Kidney360

Renal Sensing of Bacterial Metabolites in the Gut-kidney Axis

Orestes Foresto-Neto [1,2] *Bruno Ghirotto,*[1] *and Niels Olsen Saraiva Câmara* [1,2]

Abstract

Seminal works have now revealed the gut microbiota is connected with several diseases, including renal disorders. The balance between optimal and dysregulated host-microbiota interactions has completely changed our understanding of immunity and inflammation. Kidney injury is associated with accumulation of uremic toxins in the intestine, augmented intestinal permeability, and systemic inflammation. Intestinal bacteria can signal through innate receptors and induce immune cell activation in the lamina propria and release of inflammatory mediators into the bloodstream . But the gut microbiota can also modulate immune functions through soluble products as short-chain fatty acids (SCFAs). The three most common SCFAs are propionate, butyrate, and acetate, which can signal through specific G-protein coupled receptors (GPCRs), such as GPR43, GPR41, and GPR109a, expressed on the surface of epithelial, myeloid, endothelial, and immune cells, among others. The triggered signaling can change cell metabolism, immune cell activation, and cell death. In this study, we reviewed the gut-kidney axis, how kidney cells can sense SCFAs, and its implication in kidney diseases.

KIDNEY360 2: 1501–1509, 2021. doi: https://doi.org/10.34067/KID.0000292021

Introduction

The microbes that inhabit the gut, which include fungi, bacteria, viruses, archaea, and protozoans, outnumber human cells, and play a significant role in the regulation of the host immune response (1). The gut microbiota displays symbiotic relationships with humans and, depending on host genetics and environmental factors, they can be beneficial, such as mutualism and commensalism, or harmful in the case of parasitism. The balance between optimal and dysregulated host-microbiota interactions has completely changed our understanding of immunity and inflammation, and has shed light on the physiopathology of several disorders, including kidney diseases. Increased amounts of pathobionts in the gut may lead to systemic inflammation and affect distant organs, because the effect of the microbiota in immune system extends far beyond the gastrointestinal tract (1,2).

The most abundant bacteria phyla found in the human intestine include gram-positive *Firmicutes* and *Actinobacteria*, both associated with the *in-situ* promotion of homeostasis, and the gram-negative *Bacteroidetes* and *Proteobacteria*, which display LPS molecules on their surfaces, and therefore can trigger immune cell activation. The immune system has developed a series of evolutionary strategies to restrain the microbiota, limiting bacterial translocation and tissue inflammation in a steady-state condition, including mucus, high production of immunoglobulin A, induction of regulatory responses, and synthesis of antimicrobial peptides (1–3). In this sense, disruption of gut homeostasis has been associated with the development of several inflammatory diseases, such as inflammatory bowel (4), autoimmune (5), cancer (6), and kidney diseases (7).

The human intestine has epithelial and biochemical barriers that keep the microbiota apart from the host's immune cells; however, some commensals can be associated with the intestinal epithelium and modulate innate and adaptive immune responses. Innate immunity participates in the pathogenesis and progression of kidney diseases (8,9). Accordingly, it has already been demonstrated that the microbiota regulates the production of pro–IL-1β in intestinal resident macrophages through myeloid differentiation primary response 88 (MyD88) signaling (1,10). Additionally, the segmented filamentous bacteria drive the small intestinal accumulation of Th1 and Th17 cells (1), both involved in renal inflammation (11).

Products from the bacteria metabolism can affect the kidneys by several mechanisms. Some species of gut bacteria produce uremic toxins, whereas protective gut microbiota produce short-chain fatty acids (SCFAs). They can modulate the inflammatory response by several mechanisms in the intestine and other organs, including kidneys. In particular, they participate in renal physiology through the regulation of the renin-angiotensin system and cell death (11–13). In this perspective article, we explore how the microbiota-derived metabolites affect the gut-kidney axis, highlighting the role of renal SCFAs sensing in this process and in the context of kidney diseases.

[1]Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Brazil
[2]Nephrology Division, Department of Medicine, Federal University of São Paulo, Brazil

Correspondence: Niels Olsen Saraiva Camara, Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Avenue Prof. Lineu Prestes 1730, ICB IV, Sala 238, 05508000, Cidade Universitária, São Paulo, Brazil. Email: niels@icb.usp.br

Exploring the Gut-kidney Axis

An intimate connection between gut and kidney, which is called the gut-kidney axis, has been proposed in the last few years, emphasizing a bidirectional talk (11,14) (Figure 1). Kidney injury is associated with the accumulation of uremic toxins in the intestine and increased intestinal permeability. When high levels of urea reach the gut, urease-containing bacteria convert it into ammonia and ammonia hydroxide, which elevates the intestinal lumen pH, and causes mucosal damage and inflammation (7,15). In addition, abnormal kidney function and deficiency in renal excretion leads to the augmented secretion of uric acid and oxalate in the colon (16,17), favoring the proliferation of microbes capable of metabolizing these substrates. Both gut secretion and bacterial metabolism reduce the circulatory levels of these organic acids and can prevent crystal formation in kidneys (18,19). Besides its beneficial effects, metabolic changes in the intestinal microbiota can result in dysbiosis. Gut bacteria harboring p–cresol- and indole-forming enzymes are overgrown in patients with kidney diseases, and promote fermentation of tyrosine and tryptophan, with a consequent increase in circulatory levels of indoxyl sulfate, p-cresol, and p-cresyl sulfate (20). Healthy renal tubules drain these uremic toxins via organic anion transporters (OATs) localized at the basolateral and apical cell membranes (21). In addition, proximal tubules can sense uremic toxins through EGF receptors and promote their secretion by upregulating OAT1 activity (22). However, once uremic toxins such as indoxyl sulfate and p-cresol enter the renal tubular cells *via* OATs, they can stimulate the production of TGF-β1, chemokines, and free radicals, which are involved in physiologic cell processes, but can also induce oxidative stress and inflammation in both tubular and glomerular compartments, leading to interstitial fibrosis and sclerosis, when in higher concentrations (21).

Dysbiosis and lesions on the intestinal epithelium result in a loss of intestinal cell tight junction proteins and reduced mucus production, both associated with intestinal barrier dysfunction (23). These facilitate the translocation of bacteria and their toxins into the circulation, which can result in systemic inflammation or reach the kidneys (24). LPS from bacteria can be recognized by toll-like receptor-4 and trigger the signaling through MyD88, activating NF-κB and mitogen-activated protein kinase, promoting kidney inflammation (14). Our group has recently shown the deleterious effects of gut microbiota dysbiosis in kidney disease is at least in part dependent on the MyD88 signaling activation in intestinal epithelial cells and the consequent release of proinflammatory cytokines and chemokines by the intestinal epithelium (25). Taking into account that deficient excretion of renal function–associated metabolites can influence the gut microbiota composition and the products derived from the altered microbiome exert effects on kidneys, we can assume dysbiosis and kidney damage constitute a vicious cycle in kidney diseases (7).

