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Minireview

# Rev-erbα gives a time cue to metabolism

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**Abstract Normal physiological processes are under control of circadian rhythms. Moreover, certain pathological events, such as cardiovascular accidents (myocardial infarction, stroke) occur more frequently at specific times of the day. Recent observations demonstrate a causal relationship between alterations in circadian rhythmicity and metabolic disorders. Disruption of clock genes results in dyslipidemia, insulin resistance and obesity, all predisposing to atherosclerosis. The nuclear receptor Rev-erbα is part of the clock circuitry and plays an important role in keeping proper timing of the clock. Rev-erbα also regulates lipid metabolism, adipogenesis and vascular inflammation. Interestingly, Rev-erbα also cross-talks with several other nuclear receptors involved in energy homeostasis. Therefore Rev-erbα may serve to couple metabolic and circadian signals.**


*Keywords:* Circadian rhythm; Nuclear receptor; Metabolic disorder; Rev-erbα; Cardiovascular disease; Biological clock

## 1. Introduction: circadian rhythms and metabolism

The organism exerts a tight control on key metabolic events in order to assure energy homeostasis and fuel availability. Nuclear receptors are a family of transcription factors involved in the regulation of many aspects of energy homeostasis, including lipid utilisation or storage, cholesterol synthesis and elimination, insulin signalling and glucose metabolism. Abnormalities in these pathways, for instance due to genetic disorders, high caloric intake or low energy expenditure, lead to metabolic disorders such as dyslipidemia, obesity, insulin resistance and type 2 diabetes. These abnormalities often co-exist and are referred to as the metabolic syndrome [1] which also comprises an inflammatory component characterized by over-secretion of adipokines by the adipose tissue [2].

Many physiological processes are under the control of circadian ("around the day" = circa diem) rhythms that provide the organism a selective advantage by allowing its metabolism to adapt to predictable daily changes such as day–night, activity–rest cycles, and time of food availability. The master clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and consists of a complex circuitry of transcriptional/post-translational regulatory loops able to initiate and self-sustain biological rhythms. It synchronises peripheral autonomous pacemakers in order to coordinate and adjust organ physiology to environmental timing cues. Lipid and carbohydrate metabolism, hormone (insulin, leptin, and cortisol) secretion, blood pressure, coagulation factors and feeding behavior are a few examples of many aspects of mammalian physiology that are subjected to circadian oscillations. Thus, disturbance of circadian rhythms may have clinical implications in the development of dyslipidemia, obesity and cardiovascular events.

Indeed, circadian rhythms in both insulin secretion and sensitivity are altered in type 2 diabetic patients [3]. A recent clinical report revealed that sleep restriction is an independent risk factor for obesity and hypertension [4]. In the same line of evidence, components of the metabolic syndrome occur at higher frequency in shift work and night eating conditions [5,6]. Finally, circadian rhythms observed in the expression of adipokines, leptin, adiponectin are blunted in obese and diabetic animals [7] and obese humans [8,9]. These findings corroborate the existence of a link between circadian oscillations and metabolism.

A growing body of evidence shows that clock genes directly influence energy homeostasis and that deficiency in clock genes leads to metabolic disorders resembling the metabolic syndrome. Turek et al. have shown that mice with a mutated non-functional clock gene are hyperphagic, become obese and develop hyperlipidemia and hyperglycemia [10]. Another report indicates that a mutation in *clock* and *Bmal1* leads to altered circadian oscillations in plasma glucose and triglyceride levels, and mice harbouring these mutations develop glucose intolerance [11]. These observations emphasize the direct link between circadian rhythmicity and metabolism and point to a causal relationship between clock disorders and metabolic unbalance. Importantly, they suggest that clock genes themselves, directly or indirectly, are involved in the control of energy homeostasis. The nuclear receptor Rev-erbα has been identified as a clock and clock-regulated gene [12]. It is part of the core clock machinery and serves to maintain a 24-h cycle. Simultaneously, Rev-erbα plays a crucial regulatory role in metabolism. For instance, it regulates triglyceride (TG) and TG-rich lipoprotein metabolism [13] and modulates adipogenesis [14]. It may also play a determinant role in the regulation of systemic and vascular inflammatory processes [15]. Here, we will review the known physiological functions of Rev-erbα and

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discuss the potential key role of this nuclear receptor as a molecular link between circadian metabolic changes and the general clock system.

