The gut microbiota and the brain–gut–kidney axis in hypertension and chronic kidney disease

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Abstract | Crosstalk between the gut microbiota and the host has attracted considerable attention owing to its involvement in diverse diseases. Chronic kidney disease (CKD) is commonly associated with hypertension and is characterized by immune dysregulation, metabolic disorder and sympathetic activation, which are all linked to gut dysbiosis and altered host–microbiota crosstalk. In this Review, we discuss the complex interplay between the brain, the gut, the microbiota and the kidney in CKD and hypertension and explain our brain–gut–kidney axis hypothesis for the pathogenesis of these diseases. Consideration of the role of the brain–gut–kidney axis in the maintenance of normal homeostasis and of dysregulation of this axis in CKD and hypertension could lead to the identification of novel therapeutic targets. In addition, the discovery of unique microbial communities and their associated metabolites and the elucidation of brain–gut–kidney signalling are likely to fill fundamental knowledge gaps leading to innovative research, clinical trials and treatments for CKD and hypertension.

Low-grade inflammation
A chronic systemic immune response that occurs without acute clinical symptoms.

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Chronic kidney disease (CKD) affects approximately 10% of the global population and has a financial impact of ~$48 billion per year in the United States alone[1]. Hypertension is an important risk factor for CKD, and approximately 85–90% of patients with stage 3–5 CKD have hypertension[2]. Long-term hypertension leads to high intraglomerular pressure, which subsequently impairs glomerular filtration[3]. Thus, blood-pressure lowering is an important and widely used approach to slow CKD progression. Current management of early-stage CKD focuses on blood pressure control, reduction of protein and salt intake, prevention of acute kidney injury and glycaemic control[4]. No cure or strategy for prevention of CKD exists, and timely treatment is extremely challenging owing to a lack of symptoms in the early stages of the disease[5]. Moreover, with the exception of dialysis and kidney transplantation, effective treatments for end-stage renal disease (ESRD) are lacking. Thus, paradigm-shifting concepts and innovative approaches are needed to detect, manage, control and ultimately cure these diseases.

Increasing evidence indicates an important role of the gut microbiota in the development of hypertension and CKD. The gut microbiota constantly communicates with vital organ systems of the host, such as the brain[6], bone marrow[7], vasculature[8], kidney[9], immune system[10] and autonomic nervous system (ANS)[11,12]. This communication contributes to the homeostasis and health of the host. 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[13–15]. Peripheral stimuli influence the ANS to subsequently modify neural inputs to the kidney, intestine and lymphoid organs[16]. In addition, immune and gut microbiota-derived products affect renal function and have important effects on CKD[17]. 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[18].

In this Review, we provide evidence for a gut–kidney axis and its potential regulation by the brain. We describe the gut microbiota and its interactions with major components in the brain–gut–kidney axis, such as the neural, hormonal, bone marrow and immune systems, and discuss this communication in the context of CKD and hypertension.

The gut microbiota

The gut harbours trillions of microorganisms, including commensal bacteria (FIG. 1). Initial microbial colonization is generally accepted to occur transvertically during birth and to continuously evolve to a fairly stable, adult-like composition within the first 3–5 years of life[19]. However, evidence that the maternal microbiota affects the fetal microbiota has challenged this concept[20].

Key points

- The gut microbiota has crucial roles in a variety of diseases, including hypertension and chronic kidney disease (CKD).
- The gut microbiota communicates with the endocrine, nervous and immune systems to regulate host homeostasis, including blood pressure and kidney functions.
- The gut–kidney axis is mediated through metabolism-dependent and immune pathways.
- The brain–gut–kidney axis involves connections between these organs that are mediated by descending autonomic regulation from the brain and signals from the gut and the kidney, such as immune products and microbial metabolites.
- Potential therapeutic strategies for CKD and hypertension that target the gut microbiota include dietary interventions, probiotics, prebiotics, synbiotics, faecal microbiota transplant and metabolome modulation.

The gut microbiota of adults can be divided into two major enterotypes according to the dominant bacterial phylotype; both of these enterotypes are strongly associated with long-term diet[21]. The predominant bacterial population of enterotype 1 is *Bacteroides*, which predominantly metabolize protein, whereas enterotype 2 contains predominantly saccharolytic *Prevotella*. Not surprisingly, microbial metabolite profiles (for example, short-chain fatty acids (SCFAs) and bile acids) are strongly associated with enterotypes[22].

Dynamic evolution of the gut microbiota during early life begins with colonization by facultative anaerobic bacteria (predominantly Proteobacteria), followed by growth of anaerobic bacteria (generally *Lactobacillus* and *Bifidobacterium*) and, finally, diversification of bacteria — mainly different genera within the Bacteroidetes phylum — according to energy supply[19]. Neonates have an immature immune system that does not adequately respond to or defend against pathogenic invasions, which can potentially lead to severe infections. Breastfeeding and maternal interactions supply the conditions that are required for optimal development of the immune system[23]. Lactose, the primary carbohydrate of human milk, greatly promotes the growth of *Lactobacillus* and shapes the gut microbiota in infants[24]. The subsequent introduction of solid food substantially reshapes the gut microbiota, indicating that environmental factors have critical roles in determining its composition[19].

Establishment of an intact gut–blood barrier, characterized by complete physiological and immunological protection, preserves the digestive and absorptive functions of the intestine and restricts the invasion of pathogens and toxic metabolites into the circulation. This essential process depends to a great extent on the presence of a balanced gut microbiota[25]. In adults, microbial metabolic pathways in the gut are fairly stable, although, as mentioned above, environmental factors, especially diet, profoundly modify the gut microbiota[26]. Age-related changes in the gut microbiota have also been identified in the elderly population, characterized by a decrease in diversity, contraction in saccharolytic bacteria, expansion in proteolytic bacteria, increases in certain Proteobacteria and a decline in *Bifidobacterium* counts[27]. Plasma markers of increased intestinal permeability are elevated in the healthy elderly population, indicating disruption of intestinal barrier function with ageing[28]. Moreover, probiotic supplementation has been shown to have healthy lifespan-promoting effects, including suppressing chronic low-grade inflammation and increasing longevity in mice[29], indicating the importance of the gut microbiota in the maintenance of overall health.

The gut virome shows more interindividual variation and is less affected by environmental changes than is the gut microbiome[30]. However, the human gut virome carries a collection of hypervariable sequences that are considered to be a reservoir of viral evolution for adaption to a new environment[31,32]. In patients with type 1 diabetes mellitus, changes in the gut virome seem to precede the development of autoimmunity[33], indicating a potential role of the virome in disease development. Fungal communities in the gut do not seem to cause illness directly but may exhibit dysbiosis that could potentially contribute to systemic inflammation[34].