In the last decade, it has been proposed that intestinal dysbiosis-related liver damage also contributes to the progression of kidney disease, making rational the existence of a gut-liver-kidney axis (Figure 1). Intestinal barrier dysfunction allows bacterial translocation to the liver and activation of hepatocytes and immune cells, such as Kupffer cells, by bacterial components, favoring secretion of TNF-α, IL-1β, and IL-6 (26). In addition, gut microbiota metabolizes dietary choline, L-carnitine, and betaine (found in animal products such as meat and eggs, or plants such as spinach and beets), and produce trimethylamine, which is absorbed into portal circulation and oxidized by hepatic flavin-containing monooxygenases to generate trimethylamine N-oxide (TMAO). Increased TMAO levels in the blood due to variations in diet and microbiota composition, or loss of renal function (impaired excretion capacity) have been associated with reduced cholesterol clearance, increasing cholesterol-laden foam cells, and development of atherosclerotic plaques, which can affect the kidneys (27). Although it remains unclear whether TMAO directly participates of the pathogenesis of human kidney disease, or is simply a biomarker of underlying pathologies, experimental studies support the notion that TMAO plays a role in kidney and liver damage (28). Proinflammatory, prooxidant, and profibrogenic factors released in the circulation by the damaged liver affect the intestinal barrier integrity and the gut microbiota, promoting vascular and kidney tissue injury and contributing to the progression of kidney disease (26,29). In contrast, kidney dysfunction leads to accumulation of urea and uric acid, which enhance intestinal dysbiosis while impairing liver homeostasis (26).

Unlike uremic toxins, SCFAs are associated with protection against the progression of liver and kidney diseases (30,31). Although a high-fat diet is correlated with increased levels of LPS in the blood and inflammation, appropriate intake of dietary fiber is associated with higher production of SCFAs, and improvement in damaged kidney by regulating the immune response or directly interacting with kidney cells (31–33).

Microbiota-derived SCFAs in the Control of Immune Cell Metabolism: A Link to Renal Inflammation

Immune cells participate in the development of inflammatory kidney diseases through recognition of danger signals, activation of proinflammatory cascades, and release of cytokines and chemokines (11). In this context, it has been described that SCFAs produced by the gut microbiota can modulate immune cell activation in the kidneys (10,11) (Figure 2).

SCFAs are metabolites produced mainly by the gut microbiota, belonging to the *Clostridia* class, (1) through anaerobic fermentation of dietary fibers or through metabolism of amino acids, such as leucine, arginine, glycine, and lysine (34), which play a significant role in the regulation of the *in-situ* and systemic immune responses (2). The three most common SCFAs are propionate ($C_3H_6O_2$), butyrate ($C_4H_8O_2$), and acetate ($C_2H_4O_2$), which can signal through specific G-protein coupled receptors, such as GPR43 and GPR41, with a half maximal effective concentration (EC_{50}) of approximately 0.5 mM (35,36), and GPR109a, with an EC_{50} of 1.6mM for butyrate (37). These relative low potencies favor their selective activation in the gut, where the levels of SCFAs are higher, around 20–60 mM (38). These receptors are expressed on the surface of epithelial, myeloid, endothelial, and immune cells, among others (39). GPR41 can be found in adipose tissue, spleen, lymph nodes, peripheral blood mononuclear cells, kidneys, and pancreatic tissue, whereas GPR43 is located in the colonic-ileal region, adipose tissue,

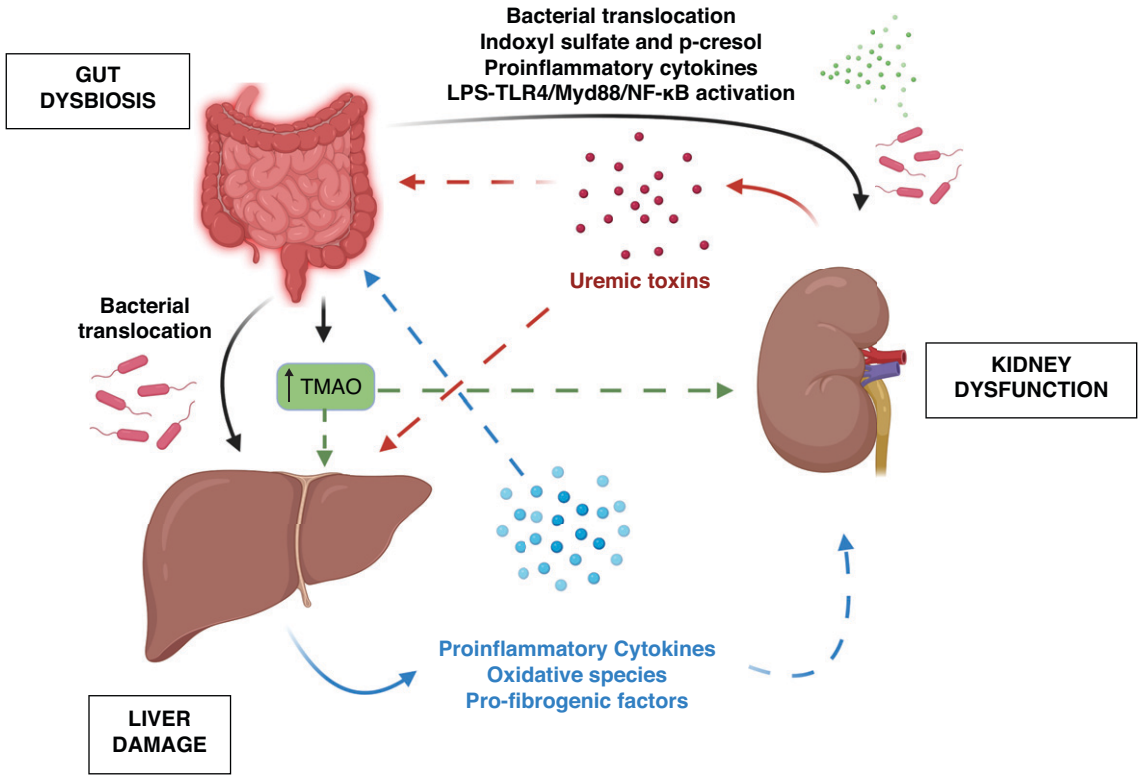

Figure 1. | **Gut microbiota dysbiosis and bacterial metabolites in the gut-liver-kidney axis.** Gut dysbiosis induces bacterial translocation to the liver, where it promotes the release of proinflammatory cytokines, oxidative species, and profibrogenic factors. These molecules can enhance the gut dysbiosis and induce kidney damage. Renal dysfunction results in the accumulation of uremic toxins, which increase gut dysbiosis and liver damage. In contrast, gut dysbiosis promotes an increased release of indoxyl sulfate, p-cresol, LPS, and proinflammatory cytokines (due to the activation of the TLR4/MyD88/NF-κB pathway by LPS), which promote kidney damage. Also, gut dysbiosis increases the production of TMAO, which can promote further liver damage and trigger kidney dysfunction. TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response 88; TMAO, trimethylamine N-oxide.

kidneys, and on the surface of monocytes (38,40). GPR109a is located mainly in the adipose tissue, but can also be found in the colon, spleen, kidneys, and on the surface of macrophages (37,40). Signaling pathways downstream of these receptors are mediated by cAMP, inositol trisphosphate, or ERK1/2 proteins (41). SCFA transport can also be mediated by the H^+/monocarboxylate transporters (MCT) or the Na^+/MCT (SMCT). Several MCT have been characterized in the human intestine by the presence of either mRNA or protein, including MCT1 (apical membranes), MCT4, and MCT5 (basolateral membranes, mainly in the distal colon), also referred to as SLC16A1, SLC16A3, and SLC16A4, respectively (42). SMCT are mainly located in the apical portion of the colon, where they regulate the transport of SCFAs from the luminal site of the colon to the intestinal epithelial cells (43). Interestingly, human SMCT1 (also known as SLC5A8) has already been associated with tumor suppression, because its inactivation correlates with the development of human colorectal cancer (44).