## 2. Clock genes and nuclear receptors: interacting partners in metabolic control

Circadian rhythms are generated by a master clock system located in the SCN. Recently, however, it was shown that peripheral self-sustained oscillators operate in virtually all cell types and autonomously generate oscillations in peripheral tissues. Feeding/fasting is the most dominant time cue for peripheral tissues [16]. The synchronization of those oscillators involves hormonal and neuronal signals from the SCN master clock which itself is reset by light via the retino-hypothalamic nerve tract. To elucidate the respective role of the central *vs* peripheral clock in the regulation of the hepatic circadian program, Schibler and colleagues have engineered a conditionally active liver clock mouse model. This was achieved by overexpressing Rev-erbα throughout the day, resulting in a suppression of Bmal1 oscillations and turning off the clock machinery [17]. In this mouse model, oscillation of most hepatic transcripts was dampened strengthening the idea that a functional liver clock is necessary to ensure proper circadian regulation of hepatic gene expression.

Under normal conditions, around 10% of hepatic transcripts oscillate diurnally [18] and microarray analyses of liver mRNA demonstrated that a large number of these genes are involved in metabolic processes such as food processing, fuel utilization/storage, etc. For instance, genes encoding enzymes and transporters involved in nutrient metabolism, cellular cholesterol homeostasis, xenobiotic detoxification or energy balance such as phosphoenolpyruvate carboxykinase (PEPCK), cholesterol 7α-hydroxylase (CYP7A1), the glucose transporter Glut2, etc., display circadian expression. As sensors of small fat-soluble molecules such as hormones or fatty acids derived from intermediate metabolism or food, nuclear receptors are key players in endocrine regulation. A recent report indicates that 28 out of 48 nuclear receptors display cyclic expression in metabolically active tissues (liver, adipose tissue, and skeletal muscle), strongly suggesting that circadian oscillations in expression of these regulatory proteins may co-ordinately entrain daily variations in their target genes and couple the peripheral clock to metabolic output [19]. In this context, Rev-erbα may play a central role in participating in the temporal coordination of metabolism.

## 3. Rev-erbα is a clock and a clock-regulated gene

At the molecular level, circadian rhythms are generated through the reciprocal regulation of two interlocked transcriptional and post-translational auto-regulatory feedback loops. In mammals, Clock (Circadian locomotor output cycles kaput), Bmal1 (Brain and muscle ARNt like protein 1), and possibly the clock paralog NPAS2, form the positive limb and activate transcription of per (Period) and cry (Cryptochrome) genes, with per1, per2, cry1 and cry2 forming the negative limb [20] (Fig. 1). Once the proteins Per and Cry reach a critical concentration, they enter the nucleus and inhibit Clock/Bmal1 transactivation, thereby repressing their own transcription. Rev-erbα transcription is activated by Clock/Bmal1 and trans-repressed by Per/Cry, resulting in circadian oscillations of Rev-erbα. In turn, Rev-erbα periodically represses Bmal1 and to a lesser extent clock transcription, thereby interconnecting the positive and negative loops. Ueli Schibler and collaborators first evidenced a critical role of Rev-erbα in the clock machinery in vivo showing that Rev-erbα-deficient mice display markedly altered circadian rhythms characterized by increased Bmal1 and Clock expression and a shorter period length than wild-type mice [12]. Moreover, light pulse delivery late in the night provoked drastic phase advances in Rev-erbα-deficient mice compared to wild-type. However, Rev-erbα-deficient mice are not arrhythmic, suggesting that Rev-erbα is required for the maintenance and robustness rather than the