Gut physiology

The small intestine (duodenum, jejunum and ileum) and large intestine (colon) differ substantially in their structure and composition. For example, goblet cells are enriched in the proximal colon, whereas Peyer's patches are primarily found in the small intestine[35,36]. In addition, the mucin layers are thinner and the microvilli are more numerous in the small intestine than in the colon. This diversity is associated with multidimensional functions that are important in host–microbiota interactions. Approximately 70% of the immune cells in the body reside in the gut; these cells maintain a balance of immune activation and tolerance to the gut microbiota[37]. The gut is also the second-most innervated organ in the body, facilitating communication with the brain[38]. The complex vascular bed of the gut enables efficient absorption of nutrients and water and maintains a gradient of oxygenation along the gastrointestinal tract[39]. The gut is one of the first major organs to encounter environmental factors such as diet, toxins and pathogens, and its interactions with endocrine, circulatory, neural and immune systems have a substantial impact on host physiological responses (FIG. 1).

Endocrines and metabolites. Enteroendocrine cells are specialized endocrine cells of the gastrointestinal tract. Upon stimulus, these cells secrete hormones that are transported via the circulation to target receptors on recipient cells and regulate intestinal and/or systemic physiological functions[40]. Gut microbial metabolites, including SCFAs that are generated by the fermentation of dietary fibre, influence the host endocrine system. For example, the SCFA propionate stimulated release of glucagon-like peptide 1 (GLP1) and the gut hormone peptide YY (PYY) from murine primary intestinal cultures via a free fatty acid receptor 2 (FFAR2)-dependent mechanism[41,42]. Another study in mice reported that PYY was induced by gut microbiota in an FFAR3-dependent manner[43]. These results suggest a role of gut-microbiota-derived SCFAs in the production of endocrine hormones.

SCFAs also have multiple roles in the maintenance of intestinal homeostasis, including control of the balance between proliferation and apoptosis of intestinal

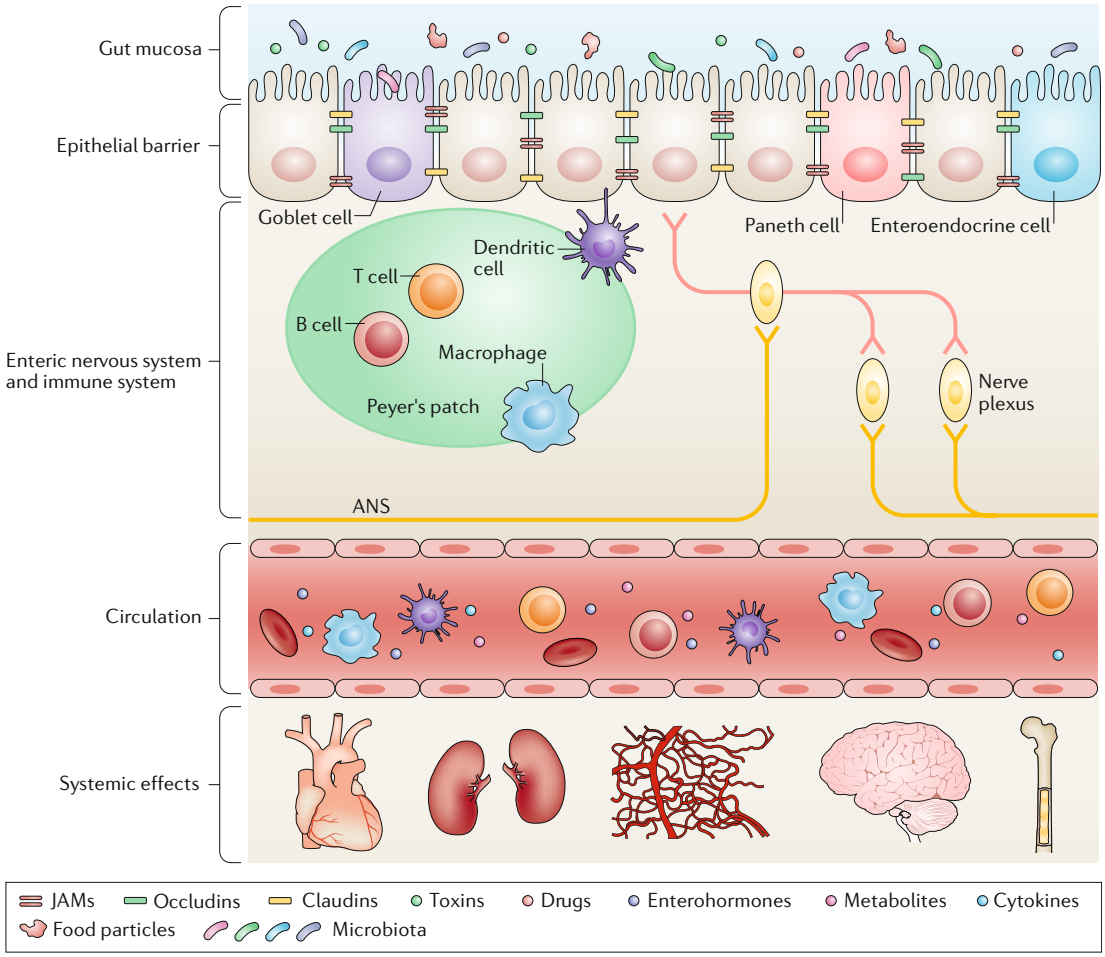

Fig. 1 | **The anatomy of the gut and its interactions with multiple systems.** The epithelial barrier, which is mainly composed of epithelial cells, goblet cells, Paneth cells and enteroendocrine cells, physically separates the gut mucosa from the submucosa. The gut mucosa is the most dynamic reservoir 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.

epithelial cells[44], induction of the secretion of endogenous antimicrobial peptides from intestinal epithelial cells[45,46] and of the differentiation of regulatory T (T_{reg}) cells[47], modulation of cytokine production[37] and maintenance of gut barrier function[48]. Therefore, enteroendocrine cell-derived hormones and gut-microbiota-derived metabolites exert profound effects on gut homeostasis.

Neural control of the gut. Intricate neural control of gastrointestinal function is achieved through the autonomic (extrinsic) and enteric (intrinsic) nervous systems[38]. The ANS conveys physiological conditions in the gut, such as acidity, levels of nutrients, osmolarity and pain, to the brain[49]. The enteric nervous system (ENS), which consists of the myenteric plexus and submucosal plexus, contributes to in situ neural communication within the intestine and connection to the ANS[38].

The ENS and its neural pathways are responsible for intestinal motor and sensory functions independent of central nervous system (CNS) control[50]. In germ-free mice, colonization of the gut microbiota is critical for the development and maturation of the ENS[51]. The gut microbiota and its metabolites are potent stimulators of the production of serotonin by enterochromaffin cells[52]. This key neurotransmitter mediates gut secretion, motility and local nerve reflexes. In addition, treatment with medium fermented by the probiotic bacteria *Bifidobacterium longum* reduced anxiety and decreased the excitability of the ileal myenteric plexus neurons in mice with infectious colitis[11], indicating communication of probiotics with the CNS via the ENS and the vagal nerve. Further investigations are required to identify the neurons that are affected by probiotics and the signals that are involved in this communication and to identify other alterations in gut microbiota that may also affect the ENS.

