

Gut microbiota–derived short-chain fatty acids and kidney diseases

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Abstract: Gut microbiota and its metabolites play pivotal roles in host physiology and pathology. Short-chain fatty acids (SCFAs), as a group of metabolites, exert positive regulatory effects on energy metabolism, hormone secretion, immune inflammation, hypertension, and cancer. The functions of SCFAs are related to their activation of transmembrane G protein-coupled receptors and their inhibition of histone acetylation. Though controversial, growing evidence suggests that SCFAs, which regulate inflammation, oxidative stress, and fibrosis, have been involved in kidney disease through the activation of the gut–kidney axis; however, the molecular relationship among gut microbiota–derived metabolites, signaling pathways, and kidney disease remains to be elucidated. This review will provide an overview of the physiology and functions of SCFAs in kidney disease.

Keywords: gut microbiome, short-chain fatty acids, kidney diseases, gut–kidney axis

Introduction

The human intestinal tract harbors a diverse and complex microbial community, which plays a pivotal role in health. In recent years, gut microbiota–derived metabolites have been shown to influence host physiology and pathology. Changes in these metabolites exert major consequences, both harmful and beneficial, to the host’s health. On one hand, metabolites – particularly, short-chain fatty acids (SCFAs) – are generally proven to promote health.^{1–3} On the other hand, uremic toxins, including indoles, ammonia, and trimethylamine N-oxide, produced by the gut microbiota enhance the development and progression of chronic kidney disease (CKD).^{4–7} An insufficiency in gut microbiota–generated SCFAs is also associated with illnesses, including inflammatory bowel disease, obesity, type 1 and 2 diabetes mellitus, autism, major depression, colon cancer, as well as kidney diseases – the focus of the discussion.^{8–11} The functions of SCFAs are mainly related to their activation of transmembrane G protein-coupled receptors (GPCRs) and their inhibition of histone acetylation (HDAC).¹² Due to their positive effects, therapeutic studies of SCFAs have been carried out both in clinical and in animal studies. However, the mechanisms of SCFAs in the gut–kidney axis have yet to be fully explored. This review will provide an overview of the physiology and functions of gut microbiota–derived SCFAs in kidney disease. Before we outline the known roles of SCFAs in renal diseases, we will first review what is known regarding the basic functions and systemic roles of SCFAs.

Gut microbiota–derived SCFAs

Definition, production, and transportation of SCFAs

SCFAs are straight-chain saturated fatty acids composed of less than six carbon atoms, among which acetate (two carbons), propionate (three carbons), and butyrate

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(four carbons) are the most abundant in the human intestinal tract.¹³ These SCFAs are the end products of fermentation by the microbiota from complex polysaccharides,¹⁴ including non-digestible dietary fibers like inulin¹⁵ and endogenous substrates like epithelial-derived mucus.¹⁶ SCFAs not only exist in the gut but also could be absorbed in the bloodstream.¹⁷ There are two main mechanisms of SCFA absorption from the gut to the circulatory system: anion exchange between SCFAs and HCO₃⁻ across the membrane and diffusive movement promoted by the pH gradient during the diffusion of protonated SCFAs.¹⁸ When entering the circulatory system, SCFAs influence several physiology process as ligands for G-protein couple receptors (GPR41, GPR43, GPR109A, and olfactory receptor 78) or as epigenetic regulators (HDAC inhibitors).²

Multiple factors affect the concentration of SCFAs in the gut, including the amount/type of fermentable carbohydrate consumption, the composition/diversity of the microbiota, and the interactions between microbes and the host. Moreover, mother-to-child transmission is involved in the gut microbiota and its metabolites; for instance, the mode of delivery (vaginal birth or caesarean section) and feeding patterns (breastfed or bottle-fed infants) play a role in the formation of intestinal microbiota and microbial products.¹⁹

Receptors and epigenetic regulation related to SCFAs

The physiological roles of SCFAs are mainly to act as ligands for GPCRs or as inhibitors of HDAC.^{2,20} GPR41 and GPR43, which are the most studied, are shown to be activated by SCFAs.²¹ GPR41 is widely distributed in adipose tissue and at low levels in the spleen, lymph nodes, bone marrow,

peripheral blood mononuclear cells, and blood vessel endothelial cells,²¹ while GPR43 is primarily expressed in immune cells, adipocytes, islets, and gastrointestinal tract. GPR43 has a potential role in inflammation and metabolic disorders.^{22–25} More importantly, GPR41 and GPR43 both are expressed in the kidney and renal arteries.²⁶ The potencies of SCFAs are different, but the rank order has remained generally consistent among different investigators (Table 1).^{21,27} Olfr78 is another key receptor for SCFAs, which is expressed on vascular smooth muscle cells, including subset of large renal vessels, renal afferent arteriole, and juxtaglomerular apparatus, where it participates in the regulation of renin secretion in response to SCFAs.^{26,28} Unlike other receptors, Olfr78 is more sensitive to acetate and propionate but not to butyrate. In addition, GPR109a is reported to express on gut epithelial cells, adipocytes, macrophages, and dendritic cells, which only respond to butyrate and not to acetate or propionate.^{29–32} Finally, when it comes to the physiological role as HDAC inhibitors, compared to propionate, butyrate is more potent in terms of pan-inhibitory activity. SCFAs affect the expression of genes with diverse functions by inhibiting the activity of HDAC to exhibit anti-tumor, anti-fibrotic, and anti-inflammatory activities.^{20,33} Additionally, SCFA-mediated inhibition of HDACs might be independent of GPCRs and GPR41 is involved in the process.³⁴

