Figure S1. Weight Gain and Fatty Liver Development after Ten Weeks of High Fat Diet Feeding (A) Weight of animals on normal chow vs. high fat diet throughout the ten weeks of feeding (N=45 per feeding group, Error bars=SEM). (B) Weights for each group of animals sacrificed at each zeitgeber time (N=5 per feeding group per zeitgeber time, Error bars=SEM). (C) Representative hematoxylin and eosin stain of livers after 3 days or 10 weeks of high fat diet feeding. (D).Oil Red O stain of livers after 3 days or ten weeks of high fat feeding. (E) Liver triglyceride accumulation in normal chow and high fat diet-fed groups after ten weeks of feeding (N=5 livers per group per time point; P=0.0079 Mann Whitney Test). (F) Blood glucose concentrations of mice fed a normal or high fat diet after 16 hours of fasting (0 minutes) and then 15, 30, 45, 60, and 120 minutes following IP glucose injection s (Diet Effect, $P<0.001$; Time Effect, $P<0.001$; Two-way ANOVA, Bonferroni post-test). (H) Average circadian food intake patterns of animals on a normal chow vs. a high fat diet for 10 weeks. (N=8 animals per feeding condition.) (I) Food intake in kcal per mouse (left panel) and normalized to total body weight (middle panel) during the light and dark phase. Percent of total calories consumed during the day and during the night (right panel) for animals on the normal chow or high fat diet for ten weeks. Data is averaged from 8 animals per feeding condition.

Figure S2: Hepatic Metabolites Peak Differentially Based on the Diet (A-F) The percent of metabolites within nucleotide, xenobiotic, carbohydrate, amino acid, lipid, and cofactors and vitamins classes that peak at a particular zeitgeber time in livers of animals fed a normal chow diet (ND) or a high fat diet (HF). Peaks of oscillatory metabolites only, divided by the total number of oscillating metabolites within the metabolic pathway are plotted.

Figure S3: BMAL1 and CLOCK Protein Expression in NC and HFD Conditions (A) BMAL1 expression at ZT0 and ZT12 in nuclear, cytoplasmic, and chromatin fractions. (B)

BMAL1 expression and phosphorylation at ZT4 and ZT16 in whole cell lysates of NC and 10-week HFD livers. (C) CLOCK protein in NC and 10-week HFD livers (whole cell lysates) at ZT0 and ZT12. (D) CLOCK occupancy of the Nampt promoter at ZT0 and ZT12 ten weeks after HFD feeding. (N=4 per zeitgeber time per feeding condition). Western blot fractions from 3 pooled livers.

Figure S4: PPARγ Ligands Elevated in the Liver after Ten Weeks of High Fat Feeding (A) Fatty acids that can serve as endogenous PPAR ligands are elevated throughout the circadian cycle. These include 15-hete, 13-hode, linolenate, and arachidonate. (B) Nocturnin (*Ccrn4l*) expression throughout the circadian cycle in NC and HFD livers after ten weeks of feeding.

Figure S5: Animal body weights and Liver Pathology on Different Feeding Regimens (A) Body weights were unaffected after three days on the high fat diet (HF) relative to the normal chow diet (NC). (B) Representative hematoxylin and eosin and Oil Red O stain of livers from animals on the NC or HF diets for three days. (C) Body weights for animals maintained on a NC or HF diet and then returned (or maintained) on the NC diet for two weeks. (N=5 animals per feeding condition; Error bars-SEM).

Supplementary Experimental Procedures:

Histological Analysis. Adult mice were sacrificed via cervical dislocation and fresh liver was rinsed with PBS and embedded in OCT. Serial sections (10μm thick) were sliced using a Leica CM1950 cryostat and mounted on Superfrost Plus Gold slides. One set of slides was stained with Hematoxylin and Eosin and another with Oil Red O as previously described {Mark, 2007 #761}. Fat vesicles were photographed at 100x magnification.

Measurement of Liver Triglycerides: Triglycerides were measured using the Triglyceride Colorimetric Assay Kit (Cayman Chemicals Company, #10010303), according to the manufacturer's instructions.

Intraperitoneal Glucose Tolerance Tests (IPGTT) : Male, age-matched (approximately 16 weeks of age) were subjected to IPGTT after ten weeks on either a normal chow diet or a high fat diet (60% kcal from fat). After 16 hours of fasting, blood glucose measurements were taken at 0 (prior to glucose injection) and 15, 30, 45, 60, and 120 minutes following glucose injection. Glucose was administered IP at a dose of 1g/kg body weight.

