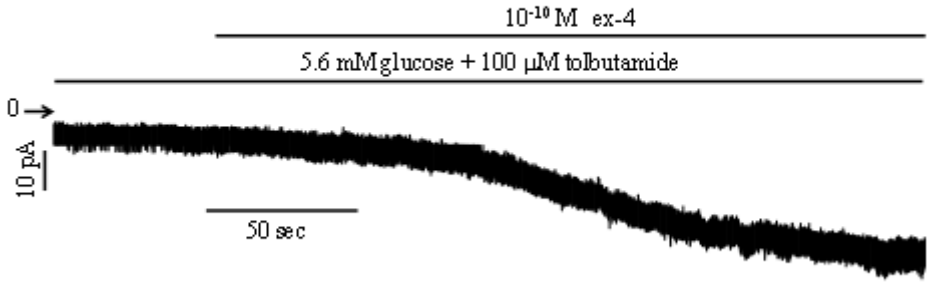
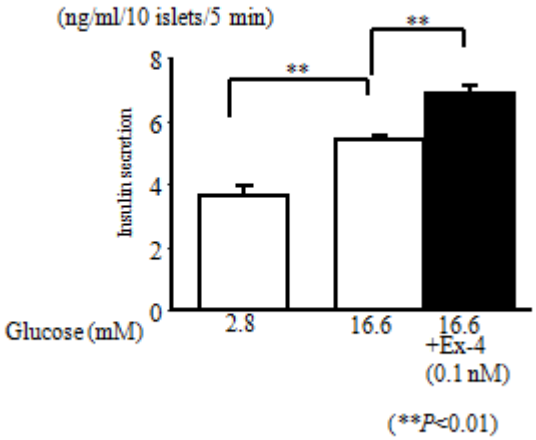
SUPPLEMENTARY DATA

Supplementary Figure 1. Exendin-4 at 10^{-10} M increased NSCC current in the presence of 5.6 mM glucose and 100 μM tolbutamide. Holding potential was held at -70 mV. Arrow indicates zero current level. This result was from a rat β-cell.

