

P006 mTOR, AMPK and GCN2 coordinate the adaptation of hepatic energy metabolic pathways in response to amino acids and insulin

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This study addressed the question of amino acid sensing in hepatocytes. We aimed to investigate whether changes in the phosphorylation state of the mammalian target of rapamycin (P-mTOR), adenosine monophosphate-activated protein kinase (P-AMPK) and general control non depressible 2 kinase (P-GCN2) transduction pathways are involved in nutrient signaling in primary culture of hepatocytes. The activation of protein translation required both high AA levels and insulin, as indicated by the increase in 4E-BP1 phosphorylation ($P < 0.01$). This was associated with an increase in P-mTOR and a reduction of P-AMPK and P-GCN2 ($P < 0.01$) suggesting, for the first time, that GCN2 is involved in sensing amino acids increase. In order to examine whether 4E-BP1 is the down stream target of mTOR, hepatocytes were incubated in the presence or absence of AICAR or Rapamycin. Surprisingly, no change in p4E-BP1 was observed by Rapamycin whereas p4EBP-1 was dramatically decreased by AIRCAR. This suggests that, in response to AA and insulin, 4E-BP1 may be not the directed downstream target of mTOR and AMPK may be involved in this effect.