

P013 PDK1, independently of PKB, is involved in the leucine-mediated stimulation of the cardiac mTOR/p70S6K pathway

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This study evaluated the putative role of PDK1 in the stimulation of cardiac p70S6K by leucine, using two genetic models, the PDK1-KO and -L155E/KI mice. In WT perfused hearts, both leucine and insulin increased p70S6K activity whereas, unlikely to insulin, leucine did not modulate PKB/Akt activity. The effect of insulin and leucine on p70S6K activity correlated with its phosphorylation state on Thr-389, the mTOR-dependent phosphorylation site, and with phosphorylation of mTOR on Ser-2448. Knowing that the insulin-dependent activation of mTOR/p70S6K requires PDK1, we investigated whether PDK1 could mediate the leucine effect. In PDK1-KO hearts, both leucine and insulin failed to induce phosphorylation of mTOR and p70S6K preventing p70S6K activation. In PDK/L155E-KI hearts, the phosphorylation, induced by insulin, of mTOR on Ser-2448 and of p70S6K on Thr-389 was preserved whereas that caused by leucine was abolished. We conclude that i) the leucine effect on the activation of both mTOR and p70S6K in the heart are independent of PKB/Akt but dependent of PDK1 and ii) the molecular mechanisms involved in the stimulation of mTOR/p70S6K by PDK1 downstream insulin and leucine are different.