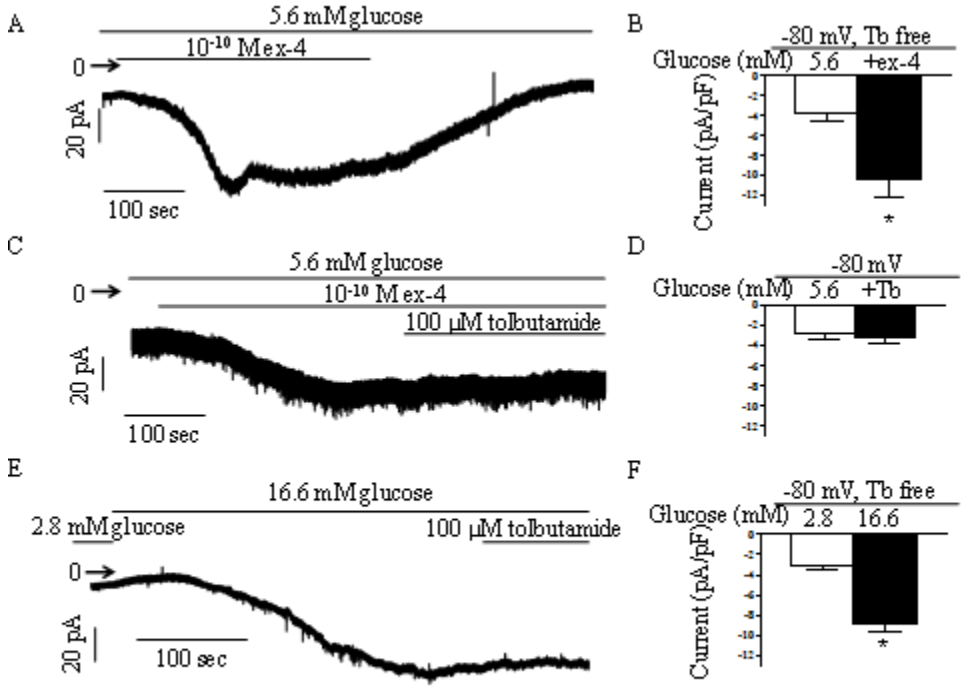


Supplementary Figure 2. Insulin secretion at glucose concentrations of 2.8 mM, 16.6 mM and 16.6 mM with ex-4. Ten rat islets were incubated for 5 min in each batch. Number of experiments was 9, results are expressed as means ± SEM, and differences were evaluated by ANOVA.



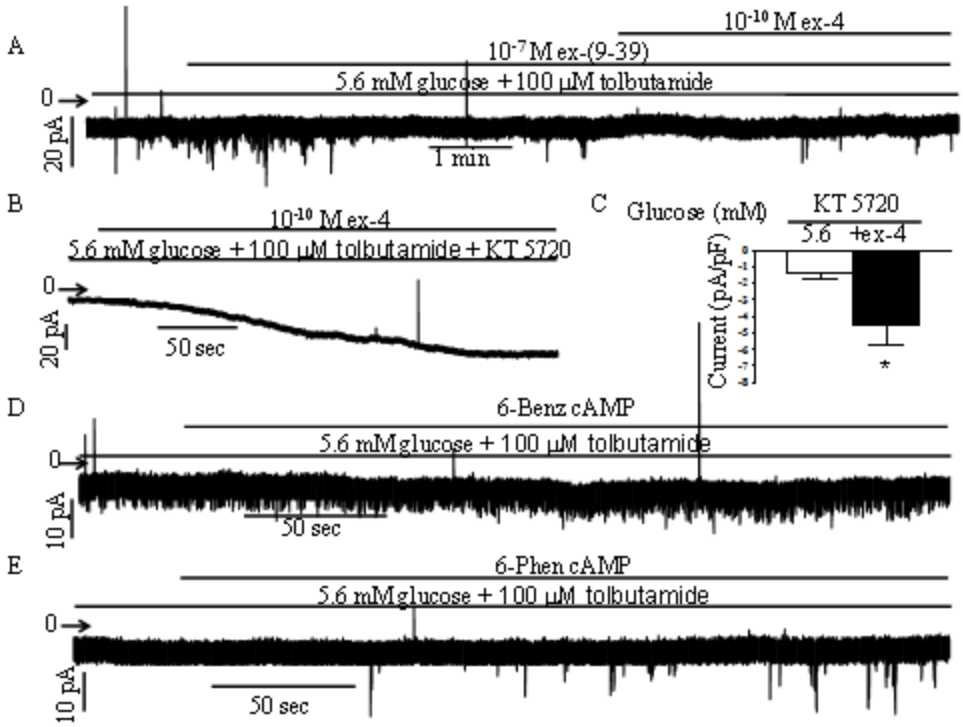
SUPPLEMENTARY DATA

Supplementary Figure 3. Effects of ex-4 and high glucose on NSCC currents in the absence of tolbutamide (Tb) at a holding potential of -80 mV. A, B: Ex-4 at 10^{-10} M was superfused at 5.6 mM glucose. C: Ineffectiveness of tolbutamide on ex-4-induced NSCC current. D: Tolbutamide alone did not affect NSCC current at 5.6 mM glucose. E, F: 16.6 mM glucose elicited an increase in NSCC current in the absence of tolbutamide and subsequent addition of tolbutamide did not influence amplitude of the current (E). Number of experiments was 6 in B, D and F. *; P<0.02 vs. control (open bars). Data were obtained from rat β-cells.



