

1 **Supplemental Data**

2 *Supplemental Data Tables*

3 Table S1. Baseline characteristics and *ADRB2* Gly16Arg genotype

	AA	GG	p-value
Number of subjects	13	12	-
Age (years)	23.4 ± 0.8	24.6 ± 0.5	0.24
Height (cm)	186 ± 2.3	185 ± 1.7	0.46
Weight (kg)	79.5 ± 1.7	81.0 ± 2.4	0.62
Body mass index (kg m ⁻²)	23.1 ± 0.4	23.7 ± 0.5	0.35
Body surface area (m ²)	2.02 ± 0.03	2.04 ± 0.04	0.80
HbA1c (% [mmol mol ⁻¹])	5.0 ± 0 [31.5 ± 0.7]	5.0 ± 0 [31.3 ± 0.7]	0.78
Creatinine (umol l ⁻¹)	74.6 ± 2.9	72.2 ± 2.0	0.47

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5 Values are mean ± SEM. Subjects homozygous for either the Arg16 allele (AA) or the Gly16 allele (GG) of the β₂-receptor
6 gene (*ADRB2*) are compared by unpaired t-test if normally distributed or by Mann-Whitney U test if not.

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8 Table S2. Comparison of plasma glucose, insulin, substrates, and circulatory measures, between *ADRB2*
9 genotype groups of AA subjects and GG subjects, at baseline before and after repeated hypoglycemia

	Baseline pre-hypoglycemia			Baseline post-hypoglycemia		
	AA	GG	p-value	AA	GG	p-value
<i>Glucose, insulin, and insulin sensitivity</i>						
Plasma glucose (mmol l ⁻¹)	4.58 ± 0.10	4.75 ± 0.13	0.34	5.39 ± 0.11	5.61 ± 0.12	0.13
Insulin (pmol l ⁻¹)	57.4 ± 7.5	46.5 ± 5.9	0.26	79.7 ± 9.5	72.1 ± 6.6	0.31
C-peptide (pmol l ⁻¹)	574 ± 40	587 ± 49	0.93	687 ± 44	686 ± 49	1.0
HOMA-IR	1.98 ± 0.29	1.66 ± 0.24	0.40	3.24 ± 0.47	3.02 ± 0.31	0.98
<i>Substrates</i>						
Lactate (mmol l ⁻¹)	0.64 ± 0.05	0.83 ± 0.11	0.15	1.24 ± 0.11	1.48 ± 0.05	0.081
Glycerol (μmol l ⁻¹)	31.9 ± 4.2	40.7 ± 5.7	0.23	26.6 ± 3.8	40.4 ± 4.9	0.037*
FFA (μmol l ⁻¹)	432 ± 46	409 ± 29	0.68	270 ± 30	247 ± 24	0.56
β-hydroxybutyrate (mmol l ⁻¹)	0.15 ± 0.04	0.16 ± 0.06	0.68	0.05 ± 0.01	0.04 ± 0.00	0.73
Alanine (μmol l ⁻¹)	221 ± 20	252 ± 26	0.24	437 ± 21	479 ± 24	0.21
<i>Circulatory measures</i>						
Heart rate (beats min ⁻¹)	57.0 ± 2.7	56.6 ± 2.5	0.91	63.2 ± 3.2	63.5 ± 2.9	0.94
Stroke volume (ml)	111.2 ± 3.9	109.5 ± 4.8	0.78	115.8 ± 3.9	114.6 ± 4.9	0.84
Cardiac output (L min ⁻¹)	6.2 ± 0.3	6.1 ± 0.3	0.79	7.1 ± 0.2	7.2 ± 0.5	0.89
Systemic vascular resistance (dyn s cm ⁻⁵)	1128 ± 59	1070 ± 49	0.64	925 ± 45	929 ± 55	0.96
Systolic pressure (mmHg)	127.9 ± 3.2	123.9 ± 3.6	0.42	124.3 ± 3.1	122.3 ± 3.3	0.67
Diastolic pressure (mmHg)	64.8 ± 1.4	60.3 ± 1.6	0.052	60.7 ± 2.0	61.3 ± 1.6	0.83
Mean arterial pressure (mmHg)	85.2 ± 1.6	79.3 ± 2.2	0.044*	80.7 ± 2.3	80.8 ± 2.1	0.96

