Cardioprotection against ischemiareperfusion injury by L-glutamate and K_{ATP} channel openers

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ABSTRACT

Acute coronary occlusion is a leading cause of morbidity and mortality in the Western world. The extent of an evolving myocardial infarction during the acute phase of coronary occlusion can be limited by rapid reestablishment of myocardial perfusion. However, metabolic therapy to the reperfused ischemic myocardium may preserve viability and represents an important therapeutic target.

From both clinical and animal experiments the amino acid L-glutamate for years has been known to possess cardioprotective effects. The underlying mechanisms are, however, unknown. Fasting and opening of ATP-sensitive potassium (K_{ATP}) channels increase myocardial ATP content during ischemia and improve post-ischemic left ventricular (LV) function. Furthermore, fasting and K_{ATP} modulation have been reported to influence glycogen content in the non-ischemic myocardium.

We hypothesized that administration of glutamate reduces infarct size after a coronary occlusion, improves myocardial hemodynamics and influences glycogen metabolism. The underlying mechanisms were hypothesized to involve K_{ATP} channels.

In an isolated perfused rat heart model we investigated the effects of glutamate administration (10 mM) on myocardial infarct size and LV function after regional no-flow ischemia. Furthermore, we investigated the effects of glutamate (10, 50 and 100 mM), fasting, and the KATP channel blocker glibenclamide on myocardial glycogen synthesis rate and content in a model of global no-flow ischemia.

Glutamate administration during reperfusion reduced myocardial infarct size by 60%, improved LV function and increased myocardial glycogen synthesis rate and content during reperfusion. These effects were abolished by glibenclamide. Pre-ischemic administration of glutamate mimics the cardioprotective effects of fasting by reducing glycogen depletion and lactate accumulation during ischemia, and improving LV function during reperfusion.

Glutamate exerts cardioprotection against ischemia-reperfusion injury through mechanisms involving L-glutamate oxidation, K_{ATP} channels, and glycogen metabolism. The thesis reports hitherto unknown aspects of myocardial glutamate metabolism, which may open up new metabolic interventions against ischemic heart disease.