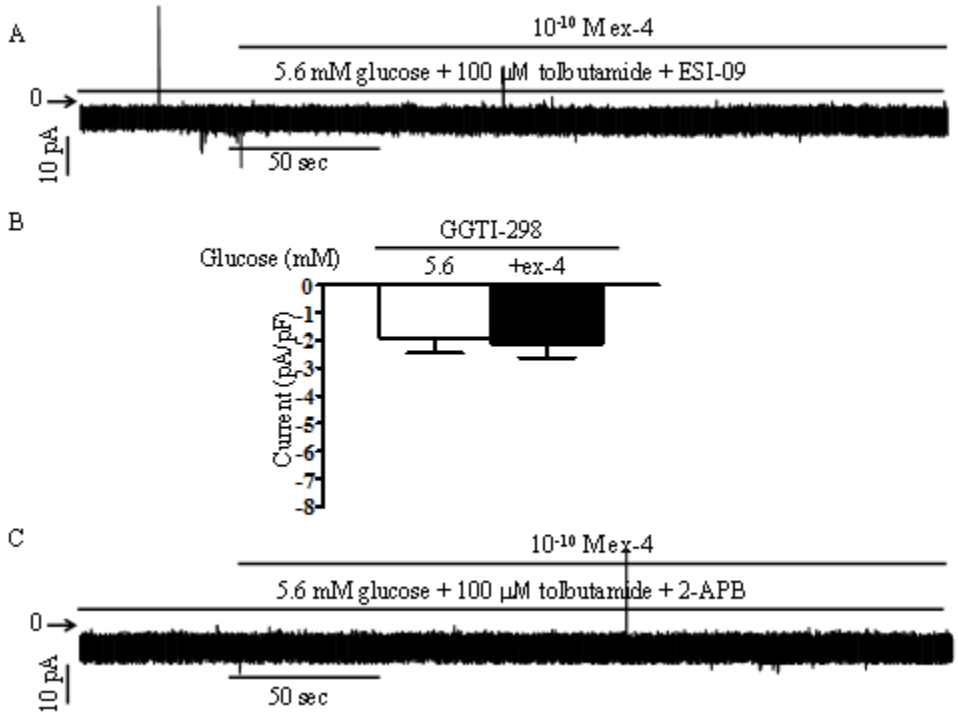
SUPPLEMENTARY DATA

Supplementary Figure 4. Original traces showing effects of ex-(9-39), KT 5720, 6-Benz cAMP and 6-Phen cAMP. A: ex-4 did not increase the current in the presence of ex-(9-39). B: KT5720, PKA inhibitor, did not influence the current increase by ex-4. C: KT5720 at 1 μM was added to the HKRB solution containing 5.6 mM glucose and 100 μM tolbutamide 5 min before exposure to ex-4. Addition of ex-4 increased the current. D and E: Traces showing effects of 6-Benz cAMP or 6-Phen cAMP on NSCC currents. Number of data points was 6. *; P<0.02 vs. control (open bars). Holding potential was -70 mV. Results from rat β-cells are shown.



