Supplementary Materials and methods

Mouse colonies
Urine was collected from 4 to 6 month old animals as follows. Mice were housed separately for one week, placed for pre-adaptation in a metabolic cage for 3 days and urine collected every 24h for the next 3 days. At the end of the collection, mice were starved for 12 hours, sacrificed by pentobarbital injection (300 mg/kg, pentobarbital sodium, USP, Abbott Laboratories North Chicago, IL60064, USA), weighed and blood collected into a tube containing 20-50 units heparin. Plasma was centrifuged and stored at -20°C until use. Organs were removed, weighed, frozen in liquid nitrogen and stored at -80°C until use.

Plasma and liver biochemistry
Glucose, cholesterol, triglycerides, ALT and AST were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Switzerland). Insulin was measured with the ultra sensitive rat/mouse insulin Elisa kit (Crystal Chem Inc (Cat No 90060), Downers Grove, IL, USA). 27-OHC was quantified by GC-MS as previously described (Burkard, et al. 2004) with 100 ng 5α-cholestan-3β,6α-diol and 100 ng stigmasterol as standards.
Triglyceride content was measured in liver homogenates with a triglyceride Quantification Kit (BioVision (Cat No K622-100), Mountain View, CA, USA).

Enzymatic assays in mouse tissues

11β-HSD1 activity in mouse liver homogenates
Reduction of E to F was used to assess 11β-HSD1 activity. Frozen liver samples were powdered and 30-50 mg tissue homogenized with 500 μl buffer containing 250 mM sucrose, 10 mM Tris Base pH 7.5 and 1 mM PMSF. Protein was quantified with a BCA™ Protein Assay Kit (Pierce Cat No 23225, Rockford, IL 61105, USA). For 11β-HSD1 assay, 10 μg protein was incubated for 30 min at 37°C in the presence of 951 mol/l β-nicotinamide adenine dinucleotide 2'-phosphate reduced tetrasodium salt (NADPH), 1.5 μmol/l cortisol and 3.2 nCi of [3H]-cortisone in sucrose buffer. The reaction was stopped by adding 30μl of a mixture containing 10 mg/ml cortisol and cortisol in methanol. Samples were spotted onto TLC plates ((G-25, UV254) Macherey-Nagel, Oensingen, Switzerland) and developed in a solvent containing chloroform-methanol (90:10 v/v). Steroids were visualized under ultraviolet light, the spots removed and counted in a Packard scintillation counter (Tri-Carb 2000CA; United Technologies, Hartford, CT, USA), and the percentage of conversion of cortisol to cortisone calculated.

11β-HSD2 activity in kidney homogenates
11β-HSD2 activity was assessed by measuring oxidation of B to A. Kidney homogenates were prepared as described above for liver from 30-50 mg of frozen tissue. Assay of 11β-HSD2 activity was performed using 10 μg protein and incubated for 90 min at 37°C in a mixture containing 200 mol/l nicotinamide adenine dinucleotide (NAD), 10 nmol/l B and 3.2 nCi of [3H]-corticosterone in sucrose buffer. The reaction was stopped by adding 30μl of a mixture containing 10 mg/ml B and A in methanol. TLC was performed as described above and the percentage of conversion of B to A calculated.