Other less abundant SCFAs include formate (CH_2O_2), isobutyrate ($C_4H_8O_{20}$), valerate ($C_5H_{10}O_2$), isovalerate ($C_5H_{10}O_2$), and 2-methylbutanoate ($C_5H_{10}O_2$), whose roles have been less explored in the literature, and deserve future investigation. GPR41 and GPR43 bind to acetate, propionate, butyrate, and formate (45), whereas GPR109a is mainly sensitive to butyrate (46). Formate can be transported through the Cl^-/formate exchanger, SLC26A6 (47); isobutyrate and valerate can be transported by SMCT1 (SLC5A8) (48); acetoacetate and beta–d-hydroxybutyrate can be transported mainly through SLC5A8 (49) and SLC5A12, although the latter has a lower affinity (50).

Immune cells display transporters and receptors for SCFAs, helping maintain homeostasis through hampering the inflammatory response in the context of several diseases. It has already been demonstrated that SCFAs induce IL-10 and expansion of $Foxp3^+$ regulatory T cells in the gut of patients with inflammatory bowel diseases (51). Patients with type 2 diabetes have a decreased level of SCFA-producing bacteria (52), indicating that, in some diseases, complex interactions between the host immune system and the microbiota may contribute to inbuilt chronic inflammation.

In innate immunity, butyrate shifts macrophage metabolism toward oxidative phosphorylation (OXPHOS) and lipid metabolism inducing their polarization to the anti-inflammatory M2 profile (53). Recent studies have focused on the molecular mechanisms through which the microbiota-derived SCFAs can regulate the metabolism of several immune cell types. During adaptive immune responses, SCFAs act on $CD8^+$ T cells, increasing OXPHOS,

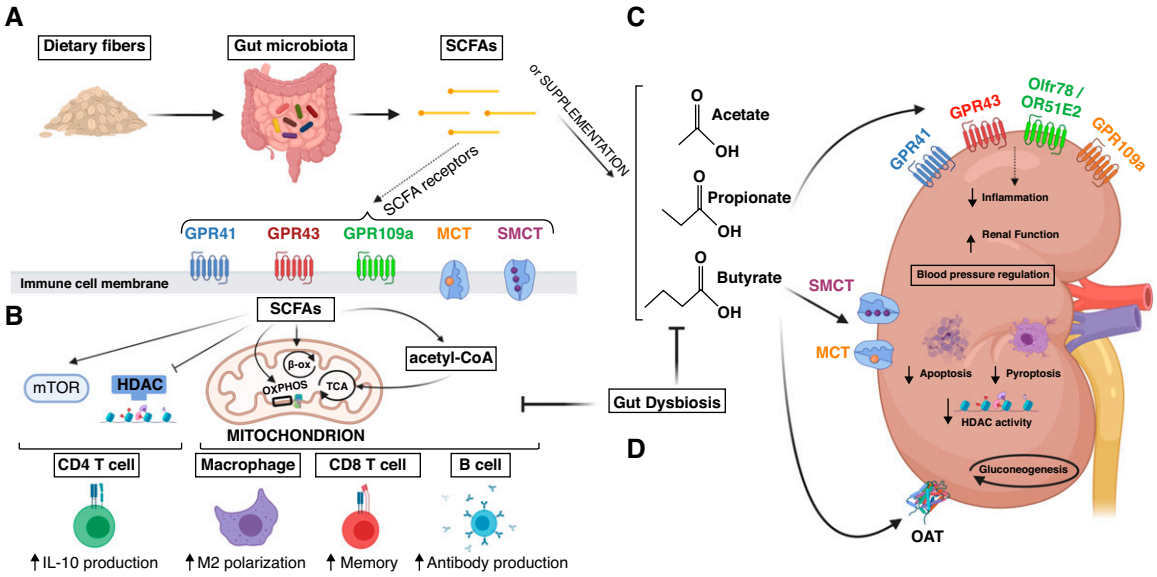

Figure 2. | **SCFAs at the control of immunometabolism and kidney function.** (A) The uptake of dietary fiber induces the production of SCFAs by the commensal gut microbiota, which signal through the G-protein coupled receptors GPR41, GPR43, and GPR109a or *via* the MCT and SMCT and regulate several metabolic processes. (B) Regarding immune cells, SCFAs activate the mTOR signaling pathway and inhibit HDAC activity, leading to increased IL-10 synthesis in CD4 T cells. They also directly influence the mitochondrial bioenergetics, by enhancing oxidative phosphorylation and β oxidation. Finally, SCFAs can be converted into acetyl-CoA and boost the activity of the tricarboxylic acid cycle. These alterations induce macrophage M2 polarization, increased memory responses in CD8 T cells and higher antibody production in B cells. (C) Acetate, butyrate, or propionate from dietary fiber/gut microbiota production or supplementation have several direct effects in kidney tissue. Signaling through the specific G-protein coupled receptors GPR41, GPR43, and GPR109a results in less inflammation and improves renal function in kidney diseases. Upon SCFA activation, Olfr78 (the murine ortholog of OR51E2) induces the secretion of renin and regulates blood pressure. SCFAs can also be transported by OATs, MCTs, and SMCTs in kidney tissue, where they can modulate the cellular metabolism by increasing gluconeogenesis and interfere in kidney integrity by inhibiting apoptosis, pyroptosis, and HDAC activity. (D) Finally, gut dysbiosis can inhibit the production of SCFAs by the microbiota and, consequently, their modulatory effects on immune cells and kidneys. SCFAs, short-chain fatty acids; MCT, H+/monocarboxylate transporters; SMCT, Na+/monocarboxylate transporters; mTOR, mammalian target of rapamycin; HDAC, histone deacetylases; acetyl-CoA, acetyl coenzyme A; Olfr78, olfactory receptor 78; OAT, organic anion transporters.

mitochondrial mass, and glycolysis through GPR41 activation, and boosting β oxidation, which is important to their differentiation into memory cells. SCFAs also modulate $CD4^+$ T cell responses, inducing IL-10 production, by inhibiting histone deacetylases (HDACs) and activating the mammalian target of rapamycin pathway. Finally, these metabolites contribute to enhance antibody production in B cells as they increase ATP production, glycolysis, fatty-acid synthesis, and β oxidation. Interestingly, SCFAs can be transported into the cytoplasm and lead to the production of acetyl-CoA through β oxidation, fueling the tricarboxylic acid cycle and stimulating OXPHOS, which usually induces an anti-inflammatory or memory profile in immune cells (53). In this context, disruptions in the gut microbiome and decreased SCFA production may affect the regulation of the immune response at different sites in the human body.

Although most studies focus on SCFAs, there are several other microbiota-derived metabolites that play a key role in regulating signaling pathways in the host, such as bile and amino acids (54). Therefore, future studies should shift their focus from SCFAs to this broader range of gut metabolites, many of which we still do not know or understand their signaling mechanisms in steady-state and disease.

