Mineralocorticoid receptor antagonism with BR-4628 protects against renal injury induced by ischemia/reperfusion

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Introduction: The main cause of acute kidney injury (AKI) is ischemia/reperfusion (IR). AKI has been associated with chronic kidney disease progression and cardiac alterations. Previous studies showed that in a rat model of kidney IR, mineralocorticoid receptor (MR) antagonism with spironolactone prevents tubular injury and renal dysfunction. Despite their benefits in renal diseases, the current MR antagonists have strong limitations like hyperkalemia, thus motivating the search of novel antagonists with safer profile.

Objective: Test the efficacy of the non-steroidal MR antagonist BR-4628 against renal injury induced by IR.

Methods: Twenty male wistar rats were divided in 4 groups: sham-operated (S), bilateral renal ischemia (IR) for 25min, treated with BR-4628 (10mg/kg) either 3 days before IR (B10-pre) or 3 hours after IR (B10-post). All groups were studied 24h after reperfusion. Blood sample was taken for creatinine and urea quantification. The right kidney was processed for molecular studies and the left for histopathological analysis.

Results: Rats with IR developed renal injury characterized by renal dysfunction, increase in tubular injury markers (Hsp72 and Kim-1), oxidized proteins and pro-inflammatory cytokines. These alterations were absent in the B10-pre and B10-post IR groups. IR induced an increased expression of the M1 macrophage markers iNOS, CCL3, TNF-alpha and MCP-1 (inflammatory phenotype) that was fully prevented with the BR-4628 pre-treatment. Furthermore we observed that in the B10-pre and B10-post groups there was a greater expression of M2 macrophage markers; IL4r, FIZZ1 and Igfr2 (wound healing phenotype), as compared to the non-treated IR group.

Conclusion: We show for the first time that the non-steroidal BR-4628 MR antagonist is effective to prevent or treat renal injury induced by IR possibly through a mechanism involving macrophage polarization towards the wound healing phenotype.

Beneficial effects of zinc on incidence and severity of ventricular reperfusion arrhythmias

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Intermittent hypoxia (IH), a major component of obstructive sleep apnea syndrome (OSA), causes several cardiovascular alterations such as hypertension, increased infarct size and ventricular arrhythmias. Indeed, IH exposure enhances the incidence of severe ventricular arrhythmias during both ischemia and reperfusion. Oxidative stress is a common feature behind the deleterious effects of both IH and ischemia-reperfusion on the myocardium. Zinc is an essential metal associated with numerous proteins and playing a vital role in various cellular functions. Its homeostasis is closely linked to the cell redox state since zinc release by oxidation can induce protein conformation changes. The resulting modification in protein activity could thus be restored by zinc administration.

Thereby, the effects of zinc supplementation were investigated in isolated perfused rat hearts presenting severe ventricular reperfusion arrhythmias following a 15-min regional ischemia. Incidence, severity and duration of ventricular arrhythmias were assessed during both ischemia and reperfusion. Three groups were compared in which zinc (pyrithione form, Zn-Pyr, 2.10⁻⁵M in DMSO), DMSO (vehicle) or pyrithione sodium (Na-Pyr) was added to the Krebs upon reperfusion. Incidence, severity and duration of ventricular arrhythmias were assessed during both ischemia and reperfusion. Three groups were compared in which zinc (pyrithione form, Zn-Pyr, 2.10⁻⁵M in DMSO), DMSO (vehicle) or pyrithione sodium (Na-Pyr) was added to the Krebs upon reperfusion. Reperfusion with Zn-Pyr significantly enhanced survival (40%) compared to DMSO or Na-Pyr (6%) (n=17 per group, p<0.05). Moreover, the time spent in sinus rhythm was significantly increased in the Zn-Pyr group compared to other groups (p<0.01). Accordingly, the duration of ventricular tachycardia/fibrillation was significantly decreased in the Zn-Pyr group (p<0.05).

Therefore, zinc administration during reperfusion improves survival in response to a severe ischemic insult. Zinc supplementation upon myocardial reperfusion procedures could thus represent a valuable approach to prevent the occurrence of arrhythmias and could be of interest in the prevention of IH- and OSA-related ventricular arrhythmias.