REVIEW

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The role of the intestinal microbiome in cognitive decline in patients with kidney disease

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ABSTRACT

Cognitive decline is frequently seen in patients with chronic kidney disease (CKD). The causes of cognitive decline in these patients are likely to be multifactorial, including vascular disease, uraemic toxins, blood–brain barrier leakage, and metabolic and endocrine changes. Gut dysbiosis is common in patients with CKD and contributes to the increase in uraemic toxins. However, the gut microbiome modulates local and systemic levels of several metabolites such as short-chain fatty acids or derivatives of tryptophan metabolism, neurotransmitters, endocannabinoid-like mediators, bile acids, hormones such as glucagon-like peptide 1 (GLP1) or cholecystokinin (CCK). These factors can affect gut function, immunity, autonomic nervous system activity and various aspects of brain function. Key areas include blood–brain barrier integrity, nerve myelination and survival/proliferation, appetite, metabolism and thermoregulation, mood, anxiety and depression, stress and local inflammation.

Alterations in the composition of the gut microbiota and the production of biologically active metabolites in patients with CKD are well documented and are favoured by low-fiber diets, elevated urea levels, sedentary lifestyles, slow stool transit times and polypharmacy. In turn, dysbiosis can modulate brain function and cognitive processes, as discussed in this review. Thus, the gut microbiome may contribute to alterations in cognition in patients with CKD and may be a target for therapeutic interventions using diet, prebiotics and probiotics.

Keywords: chronic kidney disease, cognition, exerkines, gut microbiome, short chain fatty acids

INTRODUCTION

Cognitive function declines in patients with acute kidney injury (AKI) or chronic kidney disease (CKD) at a much higher prevalence than in a healthy matched population [1, 2]. The progressive loss of brain function can affect many areas, including motor function, sleep, eating control, mood and inhibitory control, and cognitive functions such as short- and long-term memory and attention [1, 2]. Cognitive decline and CKD share common risk factors such as diabetes, obesity, hypertension, autoimmunity, genetic risk factors and lifestyle (e.g. smoking, diet, etc.), suggesting some common pathological mechanisms [1, 2].

The loss of cognitive function in patients with CKD results in a loss of quality of life for patients, a burden on their families and increased healthcare costs, and raises ethical issues such as the eligibility of these patients for kidney transplantation [3]. The increase in diseases that cause CKD, such as diabetes, obesity and hypertension, and the ageing of societies in developed countries require a better understanding of the causes of CKD and its impact on cognition in order to develop strategies to prevent or better treat cognitive decline [1, 2].

In recent years, the gut and its microbiome have emerged as an important modulator of central nervous system (CNS)

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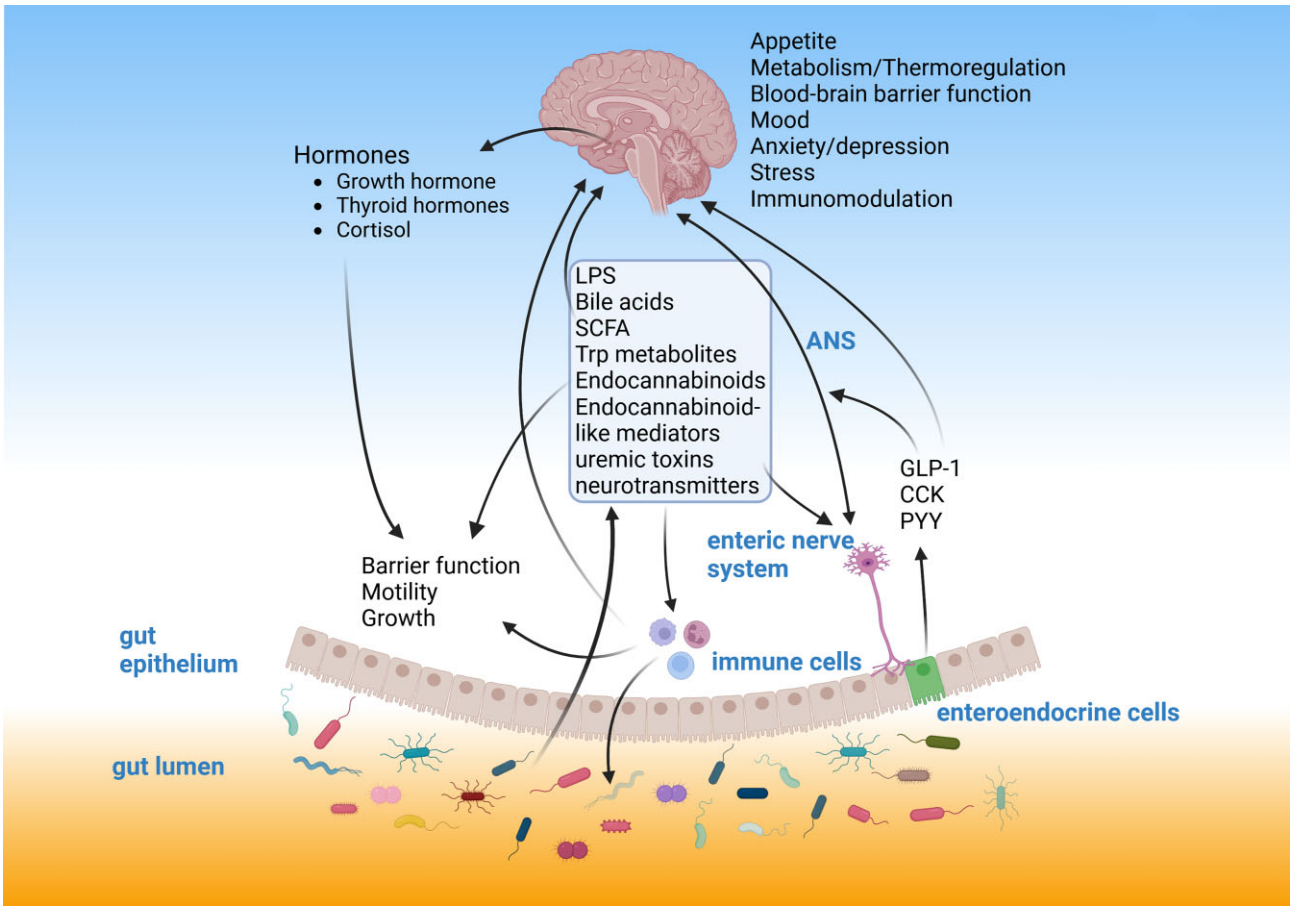

