Supplement figure legends:

Supplement figure 1: **^{13}C-amino acid, insulin, glucagon and $[Ca^{2+}]_i$ response to glucose stimulation in mouse islets.** 500 to 600 isolated and cultured normal mouse islets were pre-incubated with glucose-free KRBB for 60 min, then incubated with 4 mM amino acid mixture plus different concentrations of [U-^{13}C]glucose for another 120 min; intracellular amino acids and their ^{13}C enrichments were determined. Panel A shows insulin and glucagon secretion (*vs.* G, 0 mM, *: $p<0.05$, n=3); Panel B to F show ^{13}C-amino acid production in response to different concentrations of [U-^{13}C]glucose (B: Ala; C: Asp; D: Glu; E: GABA; F: Gln; *vs.* G, 3 mM, *: $p<0.05$, n=3). Panel G shows $[Ca^{2+}]_i$ responses to different concentrations of glucose in normal mouse islets (representative data from 3 separate experiments).

Supplement figure 2: Gene expression of 3 isoforms of Malic enzyme (1, 2 and 3), GAD and GS in normal human islets. Gene expression was detected by RT-PCR in normal human islets. Data represent 3 separate preparations of normal human islets.

Supplemental figure 3: Gene expression of GHBDH, SSA reductase, GlyR-α1 and GHBR in normal and T2D human islets. Gene expression were detected by RT-PCR in normal human islets (black filled bar, n=5), T2D-αGR (gray filled bar, n=3) and T2D-αNGR (open bar, n=3).

Supplemental Table 1: Pancreas donors' information

		Gender	Age	Race	BMI	Blood glucose and (HbA1C)*	History (years)	Treatment	*Note*
T2D	1	F	61	White	29.6	425	4	Oral medicine[#]	*αNGR*
	2	M	48	White	26.2	250	2	Oral medicine[#]	
	3	M	45	White	37	165	15	Oral medicine[#] then insulin for 5 years	
	1	M	55	White	29.9	*NA* (6.5)	4	Metformin for 4 years	*αGR*
	2	M	53	White	28.3	223 (8.3)	5	Metformin for 5 years	
	3	F	38	White	29	119 (6.5)	1	Diet	
Normal	1	M	32	Asian	27.2	113			
	2	F	22	Black	25	84			
	3	F	57	White	21.1	106			
	4	M	51	Hispanic	26.1	108			
	5	M	57	White	26.5	120			
	6	F	28	Black	19.5	83			
	7	M	56	White	24.7	123			
	8	F	33	Black	31.1	98			
	9	m	52	White	28.7	121			
	10	M	57	White	26.5	*NA*			
	11	M	53	White	31	149			
	12	M	19	Black	35	140			
	13	M	43	White	26.2	102			
	14	F	52	White	28.7	103			
	15	F	53	White	21.1	106			
	16	M	36	Black	39.5	84			
	17	F	54	Black	27.6	102			
	18	M	28	White	29.4	103			
	19	M	53	White	29	144			
	20	M	47	Black	28.6	118			
	21	M	22	White	22.4	104			

*: Blood glucose or HbA1C were measured when admitted to hospital. *NA*: data not available, [#]: details of oral medication are unknown. Note that the blood glucose values are not clearly diagnostic because of the uncontrolled circumstances surrounding admission. Normal HbA1C values in control subjects used in another study performed during the same time period as the present one were 5.7±0.05% (1). The diagnosis of T2D in this

group of subjects is thus based primarily on case histories, retrospectively validated by in vitro insulin release data and the results of the respirometry test as presented in the text.

References:

1. Doliba, N.M., Qin, W., Najafi, H., Liu, C., Buettger, C.W., Sotiris, J., Collins, H.W., Li, C., Stanley, C.A., Wilson, D.F., et al. 2012. Glucokinase activation repairs defective bioenergetics of islets of Langerhans isolated from type 2 diabetics. *Am J Physiol Endocrinol Metab* 302:E87-E102.

