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Myocardial protection from ischemic preconditioning is not blocked by sub-chronic inhibition of carnitine palmitoyltransferase I

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Abstract

Ischemic preconditioning (IP) triggers cardioprotection via a signaling pathway that converges on mitochondria. The effects of the inhibition of carnitine palmitoyltransferase I (CPT-I), a key enzyme for transport of long chain fatty acids (LCFA) into the mitochondria, on ischemia/reperfusion (I/R) injury are unknown. Here we investigated, in isolated perfused rat hearts, whether sub-chronic CPT-I inhibition (5 days i.p. injection of 25 mg/kg/day of Etomoxir) affects I/R-induced damages and whether cardioprotection by IP can be induced after this inhibition. Effects of global ischemia (30 min) and reperfusion (120 min) were examined in hearts harvested from Control (untreated), Vehicle- or Etomoxir-treated animals. In subsets of hearts from the three treated groups, IP was induced by three cycles of 3 min ischemia followed by 10 min reperfusion prior to I/R. The extent of I/R injury under each condition was assessed by changes in infarct size as well as in myocardial contractility. Postischemic contractility, as indexed by developed pressure and dP/dt_{max}, was similarly affected by I/R, and was similarly improved with IP in Control, Vehicle or Etomoxir treated animals. Infarct size was also similar in the three subsets without IP, and was significantly reduced by IP regardless of CPT-I inhibition. We conclude that CPT-I inhibition does not affect I/R damages. Our data also show that IP affords myocardial protection in CPT-I inhibited hearts to a degree similar to untreated

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animals, suggesting that a long-term treatment with the metabolic anti-ischemic agent Etomoxir does not impede the possibility to afford cardioprotection by ischemic preconditioning.

Keywords: Ischemia/reperfusion; Preconditioning; Myocardial necrosis; Mitochondria; Carnitine palmitoyltransferase

Introduction

Long chain fatty acids (LCFA) are the major oxidation fuel of the healthy heart in vivo and in vitro, while carbohydrates, especially lactate and glucose, provide the remaining energy source (Neely et al., 1969; Morgan et al., 1984; Jeffrey et al., 1995). However, in several pathological conditions cardiac glucose uptake is higher and fatty acid oxidation is likely to be reduced (Olson, 1959; Wikstrom et al., 1997; Recchia et al., 1998; Osorio et al., 2002).

Numerous studies have aimed to establish whether the oxidation of a given type of substrate vs. another energy source results in a more or less advantageous environment for cardiac energetics. The prevailing idea is that the preferential oxidation of glucose improves cardiac efficiency of the ischemic heart (Simonsen and Kjekshus, 1978; Burkhoff et al., 1991, 1995; Korvald et al., 2000) and therefore glucose oxidation is considered beneficial during myocardial hypoperfusion (Pepine and Wolff, 1999; Taniguchi et al., 2001). In fact, compared with fat oxidation, carbohydrate utilization increases the ratio between adenosine triphosphate (ATP) synthesis and consumed oxygen (Starnes et al., 1985). We recently demonstrated that inhibition of LCFA oxidation by inhibition of carnitine palmitoyltransferase I (CPT-I), a key enzyme for transport of LCFA into the mitochondria, impedes an adequate contractile response of the isolated heart to increased pre-load or flow, whereas the inotropic response to adrenergic β-receptor stimulation is insensitive to changes in substrate availability (Pagliaro et al., 2002).

The above studies suggest that inhibition of LCFA oxidation may improve cardiac efficiency of ischemic heart, but may endanger contractile function of normal perfused hearts.

Ischemic preconditioning (IP), which is obtained by brief episodes of coronary occlusion (few minutes), is well known to induce myocardial protection against the injury caused by sustained ischemia followed by reperfusion (Murry et al., 1986). Among other effects, IP induces a sort of "metabolic hibernation" characterized by a reduction in the ATP pool combined with a reduction in ATP hydrolytic rate during subsequent ischemic stress (Murry et al., 1990; Reimer, 1996; Jennings et al., 2001; Schulz et al., 2001). Mitochondrial F_0F_1 ATPsynthase may play an important role on this respect (Das and Harris, 1990; Vander Heide et al., 1996; Vuorinen et al., 1995; Green et al., 1998; Bosetti et al., 2000; Penna et al., 2004). Importantly, mitochondrial K^+_{ATP} channel activation plays a pivotal role in the pathway leading to myocardial protection by IP (Yellon and Downey, 2003; O'Rourke, 2004). Several reviews have been recently published on the critical role played by mitochondria in cardioprotection (Yellon and Downey, 2003; Marin-Garcia and Goldenthal, 2004; Murphy, 2004; O'Rourke, 2004).

All the above studies strongly suggest that mitochondrial function is crucial to obtain protection by IP. In particular, ischemia is hypothesized to promote preconditioning, via mitochondria uncoupling; thus metabolic anti-ischemic agents may act against the IP-inducing cardioprotection (Opie, 2003).