BMC Pharmacology

Oral presentation

The role of cGMP and PKG in cardioprotection

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from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):S9 doi:10.1186/1471-2210-9-S1-S9

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/S9

Interrupting blood flow to a heart (ischemia) for several minutes followed by several minutes of restored flow renders it very resistant to cell death from a subsequent much more prolonged ischemic episode. This phenomena, termed ischemic preconditioning, is the result of a complex signal transduction pathway which ultimately prevents formation of lethal mitochondrial permeability transition pores when blood flow is restored. In mapping this pathway we found that NOS was in the pathway [1] and proposed that it was involved in opening ATP-sensitive potassium channels (K_{ATP}) in the mitochondrial inner membrane. Those channels play a key role in preconditioning's mechanism. Incubating isolated heart mitochondria in cGMP + PKG + ATP opened the channel as indicated by mitochondrial swelling [2]. To test this hypothesis further the cGMP analog 8-CPT-cGMP (10 μM) was infused for 30 min starting 5 min prior to the end of 30 min of regional ischemia in an isolated rabbit heart [3]. It greatly attenuated the resulting infarction by an amount similar to that seen with preconditioning (infarct size approximately 50% of that in untreated hearts). 8-CPT's protection could be blocked by the K_{ATP} blocker 5 hydroxydecanoate confirming its position in the pathway. Because there is a medical need for an intervention that prevents myocardial infarction when given at reperfusion we looked for a method of raising cGMP that would be clinically feasible. We gave the direct guanylyl cyclase activator BAY 58-2667 (cinaciguat) to open-chest rabbits at 53 μg/kg bolus just prior to reperfusion followed by a 60 min 1.25 μg/min infusion. It reduced infarct size from 40.6% of the ischemic zone to only 16.0%. In another experiment we tested Vardenafil infusion of 140 μg/kg/h starting 5 min before coronary occlusion in the open-chest rabbit. It also greatly protected the hearts against infarction. Because it is controversial as to whether heart muscle expresses PDE 5, we transfected isolated rabbit ventricular myocytes with CNG channels selective for cGMP. In the resting cells cGMP as monitored with patch clamping was near zero and did not increase when they were exposed to 1 μM vardenafil. However, when cGMP was first increased with 1 μM BAY 58-2667 addition of vardenafil greatly increased the cGMP-dependent membrane current indicating that a vardenafil-sensitive PDE was present which is presumed to be PDE5. We conclude that raising cGMP in the reperfused heart is an effective anti-infarct strategy.

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