Figure 1: Crosstalk between gut microbiome and brain mediated by gut microbiome–derived metabolites, hormones produced by enteroendocrine cells, the enteric and autonomous nerve system (ANS), and hormones produced by the brain. Various brain functions are modulated by these pathways. Figure modified from [8].

function in health and disease. As discussed below, multiple direct and indirect mechanisms mediate the crosstalk between CNS and gut functions. Various components of the gut microbiota interact directly with the (epithelial) cells of the intestinal barrier. In addition, the gut microbiota produces metabolites that act on epithelial, sensory and immune cells embedded in the gut wall and are transported to the brain. CKD modulates the composition and function of the gut microbiota and may thereby alter gut–CNS interactions directly or indirectly by altering immunity or metabolism [4–8]. Emerging therapies aim to modulate the gut microbiota and may offer preventive and/or therapeutic opportunities in patients with CKD and cognitive decline.

This review summarizes recent developments in our understanding of gut microbiota modulation of CNS function, particularly in the context of CKD, and discusses potential preventive or therapeutic approaches targeting the gut microbiota. In the absence of experimental data directly addressing the role of microbiota in the development of cognitive decline in patients (or animal models) with CKD, we synthesize information from different fields. The review will provide an overview of potentially related areas rather than an in-depth discussion of molecular mechanisms, which would be speculative or only by analogy to established roles of microbiota in other neurological disorders. We refer the interested reader to the excellent and recent reviews that have discussed mechanisms in these areas.

THE GUT MICROBIOME AND ITS IMPACT ON THE ENTERIC, AUTONOMOUS AND CENTRAL NERVOUS SYSTEMS

The gut microbiome is made up of bacteria, yeast and viruses. Here we will focus on the bacterial component, which is the best studied of the three. The six most abundant bacterial phyla include Bacillota (Firmicutes), Bacteroidota, Actinomycetota, Pseudomonadota, Synergistota and Verrumicrobia [9]. However, Bacillota and Bacteroidota represent more than 90% of all bacteria in the healthy gut. As discussed below the composition and activity of the gut microbiota is strongly influenced by a variety of factors relevant to patients with CKD. These include diet, physical activity, drugs and metabolites cleared by the kidneys.

The activity of the gut microbiota affects brain function in a variety of ways in healthy individuals, and changes in the microbiota can therefore have profound effects on brain integrity and function as reviewed recently [4–8, 10–13] (Fig. 1). Mechanisms of gut microbiota–brain crosstalk have been excellently explained in references [14] and [15].

Briefly, data from animal models and humans suggest that the gut microbiome modulates directly and indirectly several brain functions, including response to stress, anxiety-like behaviour, depression-like behaviour, nociception, appetite and hunger, taste preferences, or metabolic regulation by the CNS. As evident from neurodegenerative diseases and the possible involvement of the

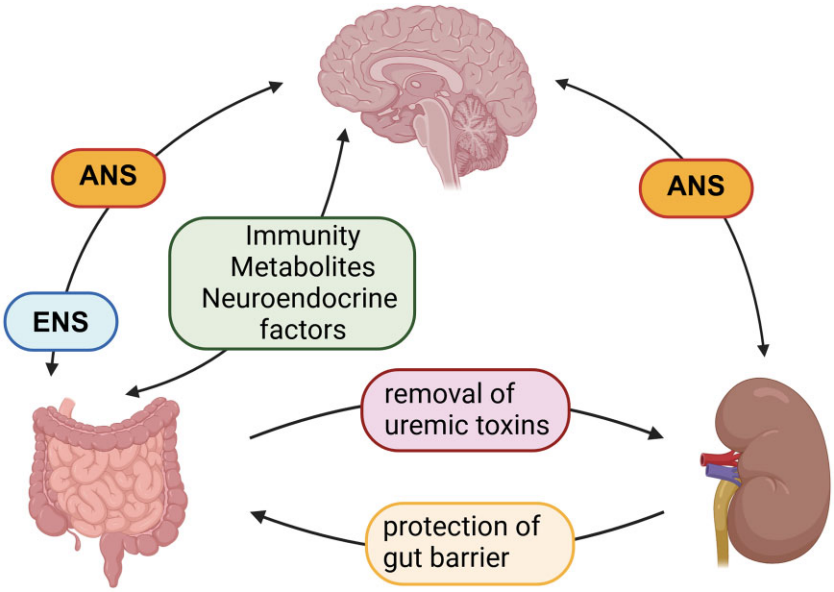

Figure 2: Interactions of gut-derived factors, kidney function and brain functions. ENS, enteric nerve system; ANS, autonomous nerve system.

gut microbiome, also motor functions, memory and other cognitive domains are influenced by the gut microbiome.

