ONLINE METHODS

All procedures were approved by the Institutional Animal Care and Use Committees at the University of Cincinnati Office or the Pennington Biomedical Research Center, in accordance with the US National Institutes of Health guide for the care and use of laboratory animals. Ghrelin and GLP-1 synthesis used *in situ* neutralization for Boc-chemistry as described previously[41]. All peptides were purified by preparative chromatography and characterized by HPLC and mass spectral analysis. MTII and SHU9119 were obtained from Bachem.

Animals. Male Wistar rats (250–350 g) purchased from Harlan were housed in individual cages at 23 °C and with a 12-h light/12-h dark cycle. Rats were allowed *ad libitum* access to water and pelleted low-fat laboratory chow (Harlan Teklad) or a high–fat content diet (ref. no. D03082706, Research Diets). For induction of diet-induced obesity, a cohort of 32 rats (250–275 g) was given *ad libitum* access to a high-fat diet (butter enriched, 0.05% cholesterol, ref. no. D03082706, Research Diets). After 11 months, the body weight range of these rats was 587–1,247 g and the eight rats at each extreme were referred to as either DIO resistant (body weight range, 587–707 g, $n = 8$) or DIO sensitive (body weight range, 947–1,247 g, $n = 8$) and studied further in comparison with a group of chow-fed rats (body weight range, 427–508 g, $n = 8$).

Male 129sv or C57BL/6 mice (12–15-weeks-old) wild-type mice purchased from Taconic or Jackson Labs, respectively, were singly housed on a 12-h light, 12-h dark cycle at 22 °C, and fed a low-fat pelleted (chow) diet with free access to food and water. *Ghrl*$^{-/-}$ and *Ghsr*$^{-/-}$ mice were obtained from Regeneron Pharmaceuticals. Male and female *Mc3r*$^{-/-}$, *Mc4r*$^{-/-}$ and wild-type C57BL/6J mice ($n = 3$–10 mice per group), bred by mating heterozygotes as described previously[10].

Body composition measurement. Body composition was measured using NMR imaging (Whole Body Composition Analyzer, EchoMRI).

Gene expression quantification. Animals were killed by decapitation in the fed (3 h after onset of light phase) or fasted state (over night, 12 h). Tissues were sampled, freeze clamped and stored at −80 °C for subsequent measurement of mRNA (**Supplementary Table 1** and **Supplementary Methods**).

Clearance analysis of HDL-C. Human HDL was purified by ultracentrifugation in KBr gradient, labeled with [cholesterol-1,2-^{3}H]cholesteryl oleoyl ether as previously described[42] and injected via tail vein in *ad libitum* chow-fed rats infused chronically icv with SHU9119 (10 nmol d^{-1}, 4 d) or saline. Blood was collected up to 6 h and plasma radioactivity was determined with a β counter. Clearance curves were averaged per treatment group and fitted with a nonlinear regression for two phase decay with least square fit. Both curves were compared with extra sum of squares *F* test (**Supplementary Methods**).

Analysis of HDL size by nondenaturing electrophoresis. We pooled 2 ml of plasma from two animals from the same group. HDL was purified by ultracentrifugation in KBr gradient and 12 μg of protein were separated in nondenaturing conditions in a 4–15% Tris glycine polyacrylamide gel. The size of HDL was compared with a High Molecular Weight marker (GE Healthcare) (**Supplementary Methods**).

Blood parameters. Trunk blood was collected in EDTA-containing tubes and stored at −80 °C until further processing for the measurement of hormones and metabolites using commercially available kits (**Supplementary Methods**).

Statistics. Results are given as mean ± s.e.m. Student's *t* test, one-way ANOVA followed by the *post hoc* Tukey test, two-way ANOVA followed by the *post hoc* Bonferroni test or extra sum of squares *F* test were performed using GraphPad Prism 5 (GraphPad Software). A two-tailed *P* value less than 0.05 was considered to be statistically significant.

41. Schnölzer, M., Alewood, P., Jones, A., Alewood, D. & Kent, S.B. *In situ* neutralization in Boc-chemistry solid-phase peptide synthesis. Rapid, high yield assembly of difficult sequences. *Int. J. Pept. Protein Res.* **40**, 180–193 (1992).
42. Pittman, R.C., Knecht, T.P., Rosenbaum, M.S. & Taylor, C.A. Jr. A nonendocytotic mechanism for the selective uptake of high-density lipoprotein–associated cholesterol esters. *J. Biol. Chem.* **262**, 2443–2450 (1987).