The functions of SCFAs

As reported, SCFAs regulate tissue-specific health, as well as systemic health, including appetite, gastrointestinal motility, colitis, metabolic syndrome, airway disease, and even carcinogenesis.^{35–37} All of these influences are derived from the complex functions of SCFAs, including influencing

Table 1 The expression and major functions of SCFAs receptors

Receptors	Ligands	Expression	Functions
GPR41 (FFAR3)	C3 > C4 > C2	Colonic, small intestinal epithelium, enteroendocrine, enteric neuronal cells, sympathetic ganglia, adipose tissue, pancreas, renal smooth muscle cells	Metabolism: regulation of gut hormones; immune: epithelia innate immunity, increases Treg generation and hematopoiesis of DCs from bone marrow; sympathetic activation
GPR43 (FFAR2)	C2, C3	Colonic, small intestinal epithelium, enteroendocrine L cells, adipose tissue, leukocytes (eosinophils, basophils, neutrophils, monocytes, dendritic cells), skeletal muscle, heart, vascular endothelium in the myometrium	Metabolism: adipocyte development, adipogenesis, anti-lipolysis, regulation of gut hormones (secretion of PYY and GLP-I); immune: innate immunity and Treg differentiation; anti-inflammation; anti-tumor activity
GPR109a	C4, niacin	Intestinal epithelial cells, adipocytes, dendritic cells, macrophages, neutrophils, hepatocytes, epidermis in squamous carcinoma	Metabolism: anti-lipolysis, HDL metabolism; immune: increases Treg generation and DC trafficking, decreases Th17 cells; anti-tumor activity
Olfr78	C2, C3	Large renal vessels, renal afferent arterioles, extrarenal vascular beds, prostate cancer, autonomic nervous system cells	Regulation of blood pressure by renin

Abbreviations: DCs, dendritic cells; GLP-I, glucagon-like peptide I; HDL, high density lipoprotein; PYY, peptide YY; SCFAs, short-chain fatty acids; Treg, regulatory T cells.

energy metabolism, evoking hormone release, and regulating immune inflammation and blood pressure.

Energy metabolism

Locally, SCFAs (butyrate preferentially) are used as fuel for colonocytes and in the maintenance of the epithelium.⁷ After absorption into the bloodstream,¹⁷ circulatory SCFAs act as a primary substrate for hepatic and adipocyte lipogenesis, as well as for intestinal gluconeogenesis, and exhibit a range of metabolic effects (Figure 1).^{38,39} For example, SCFAs activate AMP-activated protein kinases (AMPK) in the liver and muscle, thereby triggering the activation of peroxisome proliferator-activated receptors, and thus stimulating glucose uptake and fatty acid oxidation and improving glycemic control, at least in murine models.⁴⁰

Several studies reported the benefits of regulating lipid or glucose metabolism by resistant starch, which increased

SCFAs production^{41,42} or fecal transplantation of butyrate-producing bacteria.^{43,44} Administration of acetate or propionate in adipocytes of mice reduced plasma free fatty acid levels by enhancing adipogenesis and inhibiting lipolysis via the activation of GPR43.^{38,45-47} In obese hyperinsulinemia *fa/fa* rats, propionate lowered urinary glucose excretion and fasting blood glucose levels.⁴⁸ Amelioration of obesity and its comorbidities, as well as insulin resistance, was also observed in mice fed with dietary supplementation of acetate.⁴⁰ Not only in an experimental setup, but also in clinical studies, overweight adults supplemented with inulin-propionate ester for a longer term (which could be metabolized by the microbiota in the colon to propionate) showed a significant reduction in weight gain via appetite regulation.⁴⁹ Patients were advised to increase their dietary fibers, which increased concentrations of SCFAs in the gut and circulatory system; this was associated with the reduction of adverse consequences of hyperglycemia.⁵⁰

