

**P060** Elevated Intracellular Acyl-CoAs Increase the Open Probability of KATP channels In Intact Pancreatic Beta-cells  
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The activity of ATP-sensitive potassium (KATP) channels is pivotal in controlling pancreatic beta-cell excitability and consequent insulin secretion. In inside-out excised membrane patches, saturated, but not polyunsaturated, long chain acyl-CoAs (acyl-CoAs) potently activate KATP channels. Thus, elevated levels of acyl-CoAs in obese and type 2 diabetic individuals could contribute to beta-cell failure via persistent activation of KATP. However, this has not been confirmed in physiologically intact primary beta-cells. In the present study we have used adenoviral over-expression of long chain acyl-CoA synthetase-1 (AdACSL-1) to elevate specific dietary acyl-CoAs *within* primary beta-cells. Data showed a significant increase in whole-cell KATP channel activity in AdACSL-1-infected cells cultured in the presence of saturated (palmitate), but not in the presence of polyunsaturated (linoleate), fat. Single channel analysis confirmed that the increased potassium current was attributable to an increase in the open probability of KATP channels. Furthermore, AdACSL-1-infected beta-cells (+palmitate) showed a significant decrease in electrical responsiveness to glucose and tolbutamide. Our data suggest a direct link between intracellular accumulation of saturated acyl-CoAs and KATP channel activation. This has implications for our current understanding of the involvement of dietary fat in the demise of the beta-cell and development of type 2 diabetes.