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REVIEW MEDICAL BIOCHEMISTRY

Nuclear receptor protein: REV-ERB

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ABSTRACT

REV-ERB α/β proteins play critical roles in circadian rhythm regulation and are considered to be specialized members of the nuclear receptor family. These so-called "orphan" proteins, whose endogenous ligands were initially unidentified, have become exogenously interferable through synthetic agents with the discovery of their endogenous ligands. This feature has made them an important target for clinical research in recent years. Unlike other nuclear receptors, the unique structure of REV-ERB proteins allows them to perform only transcription inhibition, which makes them even more intriguing. This review summarizes the structural features of REV-ERB α/β proteins and their role in the circadian cycle. We also discuss findings in the literature on the function of REV-ERB α/β proteins in the metabolic and immune systems, emphasizing their importance in these systems.

Keywords: Circadian rhythm; nuclear receptors; orphan receptors; REV-ERB α/β.

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Nuclear receptors, constituting a vast superfamily of transcription factors, are pivotal in a range of physiological processes, including embryonic development, organ physiology, cellular differentiation, and maintaining homeostasis [1, 2]. Their importance extends to the pathological domain, where they are associated with diseases such as cancer, diabetes, rheumatoid arthritis, asthma, and hormone-resistance syndromes. This group, comprising 48 members, includes both ligand-regulated and orphan proteins integral to human physiology and pathophysiology [3]. Notable among transcription factors, nuclear receptors have the capability to bind specifically to DNA-regulatory elements, functioning as regulators of transcription that are specific to both cell type and promoter.

The structural intricacy of Nuclear Receptor Proteins (NRPs) highlights their multifaceted functions. These proteins are structured with several distinct parts: a varying N-terminal domain, a domain for DNA binding, a connecting hinge region, a universally consistent ligand-binding domain, and a varying C-terminal domain. The ligand-binding domain is particularly vital for the unique functions of NRPs, distinguished by its uniform structure yet capable of interacting with a wide array of specific ligands. This interaction is not just a simple connection but is central to how NRPs regulate cellular reactions to hormonal signals. NRPs are also skilled in complex molecular interactions involving repressors, such as NCoR and SMRT, and activators, including CBP and p300, which significantly impact the transcription process [4].

Among this diverse family of proteins, the REV-ERB α/β proteins emerge as key figures, especially noted for their regulatory roles in circadian rhythms – those intrinsic time-keeping mechanisms that govern many biological functions. The intricate dance of these rhythms influences various facets of brain functionality, from neurotransmitter dynamics to the subtleties of aging, learning, memory, and mood regulation. The role of REV-ERB α/β as nuclear receptors underscores their potential for external modulation, an attribute that renders them tantalizing targets for pharmacological interventions aimed at circadian rhythm regulation [5].

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Furthermore, the REV-ERB α/β proteins play a crucial role in metabolism, particularly in regulating lipid metabolism. Evidence of this is seen in the altered lipid profiles of REV-ERB α-deficient mice. These mice display signs of dyslipidemia and elevated levels of VLDL triglycerides [6]. These proteins are also critical regulators of hepatic glucose metabolism, directly influencing genes associated with gluconeogenesis. This regulatory action has significant effects on plasma glucose levels [7]. Their role is not confined to these aspects alone; their involvement in skeletal muscle function and adipogenesis further highlights their significance [8, 9]. The complex interplay of REV-ERB proteins within these metabolic pathways, dovetailed with their role in circadian rhythm regulation, underscores their potential as novel pharmacological targets in managing metabolic disorders like obesity, type 2 diabetes, and atherosclerosis [10].

This review aims to delve into the multifaceted roles of REV-ERB α/β proteins, illuminating their significance in cellular and physiological contexts and exploring the potential implications of their modulation in health and disease.

Molecular Structure and Function of REV-ERBs

The story of REV-ERB began with the discovery of the ear-2 and ear-3 genes by the Yamamoto group in the 1980s, which were found to encode proteins that bear a striking resemblance to steroid and T3 (thyroid hormone) receptors [5]. In similar years, Lazar and colleagues identified a protein weighing 56 kDa. This protein was named REV-ERB α and was recognized as a new member of the thyroid and steroid hormone receptor family [6].

