Pharmacological interventions against myocardial ischaemia and reperfusion injury

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg

dredagen den 18 november 2011 kl 13.00

av

Lars Karlsson

Fakultetsopponent:

Professor Guro Valen
Oslo Universitet

The thesis is based on the following papers,


II Karlsson LO, Bergh N, Grip L. Cyclosporine A, 2,5 mg/kg, does not reduce myocardial infarct size in a porcine model of ischemia and reperfusion J Cardiovasc Pharmacol Ther 2011 Maj 13. (Epub ahead of print)


IV Karlsson LO, Bergh N, Li L, Bissessar E, Bobrova I, Gross GJ, Akyürek LM, Grip L. Dose-dependent cardioprotection of enkephalin analogue Eribis peptide 94 and cardiac expression of opioid receptors in a porcine model of ischaemia and reperfusion Submitted
Pharmacological interventions against myocardial ischaemia and reperfusion injury

Lars O Karlsson, Department of Molecular and Clinical Medicine, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Sweden

ABSTRACT

Background: Ischaemic heart disease is the leading cause of death in the industrialised world. Although the concept of early restoration of coronary blood-flow constitutes an important factor to reduce the injury caused by myocardial ischaemia, reperfusion in itself can aggravate the damage to myocardial tissue, a phenomenon denoted myocardial reperfusion injury. Even though promising cardioprotective strategies have been presented in the pre-clinical setting, experience from the clinic has been largely disappointing.

Aims: To investigate whether two different pharmacological interventions, cyclosporine A (CsA) and the novel enkephalin analogue EP 94, could reduce myocardial infarct size in different porcine models of myocardial ischaemia and reperfusion. Furthermore, to examine the distribution of the opioid receptor subtypes in the porcine heart, and to investigate how this expression is affected by ischaemia and reperfusion.

Methods: Anesthetised pigs underwent balloon occlusion of the left anterior descending coronary artery, followed by reperfusion. CsA and EP 94 were administered during the end of the ischaemic insult. After the reperfusion period hearts were stained with Evans blue and 2, 3, 5-triphenyltetrazolium chloride to quantify area at risk and infarct size, respectively. mRNA and protein expression of different pro-apoptotic proteins, endothelial NO-synthetase and opioid receptor subtypes was quantified in the control and ischaemic/reperfused areas.

Results: Two different dosages of CsA did not confer cardioprotection whereas EP 94 reduced myocardial infarct size in a dose-dependant manner in our different porcine models. Immunoblotts revealed a possible mechanism for the cardioprotective effect with up-regulation of phosphorylated eNOS in pigs receiving EP 94. Furthermore, protein expression of the κ- and δ-opioid receptors was detected in the left ventricle, with an up-regulation of the δ subtype after ischemia and reperfusion. The µ-opioid receptor was not detected.

Conclusions: CsA did not reduce myocardial infarct size, whereas the novel enkephalin analogue EP 94 conferred cardioprotection in different porcine models. The κ- and δ-opioid receptors were detected in the pig left ventricle.

Keywords: myocardial ischemia, reperfusion injury, opioids, cyclosporine A