Sensing SCFAs by Kidney Cells

Once produced by gut microbiota and distributed into the bloodstream, SCFAs can reach different tissues. In kidney cells, the expression of GPR41, GPR43, Olfr78/OR51E2, and GPR109a has already been reported (40) (Figure 2). GPR41 and GPR43 were identified in human distal and collecting tubules and treatment with propionate, acetate, or butyrate was shown to reduce the TNFα-stimulated MCP-1 production by human renal cortical epithelial cells in a GPR41/43-dependent manner (55). Renal expression of GPR41 and GPR43 was reduced after ischemia and reperfusion injury, and treatment with acetate restored GPR43 expression and improved renal inflammation and dysfunction. Similar renoprotection was observed by treatment with propionate-, butyrate-, or acetate-producing bacteria in ischemic animals (32).

The murine ortholog of OR51E2 (Olfr78) has been localized in the renal afferent arteriole, part of the juxtaglomerular apparatus of the kidney, and can mediate the secretion of renin and regulate blood pressure in response to SCFAs (12). However, the mechanisms by which Olfr78 induces the expression of renin remain to be clarified. Later, Natarajan *et al.* observed that GPR41 present in the vascular endothelium

also responds to SCFAs, and participates in blood pressure regulation by mechanisms independent of the plasma renin levels (56). By binding to their receptors on enteroendocrine cells, SCFAs can also stimulate the release of serotonin (5-hydroxytryptamine), which regulates the vascular tone, and therefore affects kidney perfusion (57–59).

High expression of GPR109a was detected in murine podocytes, and treatment with sodium butyrate or high butyrate-releasing high-amylose maize starch diet ameliorated the adriamycin-induced glomerular damage, and renal inflammation and fibrosis in mice. In addition, this protective effect of butyrate was not abolished in Gpr109a$^{-/-}$ mice (31). Snelson *et al*. did not observe a GPR109a-dependent beneficial effect of high-fiber diet in experimental type 1 diabetic kidney disease (60), whereas another study showed that high-fiber diets or supplementation with acetate, butyrate, or propionate was protective against development of type 1 or type 2 diabetic kidney disease in mice. Conversely, GPR43- or GPR109a-deficient mice were not protected by the SCFAs, suggesting that renoprotection was dependent on these receptors (61). These disparate results could be due to the different fiber concentration present in the two diets. In addition, microbiota composition can vary according to several factors as age, diet, and environmental factors (62).

Islam *et al*. proposed that propionate can also cross the membranes of mouse kidney cells through the transporter OAT2 and modulates the cellular metabolism, particularly gluconeogenesis (63). Members of the membrane transport proteins MCTs and SMCTs are also expressed in kidney cells (48,64–66) and are speculated to play a role in the entry of SCFAs (Figure 2). MCT1 and MCT2 (SLC16A1 and SLC16A7) promote H^+-coupled transport of lactate, pyruvate, and SCFAs (acetate, propionate, and butyrate) (64,67). MCT1, detected on the basolateral side of the proximal tubule, may also be involved in taking up lactate or pyruvate for gluconeogenesis and β oxidation (65). Two members of the SMCT family, SLC5A8 and SLC5A12, are Na^+-coupled transporters for lactate, pyruvate, and SCFAs, expressed by tubular epithelial cells (50). The proton/amino acid transporters 1 and 2 (SLC36A1 and SLC36A2) have been shown experimentally to mediate the uptake of acetate, butyrate, and propionate by *Xenopus laevis* oocytes, and were are also detected in kidney tissue (68).

SCFAs can directly induce renal cell cytoprotection by inhibiting apoptosis, pyroptosis, and histone acetylation (Figure 2) (13,69). When administrated in two intraperitoneal dosages (200 mg/kg), 30 minutes before ischemia, and at the moment of reperfusion, acetate reversed the increase in renal HDACs activity, and prevented the reduction in DNA methylation in mice undergoing kidney ischemia and reperfusion injury (32). Administration of sodium butyrate (500 mg/kg per day, intraperitoneally) for 21 days inhibited renal HDACs activity, fibrogenesis-related gene expression, and DNA damage, and prevented the loss of renal function in diabetic rats (70). Accordingly, treatment with sodium butyrate (1 g/kg per day, 5 days per week for 12 weeks, oral administration) attenuated high glucose-induced HDAC2 upregulation and suppressed apoptosis of rat kidney tubular epithelial cells (13). Although acetate and butyrate have been largely explored in HDAC inhibition in kidney diseases, other SCFAs may also have inhibitory effect to a lesser extent. Using a reporter gene designed to measure HDACs inhibition, Waldecker *et al*. demonstrated that butyrate is effective in inhibiting HDACs in transfected HeLa cells at concentrations of ≥1 mM, whereas superior concentrations are necessary for other SCFAs (≥2 mM for valerate and ≥10 mM for propionate) (71). In MCF7 breast tumor cells, butyrate was the most potent HDAC inhibitor tested, followed by pyruvate (a substrate for acetate production) and propionate (72).

SCFAs in Human Kidney Diseases

Although still scarce, studies evaluating the effect of SCFA in the clinic have increased in recent years. The available data support the existence of a link between alterations in gut microbiome and inflammation in human kidney diseases (73,74), especially regarding the contraction of SCFA-producing bacteria (15). Wong *et al.* showed that patients with CKD exhibited significant expansion of bacterial families possessing urease and uricase, with concomitant reduction of families possessing butyrate-forming enzymes (15). Similarly, a significant reduction of butyrate-producing bacteria *Roseburia* spp. and *Faecalibacterium prausnitzii* was observed in patients with ESKD compared with healthy controls or patients with early stages of CKD (75). Wang *et al*. observed lower serum levels of SCFAs in patients with CKD and an inverse correlation between butyrate level and renal function (76).

Metagenomic analyses are useful to better understand the gut microbiota changes in patients with cardiovascular and kidney diseases. Individuals with first-grade hypertension presented lower abundance of *Faecalibacterium prausnitzii*, *Roseburia hominis*, *Ruminococcaceae* NK4A214, *Ruminococcaceae_UCG-010*, and *Christensenellaceae* R-7, which are SCFA-producing bacteria (77–79), before drug treatment. They also showed for the first time that higher fecal excretion of acetate, propionate, butyrate, and valerate, together with lower plasmatic levels are associated with hypertension in humans (80).

A case-control study performed at the West China Hospital demonstrated that patients with occasional or recurrent renal calcium oxalate stones had lower SCFAs-producing gut bacteria and metabolic pathways associated with SCFA production than the non-kidney stone controls (81). Gut dysbiosis at the species level can be observed in different stages of CKD. Metagenomics analyses showed that the top-discriminatory species between non-CKD controls and patients with early-stage CKD are *Bacteroides eggerthii, Candidatus Stoquefichus sp. KLE1796* (decreased in mild CKD), and *Cetobacterium somerae* (elevated in mild CKD). In advanced CKD, the SCFA-producing bacteria *Prevotella sp. 885* and *Roseburia faecis* were decreased, whereas *Merdibacter massiliensis* and *Clostridium glycyrrhizinilyticum* were increased in association with elevated levels of serum uremic toxin and bile acid compared to non-CKD controls (82). These results raise the possibility that specific gut microorganisms can become biomarkers for early diagnosis and prognosis monitoring of CKD. Notably, lower levels of propionic acid were highly discriminatory between non-CKD controls and patients with advanced CKD (82). Although these changes in gut microbiota and in SCFA levels have been demonstrated in kidney diseases, it is still unclear whether the expression of SCFAs receptors/

transporters is altered in immune cells or renal parenchymal cells of these patients.