Probiotics
A group of microorganisms with beneficial effects on human health.

The ENS communicates bidirectionally with the brain through the vagus nerve, which sends sensory signals from the gut to the nucleus of the solitary tract (NTS) in the CNS. In a rat model of obesity, changes in the gut microbiota induced by an energy-dense diet were associated with alterations in brain–gut vagal (NTS) communication[53], which may alter vagal satiety signalling and stimulate energy intake and adiposity[54]. A series of beneficial effects of treatment with probiotics (*Lactobacillus rhamnosus* and *B. longum*) on stress and anxiety have been demonstrated to be vagus-nerve-dependent[11,12]. Vagal afferents express receptors that sense SCFAs[55], and activation of this pathway has been implicated in glucose homeostasis[56].

Role of the gut in the immune system. The gut is the largest immune organ in the body, with a complex mucosal immune system located at its inner surface and exposed to the lumen. Lymphocytes and innate immune cells, such as macrophages and dendritic cells, are found throughout the epithelial layers[37]. Mucosal immunity is characterized by individually compartmentalized gut-associated lymphoid tissues (GALTs) that form an interface between the blood and the intestinal lymph. This structural feature enables the GALT to constantly supply mature immune cells to the intestinal epithelium and lamina propria, where mucosal immunity interacts with the gut microbiota to produce immune responses and tolerance[37]. Harmonious immune responses within the physiological range ensure intestinal and systemic homeostasis. The gut microbiota therefore has a critical role not only in determining local immune outcomes but also in maintaining systemic physiology[57].

A lack of gut microbiota leads to deficient development of the GALT[58] and abnormal systemic[59] and central immunity[60]. Germ-free animals have a substantial reduction in the levels of T helper 17 (T_H17) cells[61], B cells, immunoglobulin A (IgA) and plasma cells[62,63], an imbalance of T_H1 and T_H2 responses[64] and impaired T_{reg} cell function[65]. Intestinal infiltration of pro-inflammatory T_H17 cells is induced by segmented filamentous bacteria[66], and gut microbial diversity, particularly colonization by Bacteroidetes, is critical for balancing T_H1 and T_H2 responses[64]. T_{reg} cells are induced by a variety of bacterial groups[67,68] and by the SCFA butyrate[47], which is produced by bacterial fermentation. Innate immunity is also regulated by the gut microbiota as evidenced by reduced numbers and compromised functions of antigen-presenting cells and microglia in germ-free animals[60,69]. These findings indicate that the gut microbiota has a global impact on host immunity.

Given the aforementioned immune abnormalities, the observed alterations in gut and systemic physiological functions in germ-free mice are not surprising. These mice exhibit considerable alterations in the size and number of goblet cells in the caecum[70] (but not in the colon[71]), in mucus properties[72] and in intestinal tight junction proteins[73]. Other alterations in physiological parameters in germ-free animals include impaired blood–brain barrier integrity[74], an exaggerated hypothalamic–pituitary–adrenal response to stress[75], increased anxiety-like behaviour[76], altered neurotransmitter levels[52,77] and a reduced metabolic rate in the liver[78]. In the kd/kd mouse model of collapsing glomerulopathy, germ-free conditions postponed the onset of renal mitochondrial ultrastructural defects[79], indicating a contribution of the gut microbiota to the pathogenesis of this kidney disease. Therefore, alteration and disruption of homeostasis in the gut have negative effects on intestinal and systemic physiological functions.

The gut microbiota in hypertension

Dysregulation of multiple contributing factors has been demonstrated in hypertension[80], including the renin–angiotensin system[81,82], the ANS[82,83] and the immune system[84]. Environmental factors in association with epigenetic[85] and genetic[86] components have critical roles in the initiation, maintenance and progression of hypertension. In addition, emerging evidence indicates that the gut microbiota has an essential role in hypertension development.

Gut dysbiosis has been reported in animal models[87–89] and in patients with hypertension[87,90] (TABLE 1). Moreover, spontaneously hypertensive rats (SHRs) showed pathophysiological changes in the gut, including decreased numbers of goblet cells and villi length and increased fibrosis compared with age-matched normotensive Wistar Kyoto (WKY) controls[91]. Although these changes were more profound in adult SHRs than in juvenile SHRs that had not yet developed hypertension, the pre-hypertensive juvenile SHRs had reduced levels of multiple tight junction proteins but similar gut permeability compared with juvenile WKY rats[91]. These findings indicate that gut pathology occurs before the onset of blood pressure elevation in the SHRs. Further evidence for a causative role of gut dysbiosis in the genesis of hypertension came from faecal microbiota transplantation (FMT) experiments in which transferring dysbiotic faecal samples from patients with hypertension to germ-free mice[90] or faeces from hypertensive stroke-prone SHRs to normotensive WKY rats[92] increased blood pressure in the recipients. As gut pathophysiological changes, immune responses and autonomic responses to FMT were not evaluated, further investigation is required to identify the potential mechanisms that underlie this FMT-induced increase in blood pressure.

Finally, studies in animal models and in patients with hypertension have reported that interventions that target the gut microbiota, such as a high-fibre diet, probiotics and antibiotics, have blood-pressure lowering effects[87,92–99]. For example, salt-sensitive mice treated with *Lactobacillus murinus* had lower systolic blood pressure (SBP; ~5 mmHg) and diastolic blood pressure (DBP; ~5 mmHg) than untreated controls[92]. The findings of these studies, which are discussed further below, provide further support for a role of the microbiota in hypertension.

The gut microbiota in CKD

The gut microbiota also seems to be a key factor that mediates the onset of kidney disease. In 1984, a study using a mouse strain that developed a spontaneous renal cystic disease (CFWwd mice) reported that mice

Nucleus of the solitary tract (NTS). A brainstem region that receives and integrates peripheral afferent inputs from the baroreceptors, chemoreceptors and subdiaphragmatic organs of the gastrointestinal tract. The NTS projects selectively to the paraventricular nucleus of hypothalamus or caudal ventrolateral medulla to modulate sympathetic outflow.

T_H1 and T_H2 responses CD4+ T cells can be divided into two subsets on the basis of their pattern of cytokine production. The T_H1 response is characterized by the production of IFNγ and is generally more effective against intracellular pathogens, whereas the T_H2 response is characterized by the production of IL-4 and is generally more effective against extracellular bacteria and parasites.