Indirect Calorimetry: Calorimetry was performed as described in (Eckel-Mahan 2012), using negative-flow CLAMS hardware system cages (Columbus Instruments, Columbus, Ohio).

GW9662 Administration: GW9662 (Cayman Chemical) was prepared as previously described (Sos et al., 2011) with minor deviations. Following the preparation of 20mg/ml aliquots, GW9662 was dissolved in 50% DMSO/50% saline and administered in volumes of approximately 100 µl at a dose of 4 mg/kg. Nine week-old animals were fed a high fat diet for two weeks and then given intraperitoneal injections of vehicle (50%DMSO/50% saline) or GW9662 for 21 days, once a day. Following the final injection, animals were harvested at ZT0 and ZT12 on the following day and livers were analyzed for *Cidec* and PPARγ expression. As the drug generally increased *Pparγ* expression, *Cidec* increases were normalized to the amount of drug-induced *Pparγ* expression.

Microarray Analysis Preparation and Processing: Target Preparation/Processing for GeneChip® Analysis Isolated total RNA samples were processed as recommended by

Affymetrix, Inc. (Affymetrix Genechip® Whole Transcript Sense Target Labeling Assay Manual, Affymetrix, Inc., Santa Clara, CA) In brief, total RNA was initially isolated using TRIzol Reagent (Gibco BRL Life Technologies, Rockville, MD), and passed through an RNeasy spin column (Qiagen, Chatsworth, CA) for further clean up. Eluted total RNAs were quantified (Nanodrop) with a portion of the recovered total RNA adjust to a final concentration of 100ng/ul. All starting total RNA samples were quality assessed prior to beginning target preparation/processing steps by running out a small amount of each sample (typically 25-250ng/well) onto a RNA 6000 Nano LabChip that was evaluated on an Agilent Bioanalyzer 2100 (Agilent Technologies, Palo Alto, CA).Single-stranded, then double-stranded cDNA was synthesized from the poly(A)+mRNA present in the isolated total RNA (typically 100ng total RNA starting material each sample reaction) using the Ambion® WT Expression Kit (Life Technologies, Carlsbad, CA) and random hexamers tagged with a T7 promoter sequence. The double-stranded cDNA is then used as a template to generate many copies of antisense cRNA from an *in vitro* transcription reaction (IVT) of 16hrs in the presence of T7 RNA Polymerase. 10 ug of cRNA were input into the second cycle cDNA reaction with random hexamers that are used to reverse transcribe the cRNA from the first cycle to produce single-stranded DNA in the sense orientation. The single-stranded DNA sample is fragmented (WT Terminal Labeling Kit, Affymetrix, Inc, Santa Clara, CA) to an average strand length of 70 bases (range 40-70bp) following prescribed protocols (Affymetrix GeneChip® WT Sense Target Labeling Assay Manual). The fragmented single-stranded DNA is subsequently labeled with recombinant terminal deoxynucleotidyl transferase (TdT) and the Affymetrix proprietary DNA Labeling Reagent that is covalently linked to biotin.

Following the recommended procedure, 2 ug of this fragmented target single-stranded cDNA was hybridized at 45c with rotation for 17 hours (Affymetrix GeneChip® Hybridization Oven 640) to probe sets present on an Affymetrix GeneChip Mouse Gene 1.0 ST array (Affymetrix, 901171). The GeneChip® arrays were washed and then stained (SAPE, streptavidin-phycoerythrin) on an Affymetrix Fludics Station 450 (Fluidics protocol FS450_007). Arrays were scanned using the GeneChip Scanner 3000 7G and Command Console Software v. 3.2.3.to produce .CEL intensity files. These probe cell intensity files (*.CEL) were analyzed in Affymetrix Expression Console software v1.1.1 using the PLIER algorithm to generate probe level summarization files (*.CHP). (Algorithm: PLIER v 2.0; Quantification Scale: Linear; Quantification Type: Signal and Detection P-Value; Background: PM-GCBG; Normalization Method: Sketch-Quantile).