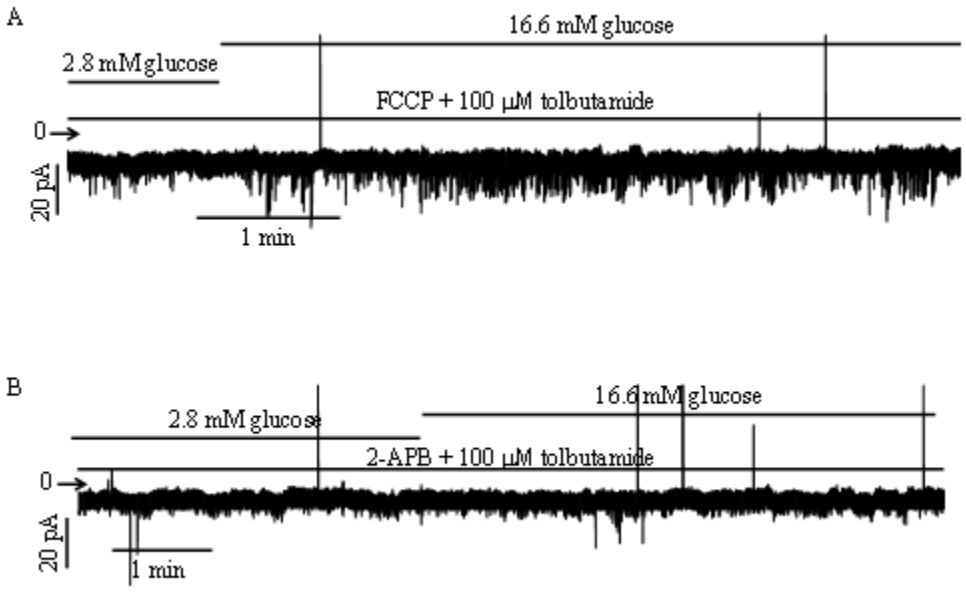
SUPPLEMENTARY DATA

Supplementary Figure 5. Ineffectiveness of ex-4 in the presence of EPAC inhibitor (A), RAP1 inhibitor (B) and TRPM2 inhibitor (C). A: ESI-09 at 10 μM prevented current increase of ex-4. B: RAP1 inhibitor, GGTI-298 (10 μM), counteracted current increases by ex-4. C: Current increase by ex-4 was also inhibited by 2-APB (10 μM). Holding potential was -70 mV. GGTI-298 was preincubated in cultured β-cells for 12 hours before use and it also was superfused during recording data at the same concentration. Results from rat β-cells are shown.

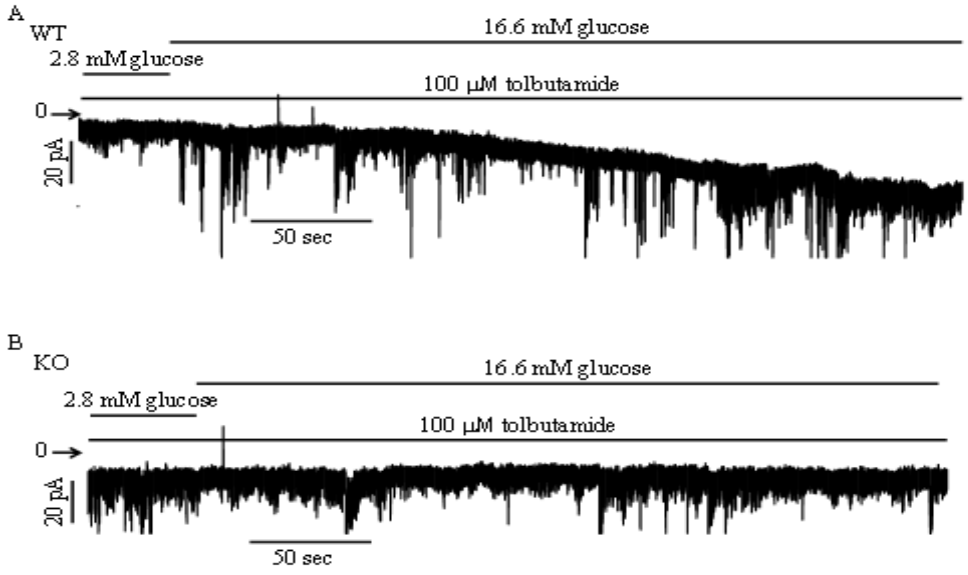


SUPPLEMENTARY DATA

Supplementary Figure 6. Original traces showing effects of 16.6 mM glucose in the presence of FCCP (A) and 2-APB (B). Holding potential was -70 mV. Results from rat β-cells are shown.

