Cardioprotective Effects of Quercetin in Ischemia-Reperfusion Injury: The Role of Oxidized CaM Kinase II

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Ischemia-reperfusion (I/R) injury during heart attack may result in significant heart damage, and new therapies are needed. The goal of this study was to determine if the flavonoid quercetin protects spontaneously beating cardiac cells from death in an in vitro model of hypoxia-reoxygenation (H/R), simulating the conditions of ischemia-reperfusion in vivo, and to establish the mechanism of quercetin's action. Cultured neonatal rat cardiac myocytes were exposed to 40 minutes mineral oil-induced hypoxia followed by two hours reperfusion with oxygenated media. Cell death, formation of reactive oxygen species (ROS), and mitochondrial membrane potential (?m) were monitored using fluorescence microscopy. The activation and oxidation of CaMKII was determined by Western blot with specific antibodies recognizing phosphorylated and oxidized forms of CaMKII. Hypoxia caused the loss of ?m, generated low levels of ROS, and reduced cell viability by 60%. Quercetin and the CaMKII inhibitor KN-93 were tested to see if they could prevent cell death. Quercetin protected cells from hypoxia-induced loss of ?m, blocked ROS formation, and increased viability to 70%. Combined treatment with quercetin and KN-93 increased cell survival to 90%. Early reoxygenation was associated with a twofold increase in ROS formation and loss of ?m. After two hours reoxygenation, over 80% of surviving cells were dead. Both quercetin and KN-93 increased cell survival during reoxygenation. Western blot revealed that quercetin strongly blocked activation and oxidation of CaMKII during reoxygenation, suggesting that CaMKII is one of the signaling molecules that is sensitive to quercetin's action.

Awards Won: