

## **Celecoxib Modulates Nitric Oxide and Reactive Oxygen Species in Kidney Ischemia/Reperfusion Injury and in Rat Aorta Model of Hypoxia/Reoxygenation**

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Ischemia/Reperfusion injury (IRI) is an unavoidable consequence of organ transplantation leading to acute renal failure which leads to development of chronic kidney disease and transition from pre-existing chronic disease to end-stage renal disease and a high mortality. [1] Although, a lot has been learned about the pathogenesis of ischemic acute renal failure, there has been very little improvement in mortality. The major aim of the current study is to examine the effect of the selective COX-2 inhibitor, celecoxib on renal biochemical and histomorphological characteristics following IRI. Part of the study is designed to investigate the effect of hypoxia/re-oxygenation on the endothelium-dependent and endothelium independent relaxation in vascular beds in-vitro and test how it is modulated by celecoxib in search for the potential mode of interaction between COX-2, NO and ROS in kidney and vascular beds after ischemia/reperfusion events.

IRI model in albino male Sprague-Dawley rats (weighing 250-300 gm) was used and various biochemical and histopathological parameters examined, namely, urea and creatinine levels, kidney lipid peroxidation [2], reduced glutathione [3], NO using Griess reaction [4], superoxide dismutase activity [5] and COX-2 levels. The above-mentioned parameters were measured in sham-operated (received an oral daily dose of the vehicle PEG 400/saline (2:1) for 7 days), IRI (received an oral daily dose of the vehicle PEG 400/saline (2:1) for 7 days followed by IRI on the 8<sup>th</sup> day), and celecoxib-treated group (received an oral daily dose of celecoxib (10 mg/kg) for 7 days followed by IRI on the 8<sup>th</sup> day). The rat isolated aortic rings served as model for hypoxia/reoxygenation where endothelium dependent and independent relaxations, using acetylcholine (ACh) sodium nitroprusside (SNP) respectively, were tested in presence and absence of celecoxib. Rats were sacrificed using an overdose of thiopental. Values are expressed as mean  $\pm$  SEM. Criteria for significance was set at  $p < 0.05$ .

Celecoxib (10 mg/kg) significantly reduced serum creatinine and urea levels and kidney malonaldehyde level, significantly increased kidney superoxide dismutase activity and reduced glutathione level and histopathological scores at 24 and 48 hours after reperfusion compared to IRI group. This was associated with a significant increase in NO level to  $0.70 \pm 0.03$  nmole/mg protein compared to  $0.37 \pm 0.01$  nmole/mg protein for IRI group. Unexpectedly, celecoxib significantly reduced COX-2 expression in kidney. Celecoxib reversed the effect of hypoxia-reoxygenation on ACh and SNP-induced relaxation in aortic rings but failed to significantly potentiate the SNP-induced relaxations in the control rings not subjected to hypoxia. Hypoxia-reoxygenation significantly impaired celecoxib-induced relaxation of aorta ( $13 \pm 2.69\%$  vs.  $36 \pm 0.84\%$ ) and this relaxation was significantly inhibited in presence

of L-NAME.

It can be concluded that Celecoxib holds the potential to beneficially affect the outcome of renal IRI by lowering the expression of COX-2 and hence reducing oxidative stress and increasing the bioavailability of NO. Direct interaction between celecoxib and NO in associated vascular beds may also be a contributing mechanism.

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