SUPPLEMENTARY DATA:

Metabolic studies

Euglycemic hyperinsulinemic clamp was performed after 12h fast, using a continuous infusion of insulin administered at the rate of 80 mU/m^2 of body surface area per minute. Blood glucose was clamped at 5.5 mmol/l for 100 min. by infusing 20% glucose at varying rates according to blood glucose measurements performed at 5 min. intervals. In fasting and at 80, 90 and 100 min, arterialised blood samples were collected for the measurement of plasma glucose and insulin concentrations, and determination of insulin-mediated glucose uptake. Graded glucose infusion consisted of consecutive 40 min. IV infusion periods of 20% glucose at 2, 4, 8, and if needed 12 and 16 mg/kg/min, respectively, in order to reach mean blood glucose levels around 20 mmol/l during the last period. These levels were maintained during the arginine test. Arterialised blood samples were obtained at baseline and every 10 min. during each glucose infusion step, and were immediately centrifuged and stored at –80°C.

Glucose disposal rate was calculated from the glucose infusion rate during the last 20 min. of the glucose clamp after accounting for inter-individual differences in glucose space, and was expressed in mg/kg of fat-free body mass. Early insulin secretion in response to an oral glucose load was calculated as the ratio [insulinemia at 30 min (I30) - fasting insulinemia (I0)]/[blood glucose at 30 min. (G30) – fasting blood glucose (G0)]. Insulin secretion in response to the graded glucose infusion was evaluated from the changes in C-peptide concentration and the pre-hepatic insulin secretion rate (ISR). ISR was derived by deconvolution assuming a two-compartment model of C-peptide clearance kinetics using version 3·4a of the ISEC software (1). The insulin response to arginine during hyperglycemia was estimated using the AUC of insulin concentrations within the 5 min. following arginine injection.

Supplementary Table 1. Primer sequences

Gene	Sequence (5'-3')
human cyclophilin	Fwd:GCAAAGTGAAAGAAGGCATGAA Rev:CCATTCCTGGACCCAAAGC
human insulin	Fwd:GCAGCCTTTGTGAACCAACA Rev:TTCCCCGCACACTAGGTAGAGA
human CHOP/GADD153	Fwd:AGAACCAGGAAACGGAAACAGA Rev:TTCATGCGCTGCTTTCCA
human XBP1	Fwd:GAAGCCAAGGGGAATGAAGT Rev:ACTGGGTCCAAGTTGTCCAG

Reference List

1. Sobngwi,E, Boudou,P, Mauvais-Jarvis,F, Leblanc,H, Velho,G, Vexiau,P, Porcher,R, Hadjadj,S, Pratley,R, Tataranni,PA, Calvo,F, Gautier,JF: Effect of a diabetic environment in utero on predisposition to type 2 diabetes. *Lancet* 361:1861-1865, 2003

Supplementary Figure 1. Expression of mutant insulins in HEK293 cells.
Cells seeded on coverslips were transfected with *INS*-GFP constructs and were fixed after 48h of expression of recombinant proteins. Fluorescence of *INS*-GFP was studied using a 63x oil-immersion lens of a spinning disc confocal microscope (see Research Design and Methods) using a 488nm laser line. Images are typical distribution of each *INS* mutant protein (n≥20). Scale bar=10μm.