Supplement table 2: Sequences of the primers of targeted genes

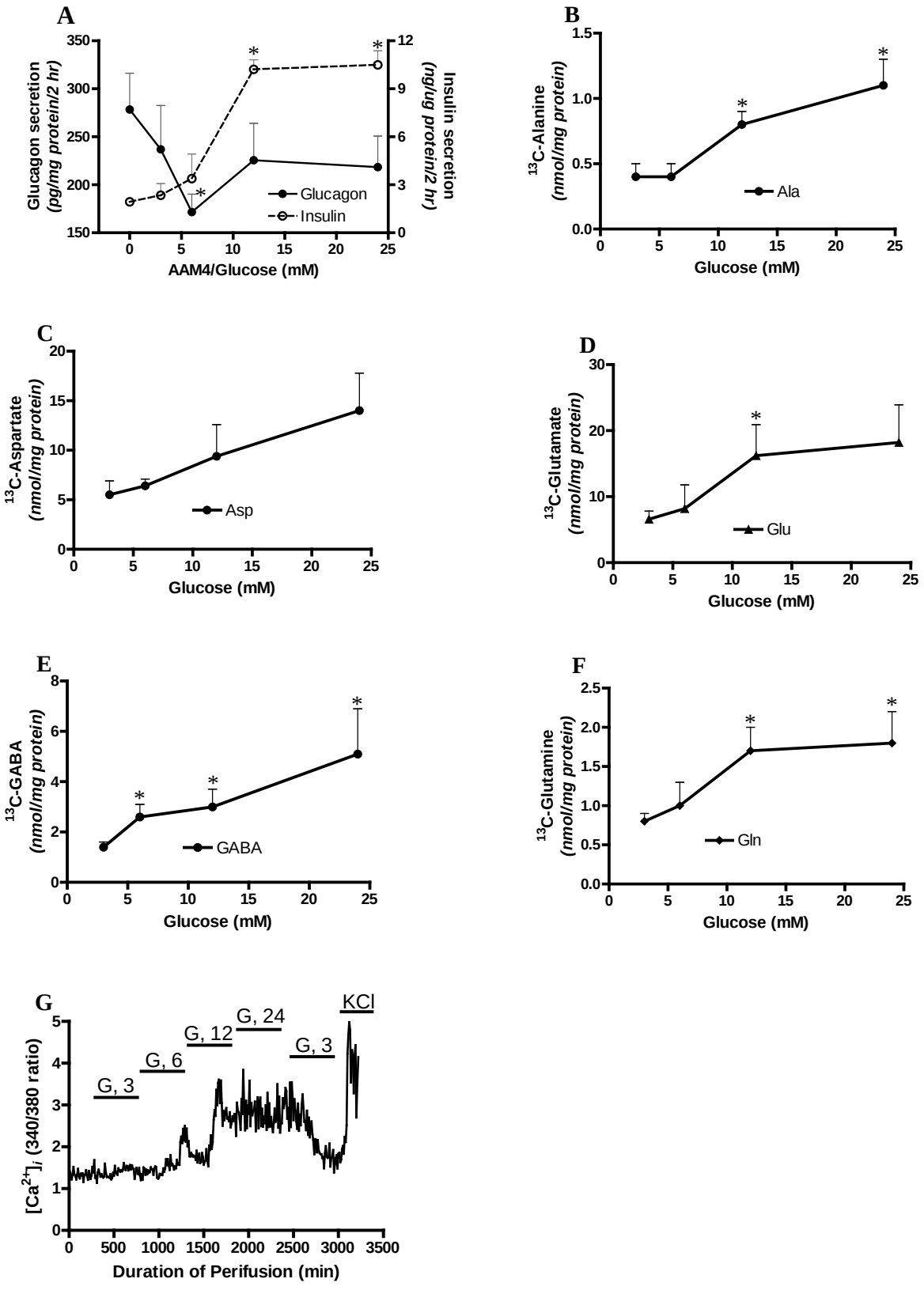
Gene	Protein	Sequence	
		forward	reverse
ACTB	beta-actin	CTCTTCCAGCCTTCCTTCCT	AGCACTGTGTTGGCGTACAG
HK1	Hexokinase 1	AGACGCACCCACAGTATTCC	CGCATCCTCTTCTTCACCTC
GAD	Glutamate Decarboxylase	TTCCTCCAAGCTTGCGTACT CACAAACTCAGCGGCATAGA*	ACCATGCGGAAGAAATTGAC ATCTGGTTGCATCCTTGGAG*
GDH	Glutamate Dehydrogenase	GGAGGTTCACCATGGAGCTA	CCTATGGTGCTGGCATAGGT
BDH1	GHB Dehydrogenase	TCACCAAGTTCGGGGTAGAG CGGCTAGTGGCAAAGCTATC*	CTTCTTGCCGTAGTCCTTGC GTTGCAGACATTGAGCTGGA*
GCK	Glucokinase	CACTGCTGAGATGCTCTTCG	CCACGACATTGTTCCCTTCT
GLRA1	Glycine receptor, alpha 1	TAGGCATCACCACTGTGCTC CAGGATCAGGCCCAACTTTA*	AGCTCCTTATGTTGCCGAGA GATGGGTCAAGGTCCAGAGA*
GLRB	Glycine receptor, beta	AGTGCCCCTGGGTATCTTCT	CCTTTTCCATCTGCTTGCTC
AKR7A2	SSA Reductase	CAGCTGGAGACGTCATTGAA TGTGGAGGAGACACTTCGTG*	GCATAGTTGGAGAGGCCAAG CATGCCCTGGTACACAGTTG*
PC	Pyruvate Carboxylase	GCCTGGGAAGGTGATAGACA	GGGTGAGGTCACCACAGTCT
TSPAN-17	GHB Receptor	GGTAGTTGGAGGCGTCATGT CAGCGGAAGATGTCCTCAAT*	GGTTGAGCTGGTCTCGAATC TGTCACTCACGAGGTTCTGG*
INS	Insulin	CTACCTAGTGTGCGGGGAAC GGAGCGTGGCTTCTTCTACA*	GCTGGTAGAGGGAGCAGATG GTGCAGCACTGATCCACAAT*
GCG	Glucagon	CATTCACAGGGCACATTCAC GAAGACAAACGCCACTCACA*	CAGCTTGGCCTTCCAAATAA CAGCATGCCTCTCAAATTCA*
ME1	Malic Enzyme, 1	ACCCTGGAAGAGAGACAGCA	AGCCAAGAATACGCTCTCCA
ME2	Malic Enzyme, 2	ATGGGCTTGTACCAGAAACG	TATGCTCTCTGGGGCTGAGT
ME3	Malic Enzyme, 3	TCACCAGGAACCCTCATCTC	TTGTCCAGGTCACTCTGATG
GLUL	Glutamine Synthetase	TGGGAGCAGACAGAGCCTAT	CAGGAATGGGCTTAGGATCA
GAPDH	Glyceraldehyde-3-phosphate Dehydrogenase	CAATGACCCCTTCATTGACC AACTTTGGCATTGTGGAAGG*	GACAAGCTTCCCGTTCTCAG GGATGCAGGGATGATGTTCT*