REV-ERB, belonging to the nuclear receptor family, comprises two similar proteins: REV-ERB α and REV-ERB β [6, 11]. The term "REV-ERB" originates from "reverse-ERB," as the Nr1d1 gene encodes REV-ERB α is antisense to the ERB α proto-oncogene gene. The Nr1d2 gene encodes the REV-ERB β isoform [6]. Both RBα and REV-ERB β have a DNA Binding Domain (DBD) with nearly identical structures, enabling specific DNA region attachment. Additionally, they share 71% of the amino acids in their Ligand Binding Domain (LBD). Their tissue expression patterns are also strikingly similar [12]. In experiments with mice lacking REV-ERB α, it was noted that REV-ERB β compensated for its absence in some tissues. Unique to nuclear receptors, REV-ERB α/β binds to specific genomic regions through two zinc fingers. However, unlike most nuclear receptors,

Highlight key points

- REV-ERB α/β, nuclear receptors, function as transcriptional repressors within the core circadian clock.
- REV-ERB links the circadian clock to immunity by modulating inflammatory signaling (e.g., via TLR4, NLRP3), neuroinflammation, and autoimmune-related TH17 pathways.
- REV-ERB integrates circadian timing with systemic metabolism through regulation of key processes in the liver, adipose tissue, skeletal muscle, and pancreas.
- As transcriptional repressors binding heme, REV-ERB α/β represent promising therapeutic targets, but strategies must carefully consider their complex, tissue-specific actions.

REV-ERBs do not have the carboxy-terminal activation function 2 (AF2) domain at the LBD's C-terminal end. This AF2 domain typically facilitates transcriptional activation by recognizing coactivator protein patterns. Consequently, the lack of AF2 implies that REV-ERBs function as transcriptional repressors, binding to the RORE sequence via their DNA-binding domain [13, 14]. This binding triggers interaction with the nuclear receptor corepressor (NCOR1) protein, which then activates histone deacetylase 3 (HDAC3) enzymes. These enzymes lead to chromatin condensation and transcription repression through a deacetylation reaction [4, 15].

REV-ERB Ligands

Within the human body, there are 48 unique nuclear receptors, each equipped with a DNA binding domain (DBD) for interacting with the genome and a ligand binding domain (LBD) for ligand attachment [16]. Notably, REV-ERB is a member of the steroid/thyroid hormone receptor superfamily. Initially, it was categorized as an orphan receptor due to the unknown nature of its endogenous ligand [17]. The breakthrough in understanding REV-ERB's natural ligand came from research on the fruit fly Drosophila, which identified the heme (an oxygen-binding molecule) molecule as an activator for the fly's E75 ortholog, a protein sharing structural similarities [18]. The following studies confirmed that heme also binds to mammalian REV-ERB, leading to the inhibition of BMAL1 and the recruitment of the nuclear receptor coactivator NCoR [19]. Structural examination revealed that REV-ERB's heme (an oxygen-binding molecule) binding site is comparable to those in other nuclear receptors, indicating the potential for synthetic ligands to influence REV-ERB's activity [20]. The discovery of the first synthetic ligand for REV-ERB, GSK4112, was

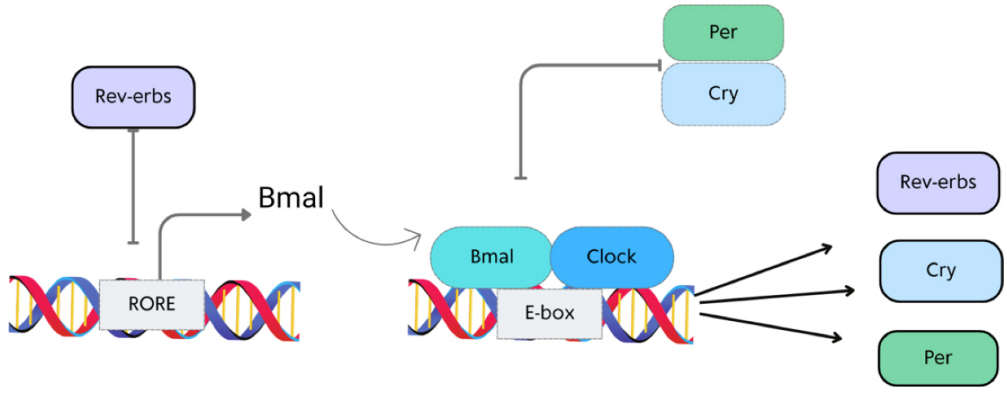

FIGURE 1. Circadian rhythm regulatory mechanism.

made possible through a biochemical screening method that employed fluorescence resonance energy transfer (FRET) technology. This seminal development created more bioavailable agonists targeting REV-ERB, with notable examples being compounds like SR9009 and SR9011 [4, 21]. Additionally, SR8278 was engineered as a specific antagonist for REV-ERB receptors [22].