11 Values are mean \pm SEM. Comparison between genotype groups of subjects homozygous for either the Arg16 allele (AA)
12 or the Gly16 allele (GG) of the β_2 -receptor gene (*ADRB2*), at baseline before and after repeated hypoglycemia (pre-
13 hypoglycemia and post-hypoglycemia, respectively), were by unpaired t-test if normally distributed or by Mann-Whitney
14 U test if not. No missing values (n=25). * $P \leq 0.05$

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16 Table S3. Comparison between subjects homozygous for the Arg16 allele and Gly16 allele of the β_2 -receptor
 17 gene (*ADRB2*), in the glucose, insulin, substrate, and circulatory responses to epinephrine, before and after
 18 repeated hypoglycemia

	Pre-hypoglycemia (D1 _{pre})			Post-hypoglycemia (D4 _{post})		
	AA	GG	p-value	AA	GG	p-value
<i>Glucose, insulin, and C-peptide</i>						
Glucose (mmol l ⁻¹ h)	2.97 ± 0.15	3.18 ± 0.20	0.42	2.68 ± .015	2.43 ± 0.26	0.15
Insulin (pmol l ⁻¹ h)	44 ± 8	93 ± 13	0.0051**	79 ± 19	108 ± 14	0.21
C-peptide (pmol l ⁻¹ h)	135 ± 52	307 ± 59	0.041*	295 ± 98	397 ± 52	0.37
<i>Substrates</i>						
Lactate (mmol l ⁻¹ h)	2.71 ± 0.21	3.15 ± 0.37	0.32	2.02 ± 0.16	2.25 ± 0.25	0.45
Glycerol (μmol l ⁻¹ h)	79 ± 12	115 ± 14	0.041*	63 ± 7	64 ± 9	0.96
FFA (μmol l ⁻¹ h)	724 ± 96	1113 ± 140	0.033*	570 ± 60	643 ± 92	0.51
β-hydroxybutyrate (mmol l ⁻¹ h)	0.34 ± 0.11	0.44 ± 0.08	0.31	0.09 ± 0.04	0.07 ± 0.02	0.68
Alanine (μmol l ⁻¹ h)	90 ± 15	43 ± 22	0.10	-44 ± 14	-76 ± 40	0.47
<i>Circulatory Measures</i>						
Heart rate (beats min ⁻¹ h)	38.2 ± 3.6	35.5 ± 2.9	0.56	29.0 ± 2.7	27.8 ± 3.4	0.77
Stroke volume (ml h)	33.6 ± 5.6	40.7 ± 5.3	0.37	24.5 ± 3.7	28.3 ± 5.5	0.58
Cardiac output (L min ⁻¹ h)	6.8 ± 0.6	7.1 ± 0.6	0.78	5.3 ± 0.4	5.4 ± 0.7	0.26
Systemic vascular resistance (dyn s cm ⁻⁵ h)	-818 ± 72	-781 ± 53	0.83	-543 ± 53	538 ± 60	0.95
Systolic pressure (mmHg h)	3.4 ± 5.3	8.3 ± 4.3	0.48	6.4 ± 4.8	7.0 ± 3.2	0.93
Diastolic pressure (mmHg h)	-14.3 ± 1.6	-14.4 ± 2.7	0.96	-10.2 ± 2.0	-12.2 ± 3.1	0.60
Mean arterial pressure (mmHg h)	-11.8 ± 2.2	-12.0 ± 2.7	0.97	-9.2 ± 2.5	-10.4 ± 2.9	0.77

