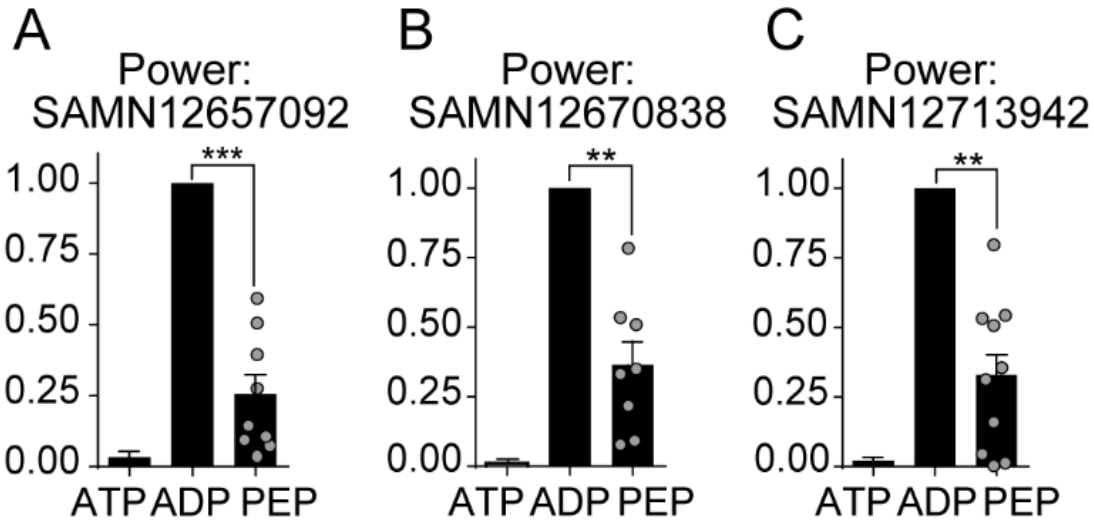

Figure S1. Membrane-associated PK is sufficient to close K_{ATP} channels in human islets, Related to Figure 1

(A-C) Analysis of K_{ATP} channel closure in terms of power for each human islet donor.
Data are shown as mean ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$ by 1-way ANOVA.

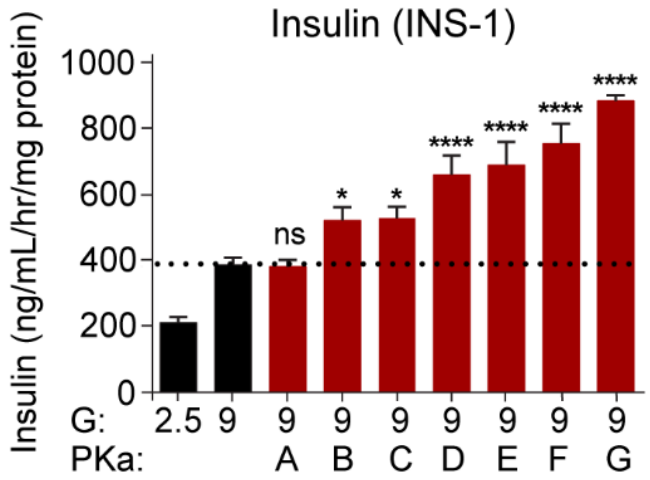

Figure S2. PK activators stimulate insulin secretion in INS-1 cells, Related to Figure 2
Effect of various PK activators on the average insulin secretion of INS-1 cells in a static incubation in 9 mM glucose (9G). A, 10 µM NIH NCGC185916-06 (Dasa-58); B, 10 µM NIH NCGC188799-02; C, 10 µM TEPP-46; D, 10 µM NIH NCGC186527-05; E, 10 µM NIH NCGC181801-02; F, 10 µM NIH NCGC188795-01; G, 10 µM NIH NCGC183333-05. Data points represent the mean of 6 technical replicates for each experiment and are shown as mean ± SEM. *$P < 0.05$, ****$P < 0.0001$ by 1-way ANOVA.

