of the cardiomyocytes. (**c**) Quantification of cross-sectional areas of the cardiomyocytes. (**d**) The ratio of HW/BW. (**e**) The ratio of LVW/BW, Scale bar = 30 μm. Data are mean ± SEM (n = 8). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs WKY; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs SHR; $^{\&}P < 0.01$ vs SHR+Choline.

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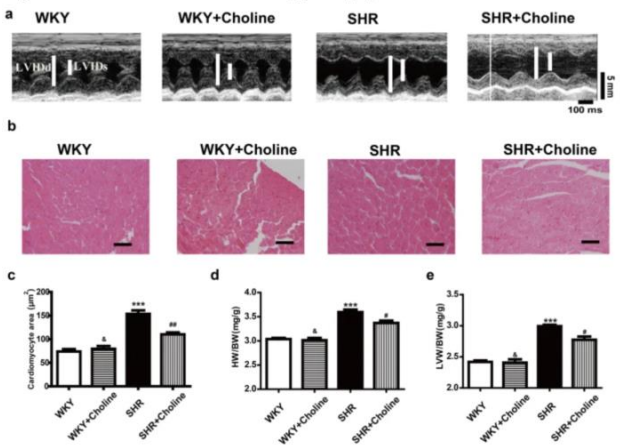

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Sympathetic Overactivity in Chronic Kidney Disease: Consequences and Mechanisms

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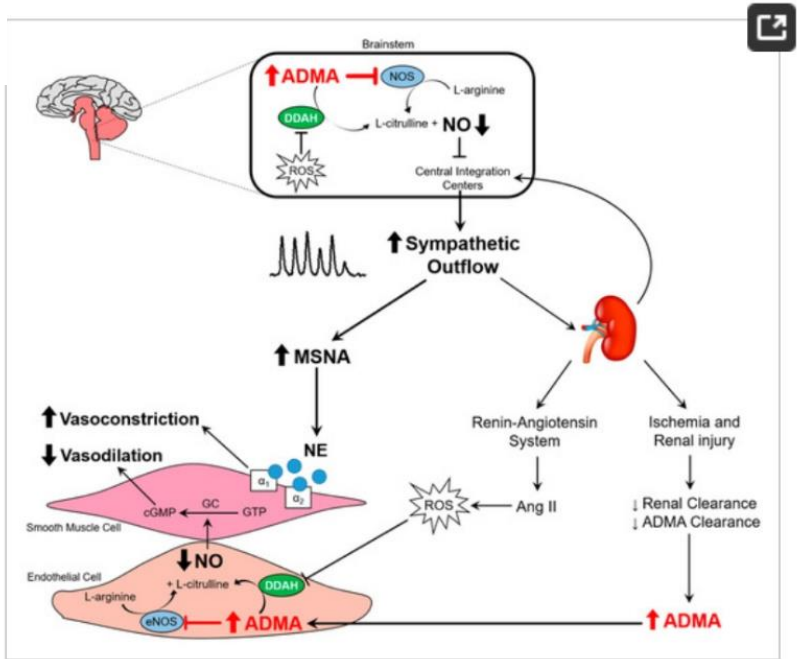

Figure 5. Schematic illustration depicting the effects of elevated ADMA in the brainstem and the peripheral circulation. Reduced dimethylarginine dimethylaminohydrolase (DDAH) activity and renal clearance of ADMA leads to elevated plasma ADMA concentrations in chronic kidney disesase (CKD). Elevated ADMA in the brainstem inhibits NOS and reduces central nitric oxide (NO) production, contributing to higher central sympathetic outflow. This greater SNA results in peripheral vasoconstriction. When prolonged, the sympathetic overactivity leads to a host of other deleterious consequences as outlined in the text of the review. In the periphery, elevated ADMA inhibits NOS and decreases NO, thereby reducing endothelium-mediated vasodilation. Greater sympathetically-mediated vasoconstriction and lower endothelium-mediated vasodilation contributes to increased vascular tone and higher blood pressure. ROS, reactive oxygen species; eNOS, endothelial nitric oxide synthase; NE, norepinephrine. ⊢ denotes inhibition. (See text for further details).

