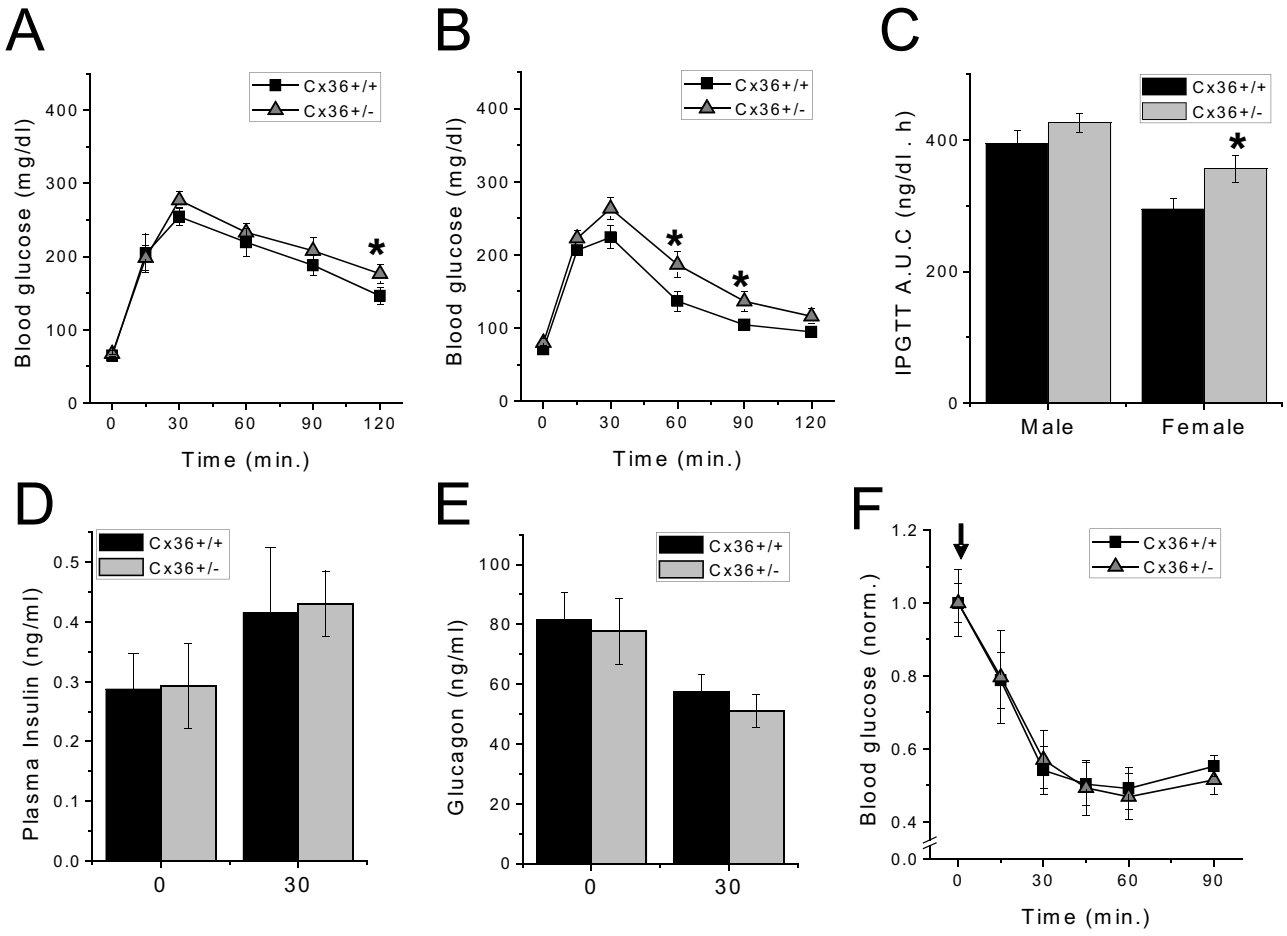
