Supplementary Information and data:

Supplementary Figure S1. RORα and RORγ exhibited a certain degree of redundancy in regulating clock gene expression. The level of *Cry1*, *Bmal1*, *Rev-Erbα*, *E4bp4*, *Per2*, *Npas2*, and *Clock* mRNA expression in liver, BAT, kidney, and small intestines from WT, $RORα^{sg/sg}$, $RORγ^{-/-}$, and $RORα^{sg/sg}RORγ^{-/-}$ DKO mice (n=4) was compared at ZT8 and ZT 22. The level of expression was normalized to that of littermate WT mice controls (black bars). Data represent mean ±SD; * P<0.05, **P<0.01, *** P<0.001 by ANOVA.

Supplementary Figure S2. Activation of *Cry1*, *Bmal1*, *Rev-Erbα*, and *E4bp4* by RORs is mediated through ROREs. (A) Location of the conserved ROREs within the regulatory regions of mouse and human *Cry1*, *E4bp4*, *Bmal1*, and *Rev-Erbα*. The core motifs of the ROREs are shown in bold and are underlined. The numbers refer to the distance to the transcription start site. (B) RORs effectively activate the *Luc* reporter driven by the RORE-containing regulatory region of *Cry1*, *Bmal1*, *Rev-Erbα*, and *E4bp4* in Huh-7 cells. Cells were co-transfected with an p3xFlag-CMV10-ROR expression vector, pCMV-β-Gal, and a pGL4.27 reporter plasmid driven by the RORE-containing regulatory region of *Cry1*, *Bmal1*, *Rev-Erbα*, or *E4bp4* or regions in which the ROREs were mutated (RORE1m, RORE2m, and RORE1m2m, respectively). 24 h later the relative luciferase reporter activities were determined as described in Experimental Procedures. The basal activity of each reporter plasmid in cells co-transfected with the empty vector was normalized to 1. Data present mean ±SEM, * P<0.01 by ANOVA.

Supplementary Figure S3. The transcriptional regulation of *Clock* by RORγ and RORα *in vivo* involves recruitment to the *Clock*(RORE). (A) RORs were able to effectively activate the (+511/+827) *Clock* proximal promoter in Huh-7. The RORE was mutated from GGGTCA to GAATCA which is designated as ROREm. (B) The inverse agonist, T0901317, represses the activation of the *Clock* promoter by both RORα and RORγ in Huh-7 cells. Data present mean ±SEM, * P<0.01 by ANOVA. (C) *Clock* mRNA expression was examined by QRT-PCR analysis in Hepa1-6 stable cells described above (n=5). The expression of *Clock* in Hepa1-6(Empty) was normalized to 1. (D) RORs and Rev-Erbα were recruited to the *Clock* promoter in Hepa1-6 cells. ChIP analysis was performed with the Hepa1-6 stable cell lines and anti-Flag M2 antibody. Hepa1-6(Empty) served as a negative control. ChIP analysis was performed with anti-ROR antibodies using liver tissues (n=4) isolated from WT, $RORα^{sg/sg}$, and $RORγ^{-/-}$ mice at CT22. QPCR amplification of a non RORE-containing distal site of the *Clock* gene was used as a negative control. Data represent mean ±SEM; ** P < 0.01, *** P < 0.001 by ANOVA.

Supplementary Figure S4. Regulation of clock genes by wild type and mutant RORs in brown adipocytes and its inhibition by T0901317. (A) Relative expression of *Cry1*, *Bmal1*, *Rev-Erbα*, *E4bp4*, and *RORα* mRNA in BAT(E), BAT(RORγ), and BAT(RORγE502Q) brown adipocytes stably expressing the empty vector, RORγ, or the RORγE502Q mutant lacking transcriptional activity. BAT(RORγ) cells were also treated for 24 h with vehicle or the ROR antagonist T0901317 (10 μM). (B) Relative expression of *Cry1*, *Bmal1*, *Rev-Erbα*, *E4bp4*, and *RORγ* in BAT(E), BAT(RORα), and BAT(RORαΔAF2) brown adipocytes stably expressing the empty vector, RORα, or the

RORαΔAF2 mutant lacking transcriptional activity. The expression of each gene in BAT(E) cells was normalized to 1. Data represent mean ±SEM; ** P < 0.01, *** P < 0.001 by ANOVA.