To avoid phosphate intake and hyperkalemia, patients with kidney diseases have dietary restrictions of fiber-rich foods, which contribute to the decrease in the production of SCFAs by the gut microbiota. It was already shown that high total fiber intake is associated with lower risk of inflammation and mortality (83) and reduced serum urea and creatinine in patients with CKD or on hemodialysis (84). Therefore, nutritional strategies aiming to increase SCFAs synthesis may benefit patients with CKD or on hemodialysis, although this warrants further investigation. A single-center nonrandomized pilot study demonstrated that supplementation with sodium propionate reduced C-reactive protein, IL-2, and IL-17, oxidative stress, gut-derived indoxyl sulfate, and p-cresyl sulfate in patients on maintenance hemodialysis. Then 4 weeks after ceasing treatment, all improved parameters deteriorated again, evidencing the renoprotective effect of the ongoing SCFA supplementation (85). Finally, Meyer *et al.* showed that propionate supplementation (participants ingested 2×500 mg propionic acid per day) reduces the systemic inflammation in patients with ESKD on dialysis and this effect was associated with the expansion of circulating regulatory T cells (86). Together, these data suggest SCFA-related treatments can become therapeutic strategies for human kidney diseases.

Kidneys and the gut are deeply interconnected, and intestinal dysbiosis can affect renal function and the increase in uremic toxins can change the gut microbiota composition (Figure 1). SCFAs are produced by commensal gut microbiota and affect the kidneys by a large range of mechanisms, including modulation of immune system and interactions with their cognate receptors and transporters present in kidney cells (Figure 2). The identification of these and other putative SCFAs receptors and transporters in renal cells will facilitate any pharmacological and nonpharmacological strategies to halt the progression of kidney diseases.

Disclosures

All authors have nothing to disclose.

Funding

This work was supported by the São Paulo Research Foundation (2017/05264-7 and 2019/02893-9), the National Council for Scientific and Technological Development, and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Brasil – Financial Code 001.

Acknowledgments

The figures were created with BioRender.com.

Author Contributions

O. Foresto-Neto, B. Ghirotto and N. Olsen Saraiva Câmara wrote the original draft, and reviewed and edited the manuscript.

References

1. Belkaid Y, Hand TW: Role of the microbiota in immunity and inflammation. *Cell* 157: 121–141, 2014 https://doi.org/10.1016/j.cell.2014.03.011
2. Blander JM, Longman RS, Iliev ID, Sonnenberg GF, Artis D: Regulation of inflammation by microbiota interactions with the host. *Nat Immunol* 18: 851–860, 2017 https://doi.org/10.1038/ni.3780
3. Zheng D, Liwinski T, Elinav E: Interaction between microbiota and immunity in health and disease. *Cell Res* 30: 492–506, 2020 https://doi.org/10.1038/s41422-020-0332-7
4. Mirsepasi-Lauridsen HC, Vrankx K, Engberg J, Friis-Møller A, Brynskov J, Nordgaard-Lassen I, Petersen AM, Krogfelt KA: Disease-specific enteric microbiome dysbiosis in inflammatory bowel disease. *Front Med (Lausanne)* 5: 304, 2018 https://doi.org/10.3389/fmed.2018.00304
5. Jamshidi P, Hasanzadeh S, Tahvildari A, Farsi Y, Arbabi M, Mota JF, Sechi LA, Nasiri MJ: Is there any association between gut microbiota and type 1 diabetes? A systematic review. *Gut Pathog* 11: 49, 2019 https://doi.org/10.1186/s13099-019-0332-7
6. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, Machado JC, Figueiredo C: Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut* 67: 226–236, 2017 https://doi.org/10.1136/gutjnl-2017-314205
7. Felizardo RJF, Watanabe IKM, Dardi P, Rossoni LV, Câmara NOS: The interplay among gut microbiota, hypertension and kidney diseases: The role of short-chain fatty acids. *Pharmacol Res* 141: 366–377, 2019 https://doi.org/10.1016/j.phrs.2019.01.019
8. Foresto-Neto O, Albino AH, Arias SCA, Faustino VD, Zambom FFF, Cenedeze MA, Elias RM, Malheiros DMAC, Camara NOS, Fujihara CK, Zatz R: NF-κB system is chronically activated and promotes glomerular injury in experimental type 1 diabetic kidney disease. *Front Physiol* 11: 84, 2020 https://doi.org/10.3389/fphys.2020.00084
9. Foresto-Neto O, Ávila VF, Arias SCA, Zambom FFF, Rempel LCT, Faustino VD, Machado FG, Malheiros DMAC, Abensur H, Camara NOS, Zatz R, Fujihara CK: NLRP3 inflammasome inhibition ameliorates tubulointerstitial injury in the remnant kidney model. *Lab Invest* 98: 773–782, 2018 https://doi.org/10.1038/s41374-018-0029-4
10. Wang J, Chen WD, Wang YD: The relationship between gut microbiota and inflammatory diseases: The role of macrophages. *Front Microbiol* 11: 1065, 2020 https://doi.org/10.3389/fmicb.2020.01065
11. Andrade-Oliveira V, Foresto-Neto O, Watanabe IKM, Zatz R, Câmara NOS: Inflammation in renal diseases: New and old players. *Front Pharmacol* 10: 1192, 2019 https://doi.org/10.3389/fphar.2019.01192
12. Pluznick JL, Protzko RJ, Gevorgyan H, Peterlin Z, Sipos A, Han J, Brunet I, Wan LX, Rey F, Wang T, Firestein SJ, Yanagisawa M, Gordon JI, Eichmann A, Peti-Peterdi J, Caplan MJ: Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proc Natl Acad Sci U S A* 110: 4410–4415, 2013 https://doi.org/10.1073/pnas.1215927110
13. Du Y, Tang G, Yuan W: Suppression of HDAC2 by sodium butyrate alleviates apoptosis of kidney cells in db/db mice and HG-induced NRK-52E cells. *Int J Mol Med* 45: 210–222, 2020 https://doi.org/10.3892/ijmm.2019.4397
14. Huang W, Zhou L, Guo H, Xu Y, Xu Y: The role of short-chain fatty acids in kidney injury induced by gut-derived inflammatory response. *Metabolism* 68: 20–30, 2017 https://doi.org/10.1016/j.metabol.2016.11.006
15. Wong J, Piceno YM, DeSantis TZ, Pahl M, Andersen GL, Vaziri ND: Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. *Am J Nephrol* 39: 230–237, 2014 https://doi.org/10.1159/000360010
16. Vaziri ND, Freel RW, Hatch M: Effect of chronic experimental renal insufficiency on urate metabolism. *J Am Soc Nephrol* 6: 1313–1317, 1995 https://doi.org/10.1681/ASN.V641313
17. Hatch M, Freel RW, Vaziri ND: Intestinal excretion of oxalate in chronic renal failure. *J Am Soc Nephrol* 5: 1339–1343, 1994 https://doi.org/10.1681/ASN.V561339
18. Chen YY, Chen DQ, Chen L, Liu JR, Vaziri ND, Guo Y, Zhao YY: Microbiome-metabolome reveals the contribution of gut-kidney axis on kidney disease. *J Transl Med* 17: 5, 2019 https://doi.org/10.1186/s12967-018-1756-4
19. Mehta TH, Goldfarb DS: Uric acid stones and hyperuricosuria. *Adv Chronic Kidney Dis* 19: 413–418, 2012 https://doi.org/10.1053/j.ackd.2012.07.014

