THE H2S-DONOR, 4-CPI, PROMOTES ANTI-ISCHEMIC EFFECTS THROUGH ACTIVATION OF CARDIAC MITOKATP AND REDUCTION OF OXIDATIVE STRESS.

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Hydrogen sulfide (H2S) is an endogenous gasotransmitter pivotally involved in the physiological regulation of cardiovascular functions. In particular, H2S exhibits cardioprotective effects in ischemia-reperfusion (I/R) models, and is considered an important mediator of "ischemic preconditioning", a self-defence cardioprotective mechanism against myocardial I/R injury. Although mechanisms of action accounting for its activity are not yet completely understood, a central role is likely to be played by mitochondrial ATP-sensitive potassium channels (mito-KATP), since anti-ischemic effects of H2S are largely inhibited by mito-KATP blockers [1]. Other mechanisms are proposed to explain cardioprotection both H2S, such as 5-phosphodiesterase inhibition and anti-inflammatory effects [2-3].

Presently, the most widely used H2S-donor is NaHS; nevertheless this agent rapidly produces H2S, and this feature may cause adverse effects. Indeed, an ideal H2S-donor should generate H2S with slower releasing rate. We have recently demonstrated the H2S-releasing properties of some aryl isothiocyanate derivatives, suggesting that isothiocyanate is a suitable H2S-donor moiety. Among these derivatives, 4-carboxyphenyl isothiocyanate (4-CPI) exhibited interesting concentration-dependent vasorelaxing effects on conductance and coronary arteries, and caused membrane hyperpolarization of vascular smooth muscle cells [4].

Here, we aimed at evaluating the cardioprotective profile of 4-CPI in ex-vivo model of I/R injury in Langendorff-perfused hearts from Wistar rats and in in-vivo model of acute myocardial infarct.

I/R period is responsible for a marked damage to the isolated rat hearts, highlighted by a 50% reduction in myocardial contractility and a high degree of tissue injury, detected by morphometric analysis. 4-CPI (0.072, 0.24 and 0.72 mg/Kg, i.p.) produced a significant improvement of functional parameters and a reduced extension of ischemic area. Moreover, dihydroethidium (DHE)-staining evidenced an elevated production of ROS in tissue slices from hearts submitted to I/R, while in myocardial samples from rats pre-treated with 4CPI (0.24mg/Kg) ROS production was significantly reduced. Finally, CSE expression was markedly lower in cardiac homogenates obtained from hearts submitted to I/R period after pre-treated with 4CPI (0.24mg/Kg).

Pre-treatment of animals with 5-hydroxydecanoic acid (5HD, 10 mg/Kg i.p.), selective blocker of mito-KATP channels, almost completely abolished the cardioprotective effects of 4CPI (0.24mg/Kg). The involvement of mito-KATP channels was further confirmed in isolated rat cardiac mitochondria, in which 4-CPI showed the typical effects of mitochondrial potassium channel activators, such as mitochondrial membrane depolarization and inhibition of calcium uptake into the mitochondrial matrix.

Finally, 4-CPI (0.24mg/Kg, i.p.) displayed protective effects also in in vivo model of acute myocardial infarct, where damaged areas were significantly reduced if compared with vehicle-treatment.

These results demonstrate that the novel H2S-donor, 4-CPI, is endowed with significant cardioprotective activity in ex-vivo and in vivo I/R models, likely to be mediated by mito-KATP channel activation.

References:

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