Brain Microglial Cytokines in Neurogenic Hypertension

Peng Shi, Carlos Diez-Freire, Joo Yun Jun, Yanfei Qi, Michael J. Katovich, Qiuhong Li, Srinivas Sriramula, Joseph Francis, Colin Sumners, Mohan K. Raizada

Abstract—Accumulating evidence indicates a key role of inflammation in hypertension and cardiovascular disorders. However, the role of inflammatory processes in neurogenic hypertension remains to be determined. Thus, our objective in the present study was to test the hypothesis that activation of microglial cells and the generation of proinflammatory cytokines in the paraventricular nucleus (PVN) contribute to neurogenic hypertension. Intracerebroventricular infusion of minocycline, an anti-inflammatory antibiotic, caused a significant attenuation of mean arterial pressure, cardiac hypertrophy, and plasma norepinephrine induced by chronic angiotensin II infusion. This was associated with decreases in the numbers of activated microglia and mRNAs for interleukin (IL) 1β, IL-6, and tumor necrosis factor-α, and an increase in the mRNA for IL-10 in the PVN. Overexpression of IL-10 induced by recombinant adenoassociated virus-mediated gene transfer in the PVN mimicked the antihypertensive effects of minocycline. Furthermore, acute application of a proinflammatory cytokine, IL-1β, into the left ventricle or the PVN in normal rats resulted in a significant increase in mean arterial pressure. Collectively, this indicates that angiotensin II induced hypertension involves activation of microglia and increases in proinflammatory cytokines in the PVN. These data have significant implications on the development of innovative therapeutic strategies for the control of neurogenic hypertension. (***Hypertension*****. 2010;56:297-303.)**

Key Words: angiotensin II ■ hypertension ■ minocycline ■ interleukin 10 ■ microglia ■ paraventricular nucleus ■ cytokine

Inflammation has been implicated in hypertension and cardiovascular diseases in both animal models and human diseases.[1,2] Increases in levels of plasma proinflammatory cytokines (PICs) and other markers of inflammation are associated with the progression of hypertension, whereas immune suppression produces beneficial outcomes.[3,4] Despite evidence for the participation of peripheral cytokines and inflammation in cardiovascular disease, little is known about their involvement in neurogenic hypertension. Studies from Francis and collaborators[5,6] have indicated that angiotensin (Ang) II–induced hypertension involves activation of tumor necrosis factor-α (TNF-α) and nuclear factor κB and production of reactive oxygen species in the brain. These observations have led us to propose that Ang II–induced neurogenic hypertension involves activation of microglial cells and production of PICs within the brain. Our objective in the present study was to test this hypothesis.

We focused on the paraventricular nucleus (PVN) and a chronic Ang II infusion rat model of hypertension for this study, based on the following rationales. First, the PVN integrates signals/inputs from circumventricular organs and other cardiovascular-relevant brain areas and transmits them to the rostroventrolateral medulla and other downstream areas to influence sympathetic nerve activity.[7] Second, chronic Ang II infusion is an established animal model of hypertension with strong neurogenic components.[8] Our studies demonstrate that Ang II–induced hypertension involves activation of microglia and increases in PIC within the PVN.

Materials and Methods

Animals

Adult male Sprague-Dawley (SD) rats (Charles River Laboratories) aged 5 weeks (n=118) were individually housed in a temperature-controlled room (22°C to 23°C) with a 14:10-hour light-dark cycle. Tap water and laboratory chow were available ad libitum. All of the experimental procedures were approved by the University of Florida Institute Animal Care and Use Committee.

Surgical Preparation

Implantation of Telemetry Transducers

Six-week–old male SD rats were anesthetized with a mixture of O_2 (1 L/min) and isoflurane (3% to 4%). Rat telemetry transducers (TA11PA-C40, DSI) were implanted into the abdominal aorta on day −10 (for minocycline experiments) or day −28 (for viral experiments), as described previously.[9] A bolus injection of buprenorphine (0.05 mg/kg SC) was administered after each surgery.

