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The transcriptional repressor Rev-erbα regulates circadian expression of the astrocyte Fabp7 mRNA

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ABSTRACT

The astrocyte brain-type fatty-acid binding protein (Fabp7) circadian gene expression is synchronized in the same temporal phase throughout mammalian brain. Cellular and molecular mechanisms that contribute to this coordinated expression are not completely understood, but likely involve the nuclear receptor Rev-erbα (NR1D1), a transcriptional repressor. We performed ChIP-seq on ventral tegmental area (VTA) and identified gene targets of Rev-erbα, including *Fabp7*. We confirmed that Rev-erbα binds to the *Fabp7* promoter in multiple brain areas, including hippocampus, hypothalamus, and VTA, and showed that *Fabp7* gene expression is upregulated in *Rev-erbα* knock-out mice. Compared to *Fabp7* mRNA levels, *Fabp3* and *Fabp5* mRNA were unaffected by *Rev-erbα* depletion in hippocampus, suggesting that these effects are specific to *Fabp7*. To determine whether these effects of *Rev-erbα* depletion occur broadly throughout the brain, we also evaluated *Fabp* mRNA expression levels in multiple brain areas, including cerebellum, cortex, hypothalamus, striatum, and VTA in *Rev-erbα* knock-out mice. While small but significant changes in *Fabp5* mRNA expression exist in some of these areas, the magnitude of these effects are minimal to that of *Fabp7* mRNA expression, which was over 6-fold across all brain regions. These studies suggest that Rev-erbα is a transcriptional repressor of *Fabp7* gene expression throughout mammalian brain.

1. Introduction

Fatty-acid binding proteins (Fabp) comprise a family of small (~15 kDa) hydrophobic ligand binding carriers with high affinity for long-chain fatty-acids for intracellular transport, and are associated with metabolic, inflammatory, and energy homeostasis pathways (Furuhashi and Hotamisligil, 2008; Storch and Corsico, 2008). These include three that are expressed in the adult mammalian central nervous system (CNS), and are Fabp3 (H-Fabp), Fabp5 (E-Fabp), and Fabp7 (B-Fabp). Fabp3 is primarily expressed in neurons, Fabp5 is expressed in various cell types, including both neurons and glia, and Fabp7 is most abundant in astrocytes and neural progenitors. While performing microarray analysis of transcripts in mouse brain to characterize novel diurnally regulated genes, Fabp7 was identified as a unique transcript elevated in multiple hypothalamic brain regions during the sleep phase (Gerstner et al., 2006). Unlike other circadian regulated gene products, Fabp7 has a synchronized pattern of global diurnal expression in adult murine brain (Gerstner et al., 2006, 2008; Gerstneret al., 2012), is regulated by the core clock gene BMAL1 (Gerstner and Paschos, 2020) and has a general role in governing aspects of sleep behavior in multiple species, including flies, mice, and humans (Gerstneret al., 2017). Fabp7 has been shown to regulate dendritic morphology and excitatory cortical neuron synaptic function (Ebrahimiet al., 2016), as well as locomotor responses to NMDA-receptor activity (Watanabeet al., 2007), and other behavioral conditions including fear memory and anxiety (Owadaet al., 2006). Therefore, Fabp7 may play an important role in regulating time-of-day dependent changes in astrocyte-derived and evolutionarily conserved plasticity-related processes (Lavialleet al., 2011; Nagaiet al., 2020; Gerstner, 2012).