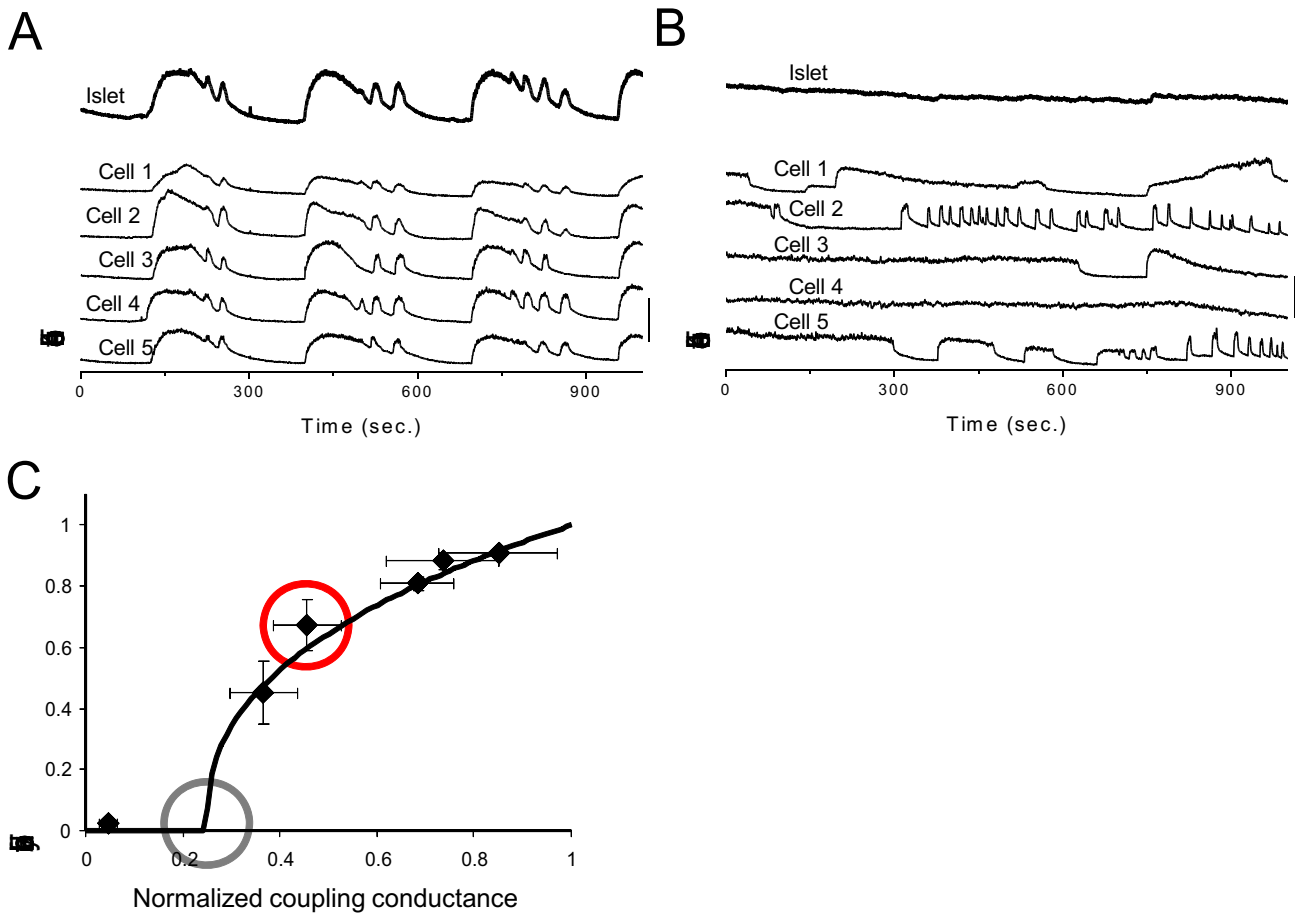
SUPPLEMENTARY DATA

