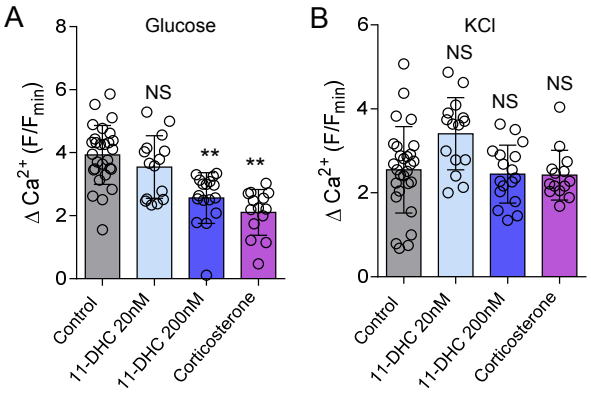
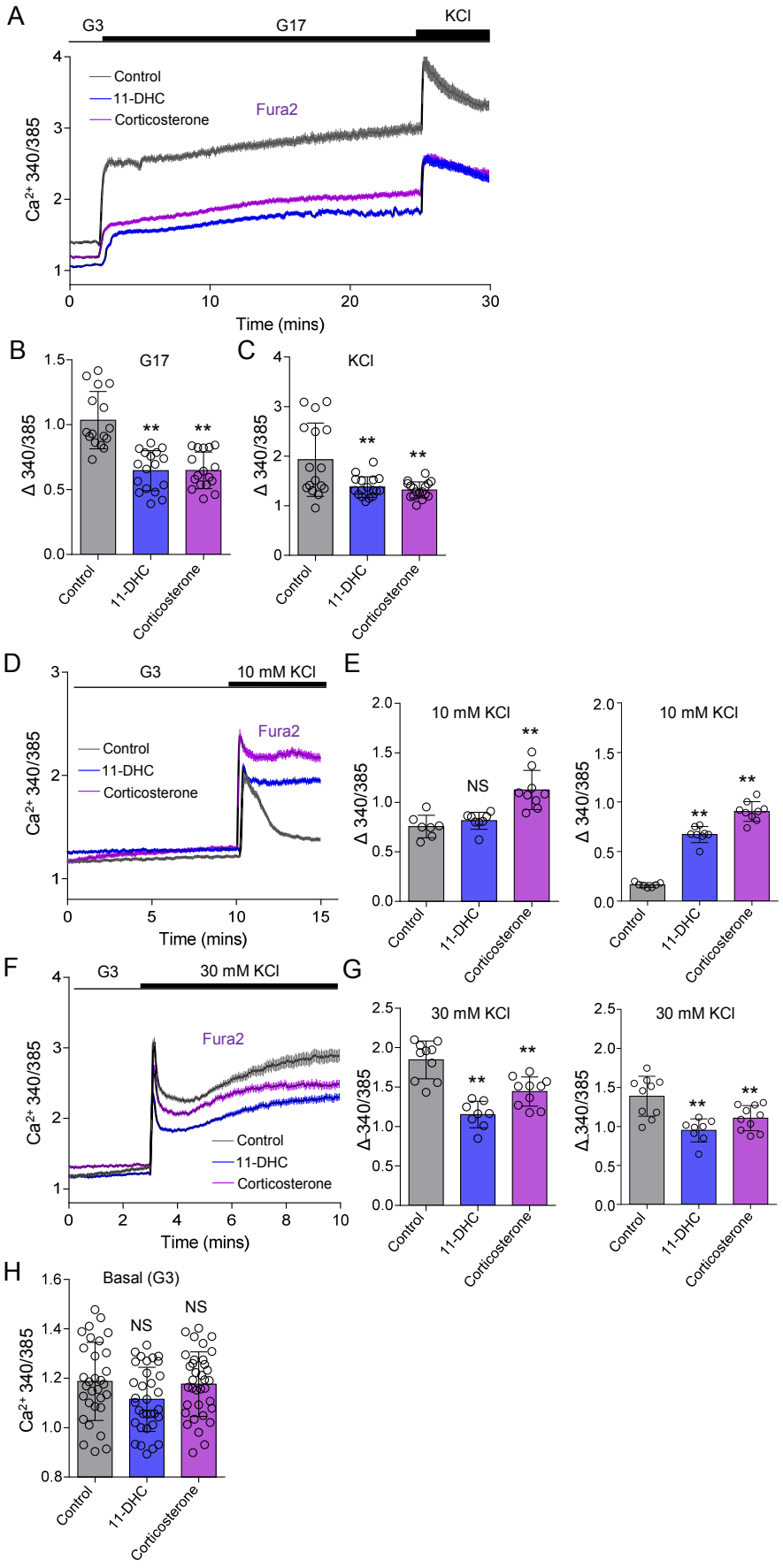
SUPPLEMENTARY DATA

