The Role of AhR in CKD-induced Cognitive Impairment through Cerebral-endothelial and BBB Function

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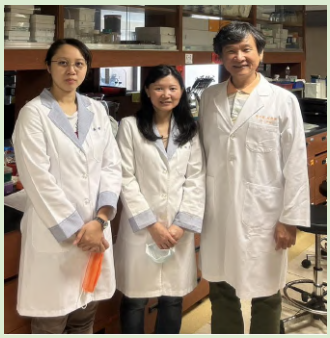
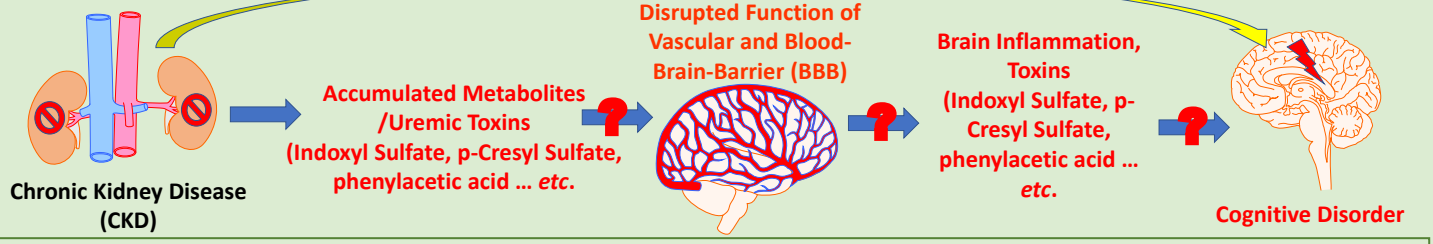


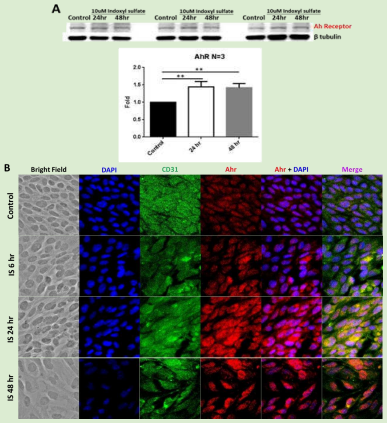
INTRODUCTION

Chronic kidney disease (CKD) is characterized as a progressing loss of renal function and known as one of well-known risk-factors of dementia. Our previous study reported that accumulation of uremic toxins, including creatinine, blood urea nitrogen (BUN), indoxyl sulfate (IS), and p-cresol sulfate (PCS), could not only induce neuronal inflammation, but also NLRP3-inflammasome-correlated astrocytic inflammation; both neuronal and astrocytic inflammation significantly contribute to CKD-triggered cognitive impairment. The mechanisms of IS and PCS leading to cognitive disorder remain unclear. The current study aims to understand how IS and PCS passing through endothelial cells and affecting endothelial physiology and BBB function, then, bring to neuronal inflammation and cognitive dysfunction eventually.

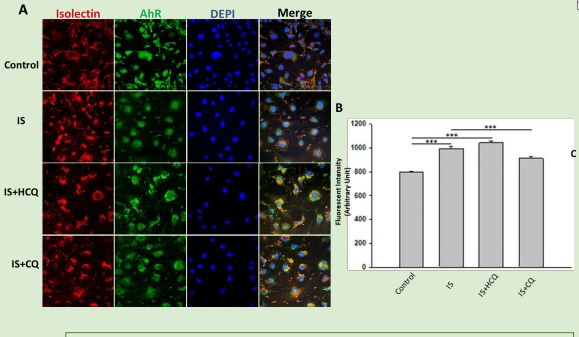


RESEARCH THEME

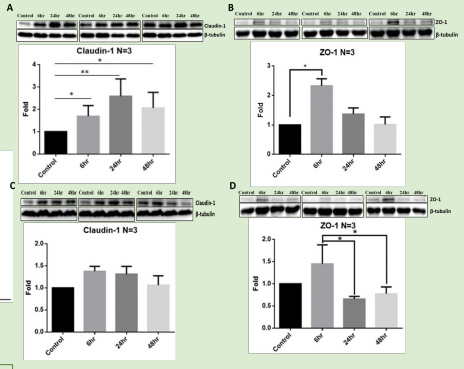
Our pilot study indicated that IS/PCS was able to enter endothelial cells and promote relocation of AhRs from cytosol to nucleus. In addition, an inhibitor of organic anion transporter peptides (OATPs) could prohibit AhR nuclear relocation. Therefore, we hypothesized that IS/PCS could enter endothelial cells via OATPs and activate AhR to regulate down-stream expression of genes. In consequence, the function of endothelial cells and BBB should be altered leading to pathogenesis of cognitive impairment.