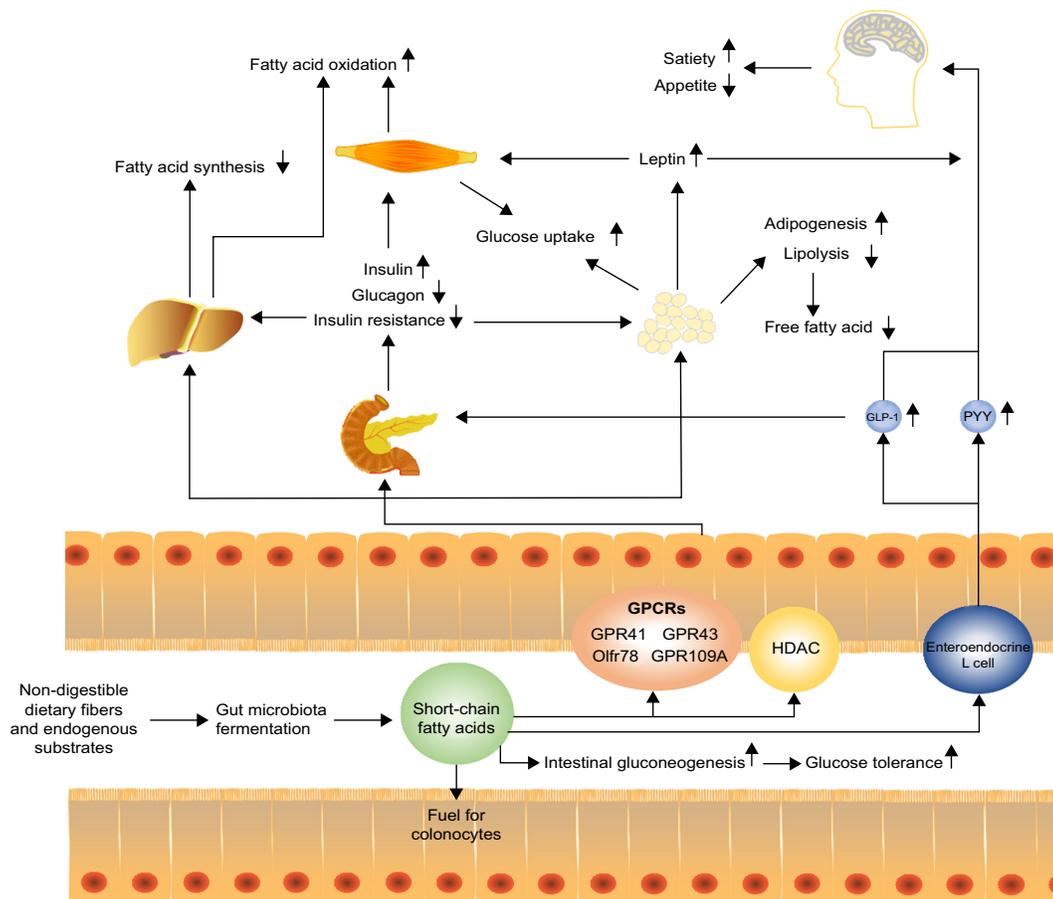


Figure 1 Short-chain fatty acids to host appetite and metabolism control. Short-chain fatty acids (SCFAs) produced via microbiota fermentation of non-digestible dietary fibers or endogenous substrates can be used as fuel for colonocytes and stimulate intestinal gluconeogenesis, which improves glucose tolerance. Moreover, SCFAs can stimulate enteroendocrine L cells to release anorexigenic hormones PYY and GLP-1. These hormones promote satiety and suppress appetite which may promote weight loss. GLP-1 increases the production of insulin and decreases the production of glucagon in the pancreas, which then increases the uptake of glucose in muscle and adipose tissues. SCFAs can also decrease fatty acid synthesis and promote fatty acid oxidation in the liver. In adipose tissue, SCFAs can increase adipogenesis and inhibit lipolysis, thereby decreasing free fatty acids. Meanwhile, SCFAs can promote the secretion of leptin that suppresses appetite.

Abbreviations: GLP-1, glucagon-like peptide 1; GPCRs, G protein-coupled receptors; HDAC, histone acetylation; PYY, peptide YY.

The benefits of SCFAs on energy metabolism could be partially explained by modulating the secretion of hormones such as peptide YY (PYY), glucagon-like peptide 1 (GLP-1), and leptin by activating GPR41 and GPR43.^{48,51,52} PYY, a gut hormone derived from enteroendocrine cells, could suppress postprandial appetite, slow gastrointestinal motility, decrease insulin secretion and sensitivity, and increase glucose uptake by SCFAs-stimulated GPR41.^{38,53–55} In contrast, GLP-1 influences peripheral metabolic effects by stimulating insulin secretion and increasing glucose tolerance. Further, GLP-1 exerts cardioprotective effects and induces beta-cell proliferation and plays a major role in decreasing epithelial permeability and increasing mucosal antibacterial defenses by GPR41 and GPR43 activation.^{56–60} SCFA-induced leptin is involved in regulating appetite and energy metabolism by GPCRs activation;⁴⁵ failure of leptin regulation is connected with obesity, hyperphagia, infertility, and immunological defects.⁶¹ In general, SCFA-activated GPR41 or GPR43 promotes hormone secretion that inhibits gastric emptying and food intake and further modulates metabolic functions both locally in the gut and distally at peripheral tissues to remain systemic in metabolic health. However, a recent study in rats showed contradictory results – acetate-induced obesity and insulin resistance.⁶² Also, SCFA concentrations were found to be higher in feces of obese humans when compared to lean controls.⁶³ This suggests that more studies are required to elucidate the true functions of SCFAs in regulating energy metabolism.