The gut microbiota modulates systemic and brain functions in different ways mostly through neuroimmune and neuroendocrine pathways that often involve vagal nerves and may be mediated by various bacteria-derived metabolites such as short chain fatty acids (SCFAs), mostly butyrate, tryptophan and secondary bile acids, as well as neurotransmitters or their modulators. These molecules interact with enteroendocrine cells, enterochromaffin cells, intestinal epithelial cells and immune cells, or circulate systemically and reach directly the brain [4]. Various neurotransmitters or other neuroactive molecules are produced or their secretion promoted by the gut microbiota including GABA, serotonin norepinephrine, acetylcholine, dopamine, oxytocin, endocannabinoids and endocannabionoid-like mediators, brain-derived neurotrophic factor (BDNF), and SCFAs [5, 16, 17]. These mediators may either directly influence brain functions or act on receptors present in epithelial cells, enteric nerve cells or the autonomous nerve system. Various bacteria-derived metabolites modulate the function of enteroendocrine or enterochromaffin cells which release different endocrine factors including glucagon-like peptide 1 (GLP1) cholecystokinin (CCK) or serotonin, which regulate brain function as well as intestinal (e.g. motility and transit time, secretion, absorptive processes) and metabolic activity (e.g. insulin secretion, pancreatic enzyme secretion). Their effects on food intake are best studied but neuroprotective actions of GLP1 are emerging [18]. The activity of the enteroendocrine and enterochromaffin cells is strongly regulated by dietary intake of carbohydrates, proteins (particularly tryptophan derivates such as in the kynurenine pathway originating from amino acid fermentation) and fat, as well as by SCFAs (via GPR43 and GPR41 receptors or epigenetic modulation) and secondary bile acids (via FXR receptors) produced by gut microbiota [4]. Gut microbiota also modulate resident immune cells that release pro- and anti-inflammatory signals affecting gut barrier integrity as well as systemic immune functions [5]. Effects of the gut microbiome extend beyond short-term regulation of brain function. Factors such as SCFAs or lipopolysaccharides (LPS) produced by gut microbes or endogenous mediators modulated by microbial products, such as BDNF, affect directly or indirectly neurogenesis, synaptic plasticity, neurotransmitter synthesis or blood–brain barrier (BBB) integrity [8] (see also below).

Gut microbiome composition and activity is also regulated by output from the CNS via the autonomous nerve system and enteric nerve system that affects gut motility and stool transit time, via regulating dietary intake (hunger and satiety), and secretion of digestive juices, bicarbonate, antimicrobial peptides and immune functions. Moreover, the regulated release of different hormones such as thyroid hormones, growth hormone and stress hormones (mostly cortisol) has profound effects of gut function and gut microbiota [4, 5] establishing a reciprocal regulation and interaction between both organs.

Kidney function can modulate the interactions between gut microbiota and brain by clearing circulating factors by filtration or active tubular secretion which is most obvious for bacteria-derived molecules that act as uraemic toxins in CKD (see below) (Fig. 2).

SEX DIFFERENCES IN THE GUT MICROBIOME BRAIN AXIS

Across the lifespan, sex differences in the diversity and composition of the gut microbiome have been found in animals and humans. Sex hormones can modulate the gut microbiome and vice versa [19]. Gut bacteria metabolize sex hormones, their precursors and metabolites, and may thereby influence sex hormone–dependent host functions [20–22]. Age-related declines in both oestrogen and testosterone have been implicated in the pathogenesis of Alzheimer's disease [23, 24]. Oestrogens may help maintain cholinergic tone, thereby reducing the deposition of β-amyloid plaques in the brain [25]. The role of the gut microbiome in sex differences in human CKD and its manifestations will require further attention.

CHANGES OF THE GUT MICROBIOME IN AKI/CKD

In AKI and CKD, changes in the gut microbiome may contribute to the manifestations of CKD and AKI (e.g. by providing precursors

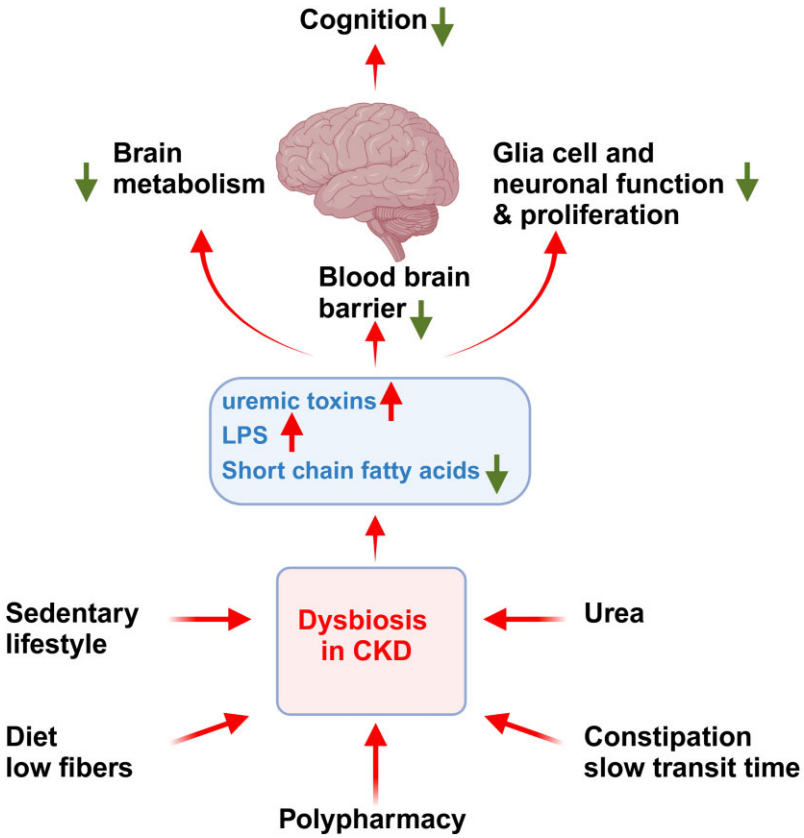

Figure 3: Factors causing intestinal dysbiosis in patients with CKD and the impact of dysbiosis on brain functions. Red arrows negative impact, green arrows positive factors reduced by dysbiosis-induced factors.

for uraemic toxins) and may also modulate the kidney resilience to injury and its ability to support brain health.