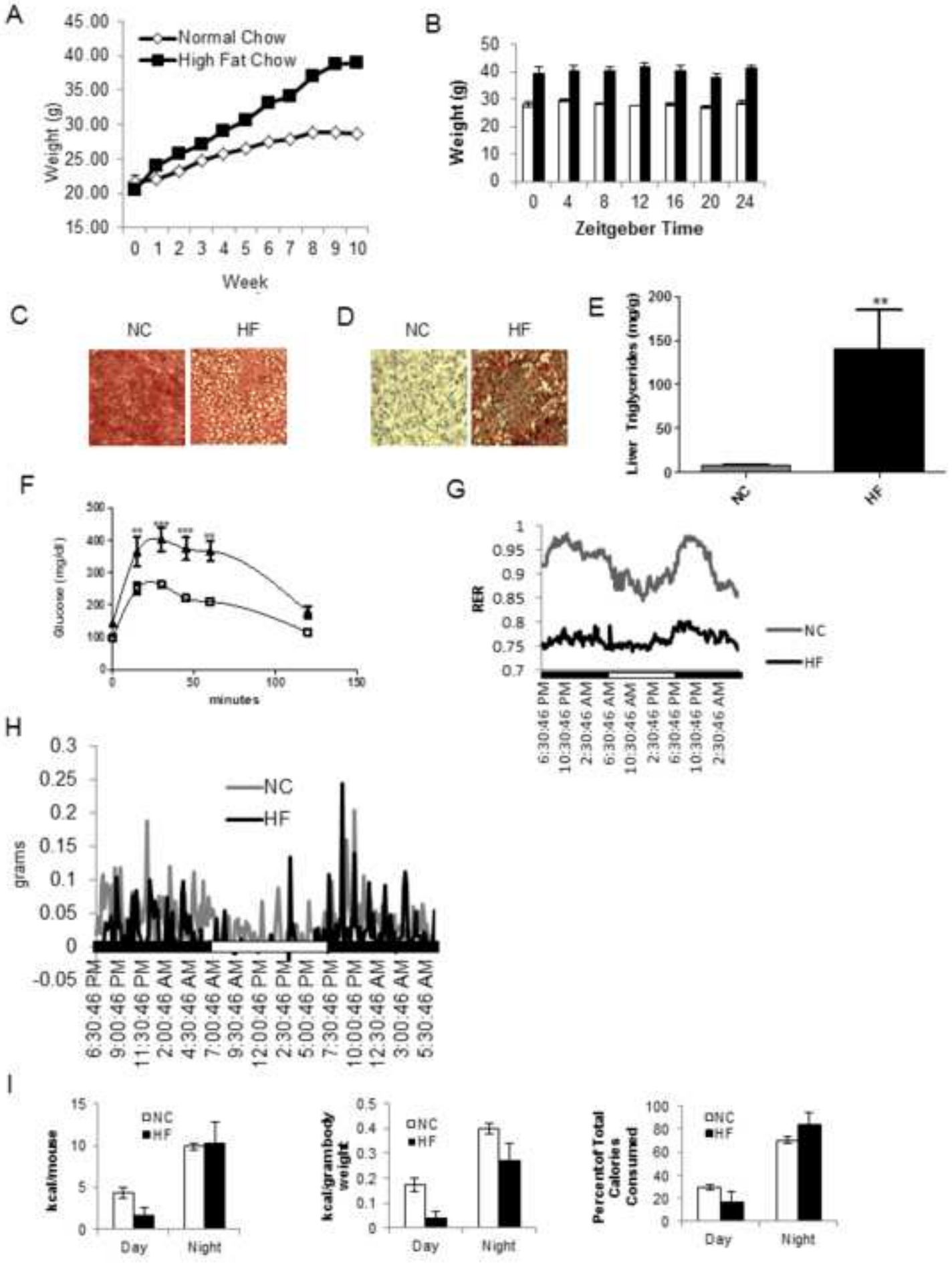
MotifMap Analysis: MotifMap is a comprehensive database of putative regulatory transcription factor binding sites which is described in (Daily et al., 2011; Xie et al., 2009) and also in (Eckel-Mahan et al., 2012). Briefly, each position weight matrix is used to scan the mouse genome for potential binding sites with every site being assigned the following three scores: (1) motif matching score (Z-score); (2) conservation score (Bayesian Branch Length Score or BBLS) which is calculated using a multiple alignment of 30 genomes from mouse to zebrafish; and (3) false discovery rate (FDR) obtained by shuffling the columns of the binding matrix and using Monte Carlo methods. We retained only those sites for which the Z-score was greater than 4.0, BBLS was greater than or equal to 0.5, and FDR less than or equal to 0.1. SREBP1 motif searches were based on (Proskura, 2004).