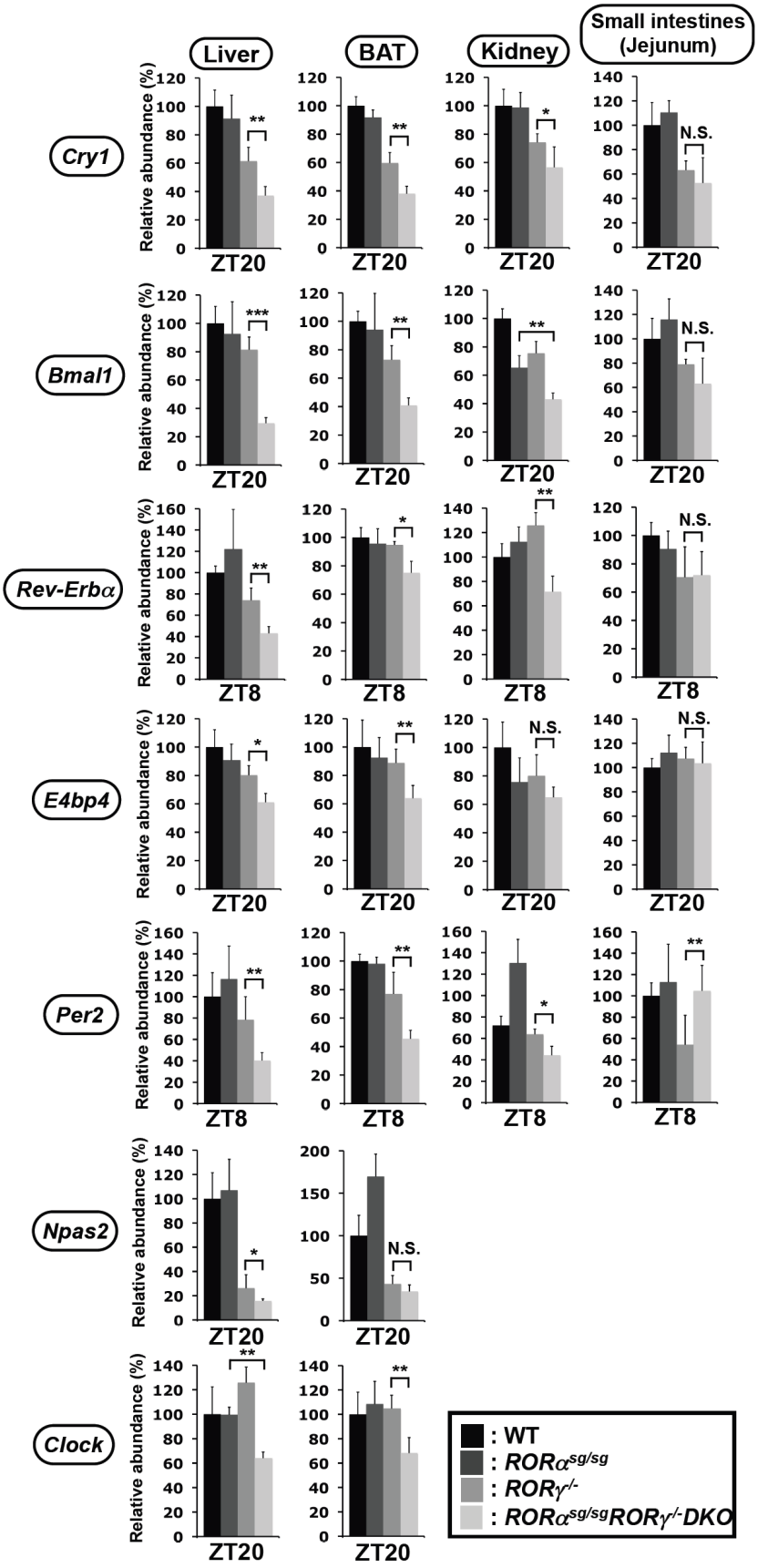
Supplementary Figure S5. Schematic presentation of the reciprocal transcriptional regulation of clock genes and *RORγ1* in peripheral tissues and the control of down-stream RORγ target genes. *In vivo*, RORγ1 modulates the peak expression of *Bmal1*, *Npas2*, *Cry1*, and *E4bp4* during ZT20-0, while Rev-Erbα represses the transcription of these clock genes, as well as *RORγ1,* during ZT8-12. Bmal1/Clock/Npas2 positively regulate the expression of *RORγ1*. RORγ1 might function as an intermediary, providing a link between the clock machinery and its regulation of metabolic genes. Bmal1/Clock and Rev-Erb regulate the rhythmic expression of *RORγ1* and as a result the rhythmic expression of downstream target genes, such as *Avpr1a*. The circadian expression of *Avpr1a* may depend on the rhythmic expression of *RORγ1* and to a certain degree on *Rev-Erb* through its regulation of *RORγ1* and/or its competition with RORγ1 for *Avpr1a*(RORE) binding.

