Electrical activity and pulsatile insulin release in islets of Langerhans from normal and diabetic rodents

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Type-2 diabetes *mellitus* (T2DM) is characterized by impaired glucose-induced insulin secretion and abnormal pulsatile insulin release both in plasma and islets of Langerhans. Glucose-induced electrical activity (EA) is one of the early steps of the stimulus-secretion coupling however its role in defective insulin secretion is yet unknown. In this work it was investigated whether EA is impaired in pancreatic β-cells from Goto-Kakizaki (GK) rats, an animal model of T2DM. The role of EA in the genesis of pulsatile insulin secretion was also investigated.

EA was recorded from single collagenase-isolated islets, using high-resistance intracellular microelectrodes. Insulin release was measured by ELISA. The correlation between the EA and insulin secretion was established by simultaneous measurements.

Challenging mouse β-cells with stimulatory glucose concentrations ([G]) evoked a bursting pattern of EA characterized by alternating hyperpolarized silent phases and depolarized active phases with superimposed spikes. In contrast, rat islets did not exhibit bursting EA. Raising [G] evoked a depolarization to a non-oscillating plateau in both GK and control Wistar (Wr) rats. This depolarization had similar amplitude but was significantly slowed in GK rats. Spiking activity was also delayed in GK islets. Accordingly, the GK dose-response curve to glucose was shifted towards higher [G]. Moreover, in GK islets both the spike frequency and amplitude were lower for every [G] tested. Two major patterns of oscillatory activity were detected in mouse islets: 1) A regular bursting pattern, synchronous with pulses of insulin secretion (1-6min^{-1}); 2) An intermittent pattern consisting of groups of bursts (0.3-0.5min^{-1}), which were accompanied by insulin pulses of similar frequency. Single rat islets often displayed insulin oscillations with periods of about 10, 2.5 in and <1min. The two fastest oscillatory components were also detected in EA, in the form of cyclic variations in the spiking frequency.

In summary: i) The data evidence major species differences in EA patterns from mouse and rat islets; ii) GK islets showed a diminished sensitivity to glucose and a markedly delayed glucose-induced depolarization and EA; iii) Despite the differences found between mouse and rat islets, pulsatile insulin release *in vitro* is driven by oscillatory EA.

In conclusion, the alterations observed in glucose-induced EA may account for the lack of the 1st phase and for the dampening of the 2nd phase of insulin secretion in GK islets. Finally, pulsatile insulin release *in vitro* is driven by oscillatory EA, thus, single islets have the potential to behave as pacemakers for pulsatile insulin release *in vivo*.