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.

that were raised in a germ-free environment rarely displayed this disease, whereas all those that were conventionally housed died of the disease[100]. Similar results were observed in the kd/kd mouse model of collapsing glomerulopathy, which spontaneously develops interstitial nephritis[79]. Transfer of these mice from specific pathogen-free (SPF) conditions to a germ-free environment resulted in a marked decrease in the incidence of this disease.

As gut dysbiosis and altered gut pathology are associated with hypertension, and hypertension is an important factor that contributes to the development of CKD, the finding that changes in the composition of the gut microbiota (TABLE 1) are associated with CKD and ESRD is not surprising[101,102]. Compared with healthy individuals, a decrease in culturable anaerobic bacteria was observed in the faeces of patients with stage 3–4 CKD[103]. By contrast, an increase in culturable aerobic bacteria was reported in the faeces of patients with CKD who were not yet on dialysis compared with healthy adults[104]. As culture of most gut bacteria is not currently possible, the fact that these findings were confirmed using non-culture-dependent methods, such as PCR or pyrosequencing, is reassuring. In addition, patients with ESRD and healthy individuals had distinct faecal microbial compositions, characterized by differences in the abundance of 190 microbial operational taxonomic units, akin to bacterial species[101]. Rats with CKD induced by 5/6 nephrectomy also differed substantially from sham controls in their abundance of bacterial taxa and showed increases in blood pressure, serum urea and creatinine levels and urinary protein levels[101].

In a study that included 30 patients with ESRD not on dialysis, bacterial DNA was detected in the blood of six (20%) patients and the bacterial genera found in the blood were overgrown in the guts of these patients[105]. Moreover, the levels of C-reactive protein and IL-6 (biomarkers of low-grade inflammation) were significantly higher in patients with circulating bacterial DNA than in those in whom bacterial DNA was not detected. These findings suggest that overgrown bacteria translocate from the gut to the blood, where they contribute to increased levels of low-grade inflammation and thus exacerbate CKD pathology.

Although different sequencing methods and bacterial taxonomic levels have been used, studies have consistently reported that animals and patients with CKD had decreases in the genus *Lactobacillus* in their gut microbiota[101,106], whereas the levels of the Enterobacteriaceae family were increased[101,105]. In patients with ESRD in China, a switch from enterotype 2 (Prevotella dominant) to enterotype 1 (Bacteroides dominant) was associated with a decrease in butyrate-producing bacteria[107]. This shift in enterotype is characterized by a change in predominant microbial metabolism from saccharolytic to proteolytic fermentation.

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 microbiota[106]. These species have a gene that encodes a tryptophanase–tyrosine phenol-lyase, suggesting that they have an important role in the production of uraemic toxins. To date, more than 80 uraemic toxins have been

Uraemic toxins
Various compounds, mainly derived from the gut microbiota, that accumulate in the blood and tissue with progression of renal failure. Some compounds exhibit high affinity for albumin and are difficult to remove by haemodialysis.

reported to accumulate in patients with CKD[108]. Most of these toxins are widely considered to contribute to uraemic syndromes. For example, the plasma levels of trimethylamine *N*-oxide (TMAO), an amine oxide metabolite of trimethylamine (TMA) that is associated with an increased risk of adverse cardiovascular events[109], are elevated in patients with CKD compared with levels in healthy individuals[110]. Consistent with this finding, a phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt) analysis showed that the expression of three genes involved in the production of TMA was also significantly increased in the gut microbiota of patients with CKD[110]. Antibiotic-treated mice that received FMT from patients with CKD showed notable elevations of TMAO in their plasma compared with mice that received FMT from healthy individuals, indicating a critical role of gut dysbiosis in the overproduction of TMAO in CKD[110]. Unfortunately, glomerular filtration rate (GFR) was not measured in these mice; therefore, the role of gut dysbiosis in the initiation and progression of CKD remains to be determined.

The gut–kidney axis

The gut–kidney axis can be subdivided into metabolism-dependent and immune pathways[9]. The metabolism-dependent pathway is primarily mediated by metabolites produced by the gut microbiota that have the capability to regulate host physiological functions. In the immune pathway, components of the immune system (for example, lymphocytes, monocytes and cytokines) have a critical role in communication between the gut and the kidney (FIG. 2). 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. Diet is increasingly recognized to be a fundamental regulator of gut microbiomes. Dietary fermentable fibres, rather than protein, are the main source of energy for gut epithelial cells[111]. With sufficient supply of dietary fibres, the protein-derived α-amino nitrogen is almost totally incorporated into the faecal biomass. Lack of dietary fibres or excessive protein or animal fats leads to overaccumulation of α-amino nitrogen, which can be converted into uraemic toxins by the gut microbiota[112]. 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[113]. Colonic transit time is a modifiable determinant of uraemic toxin production[114]. A prolonged transit time decreases the availability of carbohydrates in the colon, facilitating increased protein fermentation and expanding the proteolytic bacterial population[9]. Therefore, the colonic microbiota makes a considerable contribution to the production of uraemic toxins.

In CKD, a reduction in renal filtering capacity results in the deposition and accumulation of waste products in the blood. Accumulation of products of protein fermentation (for example, α-amino nitrogen) in the intestine and blood increases the gut intraluminal pH, deranges gut homeostasis and triggers intestinal disorders[102]. In addition, as renal function declines, the colon replaces the kidney as the primary site of excretion of urea and uric acid[115]. Constant exposure of colonic epithelial cells to urea reduces their viability and decreases epithelial barrier function in vitro[116] and disrupts colonic tight junction proteins (for example, claudin 1, occludin and zonula occludens 1) both in vitro and in vivo[116,117]. Consequently, the levels of endotoxins and bacterial products in the circulation are elevated in patients with CKD compared with healthy individuals[118,119]. Deficits in renal function associated with a leaky gut exacerbate the accumulation of metabolic wastes in the blood and may eventually cause uraemia.

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[120], 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[7]. 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.

The relationship between the bone marrow, cardiovascular system, hypertension and CKD has long been recognized[15,121]. 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 effect[15]. In a clinical setting, renal dysfunction has been found in recipients of bone marrow transplants[122], suggesting a contributory role of the bone marrow in the initiation of kidney inflammation. As the levels of pro-inflammatory cytokines positively correlate with the development of albuminuria and proteinuria, early intrarenal inflammation has been suggested as an important pathogenic mechanism in the onset of kidney disease[123]. 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 CKD[125]. Evidence also indicates that multipotent cells in bone marrow repair damaged tissues, including the vasculature and kidney, by undergoing proliferation, mobilization, differentiation and eventually incorporation into these tissues[126–128].

After exiting from the bone marrow, mature immune cells in the gut are activated by the gut microbiota in peripheral lymphoid organs, such as GALT[129]. Gut permeability leads to accumulation of bacteria and bacterial products in the circulation and substantially contributes to chronic and systemic low-grade inflammation.