Inflammation and immune regulation

Kidney disease is often related to microinflammation and dysbiosis of immune system. Although the detailed mechanisms by which the gut microbiota regulates host health and renal health have yet to be elucidated, gut microbiota-generated SCFAs, at least partly, mediate inflammatory and immune effects (Figure 2).

SCFAs modulate inflammation both in intestinal and in extra-intestinal environments via leukocyte recruitment and chemokines production. The anti-inflammatory effects of SCFAs have been well characterized at both the epithelial and immune cell levels. On one hand, SCFAs are involved in the expression of adhesion molecules in neutrophils and endothelial cells that reduce cell recruitment. On the other hand, SCFAs exert anti-inflammatory effects by suppressing the production of cytokines such as interleukin (IL)-6, IL-1 β , tumor necrosis factor- α , and nitric oxide,^{64–69} and/or by increasing the production of anti-inflammatory cytokine IL-10⁷⁰ via stimulation of GPCRs^{58,71,72} or inhibition of HDAC.⁷³

Moreover, SCFAs induce IL-10-expressing regulatory T cells to reduce inflammation.^{74–77} SCFAs also stimulate the migration of neutrophils by chemotaxis via activation of GPR43, which further leads to inflammatory responses.^{72,78,79} In clinical investigation and animal models, SCFAs have also been demonstrated to possess protective effects on inflammatory bowel conditions, allergic airway disease, and CKD, due to their inhibitory effects on pro-inflammatory cytokines and reactive oxygen species.^{37,80,81}

The generation of SCFAs was also confirmed to influence innate immunity and adaptive immunity. For innate immunity, low concentrations of butyrate stimulate intestinal epithelial cells (goblet cells) to release mucin Muc2, which enhances the gut barrier function and heightens the response to pathogens and commensal bacteria, while high concentrations of butyrate diminish the intestinal barrier function.⁸² In terms of adaptive immune system, it was illustrated that the number of colonic Tregs are influenced, or even determined, by the luminal concentration of SCFAs through GPCRs or epigenetic modification-inhibition of HDAC.^{29,59,74–77,83–85} In general, Tregs stimulated by SCFAs always decrease inflammation under certain conditions; SCFAs induce Th1 and Th17 lymphocytes production^{35,74} by cellular bioenergetic metabolism via the conversion of SCFAs to acetyl-CoA, integration into the tricarboxylic acid, and subsequent activation of mTOR.⁸⁶ SCFAs also indirectly affect T-cell differentiation patterns by exerting a broadly immunosuppressive or tolerogenic effect on antigen-presenting cells. For example, SCFAs inhibit the development of myeloid dendritic cells (DCs) from their progenitors,⁸⁷ as well as their functional maturation,^{88,89} which then limits their ability to present antigens and cytokines to make effector T cells.³⁵ Further, SCFAs act on DCs to suppress the expression of T cell-activating molecules such as major histocompatibility complex II molecules, costimulatory molecules, and cytokines leading to generation of tolerogenic T cells rather than inflammatory T cells.^{35,37} The tolerogenic effect of SCFAs on DCs could lower inflammatory responses. Although SCFAs mostly regulate the immune system to decrease inflammation, the activity of SCFAs in immune and epithelial cells may boost inflammatory responses, if not properly regulated.³⁵ Thus, the function of SCFAs still seems to be inconsistent and complex, and future studies could provide mechanistic insights into how gut microbiota-derived metabolites contribute to immune inflammation.

In addition, SCFAs exhibit apparent impacts on cell differentiation, oxidative DNA damage, and apoptosis death through autophagy.^{18,90–92} SCFAs could modulate blood pressure by regulating renin release and peripheral resistance