20 The values of plasma glucose, insulin, substrate, and circulatory responses to epinephrine before, and after repeated
21 hypoglycemia (pre-hypoglycemia, and post-hypoglycemia respectively), are indicated as the change from the preceding
22 baseline values during a 2h period (area under the curve (AUC), values are mean \pm SEM. Comparison between subjects
23 homozygous for the Arg16 allele (AA subjects) and Gly16 allele (GG subjects) of the β_2 -receptor gene (*ADRB2*) was by
24 unpaired t-test if normally distributed or Wilcoxon signed-rank test if not. No missing values (n=25). * $P \leq 0.05$; ** $P \leq$
25 0.01

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28 Table S4. Comparison of changes in baseline plasma glucose, insulin, substrates, and circulatory measures,
 29 between before and after repeated hypoglycemia, in the *ADRB2* genotype groups of AA subjects and GG
 30 subjects.

	Baseline AA Δ -values		Baseline GG Δ -values	
	(post- vs pre-hypoglycemia)	p-value	(post- vs pre-hypoglycemia)	p-value
<i>Glucose, insulin, and insulin sensitivity</i>				
Plasma glucose (mmol l ⁻¹)	0.80 \pm 0.13	0.0021**	0.86 \pm 0.16	0.00023***
Insulin (pmol l ⁻¹)	22.3 \pm 10.5	0.036*	25.6 \pm 9.5	0.021*
C-peptide (pmol l ⁻¹)	113 \pm 53	0.056	99 \pm 70	0.18
HOMA-IR	1.26 \pm 0.51	0.012*	1.36 \pm 0.43	0.013*
<i>Substrates</i>				
Lactate (mmol l ⁻¹)	0.60 \pm 0.12	0.00033***	0.65 \pm 0.12	0.00026***
Glycerol (μ mol l ⁻¹)	-5.3 \pm 2.9	0.097	-0.3 \pm 3.4	0.93
FFA (μ mol l ⁻¹)	-161 \pm 50	0.0071**	-162 \pm 38	0.0014**
β -hydroxybutyrate (mmol l ⁻¹)	-0.10 \pm 0.04	0.0024**	-0.11 \pm 0.06	0.0093**
Alanine (μ mol l ⁻¹)	216 \pm 26	0.0017**	227 \pm 30	0.000011***
<i>Circulatory measures</i>				
Heart rate (beats min ⁻¹)	6.2 \pm 1.6	0.0026**	6.9 \pm 1.5	0.00081***
Stroke volume (ml)	4.6 \pm 2.0	0.044*	5.1 \pm 1.8	0.00073***
Cardiac output (L min ⁻¹)	0.9 \pm 0.1	0.000034***	1.1 \pm 0.2	0.00073***
Systemic vascular resistance (dyn s cm ⁻⁵)	-203 \pm 31	0.00017***	-142 \pm 39	0.0038**
Systolic pressure (mmHg)	-3.5 \pm 2.5	0.19	-1.6 \pm 2.4	0.53
Diastolic pressure (mmHg)	-4.1 \pm 1.5	0.020*	0.9 \pm 1.1	0.44
Mean arterial pressure (mmHg)	-4.5 \pm 1.6	0.016*	1.5 \pm 1.4	0.30

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32 Values are mean \pm SEM. For genotype groups of subjects homozygous for either the Arg16 allele (AA) or the Gly16 allele
33 (GG) of the β_2 -receptor gene (*ADRB2*), comparison between baseline before and after repeated hypoglycemia (pre-
34 hypoglycemia and post-hypoglycemia, respectively) was by paired t-test if normally distributed or by Wilcoxon signed-
35 rank test if not. No missing values (n=25). * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

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37 Table S5. Comparison of changes in the glucose, insulin, and substrate responses to epinephrine before and
 38 after repeated hypoglycemia, in subjects homozygous for the Arg16 allele and Gly16 allele of the β_2 -receptor
 39 gene (*ADRB2*)