Low-grade inflammation has a critical role in the maintenance of many chronic diseases, including hypertension and CKD[130,131]. A number of studies have

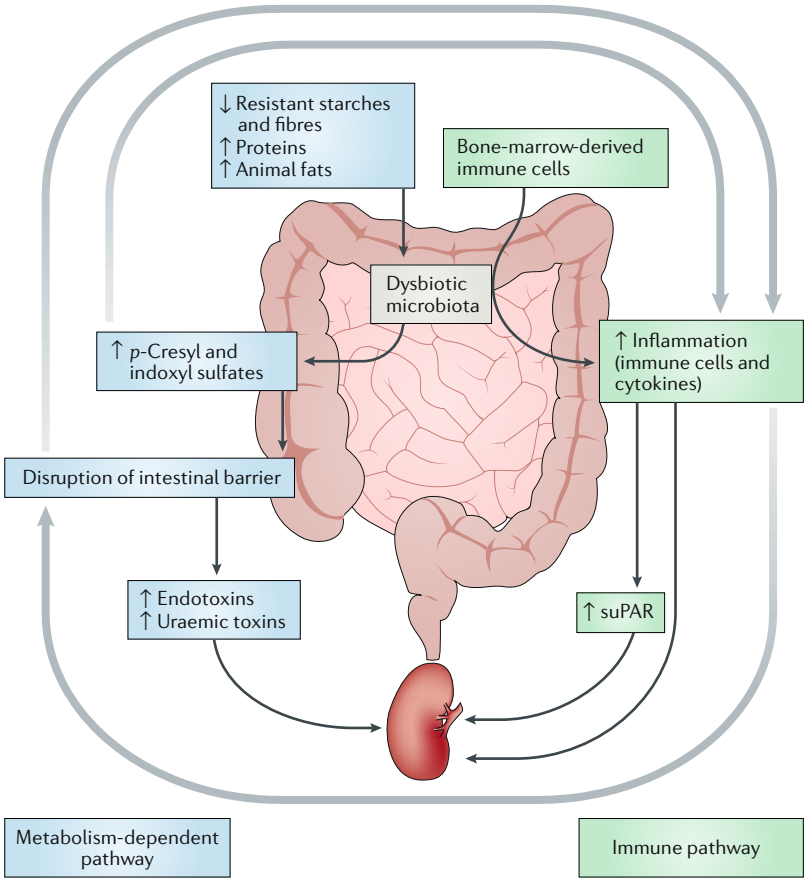

Fig. 2 | **The metabolism-dependent and immune pathways of the gut–kidney axis.** In the metabolism-dependent pathway, dysbiosis induced by an imbalanced diet (for example, a diet that is low in dietary fibres and high in protein and animal fats) leads to overproduction and accumulation of *p*-cresyl and indoxyl sulfates in the intestine. This accumulation disrupts the gut barrier and thus increases gut permeability. Consequently, influx of endotoxins and uraemic toxins into the kidney via the circulation contributes to renal inflammation. In the immune pathway, immune cells originating from the bone marrow encounter dysbiotic microbiota and become overactivated within the intestine. Inflammatory cells, cytokines and soluble urokinase plasminogen activator surface receptor (suPAR) generated in the gut contribute to renal inflammation via the circulation. Crosstalk between metabolism-dependent and immune pathways is achieved through the contributory effects of dysbiotic metabolites on intestinal and renal immunity, inflammation-induced gut barrier disruption and the resultant influx of dysbiotic metabolites into the kidney through the circulation.

demonstrated contributory roles for macrophages[132], T cells[133] and B cells[134] in the genesis of hypertension. For example, the blood pressure of germ-free mice is comparable to that of conventionally raised mice[8], but angiotensin-II-induced increases in blood pressure are blunted in germ-free mice, likely owing to inefficient induction of oxidative stress and inflammation by angiotensin II[8]. In the prehepatic portal hypertension model, mice with absent intestinal bacteria exhibited lower portal pressure than controls with intestinal microbiota; this lower portal pressure was associated with reduced densities of intestinal lymphatic and blood vessels[135]. These data suggest the involvement of gut microbiota in the immune-cell-mediated genesis of hypertension.

The gut microbiota also has a crucial role in systemic metabolic syndrome and CKD[136–138]. Mice with adenine-induced renal failure housed in germ-free conditions had significantly lower levels of uraemic toxins than those housed in SPF conditions[138]. However, more severe renal damage was observed in the germ-free mice, presumably owing to reduced production of renoprotective SCFAs and inefficient utilization of amino acids compared with the SPF mice. This finding highlights the importance of maintaining an exquisitely balanced gut microbiota in CKD.

Communication between the pathways. The gut microbial metabolites *p*-cresyl sulfate and indoxyl sulfate bind albumin in the circulation[139] and are rapidly released from albumin immediately before being eliminated by tubular secretion[140]. The levels of *p*-cresyl and indoxyl sulfates increase concomitantly with CKD progression[141], and this increase has been attributed to decreased renal clearance[142] and increased production due to gut dysbiosis[138]. Gut-microbiota-derived uraemic toxins induce inflammation in the gastrointestinal tract, as evidenced by increased intestinal permeability in patients and animals with uraemia[143,144], increased penetration of bacteria across the intestinal wall in uraemic rats[145], the detection of endotoxaemia in patients with ESRD[105,119] and histological evidence of chronic enterocolitis in patients on dialysis[146]. Pathological accumulation of *p*-cresyl and indoxyl sulfates in the circulation results in systemic inflammation in blood vessels, endothelial dysfunction[147], insulin resistance[148] and activation of the renin–angiotensin–aldosterone system[149], which are all common features of hypertension and CKD. Furthermore, high concentrations of uraemic toxins in plasma due to CKD lead to increased concentrations of these toxins in the gastrointestinal tract, where they affect the composition of the gut microbiome[106]. 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 *p*-cresol-forming bacteria, contraction of families of SCFA-producing bacteria has been reported in patients with ESRD compared with healthy individuals[150,151]. These changes included reductions in the Lactobacillaceae and Prevotellaceae families, which express genes that encode butyrate-forming enzymes (phosphotransbutyrylase and butyrate kinase)[150], and in the butyrate-producing bacteria *Roseburia* spp. and *Faecalibacterium prausnitzii*[151]. Beneficial effects of butyrate on colonic inflammation have been reported[152]. Moreover, in uninephrectomized rats, infusion of sodium butyrate into the intramedullary area of the kidney resulted in improvement in angiotensin-II-induced glomerulosclerosis, renal fibrosis and urinary albumin levels and led to decreases in the levels of (pro)renin receptor, angiotensinogen, renin, angiotensin-I-converting enzyme and renal inflammatory markers[153]. In the deoxycorticosterone acetate (DOCA) hypertension model, a high-fibre diet that promoted the growth of acetate-producing bacteria and acetate supplementation attenuated renal fibrosis[95]. These findings indicate that SCFAs regulate immune responses and attenuate kidney pathology.