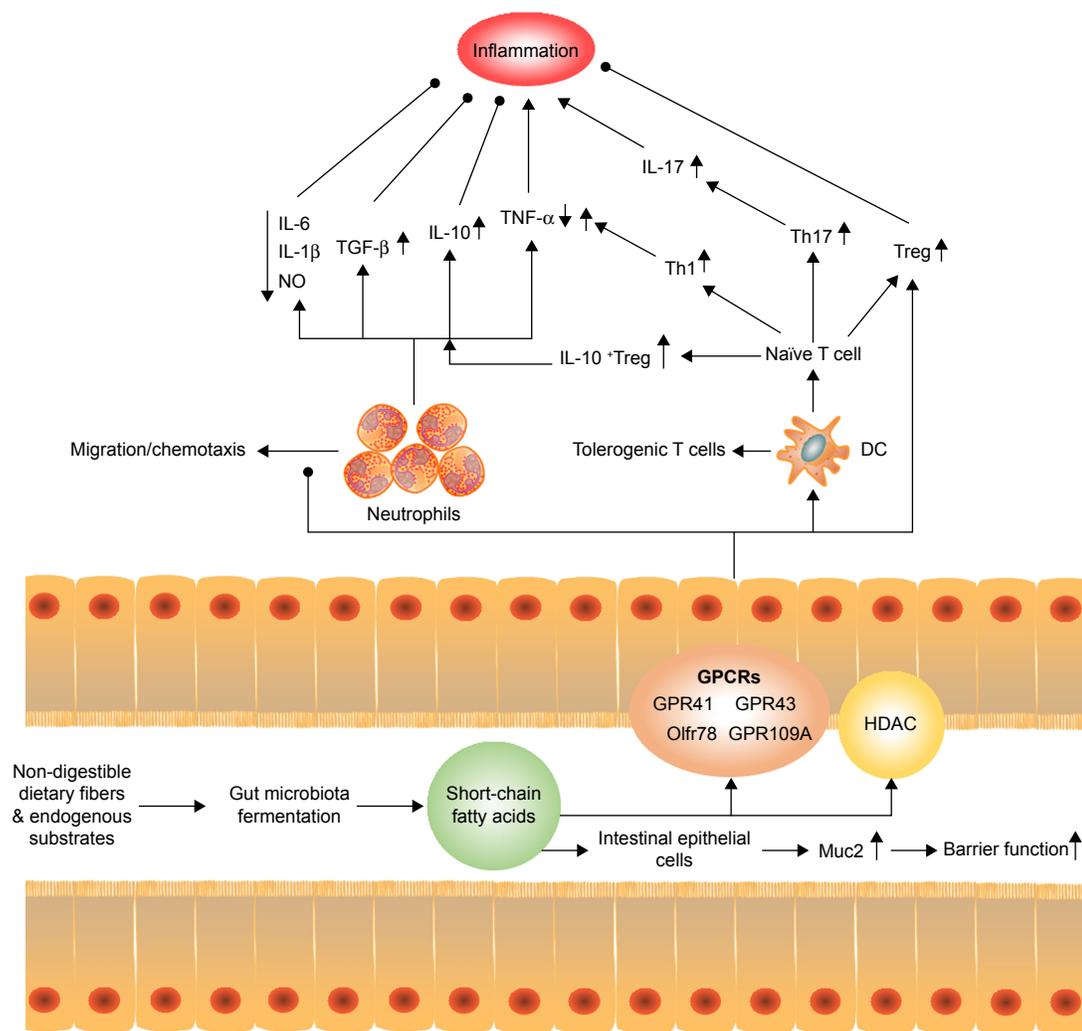


Figure 2 Regulation of short-chain fatty acids to host inflammation and immune. SCFAs can stimulate intestinal epithelial cells to release Muc2, which enhance the gut barrier function and heighten the response to pathogens and commensal bacteria. Moreover, SCFAs can reduce the recruitment of neutrophils under certain condition, with an increase in the levels of TGF- β , IL-10 and a decrease in the levels of IL-6, IL-1 β , NO, and TNF- α to inhibit inflammation. Meanwhile, SCFAs promote T-cell production of IL-10 and Treg to prevent inflammatory responses. On the other hand, SCFAs act on DCs to limit the expression of T cell-activating molecules such as MHC II molecules and costimulatory molecules, leading to the generation of tolerogenic T cells rather than inflammatory T cells. The tolerogenic effect of SCFAs on DCs can lower inflammatory responses. However, the direct effect of SCFAs on T cells enhances the generation of Th1 and Th17 cells to boost immunity to fight pathogens, which means that activation of SCFAs for immune cells and epithelial cells may increase inflammatory responses, if not properly regulated.

Abbreviations: DCs, dendritic cells; FAs, short-chain fatty acids; GPCRs, G protein-coupled receptors; HDAC, histone acetylation; NO, nitrous oxide; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α .

via Olfr78 and Gpr41 expressed on the afferent arteriole (juxtaglomerular apparatus) and smooth-muscle cells of the small resistance vessels.^{93–95} So, the functions of SCFAs in most parts are contradictory; it is now becoming clear that gut microbiota-derived metabolites play a central role in host physiology.⁹⁶

SCFAs in kidney diseases

In recent years, considerable studies have explored a new and exciting area: the interaction between the gut microbiome and kidney disease, and have reported that alteration of intestinal microbiota in CKD is an important indicator of impaired

renal function and progression of CKD.⁹⁷ Kidney disease is often related to malnutrition, hypertension or hypotension, microinflammation, dysbiosis of immune system, and multiple oxidative stress, which could be reversed by SCFAs (Figure 3). Furthermore, growing evidence has highlighted that SCFAs exhibited positive effects on kidney disease in both experimental animals and patients.