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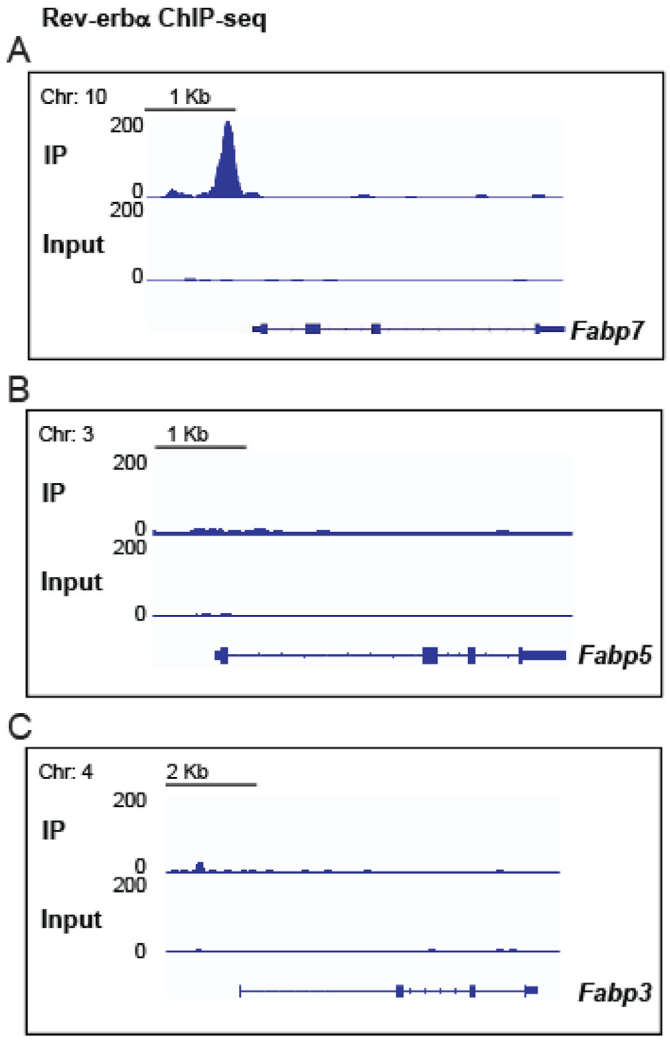

Fig. 1. ChIP-seq binding profile of Rev-erbα around the *Fabp7* locus (A), but not in the *Fabp5* (B) or *Fabp3* (C) loci in the VTA of WT mice.

Table 1
The top 20 Rev-erbα binding site loci, peak score, distance to the translational start site (TSS), and gene names, as identified by Rev-erbα ChIP-seq.

Chromosome	Peak Score	Distance to TSS	Gene Name
chr14	151.18628	506	Nr1d2
chr1	139.22659	−2189	Igsf8
chr11	135.35667	−27206	Hlf
chr7	131.72737	2519	Dbp
chr7	102.16678	−206	Dbp
chr2	102.00463	10184	Cry2
chr11	97.30782	1526	Nr1d1
chr6	95.75218	9516	Bhlhe41
chr3	94.62258	−69	Ciart
chr6	81.56895	−1171	Bhlhe40
chr6	80.73732	83133	Lsm3
chr2	76.52149	401	Aven
chr11	76.4099	−4068	Per1
chr10	**74.53577**	**−153**	**Fabp7**
chr15	71.89268	−459	Tef
chr9	67.80914	−112	Nptn
chr1	62.37303	−197	Coq10b
chr16	61.30798	−793	Ubald1
chr7	60.32358	37	Arntl
chr15	59.34713	45290	Nfam1

Here we were interested in validating findings that *Fabp7* is a target of Rev-erbα (Schnellet al., 2014) and determining whether *Fabp7* mRNA is regulated by Rev-erbα across multiple brain areas. We also wanted to examine whether these effects are specific to *Fabp7*, or whether other Fabps expressed in the CNS are similarly affected.

2. Results

Since the time-of-day profile of *Fabp7* mRNA expression is abolished in BMAL1 KO mice (Gerstner and Paschos, 2020), we performed bioinformatic analysis to locate core canonical E-box elements (CACGTG) within the *Fabp7* promoter. We did not detect any canonical E-box elements, so we considered whether other cis-acting elements influenced by circadian output in the *Fabp7* promoter exist. Analysis of the promoter for *Fabp7* gene revealed several sites known to be involved in the metabolic arm of the clock (Choet al., 2012; Buggeet al., 2012; Zhanget al., 2015), including multiple sites for the transcriptional co-repressor nuclear receptor Rev-erbα (NR1D1), termed Rev-erbα response elements (RORE) (Table S1).

To determine whether these RORE sites were functional, we performed chromatin immunoprecipitation experiments followed by DNA-sequencing (ChIP-seq) on tissue from the ventral tegmental area (VTA), a brain region known to regulate motivational/reward behaviors (Morales and Margolis, 2017; Russo and Nestler, 2013), wakefulness, and sleep (Takataet al., 2018; Yuet al., 2019; Eban-Rothschild et al., 2016). Here we identified positive Rev-erbα interactions within the first kilobase upstream of the transcription start site of the *Fabp7* promoter, but not in the *Fabp3* or *Fabp5* promoters (Fig. 1A–C). The top 20 Rev-erbα binding site loci, peak score, distance to the translational start site and gene names are listed in Table 1. Gene Ontology (GO) analysis revealed significant enrichment of several biological processes, molecular functions, and cellular components (Table 2) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis shows the top 20 pathways in Rev-erbα ChIP-seq genes (Fig. 2). The complete list of Rev-erbα ChIP-seq genes is provided in [SUPPLEMENTAL dataset 1].