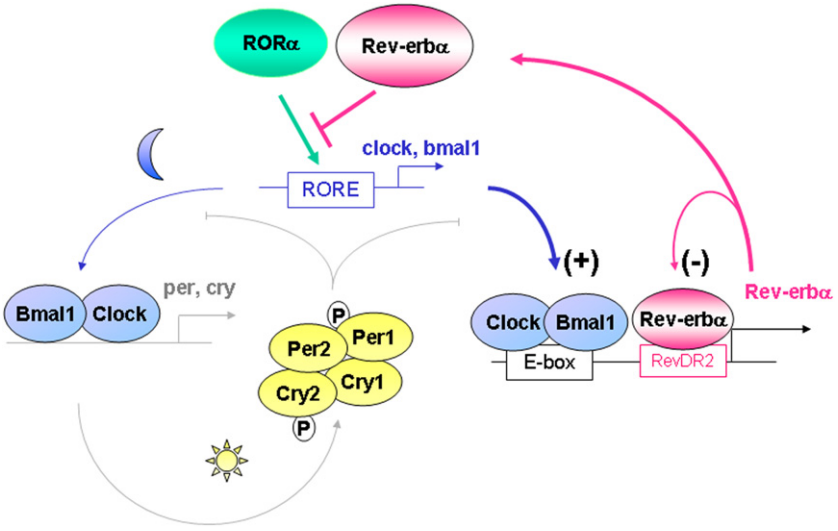


Fig. 1. Rev-erbα is a clock and a clock-controlled gene. The cartoon depicts a simplified model of the circadian machinery in which Rev-erbα links the positive (Clock/Bmal1) and the negative (Per/Cry) limb of the pacemaker. Rev-erbα serves to ensure proper phase length and strengthens circadian rhythms.

generation of circadian rhythms. A ROR/Rev-erbα loop exists in which ROR and Rev-erbα compete for the regulation (induction *vs* repression) of the positive limb [21,22]. Of note, Rev-erbβ also displays a strong diurnal expression pattern and represses Bmal1 transcription [23]. Since the three ROR isoforms do not all cycle in the same tissues, we hypothesize that the ratio between each isoform of ROR and Rev-erb might affect the regulation of the positive limb in a tissue-specific manner and may offer the opportunity to finely tune the circadian network to nutrient and energy metabolism.

Post-translational mechanisms (i.e. protein phosphorylation) are likely to play a regulatory role as well. They influence per and cry protein stability and may therefore be critical to their activity [24]. Lazar and colleagues have recently shown that the glycogen synthase kinase (GSK)3 stabilizes the Rev-erbα protein and that lithium, a potent inhibitor of GSK3, induces Rev-erbα degradation. In the presence of a mutant form of Rev-erbα, that is resistant to degradation by lithium, a serum shock could not initiate circadian oscillation in cells [25]. Rev-erbα protein stability is therefore crucial for circadian rhythm initiation, maintenance and synchronisation after serum shock.

## 4. Rev-erbα: an orphan nuclear receptor with atypical features

Rev-erbα belongs to the superfamily of nuclear receptors. It is still considered as an "orphan receptor" since no ligand has been identified sofar. Furthermore, it lacks the AF2 ligand-dependent transactivation domain and its ligand binding pocket is filled up by amino-acid side chains leaving little room to accommodate a putative ligand [26]. Rev-erbβ, the other isotype of the Rev-erb family sharing high homology with Rev-erbα, has still not been adopted either.

Rev-erbα is encoded on the opposite strand of the thyroid receptor (TR)α gene [27]. The Rev-erbα gene overlaps with 269 nucleotides the splice variant TRα2 and it has been suggested that Rev-erbα may influence the TRα1/TRα2 ratio, thereby possibly altering TRα signalling. However this hypothesis has sofar not been corroborated in vivo and Rev-erbα-deficient mice have been shown to have TRα1 and TRα2 levels within the normal range ([28], and C. Fontaine and B. Staels, unpublished data). Triqueneaux et al. recently demonstrated that alternative promoter and splicing site usage gives rise to two Rev-erbα isoforms Rev-erbα1 and Rev-erbα2 [29].