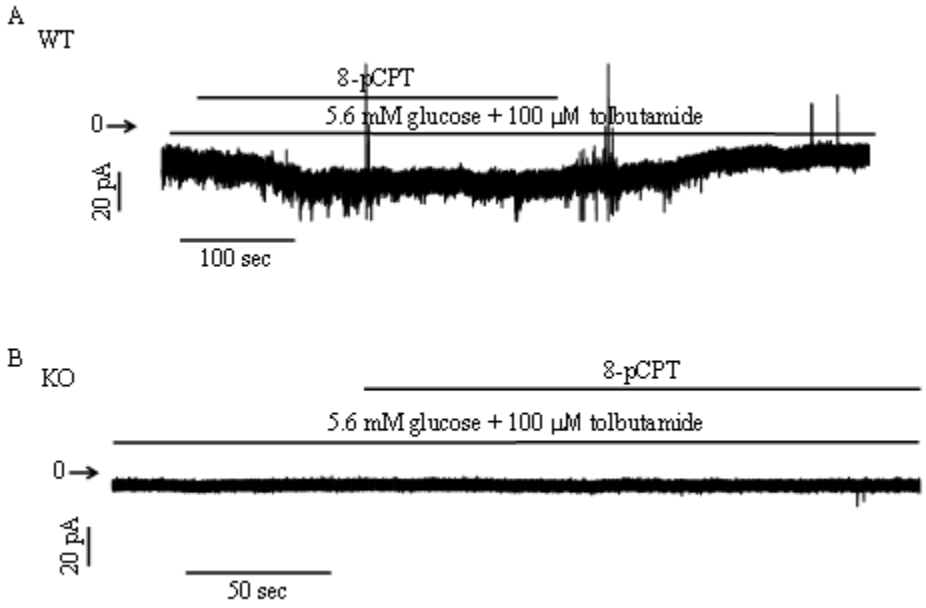


Supplementary Figure 7. Current traces recorded in wild-type (A) and TRPM2 KO (B) mice and effects of 16.6 mM glucose. In KO mice, high glucose did not increase TRPM2-channel current. Holding potential was -70 mV.

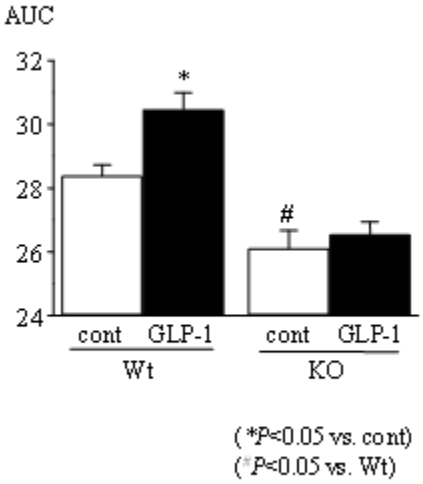


SUPPLEMENTARY DATA

Supplementary Figure 8. Current traces in wild-type (A) and KO (B) mice testing effects of 8-pCPT. Holding potential was -70 mV.



Supplementary Figure 9. AUC (area under the curve of $[Ca^{2+}]_i$ response to 10^{-10} M GLP-1) in islets isolated from wild-type (Wt) and KO mice. Means ± SEM are shown and were compared by ANOVA. Glucose concentration was 8.3 mM. AUC was measured from $[Ca^{2+}]_i$ response during 20-min exposure of cells to 8.3 mM glucose.



SUPPLEMENTARY DATA

Supplementary Figure 10. Depolarization by EPAC activator is mediated by TRPM2 channel. Membrane potentials were measured in control (white bars; -68.0 ± 1.4 mV in WT, -70.0 ± 1.0 mV in KO), in the presence of 100 μM tolbutamide (black bars; -29.0 ± 1.8 mV in WT, -26.3 ± 1.7 mV in KO) and in the presence of tolbutamide + 10 μM 8-pCPT-AM (red bars; -19.9 ± 1.1 mV in WT, -25.6 ± 1.5 mV in KO) in β-cells from wild-type and KO mice. *; P<0.01 vs. tolbutamide.