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New insights into mechanisms underlying cognitive impairment in chronic kidney disease

Mickaël Bobot[1,2,3] and Stéphane Burtey[1,2]

Chronic kidney disease (CKD) is associated with an increased risk of cognitive impairment. Patients with CKD display an increased permeability of the blood–brain barrier. Zimmermann *et al.* highlighted the implication of potassium efflux in the microglia and its activation, the activation of the interleukin-1b/interleukin-1R pathway, linked to blood–brain barrier permeability and cognitive impairment in CKD. Along with uremic toxicity, this study provides new solid insights about pathophysiological mechanisms of cognitive impairment in CKD, and potential therapeutic targets.

Kidney International (2024) **106,** 1020–1022; https://doi.org/10.1016/j.kint.2024.09.008

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Chronic kidney disease (CKD) is associated with an increased risk of cognitive impairment.[1] Cognitive impairment is a frequent and underestimated burden in patients with CKD, complexifying their care. Cognitive impairment concerns 30% to 80% of patients with end-stage kidney disease (ESKD). The specific pathophysiological mechanisms of cognitive impairment in CKD are, however, incompletely understood. Classic risk factors of cognitive impairment, like diabetes, which is highly prevalent in the population with CKD, notably in high-income countries, are known to increase the risk of cognitive impairment in both general and CKD populations. However, this risk factor, like others, such as hypertension, do not fully explain the high prevalence, earliness, and severity of cognitive impairment in CKD. Therefore, mechanisms more specifically linked to CKD are suspected. Water and electrolyte imbalance is associated with impaired cognitive performance, notably hyponatremia and acidosis, especially in patients with ESKD. In addition, uremic toxin accumulation seems an important specific mechanism involved in CKD.

The blood–brain barrier (BBB) is a highly selective physiological barrier separating the brain parenchyma from the blood and guarantying the protection of central nervous system cells from circulating pathogens and neurotoxic compounds.[2] The BBB is composed of a nonfenestrated endothelium, pericytes, basal lamina, and astrocyte feet. Rupture of the BBB, particularly after an ischemic process, will lead to inflammatory processes in the brain, and activation of microglial cells, the main immune cells of the central nervous system. BBB permeability could increase through several mechanisms: cerebral endothelial dysfunction, loss of endothelial tight junctions, decreased expression of efflux transporters, alteration of basement membrane, or pericyte degeneration, leading to impaired endothelial transcytosis. BBB disruption is a major mechanism involved in several neurodegenerative diseases,[3] but also in systemic diseases, like diabetes or hypertension. The main mechanisms involved in BBB dysfunction could be different, depending on the underlying disease. BBB disruption is clearly associated with cognitive impairment in these diseases.[4]

In preclinical research, BBB permeability also appears as a crucial mechanism of brain dysfunction in CKD. In several rodent models of CKD, we previously highlighted that animals fed with an adenine-rich diet displayed important serum accumulation of indoxyl sulfate, which activates aryl hydrocarbon receptor (AhR), and was associated with cognitive impairment (notably impaired short-term memory), and increased BBB permeability compared with control animals. We observed a correlation between BBB permeability and cognitive

[1]*Centre de Néphrologie et Transplantation Rénale, Hôpital de la Conception, Assistance Publique - Hôpitaux de Marseille, Marseille, France;* [2]*Aix Marseille Univ, INSERM 1263, INRAE 1260, Centre de Recherche en CardioVasculaire et Nutrition, Marseille, France; and* [3]*Centre Européen de Recherche en Imagerie Médicale, Aix-Marseille University, Marseille, France*

Correspondence: *Mickaël Bobot, Service de Néphrologie et Transplantation Rénale, 147 boulevard Baille, 13005 Marseille, France. E-mail: mickael.bobot@ap-hm.fr*

