

P006 Long term high fat feeding results in reduced exocytosis and altered calcium signalling

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Glucose intolerance and altered glucose induced insulin secretion (GIIS) are both *in vitro* and *in vivo* landmarks of long term high fat (40%) feeding in C57/bl6ox mice. When compared to controls, pancreatic islets (or beta cells) isolated from high fat fed mice showed the following features: 1) reduced GIIS but normal insulin content. 2) increased pancreatic beta cell area. 3) impairment of peak Ca^{2+} transient elicited by both glucose and tolbutamide, as well as a slight attenuation in glucose induced Ca^{2+} oscillations but Ca^{2+} response to KCl was not different from controls (as measured by microfluorimetry). 4) reduction in 1st phase insulin secretion in the high fat group, followed by a smaller but significant reduction in 2nd phase insulin secretion (as measured by islet perfusion). The response to tolbutamide was likewise reduced. 5) Ca^{2+} currents and K_{ATP} conductance were unchanged. 6) Membrane potential recordings were unchanged. 7) Using whole cell capacitance measurements, we established that during a 10-step train of membrane depolarisations, the first step of capacitance increase is largely reduced in islets isolated from high fat fed animals whereas the second phase is identical to control islets. Together, these results demonstrate the plurality of the effects exerted by high fat feeding on beta cells. We hypothesise that granule docking is impaired and leads to impairment of 1st phase insulin secretion whilst the calcium oscillation pattern is perturbed, leading to the impairment of 2nd phase insulin secretion.