MECHANISMS IN WHICH PRECONDITIONING AND MITOCHONDRIAL ATP-SENSITIVE K^+ CHANNELS PROTECT AGAINST DAMAGE PROMOTED BY ISCHEMIA/REPERFUSION

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Heart ischemia followed by reperfusion results in impairment of cellular and mitochondrial functionality due to opening of mitochondrial permeability transition (MPT) pores. Preconditioning or mitochondrial ATP-sensitive K^+ channel (mitoK$_{ATP}$) opening rescues cells from ischemic damage. Here we investigate the signaling mechanisms that activate mitoK$_{ATP}$ during preconditioning and the role of these channels in cardioprotection. Using cardiac HL-1 cells, we demonstrate that increases in reactive oxygen species (ROS) observed during preconditioning are not inhibited by mitoK$_{ATP}$ antagonists, suggesting they occur upstream of channel activity. Consistent with this, catalase addition to perfused rat heart and HL-1 cells prevented the beneficial effect of preconditioning, but not of mitoK$_{ATP}$ opening. On the other hand, 2-mercaptopropionylglycine prevented cardioprotection in both cases, suggesting this compound may present effects other than scavenging ROS. Indeed, tiol reducing agents impaired diazoxide-mediated activation of mitoK$_{ATP}$. Examining how mitoK$_{ATP}$ can be activated during preconditioning, we found that endogenous or exogenous ROS strongly enhance mitoK$_{ATP}$ activity, suggesting that increments in ROS release may activate mitoK$_{ATP}$. MitoK$_{ATP}$ prevented Ca^{2+} uptake and ROS formation, conditions that favor the opening of MPT pores under ischemic conditions. MitoK$_{ATP}$ opening decreased ROS generation during both ischemia and reperfusion, avoiding cellular damage. On the other hand, MPT inhibition prevented oxidative stress only during simulated reperfusion, but protected cells in a manner indistinguishable from mitoK$_{ATP}$ opening. Collectively, our results suggest that mitoK$_{ATP}$ acts as a ROS sensor that decreases mitochondrial ROS generation in response to enhanced local levels of oxidants. As a result, these channels regulate mitochondrial redox state under physiological conditions and prevent oxidative stress under pathological conditions, inhibiting MPT opening and ischemic cardiac damage.
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