THE COMPOSITION OF THE GUT MICROBIOME IN KIDNEY DISEASE

Dysbiosis of the gut microbiome has been recognized as a key contributor to the pathogenesis of both AKI and CKD, influencing disease progression and therapeutic outcomes. In kidney disease, disruption of the balance of the gut microbiota leads to a reduction in microbial diversity by promoting a shift in community structure, increasing the abundance of proteolytic bacteria and decreasing saccharolytic populations. These changes alter the bacterial metabolite output, and increase intestinal barrier permeability and systemic inflammation, which can exacerbate kidney damage [26–28].

When discussing gut microbiome alterations in patients with CKD in comparison with healthy individuals, important confounding factors must be considered, as recently discussed [29]. These confounders include not only estimated glomerular filtration rate, but also age, lifestyle factors such as sedentary lifestyle or exercise, differences in diet (especially fibre and water intake), comorbidities known to influence the gut microbiome (diabetes, hypertension, inflammatory diseases), host genetics, time of sampling (day and season), medications and stool transit time (often reduced in patients with advanced stages of CKD). Unfortunately, many previous studies were either unaware of these confounders or ignored their importance, and future studies need to be designed to include these variables in the analyses [29]. Similarly, the changes in gut microbiome composition discussed below must be interpreted with caution, as many studies were also too small to account for all confounders.

In mice, ischaemia–reperfusion injury, a model for AKI, higher abundance of *Clostridium*, *Ruminococcus* and Enterobacteriaceae and lower abundance of *Bifidobacterium* and *Lactobacilli* was found [30]. The role of the gut microbiome in also modulating the outcome from AKI has been recently reviewed [31]. Patients with CKD show significant changes in the composition of their gut microbiota, including a relative decrease in Prevotellaceae and *Roseburia* and an increase in pathobionts such as Enterobacteriaceaecae, Streptococcaceae and *Enterococcus* [32]. This is associated with an overall decrease in the production of SCFAs such as butyrate and an increase in urease activity [33, 34]. Similarly, changes in the diversity of the gut microbiome have been reported in patients on haemodialysis or peritoneal dialysis [35].

The causes of dysbiosis in patients with CKD are multifactorial (Fig. 3). Major contributors are elevated plasma urea levels, often sedentary lifestyles (especially in haemodialysis patients), low-fibre diets, constipation and slow stool transit times, and polypharmacy. In CKD, the intestinal epithelium secretes urea into the intestinal lumen, where it is hydrolysed by bacterial ureases to ammonia and binds protons (i.e. raises the intraluminal pH) to form ammonium. Higher luminal pH and urea levels favour the growth of bacteria that use urea as an energy source. Whether high urease activity is beneficial or detrimental remains an open question. Ammonia is well known as a neurotoxic agent in hepatic encephalopathy, while recent data in mice suggest that gut-derived ammonia may be an important precursor for brain metabolism to produce glutamine, glutamate and GABA [36]. Low levels of glutamate and GABA are associated with

depressive-like behaviour in mice and restoring brain glutamine levels in mice with reduced intestinal ammonia production reversed depression.

Diet has a profound effect on the diversity and activity of the gut microbiome [37–39]. Patients with CKD have dietary patterns that favour loss of diversity and dysbiosis. This is partly due to the specific dietary advice given to patients with CKD, which includes restricting fruit, vegetables and nuts (to control potassium), as well as some other high-fibre foods, all of which are essential to support butyrate-producing bacteria. Low-protein diets also modulate the gut microbiome, increasing Lactobacillaceae, Bacteroidaceae and *Streptococcus anginosus*, while decreasing *Roseburia faecis* and *Bacteroides eggerthii*. Keto analogue diets also affect microbiome composition [9].

Diets low in fibre are also associated with another cause of dysbiosis, as fibre is important in binding water (and other toxins) and accelerating stool transit time. Low fibre in combination with hyperkalemia and water restriction, autonomic neuropathy, low physical activity, and potassium and phosphate binders can promote constipation [40]. Low stool transit time increases dysbiosis also independently from the presence of CKD [41, 42].

Low physical activity in patients with CKD [43] is another risk factor for dysbiosis. High physical activity in non-CKD individuals is associated with higher microbiota diversity and higher production of SCFAs [44]. Physical activity also associates with shorter stool transit times, reduced levels of bile acids and generally lower levels of systemic and intestinal inflammation, also increasing intestinal barrier function [45].

Patients with CKD are often exposed to a variety of medications, including different classes of antihypertensives, sodium-glucose cotransporter 2 (SGLT2) inhibitors, antidiabetic drugs such as metformin, laxatives, proton pump inhibitors, iron supplements, phosphate binders, vitamin D supplements and antibiotics [46, 47]. In patients with cancer, use of chemotherapy and radiotherapy usually contribute to alterations of the gut microbiota [48]. Polypharmacy is associated with poorer clinical outcomes and has a profound effect on the microbiota. Most of the drugs listed above are associated with multiple changes in the microbiota, even in patients without CKD [9]. The loss of microbial diversity caused by these drugs predisposes pathogenic bacteria to overgrowth, as exemplified by the increased risk of *Clostridium difficile* infection in patients with CKD [49]. Many non-antibiotic drugs have been recently shown to influence microbiota biology, including some commonly used in CKD such as vitamin D [50–53].