Its orphan status and the peculiar arrangement of its genomic locus are not the only atypical characteristics of this nuclear receptor. Rev-erbα displays a hydrophobic region to which co-repressors such as NCoR are recruited [26]. As a consequence Rev-erbα behaves as a constitutive repressor of transcription. Rev-erbα binds either as a monomer to a specific response element (RevRE) consisting of a 6 bp core motif (A/G)GGTCA flanked by an A/T-rich 5′ sequence, or as a homodimer to a RevDR2 element composed of a direct repeat of the core motif spaced by two nucleotides [30,31] (Fig. 2). Rev-erbα also competes on these sites with the closely related RAR-related orphan receptors RORs [32]. Indeed, RORα and Rev-erbα are co-expressed in many tissues and share the

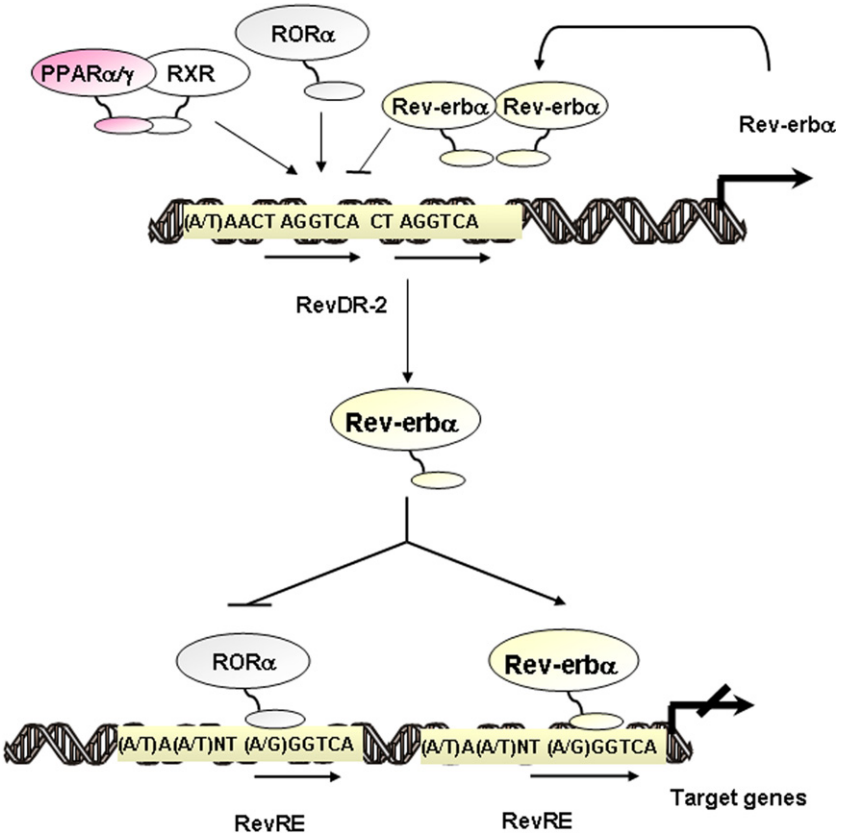


Fig. 2. Control of Rev-erbα transcription. Rev-erbα negatively regulates expression of its target genes by binding to specific monomeric (RevRE) or dimeric (RevDR-2) response elements. Rev-erbα also competes for binding with transcriptional activators such as ROR or PPARs.

same response elements but have opposite effects on transcription (activation *vs* repression, respectively). A good example of that competition is the regulation of Rev-erbα itself: the Rev-erbα promoter contains a RevDR-2 site to which it binds and represses its own transcription [33]. RORα binds to the same sequence and activates Rev-erbα transcription [34].

The peroxisome proliferator-activated receptors (PPAR)α and γ also bind to the RevDR-2 sequence in the Rev-erbα gene promoter and activate its transcription [14,35]. Thus ligands of PPARα (such as the fibrate class of hypolipemiants) and PPARγ (such as the insulin sensitizing thiazolidinediones) have been shown to increase Rev-erbα expression and, interestingly, Rev-erbα may mediate some of their physiological effects (see below).

Rev-erbα is expressed in many tissues such as the liver, white and brown adipose tissue, muscle, brain, and cell types such as endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and macrophages [15,27,32,36]. Its expression increases during the differentiation of pre-adipocytes into mature adipocytes [14,37]. In vitro data had suggested that its expression decreases during myogenesis, but Rev-erbα has been reported to be highly expressed in muscle from adult mice [38]. A major characteristic of Rev-erbα expression is its very robust circadian regulation in vitro in serum-synchronised fibroblasts [39], ex vivo in primary cultures of rat hepatocytes [40], as well as in vivo in brain, liver, muscle, pancreas and white and brown adipose tissue [18,19,40–42].

