AMPK inibe IGF-I

Lembrar que as antocianinas do reino vegetal estimulam a AMPK, sendo tais substâncias mais um presente da Natureza para os seres humanos no tratamento das células doentes que chamam de câncer. Jose de Felippe Junior

AMP-activated protein kinase inhibits IGF-I signaling and protein synthesis in vascular smooth muscle cells via stimulation of insulin receptor substrate 1 S794 and tuberous sclerosis 2 S1345 phosphorylation.


Department of Medicine, University of North Carolina, School of Medicine, Chapel Hill, North Carolina 27705, USA.

Abstract

AMP-activated protein kinase (AMPK) inhibits IGF-I actions, but the mechanism by which AMPK functions is undefined. This study identified signaling events that were induced by AMPK that mediated inhibition of IGF-I-stimulated phosphoinosotide-3-kinase (PI3K) pathway activation. The AMPK activator metformin stimulated AMPK Thr172 phosphorylation and inhibited IGF-I-stimulated phosphorylation of Akt/tuberous sclerosis 2 (TSC2)/mammalian target of rapamycin (mTOR)/p70S6 kinase (p70S6K). Expression of constitutively active forms of AMPK suppressed IGF-I-stimulated activation of Akt/TSC2/mTOR/p70S6K and protein synthesis, whereas AMPK knockdown resulted in enhanced responses to IGF-I. To determine the mechanism by which AMPK inhibited IGF-I signaling, the role of insulin receptor substrate-1 (IRS-1) was examined. Both metformin and constitutively activated AMPK enhanced phosphorylation of IRS-1 Ser794, which led to decreased IRS-1 tyrosine phosphorylation and recruitment of the p85 subunit of PI3K. Overexpression of IRS-1 S794A was associated with increased IGF-I-stimulated IRS-1 tyrosine phosphorylation, p85 association, and protein synthesis. To determine whether other signaling molecules mediated the effect of AMPK, TSC2 function was examined. Cells overexpressing TSC2/S1345A (the site of AMPK phosphorylation) were less responsive to metformin-induced inhibition of p70S6 kinase. These findings are relevant to whole animal physiology because administration of metformin to mice resulted in inhibition of IGF-I-stimulated phosphorylation of Akt/mTOR/p70S6K. In conclusion, AMPK functions to inhibit IGF-I-stimulated PI3K pathway activation through stimulation of IRS-1 serine 794 phosphorylation. Because IGF-I is an important stimulant of the anabolic response, this effect of AMPK could account for part of its inhibitory effect on protein synthesis, thus allowing more efficient energy use by other cellular processes.

PMID: 20363874