Circadian Rhythm

The circadian rhythm, derived from the Latin words "circa" (meaning about) and "diem" (day), is a fundamental aspect of the biological clock system inherent to organisms. This internal biological timer, prevalent across almost all life forms, including humans, is pivotal for anticipating and adapting to daily environmental changes. Such a clock enables organisms to fine-tune their physiological and behavioral responses in anticipation of the diurnal cycle's demands [7, 8].

Historically, medical luminaries like Hippocrates and Galen recognized the 24-hour rhythm associated with febrile conditions. This rhythmic pattern, evident in plants and animals and persisting on a roughly 24-hour cycle, was long acknowledged as a natural phenomenon. However, Jean Jacques d'Ortous de Mairan (1729) challenged this perception by demonstrating plant rhythmicity in a controlled, dark environment, thereby hinting at an intrinsic biological mechanism.

The discovery of the "Period" gene and its role in circadian rhythms, which garnered the Nobel Prize in Physiology or Medicine in 2017 for Jeffrey C. Hall, Michael Rosbash, and Michael W. Young, is a landmark in biological and medical research. This gene, vital for the normal daily biological rhythm, was first isolated using fruit flies. It encodes a protein, PER, that accumulates at night and degrades during the day [23–26]. This discovery revealed the intricate mechanisms of our internal biological clock, showing how it synchronizes with Earth's revolutions and regulates critical functions like behavior, hormone levels, sleep, body temperature, and metabolism.

The circadian rhythm is a clock-like mechanism in nearly all body cells. Each cell acts as a basic unit of circadian timing, with gene expression oscillations being the primary driver of rhythmicity. While many of these rhythmically expressed genes are tissue-specific, a shared clock mechanism exists at the cellular level, primarily operating through interconnected molecular loops where "clock" genes inhibit their protein products [26].

In the circadian systems of mammals, core clock genes display rhythmic patterns driven by a well-conserved biological process involving autonomous transcriptional-translational feedback loops. This autonomous system consists of interconnected negative feedback loops at the cellular level. Central elements of this system are BMAL1 (Brain and muscle ARNT-like protein 1) along with either CLOCK (Circadian locomotor output cycles caput) or NPAS2 (Neuronal PAS domain-containing protein 2) (Fig. 1). These components control the expression of the Period (PER) and Cryptochrome (CRY) genes. Subsequently, the PER and CRY proteins counteract the activity of the BMAL1/CLOCK transcription factors, culminating in cyclical variations in protein expression levels [10, 27].

The CLOCK-BMAL1 complex plays a significant role in initiating the transcription of REV-ERB α/β, leading to an increase in REV-ERB α protein levels, which subsequently results in the inhibition of BMAL1 transcription (Fig. 1). This mechanism is intricately linked to the pivotal role of REV-ERB α and β, members of the nuclear receptor family, in regulating circa-

dian rhythms and metabolic processes. Upon binding to DNA, REV-ERB α/β promotes the recruitment of nuclear receptor corepressor 1 (NCOR1), initiating a cascade that suppresses gene expression. This recruitment enhances the localization and functionality of REV-ERB at the promoter regions of target genes, setting off transcriptional repression. Following this, the complex attracts histone deacetylase 3 (HDAC3), an enzyme that removes acetyl groups from histone proteins, leading to chromatin condensation and further inhibition of gene expression. The interplay between the CLOCK-BMAL1 complex, REV-ERB α/β, NCOR1, and HDAC3 is instrumental in modulating cellular functions, particularly regulating circadian and metabolic pathways [28, 29]. REV-ERB expression peaks during the day (ZT 6–12), repressing gene expression at complex RORE sites [30]. Conversely, at night (ZT 18 to 24), when REV-ERB expression is lower, ROR proteins bind to RORE sites and promote the transcription of numerous genes by histone acetylation [30].

In studies utilizing mouse models, it has been observed that the expression levels of REV-ERB α mRNA demonstrate significant circadian variations across a range of tissues [31]. While the sole deficiency of REV-ERB α does not induce arrhythmic behaviors, the concurrent absence of both REV-ERB α and β leads to the onset of arrhythmia [31–33]. Moreover, the deliberate removal of REV-ERB α in these models is associated with a reduction in the duration of behavioral rhythms by about 30 minutes under circumstances lacking daily light cues [31]. This underscores the nuanced role of REV-ERB α in the regulation of circadian rhythms, particularly in environments without natural light indicators. These results highlight the complex mechanisms underlying circadian regulation and emphasize the critical importance of REV-ERB α/β in this process.

REV-ERB: Immune Responses

The research on REV-ERB underscores its critical role in the immune system, emphasizing the intersections between circadian rhythms, inflammation, and autoimmune diseases. The interplay between REV-ERB and TLR4, a crucial immune receptor, is a focal point of interest. One study reveals how REV-ERB suppresses TLR4, thereby dampening the inflammatory response [10]. Conversely, another study notes that REV-ERB dysfunction increases TLR4 expression, which could intensify inflammation [34]. NR1D1 regulates the expression and activity of the NLRP3 inflammasome complex according to circadian rhythms. Nr1d1 deficiency leads to increased production of IL1B and IL18 in mice, resulting in more severe acute peritonitis and hepatitis [35]. These findings collectively point to a critical circadian control of immune responses mediated by REV-ERB, offering insight into managing various inflammatory conditions.

Numerous investigations have highlighted the crucial role of REV-ERB proteins in neuroinflammation, particularly within the brain. In experiments with mice lacking REV-ERB α (REV-ERB α−/− knockout mice), there has been an observed increase in microglial activation and neuroinflammation in the hippocampus. This neuroinflammation was further exacerbated following lipopolysaccharide (LPS) injection. In contrast, stimulating REV-ERB α has been shown to reduce LPS-induced neuroinflammation. Additionally, research has shown that the absence of REV-ERB α eliminates the daily variations in microglia, potentially resulting in a continuous state of enhanced phagocytosis [36].

Furthermore, REV-ERB's involvement in autoimmune diseases is evident through its regulation of TH17 cells. A study shows that deletion of REV-ERB leads to increased IL17 expression and exacerbates symptoms in TH17-mediated immune diseases. This suggests that REV-ERB has a regulatory influence on autoimmune diseases via its impact on TH17 cells [37]. These investigations collectively position REV-ERB as a key player in immune regulation, suggesting potential therapeutic approaches for inflammatory and autoimmune diseases by targeting REV-ERB's modulation of immune responses and circadian rhythms.

REV-ERB in Metabolic Regulation

The human liver, being the primary metabolic organ, is pivotal in processes such as lipogenesis, glycogenesis, gluconeogenesis, glycogenolysis, and maintaining energy balance. Extensive research has been conducted to understand the impact of REV-ERB on liver functions. Notably, the suppression of REV-ERB α or REV-ERB β in mice led to hepatic steatosis, commonly known as fatty liver [38]. In a separate study, REV-ERB α was found to influence cholesterol metabolism by downregulating the LRH-1 receptor and regulating CYP7A1 [39]. Additionally, REV-ERB α is known to impact lipid metabolism through its role in suppressing the expression of ApoC-III, a key protein involved in the transportation of lipids [40]. Furthermore, REV-ERB's regulatory ef-

fect extends to the transformation of cholesterol into bile acids, essential for digesting dietary fats and oils. This transformation involves the suppression of transcription factor E4BP4 and signaling molecule SHP in the liver, mediated by REV-ERB [21]. Additional studies have highlighted REV-ERB α's significant role in repressing hepatic gluconeogenic gene expression and reducing glucose production. These insights underscore REV-ERB α's vital role in coordinating glucose homeostasis and overall energy metabolism, marking it as a key regulatory element [41].