Supplementary Figure 1. Phenotype of $Cx36^{+/-}$ mice. **A)** Intra-peritoneal glucose tolerance test on male $Cx36^{+/+}$ mice (solid squares) and $Cx36^{+/-}$ mice (grey triangles), each of 16 weeks age, following 2g/kg b.w. IP glucose injection. n=6 littermate mice in each group. **B)** Intra-peritoneal glucose tolerance test on female mice of 16 weeks age, as in A. n=8 littermate mice in each group. **C)** Area under the curve of the glucose excursions during IPGTT in A and B. **D)** Plasma insulin measurements in male mice aged 16 weeks before (0) and 30 minutes after 3g/kg b.w. IP glucose injection (black bars $Cx36^{+/+}$ mice, grey bars $Cx36^{+/-}$ mice). n=8 littermate mice in each group. **E)** Plasma glucagon measurements in male mice aged 16 weeks, before and 30 minutes after IP glucose injection, as in D. n=7 littermate mice in each group. **F)** Insulin tolerance test following 0.075U/kg IP insulin injection. n=10 littermate mice in each group. * indicates significant difference ($p<0.05$, 2-tailed student's t-test) at each time point comparing measurements in $Cx36^{+/+}$ and $Cx36^{+/-}$ mice.



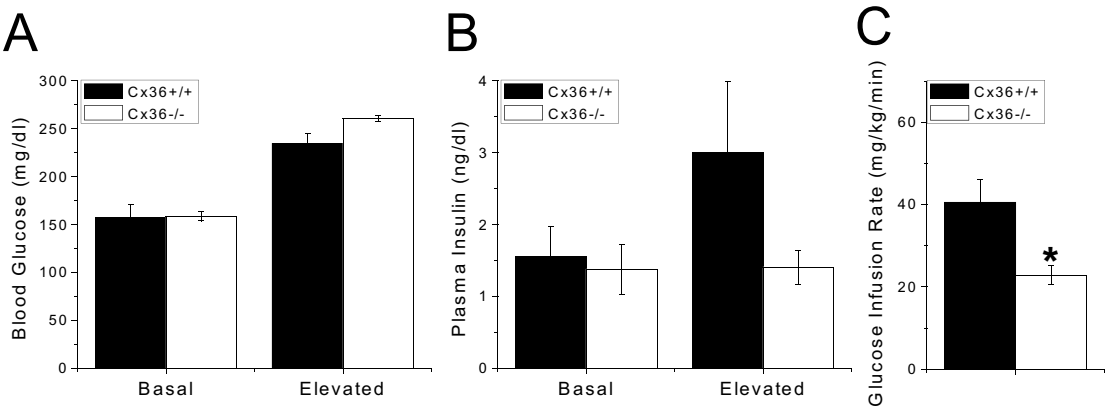
SUPPLEMENTARY DATA

Supplementary Figure 2. A) Time course of $[Ca^{2+}]_i$ in a representative $Cx36^{+/+}$ islet stimulated with 11mM glucose, as shown through Fluo4 fluorescence. Data is displayed as the fluorescence intensity averaged over the whole islet (top, bold), and a number of cells within the islet studied. **B)** As in A for a representative $Cx36^{-/-}$ islet stimulated with 11mM glucose. Vertical scale bar in A,B indicates a 100% increase in Fluo4 fluorescence. **C).** Variation in the synchronization of calcium oscillations (% of cells that are synchronized) versus the level of gap junction coupling conductance (normalized), modified from that in [Benninger et al. *BiophysJ* (2008) **95** p5048]. Filled diamonds indicate experimental data (mean±s.e.m.); solid line indicates prediction derived from multicellular model of islet electrical activity [Benninger et al. *BiophysJ* (2008) **95** p5048]. Circled in red is the coordination of $[Ca^{2+}]_i$ oscillations (~70%) upon a ~50% loss of gap junction conductance (islets of $Cx36^{+/-}$ mice). Circled in grey is coordination in $[Ca^{2+}]_i$ oscillations (~0%) upon a loss of ~75% gap junction conductance (model prediction); showing a much greater reduction in synchronization and similar to that in the absence of any gap junction conductance (e.g. in $Cx36^{-/-}$ mice).