Supplementary Table S1. A series of nucleotide sequences for QPCR primers

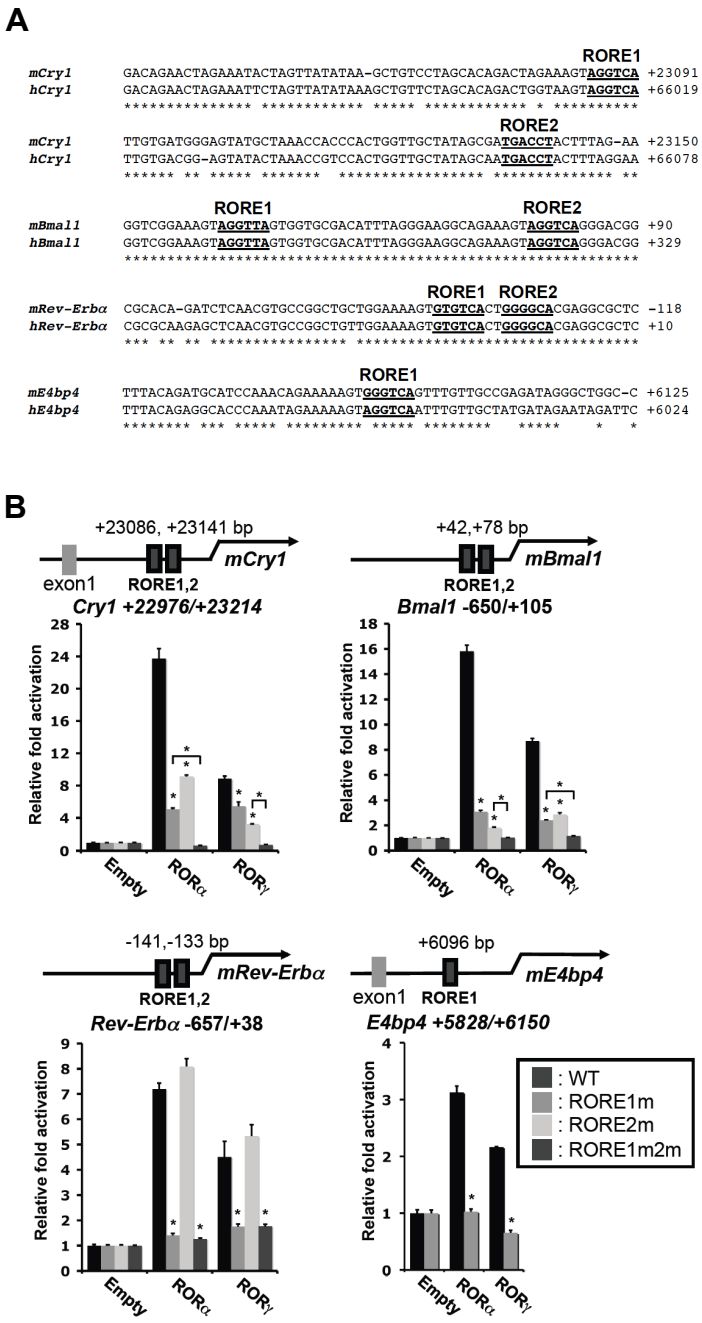
Gene	Sense primer	Antisense primer
mRORα1	GAGGTATCTCAGTCACGAAG	AACAGTTCTTCTGACGAGGACAGG
mRORα4	TGTGATCGCAGCGATGAAAG	AACAGTTCTTCTGACGAGGACAGG
mRORγ	ACTACGGGGTTATCACCTGTGAG	GTGCAGGAGTAGGCCACATTAC
mGapdh	AGTATGACTCCACTCACGGCAAAT	GTCTCGCTCCTGGAAGATGGT
mBmal1	AACCTTCCCGCAGCTAACAG	AGTCCTCTTTGGGCCACCTT
mNpas2	CGCAGATGTTCGAGTGGAAAG	GTGCATTAAAGGGCTGTGGAG
mCry1	AGGAGGACAGATCCCAATGGA	GCAACCTTCTGGATGCCTTCT
mRev-Erbα	CATGGTGCTACTGTGTAAGGTGTGT	CACAGGCGTGCACTCCATAG
mE4bp4	ACGGACCAGGGAGCAGAAC	GGACTTCAGCCTCTCATCCATC
mClock	GGCGTTGTTGATTGGACTAGG	GAATGGAGTCTCCAACACCCA
mPer2	AGAACGCGGATATGTTTGCTG	ATCTAAGCCGCTGCACACACT
mAvpr1a	CAATGTCCGAGGGAAGACAG	AATGCTCTTCACGCTGCTGAC

