

**P016** Long chain acyl-CoA esters increase activity of the sodium-calcium exchanger NCX1.3: Implications for the dietary regulation of pancreatic beta-cell excitability.

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Sodium-calcium exchanger (NCX) activity contributes to beta-cell calcium homeostasis by extruding  $\text{Ca}^{2+}$ , thus restoring the beta-cell to its resting state. NCX1.3 is an abundantly expressed beta-cell isoform and increases in NCX1.3 activity therefore lead to increased  $\text{Ca}^{2+}$  extrusion and a reduction in insulin secretion. We have previously demonstrated that long chain acyl-CoA esters (acyl-CoAs) activate the  $\beta$ -cell  $\text{K}_{\text{ATP}}$  channel. Therefore in this study we determined the effects of acyl-CoAs on NCX1.3 activity. Inside-out patch-clamp experiments were performed on recombinant NCX1.3 transiently over-expressed in tsA201 cells. Acyl-CoAs (1  $\mu\text{M}$ ) with differing sidechains were perfused across the inner surface of membrane patches. Palmitoyl-CoA (C16:0), stearoyl-CoA (C18:0), and oleoyl-CoA (C18:1) significantly decreased the inactivation process leading to increased forward mode activity. Interestingly, NCX1.3 inactivation was unaltered by polyunsaturated acyl-CoAs n-6 linoleoyl-CoA (C18:2) and n-3 docosahexaenoyl-CoA (C22:6) or the shorter chain decanoyl-CoA (C10:0) suggesting that there is a saturation- and acyl chain length-dependent effect of acyl-CoAs. We demonstrate for the first time that increases in saturated long chain intracellular acyl-CoAs may contribute to impaired insulin secretion via increased  $\text{Ca}^{2+}$  extrusion, further emphasizing the importance of dietary fat in the aetiology of type 2 diabetes.