Chronic kidney disease linked to brain inflammation and cognitive decline

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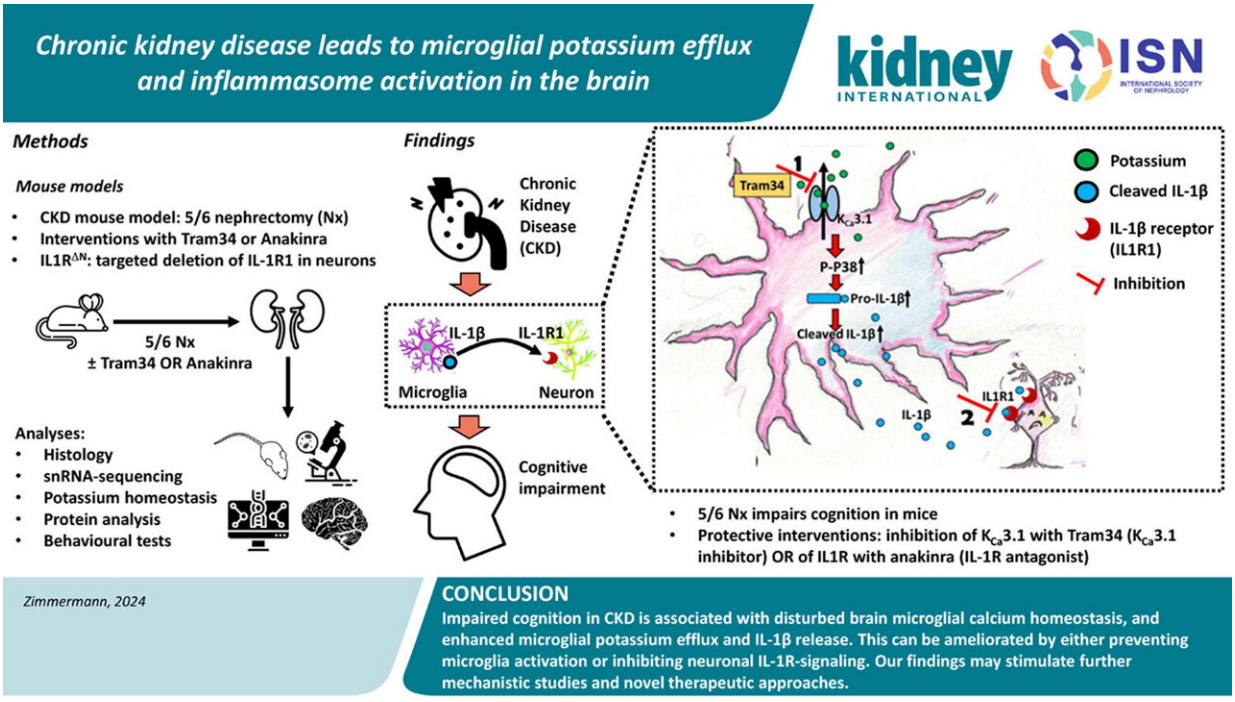

Credit: *Kidney International* (2024). DOI: 10.1016/j.kint.2024.06.028

Cognitive impairment is one of the burdens for patients suffering from chronic kidney disease. It can severely impair quality of life and often leads to an increased risk of dementia in those affected. Studies show that a kidney transplant can reverse cognitive impairment—indicating that this disorder can be treated. However, the exact mechanisms that lead to cognitive impairment are largely unclear.

A new study conducted by the University of Leipzig Medical Center provides important findings from basic research that could be used to develop therapeutic approaches for chronic kidney disease. The results have been published in the journal *Kidney International*.

Microglia are specialized immune cells in the brain that play a key role in the transformation of neuronal functions. The activation of these cells is often associated with inflammatory processes, which in turn influence the brain and cognitive functions.

"In the present study, we were able to show that chronic kidney disease (CKD) leads to an activation of microglial cells, which has a number of negative effects on the brain and in particular disrupts the homoeostasis of potassium in the nerve cells," explains Dr. Dr. Silke Zimmermann, first author of the study and researcher at the University of Leipzig Medical Center.

To investigate the mechanisms of chronic kidney disease in the brain, the Leipzig researchers established a surgical mouse model in which 5/6 of the kidney tissue was removed. The study data showed that these mice performed worse in cognitive tests and exhibited reduced neuronal potassium turnover.

Analysis of gene expression showed that several signaling pathways linked to diseases such as Alzheimer's, Huntington's and Parkinson's were affected in the neuronal cell clusters of the mouse models with chronic kidney disease.

The analyses of the experimental approaches, both in cell cultures and in mouse models, showed that chronic kidney disease disrupts the barrier of the brain endothelial cells. The Leipzig researchers therefore showed that the progressive uremic toxicity in kidney failure alters vascular permeability in the brain.

This disruption of the blood-brain barrier enables toxic substances to reach the brain and trigger inflammatory reactions. This process in turn impairs the balance of potassium in the microglial cells.

The researchers succeeded in restoring potassium homoeostasis in the cells by blocking a receptor on the nerve cells with an inhibitor—which also reduced cognitive impairment.

"We have therefore succeeded in identifying a mechanism in the brain that has a central function in the development of impaired cognition. And we believe that it is sufficient to treat this mechanism in order to improve cognition in affected patients," says Professor Berend Isermann, corresponding author of the current study.

"Our research shows that the regulation of potassium efflux in microglial cells and the preservation of neuronal function could be promising approaches for the treatment of cognitive impairment.

"We hope that our findings will help to further decipher these mechanisms and develop targeted therapies for cognitive impairment in chronic kidney disease.

"Another vision we have is to investigate novel biomarkers that can indicate the development of cognitive impairment at an early stage," says Dr. Dr. Zimmermann, clinician scientist at the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics. She led the basic research project together with institute director Professor Berend Isermann.

More information: Silke Zimmermann et al, Chronic kidney disease leads to microglial potassium efflux and inflammasome activation in the brain, *Kidney International* (2024). DOI: 10.1016/j.kint.2024.06.028

Provided by Leipzig University