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	8,89,90,101,103–106
• 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.

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[15,87,91,154–159]. Emerging evidence has led to expansion of this concept to that of the brain–gut–kidney axis[9,118,160,161] (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).

Sympathetic nervous system and brain. The occurrence of increased SNS activity in hypertension and CKD is well established[83,162]. Efferent fibres of the SNS innervate the renal vasculature and juxtaglomerular cells, and afferent fibres convey mechanical and chemical information from the kidney[163]. Rapid turnover of noradrenaline in autonomic brain centres has been shown in rats with 5/6-nephrectomy-induced CKD[164]. In addition, the sympathetic dampening agent moxonidine lowers urinary albumin excretion and reduces glomerulosclerosis in subtotally nephrectomized rats[165]. 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[166].

The SNS directly innervates both primary (bone marrow) and secondary (spleen) immune organs[80]. Expression of adrenergic receptors on immune cells residing in immune organs indicates regulatory effects of sympathetic catecholamines on the immune system[154,167]. Both anti-inflammatory and pro-inflammatory effects of adrenergic signalling have been demonstrated, depending upon the subtype of adrenergic receptors expressed[167], the level of activation of specific cell types and the stage of disease progression[168]. However, persistent activation of the SNS results in changes in signalling within immune organs and cells towards pro-inflammatory pathways[168], as observed in hypertension and CKD[169,170].

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[163]. An impaired renorenal reflex in hypertension and CKD leads to augmented sympathetic excitation to the blood vessels, heart and kidney[161].

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 outflow[171]. Neuroinflammation in central sympathetic regions is observed in hypertension[172,173], and the central renin–angiotensin system has an important role in mediating neuroinflammation[174]. In CKD, indoxyl sulfate increases neuroinflammation, which may facilitate the neurodegeneration that has been observed in some patients[175]. In the 5/6 nephrectomized mouse, renal denervation lowers blood pressure, and reduced sympathetic nerve activity is associated with increased GABA input into the PVN[176], indicating crosstalk between the kidney and the brain in the context of hypertension and CKD.

In cross-sectional and longitudinal studies, each 10 ml/min/1.73 m^2 reduction in estimated GFR (eGFR) below 60 ml/min/1.73 m^2 was associated with an approximately 11% increase in the prevalence of cognitive impairment[177,178]. Other studies failed to identify statistically significant correlations between eGFR and cognitive impairment but reported that albuminuria and the rate of eGFR decline were associated with cognitive decline[179–181]. Uraemic guanidino compounds with neuroexcitatory effects have been found in brain regions responsible for cognition (thalamus and mammillary bodies) in patients with CKD[182], suggesting a direct role of these compounds in cognitive impairment.

Another potential mechanism that links cognitive impairment to the gut–brain–kidney axis is dysregulation of the tryptophan kynurenine pathway. Such dysregulation was associated with eGFR decline and CKD incidence in a population-based study[183]. Germ-free mice had reduced kynurenine pathway activity that was normalized by colonization of a conventional gut microbiota[184]. This finding indirectly suggests a role of immune activation in the regulation of the kynurenine pathway. Activation of Toll-like receptor 3 (TLR3) in peripheral monocytes facilitates production of the metabolite quinolinic acid[185] (an end product of the kynurenine pathway), which is an excitotoxin with high affinity for glutamate *N*-methyl-d-aspartate (NMDA) receptors[186]. As TLR3 is abundantly expressed in the

Paraventricular nucleus of hypothalamus
(PVN). An important region in the central nervous system that contributes to sympathetic nervous system efferent transmission. Stimulation of the PVN with inflammatory cytokines or angiotensin II increases sympathetic outflow.

Rostral ventrolateral medulla
(RVLM). The RVLM receives projections from the paraventricular nucleus of hypothalamus and caudal ventrolateral medulla to control sympathetic activity associated with cardiovascular functions.

Kynurenine pathway
The kynurenine pathway catabolizes approximately 95–99% of ingested tryptophan that is not utilized for protein synthesis in mammalian cells. Dysregulation of the kynurenine pathway results in overproduction of quinolinic acid, which has been implicated in inflammatory neurological diseases, such as Alzheimer and Huntington diseases.

brain[187], abnormal activation of NMDA receptor signalling by quinolinic acid might be at least partially responsible for numerous neurological diseases[186,188].

Abnormal sympathetic drive to the bone marrow in hypertension and CKD dramatically shifts the immune properties of haematopoietic cells to a pro-inflammatory state, and the release of these inflammatory immune cells from the bone marrow contributes to the pathogenesis of hypertension and CKD[15,156,189]. Therefore, the immune pathway of the brain–kidney axis involves input from the CNS and/or SNS to the bone marrow and the effects of inflammatory cells released from the bone marrow on the kidney.

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 interference[190–192]. The gut microbiome has been shown to induce host epigenetic changes that might contribute to the development of cancer[193,194], and notable changes in epigenetic modifications have been reported in hypertension and CKD[85,195]. For example, podocyte-specific inactivation of Dicer, one of the enzymes responsible for production of microRNAs, results in proteinuria and glomerulosclerosis[196]. 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[197]. 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 promoter[198]. 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[199].

In germ-free mice, colonization by gut microbiota normalized the deregulation of microRNA in the amygdala and prefrontal cortex of the brain[200], indicating an epigenetic connection between the gut and the brain. The chromatin accessibility of intestinal intraepithelial lymphocytes was quantitatively changed in germ-free mice colonized by conventional microbiota, resulting in determination of functional features of host immune cell lineages[201]. Epigenetic inheritance may explain much of the heritability of hypertension[202]. For example, in mice, perinatal exposure to a high-fat, high-sucrose diet epigenetically primed the central renin–angiotensin system leading to hypertension, potentially owing to limited plasticity of the autonomic system[202]. Unfortunately, the effects of this diet on the gut microbiome were not investigated in this study.

Together, the available data suggest that epigenetic changes mediated by the gut microbiota are involved in the pathogenesis of dysbiosis-associated hypertension and CKD. However, further studies are needed to provide direct evidence of a role of the microbiota in the induction of host epigenetic changes in these diseases.

Excitotoxin
A collection of chemical compounds that overactivate and exhaust neurons by binding to their receptors.