20. Heaney LM, Davies OG, Selby NM: Gut microbial metabolites as mediators of renal disease: do short-chain fatty acids offer some hope? *Future Sci OA* 5: FSO384, 2019 https://doi.org/10.4155/fsoa-2019-0013
21. Liu WC, Tomino Y, Lu KC: Impacts of indoxyl sulfate and p-cresol sulfate on chronic kidney disease and mitigating effects of AST-120. *Toxins (Basel)* 10: 367, 2018 https://doi.org/10.3390/toxins10090367
22. Jansen J, Jansen K, Neven E, Poesen R, Othman A, van Mil A, Sluijter J, Sastre Torano J, Zaal EA, Berkers CR, Esser D, Wichers HJ, van Ede K, van Duursen M, Burtey S, Verhaar MC, Meijers B, Masereeuw R: Remote sensing and signaling in kidney proximal tubules stimulates gut microbiome-derived organic anion secretion. *Proc Natl Acad Sci U S A* 116: 16105–16110, 2019 https://doi.org/10.1073/pnas.1821809116
23. Vaziri ND, Yuan J, Norris K: Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in chronic kidney disease. *Am J Nephrol* 37: 1–6, 2013 https://doi.org/10.1159/000345969
24. Felizardo RJ, Castoldi A, Andrade-Oliveira V, Câmara NO: The microbiota and chronic kidney diseases: A double-edged sword. *Clin Transl Immunology* 5: e86, 2016 https://doi.org/10.1038/cti.2016.36
25. Watanabe IKM, Andrade-Silva M, Foresto-Neto O, Felizardo RJF, Matheus MAC, Silva RC, Cenedeze MA, Honda TSB, Perandini LAB, Volpini RA, Pacheco-Silva A, Câmara NOS: Gut microbiota and intestinal epithelial Myd88 signaling are crucial for renal injury in UUO mice. *Front Immunol* 11: 578623, 2020 https://doi.org/10.3389/fimmu.2020.578623
26. Raj D, Tomar B, Lahiri A, Mulay SR: The gut-liver-kidney axis: Novel regulator of fatty liver associated chronic kidney disease. *Pharmacol Res* 152: 104617, 2020 https://doi.org/10.1016/j.phrs.2019.104617
27. Zeisel SH, Warrier M: Trimethylamine N-oxide, the microbiome, and heart and kidney disease. *Annu Rev Nutr* 37: 157–181, 2017 https://doi.org/10.1146/annurev-nutr-071816-064732
28. Tan X, Liu Y, Long J, Chen S, Liao G, Wu S, Li C, Wang L, Ling W, Zhu H: Trimethylamine N-oxide aggravates liver steatosis through modulation of bile acid metabolism and inhibition of farnesoid x receptor signaling in nonalcoholic fatty liver disease. *Mol Nutr Food Res* 63: e1900257, 2019 https://doi.org/10.1002/mnfr.201900257
29. Targher G, Byrne CD: Non-alcoholic fatty liver disease: An emerging driving force in chronic kidney disease. *Nat Rev Nephrol* 13: 297–310, 2017 https://doi.org/10.1038/nrneph.2017.16
30. Zhou D, Chen YW, Zhao ZH, Yang RX, Xin FZ, Liu XL, Pan Q, Zhou H, Fan JG: Sodium butyrate reduces high-fat diet-induced non-alcoholic steatohepatitis through upregulation of hepatic GLP-1R expression. *Exp Mol Med* 50: 1–12, 2018 https://doi.org/10.1038/s12276-018-0183-1
31. Felizardo RJF, de Almeida DC, Pereira RL, Watanabe IKM, Doimo NTS, Ribeiro WR, Cenedeze MA, Hiyane MI, Amano MT, Braga TT, Ferreira CM, Parmigiani RB, Andrade-Oliveira V, Volpini RA, Vinolo MAR, Mariño E, Robert R, Mackay CR, Camara NOS: Gut microbial metabolite butyrate protects against proteinuric kidney disease through epigenetic- and GPR109a-mediated mechanisms. *FASEB J* 33: 11894–11908, 2019 https://doi.org/10.1096/fj.201901080R
32. Andrade-Oliveira V, Amano MT, Correa-Costa M, Castoldi A, Felizardo RJ, de Almeida DC, Bassi EJ, Moraes-Vieira PM, Hiyane MI, Rodas AC, Peron JP, Aguiar CF, Reis MA, Ribeiro WR, Valduga CJ, Curi R, Vinolo MA, Ferreira CM, Câmara NO: Gut bacteria products prevent AKI induced by ischemia-reperfusion. *J Am Soc Nephrol* 26: 1877–1888, 2015 https://doi.org/10.1681/ASN.2014030288
33. Maciejewska D, Skonieczna-Zydecka K, Lukomska A, Gutowska I, Dec K, Kupnicka P, Palma J, Pilutin A, Marlicz W, Stachowska E: The short chain fatty acids and lipopolysaccharides status in Sprague-Dawley rats fed with high-fat and high-cholesterol diet [published online ahead of print, June 13, 2018]. *J Physiol Pharmacol* https://doi.org/10.26402/jpp.2018.2.05
34. Neis EP, Dejong CH, Rensen SS: The role of microbial amino acid metabolism in host metabolism. *Nutrients* 7: 2930–2946, 2015 https://doi.org/10.3390/nu7042930
35. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Steplewski KM, Murdock PR, Holder JC, Marshall FH, Szekeres PG, Wilson S, Ignar DM, Foord SM, Wise A, Dowell SJ: The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem* 278: 11312–11319, 2003 https://doi.org/10.1074/jbc.M211609200
36. Le Poul E, Loison C, Struyf S, Springael JY, Lannoy V, Decobecq ME, Brezillon S, Dupriez V, Vassart G, Van Damme J, Parmentier M, Detheux M: Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* 278: 25481–25489, 2003 https://doi.org/10.1074/jbc.M301403200
37. Elangovan S, Pathania R, Ramachandran S, Ananth S, Padia RN, Lan L, Singh N, Martin PM, Hawthorn L, Prasad PD, Ganapathy V, Thangaraju M: The niacin/butyrate receptor GPR109A suppresses mammary tumorigenesis by inhibiting cell survival. *Cancer Res* 74: 1166–1178, 2014 https://doi.org/10.1158/0008-5472.CAN-13-1451
38. Ang Z, Ding JL: GPR41 and GPR43 in obesity and inflammation: Protective or causative? *Front Immunol* 7: 28, 2016 https://doi.org/10.3389/fimmu.2016.00028
39. Sivaprakasam S, Prasad PD, Singh N: Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. *Pharmacol Ther* 164: 144–151, 2016 https://doi.org/10.1016/j.pharmthera.2016.04.007
40. Gong J, Noel S, Pluznick JL, Hamad ARA, Rabb H: Gut microbiota-kidney cross-talk in acute kidney injury. *Semin Nephrol* 39: 107–116, 2019 https://doi.org/10.1016/j.semnephrol.2018.10.009
41. Kimura I, Ichimura A, Ohue-Kitano R, Igarashi M: Free fatty acid receptors in health and disease. *Physiol Rev* 100: 171–210, 2020 https://doi.org/10.1152/physrev.00041.2018
42. Gill RK, Saksena S, Alrefai WA, Sarwar Z, Goldstein JL, Carroll RE, Ramaswamy K, Dudeja PK: Expression and membrane localization of MCT isoforms along the length of the human intestine. *Am J Physiol Cell Physiol* 289: C846–C852, 2005 https://doi.org/10.1152/ajpcell.00112.2005
43. Paroder V, Spencer SR, Paroder M, Arango D, Schwartz S Jr, Mariadason JM, Augenlicht LH, Eskandari S, Carrasco N: Na(+)/monocarboxylate transport (SMCT) protein expression correlates with survival in colon cancer: Molecular characterization of SMCT. *Proc Natl Acad Sci U S A* 103: 7270–7275, 2006 https://doi.org/10.1073/pnas.0602365103
44. Li H, Myeroff L, Smiraglia D, Romero MF, Pretlow TP, Kasturi L, Lutterbaugh J, Rerko RM, Casey G, Issa JP, Willis J, Willson JK, Plass C, Markowitz SD: SLC5A8, a sodium transporter, is a tumor suppressor gene silenced by methylation in human colon aberrant crypt foci and cancers. *Proc Natl Acad Sci U S A* 100: 8412–8417, 2003 https://doi.org/10.1073/pnas.1430846100
45. Pluznick JL: Gut microbiota in renal physiology: focus on short-chain fatty acids and their receptors. *Kidney Int* 90: 1191–1198, 2016 https://doi.org/10.1016/j.kint.2016.06.033
46. Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, Browning DD, Mellinger JD, Smith SB, Digby GJ, Lambert NA, Prasad PD, Ganapathy V: GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Res* 69: 2826–2832, 2009 https://doi.org/10.1158/0008-5472.CAN-08-4466
47. Xie Q, Welch R, Mercado A, Romero MF, Mount DB: Molecular characterization of the murine Slc26a6 anion exchanger: functional comparison with Slc26a1. *Am J Physiol Renal Physiol* 283: F826–F838, 2002 https://doi.org/10.1152/ajprenal.00079.2002
48. Gopal E, Fei YJ, Sugawara M, Miyauchi S, Zhuang L, Martin P, Smith SB, Prasad PD, Ganapathy V: Expression of slc5a8 in kidney and its role in Na(+)-coupled transport of lactate. *J Biol Chem* 279: 44522–44532, 2004 https://doi.org/10.1074/jbc.M405365200
49. Martin PM, Gopal E, Ananth S, Zhuang L, Itagaki S, Prasad BM, Smith SB, Prasad PD, Ganapathy V: Identity of SMCT1 (SLC5A8) as a neuron-specific Na+-coupled transporter for active uptake of L-lactate and ketone bodies in the brain. *J Neurochem* 98: 279–288, 2006 https://doi.org/10.1111/j.1471-4159.2006.03878.x

