Losartan protects the heart against ischemia/reperfusion injury: sirtuin3 involvement

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Introduction: Sirtuin-3 (SIRT3) deacetylase protects the heart against oxidative stress via survival factors upregulation. Clinical and experimental studies have demonstrated that activation of systemic and local renin-angiotensin system (RAS) is implicated in ischemia-induced cardiac injury. However, the relation between RAS and SIRT3 in pathophysiology of myocardial ischemia reperfusion is unknown. In this study, the cardiac transcription and expression of SIRT3 levels was examined in response to ischemia reperfusion in untreated and losartan treated rats.

Methods: Rats were divided into control group, losartan group (L), and ischemia reperfusion (IR) groups with (L+IR) or without losatran pretreatment. Some rats were included as sham-operated and saline groups. IR was induced by left anterior descending artery occlusion. SIRT3 protein levels were determined by Western blot technique. The genes expression was specified by realtime RT-PCR. Arrhythmias were assessed according to the Lambeth conventions.

Results: In L+IR group a significant reduction was noted in the number of ventricular ectopic beats (VEBs) and episodes of ventricular tachycardia (VT) (VEBs: $P<0.001$; VT: $P<0.01$ vs. IR). In IR group, SIRT3 protein level was decreased in the ischemic tissue by 26.7±5.9% ($P<0.01$ vs. Control). However, in the non-ischemic tissue the changes of SIRT3 protein content were not significant. In L+IR group SIRT3 protein levels in the ischemic part of Left ventricle were significantly different from IR group ($P<0.001$). SIRT3 mRNA level did not change significantly among the experimental groups. Thioredoxin-1 and catalase transcription level was increased in L+IR group compared to IR group ($P<0.01$).

Conclusion: A decreased SIRT3 protein levels subsequent to IR might be a novel signaling mechanism involved in IR injury. Losartan at non–hypotensive dose exerts anti-ischemic effects in part by normalizing the SIRT3 protein level and upregulating the survival factors encoding genes transcription in ischemic tissue of the heart.

Keywords: SIRT3; Renin-angiotensin system; Ischemia reperfusion; Losartan