Supplementary Table S2. A series of nucleotide sequences for ChIP-QPCR primers

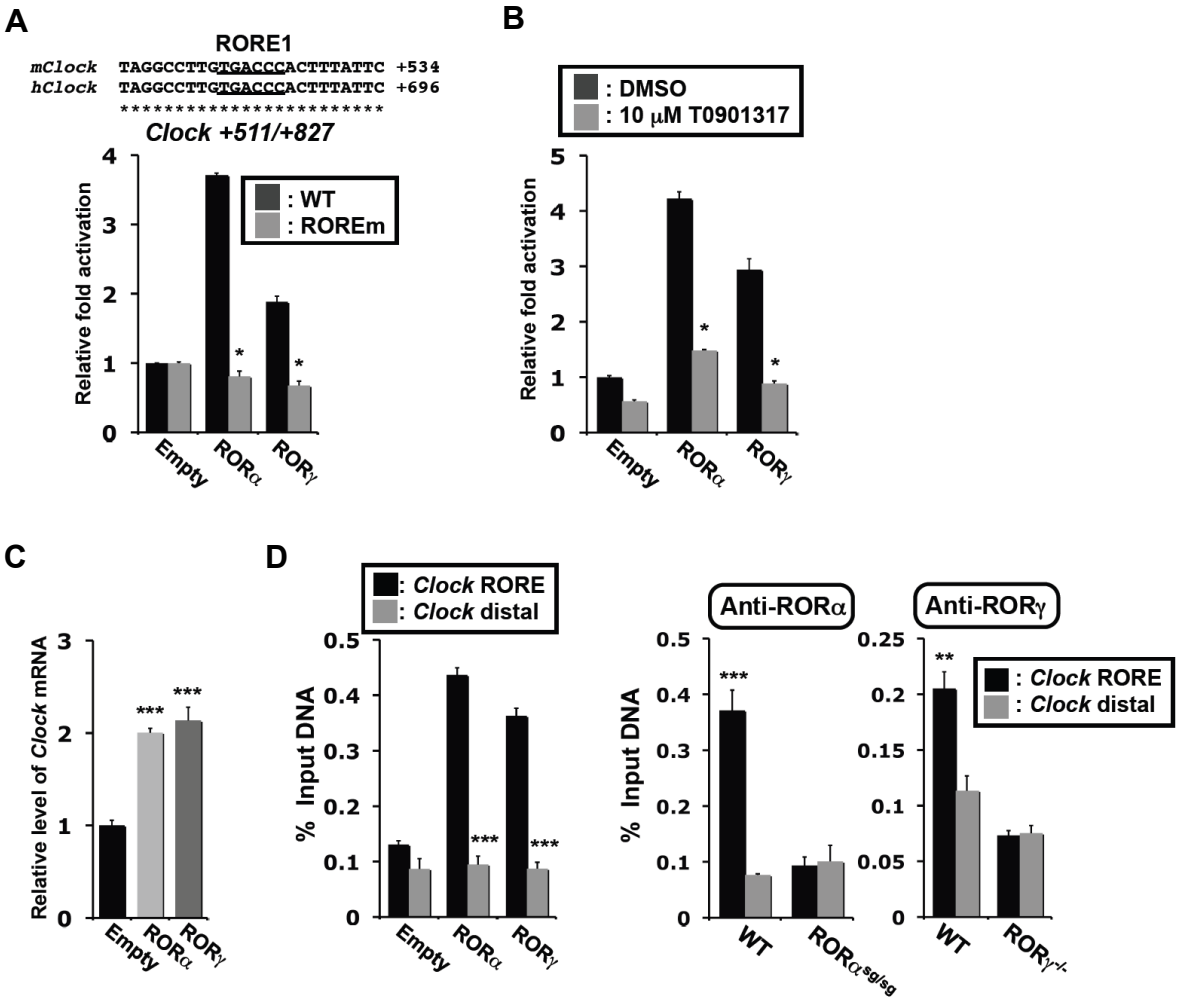
Gene	Sense primer	Antisense primer
mCry1 E-box	GCGAGAACTCAGGTCGTGAG	GCTTCTCATTGGGCGGCATG
mRORγ -1179/-1042	GCTAAGAACGGCTATTCCTCCTAATC	TTCGCTCCCAGCATTCCATTC
mRORγ -160/-70	CAAGGCCTGGCAAAAACTCAG	GACCAGTGTCTGGAGTCTTGAG
mRORγ distal	AAGCACAGAATAGTGCTTGGGTAC	ACCTTCATCTTCTGGCTGGAG
mBmal1 RORE1,2	GGATTGGTCGGAAAGTAGGTTAG	GGTAAACAGGCACCTCCGTC
mCry1 RORE1,2	TCAGTAGCAGTGGGATTATGTTGTATC	GAAGTGGCATAAGGAAGTTACTACATGT
mCry1 RORE3	GATGTGGCTTGTGCCATTCTAAG	CTATGCTAGAGGAAGGGCATCTC
mRev-Erbα-RORE1,2	GTAGACTACAAATCCCAACAATCCTG	TGGAGCAGGTACCATGTGATTC
mE4bp4-RORE1	GCAGTGAGAGATGGCTCATGTG	GAAGTCACTCAGCAGTCCAAAGTC