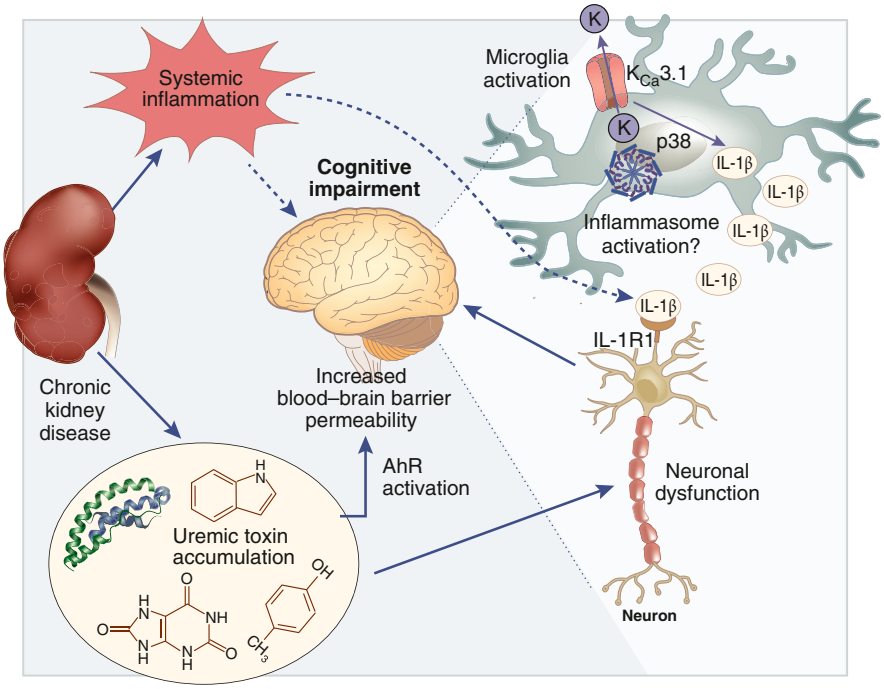

Figure 1 | Mechanisms of chronic kidney disease (CKD)–induced cognitive impairment. The degradation of kidney function leads to the accumulation of uremic toxins and systemic inflammation. Accumulation of indoxyl sulfate leads to an activation of aryl hydrocarbon receptor (AhR) that increased the blood–brain barrier (BBB) permeability. The increased BBB permeability is associated with cognitive impairment. In the study of Zimmermann *et al.*,[8] the BBB permeability is associated with the activation of the microglia, leading to an activation of the KCa3.1 channel. This potassium efflux channel activation induced the phosphorylation of p38 and so increased production of interleukin (IL)-1b by the microglia, leading to an increased production of IL-1b by the microglia. This leads to an activation of IL1-R1 in the neurons and to neuronal dysfunction, playing a role in the CKD-induced cognitive impairment. The activation of inflammasome could play a role in the microglial activation. The uremic toxins, like indoxyl sulfate, could directly impair the neuronal function. In addition, systemic inflammation associated with both CKD and uremic toxin accumulation, characterized by the accumulation of IL-1b, could activate the neuronal IL1-R in addition to local production.

impairment, as well as with serum indoxyl sulfate concentrations. Furthermore, indoxyl sulfate overload in the same model was associated with greater cognitive impairment and even more increased BBB permeability, for equivalent kidney function. AhR-knockout mice were protected against BBB disruption and cognitive impairment induced by indoxyl sulfate administration.[5] Thus, BBB dysfunction appears to be an important mechanism of cognitive impairment in CKD, under the influence of AhR activation by indoxyl sulfate. Its exact mechanism is still unknown. One hypothesis is that this BBB disruption is the result of AhR-mediated endothelial dysfunction in the brain vessels, following the accumulation of indoxyl sulfate during CKD. Indeed, the endothelial toxicity of indoxyl sulfate is well recognized, and AhR is highly expressed in the human BBB.[5]

Recently, 2 clinical studies confirmed this proof of concept in humans. The study of Gupta *et al.* found an increased BBB permeability, quantified by cerebral technetium-99m–diethylene-triamine-pentaacetate (^{99m}Tc-DTPA) single-photon emission computed tomography/computed tomography imaging, in patients with ESKD compared with control participants,[6] BBB permeability was correlated with some aspects of cognitive impairment. Especially functions such as immediate and delayed recall were the most affected. The BREIN (Blood-BRain barrier Evaluation In Nephrology) study confirmed these results and found an increased BBB permeability in patients with ESKD on hemodialysis compared with matched healthy volunteers. Patients with ESKD also had a higher prevalence of cognitive impairment, particularly in short-term memory, language, and attention functions, and BBB permeability was inversely correlated with global Montreal Cognitive Assessment score in these patients.[7]

This BBB disruption could have several consequences. It could increase the passage of drugs into the brain parenchyma through the BBB, explaining the greater frequency of drug neurotoxicity in patients with CKD. Chronic BBB disruption and cerebral endothelial dysfunction could also explain the important prevalence of cerebral white matter lesions and a much higher risk of severe stroke in these patients.

