SUPPLEMENTAL EXPERIMENTAL PROCEDURES

Western blot analysis of NNT expression – About 200 islets were homogenized in lysis buffer (10 mmol/l Tris pH 7.4, 150 mmol/l NaCl, 1% Triton X-100, 1% sodium deoxycholate, 0.1 SDS, 5 mmol/l sodium fluoride) supplemented with 1 µg/ml pepstatin and 1 mmol/l phenylmethylsulfonyl fluoride. After 40 min incubation on ice, the homogenates were centrifuged for 10 min at 13000 rpm. Protein concentration of the supernatant fraction was determined using the Pierce TM BCA Protein Assay Kit. Small pieces of heart from N-mice and J-mice were used as positive and negative control for NNT. Protein extracts (35 µg per lane) were separated on a 7% polyacrylamide gel and transferred on a PVDF membrane. The membrane was blocked overnight at 4°C with 5% non-fat milk in Tris-buffered saline containing 0.1% Tween 20 (TBST), then incubated for 2 h at room temperature with 1 µg/ml NNT antibody or 0.2-0.4 µg/ml anti-actin antibody in 1% non-fat milk TBST. After rinsing, the membrane was incubated for 1 h at room temperature with an anti-rabbit peroxidase-conjugated antibody diluted 1:10000 in 1% non-fat milk TBST. The chemiluminescent signal was revealed with SuperSignal™ West Femto or West Pico Chemiluminescent Substrate (ThermoFisher Scientific) and quantified with a ChemiDoc MP Imaging System (Bio-Rad).

Measurement of pyridine nucleotides with NAD/NADH-Glo™ and NADP/NADPH-Glo™ Assays (Promega) - For each sample, the oxidized form NAD^+ (or $NADP^+$) was assayed after selective destruction of NADH (or NADPH) by 15 min incubation at 60°C in an acidic solution, while NADH (or NADPH) was assayed after selective destruction of NAD^+ (or $NADP^+$) by 15 min incubation at 60°C in a basic solution. After pH neutralization with Tris or HCl-Tris, the amount of pyridine nucleotide in each sample was determined in parallel with standard curves of the corresponding nucleotide (Sigma), according to manufacturer's instructions.

Measurement of oxygen consumption rate - Oxygen consumption by isolated islets was measured in a flow culture system. Oxygen consumption rate was determined as the difference between inflow and outflow oxygen tension, times the flow rate (60 µL/min), as measured by the phosphorescence lifetime of an oxygen-sensitive dye painted on the inside of the perifusion chamber using an MFPF-100 multi-frequency phase fluorometer lifetime measurement system (TauTheta Instruments, Boulder, CO). The dye was excited and detected by a single bifurcated 2

mm optical fiber (TauTheta part no. SFO-026) where one fiber was illuminated with a 405-nm light emitting diode and the other was connected to the phosphorometer.