Clinical investigations of gut microbiota-derived SCFAs

Recently, multiple studies focusing on microbiota in CKD or end-stage renal disease (ESRD) patients have reported a

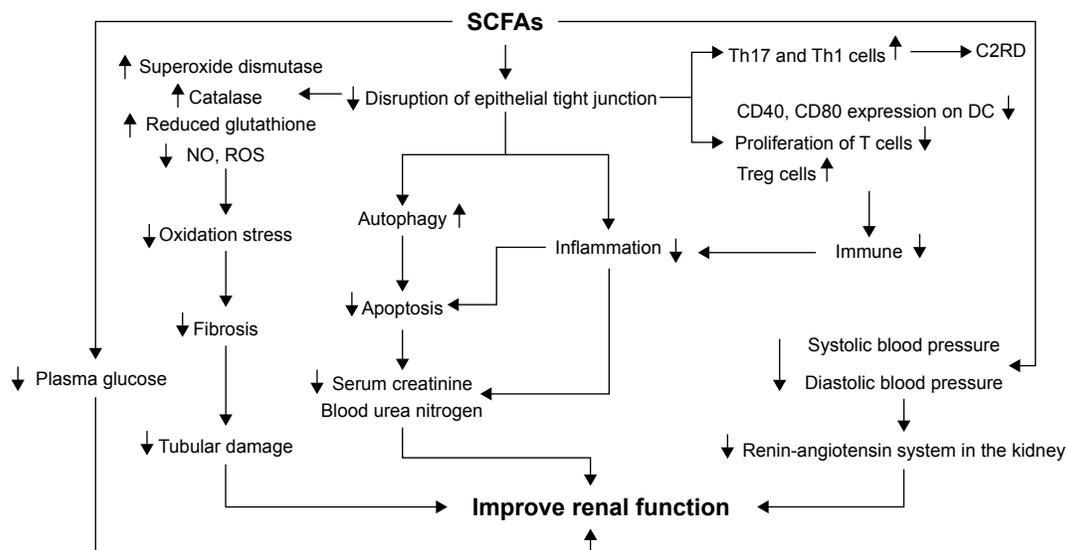


Figure 3 Regulation of short-chain fatty acids to improve kidney function SCFAs can decrease the disruption of epithelial tight junction. After getting absorbed in blood, SCFAs can suppress oxidation stress by increasing superoxide dismutase, catalase, and reduced glutathione, and by decreasing nitric oxide (NO) and reactive oxygen species (ROS), which can lead to the decline of renal fibrosis and amelioration of tubular damage. In addition, SCFAs can also inhibit apoptosis by promoting autophagy and suppressing inflammation by regulating immune system, thereby decreasing serum creatine as well as blood urea nitrogen to improve renal function. Regulation of SCFAs on blood pressure and plasma glucose may help to ameliorate renal function in chronic kidney diseases. However, SCFAs can also increase Th17 and Th1 cells to promote acetate- or C2-induced renal disease (C2RD) under certain condition, as the negative outcomes of SCFAs on kidney.

Abbreviation: SCFAs, short-chain fatty acids.

correlation between dysbiosis and CKD.^{7,98} Compared with control groups, patients with CKD or ESRD have altered microbiota⁹⁹ with increased bacteria that possessed urease, uricase, p-cresol-, and indole-forming enzymes and reduced bacteria that possessed SCFA-forming enzymes.¹⁰⁰ Uremic toxicities produced by microbiota could not only worsen the intestinal environment and alter its composition, but also affect cardiovascular disease progression and mortality in patients with CKD and ESRD.^{101–105} For treatment of these toxicities, dietary fiber supplementation in a group of chronic hemodialysis patients was reported to reduce serum concentration of indoxyl sulfate and p-cresol sulfate,¹⁰⁶ and the use of indoxyl sulfate-binding agent, AST-120, in pre-dialysis CKD patients also improved uremic symptoms, enhanced 5-year survival rate, and potentially delayed the onset of uremia.^{107,108} Compared to gut microbiota-generated toxicities, there were few studies that focused on SCFAs in CKD/ESRD patients, and most studies were related to dietary management. For instance, in ESRD patients, reduced dietary fiber intake was associated with a reduction in the population of butyrate-forming bacteria,¹⁰⁰ and after improving dietary management, colonic-CKD pathology ameliorated.¹⁰⁹ On the whole, these observations suggest the potentially beneficial effects of fiber-rich diets on CKD progression. However, despite indirect positive effects of SCFAs on remission of CKD/ESRD, direct effects on kidney diseases are still in the experimental stage and require further study.

Experimental studies of SCFAs in animals

In recent decades, a small but growing number of animal experiments focusing on SCFAs in kidney disease have been reported using different models. However, these are mainly divided into two parts: acute kidney injury (AKI) and CKD (Table 2).

AKI

Regarding AKI, researchers have expanded the role of acetate to explain the gut–kidney connection in several animal models, including ischemia-reperfusion injury, contrast-induced nephropathy (CIN), and gentamicin-induced nephrotoxicity. Though various mechanisms were reported, most of these studies suggest that decreasing inflammation and enhancing antioxidant activity by SCFAs may result in the improvement of renal function.

In the ischemia-reperfusion injury model, treatment with acetate or acetate-producing bacteria could reduce kidney injury.² The key mechanism of action of SCFAs against kidney injury was suggested to be the reduction of inflammatory cytokines and chemokines locally and systemically, as well as the inhibition of production of reactive oxygen species (ROS), apoptosis, and chromatin modification.² It is also interesting to note that in the ischemia-reperfusion models of other tissues, SCFAs¹ or SCFA-producing bacteria¹¹⁰ have been shown to exhibit protective effects, implying that the underlying mechanism may be common across tissues.