Chromatin Immunoprecipitation: Chromatin immunoprecipitation experiments were performed as previously described (Eckel-Mahan 2012) with slight modifications.

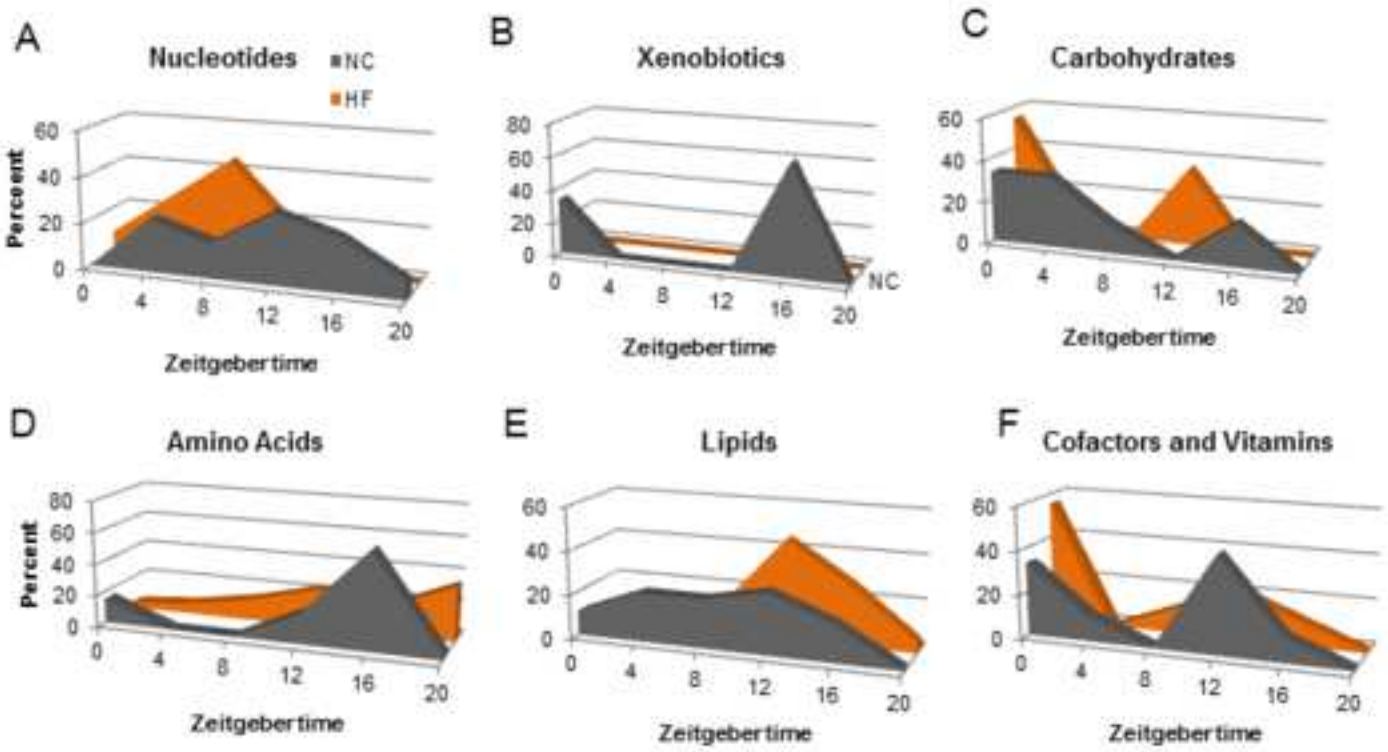
Approximately 200 mg of tissue was used per replicate. Antibodies for chromatin immunoprecipitation included 2 µg BMAL1 (Abcam #3350), 2 µg PPARγ (Santa Cruz, H-100), 1 µg CLOCK (Santa Cruz C-19, sc-6927), and 3 µg H3K4me3 (Active Motif, #39160). The primers for ChIP were obtained as designated below or designed by Primer 3 (v. 0.4.0) and are as follows: *Cidec* PPRE and nonPPRE (Matsusue et al., 2008)**,** *Pcx*PPRE and nonPPRE (Jitrapakdee et al., 2005)**,** *Upp2* (Eckel-Mahan et al., 2012). *Dbp*i1 and *Dbp*E1 ChIP primers are based on (Ripperger and Schibler, 2006), and *Nampt* primers are based on (Nakahata et al., 2009).