*: primers for mouse

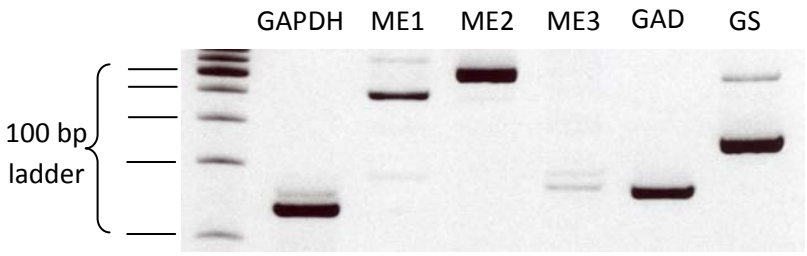
Supplement Table 3: Intracellular amino acid (*nmol/mg islets protein*) responses to 5, 10 and 25 mM glucose in normal human islets

	G, 0		**G, 5 mM**		**G, 10 mM**		**G, 25 mM**	
	VGB (mM)		**VGB (mM)**		**VGB (mM)**		**VGB (mM)**	
n=4	**0**	**1.55**	**0**	**1.55**	**0**	**1.55**	**0**	**1.55**
Alanine	2.1±0.3	2.0±0.1	3.5±0.3[a]	3.7±0.5 [a]	3.9±0.3[a]	3.7±0.6 [a]	5.2±0.8[a]	6.6±2.2[a]
Arginine	16.4±1.7	19.7±4.8	16.8±3.2	19.8±3.6	16.4±2.1	16.5±2.1	18.2±2.7	20.8±3.1
Aspartate	13.3±2.5	12.4±3.1	10.5±2.1[a]	8.0±1.7[a]	9.6±1.4	7.8±1.6[a]	10.1±1.7[a]	8.5±1.4[a]
GABA	23.1±2.0	36.1±2.4*	17.7±2.3[b]	31.9±2.5*	13.8±1.2[b]	31.2±2.1*	14.4±1.8[a]	31.8±1.8*
Glutamate	23.5±2.3	23.7±2.3	32.7±5.6	28.3±4.0	30.1±4.1	27.2±3.9	33.5±5.4[a]	33.2±5.1[a]
Glutamine	1.1±0.1	1.2±0.0	1.1±0.4	1.8±0.4	1.5±0.2	1.6±0.3	1.6±0.2	2.8±1.2
Sum	*81±8*	*80*±17	*84±13*	*93*±10	*76±8*	*88*±8	*85±12*	*104*±10

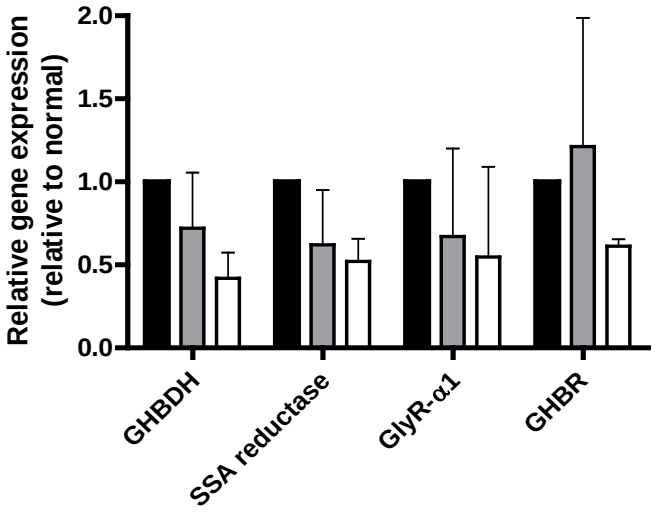
vs. G 0, *a*: $p<0.05$, *b*: $p<0.01$; *vs.* VGB 0, *: $p<0.01$.



Supplement Figure 1



Supplemental figure 2



Supplemental figure 3