Table 2 Applications of SCFAs in animal models of kidney injury

Diseases	Administration	Effect of SCFAs on disease models	References
AKI			
Ischemia reperfusion injury	C2, C3, and C4 C2-producing bacteria	Improve renal function Decrease local and systemic inflammation, oxidative cellular stress, cell infiltration/activation Decrease apoptosis and increase autophagy Decrease HDACs activity Modulate chromatin modification enzymes	2
Contrast-induced nephrotoxicity	C4	Improve renal function Decrease kidney IL-6 and lipid peroxidation Decrease kidney NF- κ B and pI κ B α	111
Gentamicin-induced nephrotoxicity	C4	Improve renal function Improve body weight and food and water intake Increase superoxide dismutase, catalase, and reduced glutathione Increase inducible prohibitin	112
Ureteritis and hydronephrosis	C2, C3, and C4	All major SCFAs have acetate- or C2-induced renal disease (C2RD) activity Develop inflammatory responses and hyperplasia leading to ureteral obstruction Increase inflammatory Th17 and Th1 cells Gpr41 $^{-/-}$ and Gpr43 $^{-/-}$ mice also develop C2RD	117
CKD			
Diabetic nephropathy	C4	Improve renal function Decrease plasma glucose Decrease fibrosis and collagen deposition Decrease apoptosis Decrease HDACs activity Decrease activation of NF- κ B and DNA damage	115
Chronic kidney disease	High-fiber diet	Improve renal function Decrease inflammation Decrease oxidative stress Decrease disruption of colonic epithelial tight junction Decrease nuclear factor erythroid 2-related factor 2 (Nrf2) Decrease activation of NF- κ B	80
DOCA-salt hypertensive	High-fiber diet C2	Decrease systolic blood pressure and diastolic blood pressure, cardiac fibrosis and left ventricular hypertrophy Decrease renal fibrosis Downregulate cardiac and renal Egr1 Downregulate renin-angiotensin system in the kidney and MAPK signaling in the heart	116
Normal	C2, C3, and C4	C4 decreases pro-inflammatory cytokine C3/C4 increase Treg cells	75

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HDAC, histone acetylation; IL, interleukin; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor- κ B; SCFAs, short-chain fatty acids.

CIN is another form of AKI with exposure contrasting that of the media. A study showed that sodium butyrate protected against kidney injury by inhibiting inflammatory and oxidative tubular damage, with nuclear factor- κ B signal pathway playing key roles in the development of CIN.¹¹¹ However, the study did not exclude other potential mechanisms by which SCFAs may take part in inflammatory response, such as inhibition of HDAC, given that the regulatory mechanisms of SCFAs are extremely complex.

The effect of acute and chronic treatment of sodium butyrate in gentamicin-induced nephrotoxicity was also assessed. In an animal experimental model, kidney injury was

attenuated by long-term oral administration of sodium butyrate via enhanced renal antioxidant enzymes activity, which promoted the expression of prohibitin protein¹¹² and increased the levels of superoxide dismutase, catalase activity, and reduced glutathione.³³ Another drug-induced nephropathy, paracetamol-induced nephrotoxicity, was reported to be protected by ethyl acetate extract of *Zingiber zerumbet* rhizome. This process was also probably mediated by its antioxidant properties.¹¹³

Taking into account all of these recent studies, they have almost included all main types of AKI experimental models and have shown the positive effects of acetate or butyrate to

improve renal function. Although the results are exciting, they are still not sufficient to drop the veil of SCFAs, and the underlying mechanism still remains unclear; therefore, more studies are that focus on SCFAs are needed.

CKD

Supposing that SCFAs play a significant role in AKI, it might be of interest to define their role in the development and progression of CKD. Increasing dietary fiber in CKD rats showed similar results to clinical research, with significantly improved intestinal epithelial tight junctions, reduced oxidative stress and inflammation, and less severe renal dysfunction.⁸⁰ Besides increasing SCFAs in uremic rats could improve kidney function, and neutralizing bacteria-derived uremic toxin indoxyl sulfate inside the gut could also delay the progression of CKD and cardiovascular disease.¹¹⁴ The direct effects of SCFAs on kidney disease have been studied in juvenile diabetic rats by administering butyrate post-treatment; the results showed that SCFAs not only decreased plasma glucose, creatinine, and urea but also improved renal histological alterations (including fibrosis and collagen deposition), apoptosis, and DNA damage.¹¹⁵ Supplementation of acetate was reported to attenuate glomerular and tubulointerstitial fibrosis in the DOCA-salt mice.¹¹⁶