Co-Immunoprecipitation: For immunoprecipitation of CLOCK, 3 µg of antibody (Bethyl Laboratories) was used per 2 mg whole cell lysates. Western blot analysis was performed on immunoprecipitated protein with a different CLOCK antibody (S-19, Santa Cruz Biotechnology).

Supplemental Figure



Supplemental Figure



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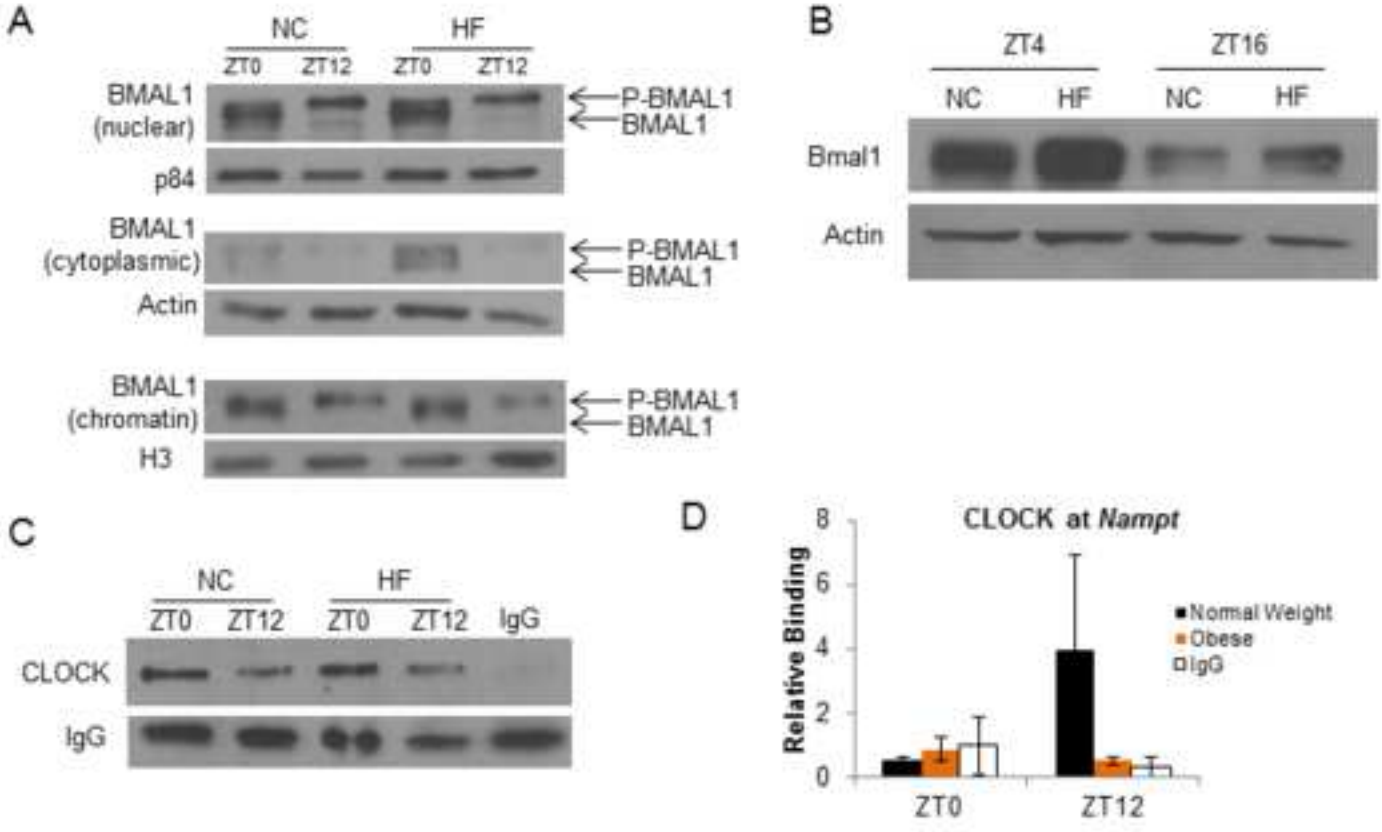
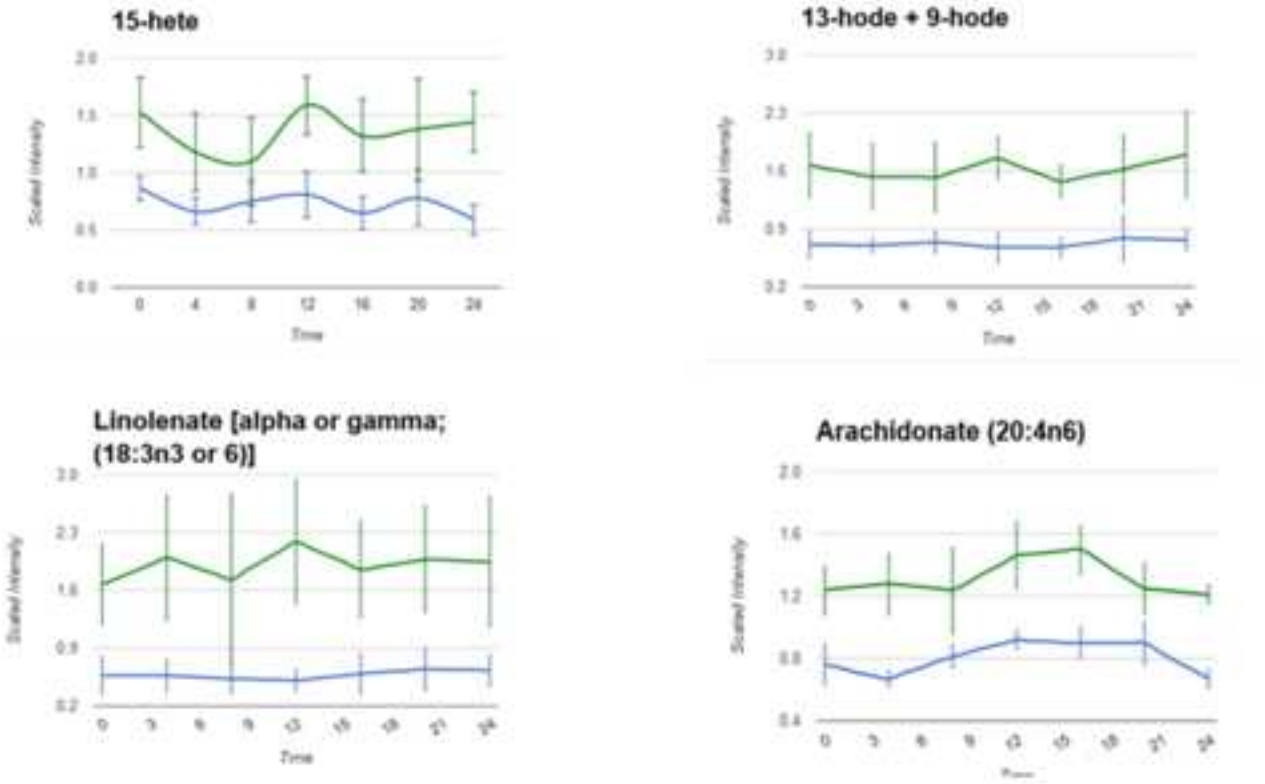