To confirm that Rev-erbα binds the *Fabp7* promoter in multiple brain regions, we compared Rev-erbα binding in the *Fabp7* promoter against the negative control *insulin*, and the positive control *NPAS2* in WT and Rev-erbα KO mice. We observed Rev-erbα binding to the *Fabp7* and *NPAS2* promoters in WT, but not Rev-erbα KO mice, in both hippocampus (Fig. 3A) and hypothalamus (Fig. 3B). Binding of Rev-erbα was not observed for *insulin*, regardless of genotype (Fig. 3A and B). Since BMAL1 is known to transactivate Rev-erbα (Mohawk et al., 2012; Albrecht, 2012), a transcriptional repressor, BMAL1 could influence *Fabp7* gene expression (Gerstner and Paschos, 2020) indirectly through Rev-erbα.

To test the hypothesis that Rev-erbα represses *Fabp7* gene expression, we examined the diurnal profile of *Fabp7* mRNA in Rev-erbα KO mice. If *Fabp7* expression is repressed by Rev-erbα, this predicts that *Fabp7* mRNA should be elevated in the Rev-erbα KO. We confirmed that *Fabp7* mRNA is elevated in hippocampus of Rev-erbα KO mice, while *Fabp3* and *Fabp5* mRNA levels are not affected (Fig. 4A–C). To determine whether time-of-day mRNA levels are affected by Rev-erbα, we analyzed the normalized mRNA expression for *Fabp3*, *Fabp5*, and *Fabp7* from six time-points over 24h of Rev-erbα KO and WT mice. While *Fabp3* (Fig. 4D) and *Fabp5* (Fig. 4E) mRNA do not oscillate in WT mice and remain unaffected in Rev-erbα KOs, the *Fabp7* mRNA circadian oscillation is disrupted in the Rev-erbα KO compared to WT hippocampus (Fig. 4F). Since *Fabp7* expression is diurnally regulated throughout murine brain (Gerstner et al., 2006; Gerstner, 2008; Gerstneret al., 2012), we wanted to determine if *Fabp7* mRNA levels were regulated by Rev-erbα broadly in multiple brain regions. Analysis of multiple brain regions including striatum, VTA, cerebellum, hippocampus, hypothalamus, and cortex of Rev-erbα KO compared to WT mice revealed analogous increases in *Fabp7* mRNA levels (~6–15 fold), but not *Fabp3* or *Fabp5* mRNA levels (Fig. 5).

Table 2
Analysis of Gene Ontology in Rev-erbα ChIP-seq genes. Highest fold enriched Gene Ontology classes for Biological Process, Molecular Function and Cellular Component are listed with most highly enriched on top.

PANTHER GO-Slim Biological Process	Number of Genes	Fold Enrichment	Raw P-value	FDR
circadian regulation of gene expression	11	10.65	0.000000207	0.00000705
neg. reg. of transforming growth factor beta receptor signaling pathway	4	10.33	0.0021	0.0312
regulation of circadian rhythm	4	8.85	0.00314	0.0448
chondroitin sulfate proteoglycan biosynthetic process	5	6.46	0.00272	0.0393
protein demethylation	5	6.46	0.00272	0.0391
protein autophosphorylation	10	3.87	0.000719	0.0118
regulation of actin filament organization	15	2.8	0.000803	0.013
response to abiotic stimulus	16	2.75	0.000638	0.0106
positive regulation of transcription by RNA polymerase II	38	2.52	0.00000206	0.0000599
regulation of cellular component size	17	2.42	0.00196	0.0295
positive reg. of nucleobase-containing compound metabolic process	54	2.34	9.73E-08	0.00000342
PANTHER GO-Slim Molecular Function				
demethylase activity	9	5.17	0.000228	0.00452
flavin adenine dinucleotide binding	10	4.56	0.000242	0.00463
transcription coregulator activity	40	3.04	8.74E-09	0.000000606
phosphoprotein phosphatase activity	19	2.21	0.00295	0.0409
small molecule binding	44	1.76	0.000706	0.0112
protein kinase activity	51	1.62	0.00177	0.0266
PANTHER GO-Slim Cellular Component				
vacuolar membrane	13	2.76	0.00196	0.0344
Golgi membrane	14	2.55	0.00255	0.0418
transcription regulator complex	31	2.54	0.0000114	0.000386
neuron projection	42	1.72	0.00181	0.0328
transferase complex	50	1.69	0.000921	0.0187
bounding membrane of organelle	43	1.66	0.00248	0.0421
nucleoplasm	54	1.65	0.000836	0.0185
chromatin	67	1.56	0.000896	0.019

Together, these data suggest that the circadian clock control of Fabp7 mRNA expression requires Rev-erbα broadly across many brain regions.