50. Ganapathy V, Thangaraju M, Gopal E, Martin PM, Itagaki S, Miyauchi S, Prasad PD: Sodium-coupled monocarboxylate transporters in normal tissues and in cancer. *AAPS J* 10: 193–199, 2008 https://doi.org/10.1208/s12248-008-9022-y
51. Sun M, Wu W, Chen L, Yang W, Huang X, Ma C, Chen F, Xiao Y, Zhao Y, Ma C, Yao S, Carpio VH, Dann SM, Zhao Q, Liu Z, Cong Y: Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. *Nat Commun* 9: 3555, 2018 https://doi.org/10.1038/s41467-018-05901-2
52. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J: A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 490: 55–60, 2012 https://doi.org/10.1038/nature11450
53. Michaudel C, Sokol H: The gut microbiota at the service of immunometabolism. *Cell Metab* 32: 514–523, 2020 https://doi.org/10.1016/j.cmet.2020.09.004
54. Agus A, Clément K, Sokol H: Gut microbiota-derived metabolites as central regulators in metabolic disorders. *Gut* 70: 1174–1182, 2020 https://doi.org/10.1136/gutjnl-2020-323071
55. Kobayashi M, Mikami D, Kimura H, Kamiyama K, Morikawa Y, Yokoi S, Kasuno K, Takahashi N, Taniguchi T, Iwano M: Short-chain fatty acids, GPR41 and GPR43 ligands, inhibit TNF-α-induced MCP-1 expression by modulating p38 and JNK signaling pathways in human renal cortical epithelial cells. *Biochem Biophys Res Commun* 486: 499–505, 2017 https://doi.org/10.1016/j.bbrc.2017.03.071
56. Natarajan N, Hori D, Flavahan S, Steppan J, Flavahan NA, Berkowitz DE, Pluznick JL: Microbial short chain fatty acid metabolites lower blood pressure via endothelial G protein-coupled receptor 41. *Physiol Genomics* 48: 826–834, 2016 https://doi.org/10.1152/physiolgenomics.00089.2016
57. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY: Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. [Published correction appears in *Cell* 163: 258, 2015] *Cell* 161: 264–276, 2015 https://doi.org/10.1016/j.cell.2015.02.047
58. Silva YP, Bernardi A, Frozza RL: The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol (Lausanne)* 11: 25, 2020 https://doi.org/10.3389/fendo.2020.00025
59. Blackshear JL, Orlandi C, Hollenberg NK: Serotonin and the renal blood supply: Role of prostaglandins and the 5HT-2 receptor. *Kidney Int* 30: 304–310, 1986 https://doi.org/10.1038/ki.1986.185
60. Snelson M, Tan SM, Higgins GC, Lindblom RSJ, Coughlan MT: Exploring the role of the metabolite-sensing receptor GPR109a in diabetic nephropathy. *Am J Physiol Renal Physiol* 318: F835–F842, 2020 https://doi.org/10.1152/ajprenal.00505.2019
61. Li YJ, Chen X, Kwan TK, Loh YW, Singer J, Liu Y, Ma J, Tan J, Macia L, Mackay CR, Chadban SJ, Wu H: Dietary fiber protects against diabetic nephropathy through short-chain fatty acid-mediated activation of G protein-coupled receptors GPR43 and GPR109A. *J Am Soc Nephrol* 31: 1267–1281, 2020 https://doi.org/10.1681/ASN.2019101029
62. Laukens D, Brinkman BM, Raes J, De Vos M, Vandenabeele P: Heterogeneity of the gut microbiome in mice: Guidelines for optimizing experimental design. *FEMS Microbiol Rev* 40: 117–132, 2016 https://doi.org/10.1093/femsre/fuv036
63. Islam R, Anzai N, Ahmed N, Ellapan B, Jin CJ, Srivastava S, Miura D, Fukutomi T, Kanai Y, Endou H: Mouse organic anion transporter 2 (mOat2) mediates the transport of short chain fatty acid propionate. *J Pharmacol Sci* 106: 525–528, 2008 https://doi.org/10.1254/jphs.SC0070291
64. Halestrap AP, Price NT: The proton-linked monocarboxylate transporter (MCT) family: Structure, function and regulation. *Biochem J* 343: 281–299, 1999 https://doi.org/10.1042/bj3430281
65. Becker HM, Mohebbi N, Perna A, Ganapathy V, Capasso G, Wagner CA: Localization of members of MCT monocarboxylate transporter family Slc16 in the kidney and regulation during metabolic acidosis. *Am J Physiol Renal Physiol* 299: F141–F154, 2010 https://doi.org/10.1152/ajprenal.00488.2009
66. Fishbein WN, Merezhinskaya N, Foellmer JW: Relative distribution of three major lactate transporters in frozen human tissues and their localization in unfixed skeletal muscle. *Muscle Nerve* 26: 101–112, 2002 https://doi.org/10.1002/mus.10168
67. Halestrap AP, Meredith D: The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. *Pflugers Arch* 447: 619–628, 2004 https://doi.org/10.1007/s00424-003-1067-2
68. Foltz M, Boll M, Raschka L, Kottra G, Daniel H: A novel bifunctionality: PAT1 and PAT2 mediate electrogenic proton/amino acid and electroneutral proton/fatty acid symport. *FASEB J* 18: 1758–1760, 2004 https://doi.org/10.1096/fj.03-1387fje
69. Gu J, Huang W, Zhang W, Zhao T, Gao C, Gan W, Rao M, Chen Q, Guo M, Xu Y, Xu YH: Sodium butyrate alleviates high-glucose-induced renal glomerular endothelial cells damage via inhibiting pyroptosis. *Int Immunopharmacol* 75: 105832, 2019 https://doi.org/10.1016/j.intimp.2019.105832
70. Khan S, Jena G: Sodium butyrate, a HDAC inhibitor ameliorates eNOS, iNOS and TGF-β1-induced fibrogenesis, apoptosis and DNA damage in the kidney of juvenile diabetic rats. *Food Chem Toxicol* 73: 127–139, 2014 https://doi.org/10.1016/j.fct.2014.08.010
71. Waldecker M, Kautenburger T, Daumann H, Busch C, Schrenk D: Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. *J Nutr Biochem* 19: 587–593, 2008 https://doi.org/10.1016/j.jnutbio.2007.08.002
72. Thangaraju M, Gopal E, Martin PM, Ananth S, Smith SB, Prasad PD, Sterneck E, Ganapathy V: SLC5A8 triggers tumor cell apoptosis through pyruvate-dependent inhibition of histone deacetylases. *Cancer Res* 66: 11560–11564, 2006 https://doi.org/10.1158/0008-5472.CAN-06-1950
73. Li F, Wang M, Wang J, Li R, Zhang Y: Alterations to the gut microbiota and their correlation with inflammatory factors in chronic kidney disease. *Front Cell Infect Microbiol* 9: 206, 2019 https://doi.org/10.3389/fcimb.2019.00206
74. Chung S, Barnes JL, Astroth KS: Gastrointestinal microbiota in patients with chronic kidney disease: A systematic review. *Adv Nutr* 10: 888–901, 2019 https://doi.org/10.1093/advances/nmz028
75. Jiang S, Xie S, Lv D, Zhang Y, Deng J, Zeng L, Chen Y: A reduction in the butyrate producing species Roseburia spp. and Faecalibacterium prausnitzii is associated with chronic kidney disease progression. *Antonie van Leeuwenhoek* 109: 1389–1396, 2016 https://doi.org/10.1007/s10482-016-0737-y
76. Wang S, Lv D, Jiang S, Jiang J, Liang M, Hou F, Chen Y: Quantitative reduction in short-chain fatty acids, especially butyrate, contributes to the progression of chronic kidney disease. *Clin Sci (Lond)* 133: 1857–1870, 2019 https://doi.org/10.1042/CS20190171
77. Flint HJ, Bayer EA, Rincon MT, Lamed R, White BA: Polysaccharide utilization by gut bacteria: Potential for new insights from genomic analysis. *Nat Rev Microbiol* 6: 121–131, 2008 https://doi.org/10.1038/nrmicro1817
78. Chassard C, Bernalier-Donadille A: H2 and acetate transfers during xylan fermentation between a butyrate-producing xylanolytic species and hydrogenotrophic microorganisms from the human gut. *FEMS Microbiol Lett* 254: 116–122, 2006 https://doi.org/10.1111/j.1574-6968.2005.00016.x
79. Waters JL, Ley RE: The human gut bacteria Christensenellaceae are widespread, heritable, and associated with health. *BMC Biol* 17: 83, 2019 https://doi.org/10.1186/s12915-019-0699-4
80. Calderón-Pérez L, Gosalbes MJ, Yuste S, Valls RM, Pedret A, Llauradó E, Jimenez-Hernandez N, Artacho A, Pla-Pagà L, Companys J, Ludwig I, Romero MP, Rubió L, Solà R: Gut metagenomic and short chain fatty acids signature in hypertension: A cross-sectional study. *Sci Rep* 10: 6436, 2020 https://doi.org/10.1038/s41598-020-63475-w
81. Liu Y, Jin X, Hong HG, Xiang L, Jiang Q, Ma Y, Chen Z, Cheng L, Jian Z, Wei Z, Ai J, Qi S, Sun Q, Li H, Li Y, Wang K: The