Supplemental Figure

A



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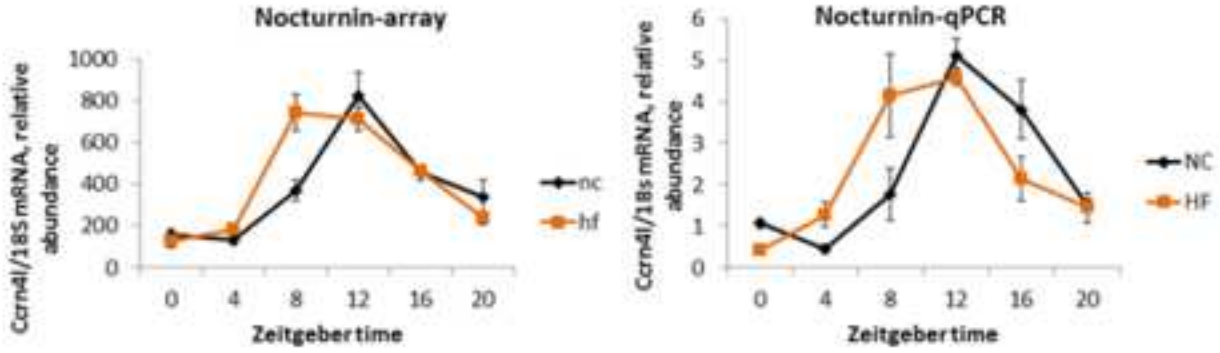

Supplemental Figure