The recently published article by Zimmermann *et al.* proposes an interesting and convincing explanation that linked the BBB permeability to neuronal dysfunction in the context of CKD,[8] focusing on potassium efflux in microglia, neurons, and interleukin (IL)-1b/IL-1R1 pathway by performing complementary *in vitro* and *in vivo* experiments, performing single-cell analyses,

and using human samples. Mice subjected to 5/6 nephrectomy displayed impaired learning and memory, increased BBB permeability, and impairment in potassium turnover in neurons. In an *in vitro* model of BBB, permeability was higher when endothelial cells were exposed to the serum of patients with CKD. Increased activation of microglia was highlighted in both mouse with CKD and patients with CKD, in relation to impaired calcium homeostasis and microglial potassium efflux. Inhibition of KCa3.1 channel with triarylmethane-34 (TRAM34) prevents potassium efflux in the microglia and ameliorates cognitive impairment in mice with CKD. Microglial exposed to CKD plasma produced more IL-1b. Inhibition of the receptor IL-1R1 by using anakinra improved both microglial potassium efflux and cognitive performances in mice with CKD.

These findings highlight that BBB permeability is associated with the activation of the microglia, leading to an activation of the KCa3.1 channel. This potassium efflux channel activation induced the phosphorylation of p38 and so increased production of IL-1b by the microglia. This leads to an activation of IL1-R in the neurons and to neuronal dysfunction, playing a role in the CKD-induced cognitive impairment. The activation of inflammasome certainly plays a role in the production of IL-1b by the microglia, but this must be confirmed experimentally.

Numerous studies have reported a link between BBB disruption and neuroinflammatory processes in the context of cerebral aggression, notably in stroke. It could be of great interest to know if the mechanism activating microglial involved also KCa3.1, like during CKD. Several studies have reported chronic increases in systemic inflammatory processes in murine CKD models and in patients with CKD. CKD leads to increased circulating concentrations of proinflammatory cytokines, such as IL-1b, IL-6, and tumor necrosis factor-α, playing an important role in cardiovascular complications of CKD. It is tempting to imagine that the accumulation of circulating IL-1b could further activate the neuronal IL1-R1 in addition to local production by microglia. Astrogliosis, an abnormal increase of the number of reactive astrocytes, is frequently observed after central nervous system injury following BBB disruption and neuron death. It has also been demonstrated in CKD models in mice. Astrogliosis can lead to a vicious cycle, exacerbating neuroinflammation by activating the microglia through cytokine production, but can also increase the production of excitotoxic glutamate or neurotoxic reactive oxygen species and further alter BBB permeability. Uremic toxins, like indoxyl sulfate, could also directly impair the neuronal function. Indeed, Adesso *et al.* have reported that indoxyl sulfate exposition increased neuroinflammation and neuronal cell death *in vitro* and *in vivo*.[9] Thus, uremic toxicity could play a central role in brain impairment in CKD through its effects on BBB permeability, by promoting local and systemic inflammation and through potential direct neurotoxicity. Infectious diseases, which are particularly frequent in patients with ESKD, could lead to neuroinflammation in these patients, with unknown effects on long-term cognitive performances. However, some chronic infectious diseases, like HIV, are also known to be associated with BBB disruption and cognitive impairment by themselves. The potential mechanisms involved in CKD-induced cognitive impairment are summarized in Figure 1.

The article of Zimmermann *et al.* provides an important stone in the complex way to understand the mechanisms of the impaired cognition in CKD. They emphasized the primordial role of BBB permeability as a critical event. Numerous questions are not resolved. Do uremic toxins play a role in the activation of KCa3.1? Is there an activation of the inflammasome in microglia and how? Could systemic inflammation activate the IL1-R1 in neurons? The changes in other brain cell populations, like astrocytes and pericytes, as well as the specific impact of high blood pressure during CKD on these cerebral changes are also yet to be deciphered. Understanding the mechanisms leading to impaired cognition could help nephrologists to improve cognitive impairment in patients and their quality of life.

In just a few years, the progress in understanding cognition during CKD has provided us many molecular targets from the control of the BBB permeability by AhR, to the neuronal dysfunction induced by the activation of IL1-R1 through activation of microglia. Modulation of BBB permeability and inflammation in the brain are 2 promising strategies to improve cognitive function in patients with CKD.

DISCLOSURE

All the authors declared no competing interests.

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