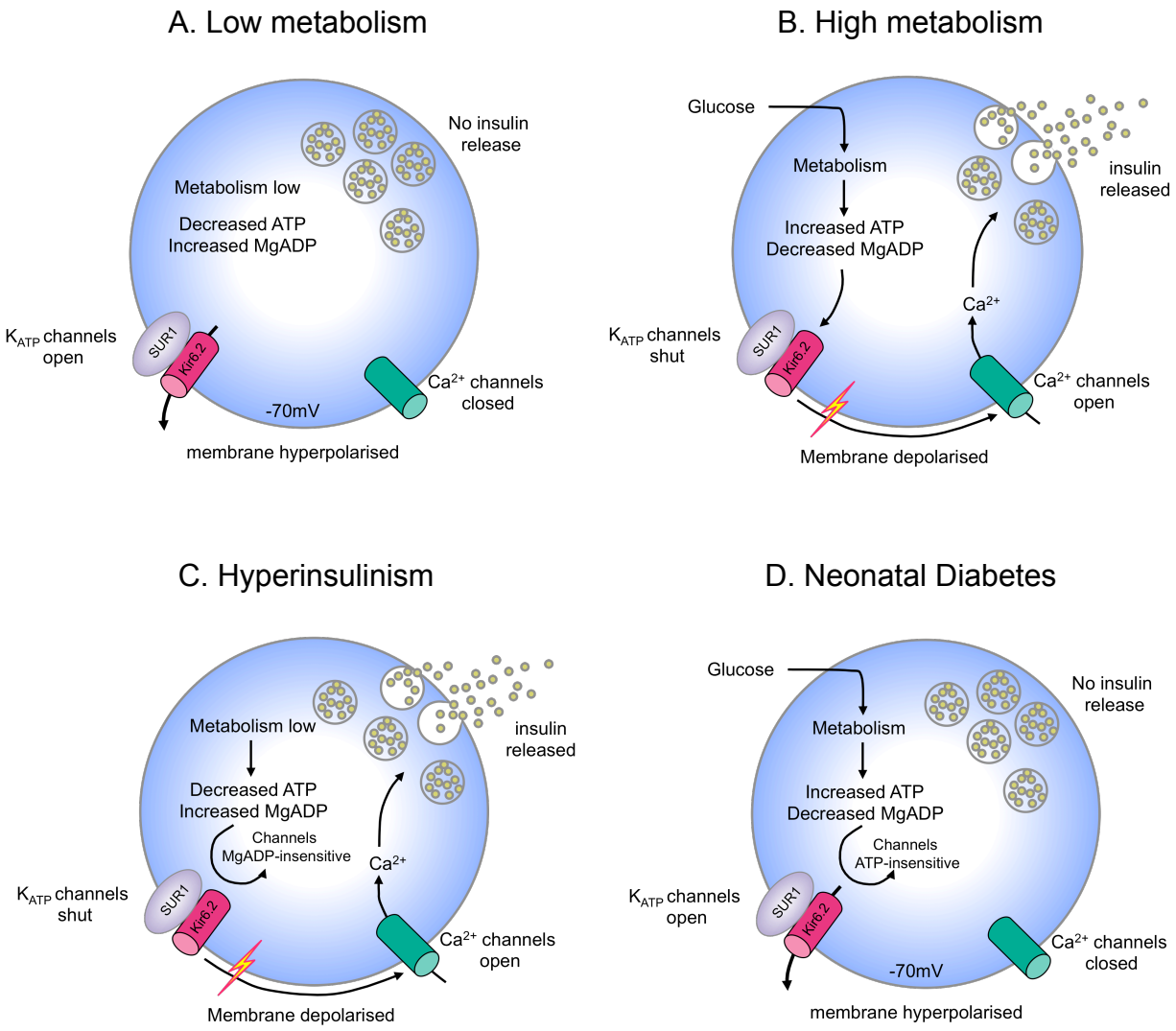
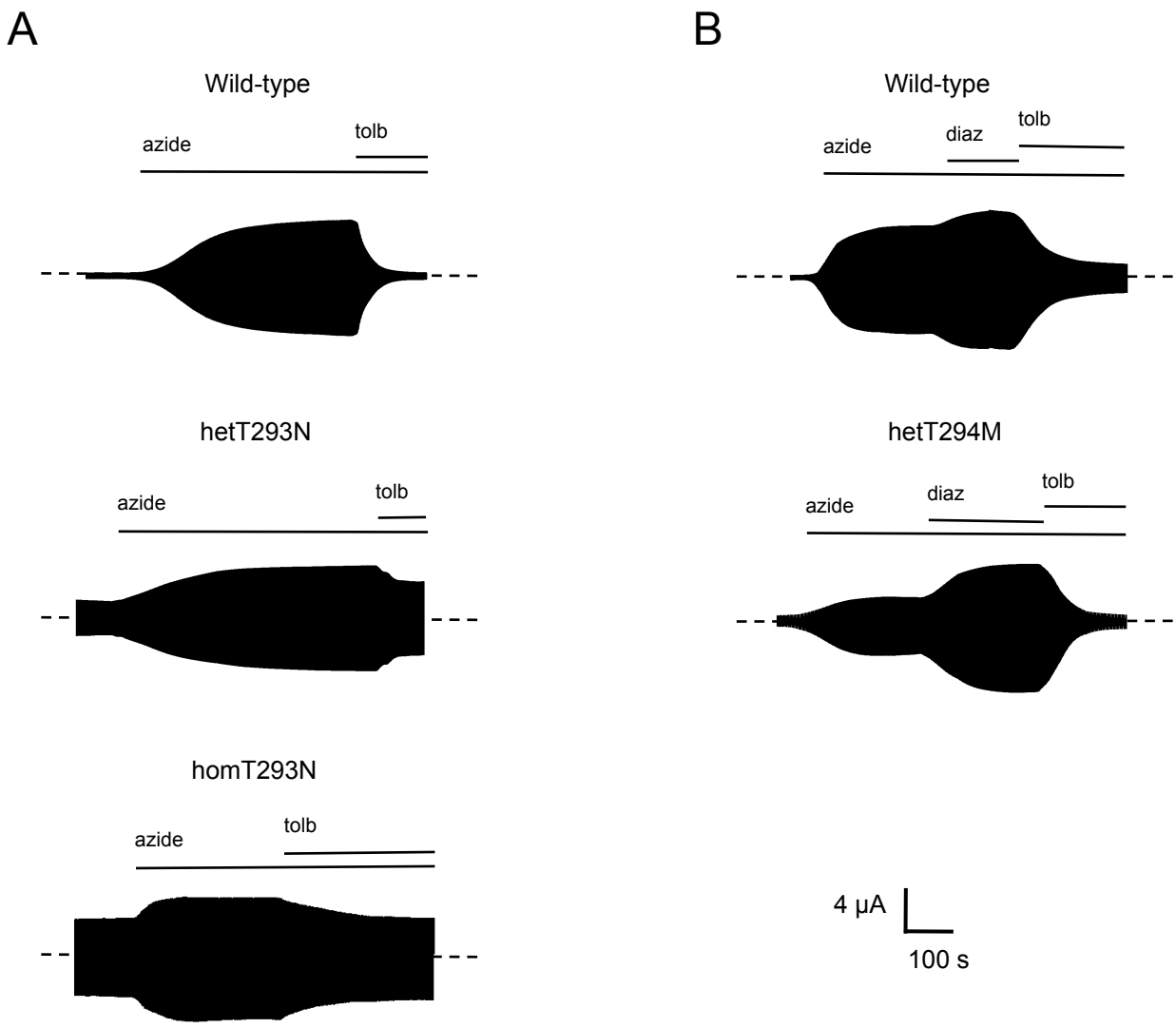