In mammalian biology, adipose tissue is differentiated into three main types: white adipose tissue (WAT), primarily used for storing energy; brown adipose tissue (BAT), which facilitates energy expenditure via thermogenesis; and beige adipose tissue, which displays properties that are a blend of those found in WAT and BAT [42]. REV-ERB α is integral to the modulation of heat production in brown adipose tissue (BAT). The cyclical pattern of REV-ERB α expression in mouse BAT is most prominent at Z10, displaying a reverse correlation with the rhythm of body temperature. The absence of REV-ERB α in mice leads to a notable decrease in the variation of body temperature, a consequence of the uncontrolled expression of Uncoupling Protein 1 (UCP1) in BAT, a key target of REV-ERB α [43]. Mice either genetically deficient in REV-ERB α or experiencing low levels of REV-ERB α expression exhibited increased resistance to extreme cold conditions. REV-ERB α is instrumental in modulating the expression of Ucp1, a vital protein in brown adipocytes, synchronizing its action with the circadian cycle and variations in environmental temperature [43].

Research into the function of REV-ERB α in skeletal muscle reveals that its overexpression enhances mitochondrial content and activity, primarily through the modulation of the AMP-activated protein kinase (AMPK) pathway [44]. Conversely, inhibiting REV-ERB α has been linked to decreased exercise capacity due to reduced mitochondrial content and functionality. REV-ERB α also impacts various genes associated with autophagy and mitophagy in muscle tissue, predominantly through direct repression. This indicates that REV-ERB α may inhibit mitochondrial autophagy in muscle cells, thereby augmenting mitochondrial quantity and the oxidative capacity of myocytes [44]. These findings imply that activating REV-ERB α in skeletal muscle could potentially increase resistance to muscle fatigue and improve exercise performance.

Recent research involving mice has revealed that REV-ERB α plays a crucial role in the functionality of both insulin-producing β-cells and glucagon-producing α-cells in pancreatic islets. Specifically, it has been found that insulin secretion, which is dependent on glucose levels, is enhanced during periods when REV-ERB α expression is at its peak [45]. Additionally, REV-ERB α has been identified as a promoter of glucagon release from islet α cells [46]. Interestingly, the influence of REV-ERB α on lipogenic genes in mouse islets shows a resemblance to its effects in the liver [47].

Studies in SCN GABA neurons have shown that increased levels of REV-ERB at the end of the sleep cycle reduce the firing rate of SCN GABA neurons during waking, which increases insulin sensitivity and suppresses liver glucose production [48]. In REV-ERB α/β GABA neuron-specific knockout (KO) mice, glucose and insulin metabolism were impaired without altering behavior and feeding, but this was restored when REV-ERB α was re-expressed [48].

Discussion

In this review, we delve into the role of REV-ERB α/β proteins, classified as nuclear receptors, in circadian rhythm and human physiology. As target molecules in clinical research, the dilemma arises whether to focus on REV-ERB α, REV-ERB β, or both REV-ERB α/β. This decision is complex due to their interrelated functions.

When examining the influence of REV-ERB α/β on circadian rhythms, it's important to note that the lack of REV-ERB α by itself does not lead to behavioral arrhythmicity. However, the simultaneous absence of both REV-ERB α and β is crucial for the development of behavioral arrhythmia. This indicates a compensatory mechanism where REV-ERB β may replace REV-ERB α in maintaining and generating rhythm. Research has shown that the isolated absence of REV-ERB α shortens the circadian cycle by 30 minutes but does not disrupt its rhythm [49]. Conversely, the absence of REV-ERB β showed no significant changes in circadian activity rhythms. The combined deficiency of both REV-ERB α and β led to more pronounced alterations in circadian rhythms, characterized by decreased activity levels and rhythm fragmentation, indicating a synergistic role in circadian regulation [50].

Furthermore, in experiments involving REV-ERB α gene-deleted mice, a slight shortening of the circadian rhythm and an enhanced phase-shift response to envi-

ronmental stimuli were observed. The administration of a REV-ERB α ligand at varying circadian phases demonstrated phase-dependent, bidirectional modulations (either delay or advance) in Per2 and Bmal1 gene expression rhythms. This highlights REV-ERB α's significant role in modulating the circadian clock's response to environmental cues [51].

Circadian rhythm amplitude, a vital aspect of human health, is another parameter of interest. Amplitude, defined as the variance between a gene's peak and trough expression levels, directly influences the gene's biological effectiveness within the cycle. This amplitude has been associated with physiological aspects, disease manifestation, sleep disorders, and aging. A particular study underscored the influence of REV-ERB α on circadian amplitude, elucidated through the involvement of the F-box protein FBXW7 [52]. This process entails CDK1 (cyclin-dependent kinase 1) performing specific phosphorylation on REV-ERB α, subsequently leading to FBXW7-mediated ubiquitination and proteasomal degradation of REV-ERB α. This intricate interplay between REV-ERB α and the F-box protein FBXW7 underlines the nuanced regulation of circadian rhythm amplitude, demonstrating how post-translational modifications can pivotally influence circadian biology [52].