3. Discussion

The astrocyte *Fabp7* gene expression is known to cycle in a synchronized fashion throughout the mammalian CNS (Gerstner et al., 2006; Gerstner, 2008; Gerstneret al., 2012; Schnellet al., 2014). Previous studies have shown *Fabp7* circadian gene expression is under control of the core clock transcription factor BMAL1 (Gerstner and Paschos, 2020), however the *Fabp7* promoter lacks a canonical E-box element, suggesting that BMAL1 may indirectly exert its effects on *Fabp7* circadian expression via Rev-erbα, a transcriptional repressor, and known BMAL1 target (Guillaumond et al., 2005). Here we provide evidence that *Fabp7*

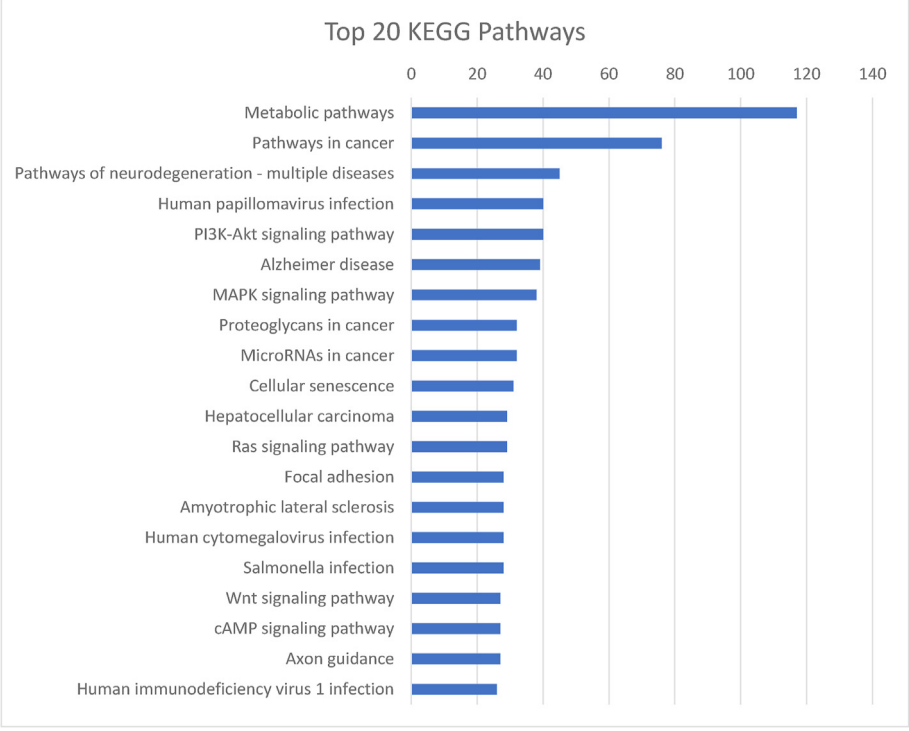

Fig. 2. Analysis of the top 20 KEGG pathways enriched in Rev-erb ChIP-seq genes plotted with number of hits per pathway.

