Editorial

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A troubled mind troubles the kidney: a brain-to-kidney axis?

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See the article "Associations among Alzheimer disease, depressive disorder, and risk of end-stage kidney disease in elderly people".

Dementia and depression are among the so-called 3Ds (dementia, depression, and delirium), which are most frequently encountered in geriatric psychiatry [1]. A recent report by Kang et al. [2] has shown that older adults (aged >60 years) with Alzheimer dementia (AD) or depression have increased risk of end-stage kidney disease (ESKD) by 67% and 44%, respectively [2]. These figures seem to go beyond the common expectation that aging-associated illnesses are more likely to coexist.

It is recognizable that impaired renal function can increase the risk to brain health in various ways. Chronic kidney disease (CKD) has been associated with increased risk of depression, anxiety, and cognitive decline [3]. However, the opposite relationship has not been studied well. A recent study of Kang et al. [2] highlights the topic by supporting the existence of a brain-to-kidney axis [4]. This concept has been proposed based on findings that acute brain injuries from trauma or ischemic or hemorrhagic stroke coincide with acute kidney injury [5]. However, it is unknown which factors could be involved in such long-term crosstalk between depression, dementia, and ESKD. First, any factors that mediate brain and kidney function could mediate the relationship bidirectionally (Fig. 1A). For instance, humoral factors such as proinflammatory cytokines can arise from pathological conditions of either of the two organs and affect the other. Indeed, depression and AD have long been associated with systemic as well as neuronal inflammation [6,7]. Second, metabolic conditions such as hypertension, diabetes, and hypercholesterolemia may contribute to the link since they cause vascular dysfunction (Fig. 1B); not only vascular dementia but also AD have been related to vascular pathology. Vascular dysfunction has also been regarded as an important depressogenic factor, especially in elderly depression, which prompted the term, 'vascular depression' [8]. The brain and kidney share a common feature of microvasculature, function of which is crucial to their normal operation. This common microvascular pathogenesis might have influenced the brain first (inducing depression or dementia) and then the kidney, resulting in ESKD as a final step. As well as vasculopathy, several adipokines (adiponectin, leptin, and clusterin)

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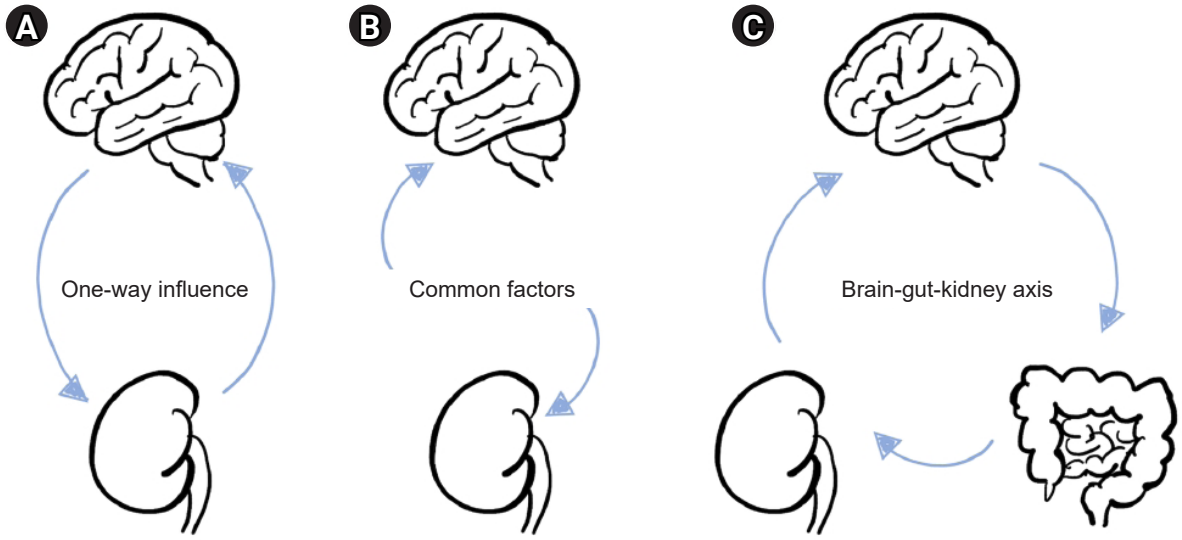

Figure 1. Proposed model for a brain-kidney axis. (A) Factors initiated by the brain can affect the kidney and vice versa. For instance, circulating cytokines associated with neuroinflammation can damage the kidney. (B) Common factors may influence both organs but do so sequentially. Hypertension, diabetes, and other metabolic/vascular risk factors may affect the brain first, causing depression or dementia, and then the kidney. (C) The brain-gut-kidney axis [13] involves inflammation, metabolic dysfunction, and sympathetic activation as mediators of brain-kidney crosstalk, and gut microbiota are highly involved in this interplay.

and myokines (irisin) could mediate or moderate the relationship between metabolic disease and AD [9–11]. These proteins might have the potential to convey or implicate dysfunctions in the kidney as well. Third, attention should be paid to a recent conceptualization of 'brain-gut-kidney axis' (Fig. 1C). This may be an extended concept based on the above-mentioned pathways between the brain and kidney, suggesting that the gut microbiome can affect both the brain and kidney through metabolic, immune, and autonomic nervous systems [12,13].

Future study efforts should aim to elucidate clinical and therapeutic implications of the brain-kidney axis. First, as mentioned above, gut microbiota could be added as a key potential mediator between brain and kidney functions. Second, the long-term influence of antidementics or antidepressants on kidney function should be reexamined. Third, a prospective study should identify metabolic, immune, or microbiotic factors, which are commonly found in patients who have simultaneous depression/dementia and ESKD/CKD compared to those who have only one. Such studies will provide valuable information on a promising target of intervention with which renal function may be protected in elderly patients with depression or dementia. Given the high prevalence of these conditions in old age, the impact of such intervention would be not insignificant, as suggested by Kang et al. [2].

Conflicts of interest

The author has no conflicts of interest to declare.

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Conceptualization, Project administration, Supervision, Visualization: EK
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