Beyond circadian rhythms, the REV-ERB α/β proteins have significant impacts on metabolic and immune systems. REV-ERB α orchestrates rhythmic epigenomic reshaping and lipid metabolism in the liver by suppressing genes like cholesterol, bile acid, and apolipoprotein CIII [38–40]. It also regulates thermogenesis in brown adipose tissue through uncoupling protein 1 (UCP1) and affects mitochondrial activity in skeletal muscle via AMPK, substantially influencing physical conditioning [42–44]. Additionally, REV-ERB α modulates insulin and glucagon secretion in pancreatic islets through rhythmic expression [45, 46]. Furthermore, in macrophages, REV-ERB α suppresses inflammatory signaling, linking the circadian clock to immune functions. These insights suggest that REV-ERB α/β could serve as a bridge between the circadian cycle and other physiological systems. The role of REV-ERB α/β proteins, which are nuclear receptors involved in circadian rhythm, indicates their potential as external targets for therapeutic interventions in metabolic, inflammatory, and behavioral disorders. However, given the complexity of their tissue-specific effects, careful consideration of timing and selectivity is imperative in therapeutic applications.

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REFERENCES

1. Gustafsson JA. Historical overview of nuclear receptors. J Steroid Biochem Mol Biol 2016;157:3-6. [CrossRef]
2. Kininis M, Kraus WL. A global view of transcriptional regulation by nuclear receptors: gene expression, factor localization, and DNA sequence analysis. Nucl Recept Signal 2008;6:e005. [CrossRef]
3. McKenna NJ, Cooney AJ, DeMayo FJ, Downes M, Glass CK, Lanz RB, et al. Minireview: evolution of NURSA, the Nuclear Receptor Signaling Atlas. Mol Endocrinol 2009;23:740-6. Erratum in: Mol Endocrinol 2009;23:1522. [CrossRef]
4. Kojetin DJ, Burris TP. REV-ERB and ROR nuclear receptors as drug targets. Nat Rev Drug Discov 2014;13:197-216. [CrossRef]
5. Miyajima N, Kadowaki Y, Fukushige S, Shimizu S, Semba K, Yamanashi Y, et al. Identification of two novel members of erbA superfamily by molecular cloning: the gene products of the two are highly related to each other. Nucleic Acids Res 1988;16:11057-74. [CrossRef]
6. Lazar MA, Hodin RA, Darling DS, Chin WW. A novel member of the thyroid/steroid hormone receptor family is encoded by the opposite strand of the rat c-erbA alpha transcriptional unit. Mol Cell Biol 1989;9:1128-36. [CrossRef]
7. Rosbash M. The implications of multiple circadian clock origins. PLoS Biol 2009;7:e62. [CrossRef]
8. Pittendrigh CS. Temporal organization: reflections of a Darwinian clock-watcher. Annu Rev Physiol 1993;55:16-54. [CrossRef]
9. Takahashi JS. Transcriptional architecture of the mammalian circadian clock. Nat Rev Genet 2017;18:164-79. [CrossRef]
10. Crumbley C, Burris TP. Direct regulation of CLOCK expression by REV-ERB. PLoS One 2011;6:e17290. [CrossRef]
11. Bonnelye E, Vanacker JM, Desbiens X, Begue A, Stehelin D, Laudet V. Rev-erb beta, a new member of the nuclear receptor superfamily, is expressed in the nervous system during chicken development. Cell Growth Differ 1994;5:1357-65.
12. Guillaumond F, Dardente H, Giguère V, Cermakian N. Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. J Biol Rhythms 2005;20:391-403. [CrossRef]
13. Zhao Q, Khorasanizadeh S, Miyoshi Y, Lazar MA, Rastinejad F. Structural elements of an orphan nuclear receptor-DNA complex. Mol Cell 1998;1:849-61. [CrossRef]
14. Burke L, Downes M, Carozzi A, Giguère V, Muscat GE. Transcriptional repression by the orphan steroid receptor RVR/Rev-erb beta is dependent on the signature motif and helix 5 in the E region: functional evidence for a biological role of RVR in myogenesis. Nucleic Acids Res 1996;24:3481-9. [CrossRef]