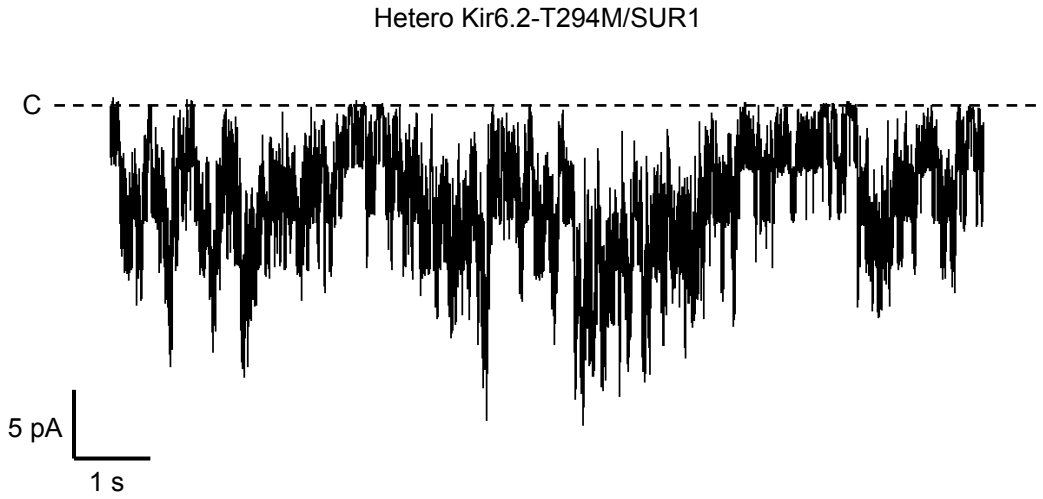
Supplementary Figure 1 Stimulus-secretion coupling in pancreatic beta-cells.