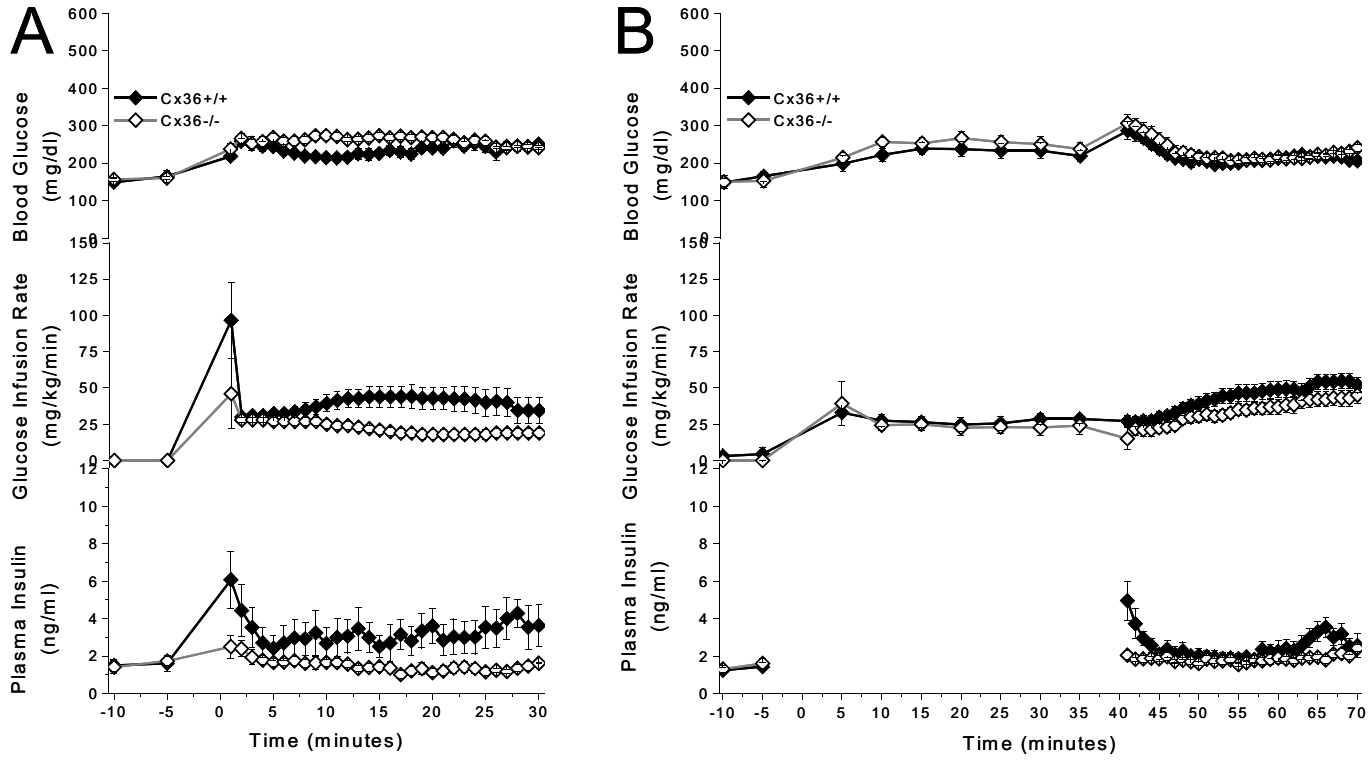


SUPPLEMENTARY DATA

Supplementary Figure 3. A) Time averaged blood glucose in male littermate $Cx36^{+/+}$ mice (black bars) and $Cx36^{-/-}$ mice (white bars) at 16-18 weeks of age before and during the hyperglycemic clamp, 5 minutes after the start of glucose infusion. n=5 mice from each group . **B)** Time-averaged plasma insulin levels corresponding to measurements made in A. **C)** Mean time-averaged glucose infusion rate required to establish glucose clamp A.



Supplementary Figure 4. A) Mean time-course of blood glucose (top), glucose infusion rate (middle) and plasma insulin (bottom) in male littermate $Cx36^{+/+}$ mice (black bars) and $Cx36^{-/-}$ mice (white bars) during the rapid sampling hyperglycemic clamp, for the protocol where blood is sampled immediately after the start of glucose infusion. n=5 mice from each group . **B)** Mean time-course of blood glucose (top), glucose infusion rate (middle) and plasma insulin (bottom) in male littermate $Cx36^{+/+}$ mice (black bars) and $Cx36^{-/-}$ mice (white bars) during the rapid sampling hyperglycemic clamp, for the protocol where blood is sampled 40 minutes after the start of glucose infusion. n=10,8 mice in $Cx36^{+/+}$, $Cx36^{-/-}$ groups respectively.



