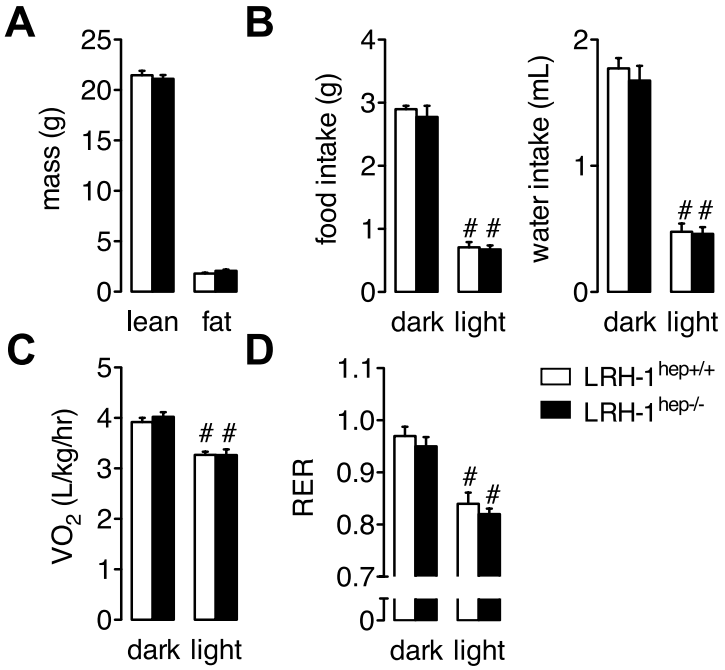

Figure S1. Body composition, energy homeostasis and substrate utilization in LRH-1$^{hep+/+}$ (white bars) and LRH-1$^{hep-/-}$ (black bars) mice. (**A**) Lean and fat masses, determined by EchoMRI. (**B**) Food and water intake during dark and light phases, determined by Comprehensive Lab Animal Monitoring (CLAMS). (**C**) Oxygen consumption during dark and light phases, determined by CLAMS. (**D**) Respiratory exchange ratio (RER) during dark and light phases, determined by CLAMS. Data represent means ± SEM (n=8/genotype). $^{\#}p<0.05$ versus dark.

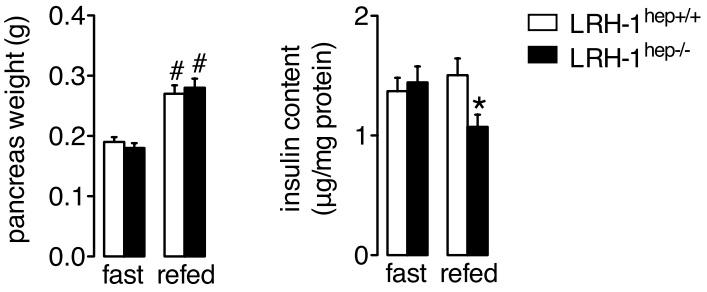

Figure S2. Pancreas weight and pancreatic insulin content in 24-hour fasted and 6-hour refed LRH-1$^{hep+/+}$ (white bars) and LRH-1$^{hep-/-}$ (black bars) mice. Data represent means ± SEM (n=5-8/genotype). *p<0.05 versus LRH-1$^{hep+/+}$, #p<0.05 versus fast.