Supplementary Figure 1. Delta Ca^{2+} rises in response to glucose and KCl at high glucose in glucocorticoid-treated islets. *A*: Gluococorticoids significantly impair the amplitude of Ca^{2+} responses to glucose. *B*: As for *A*, but Ca^{2+} responses to 10 mM KCl (amplitude measured *versus* 17 mM glucose; G17). *P<0.05, **P<0.01 and NS, non-significant; one-way ANOVA (Bonferroni's post hoc test). 11-DHC and corticosterone were applied at 200 nM or 20 nM, respectively. Data represent the mean ± S.D. N numbers as for Figure 1.



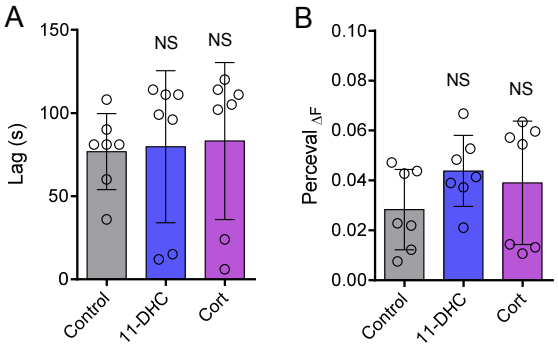
Supplementary Figure 2. Glucocorticoids impair Ca^{2+} responses to glucose and KCl at high glucose as measured using Fura2. *A:* Ratiometric Fura2 recordings showing glucose- and glucose + 10 mM KCl-stimulated Ca^{2+} rises in mouse islets treated for 48 hrs with 11-DHC or corticosterone (mean ± S.E.M intensity-over-time traces shown) (*n* = 16-17 islets from 4 animals). *B-C*: Summary bar graphs showing a significant reduction in the amplitude of glucose- (*B*) and 10 mM KCl- (*C*) stimulated Ca^{2+} rises following treatment with either glucocorticoid (KCl amplitude measured *versus* 17 mM glucose; G17). *D*: Peak Ca^{2+} responses to 10 mM KCl at low (3 mM) glucose are not affected or significantly increased by 11-DHC or corticosterone exposure, respectively. Sustained Ca^{2+} responses to 10 mM KCl at low (3 mM) glucose are significantly increased by both glucocorticoids. *E:* As for *D*, but summary bar graph (peak Ca^{2+} responses, left panel; sustained Ca^{2+} responses, right panel) (*n* = 7-9 islets from 2 animals). *F*: Peak and sustained Ca^{2+} responses to 30 mM KCl at low (3 mM) glucose are significantly reduced by treatment with 11-DHC or corticosterone (*n* = 31-35 islets from 9 animals). *G:* As for *F*, but summary bar graph (peak Ca^{2+} responses, left panel; sustained Ca^{2+} responses, right panel) (*n* = 31-35 islets from 9 animals). *H:* Glucocorticoid does not significantly alter the Fura2 340/385 ratio (*n* = 8-10 islets from 3 animals). G3 = 3 mM glucose; G17 = 17 mM glucose. **P<0.01 and NS, non-significant; one-way ANOVA (Bonferroni's posthoc test). 11-DHC and corticosterone were applied for 48 hrs at 200 nM or 20 nM, respectively. Unless otherwise stated, data represent the mean ± S.D.