(***A***) When extracellular glucose, and thus beta-cell metabolism, are low K_{ATP} channels are open. Consequently, the cell membrane is hyperpolarised. This keeps voltage-gated Ca^{2+} channels closed, so that Ca^{2+} influx remains low and insulin secretion is inhibited. (***B***) When extracellular glucose increases, glucose metabolism generates ATP at the expense of MgADP, thereby closing K_{ATP} channels. This leads to membrane depolarization, opening of voltage-gated Ca^{2+} channels, Ca^{2+} influx and insulin secretion. (***C***) Loss-of function mutations in K_{ATP} channel genes lead to a lack of K_{ATP} channel activity, either because of a reduced channel density or an inability to of the channel respond to the stimulatory effects of MgADP. Consequently, the membrane is permanently depolarised, causing continuous Ca^{2+} channel activity and Ca^{2+} influx. This produces persistent and unregulated insulin secretion. (***D***) Gain-of function mutations in K_{ATP} channel genes cause the channel to be open even when metabolism and cellular ATP levels are high. Consequently, the membrane remains hyperpolarised, preventing opening voltage-gated Ca^{2+} channels, Ca^{2+} influx and insulin secretion, even when blood glucose levels are high. This leads to diabetes.



Supplementary Figure 2

*(**A**)* Representative wild-type, hetT293N and homT293M whole-cell currents evoked by a voltage step from -10mV to -30mV. The bars indicate the application of 3mM azide or 0.5mM tolbutamide (tolb). The dashed line indicates the zero current level.
(***B***) Representative wild-type and hetT294M whole-cell currents evoked by a voltage step from -10mV to -30mV. The bars indicate the application of 3mM azide, 340μM diazoxide or 0.5mM tolbutamide.



Supplementary Figure 3

Representative single K_{ATP} channel currents recorded at –60mV from inside-out patches from oocytes injected with SUR1 and a 1:1 ratio of Kir6.2 and Kir6.2-T294M to simulate the heterozygous state. The dashed line indicates the zero current level. C, closed state.