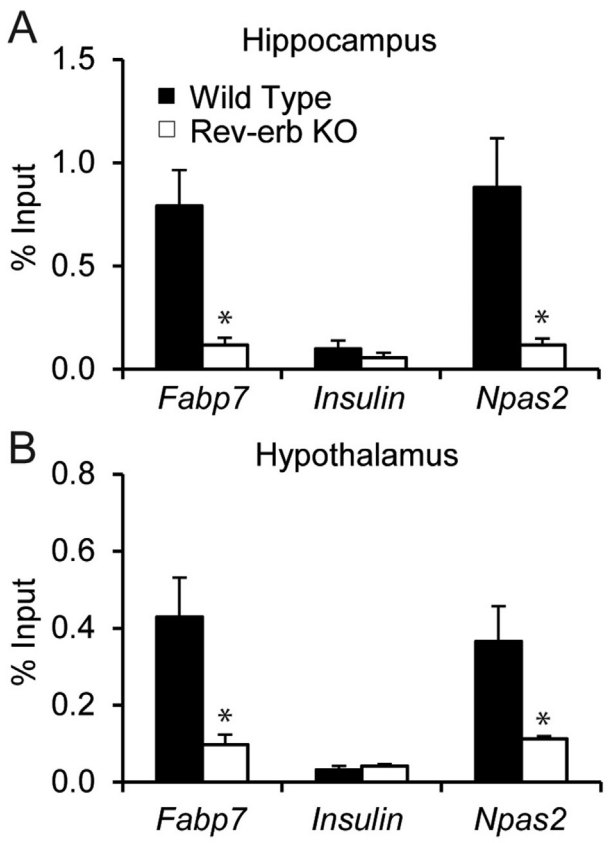

Fig. 3. ChIP-qPCR measurements of Rev-erbα relative occupancy at *Fabp7* locus, *Insulin* locus (negative control) and *Npas2* locus (positive control) in hippocampus (A) and hypothalamus (B) of WT and Rev-erbα KO mice. Data are expressed as the percent of input and are the mean ± SEM. (Student's *t*-test, *p < 0.05, n = 3 per group).

contains canonical ROREs and that Rev-erbα binds to the RORE regions in the *Fabp7* gene locus in the VTA (Fig. 1A). The current study validates a previous report that also showed Rev-erbα binding to *Fabp7* in the hippocampus (Schnellet al., 2014) (Fig. 3A), and extends these findings to show this also occurs in the hypothalamus (Fig. 3B). Taken together, these results suggest that the coordinated and synchronized expression of Fabp7 transcription is controlled by Rev-erbα direct binding in multiple brain regions throughout mammalian brain.

Rev-erbα KO mice showed a greater than 6-fold increase in *Fabp7* mRNA expression across multiple brain areas, including cerebellum, cortex, hippocampus, hypothalamus, striatum, and VTA, compared to WT mice. We also observed minimal, but significant, reduction in *Fabp5* mRNA in a few brain areas (cerebellum, hypothalamus, and VTA; Fig. 5) and no differences in *Fabp3* mRNA in any brain region, in Rev-erbα KO compared to WT mice. These reductions in *Fabp5* mRNA may represent compensatory mechanisms that are in response to the large increases in *Fabp7* mRNA expression in glial cells, however, to rule out a direct role of Rev-erbα in transcriptional regulation of these other Fabp types throughout brain, binding assays for Rev-erbα at their respective genetic loci across multiple brain regions would be required. Recently, local oscillators have been discovered in multiple brain regions throughout the mammalian brain (Paulet al., 2019), therefore it will be important to determine the extent to which *Fabp7* oscillations require 'global' vs. 'local' coordinated control. Stability of Rev-erbα and the role of degradation processes that control the protein half-life in downstream signaling may also contribute to alterations in periodicity of gene expression (DeBruyne et al., 2015). Future studies determining the cell-type specificity of these observations are also needed to better understand lipid-mediated signaling cascades (Gooley and Chua, 2014; Gooley, 2016) downstream of circadian- and metabolically (Buggeet al., 2012; Kumar Jha et al., 2015; Bass and Takahashi, 2010; Eckel-Mahan and Sassone-Corsi, 2013) driven changes in Rev-erbα expression both within and between neurons and glia.

Understanding the molecular and cellular components that regulate *Fabp7* expression will have important implications for public health. For example, pathological states associated with *Fabp7* overexpression exist for a variety of diseases, including multiple types of cancer (Zhouet al., 2015; Liuet al., 2012; Mita et al., 2010; Corderoet al., 2019; Kagawaet al., 2019; Maet al., 2018), and neurodegenerative disease, including Alzheimer's disease (Teunissenet al., 2011; Johnsonet al., 2018). Given the role of the circadian clock in cancer (Masri and Sassone-Corsi, 2018; Sulli et al., 2018, 2019) and neurodegeneration (Musiek and Holtzman, 2016; Hood and Amir, 2017; Lanannaet al., 2020), future studies determining the role in how circadian *Fabp7* and *Fabp7* lipid-signaling may feedback onto metabolic (Choet al., 2012; Bass and Takahashi, 2010; Panda, 2016) and inflammatory pathways (Carteret al., 2016; Scheiermann et al., 2013; Castanon-Cervanteset al., 2010) may provide novel links between clock-regulated mechanisms, fatty-acid pathways, and disease.

