MECHANISMS OF ADENOSINE MONOPHOSPHATE-ACTIVATED PROTEIN KINASE-INDUCED PRECONDITIONING IN ISCHEMIA/REPERFUSION

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Abstract

We have previously demonstrated that consuming ethanol (ethanol preconditioning or EPC) at low levels 24 hrs prior to ischemia/reperfusion (I/R) prevents postischemic leukocyte-endothelial cell adhesive interactions (LEI) by a mechanism that is initiated by nitric oxide (NO) formed by endothelial NO synthase (eNOS). Recent work indicates that: 1) ethanol increases the activity of 5'-AMP-activated protein kinase (AMPK), 2) AMPK phosphorylates eNOS at Ser1177, resulting in activation, 3) NO from eNOS can activate ATP-sensitive potassium channels (K_{ATP}), and 4) NO has been shown to induce heme oxygenase-1 (HO-1) protein expression. In light of these observations, we postulated that AMPK activation may trigger the development of an anti-inflammatory phenotype similar to that induced by antecedent ethanol ingestion, and that this effect was mediated by eNOS, K_{ATP}, and HO-1. C57BL/6J, eNOS-/-, AMPKα1-/-, and AMPKα2-/- mice were treated with EPC or the AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) 24 hrs prior to I/R (AICAR-PC) in the presence or absence of inhibitors of the proposed mediators. I/R induced a marked increase in LEI relative to sham control mice. The postischemic increase in LEI was prevented by preconditioning with AICAR 24 hrs prior to I/R. AICAR-PC appears to be mediated by eNOS, K_{ATP}, and HO, as it was ineffective at reducing LEI in the eNOS-/-, AMPKα1-/-, or AMPKα2-/- mice or wild-type mice treated with the inhibitors of the proposed mediators. Our results indicate that AMPK agonists produce an anti-inflammatory phenotype in postcapillary venules by an eNOS, K_{ATP}, and HO-dependent mechanism.