Medical Xpress

Researchers discover new therapeutic approach for cardiorenal syndrome type 2

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A study in the *Journal of the American Society of Nephrology* suggests a new therapeutic approach to treat the development of chronic kidney disease secondary to chronic heart failure, known as cardiorenal syndrome type 2.

In the journal's June 13 online edition, researchers at Cincinnati Children's Hospital Medical Center suggest inhibiting G protein-coupled receptors (GPCR) could prevent renal damage in cardiorenal syndrome type 2 (CRS2), and could also prevent acute kidney injury (AKI).

According to the researchers, chronic stimulation of GPCR receptors, specifically G-protein βγ (Gβγ) subunit signaling, plays a major role in chronic kidney disease (CKD) and AKI. In the study, researchers used a novel small molecular inhibitor (gallein) to target and block Gβγ signaling and protect renal function.

Prior to this study, GPCR-Gβγ signaling was connected to heart failure, but little was known about the role of GPCR-Gβγ signaling in kidney injury.

All patients, adult and pediatric, who have any sort of invasive cardiac procedure that requires them to go on a heart-lung bypass are at significant risk for cardiac injury and kidney injury. According to the National Kidney Foundation, CRS2 costs the healthcare system $30 billion each year.

"Developing chronic kidney disease secondary to chronic heart failure is clinically associated with organ failure and reduced survival," said Burns Blaxall, PhD, FAHA, FACC, FAPS, lead author of the study and director of Translational Science at the Cincinnati Children's Heart Institute. "GPCR-Gβγ inhibition therapy could prevent both chronic and acute kidney damage in chronic heart failure patients, thereby improving their chances of survival and quality of life."

The researchers used two mouse models during the study— a model of CRS2 they generated and an AKI model. Study data shows that the CRS2 model developed by the researchers most accurately simulates the disease progression affecting patients.

Previous studies have shown that elevated neurohormonal signaling of the sympathetic nervous system and vascular endothelin (ET) system play a key role in kidney and heart damage in cardiorenal syndrome. The sympathetic nervous system and endothelin system (which is important to the circulatory system) utilize adrenergic and ET receptors respectively, both of which are GPCRs.

Study results show that using gallein to inhibit GPCR-Gβγ signaling in mouse models reverses CRS2 disease progression and AKI, including ET system activation, fibrosis, inflammation, tissue damage and renal dysfunction.

"The future direction of this research will be to further investigate whether this approach applies to both pediatric and adult patients and to figure out the best time to deliver the therapy," said Prasad Devarajan, Director of the Division of Nephrology at Cincinnati Children's and co-lead author of the study. "The goal is to one day use this therapeutic approach for anyone going on heart-lung bypass in addition to anyone who has heart failure to prevent acute and chronic kidney injury."