4. Materials and methods

Animals. The *Rev-erbα* knock out (KO) mice were obtained from B. Vennström and were backcrossed for >7 generations with C57/Bl6 mice. Mice (N = 3–7 per group) were housed under standard 12h-light/12h-dark (LD) cycles and were sacrificed at specific times (zeitgeber time (ZT) 2, 6, 10, 14, 18, 22 with ZT0 corresponding to 7 a.m.). Animal care and use procedures followed the guidelines of the Institutional Animal Care and Use Committee of the University of Pennsylvania in accordance with the guidelines of the US National Institutes of Health.

Chromatin immunoprecipitation (ChIP). ChIP experiments were performed as previously described (Fenget al., 2011) with minor changes. Mouse brain tissue was harvested at ZT10, minced and cross-linked in 1% formaldehyde for 20min, followed by quenching with 1/20 volume of 2.5M glycine solution for 5 min, and then two washes with PBS. Cell lysates with fragmented chromatin were prepared by probe sonication in ChIP dilution buffer (50 mM HEPES, 155 mM NaCl, 1.1% Triton X-100, 0.11% sodium deoxycholate, 0.1% SDS, 1 mM phenylmethylsulfonyl fluoride [PMSF], and a complete protease inhibitor tablet [pH 7.5]). Proteins were immunoprecipitated in ChIP dilution buffer, using 1 μg of Rev-erbα antibody (Cell signaling). Cross-linking was reversed overnight at 65 °C in elution buffer (50 mM Tris-HCL, 10 mM EDTA, 1% SDS, pH8), and DNA isolated using phenol/-chloroform/isoamyl alcohol. Precipitated DNA was analyzed by quantitative PCR or high-throughput sequencing.

ChIP-qPCR. Precipitated DNA was analyzed by quantitative PCR, using the following primers: Fabp7, forward: 5′-GGG GAT CAG GAT TGT GAT GT-3'; Fabp7, reverse: 5′-AGA TGG CTC CAA TCC TCC TT-3'; Arbp, forward: 5′- CTG GGA CGA TGA ATG AGG AT-3'; Arbp, reverse: 5′- AGC AGC TGG CAC CTA AAC AG-3'; Npas2, forward: 5′-TTG CAG AAG CTT GGG AAA AG-3'; Npas2, reverse: 5′-TTT CCT GTG GGA GGA GAC AG-3'.

ChIP-seq and cistromic analysis. For ChIP-seq, material from three mice was pooled prior to library generation. ChIP DNA was prepared for sequencing according to the amplification protocol provided by Illumina, using adaptor oligo and primers from Illumina, enzymes from New England Biolabs and PCR Purification Kit and MinElute Kit from Qiagen. Deep sequencing was performed by the Functional Genomics Core (J. Schug and K. Kaestner) of the Penn Diabetes Endocrinology Research Center using the Illumina HiSeq2000, and sequences were obtained using the Solexa Analysis Pipeline. Sequenced reads were aligned to the mouse