Because Rev-erbα has no known ligand, circadian variations in its expression, regulation by other nuclear receptors, competition for binding to shared response elements and post-transcriptional modifications are likely to play crucial roles in the modulation of its activity. In rodents, Rev-erbα expression is maximal during the light phase (around 4:00pm) and decreases to reach a nadir during the dark phase. Thus not only is Rev-erbα a clock gene but also a clock-regulated gene which may have potential metabolic implications. Indeed, Rev-erbα likely only modulates transcription of its target genes when its expression is sufficient, while its activity is strongly reduced at night.

Feeding time is one of the major time cues in the synchronization of the peripheral clock [16], and time restriction to the light instead of the dark phase in food availability inverses the phase of circadian expression in mouse liver without affecting SCN circadian gene expression. Of interest is the fact that glucocorticoids interfere in that process since mice harbouring a hepato-specific deletion of the glucocorticoid receptor (GR) invert their circadian liver gene expression more rapidly after day-time shift of food availability [43]. Interestingly, Rev-erbα expression is down-regulated by glucocorticoids [40], and Rev-erbα may therefore play a role in phase adjustment to food availability.

## 5. Rev-erbα and the metabolic syndrome

Dysregulations in metabolic pathways involved in lipid and carbohydrate metabolism, and insulin signalling lead to metabolic disorders such as obesity, dyslipidemia, insulin resistance and eventually type 2 diabetes and hypertension. As other members of the nuclear receptor family, Rev-erbα has emerged as a key regulator of diverse physiological processes such as maintenance of energy homeostasis, adipogenesis and inflammation.

### *5.1. Lipid and lipoprotein metabolism*

The expression of apolipoprotein (apo) A–I, a major constituent of high density lipoproteins (HDL), is repressed by Rev-erbα in rats [44]. Rev-erbα is induced by PPARα and may mediate the fibrate-induced reduction of apoA-I gene expression and plasma HDL-cholesterol levels in rats (Fig. 3). This regulation is lost in humans due to evolutionary sequence differences in the RevRE present in the apoA-I gene promoter. In contrast, Rev-erbα represses both mouse and human apoC-III

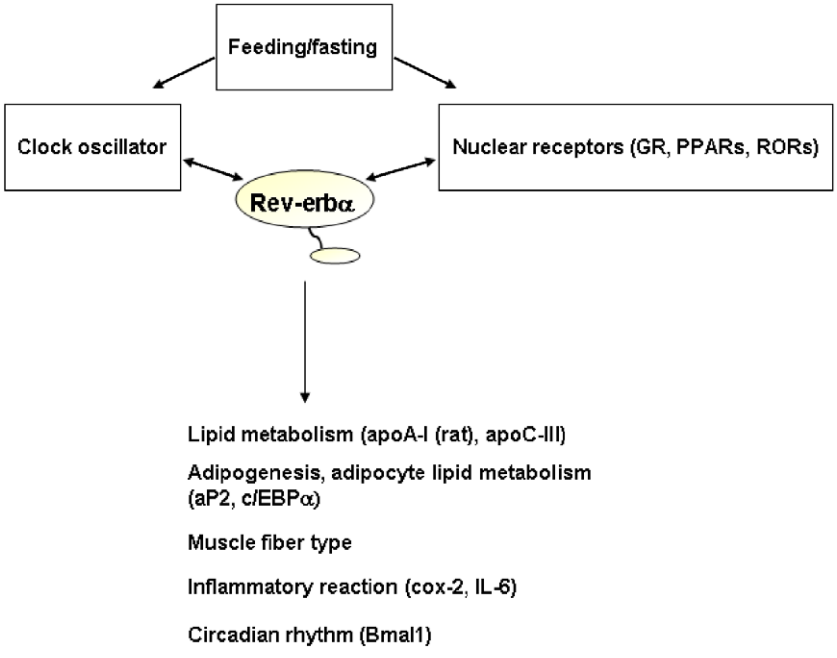


Fig. 3. Rev-erbα couples circadian rhythms and metabolic functions. Rev-erbα integrates signals from the circadian pacemaker and other nuclear receptor signalling pathways to bring about flexibility in the metabolic adjustments to environmental cues.