Role of gut-derived uraemic toxins in CKD and AKI

Uraemic toxins, as classified by the EUTox working group, include small water-soluble molecules, middle-sized molecules and protein-bound uraemic toxins (PBUTs), which accumulate due to reduced clearance [54]. Notably, plasma levels of these toxins rise with worsening kidney function, peaking in kidney failure [55]. Additionally, renal replacement therapies like haemodialysis and peritoneal dialysis are less effective at removing middle-sized and PBUTs, leading to their accumulation in various organs and tissues [56].

The primary uraemic toxins derived from the gut microbiota include indoxyl sulfate, p-cresyl sulfate and trimethylamine N-oxide (TMAO). They are produced through the fermentation of proteins and amino acids by gut bacteria. Indoxyl sulfate and p-cresyl sulfate are generated from tryptophan and tyrosine, respectively, and are associated with vascular damage, endothelial dysfunction and increased cardiovascular risk [57, 58]. TMAO, derived from dietary choline and carnitine, has been linked to cognitive decline and atherosclerosis and adverse cardiovascular outcomes in CKD patients [59–62]. These toxins exert their deleterious effects by inducing oxidative stress, inflammation and fibrosis [63]. PBUTs cause multi-organ damage and, by increasing in the systemic circulation, contribute to multiple comorbidities such as cardiovascular disease, immune dysfunction, malnutrition and inflammation [64].

The condition can be replicated in animal models where induction of renal failure increases accumulation of various uraemic toxins that affect BBB integrity and cognitive functions, as well as other organ functions (e.g. cardiovascular functions) [65–69].

The gut microbiota and kidney and brain resilience

Humans, their ancestors and their gut microbiome have been sharing metabolites for millions of years, so it is not surprising that the microbiota produce metabolites that enhance the resilience of human tissues to injury [70]. For example, dietary fibre is metabolized to SCFAs such as acetate, propionate and butyrate, all of which have been associated with improved health outcomes in multiple preclinical and clinical contexts [71]. The interaction between diet, microbiota and host is so close and relevant to health that even maternal dietary fibre has a long-term effect on the cardiometabolic health of offspring, an effect mediated by SCFAs and their receptors [72]. In addition to activating specific receptors, SCFAs modulate the epigenome, as exemplified by butyrate inhibition of histone deacetylase, and protect the brain [73, 74]. Microbiota production of SCFAs can be perturbed by the metabolic conditions of uraemia itself, as discussed below, but also by metabolic diseases that cause CKD, as exemplified by lyso-Gb3, a metabolite accumulated in Fabry disease that decreases butyrate production [75].

A link has been established between microbiota-derived SCFAs and kidney and brain resilience. For example, butyrate is renoprotective and prevents nephrotoxic AKI in mice by preserving the expression of renoprotective factors such as alpha-klotho, PGC1α and Nlrp6 [76], which are lost during AKI and CKD and have anti-inflammatory activity [77–80]. Indeed, alpha-klotho administration reproduced the renoprotective effects of butyrate, including reduced renal inflammation [76]. Interestingly, prophylactic butyrate administration was not protective: butyrate had to be administered during AKI. This has important clinical implications if translated to humans: most AKI episodes occur in the hospital, where antibiotic use, fasting, reduced food intake and parenteral nutrition interfere with fibre delivery to the gut microbiota and the microbiota's ability to produce butyrate.

Reduced renal production of alpha-klotho during renal injury has systemic effects that may involve the brain, as renal tubular cells are the major source of circulating alpha-Klotho levels [81], alpha-klotho deficiency causes cognitive impairment in mice [82] and partially reproduces the transcriptome of brain dementia [83], plasma alpha-klotho levels are associated with cognition in humans [84, 85], and maintaining or increasing circulating alpha-klotho levels by various means, including parenteral administration, protects against cognitive deficits in both mice and rhesus monkeys [86, 87]. A key mediator of brain protection by circulating alpha-klotho is CXCL4/platelet factor 4 (PF4), a platelet-derived cytokine that crosses the BBB and may account for the brain-rejuvenating effect of blood in young mice [88–90]. Indeed, increasing PF4 levels may be one of the anti-inflammatory pathways triggered by alpha-klotho [90].