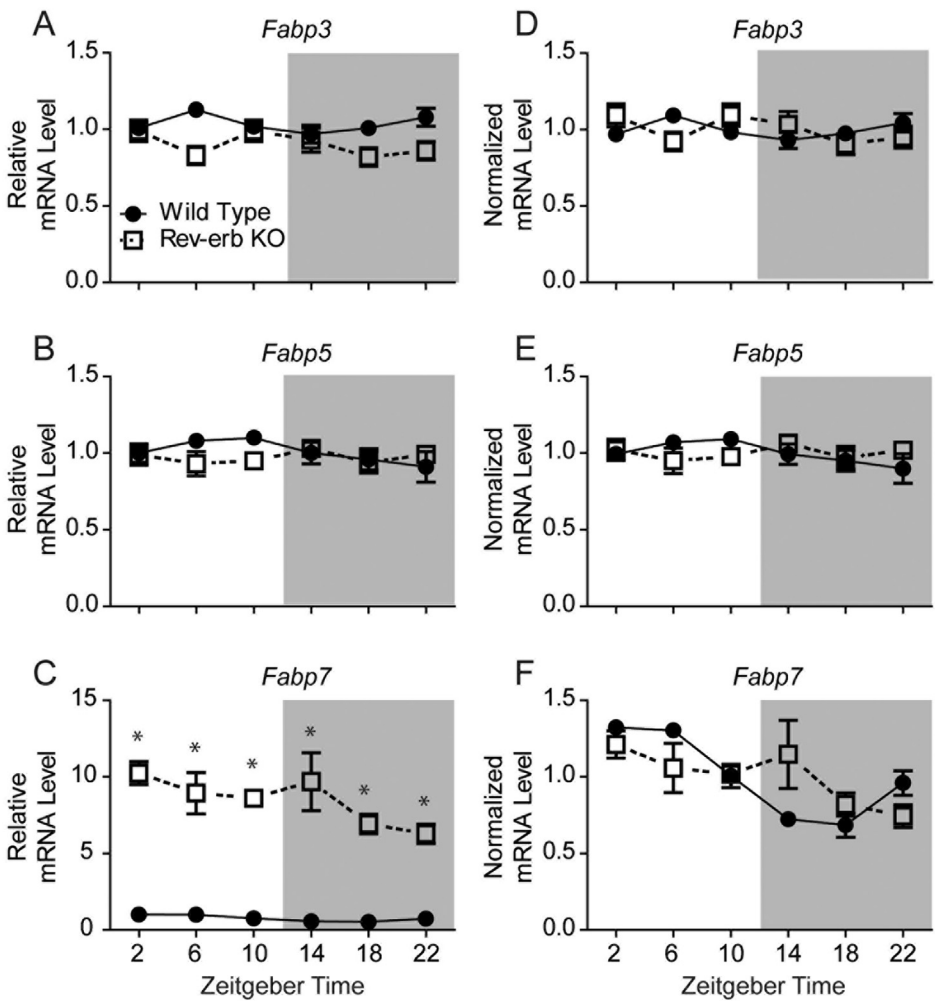

Fig. 4. A–C: Relative hippocampal mRNA expression of various Fabps in Rev-erbα KO vs. WT mice under normal (LD) conditions. Levels of *Fabp3* (A) or *Fabp5*. (B) are unaffected by Rev-erbα deficiency, however, *Fabp7* shows a significant increase in expression based on genotype. *$p < 0.001$, N = 4–7 per group, Student's t-test. ZT = zeitgeber time. Hippocampal mRNA expression normalized to genotype to visualize the circadian rhythmicity of *Fabp3* (D), *Fabp5* (E), and *Fabp7* (F). *Fabp7* circadian rhythmicity was significantly disrupted in Rev-erba KO mice (adj. p = 0.184; JTK_Cycle) compared to WT mice (adj. $p < 0.001$; JTK_Cycle).

reference genome (mm9) and peak calling was performed with HOMER (Heinzet al., 2010). ChIP-seq data are deposited in NCBI GEO GSE67973 (Zhang et al., 2015), for GSM1659684 and GSM1659685 datasets.

4.1. MEME package

Analysis of the Fabp7 promoter was done using the MEME package (http://meme.nbcr.net/meme/). 2000 base pairs upstream and 2000 base pairs downstream of the murine Fabp7 transcription start site (TSS) was used for promoter analysis. Reference to site location of cis-elements were expressed 0–4000, with 2000 being at the TSS.

4.2. GO and KEGG analysis

Gene ontology analysis was performed on the ranked list of Rev-erbα ChIP-seq genes with peak score >2 [SUPPLEMENTAL dataset 1], using Panther GO-Slim against the mouse gene list (http://geneontology.org release 2021-01-01: 44,091; (Ashburneret al., 2000; The Gene Ontology resourc, 2021). Top non-redundant categories are presented.

KEGG pathway analysis was performed on the same gene list using KEGG Mapper https://www.genome.jp/kegg/tool/map_pathway1.html (Kanehisa and Sato, 2020) against mouse pathways.

4.3. qPCR

Total RNA was extracted from tissue using the RNeasy Mini Kit (QIAGEN) and treated with DNase (QIAGEN). The RNA was reversed transcribed using the High-Capacity cDNA Reverse Transcription kit (Applied Biosystems) and analyzed by quantitative PCR. Quantitative PCR was performed with Power SYBR Green PCR Mastermix on the PRISM 7500 (Applied Biosystems). Gene expression was normalized to mRNA levels of housekeeping gene 36B4 and the level of the gene of interest in the control samples. Circadian oscillations in gene expression were calculated using JTK_cyclev3.1 scripts (Hughes et al., 2010) run on R. Amplitude confidence intervals were calculated according to Miyazaki et al. (2011).