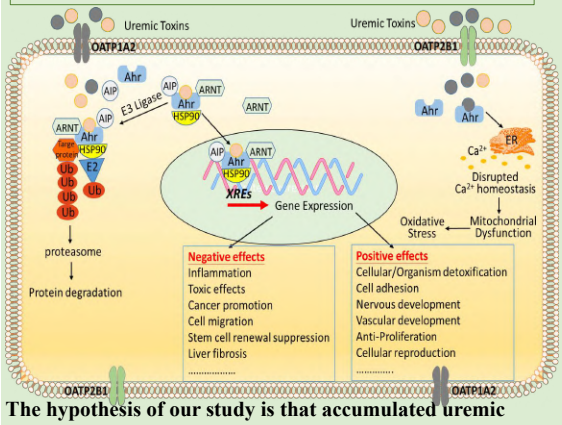
Indoxyl sulfate (IS) treatment enhanced expression of aryl hydrocarbon receptor (AhR, panel A) and relocated to nuclei in primary cerebral-vessel endothelial cells (panel B).



The inhibitor of organic anion transporting polypeptide 1 (OATP1), chloroquine (CQ), prohibited aryl hydrocarbon receptor (AhR) translocation into nuclei, but not hydroxylchloroquine (HCQ), in indoxyl sulfate (IS) treated primary cerebral-vessel endothelial cells.

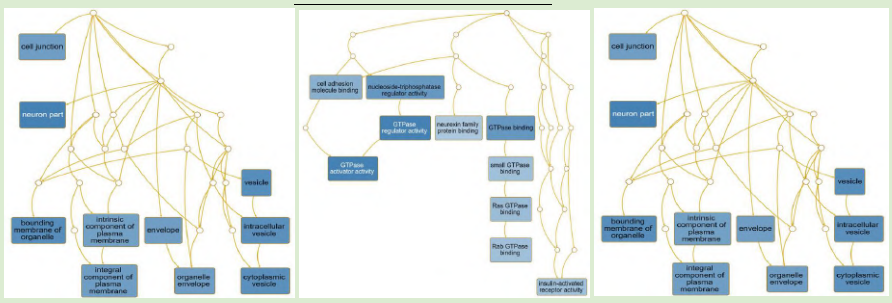


Treatments of indoxyl sulfate (IS) and p-cresol sulfate (PCS) disrupted expression of the tight-junction molecules, claudin-1 and ZO-1, in primary endothelial cells. The results also implied the disrupted protein homeostasis that could lead dysfunction of endothelial permeability.



The hypothesis of our study is that accumulated uremic toxins, especially protein-bound indoxyl sulfate (IS) and p-cresyl sulfate (PCS), enter and leave endothelial cells via organic acid transporter peptide 1A2 (OATP1A2) and organic acid transporter peptide 2A1 (OAPT2B1) or others, in following, the cellular IS or PCS binds aryl hydrocarbon receptor (AhR) changing cellular physiology and gene expression, these continuous processes result in pathogenesis of cognitive impairment.

FURTHER STUDY



The sequencing results of AhR ChIP-DNA fragments were analyzed by WebGestalt and DAVID Bioinformatics, which indicated as many as 522 genes were regulated by IS-activated AhR and suggested AhR-regulated genes involving in function of cell junction, cell adhesion, integral component of membrane, organelle envelope, cytoplasmic vesicle, intracellular transport, G-protein signaling, cell-cell signaling, and neuronal protection.

In our further study, the prominent OATs/OATPs are in response to IS/PCS transportation in cerebral-endothelial cells. Moreover, we will characterize the AhR regulated genes how they alter endothelial physiology and function.