SUPPLEMENTARY DATA

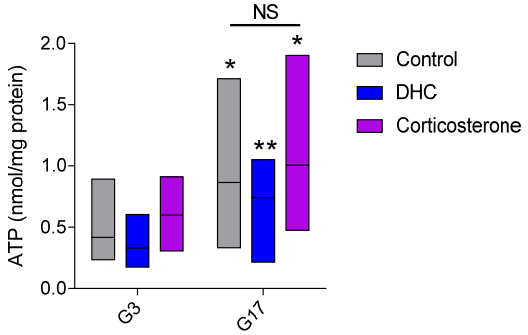


SUPPLEMENTARY DATA

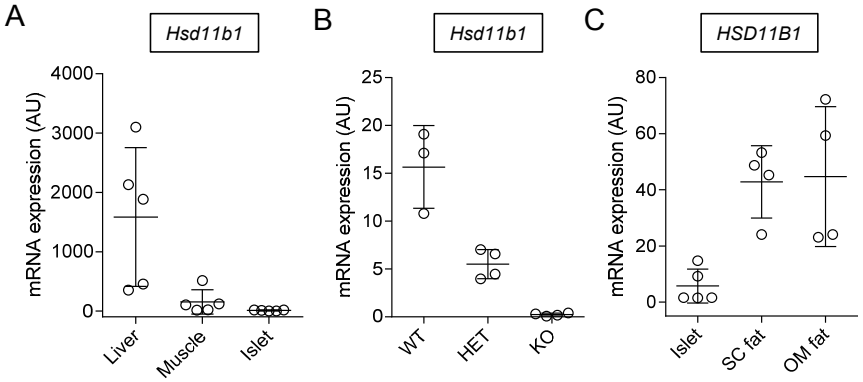
Supplementary Figure 3. Glucocorticoids do not influence the time to onset or amplitude of ATP/ADP responses to glucose. *A:* Bar graph showing no effect of 11-DHC or corticosterone (Cort) on the time to the initial decrease in ATP/ADP. *B*: As for, A but amplitude of the decrease. 11-DHC and corticosterone were applied for 48 hrs at 200 nM or 20 nM, respectively. NS, non-significant; one-way ANOVA (Bonferroni's posthoc test). Data represent the mean ± S.D.



Supplementary Figure 4. Glucocorticoids do not affect glucose-stimulated ATP production. High (17 mM) glucose concentration significantly increases ATP levels under all conditions examined. No differences were detected between control-, 11-DHC- and corticosterone-treated islets (*n* = 12 animals). 11-DHC and corticosterone were applied for 48 hrs at 200 nM or 20 nM, respectively. *P<0.05, **P<0.01; Student's t-test. NS, non-significant; one-way ANOVA. Data represent the mean and range.

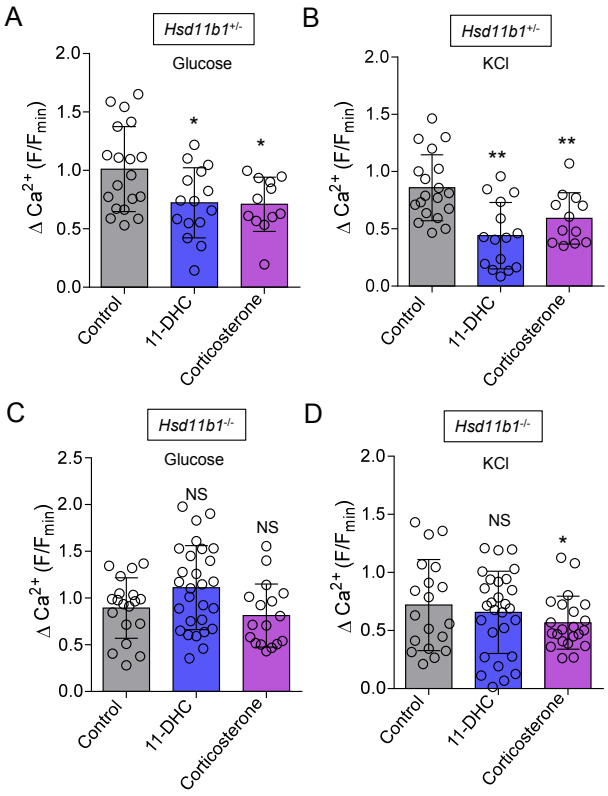


Supplementary Figure 5. *Hsd11b1* and *HSD11B1* mRNA expression in mouse and human tissue. *A*: Relative *Hsd11b1* gene expression in muscle, liver and islets in mice (*n* = 5 animals). *B*: *Hsd11b1* is expressed in islets from *Hsd11b1*$^{+/+}$ and *Hsd11b1*$^{+/-}$ mice, but not *Hsd11b1*$^{-/-}$ animals (*n* = 3-4 animals). *C*: *HSD11B1* levels in human islets are only an order of magnitude lower than in subcutaneous (SC) and omental (OM) fat (*n* = 4-5 donors). Data represent the mean ± S.D.