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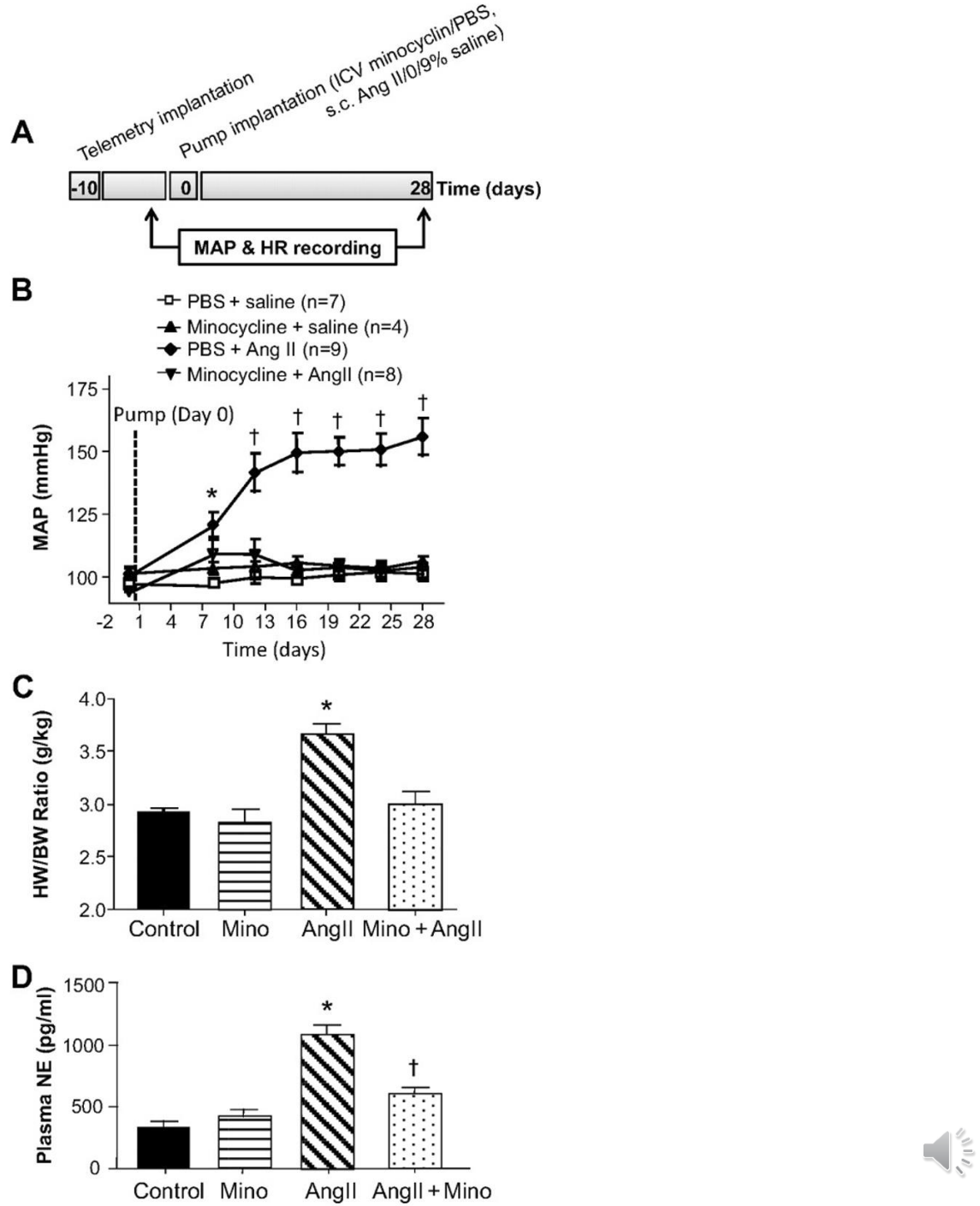

- **Epigenetic factors.**
- Epigenetic factors might also have a role in the brain–gut–kidney axis.

- Microbial metabolites including folate, butyrate and acetate are cofactors and allosteric regulators of epigenetic processes such as DNA methylation, histone acetylation and RNA interference190–192.

- The gut microbiome has been shown to induce host epigenetic changes that might contribute to the development of cancer193,194, and notable changes in epigenetic modifications have been reported in hypertension and CKD85,195.

- For example, podocyte-specific inactivation of Dicer, one of the enzymes responsible for production of microRNAs, results in proteinuria and glomerulosclerosis196.

- In a genome-wide DNA methylation study of human kidney tubules, several genes that are associated with kidney fibrosis were characterized by methylation changes and alterations of downstream transcript levels in CKD samples compared with controls.

In a rat model of salt-sensitive hypertension, stimulation of sympathetic signalling led to reduced expression of a regulator of sodium reabsorption, protein kinase lysine-deficient 4 (WNK4), owing to hyperacetylation of the promoter198.