	AA Δ -values		GG Δ -values		GG vs AA Δ -values	
	(post vs pre hypo)	P-value	(post vs pre hypo)	P-value	GG vs AA Δ -values	P-value
<i>Glucose, insulin, and C-peptide</i>						
Glucose (mmol l ⁻¹ h)	-0.29 \pm 0.12	0.050	-0.75 \pm 0.22	0.011*	-0.46 \pm 0.24	0.059
Insulin (pmol l ⁻¹ h)	35 \pm 15	0.039*	15 \pm 12	0.22	-19 \pm 19	0.32
C-peptide (pmol l ⁻¹ h)	160 \pm 63	0.027*	90 \pm 51	0.11	-69 \pm 82	0.39
<i>Substrates</i>						
Lactate (mmol l ⁻¹ h)	-0.69 \pm 0.24	0.017*	-0.89 \pm 0.24	0.0033**	-0.21 \pm 0.35	0.55
Glycerol (μ mol l ⁻¹ h)	-16 \pm 9	0.11	-52 \pm 10	0.00020***	-35 \pm 13	0.008
FFA (μ mol l ⁻¹ h)	-154 \pm 106	0.17	-470 \pm 139	0.0063**	-315 \pm 173	0.069
β -hydroxybutyrate (mmol l ⁻¹ h)	-0.26 \pm 0.10	0.014*	-0.37 \pm 0.09	0.0016**	-0.11 \pm 0.14	0.41
Alanine (μ mol l ⁻¹ h)	-133 \pm 24	0.00011***	-119 \pm 39	0.0054**	14 \pm 45	0.74
<i>Circulatory Measures</i>						
Heart rate (beats min ⁻¹ h)	-9.2 \pm 3.3	0.016*	-7.7 \pm 3.0	0.025*	1.4 \pm 4.4	0.75
Stroke volume (ml h)	-9.1 \pm 3.8	0.036*	-12.4 \pm 4.0	0.011*	-3.3 \pm 5.6	0.55
Cardiac output (L min ⁻¹ h)	-1.5 \pm 0.5	0.0052**	-1.6 \pm 0.4	0.013*	-0.2 \pm 0.6	0.82
Systemic vascular resistance (dyn s cm ⁻⁵ h)	275 \pm 61	0.00070***	244 \pm 56	0.0042**	-32 \pm 83	0.71
Systolic pressure (mmHg h)	3.0 \pm 7.3	0.69	-1.3 \pm 4.0	0.75	-4.3 \pm 8.5	0.61
Diastolic pressure (mmHg h)	4.0 \pm 2.7	0.17	2.2 \pm 2.5	0.40	-1.8 \pm 3.7	0.63
Mean arterial pressure (mmHg h)	2.6 \pm 3.5	0.47	1.6 \pm 2.7	0.55	-1.0 \pm 4.4	0.82

41 The values of plasma glucose, insulin, substrate, and circulatory responses to epinephrine are indicated as the change
42 from baseline during a 2h period (area under the curve (AUC), values are mean \pm SEM. For genotype groups either
43 homozygous for the Arg16 allele (AA) or homozygous for the Gly16 allele (GG) of the β_2 -receptor gene (*ADRB2*),
44 comparison between the pre-hypoglycemia and post-hypoglycemia epinephrine response is by paired t-test if normally
45 distributed or by Wilcoxon signed-rank test if not. Comparison between the AA and GG genotype groups Δ -values (pre-
46 hypoglycemia versus post-hypoglycemia) is by linear mixed model (LMM). No missing values (n=25). * $P \leq 0.05$; ** $P \leq$
47 0.01; *** $P \leq 0.001$.

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51 *Supplemental Data Figure legends*

52 Figure S1 Hypoglycemia trial overview

53 The study protocol consisted of 2 consecutive hypoglycemia trial days. An insulin-glucose clamp constituted
54 by a continuous infusion of insulin $1.5 \text{ mU kg}^{-1} \text{ min}^{-1}$ and a variable infusion of 20% glucose was used to regulate
55 plasma glucose. Plasma glucose was measured every 10 min during euglycemia periods E1 to E4 (5 to 6 mmol
56 l^{-1}) and every 5 min during hypoglycemia periods H1 to H3 (2.3 to 2.7 mmol l^{-1}).

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