

**P024** Glucose-Mediated Changes in Intracellular ATP Concentration Regulate eIF2 $\alpha$  Phosphorylation but not Protein Synthesis in Pancreatic  $\beta$ -cells

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In response to an increase in extracellular glucose concentration from 2mM to 20mM, pancreatic  $\beta$ -cells exhibit an approximately two fold increase in the rate of protein synthesis. We have previously demonstrated that this increase in the rate of protein synthesis at high glucose parallels an increase in the availability of the translational ternary complex (eIF2.GTP:Met-tRNA<sub>i</sub>), and the dephosphorylation of eIF2 $\alpha$ . We have therefore investigated the mechanisms by which glucose regulates the phosphorylation of eIF2 $\alpha$  and rate of protein synthesis. We show that the mitochondrial metabolism of glucose is required for both eIF2 $\alpha$  dephosphorylation and stimulation of protein synthesis at high glucose, and neither effect is regulated by an autocrine effect of insulin. Interestingly, artificially altering cellular ATP concentrations shows that changes in intracellular ATP levels parallel changes in eIF2 $\alpha$  phosphorylation, but do not parallel changes in the rate of protein synthesis in response to glucose. Furthermore, although decreases in cellular ATP cause activation of AMPK, pharmacological activation of AMPK has no effect on either eIF2 $\alpha$  phosphorylation or rate of protein synthesis. In conclusion, glucose mediated changes in intracellular ATP concentration regulate eIF2 $\alpha$  phosphorylation but not protein synthesis in pancreatic  $\beta$ -cells.