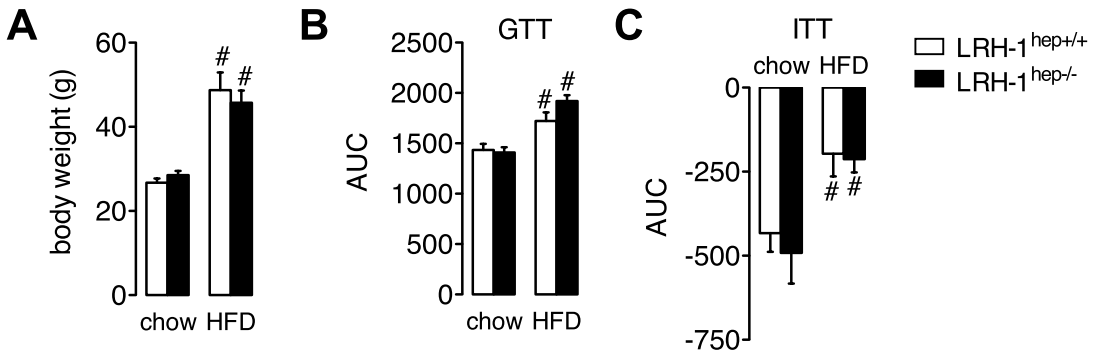

Figure S3. High-fat feeding experiments in LRH-1$^{hep+/+}$ and LRH-1$^{hep-/-}$ mice. (**A**) Body weight in chow and high-fat diet fed LRH-1$^{hep+/+}$ (white bars) and LRH-1$^{hep-/-}$ (black bars) mice after 26 weeks of dietary intervention. (**B**) Glucose AUC during oral glucose tolerance tests in chow and high-fat diet fed LRH-1$^{hep+/+}$ (white bars) and LRH-1$^{hep-/-}$ (black bars) mice. (**C**) Glucose AUC during intraperitoneal insulin tolerance tests in chow and high-fat diet fed LRH-1$^{hep+/+}$ (white bars) and LRH-1$^{hep-/-}$ (black bars) mice. Data represent means ± SEM (n=5-9/genotype). $^{\#}p<0.05$ versus chow.

Supplemental Methods

Animal studies

Food and water intake, O_2 consumption and substrate utilization in LRH-1$^{hep-/-}$ and LRH-1$^{hep+/+}$ mice were monitored using the Comprehensive Lab Animal Monitoring System (CLAMS) (Columbus Instruments, Columbus, OH). Measurements were performed under a 12/12 hr dark/light cycle (lights on 7am-7pm) during 48 hours with ad libitum access to regular chow and drinking water. Prior to these measurements, lean and fat masses were quantified by EchoMRI, after which the animals were habituated in the CLAMS system during 24 hours.

For fasting-refeeding experiments, 24 hour-fasted in LRH-1$^{hep-/-}$ and LRH-1$^{hep+/+}$ mice were sacrificed at 7am. Refed mice were fasted for 24 hours, starting at 7am, and were subsequently refed with normal chow diet during 6 hours. Animals were sacrificed by cardiac puncture under isoflurane anesthesia, and pancreas, gastrocnemius muscle, epididymal fat and hypothalamus were quickly snap-frozen. Pancreatic insulin was isolated as described (1) quantified by ELISA (Crystal Chem Inc.) and normalized for protein content (Lowry, BioRad). RNA isolated from muscle, fat and hypothalamus samples using Tri Reagent was subjected to qPCR analysis. Primer sequences are listed in Table S1. Gene expression levels were normalized for 36B4 (muscle and fat) or 18S (hypothalamus).

For high-fat feeding experiments, animals were fed either regular chow (Teklad #2016, Harlan) or a high-fat diet (D12330; Research Diets) during 26 weeks. Glucose tolerance tests were performed following an oral glucose bolus (2 g/kg) in 16-hour fasted mice (7pm-11am). Area under the curve (AUC) was calculated from blood glucose measurements at 0, 15, 30, 60, and 120 minutes. Insulin tolerance tests were performed following an intraperitoneal insulin bolus (0.75 U/kg) in 4-hour fasted mice (9am-1pm). Area under the curve (AUC) was calculated from blood glucose measurements at 0, 30, 60, 90, 120 and 150 minutes.

References

1. Maida, A., Lovshin, J.A., Baggio, L.L., and Drucker, D.J. 2008. The glucagon-like peptide-1 receptor agonist oxyntomodulin enhances beta-cell function but does not inhibit gastric emptying in mice. *Endocrinology* 149:5670-5678.

