**Supplemental Figure 1:** Generation of a targeting vector for deletion of the *HSD11B1* gene. (A) 11β-HSD1 gene targeting strategy. Wild type allele and targeting vector (top), targeted and conditional allele (middle) and the 11β-HSD1 deleted allele (bottom). The Cre used for the deletion of the *HSD11B1* gene globally was Rosa26-Cre and for the liver-specific 11β-HSD1 knock-out mice it was Albumin-Cre. Open rectangles - exon number. DTA - diphtheria toxin A fragment gene cassette. E - EcoRI site. S - StuI site. Triangle - loxP site. Arrow - oligos used for genotyping. (B) Southern blot analysis of the targeted heterozygous ES clones. Genomic DNA was digested with EcoRI and StuI and probed with a 5' flanking probe shown in (A). Expected sizes of DNA fragments of the wild-type and mutant alleles are indicated in (A). Lane 1, marker; Lane 2 and 3, targeted clones.

**Supplemental Figure 2:** Liver 11β-HSD1 knock-out (LKO) mice have 11β-HSD1 gene expression and activity knocked out in liver only without altering their metabolic profile. (A) 11β-HSD1 gene expression (n=7) and (B) enzyme activity (n=6) in brain, epididymal adipose and liver. (C) Body weight (n=12). (D) Glucose (n=11-12) and (E) Insulin (n=11-12) excursion during an oral glucose tolerance test (OGTT). (F) Adrenal gland weight (n=12). (G) Circulating corticosterone at nadir and peak (n=11-12). (H) Plasma ACTH at nadir and peak (n=5-6). (I) Plasma pro-opiomelanocortin (POMC; n=12) in LKO and wild-type floxed littermate control (WTf/f) mice. Data expressed as mean ± SEM. * P<0.05, *** P<0.001 vs. WTf/f controls.

**Supplemental Figure 3:** Global 11β-HSD1 knock-out (GKO) mice have complete gene knock-out but have a similar metabolic profile to WT mice. (A) 11β-HSD1 gene expression (n=7) and (B) enzyme activity (n=6) in brain, epididymal adipose and liver. (C) Body weight (n=12). (D) Glucose (n=11-12) and (E) insulin (n=12) excursion during an oral glucose tolerance test (OGTT). (F) Adrenal gland weight (n=12). (G) Circulating corticosterone at nadir and peak (n=12). (H) Plasma ACTH at nadir and peak (n=6). (I) Plasma pro-opiomelanocortin (POMC; n=12) in WT and GKO mice. Data expressed as mean ± SEM. *** P<0.001 vs. WT controls.
Supplemental Figure 3

A

11β-HSD1 mRNA expression (AU)

Brain  Adipose  Liver

WT  GKO  WT  GKO  WT  GKO

***  ***  ***

B

% Conversion/100mg tissue

Brain  Adipose  Liver

WT  GKO  WT  GKO  WT  GKO

***  ***  ***

C

Body Weight (g)

WT  GKO

D

Glucose (mmol)

Time (mins)

WT  GKO

E

Insulin (pmol)

Time (mins)

WT  GKO

F

Adrenal Weight (mg)

WT  GKO

***

G

Nadir  Peak

Corticosterone (nmol)

WT  GKO  WT  GKO

H

Nadir  Peak

ACTH (pg/mL)

WT  GKO  WT  GKO

I

POMC (pmol/L)

WT  GKO