Ischemic Preconditioning Enhances Fatty Acid-Dependent Mitochondrial Uncoupling

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Ischemic preconditioning (IP) is a procedure in which sub-lethal episodes of ischemia, each separated by brief periods of reperfusion, protect the heart against subsequent lethal ischemia. Cardioprotection has previously been related to changes in mitochondrial redox state, energy metabolism and ion transport. Our study tested the hypothesis that ischemic preconditioning changes mitochondrial fatty acid (FA) transport. We found that IP does not alter mitochondrial membrane integrity or FA levels, but enhances membrane potential decreases when FA are present, in an ATP-sensitive manner. FA hydroperoxides had equal effects in control and preconditioned mitochondria, while GTP did not abrogate the IP effect, suggesting uncoupling proteins were not involved. Conversely, thiol reductants and atractyloside, which inhibits the adenine nucleotide translocator, eliminated the differences in responses to FA. Together, our results suggest that IP leads to thiol oxidation and activation of the adenine nucleotide translocator, resulting in enhanced FA transport and mild mitochondrial uncoupling. The results obtained suggest an elegant negative feedback mechanism triggered by IP which can control redox balance in mitochondria.