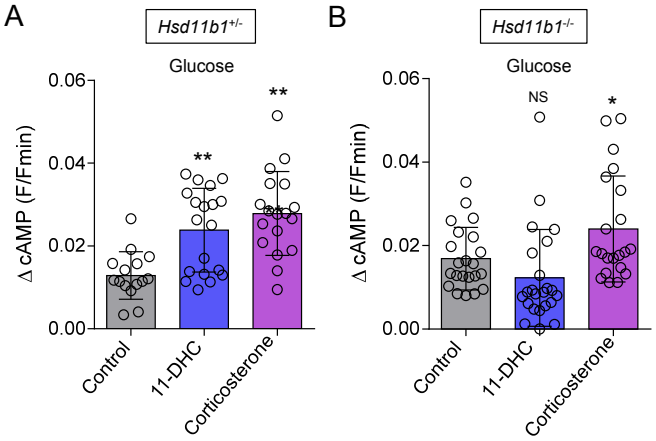
SUPPLEMENTARY DATA

Supplementary Figure 6. 11-DHC suppresses delta Ca^{2+} rises in *Hsd11b1*$^{+/-}$ but not *Hsd11b1*$^{-/-}$ islets. *A*: Both 11-DHC and corticosterone significantly impair the amplitude of Ca^{2+} responses to glucose in *Hsd11b1*$^{+/-}$ islets. *B*: As for *A*, but 10 mM KCl (amplitude measured *versus* 17 mM glucose; G17). *C*: Deletion of *Hsd11b1* (*Hsd11b1*$^{-/-}$) restores Ca^{2+} responses to glucose. *D*: As for *A*, but 10 mM KCl (amplitude measured *versus* 17 mM glucose; G17). Data represent the mean ± S.D. *P<0.05, **P<0.01 and NS, non-significant; one-way ANOVA (Bonferroni's post hoc test). 11-DHC and corticosterone were applied for 48 hrs at 200 nM or 20 nM, respectively. Data represent the mean ± S.D. N numbers as for Figure 5.

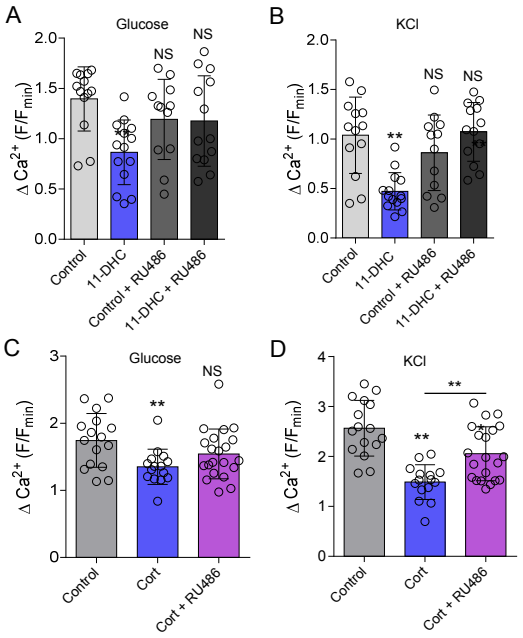


SUPPLEMENTARY DATA

Supplementary Figure 7. 11-DHC augments delta cAMP rises in *Hsd11b1*$^{+/-}$ but not *Hsd11b1*$^{-/-}$ islets. *A*: Both 11-DHC and corticosterone potentiate cAMP responses to glucose in *Hsd11b1*$^{+/-}$ islets. *B*: Only corticosterone potentiates cAMP responses to glucose in *Hsd11b*$^{-/-}$ islets. *P<0.05, **P<0.01 and NS, non-significant; one-way ANOVA (Bonferroni's post hoc test). 11-DHC and corticosterone were applied for 48 hrs at 200 nM or 20 nM, respectively. Data represent the mean ± S.D. N numbers as for Figure 6.