SUPPLEMENTARY DATA

Supplementary Figure 5. A) Mean pulse analysis parameters for T40 group $Cx36^{+/+}$ and $Cx36^{-/-}$ mice. Average represents the mean of the mean pulse parameter for each time-course. S.D. represents the mean of the standard deviation of the pulse parameter for each time course. **B)** As in A for T0 group, $Cx36^{+/+}$ and $Cx36^{-/-}$ mice, with analysis starting 5 minutes after glucose infusion. * indicates significant difference $p<0.05$, † indicates marginally significant difference $p=0.05$ to 0.15.

A) Pulse parameters for insulin time course starting t=40				
Parameter (unit)	**Mean of**	**Cx36+/+**	**Cx36-/-**	***P* value**
Pulse Interval (min.)	Average S.D.	4.36 ± 0.56 1.8 ± 0.38	4.15 ± 0.56 1.9 ± 0.23	0.79 0.71
Pulse duration (min.)	Average S.D.	3.03 ± 0.38 1.67 ± 0.26	2.90 ± 0.47 1.70 ± 0.21	0.83 0.89
Peak Pulse height (pMol)	Average S.D.	3.23 ± 0.71 0.78 ± 0.14	2.32 ± 0.26 0.51 ± 0.19	0.25 0.28
Peak Pulse height (% increase)	Average S.D.	145% ± 7% 43% ± 9%	136% ± 3% 23% ± 4%	0.24 0.066 †
Mean pulse height (% increase)	Average S.D.	117% ± 2% 11% ± 1%	116% ± 2% 10% ± 2%	0.72 0.56
Pulse Area (pMol / pulse)	Average S.D.	2.28 ± 0.41 2.20 ± 0.44	1.16 ± 0.24 1.82 ± 1.01	**0.036 *** 0.74
Pulse amplitude (pMol)	Average S.D.	0.86 ± 0.17 0.63 ± 0.14	0.60 ± 0.09 0.47 ± 0.18	0.19 0.50
Non-pulse component (pMol)	Average S.D.	2.29 ± 0.54 0.57 ± 0.14	1.72 ± 0.19 0.25 ± 0.05	0.34 0.064 †

B) Pulse parameters for insulin time course starting t=5				
Parameter (unit)	**Mean of**	**Cx36+/+**	**Cx36-/-**	***P* value**
Pulse Interval (min.)	Average S.D.	4.34 ± 0.70 2.39 ± 0.76	4.26 ± 0.45 1.02 ± 0.48	0.92 0.17
Pulse duration (min.)	Average S.D.	2.99 ± 0.47 1.37 ± 0.33	3.36 ± 0.48 1.90 ± 0.59	0.60 0.46
Peak Pulse height (pMol)	Average S.D.	3.57 ± 0.98 0.52 ± 0.17	1.56 ± 0.23 0.29 ± 0.08	0.11 0.27
Peak Pulse height (% over basal)	Average S.D.	141% ± 9% 22% ± 3%	134% ± 6% 33% ± 16%	0.57 0.54
Mean pulse height (% over basal)	Average S.D.	116% ± 3% 8% ± 2%	114% ± 3% 10% ± 4%	0.60 0.64
Pulse Area (pMol / pulse)	Average S.D.	1.82 ± 0.32 1.38 ± 0.32	0.92 ± 0.13 0.90 ± 0.17	**0.050 *** 0.64
Pulse amplitude (pMol)	Average S.D.	0.93 ± 0.20 0.43 ± 0.06	0.35 ± 0.05 0.21 ± 0.05	**0.045 *** 0.032 *
Non-pulse component (pMol)	Average S.D.	2.72 ± 0.82 0.48 ± 0.12	1.2 ± 0.17 0.32 ± 0.7	0.14 0.28