Supporting Information Methods

Human Experiments Twenty-three Caucasian obese, insulin-resistant (IR) patients (52 ± 2 years; 97 ± 3 kg; LDL 3.1 ± 0.1 mmol/L; HDL 1.1 ± 0.1 mmol/L; triglycerides 2.6 ± 0.5 mmol/L) and 19 age-matched healthy Caucasian males (54 ± 2 years; 77 ± 3 kg*; LDL 3.1 ± 0.1 mmol/L; HDL 1.4 ± 0.1 mmol/L*; triglycerides 1.1 ± 0.1 mmol/L*; *P<0.05 compared with obese-IR cohort) volunteered for this study. The protocol was approved by the Alfred Hospital Ethics Committee, and conducted in accordance with the Declaration of Helsinki of the World Medical Association. Skeletal muscle biopsy samples were obtained in the morning after an overnight fast, snap frozen in liquid nitrogen and stored at -80^{o}C.

Glucose and insulin tolerance tests, insulin signaling experiments and protein analysis. Glucose and insulin tolerance tests were performed after 16 weeks. Food was withdrawn from mice the night before experiments. Mice were placed in restrainers and blood samples were obtained by tail bleeding and analyzed for glucose (HemoCue, Ängelholm, Sweden) immediately before and at 15, 30, 60, 90 and/or 120 min after an IP glucose (1 g/kg in 0.9% NaCl) or insulin (0.75 U/kg) injection. For insulin signaling experiments, mice were anaesthetized with sodium pentobarbital (0.05 mg/g) before an IP injection of insulin (1.5U/kg) or saline (basal measures). Within 5 min of insulin injection, tissues were excized and snap frozen in liquid nitrogen. All antibodies except for anti HSP72 and anti HSF-1 (purchased from Stressgen Bioreagents) were obtained from Cell Signaling.

BGP-15 Hyperinsulinemic Euglycemic Clamp experiments. Male leptin deficient (*ob/ob*) mice, 4 weeks of age, were given standard rodent chow and water *ad libitum*

and housed in a controlled environment with a 12:12 light dark cycle. All experimental procedures were approved by the University of California, San Diego Animal Subjects Committee in accordance with the National Institutes of Health Guidelines. Animals were weighed and randomly divided into Control (Vehicle treated; 200 µl saline by oral gavage) or BGP-15 (15 mg/kg/day in 200 µl saline; N-Gene Research Laboratories Inc.) and treated for 15 d by oral gavage. After 12 d animals were chronically cannulated under single dose anesthesia (Ketamine, Xylazine, Acepromazine Maleate) in the right jugular vein with dual catheters (Micro-Renathane MRE 025, 0.025-inch outer diameter, 0.012-inch inner diameter; Braintree Scientific Inc., Braintree, MA). Mice were then placed in an isothermic environment for a 24 h period following surgery to maintain body temperature. Administration of the Control or BGP-15 was continued during the three day post-surgical recovery period. On day 15 animals were fasted for 6 h prior undergoing a euglycemic hyperinsulinemic clamp.