15. Kim YH, Marhon SA, Zhang Y, Steger DJ, Won KJ, Lazar MA. Rev-erbα dynamically modulates chromatin looping to control circadian gene transcription. Science 2018;359:1274-7. [CrossRef]
16. Evans RM. Journal of Molecular Endocrinology 25th anniversary special issue. J Mol Endocrinol 2013;51:E1-3. [CrossRef]
17. Lazar MA, Jones KE, Chin WW. Isolation of a cDNA encoding human Rev-ErbA alpha: transcription from the noncoding DNA strand of a thyroid hormone receptor gene results in a related protein that does not bind thyroid hormone. DNA Cell Biol 1990;9:77-83. [CrossRef]
18. Reinking J, Lam MM, Pardee K, Sampson HM, Liu S, Yang P, et al. The Drosophila nuclear receptor e75 contains heme and is gas responsive. Cell 2005;122:195-207. [CrossRef]
19. Raghuram S, Stayrook KR, Huang P, Rogers PM, Nosie AK, McClure DB, et al. Identification of heme as the ligand for the orphan nuclear receptors REV-ERBalpha and REV-ERBbeta. Nat Struct Mol Biol 2007;14:1207-13. [CrossRef]
20. Pardee KI, Xu X, Reinking J, Schuetz A, Dong A, Liu S, et al. The structural basis of gas-responsive transcription by the human nuclear hormone receptor REV-ERBbeta. PLoS Biol 2009;7:e43. [CrossRef]
21. Solt LA, Wang Y, Banerjee S, Hughes T, Kojetin DJ, Lundasen T, et al. Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. Nature 2012;485:62-8. [CrossRef]
22. Kojetin D, Wang Y, Kamenecka TM, Burris TP. Identification of SR8278, a synthetic antagonist of the nuclear heme receptor REV-ERB. ACS Chem Biol 2011;6:131-4. [CrossRef]
23. Reddy P, Zehring WA, Wheeler DA, Pirrotta V, Hadfield C, Hall JC, et al. Molecular analysis of the period locus in Drosophila melanogaster and identification of a transcript involved in biological rhythms. Cell 1984;38:701-10. [CrossRef]
24. Bargiello TA, Jackson FR, Young MW. Restoration of circadian behavioural rhythms by gene transfer in Drosophila. Nature 1984;312:752-4. [CrossRef]
25. Bargiello TA, Young MW. Molecular genetics of a biological clock in Drosophila. Proc Natl Acad Sci U S A 1984;81:2142-6. [CrossRef]
26. Takahashi JS. Transcriptional architecture of the mammalian circadian clock. Nat Rev Genet 2017;18:164-79. [CrossRef]
27. Griffett K, Burris TP. The mammalian clock and chronopharmacology. Bioorg Med Chem Lett 2013;23:1929-34. [CrossRef]
28. Gilles-Gonzalez MA, Gonzalez G. Signal transduction by heme-containing PAS-domain proteins. J Appl Physiol (1985) 2004;96:774-83. [CrossRef]
29. Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci 2003;4:649-61. [CrossRef]
30. Papazyan R, Zhang Y, Lazar MA. Genetic and epigenomic mechanisms of mammalian circadian transcription. Nat Struct Mol Biol 2016;23:1045-52. [CrossRef]
31. Bois-Joyeux B, Chauvet C, Nacer-Chérif H, Bergeret W, Mazure N, Giguère V, et al. Modulation of the far-upstream enhancer of the rat alpha-fetoprotein gene by members of the ROR alpha, Rev-erb alpha, and Rev-erb beta groups of monomeric orphan nuclear receptors. DNA Cell Biol 2000;19:589-99. [CrossRef]
32. Yang X, Downes M, Yu RT, Bookout AL, He W, Straume M, et al. Nuclear receptor expression links the circadian clock to metabolism. Cell 2006;126:801-10. [CrossRef]
33. Lanz RB, Jericevic Z, Zuercher WJ, Watkins C, Steffen DL, Margolis R, et al. Nuclear Receptor Signaling Atlas (www.nursa.org): hyperlinking the nuclear receptor signaling community. Nucleic Acids Res 2006;34:D221-6. [CrossRef]
34. Cho H, Zhao X, Hatori M, Yu RT, Barish GD, Lam MT, et al. Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. Nature 2012;485:123-7. [CrossRef]
