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The effect of Neprilysin and renin inhibition on the renal dysfunction following ischemia-reperfusion injury in the rat

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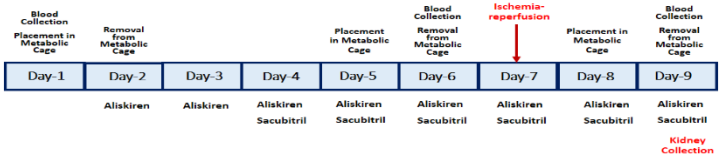
Introduction

Renal ischemia-reperfusion injury (IRI) is an invariable consequence of conditions such as renal transplantation. The inhibition of several systems involved in the pathophysiology of the IRI-induced renal alterations have been shown to have beneficial effect on renal functions. This study focuses on the renin-angiotensin system (RAS) and the natriuretic peptide (NP) systems.

Neprilysin (NEP) is the key enzyme for degradation of NPs. The effect of NEP inhibition on the IRI-induced renal alterations has not been investigated and will be investigated in this research. The second aim was to investigate if combining the NEP inhibition to RAS inhibition would have further protective value in IRI.

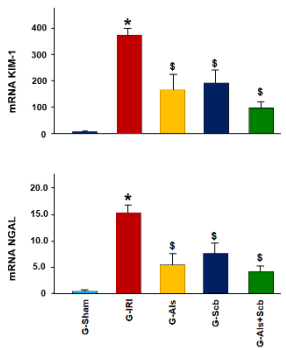
Methodology

Male Wistar rats underwent bilateral renal ischemia for 20 minutes (G-IRI) and the functional parameters were determined before and after recovery from the IRI. G-Als, G-Scb and G-Als+Scb underwent similar protocol but received Aliskirin (renin inhibitor), Sacubitril (NEP inhibitor) and combination of both pre- and post-IRI, respectively. G-Sham underwent sham surgery and did not receive treatment (Figure-1). Gene expression of renal injury, inflammatory, fibrosis, and apoptotic markers was analysed by real time PCR of kidney tissues.

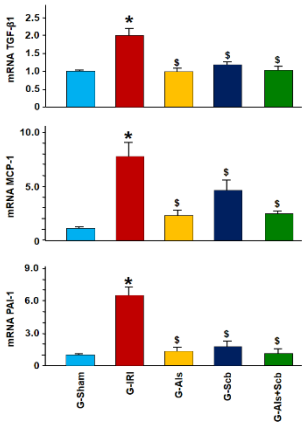


Results

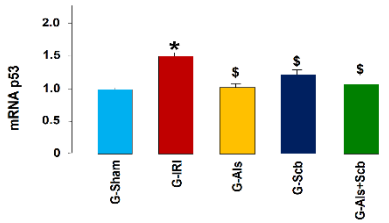
IRI caused significant alterations in all renal functional parameters, markers of acute renal injury, pro-inflammatory and pro-fibrotic cytokines and histological features. All these alterations were significantly attenuated in G-Als, G-Scb and G-Als+Scb. The attenuations in the alterations in serum creatinine, creatinine clearance and histological features were larger in G-Als+Scb compared to either G-Als or G-Scb.



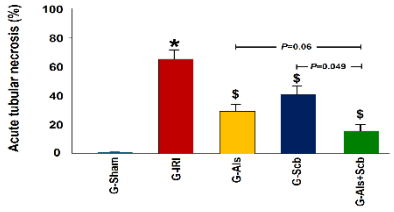
The gene expression of two of markers of acute renal injury (KIM-1 and NGAL) in all the groups. Values represent mean±SEM.
* and $ indicate statistical significance when compared to the G-Sham and G-IRI, respectively.



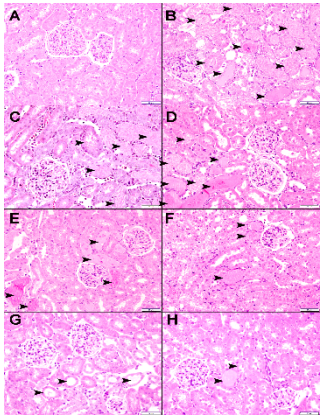
The gene expression of the pro-inflammatory and pro-fibrotic cytokines TGF-β1, PAI-1 and MCP-1 genes in all groups. Values represent mean±SEM.
* and $ indicate statistical significance when compared to the G-Sham and G-IRI, respectively.



The gene expression of the pro-apoptotic p53 gene in all groups. Values represent mean±SEM.
* and $ indicate statistical significance when compared to the G-Sham and G-IRI, respectively



The degree of acute tubular necrosis (in percentage) in all the groups.
* and $ indicate statistical significance when compared to the G-Sham and G-IRI, respectively.



The histological features in all the experimental groups. A: The kidneys in G-Sham showing normal architecture and histology. B: represents the histological features in the G-IRI with acute tubular necrosis (arrowhead) with dilated tubules and intratubular secretion. C&D, E&F and G&H show the histological features in G-Scb, G-Als and G-Als+Scb, respectively with variable degrees of acute tubular necrosis. Among the three groups, the least degree of acute tubular necrosis, is shown in G-Als+Scb.

Conclusion

RAS blockade by the use of aliskiren or sacubitril separately led to significant attenuation in the renal IRI-induced renal dysfunction. The combination of aliskiren and sacubitril in IRI was more effective than either one alone.