Pathogenesis of hypertension and CKD. On the basis of the available evidence, we propose a triangular brain–gut–kidney hypothesis for the pathogenesis of hypertension and CKD (FIG. 3). Environmental, dietary and other pro-hypertensive and/or CKD-relevant stimuli are perceived at the autonomic brain regions, where they are integrated into signals that lead to increased sympathetic nervous drive to the gut and bone marrow. Sympathetic drive to the bone marrow shifts the balance of physiological inflammation towards overactivation, which perpetuates low-grade systemic inflammation and results in a reduction in the production of pluripotent stem cells from the bone marrow for vascular, intestinal and renal repair. Activation of the SNS initiates a sequence of events in the gut that leads to increased gut wall permeability, dysbiosis, migration of pro-inflammatory cells from the bone marrow and the release of microbial products and metabolites into the blood. The resulting imbalance in the plasma metabolome adversely affects various cardio-renal tissues; for example, accumulation of uraemic toxins or a lack of SCFAs leads to activation of systemic and tissue inflammation[147,203]. In addition, activation of renal sympathetic nerve activity might directly influence renal physiology, altering body fluid balance and plasma metabolite secretion and retention. These events culminate in the development of CKD and hypertension. Consistent with our hypothesis, transplantation of bone marrow[15,122], gut microbiota[90] or kidney[204] has been demonstrated to induce disorders not only in the organs of the proposed brain–gut–kidney axis but also in the interconnected pathways of this axis. Therefore, the brain–gut–kidney hypothesis represents a novel conceptual shift that can potentially be applied in clinical settings.

Potential therapeutic strategies

According to the brain–gut–kidney axis hypothesis, treatments that target the brain, the SNS or the gut could potentially be beneficial for patients with hypertension and/or CKD. Consistent with this postulate, intracerebroventricular administration of minocycline suppresses microglial and sympathetic activation and lowers blood pressure in animal models of hypertension[205]. Moreover, beneficial effects of renal denervation, which targets sympathetic drive, have been reported in patients with resistant hypertension and CKD[206,207]. Modulation of the gut microbiota reduces systemic inflammation and SNS activity, both of which contribute to hypertension and CKD[80,162,208]. Therefore, various approaches to modulate the gut microbiota are being explored for the treatment of these diseases.

Dietary interventions. Most patients with CKD are advised to limit their intake of sodium, protein, potassium, cholesterol and phosphorus, whereas patients with hypertension are advised to avoid sodium and cholesterol. By contrast, foods rich in fibre, vitamins and minerals are highly recommended. The Dietary Approach to Stop Hypertension (DASH) diet of the National Kidney Foundation was developed for the treatment of hypertension and kidney disease according to these principles[209].

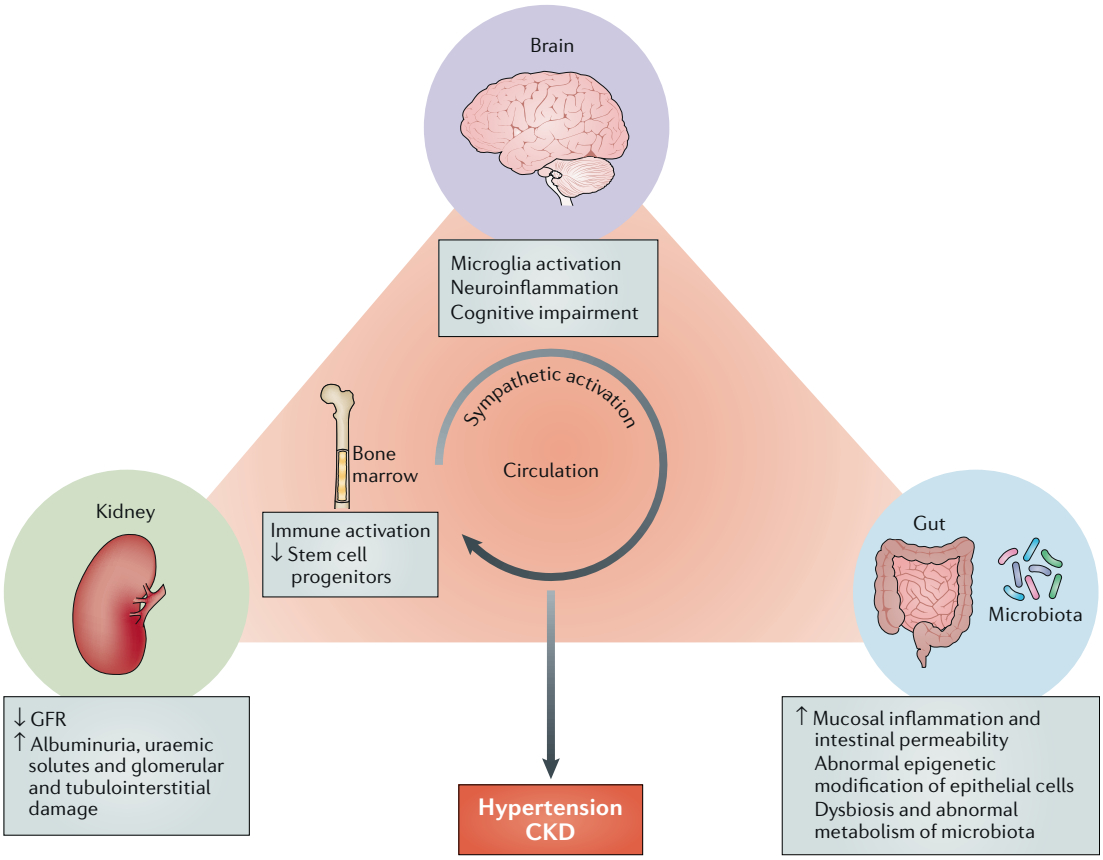

Fig. 3 | **The brain–gut–kidney axis hypothesis for the pathogenesis of hypertension and CKD.** Sympathetic activation is a common feature in disorders of the brain, gut and kidney. Persistent microglial activation and neuroinflammation in presympathetic regions of the brain responsible for sympathetic 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).

In DOCA-salt hypertensive mice, a high-fibre diet led to substantial reductions in both SBP and DBP (~20 mmHg)[95]. Clinical studies have shown a moderate blood-pressure lowering effect of dietary fibre[210,211]. Moreover, a meta-analysis of 25 randomized placebo-controlled trials reported that high versus low dietary fibre intake was associated with a modest but statistically significant reduction in DBP (1.65 mmHg) but not in SBP[97]. Importantly, more pronounced blood pressure reductions were found when the analysis was restricted to trials conducted in patients with hypertension (SBP 5.95 mmHg, DBP 4.2 mmHg) or to trials with long interventions (≥8 weeks; SBP 3.12 mmHg, DBP 2.57 mmHg).

A meta-analysis of 14 controlled feeding trials involving 143 participants with CKD showed that supplementation of dietary fibre intake significantly reduced serum levels of uraemic toxins, urea and creatinine[212]. Similarly, a study that investigated the association of dietary fibre intake with CKD-related parameters in 157 patients in China reported that a fibre intake of ≥25 g per day compared with <25 g per day was associated with a smaller reduction in eGFR and lower levels of serum C-reactive protein, indoxyl sulfate, cholesterol and IL-6 during 18 months of follow-up[213]. Thus, high fibre intake seems to retard loss of GFR and is negatively associated with cardiovascular risk. However, caution must be used when selecting high-fibre foods with high potassium contents. Therefore, a need exists to identify or formulate low-potassium, high-fibre foods for patients with CKD.