Supplementary Figure 8. R486 blocks the effects of glucocorticoids on Ca^{2+} rises. *A*: RU486 prevents 11-DHC from impairing Ca^{2+} responses to glucose. *B*: As for *A*, but 10 mM KCl (amplitude measured *versus* 17 mM glucose; G17). *C*: RU486 prevents corticosterone (Cort) from impairing Ca^{2+} responses to glucose. *D*: As for *C*, but 10 mM KCl (amplitude measured *versus* G17). *P<0.05, **P<0.01 and NS, non-significant; one-way ANOVA (Bonferroni's post hoc test). 11-DHC and corticosterone were applied for 48 hrs at 200 nM or 20 nM, respectively. Data represent the mean ± S.D. N numbers as for Figure 7.



SUPPLEMENTARY DATA

Supplementary Table 1. Human islet donor characteristics.

Age	Gender	BMI	Source
55	F	26	Milan
49	F	23.9	Milan
73	F	28.4	Alberta
71	F	35.5	Alberta
54	M	26.5	Milan
57	F	26	Milan
64	M	24.5	Pisa
44	M	34.4	Alberta

Supplementary Table 2. Epac2-camps single and dual channel fluorescence in mouse islets during maximal stimulation with forskolin. NS, non-significant *versus* control, one-way ANOVA (Bonferroni's post hoc test).

Treatment	YFP intensity ± SD (AU)	CFP/YFP ± SD
Control	$2.3 \times 10^4 \pm 6.7 \times 10^3$	1.08 ± 0.03
11-DHC	$2.4 \times 10^4 \pm 8.8 \times 10^{3\ NS}$	$1.08 \pm 0.05^{\ NS}$
Corticosterone	$2.7 \times 10^4 \pm 5.0 \times 10^{3\ NS}$	$1.07 \pm 0.04^{\ NS}$

Supplementary Table 3. Primer sequences

Gene	Forward	Reverse
Ins1	GCTGGTGGGCATCCAGTAA	AATGACCTGCTTGCTGATGGT
Pdx-1	CCAAAGCTCACGCGTGGA	TGTTTTCCTCGGGTTCCG
Nkx6.1	GCCTGTACCCCCCATCAAG	GTGGGTCTGGTGTGTTTTCTCTT
Cacna1d	GAAGCTGCTTGACCAAGTTGT	AACTTCCCCACGGTTACCTC
Cacna1c	CCAACCTCATCCTCTTCTTCA	ACATAGTCTGCATTGCCTAGGAT
Cacnb2	GCAGGAGAGCCAGATGGA	TCCTGGCTCCTTTTCCATAG
Adcy1	CGGAATTGCATGCCTTGAA	TCCATTCTTTTGTGCATGCTACAT
Adcy5	CTTCACCAGCCCCAAGAAAC	GAAGCGGCAGAGCACAGAAC
Adcy6	AGCCTTGGATAGGAAGGGACTACT	CTCCCTGCTTTGGCTTATATACCT
Adcy8	TTGGGCTTCCTACACCTTGACT	CGGTAGCTGTATCCTCCATTGAG
Adcy9	CATACAGAAGGCACCGATAG	CCGAACAGGTCATTGAGTAG
β-actin	CGAGTCGCGTCCACCC	CATCCATGGCGAACTGGTG

SUPPLEMENTARY DATA

Supplementary Table 4. Basal intracellular Ca^{2+} concentration in human islets. Free Ca^{2+} concentrations were calculated using $K_d*(F-F_{min})/(F_{max}-F)$ where F_{max} and F_{min} represent fluorescence in the presence of 10 µM ionomycin or 0.1% Triton + 5 mM EGTA, respectively, and K_d = 389 nM. NS, non-significant *versus* control, one-way ANOVA (Bonferroni's post hoc test).

Treatment	Ca^{2+} concentration ± SD (nM)
Control	61.1 ± 16.2
Cortisone	60.9 ± 18.2 ^{NS}
Cortisol	52.7 ± 19.8 ^{NS}

Supplementary Table 5. Effect of KCl concentration on amplitude Ca^{2+} responses at 3 mM glucose. **P<0.01 *versus* 3 mM glucose + 10 mM KCl, Student's t-test.

Treatment	ΔCa^{2+} ± SD (340/385)
3 mM glucose + 10 mM KCl	0.76 ± 0.12
3 mM glucose + 30 mM KCl	1.85 ± 0.24**