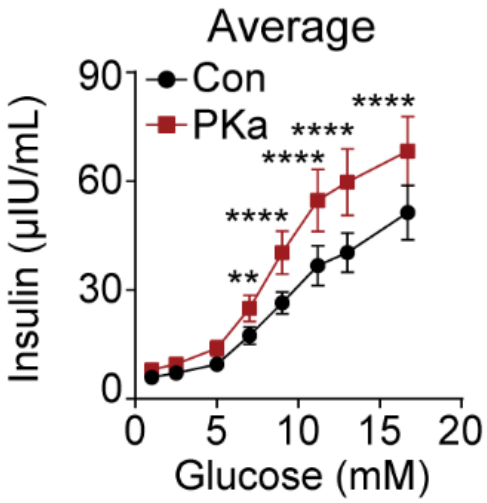

Figure S3. PK activators enhance average insulin secretion from healthy human islets, Related to Figure 2

Average insulin secretion in the absence or presence of PKa from all 10 donors from Figure 3 in static incubation assays.

Data points represent the mean of 4 technical replicates and are shown as mean ± SEM. $^{**}P < 0.01$, $^{****}P < 0.0001$ by 1-way ANOVA.

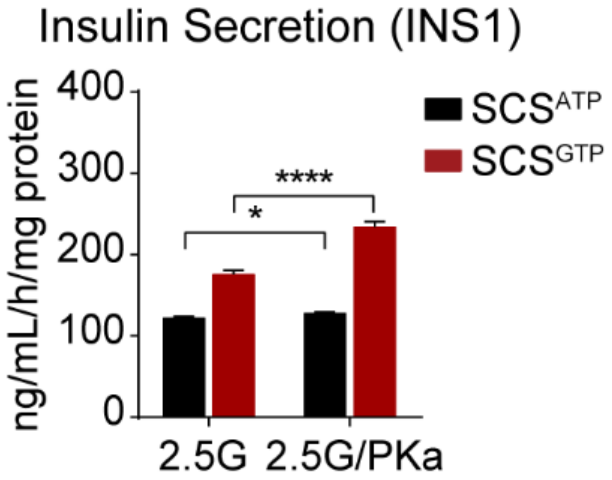

Figure S4. PK activation in INS1 832/13 cells overexpressing ATP and GTP-producing isoforms of succinyl CoA synthetase slightly elevates insulin secretion, Related to Figure 6

Insulin secretion from PKa- or vehicle-treated INS1 832/13 cells stably overexpressing the ATP and GTP-producing isoforms of succinyl CoA synthetase (SCS^{ATP} and SCS^{GTP}, respectively) (n = 6) in response to 2.5 mM glucose (2.5G).

Data are shown as mean ± SEM. *P < 0.05, ****P < 0.0001 by t-test.

Donor	Age (years)	Sex	BMI	HbA1c %
SAMN12657092	42	F	32.7	N/A
SAMN12670838	40	M	30.7	N/A
SAMN12713942	41	M	23.5	N/A
R073	74	F	28.3	5.4
R034	76	F	23.7	5.9
H1009	52	M	34.2	N/A
R081	68	M	23.7	5.9
R082	65	F	24.9	5.4
R076	63	F	26.5	N/A
H108	32	F	36.2	5.0
CHI 7/29	30	N/A	30	N/A
R075	27	M	26.2	5.4
R066	44	M	32.2	N/A
CHI R34	59	M	20.71	N/A
AVG*±*SEM	50.9±4.4		28.11±1.25	5.60±0.17

Table S1. Human Islet Donors, Related to Figures 1-4
Summary characteristics of donors studied. BMI – Body Mass Index, HbA1c – glycated hemoglobin.

Amino acid	Concentration at 1x (µM)
Alanine	2100
Glutamine	600
Glycine	700
Valine	550
Leucine	500
Serine	350
Arginine	200
Lysine	218
Threonine	121

Table S2. Physiological amino acid mixture concentrations, Related to Figure 4