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Antioxidant Therapies in a Model of Intermittent Liver Ischemia in Rats

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Introduction: The Pringle's Maneuver is the most common situation of clinical liver ischemia. There is no therapy available to prolong the maximum period of liver ischemia tolerated by the patient. Previous experiments performed in our Laboratory have proved that superoxide-dismutase (SOD) and folinic acid are useful drugs in reducing reperfusion damage both in the liver and the gut.

Methods: Female Sprague-Dawley rats, weighing 220 g were used. Liver ischemia was induced by cross-clamping the hepatic pedicle with a Yassargil clip for twenty minutes, releasing the clamp for five minutes; this procedure was repeated four times in each animal and then a 70% hepatectomy was performed. Prior to restoring the blood flow to the liver, 0.2 ml of saline were administered through the left iliac vein. Blood samples were obtained from the jugular vein on days 1, 2 and 7. Survival rate was recorded daily until day 7, when the animals were sacrificed, and the liver and body weights were recorded in order to calculate the percentage of liver-mass recovery. Serum total bilirubin (Bi), γ-GT, ALT, LDH and PA were assessed. Three groups of animals have been considered. The control group received only saline (0.2 ml ×4), while the second received SOD (9.000 IU/kg ×4) and the third folinic acid (2.5 mg/kg ×4) prior to each reperfusion period of the liver.

Results: The survival rate was 36% in the control group, and 30% in the one receiving SOD. On the other hand, this figure reached a surprising 64% in the group treated with folinic acid ($p < 0.05$). In the control group GGT was elevated on the 7th day (9.8 vs. 3.9 IU/l) and both treatments significantly reduced this difference (4.8 and 4.1 IU/l). Serum levels of Bi were increased through out the whole experiment, and SOD significantly decreased them, reaching normal values (1.1 vs. 0.6 mg/l; $p < 0.05$). However, the administration of folinic acid had no effect. Liver weight reached normal values by the 7th day in the control groups, leaving no room for any improvement in the treated groups.

Conclusions: Recovery of liver weight is not affected by intermittent liver ischemia. SOD has proved to be more effective than folinic acid on liver function. However, only folinic acid increased the survival rate following four periods of 20 minutes of liver ischemia plus 70% hepatectomy in the rat.

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Ischemic Preconditioning Prevents Reperfusion Heart Injury in Cardiac Hypertrophy by Activation of Mitochondrial Potassium Sensitive ATP Channels

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Introduction: Cardiac hypertrophy has been demonstrated to decreases the ATP sensitive Potassium channels (KATP), the major protective mechanism during energy depletion, a common condition seen in reperfusion after open heart surgery. In this study we have demonstrated the role of ischemic preconditioning (IP) in preventing the reperfusion injury of the hypertrophied heart by activation of the depleted KATP channels.

Methods: Pressure overload left ventricular hypertrophied male Wistar subjected to IP protocols by 4 episodes of 3 minutes ischemia each being separated by 10 minutes reperfusion, followed by 30 minutes of sustained ischemia and 120 minutes of reperfusion with or without treating the rats with KATP channel antagonists 5-Hydroxydecanoic acid (10 mg/kg/iv) or glibenclamide (1 mg/kg/iv), 10 minutes before sustained ischemia.

Results: IP resulted in (a) less incidence of ventricular arrhythmias (b) less area of myocardial infarction (9.3% vs. 48.1%, IP to control) (c) less tissue water content (976.5% vs. 4.8%, IP to control) (d) well preserved myocardial ATP content ($p < 0.001$ from control) content and (e) much fewer apoptotic cells (4.7% vs. 13.2%, IP to control). Pre treating the rats with the KATP channel inhibitors before sustained ischemia resulted in inhibition of these protective effects of IP on cardiac hypertrophy.

Conclusion: The above results therefore suggest to us that IP by activation of KATP channels can afford protection against the ischemia-reperfusion injury in the hypertrophied heart.

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Activation and Nuclear Translocation of Nuclear Factor-κB and Activator Protein-1 in the Preconditioned Myocardium

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Introduction: Nuclear Factor (NF)-κB and Activator Protein (AP)-1 transcription factors play important role in the signal transduction of delayed ischaemic preconditioning (PC) to generate the delayed myocardial protection. Because there is no data about the dynamics of activation of these factors, we aimed to monitor the time fluctuation of the NF-κB and AP-1 induction in an in vivo animal model. Furthermore we measured the induction rate of these factors using repeated cycles of PC.

Methods: Following median thoracotomy anaesthetized animals (24 New Zealand White rabbits) were subjected to ischaemic PC, occluding the left anterior descendent coronary artery (LAD) for 5 min. After 10 and 30 min, 1, 2, 3, and 4 hours reperfusion (R) period tissue samples were taken from the ischaemic myocardium and measured the DNA binding activity of the transcription factors with electrophoretic mobility shift assay (EMSA). Further 12 animals were subjected to 2×-, 3×-, 4×-5 min ischaemic PC, and after 30 min reperfusion period we investigated the possible modulation in NF-κB and AP-1 induction.

Results: Our result shows significant, biphasically increased NF-κB activity with peak levels at 30 min and at 3 hour of reperfusion in preconditioned myocardium (2.40 and 2.66 fold vs. control; densitometric data). AP1 increased monophasically, with peak level at 1 hour of reperfusion (6.2 fold vs. control). Repeated PC stimuli