relationship between gut microbiota and short chain fatty acids in the renal calcium oxalate stones disease. *FASEB J* 34: 11200–11214, 2020 https://doi.org/10.1096/fj.202000786R
82. Wu IW, Gao SS, Chou HC, Yang HY, Chang LC, Kuo YL, Dinh MCV, Chung WH, Yang CW, Lai HC, Hsieh WP, Su SC: Integrative metagenomic and metabolomic analyses reveal severity-specific signatures of gut microbiota in chronic kidney disease. *Theranostics* 10: 5398–5411, 2020 https://doi.org/10.7150/thno.41725
83. Krishnamurthy VM, Wei G, Baird BC, Murtaugh M, Chonchol MB, Raphael KL, Greene T, Beddhu S: High dietary fiber intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. *Kidney Int* 81: 300–306, 2012 https://doi.org/10.1038/ki.2011.355
84. Chiavaroli L, Mirrahimi A, Sievenpiper JL, Jenkins DJ, Darling PB: Dietary fiber effects in chronic kidney disease: A systematic review and meta-analysis of controlled feeding trials. *Eur J Clin Nutr* 69: 761–768, 2015 https://doi.org/10.1038/ejcn.2014.237
85. Marzocco S, Fazeli G, Di Micco L, Autore G, Adesso S, Dal Piaz F, Heidland A, Di Iorio B: Supplementation of short-chain fatty acid, sodium propionate, in patients on maintenance hemodialysis: Beneficial effects on inflammatory parameters and gut-derived uremic toxins, a pilot study (PLAN Study). *J Clin Med* 7: 315, 2018 https://doi.org/10.3390/jcm7100315
86. Meyer F, Seibert FS, Nienen M, Welzel M, Beisser D, Bauer F, Rohn B, Westhoff TH, Stervbo U, Babel N: Propionate supplementation promotes the expansion of peripheral regulatory T-cells in patients with end-stage renal disease. *J Nephrol* 33: 817–827, 2020 https://doi.org/10.1007/s40620-019-00694-z

Received: January 18, 2021 **Accepted**: June 28, 2021