



Abstract Type : Poster exhibition

Abstract Submission No.: A-0620

Abstract Topic : Basic Research

Proteomic alternation of leukotriene antagonist treatment in hypertensive nephropathy

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Objectives : Hypertensive nephropathy, resulting from hypertension-induced kidney damage is the second most major cause of end-stage renal disease (ESRD) after diabetes. Leukotrienes, inflammatory mediators derived from the arachidonic acid metabolic pathway, are essential for immune response and inflammation regulation involved in immune-mediated inflammatory diseases. Leukotriene receptor antagonists (LTRAs) known to have beneficial effects on vascular endothelial cell function, whereas their specific effects on hypertensive nephropathy-induced ESRD remain unclear.

Methods : LTRAs were treated to spontaneously hypertensive rat (SHR) after left kidney uninephrectomy, and kidney tissue was collected after 10 weeks. The kidney tissue was analyzed using mass spectrometry for identifying therapeutic effects in the global proteome.

Results : Firstly, we identified that LTRAs treatment restored blood pressure and urine protein induced by hypertensive nephropathy. Also, LTR, target of LTRAs, and AT1R related to hypertension were decreases in LTRAs-treated rat in immunohistochemistry assay in both kidney tubular and glomerular. Comparison between kidney injury in the normal blood pressure groups and hypertension-induced kidney damage revealed that significant alternation in global proteome. Additionally, these proteome alternation in the kidney failure of hypertensive rats are associated with kidney injury such as apoptosis, the TGF- β signaling pathway, chemokines, and reactive oxygen species (ROS) pathways. These results showed severe kidney injury caused by hypertensive nephropathy. And then, we also verified that the protein clusters restored by LTRAs were associated with hypertension-related mechanisms like shear stress and the apelin signaling pathway and the FoxO and MAPK signaling pathways. In the MAPK signaling components, the expression of Raf was found to be significantly upregulated in hypertensive nephropathy and restored by LTRA treatment. These findings suggest a novel role of Raf in hypertensive nephropathy and highlight the potential therapeutic benefits of LTRA treatment.



Conclusions : We identified potential effects of LTRAs in chronic kidney diseases and it could be a potential therapeutic option for hypertensive nephropathy.