Supplemental Table 1. qPCR and ChIP primer sequences.

Gene	Forward primer	Reverse primer
18S	GGGAGCCTGAGAAACGGC	GGGTCGGGAGTGGGTAATTTT
36B4	AGATTCGGGATATGCTGTTGG	AAAGCCTGGAAGAAGGAGGTC
Acc1	GACAGACTGATCGCAGAGAAAG	TGGAGAGCCCCACACACA
Acc2	CCCAGCCGAGTTTGTCACT	GGCGATGAGCACCTTCTCTA
Agrp	GCGGAGGTGCTAGATCCACA	AGGACTCGTGCAGCCTTACAC
B2mg	TTCTGGTGCTTGTCTCACTG	TATGTTCGGCTTCCCATTCT
ChREBP	AAGCTAGGATTCGACACCCT	CAGCGTTGAGCTCCTCTATT
Cycs	ACCAAATCTCCACGGTCTGTT	TCCGAACACTCGAACTTCTCA
Cyp8b1	CAAAGCCCCAGCGCCT	TTCGACTTCAAGCTGGTCGA
Fas	AGCTTCGGCTGCTGTTGGAAGT	TCGGATGCCTCTGAACCACTCACA
G6pdh	GAACGCAAAGCTGAAGTGAGACT	TCATTACGCTTGCACTGTTGGT
Gck	ACATTGTGCGCCGTGCCTGTGAA	AGCCTGCGCACACTGGCGTGAAA
Glut4	ACTCTTGCCACACAGGCTCT	CCTTGCCCTGTCAGGTATGT
Hk1	GAGGTCTACGACACCCCAGA	GAAGTCTCCGAGGCATTCAG
Hk2	CCGCCGTGGTGGACAAGATA	AGCAGTGATGAGAGCCGCTC
Ldh	ACTTGGCGGATGAGCTTGC	TGCGTCAGTGCCCAGTTCTG
Lrh-1	TCATGCTGCCCAAAGTGGAGA	TGGTTTTGGACAGTTCGCTT
L-pk	GGGCCGCATCTACATTGAC	GTCCCTCTGGGCCAATTTT
Npy	CTCCGCTCTGCGACACTACA	AATCAGTGTCTCAGGGCTGGA
Pdk4	GCA TTT CTA CTC GGA TGC TCA TG	CCA ATG TGG CTT GGG TTT CC
Pgc-1α	TGAGCGAACCTTAAGTGTGGA	CAAGAGGGCTTCAGCTTTGG
Pomc	ACCTCACCACGGAGAGCAAC	GCGAGAGGTCGAGTTTGCA
Scd1	CCGGAGACCCCTTAGATCGA	TAGCCTGTAAAAGATTTCTGCAAACC
Shp	CTTTCTGGAGCCTTGAGCTGG	GTTGAAGAGGATCGTGCCCTT
Sr-b1	TTGGCCTGTTTGTTGGGATG	GGATTCGGGTGTCATGAAGG

Promoter	**Forward primer**	**Reverse primer**
GCK1	AGATGGCAAGTGATAGACAAG	TGTGTATGCAAGCATGCGTG
GCK2	CACGCATGCTTGCATACACA	GGGAGTGAGTAAACTGAAGG

GCK3	ATTCAGGCATGAGCTCAACC	GTATGACAGGGTACATAGGG
GCK4	AGGTCTAGGAGGTGTCTGAA	GAGAAGATTCAGGTCCTCTG
GCK5	AGCCTGTCTCATAGCCCTGT	AGCCAAGGACTTCTGCACTA
GCK6	ATTAGTGCAGAAGTCCTTGG	AAGTAGAGATGTTCCTGACT
GAPDH	AGTGCCAGCCTCGTCCCGTAGACAAAATG	AAGTGGGCCCCGGCCTTCTCCAT