Probiotics, prebiotics and synbiotics. The therapeutic use of probiotics, prebiotics and synbiotics is an area of increasing interest among renal health-care professionals. A meta-analysis of nine clinical trials with a total of 543 participants demonstrated that probiotic consumption modestly but significantly reduced both SBP (3.65 mmHg) and DBP (2.38 mmHg) in populations with baseline BP ≥135/85 mmHg[98]. Probiotics that contained multiple rather than single species of bacteria,

Prebiotics
Food ingredients that promote growth of beneficial microorganisms.

Synbiotics
Combinations of prebiotics and probiotics.

a longer duration of the intervention (≥8 weeks) and higher daily doses (≥10^{11} colony-forming units) were associated with more effective blood-pressure lowering in this study. Notably, the conclusions of the individual trials included in this meta-analysis were inconsistent, likely owing to substantial differences in participant numbers, baseline blood pressures, treatment durations and type and dose of probiotics.

Numerous clinical trials and experimental studies in CKD have shown that the administration of prebiotics, probiotics and synbiotics can reduce the levels of uraemic *p*-cresyl and indoxyl sulfates and inflammatory mediators[160,214,215] and attenuate colonic epithelial tight junction disruption[215], resulting in substantial improvements in endotoxaemia, blood urea nitrogen levels and quality of life[160,216]. A diet with high levels of resistant starch (a prebiotic) favourably altered the gut microbiota and caecal, serum and urine metabolite profiles in rats with adenine-induced CKD[217].

As the abundance of *Lactobacillus* is decreased in CKD[101,106], this bacterium is one of the most common probiotics used in CKD studies. In patients with uraemia undergoing haemodialysis, oral administration of a preparation of antibiotic-resistant lactic acid bacteria (known as Lebenin) restored the composition of the gut microbiota to normal and inhibited the accumulation of uraemic toxins in the blood[218]. Such beneficial effects of *Lactobacillus* could be the result of effects of this bacteria on the permeability and immune status of the gut epithelium.

Antibiotics. Manipulation of the gut microbiota through the use of antibiotics influences blood pressure and may be a useful intervention for hypertension control. For example, in rats with angiotensin-II-induced hypertension, minocycline administration changed the gut microbiota and lowered blood pressure[87]. Administration of propionate has also been reported to modulate blood pressure in mice, likely via binding to the G protein-coupled receptor 41 (GPR41) and olfactory receptor 78 (OLFR78; also known as OR51E2)[93,94]. In a case of patient with treatment-resistant hypertension, antibiotic therapy using a combination of vancomycin, rifampin and ciprofloxacin decreased SBP by ~70 mmHg in the absence of antihypertensive drugs[99].

As the kidney has an important role in the elimination of metabolites, drug use in patients with CKD requires caution to minimize the risk of adverse effects owing to the accumulation of active metabolites[219,220]. For example, antibiotic treatment of *Escherichia coli* O157:H7 infection increases the risk of haemolytic uraemic syndrome[221]. In contrast to *Lactobacillus*, the population of Enterobacteriaceae of the Proteobacteria phylum is expanded in CKD[101,105]. Bacteriophage therapy against Enterobacteriaceae has been proposed as an alternative strategy to antibiotics for controlling this bacterial population[222,223].

Faecal transplantation. FMT and transplantation of sterile faecal filtrate (FFT), which is enriched in all components of the gut contents except bacteria and particulate matter, are alternative approaches to modify the gut microbiota. To our knowledge, no studies of FMT or FFT for the treatment of patients with hypertension or CKD have been published to date. However, FMT and FFT have been utilized for the treatment of *Clostridium difficile* infection, which is a common complication in patients with CKD, particularly in those undergoing haemodialysis[224–226]. Following successful treatment of *C. difficile* infection by FFT transplantation, the gut microbiota of a patient with loss of renal function resembled that of the faecal donor with remarkable elimination of Proteobacteria, which had dominated before FFT[226]. The risk of secondary infection may be lower with FFT than with FMT, as FFT does not involve the transfer of live bacteria[226]. Further investigation is needed to understand how the various components of sterile faecal filtrate, including viruses (that is, bacteriophages sensu stricto), bacterial DNA and metabolites, lead to long-term changes in the gut microbiota.

Metabolite modulation. Haemodialysis removes most uraemic toxins with the exception of protein-bound uraemic toxins such as indoxyl sulfate and *p*-cresyl sulfate, which bind serum albumin[227]. The spherical carbon adsorbent AST-120 absorbs indole produced in the intestine and thereby reduces serum and urinary levels of indoxyl sulfate[228]. AST-120 has been approved as a treatment to delay the initiation of haemodialysis in patients with CKD in Japan but not in Europe or the United States, owing to a lack of proof of an unequivocal therapeutic benefit in large randomized clinical trials with hard renal and cardiovascular end points[228].

To date, metabolomics studies of hypertension are limited, but changes in lipid and fatty acid profiles have been reported[229]. In addition, numerous plasma metabolites have been associated with longitudinal eGFR[183] or cross-sectional eGFR decline[230] in the general population. In particular, metabolites of the spermidine and kynurenine pathways are associated with the gut microbiota as well as the physiology of the host[231,232]. Such metabolites are potential therapeutic targets for the prevention of disease progression in CKD.

Conclusions and future perspectives

The gut microbiota has a critical role in a variety of diseases, including hypertension and CKD. Thus, we propose expansion of our brain–gut axis hypothesis for the pathogenesis of hypertension to explain the role of communication between the gut, the brain and the kidney in CKD. Numerous studies have demonstrated pathways that connect the brain and the gut in hypertension, but relatively little is known about the role of brain–gut–kidney connections in CKD pathogenesis. In particular, whether sympathetic activation to the bone marrow and gut is increased in CKD and whether changes in kidney function are associated with increased gut permeability remain to be addressed. Further studies in the settings of hypertension and CKD are needed to elucidate the mechanisms and provide proof of concept for the brain–gut–kidney axis.

Potential therapeutic strategies for CKD and hypertension that target the gut microbiota are already being investigated. However, whether hypertension and

CKD are associated with specific gut microbial profiles and microbial metabolomes remains unclear. Such profiles could provide useful biomarkers for establishing disease diagnosis and severity as well as potential therapeutic targets. The gut epithelium is dynamic, has high regenerative capacity and is epigenetically modified by the gut microbiota and their metabolites[194]. Therefore, targeting epigenetic modification of epithelia might be a promising direct approach to control the progression and perhaps also the initiation of gut-dysbiosis-associated diseases. Large-scale, well-controlled translational and preclinical studies are required to evaluate the therapeutic implications of the brain–gut–kidney hypothesis.

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Competing interests
The authors declare no competing interests.