mGapdh	GTATGACTCCACTCACGGCAAAT	GTCTCGCTCCTGGAAGATGGT
mBmal1 distal	GCCTGCCTCTTGGAGGATG	GGCATCTGGCACTGAGGAG
mCry1 distal	CCAGCCTTGTCTACAGAGTAAGTTC	GAGAACAGAACTACAGAACTAACAACTGTG
mRev-Erbα distal	CATGGTGCTACTGTGTAAGGTGTGT	CACAGGCGTGCACTCCATAG
mE4bp4 distal	GCTGCCCAAGGGACTCACT	GATGGATGAGAGGCTGAAGTCC
mBmal1 +661/+745	CTTGCCTGGTCAACCCTTCTAC	TACGGACTCCCCGACTTGAC
mBmal1 -355/-284	CTCAGCGAGCTTTAGACCTGAG	ACCAATTGGCACGCTCTGTG
mBmal1 3' end	TACAGGGCTGGTTCATCCACTTC	CTAAGCTGGTAGCATGGAAGAAGTC
mClock RORE	TAGGCCTTGTGACCCACTTTATTC	TCCAAACGTGCCCGAGTG
mClock distal	ACAGAGTTCTGATGGTCAGTCACAC	GAATGGAGTCTCCAACACCCA
mClock distal	ACAGAGTTCTGATGGTCAGTCACAC	GAATGGAGTCTCCAACACCCA
mAvpr1a RORE	CGACCTTTGTATTTTCCATCCATC	CACACGCAGAGCAAGATTGAAG