4.4. Primers

36B4 Forward TCC-AGG-CTT-TGG-GCA-TCA.
36B4 Reverse CTT-TAT-CAG-CTG-CAC-ATC-ACT-CAG-A
Fabp3 Forward CTG-ACT-CTC-ACT-CAT-GGC-AGT-GT
Fabp3 Reverse GCC-AGG-TCA-CGC-CTC-CTT
Fabp5 Forward CGA-CAG-CTG-ATG-GCA-GAA-AAA
Fabp5 Reverse GAC-CAG-GGC-ACC-GTC-TTG
Fabp7 Forward CTC-TGG-GCG-TGG-GCT-TT
Fabp7 Reverse TTC-CTG-ACT-GAT-AAT-CAC-AGT-TGG-TT

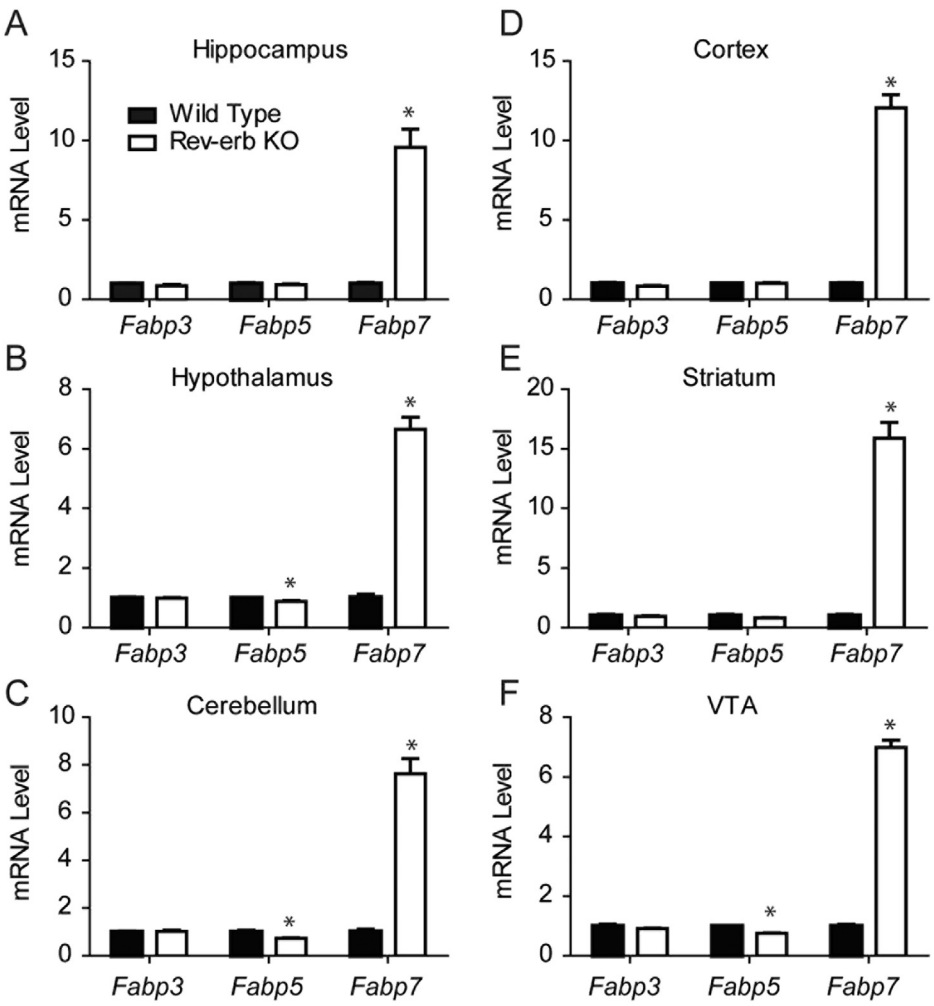

Fig. 5. A–F: Relative mRNA expression from various brain regions of Fabps in Rev-erbα KO vs. WT mice. Levels of *Fabp3* mRNA are not affected by loss of Rev-erbα, while lower levels of *Fabp5* mRNA are observed in Hypothalamus (B), Cerebellum (C), and VTA (F) based on Rev-erbα deficiency compared to WT. *Fabp7* mRNA, however, shows significant increases in expression in Rev-erbα KO compared to WT in all brain regions studied. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, N = 3–5 per group, Student's t-test.

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CRediT author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Peer Review Overview and Supplementary data

A Peer Review Overview and (sometimes) Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.crneur.2021.100009.

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