gene expression after binding to a RevRE site located in the apoC-III gene promoter adjacent to the TATA box [13]. Expression of apoC-III has been positively correlated with the risk of cardiovascular disease, and Rev-erbα may thus act on factors determining atherosclerosis risk. In vivo, Rev-erbα-deficient mice display increased hepatic apoC-III expression, plasma triglycerides (TG) and TG-rich very low density lipoprotein (VLDL) particles [13,45]. Both apoA-I and apoC-III are also regulated by RORα illustrating the cross-talk of these nuclear receptors on common target genes. While Rev-erbα represses both apolipoproteins, RORα activates their transcription after binding to the same response element [46,47]. Moreover, staggerer mice which lack a functional RORα gene display lowered apoA-I and apoC-III levels [47,48]. More recently, it has been suggested that Rev-erbα might repress the expression of elovl3, a fatty acid elongase involved in very long chain fatty acid (VLCFA) metabolism although the in vivo relevance of this regulation is lacking [49]. Finally, Rev-erbα inhibits the expression of the enoylCoA hydratase/3-hydroxyacylCoA dehydrogenase involved in the peroxisomal β-oxidation pathway [50], and of the microsomal cytochrome P450 fatty acid ω-hydroxylase [51] by competing with another nuclear receptor, namely PPARα. PPARα has been shown to bind to the Bmal1 promoter and regulate its expression [52] while the clock/Bmal1 heterodimer reciprocally regulates PPARα [53]. This constitutes another interconnection in which a Rev-erbα/PPARα regulatory loop may control lipid metabolism in a circadian-dependent manner.

Rev-erbα is also expressed in skeletal muscle where it appears to influence the myosin fiber type. Indeed, in the soleus (''red'') muscle, Rev-erbα-deficient mice exhibit an increase in the myosin heavy chain isoform specific of type I (β/slow-twitch) muscles, which have a high content in mitochondria, are involved in aerobic lipid metabolism and exhibit prolonged exercise-induced energy mobilization [38]. Rev-erbβ has also been implicated in the regulation of muscle lipid metabolism since ectopic expression of a dominant negative form increases expression of genes involved in fatty acid uptake [54]. Rev-erbβ may also affect the expression of IκB and cytokines such as IL-6, although a concomitant increase in RORα expression in the presence of the exogenous dominant negative Rev-erbβ might also contribute to this observation.

Together these data support a physiological role of Rev-erbα (and β) in intracellular as well as plasma lipid and lipoprotein metabolism. These actions may influence the development of pathologies such as type 2 diabetes and atherosclerosis, but further studies are required to explore these potential activities of Rev-erbα.

### 5.2. Adipocyte physiology

Rev-erbα expression is induced during the adipogenic process [14,37]. Furthermore, ectopic Rev-erbα expression in 3T3L1 pre-adipocytes promotes their differentiation into mature adipocytes and enhances lipid storage [14]. This action of Rev-erbα is further enhanced by treatment with the PPARγ ligand rosiglitazone. As previously mentioned, PPARγ ligands induce Rev-erbα expression and Rev-erbα may therefore transduce some of PPARγ's physiological effects. Indeed, Rev-erbα over-expression increases the expression of the PPARγ target genes aP2 and CCAAT/enhancer-binding protein (c/EBP)α, but has no effect on c/EBPβ or SREBP-1 gene expression. Together these data indicate a role for Rev-erbα in adipocyte differentiation and physiology and identify Rev-erbα as an adipogenic gene downstream of PPARγ. Another intriguing issue is the well-documented association between alteration in feeding periods seen in night shift or sleep restriction and weight gain. The mechanisms involved therein have never been clearly elucidated. In this regard it is very interesting to note that Rev-erbα can directly link the adipogenic process and the master clock system. A large number of transcripts (leptin, adipokines, and clock genes and nuclear receptors) cycle in adipose tissue. Some functions of adipose tissue such as lipolysis and free fatty acid release display circadian pulsatility. This aspect deserves further investigations to better characterize the adipose clock system and its function in the regulation of lipid storage, adipokine synthesis, and secretion of peptides involved in the (central) control of satiety and food intake.