Supplemental Figure 1



Supplemental Figure 2



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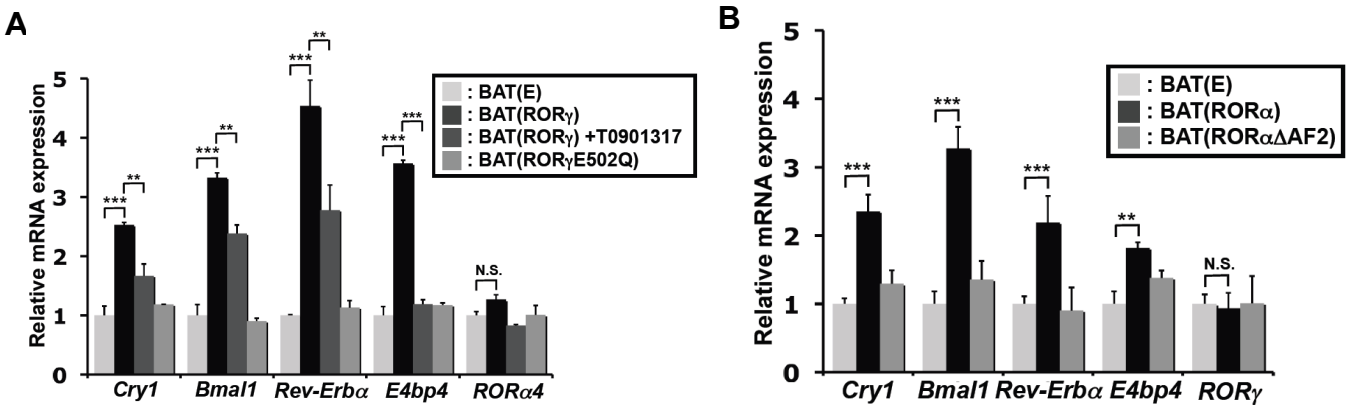
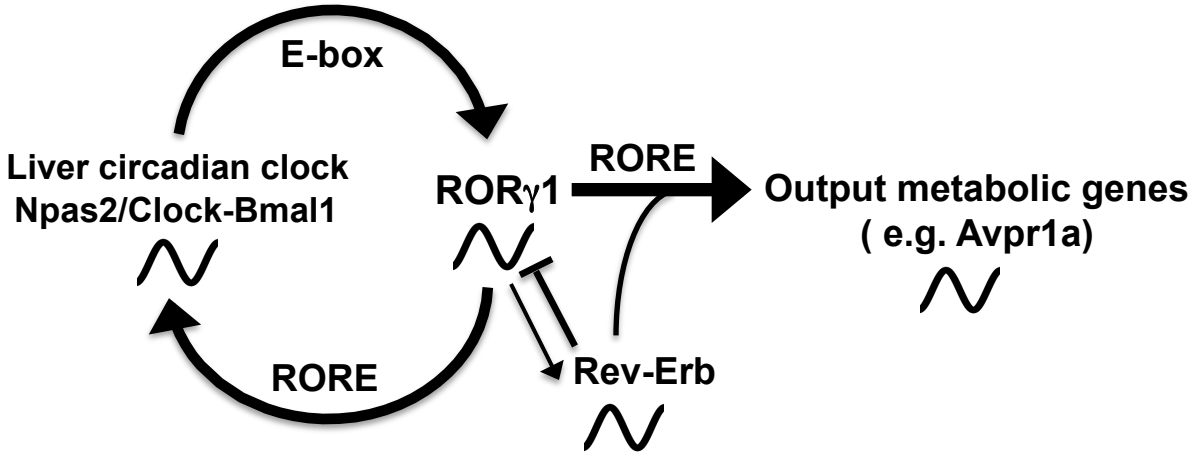


Supplemental Figure 4



Supplemental Figure 5