35. Baxter M, Ray DW. Circadian rhythms in innate immunity and stress responses. Immunology 2020;161:261-7. [CrossRef]
36. Griffin P, Sheehan PW, Dimitry JM, Guo C, Kanan MF, Lee J, et al. REV-ERBα mediates complement expression and diurnal regulation of microglial synaptic phagocytosis. Elife 2020;9:e58765. [CrossRef]
37. Chang C, Loo CS, Zhao X, Solt LA, Liang Y, Bapat SP, et al. The nuclear receptor REV-ERBα modulates Th17 cell-mediated autoimmune disease. Proc Natl Acad Sci U S A 2019;116:18528-36. [CrossRef]
38. Bugge A, Feng D, Everett LJ, Briggs ER, Mullican SE, Wang F, et al. Rev-erbα and Rev-erbβ coordinately protect the circadian clock and normal metabolic function. Genes Dev 2012;26:657-67. [CrossRef]
39. Zhang T, Zhao M, Lu D, Wang S, Yu F, Guo L, et al. REV-ERBα regulates CYP7A1 through repression of liver receptor homolog-1. Drug Metab Dispos 2018;46:248-58. [CrossRef]
40. Raspé E, Duez H, Mansén A, Fontaine C, Fiévet C, Fruchart JC, et al. Identification of Rev-erbalpha as a physiological repressor of apoC-III gene transcription. J Lipid Res 2002;43:2172-9. [CrossRef]
41. Yin L, Wu N, Curtin JC, Qatanani M, Szwergold NR, Reid RA, et al. Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways. Science 2007;318:1786-9. [CrossRef]
42. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev 2004;84:277-359. [CrossRef]
43. Gerhart-Hines Z, Feng D, Emmett MJ, Everett LJ, Loro E, Briggs ER, et al. The nuclear receptor Rev-erbα controls circadian thermogenic plasticity. Nature 2013;503:410-3. [CrossRef]
44. Woldt E, Sebti Y, Solt LA, Duhem C, Lancel S, Eeckhoute J, et al. Rev-erb-α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. Nat Med 2013;19:1039-46. [CrossRef]
45. Vieira E, Marroquí L, Batista TM, Caballero-Garrido E, Carneiro EM, Boschero AC, et al. The clock gene Rev-erbα regulates pancreatic β-cell function: modulation by leptin and high-fat diet. Endocrinology 2012;153:592-601. [CrossRef]
46. Vieira E, Marroquí L, Figueroa AL, Merino B, Fernandez-Ruiz R, Nadal A, et al. Involvement of the clock gene Rev-erb alpha in the regulation of glucagon secretion in pancreatic alpha-cells. PLoS One 2013;8:e69939. [CrossRef]
47. Feng D, Liu T, Sun Z, Bugge A, Mullican SE, Alenghat T, et al. A circadian rhythm orchestrated by histone deacetylase 3 controls hepatic lipid metabolism. Science 2011;331:1315-9. [CrossRef]
48. Ding G, Li X, Hou X, Zhou W, Gong Y, Liu F, et al. REV-ERB in GABAergic neurons controls diurnal hepatic insulin sensitivity. Nature 2021;592:763-7. Erratum in: Nature 2021;595:E2. [CrossRef]
49. Preitner N, Damiola F, Lopez-Molina L, Zakany J, Duboule D, Albrecht U, et al. The orphan nuclear receptor REV-ERBalpha con-

trols circadian transcription within the positive limb of the mammalian circadian oscillator. Cell 2002;110:251-60. [CrossRef]
50. Ikeda R, Tsuchiya Y, Koike N, Umemura Y, Inokawa H, Ono R, et al. REV-ERBα and REV-ERBβ function as key factors regulating Mammalian Circadian Output. Sci Rep 2019;9:10171. [CrossRef]
51. Meng QJ, McMaster A, Beesley S, Lu WQ, Gibbs J, Parks D, et al. Ligand modulation of REV-ERBalpha function resets the peripheral circadian clock in a phasic manner. J Cell Sci 2008;121:3629-35. [CrossRef]
52. Zhao X, Hirota T, Han X, Cho H, Chong LW, Lamia K, et al. Circadian amplitude regulation via FBXW7-targeted REV-ERBα degradation. Cell 2016;165:1644-57. [CrossRef]