### 5.3. Inflammation control

Rev-erbα is expressed in different cell types of the vascular wall, namely ECs and VSMCs [15] as well as in cells from the immune system such as macrophages ([15,55] and C. Fontaine and B. Staels, unpublished data). Rev-erbα increases tumor necrosis factor (TNF)α-induced nuclear factor κB (NFκB) activation in VSMCs [15]. Furthermore, Rev-erbα over-expression in these cells resulted in an increased expression of the pro-inflammatory interleukine (IL)-6 and cycloxygenase (cox)-2 [15].

Rev-erbα is highly expressed in chondrocytes, a cell type found in cartilage releasing cytokines and matrix metalloproteinases (MMP) [56]. Rev-erbα expression is increased in cartilage under conditions of catabolic degradation such as osteoarthritis. In these cells, Rev-erbα induces the expression of MMP-13 and aggrecanase and may amplify the degradation process [57]. These data together with those reported in vascular cell types support the concept of a general implication of Rev-erbα in the inflammatory process.

### 5.4. Fibrinolysis cascade

The plasminogen activator inhibitor (PAI)-1 inhibits the fibrinolysis cascade and may promote the development of atherothrombosis [58]. PAI-1 expression oscillates diurnally, peaking late in the night. This PAI-1 peak correlates to minimal fibrinolytic activity and is associated with higher frequency of acute thrombotic events [58]. RORα and Rev-erbα compete for the regulation of PAI-1 gene transcription: Rev-erbα represses RORα-mediated induction of PAI-1 transcription [59].

## 6. Conclusion and perspectives

We have reviewed data identifying Rev-erbα as a component of the clock machinery and a crucial player in the maintenance of circadian fluctuations. A growing body of evidence also indicates that Rev-erbα regulates lipid metabolism and vascular inflammation and suggests it might play a modulatory role in the development of cardio-vascular disease. Atherosclerosis is a complex chronic inflammatory disease of the vascular wall associated with metabolic abnormalities (i.e. dyslipidemia, glucose disorders). The inflammatory reaction is initiated by the accumulation of modified lipoproteins in the sub-endothelial space of the vessels, resulting in the activation of ECs which

in turn secrete chemoattractant and adhesion molecules [60]. Monocytes are recruited to the lesion site, differentiate into macrophages which take up cholesterol and further amplifiy the inflammatory reaction by secreting pro-inflammatory cytokines and matrix metalloproteinases [60–62]. This ultimately results in the rupture of unstable atherosclerotic plaques, and acute occlusion by thrombosis leading to myocardial infarction and stroke [60]. Since Rev-erbα regulates plasma lipid and lipoprotein metabolism and the inflammatory reaction, and may modulate the fibrinolysis cascade, Rev-erbα is likely to modulate the onset of the atherogenic process and its consequences in terms of acute cardiovascular events. It would be therefore of interest in the future to determine whether Rev-erbα plays a role in atherosclerosis development.

Another exciting field is the link between circadian rhythm disorders and the development of obesity. We hypothesize that Rev-erbα may act as a molecular link between the adipogenic process and the clock circuitry, although further studies are required to establish the role of Rev-erbα in the modulation of adipose tissue physiology by the clock system. This will help get insights as to how feeding behaviour may influence the clock system and reciprocally how the central and/or peripheral pacemakers, via neuronal or hormonal signals, control appetite, energy balance and body fat mass. Moreover, such studies will help unravel whether alteration in the adipose clock system can promote the development of obesity (and reciprocally).

Further studies are awaited to get further insights into Rev-erbα's in vivo physiological role. It becomes clear that Rev-erbα is at the crossroad of several regulatory loops involving other nuclear receptors that participate in the control of energy homeostasis. We propose that Rev-erbα is able to integrate both circadian cues and signalling from other nuclear receptors and bring about the flexibility required for metabolic adjustments.

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