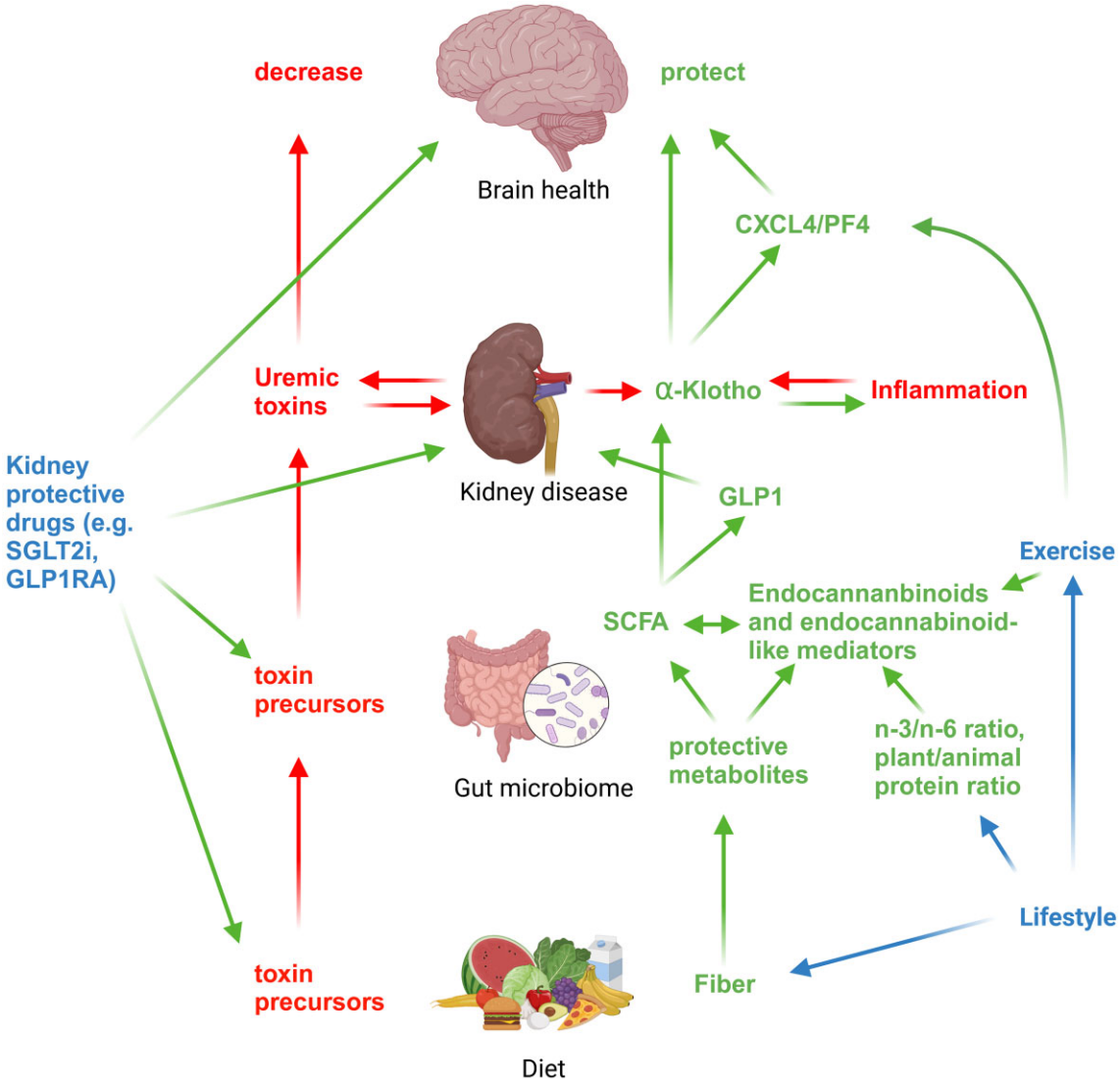

Figure 4: Kidney disease has a two-hit impact on brain health by promoting toxin availability and decreasing resilience to injury. Kidney disease is characterized by the loss of multiple kidney functions, ranging from excretion of uraemic toxins to production of tissue protective and antiaging factors such as alpha-klotho. Gut microbiota products, such as SCFAs (such as butyrate), are instrumental in preserving the kidney production of Klotho (determining circulating Klotho levels), which are also preserved by novel kidney protective drugs. SCFAs also promote the secretion of GLP1. Circulating alpha-klotho preserves brain health by increasing availability of the exerkine (i.e. also released in response to exercise) CXCL4/platelet factor 4 (PF4). Closing the circle on the relationship between lifestyle, kidney and brain health, and kidney protective medications, other microbiota products such as endocannabinoid metabolites, regulate motivation of exercise and GLP1 receptor agonists modulate diet. Blue arrows indicate modulation, red arrows indicate a negative impact and green arrows indicate positive impact.

Butyrate and Nlrp6 also protect against gut inflammation [91, 92]. Gut inflammation may spread systemically to reduce renal alpha-Klotho expression. Indeed, systemic inflammation decreases renal alpha-Klotho production, and anti–tumour necrosis factor antibodies preserve renal alpha-Klotho in the presence of gut inflammation [79, 93].

As PF4 is an exerkine, i.e. a signalling molecule released in response to acute and/or chronic exercise [25], the interaction of diet (fibre), butyrate-producing microbiota and renal-derived alpha-klotho is at the crossroads of lifestyle (healthy diet plus exercise-induced exerkines) and drugs for the prevention and treatment (e.g. via strategies such as SGLT2 inhibitors and GLP1 receptor agonists) of kidney disease and its effects on the brain [94–98]. These novel kidney-protective drugs may also have beneficial effects on gut microbiota [99–101] and brain health, and conversely, SCFAs promote GLP1 secretion [100]. Other microbiota products may contribute to healthy brain ageing by interacting with lifestyle. For example, microbiome-dependent production of endocannabinoid metabolites in the gut increases dopamine levels in the ventral striatum during exercise, thereby increasing motivation to exercise [102], again linking microbiota to renal health via exercise dependent alpha-Klotho, healthy lifestyle and delayed brain ageing.

Overall, all studies on the adverse brain effects of uraemic toxins formed in AKI or CKD should be viewed conceptually as a double hit: in addition to injury-inducing uraemic toxins, AKI and CKD are characterized by Klotho depletion, which reduces the resilience of the brain and other tissues to insults. (Figure 4).

The altered gut microbiome and its links to cognition in CKD

As discussed above, several metabolites produced by the healthy or dysbiotic microbiome affect key brain structures and functions. It is therefore not surprising that changes in the gut microbiome observed in animal models or in patients with CKD may be associated with or cause cognitive dysfunction. Some of these effects on the brain are briefly discussed below.