However, there are still several negative outcomes of SCFAs on kidney injury. After chronically increasing oral doses of SCFAs to higher than physiological levels in mice, Th1 and Th17 cells were observed to generate in the ureteropelvic junction and proximal part of the ureter, which induced inflammation and led to kidney hydronephrosis,

hereafter called acetate- or C2-induced renal disease (C2RD).¹¹⁷ It was indicated that C2RD was not conducted by GPR41/GPR43,¹¹⁷ but the underlying mechanism is still not clear. However, SCFAs were confirmed to play a dual role in the inflammation system depending on the stimulus concentration in kidney disease, consistent with the aforementioned inflammation of SCFAs. Besides C2RD, mice fed a high-fiber diet had increased gut butyrate and were more susceptible to infection with *Escherichia coli*,¹¹⁸ as well as enhanced Gb3 levels in the gut and kidney, which resulted in severe kidney damage.¹¹⁹

Despite growing interest in SCFAs, many problems involving chronic kidney injury have not yet been answered and are still disputed. Unlike the positive effects of SCFAs on AKI models that have been observed, the influence of SCFAs on CKD seems to be more controversial. This enhances the importance of SCFAs concentrations when testing the benefits of SCFAs in kidney disease and encourages further studies to identify the pharmacological concentration. Importantly, the benefits of SCFAs on diabetic nephropathy, the leading cause of ESRD worldwide, should be paid more attention to, because of the positive effects of SCFAs on regulation of energy metabolism and immune inflammation.

Experimental studies of SCFAs in kidney cells

Researchers have explored not only the in vivo effects of SCFAs but also their mechanism of action on kidney cells (Table 3). When glomerular mesangial cells (GMCs) are induced by high glucose and lipopolysaccharide (LPS),

Table 3 Applications of SCFAs in different kidney cells

Diseases	Cell types	Cell administration	Effects	References
AKI induced by IRI	BM-DCs HK-2 cells	C2, C3, and C4	Decrease BM-DCs activation, APC function, NF- κ B activation and nitric oxide production, ROS production Inhibit HIF-1 α translocation to the nucleus, lactate production, and VEGF expression under hypoxia	2
Ureteritis and hydronephrosis	Renal T cells	C2, C3, C4	Rapamycin decreases T cells	117
Diabetic nephropathy	GMCs	C2, C3, C4 GPR43 agonist	Inhibit GMCs proliferation Decrease inflammation Decrease ROS and oxidative stress Decrease ICAM-1	121
Normal	HK-2 cells	Dietary supplementation with gum arabic (SUPERGUM)	C4 decreases TGF- β 1 generation and TGF- β 1-dependent signaling	122
Normal	CD4+ T cells CD11c+ DCs Foxp3 induction	C4	Decrease pro-inflammatory cytokine Increase Treg induction	75
Normal	Porcine kidney cells	C4	Upregulate WT1 expression	127

Abbreviations: APC, antigen presenting cells; BM-DCs, bone marrow dendritic cells; GMCs, glomerular mesangial cells; HIF-1 α , hypoxia inducible factor-1 α ; HK-2 cells, epithelial kidney cell line; ICAM-1, intercellular adhesion molecule-1; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; TGF- β 1, transforming growth factor- β 1; VEGF, vascular endothelial cell growth factor; WT1, Wilms tumor 1.

the pharmacological concentrations of SCFAs accompanied with GPR43 agonist diminish renal inflammation by decreasing MCP-1 and IL-1 β . Inflammation and oxidative stress are inseparably linked, as each causes and strengthens the other, which could cause glomerulosclerosis, tubular atrophy, and fibrosis.¹²⁰ Therefore, besides decreasing inflammation, SCFAs inhibit ROS generation induced by high glucose and LPS in GMCs¹²¹ and HK-2 human kidney epithelial cells after hypoxia.² In addition to GMCs, elevated concentration of butyrate in proximal tubular epithelial cells was described to prevent TGF- β 1 generation,¹²² which is involved in renal fibrosis, and its antagonistic action has been proposed as a potential therapeutic target.^{123–125} In porcine kidney fibroblast, WT1, involved in cell proliferation and development, was markedly enhanced along with an increase in sodium butyrate levels and by prolonging the treatment.^{126,127}

These investigations of SCFAs on kidney resident cells (glomerular cells and tubular cells), which concentrate on inflammation, ROS, and fibrosis, are in agreement with the findings from animal experiments and provide more potential pathways to understand the mechanisms. However, future studies are still required to focus more on the interaction among SCFAs-associated molecular patterns and metabolism, inflammation, and immune system in order to clarify the molecular mechanisms behind kidney injury in the pathogenesis of kidney disease.

Conclusion

In summary, the function of gut microbiota-derived SCFAs in kidney disease has become an exciting area in recent years. SCFAs play extensive roles in host physiology, such as regulation of energy metabolism, immune inflammation, and blood pressure by recognizing their receptors and inhibiting HDACs. However, the entire field of SCFAs in kidney disease is still in its infancy. It has now been reported that the main beneficial effects of SCFAs on kidney function were by decreasing inflammation and enhancing antioxidant activity. Nevertheless, there are still few related studies, and all the concerned studies are either preliminary or controversial. Thus, in coming years, more explorations will be needed to better understand these pathways and their potential implications.

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Disclosure

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