Moreover, upregulation of angiotensin-converting enzyme 1 in SHR compared with WKY controls was associated with multiple epigenetic modifications in several tissues, such as the adrenal gland, aorta, heart and kidney.

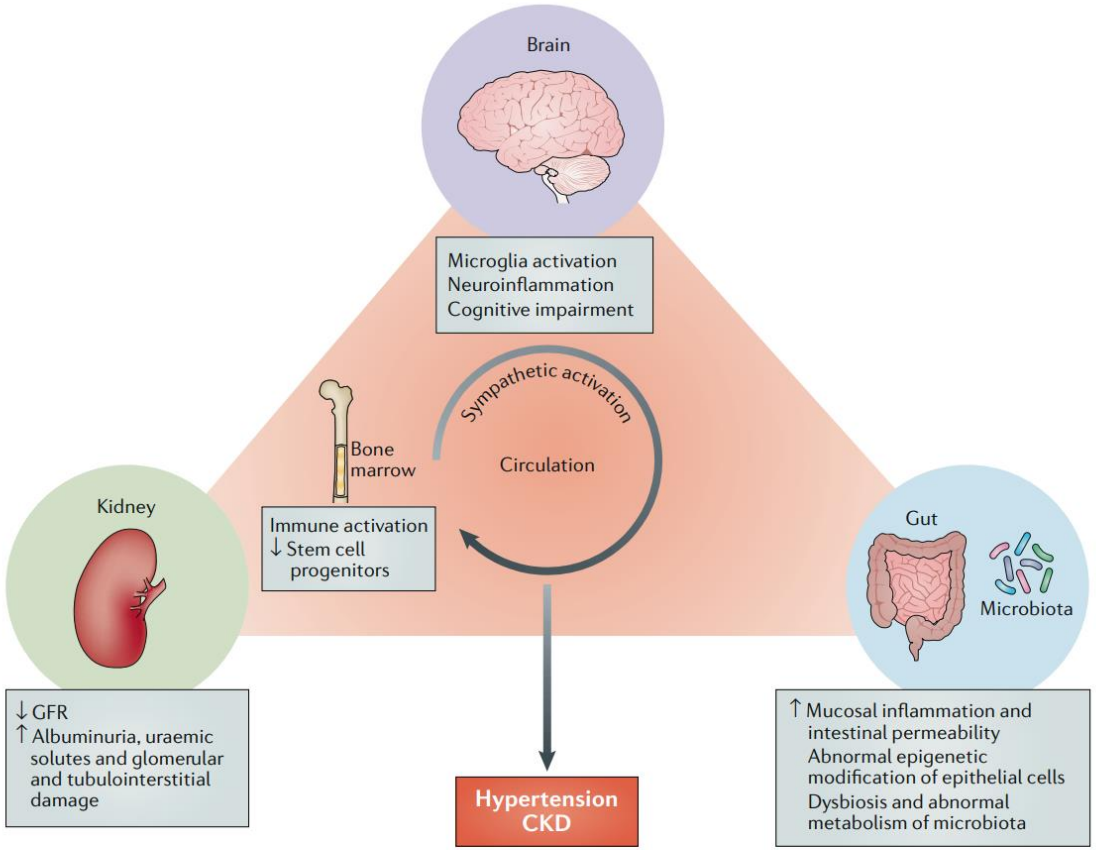

Fig. 3 | **The brain–gut–kidney axis hypothesis for the pathogenesis of hypertension and CKD.** Sympathetic activation is a common feature in disorders of the brain, gut and kidney. Persistent microglial activation and neuroinflammation in presympathetic regions of the brain responsible for sympathetic outflow contribute to an increase in blood pressure and to pathogenesis in the gut and kidney. Immune cells that develop in the bone marrow are activated by microbiota in the gut and enter the circulation; these cells contribute to gut and kidney inflammation. Local mucosal immunity is also regulated by the intestinal environment owing to close communication between the gut and the gut microbiota. Dysbiosis and disorders in intestinal metabolism result in an imbalance of intestinal homeostasis, which is characterized by increased mucosal inflammation, intestinal permeability and abnormal epigenetic modification of epithelial cells. A decline in renal function leads to reduced glomerular filtration rate (GFR), increased albuminuria and uraemic toxins and glomerular and tubulointerstitial damage. These pathological events in the brain, gut and kidney substantially contribute to the development of hypertension and chronic kidney disease (CKD).

THANK YOU