Alpha-klotho

Reduced effects of SCFAs on alpha-klotho and cognition as discussed above.

The BBB

Direct effects of uraemic toxins on the integrity of the BBB are well documented and loss of barrier function is implicated in several brain pathologies [103–105]. The BBB is disrupted both in animal models of CKD [66] and in patients with kidney failure [106]. Several toxins released by bacteria, such as LPS or uraemic toxins derived from bacterial products such as indoxyl sulfate, impair BBB integrity by acting on the toll-like receptor 4 (TLR4), or the aryl hydrocarbon receptor (AhR), respectively [67, 68]. Elevated urea levels also activate matrix metalloproteinase-2, leading to BBB breakdown [107].

Vascular damage

CKD is a major risk factor for vascular damage and dysfunction. Vascular damage promotes and causes neurodegenerative disease and cognitive decline [108, 109]. Several uraemic toxins such as phosphate, parathyroid hormone, fibroblast growth factor 23, urea, and the bacteria-derived toxins p-cresyl sulphate and indoxyl sulphate create a vascular milieu characterized by oxidative stress, reduced NO production and a proinflammatory state [110–112].

Neurotransmitters

Loss of BBB integrity in patients with CKD favours penetration of uraemic toxins and other molecules into the brain parenchyma. Increased bacterial metabolism of amino acids such as tryptophan can lead to depletion of this amino acid, which is the essential precursor for the synthesis of the neurotransmitters serotonin and melatonin. In rats with CKD, the bacterial metabolites p-cresyl sulphate, indoxyl sulphate and the tryptophan metabolites kynurenine, kynurenic acid, 3-hydroxykynurenine, anthranilic acid, xanthurenic acid, 5-hydroxyindoleacetic acid, picolinic acid and quinolinic acid increased, while serotonin and tyrosine decreased. Animals should show anxiety-like behaviour and cognitive deficits [113, 114].

Endocannabinoid-like mediators produced by the host in manner influenced by bacteria may act on local receptors that modulate gut barrier integrity and mediate or counteract some of the adverse effects of a high-fat diet on low-grade inflammation and the gut barrier [115]. Such mediators include the endocannabinoids and the *N*-acyl-serotonins, which can also counteract depression-like symptoms in animals [116]. Additionally, gut microbiota can also alter the levels of endocannabinoids and endocannabinoid-like mediators in the brain, in a manner predicted to affect mood [117]. Finally, gut bacteria produce endocannabinoid-like molecules, such as the *N*-acyl-glycines [118], which are known to affect the brain via PPARα [119] or the lysophosphatidylcholine receptor G2A/GPR132 [118].

Neuroinflammation/oxidative stress

Uraemic toxins such as indoxyl sulfate are neurotoxic [120] and cause systemic and local inflammation [121]. Indoxyl sulfate also causes astrocytosis via stimulation of AhR and neuronal cell death [122]. Similarly, homocysteine levels increase in CKD due to reduced folic acid production by colonic bacteria [123], and exacerbate neuroinflammation [124]. Dysbiosis and loss of intestinal barrier function causes invasion of bacteria, and local intestinal and systemic inflammation that includes increased circulation of proinflammatory cytokines and LPS that also affect brain [11].

Myelinization

The first step in the production of 4-ethylphenol (4-EP) from tyrosine is mediated by *Bacteroides ovatus*. 4-EP is then sulphated by human metabolism to 4-ethylpheyl-sulfate which can enter the brain [125]. There it reduces synthesis of the myelin sheath by oligodendrocytes ultimately affecting neuronal function. In patients with CKD, 4-EP clearance by the kidneys is reduced, and in mice, elevated levels of 4-EP reduce brain myelination and cause anxiety and depressive-like behaviour [125]. Elevated levels of 4-EP have also been found in patients with anxiety and autism [126]. It remains to be tested whether targeting 4-EP levels can affect brain health in people with CKD.

THE GUT MICROBIOME AS THERAPEUTIC TARGET

Based on the changes in gut microbiome in patients with CKD, the changes in gut microbiome–derived metabolites, and established and emerging links to brain pathologies, modulation of the gut microbiome is becoming a viable therapeutic target. Next to kidney replacement therapies, several and potentially synergistic strategies are plausible but will require controlled clinical trials before becoming recommended therapies (Fig. 5).

Physical activity

Physical activity has been shown to have beneficial effects in cognitive decline [127] and may act via release of exerkines on brain as discussed above. Physical activity also modulates the gut microbiome [44, 128]. Most studies in humans are cross-sectional and only few longitudinal studies exist. However, exercise is associated with higher microbiome diversity and higher production of SCFAs [45, 128, 129]. No studies have addressed the effect of exercise on the gut microbiome in patients with CKD to date.

Diet and nutrition

Dietary interventions in patients with CKD traditionally aim to prevent hyperkalemia, overhydration or high phosphate loads while providing sufficient protein and other nutrients [130]. A recent trial, the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND diet trial) provided no evidence for a benefit in a non-CKD population at risk for dementia [131, 132]. However, this population had normal kidney function, had been selected based on a family history of dementia and follow-up was only over 3 years. No information on gut microbiome was provided. In contrast, high adherence to a 1-year Mediterranean diet intervention led to improvement of global cognition and episodic memory [133, 134]. High diet adherence was further associated with specific microbiome alterations, increased SCFAs and decreased secondary bile acids and p-cresol production [133, 134]. An ideal diet for higher gut microbiome diversity and activity needs to contain sufficient amounts of dietary fibre which not only provides the

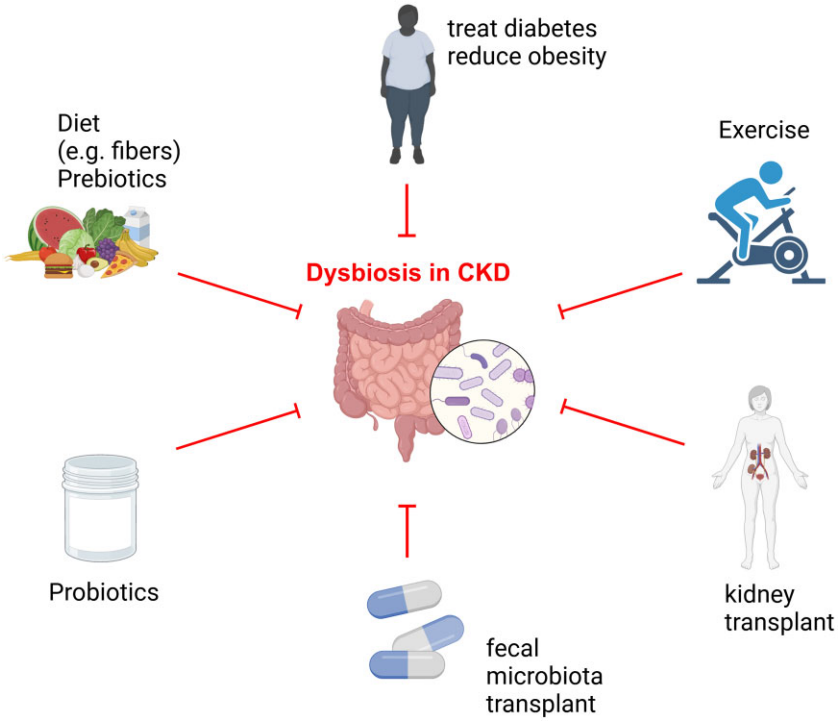

Figure 5: Strategies targeting the gut microbiome to improve cognitive function in patients with CKD.

source for SCFAs production but will also accelerate stool transit times and has the capacity to bind uraemic toxins. If fibres cannot be provided in the form of fruits, vegetables, whole grain products, and pulses and nuts, direct supplementation of fibres may be considered [135, 136]. Accordingly, even a very short period (2 days) of a Mediterranean-like diet, in individuals coming from a 12-day western-like diet, was recently shown to produce effects on circulating SCFAs and endocannabinoid-like mediators that are predicted to be beneficial for dysmetabolism and other potential consequences of gut dysbiosis [137]. Moreover, novel potassium binders may allow for a more liberal diet and even decrease ammonia absorption and serum urea levels, although their impact on the gut microbiome is still incompletely understood [138, 139].

Probiotic and prebiotic supplements

Modulation of the gut microbiota with probiotics (live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [140]), prebiotics (substrates, that are selectively utilized by host microorganisms conferring a health benefit [141]) or synbiotics (a combination of pro-and prebiotics) has been studied for prevention or improvement of cognitive decline as well as for correction of kidney disease associated dysbiosis and uraemic toxin production. Meta-analyses of randomized controlled trials testing the impact of probiotics on cognitive decline found improvement of cognitive functions in participants with impaired cognition [142, 143]. Fewer studies addressed the potential of prebiotic supplementation. A recent 12-week intervention with inulin and fructo-oligosaccharides improved cognitive functions in elderly twin pairs [144].

Pro-, pre- and synbiotic interventions in CKD patients have been analysed in meta-analyses [145–149]. In general, no improvement of kidney function but lower levels of uraemic toxins (p-cresol, indoxyl sulphate) and circulating markers of inflammation (e.g. C-reactive protein, interleukin-6) were reported. Yet, the impact on uraemic toxins differed between studies, likely reflecting the heterogeneity of probiotics (strain-specific properties) and prebiotics (chemical structures), but also the heterogeneity of participating patients with CKD. Likewise, the few studies that included the effect of biotic interventions on the gut microbiota of kidney disease patients found diverging results [150–154].

Currently, the impact of pro- or prebiotic interventions on uraemic toxins and inflammatory markers looks promising, but whether this translates into improvement of CKD-associated cognitive decline has not been addressed and more evidence from currently ongoing trials is needed [29]. More recently they were also reported to have potentially beneficial effects on brain (and kidney) health [70, 155].

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) has emerged as a treatment for severe intestinal dysbiosis as in patients with recurrent *C. difficile* infections or patients with inflammatory bowel disease [156, 157]. Despite some evidence from animal studies, that transfer of bacteria from healthy donor animals or humans could have beneficial effects on parameters of kidney function, fibrosis and inflammation [158], no controlled studies have been reported to date. A retrospective analysis of patients who underwent FMT for treatment of inflammatory bowel disease or functional bowel disease suggested that patients with reduced kidney function experienced an improvement after FMT [159]. FMT is also in early clinical development for brain protection, although not yet in the context of CKD [160].

SUMMARY AND CONCLUSION

The gut microbiome communicates with various organs and systemic functions including the brain and thereby modulates important aspects of brain function including brain metabolism,

cognition, mood and autonomous nerve system outflow. In patients with CKD, profound changes in the composition of the gut microbiome occur and likely participate in pathological alterations of brain function. Based on animal data and observational human studies, several pathways may be implicated in the decline of cognitive function. Increasing understanding of which components of the gut microbiome are relevant for human health and how to manipulate the gut microbiome may provide opportunities to improve healthcare for patients with CKD and cognitive decline. Controlled clinical trials are necessary to test the effectiveness of targeted interventions to restore microbiome functions and to examine whether these measures improve kidney function and prevent or even reverse cognitive decline.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

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APPENDIX

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