Circadian Regulation of the Hepatic Endobiotic and Xenobitoic Detoxification Pathways: The Time Matters

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Circadian Regulation of the Hepatic Endobiotic and Xenobitoic Detoxification Pathways: The Time Matters

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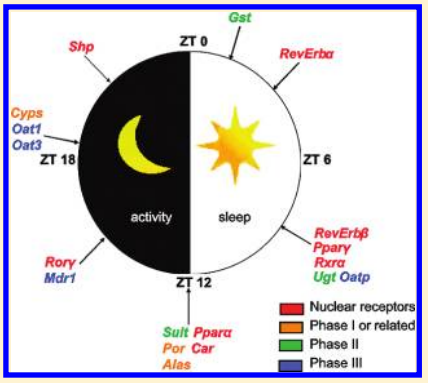
ABSTRACT: Metabolic processes have to be regulated tightly to prevent waste of energy and to ensure sufficient detoxification. Most anabolic processes operate in a timely manner when energy intake is the highest, while catabolism takes place in energy spending periods. Endobiotic and xenobiotic metabolism are therefore under circadian control. Circadian regulation is mediated through the suprachiasmatic nucleus (SCN), a master autonomous oscillator of the brain. Although many peripheral organs have their own oscillators, the SCN is important in orchestrating and entraining organs according to the environmental light cues. However, light is not the only signal for entrainment of internal clocks. For endobiotic and xenobitoic detoxification pathways, the food composition and intake regime are equally important. The rhythm of the liver as an organ where the major metabolic pathways intersect depends on SCN signals, signals from endocrine tissues, and, importantly, the type and time of feeding or xenobiotics ingestion. Several enzymes are involved in detoxification processes. Phase I is composed mainly of cytochromes P450, which are regulated by nuclear receptors. Phase II enzymes modify the phase I metabolites, while phase III includes membrane transporters responsible for the elimination of modified xenobiotics. Phases I–III of drug metabolism are under strong circadian regulation, starting with the drug-sensing nuclear receptors and ending with drug transporters. Disturbed circadian regualtion (jet-lag, shift work, and dysfunction of core clock genes) leads to changed periods of activity, sleep disorders, disturbed glucose homeostasis, breast or colon cancer, and metabolic syndrome. As many xenobiotics influence the circadian rhythm of the liver, bad drug administration timing can worsen the above listed effects. This review will cover the major hepatic circadian regulation of endogenous and xenobiotic metabolic pathways and will provide examples of how good timing of drug administration can change drug failure to treatment success.



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BASICS OF THE CIRCADIAN REGULATION OF METABOLIC PROCESSES

Metabolism is a common expression for all active processes in living organisms. It is divided to anabolism and catabolism, and the regulation of these is extremely important to not waste energy. The reactions involved in anabolism as well as catabolism are precisely controlled through rate limiting enzymes. Most anabolic processes are performed at the time of day when

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energy intake is highest, while catabolism takes place in energy spending periods. With the daily activity of man, anabolic processes are expected in the bright part of day,[1] therefore the rate limiting enzymes are under circadian control.[2] To make this control possible, organisms contain an internal clock which can detect the changes of day and night.

The patterns of activity/sleep, eating/fasting, etc. show that our lives are under the control of an internal clock. This clock is in the hypothalamus of the brain in the suprachiasmatic nucleus (SCN), a region above the optical chiasm (reviewed in refs 3 and 4). SCN receives photic signals from ganglion cells in the retina (melanopsin cells), which enables SCN to sense the start of each day at dawn. The major quality of the circadian clock is that it is maintained also in constant darkness (free running conditions), while light at dawn serves as a resetting signal to set our clocks to approximately 24 h.[5,6] The clock responsible for circadian regulation in free running conditions is represented by a set of transcription activators and repressors. The genes encoding the core clock components are transcribed periodically and are involved in transcriptional−translational−post-translational modification loops that serve autoregulation as well as the regulation of circadian expression of output genes. The first core clock gene identified was Circadian locomotor output cycles kaput (*Clock*).[7,8] It is accompanied by transcription factors Brain and muscle Arnt-like protein-1 (*Bmal1*) and Neuronal PAS domain protein 2 (*Npas2*) as activators and *Period* (*Per*) 1 and 2 and *Cryptochrome* (*Cry*) 1 and 2 as repressors. On the protein level, BMAL1 interacts with CLOCK or NPAS2 and binds to E-box DNA elements in promoter regions of different genes, among others, also to promoters of repressors *Per1,2* and *Cry1,2*.[7,9−13] After transcription, PER heterodimerizes with one of the CRY proteins, and they bind to the BMAL1/CLOCK (NPAS2) complex and attenuate its activity. As a consequence, the transcription of *Per* genes is stopped, completing the first autoregulatory loop. When the pool of PER and CRY proteins is diminished due to protein degradation, PER and CRY are removed from the BMAL1/CLOCK complex, and transcription is reactivated.[14−16] The degradation of PER and CRY is controlled trough post-translational mechanisms via phosphorylation by Casein Kinase 1ε and δ (CK1ε and CK1δ). They tag PER and CRY for ubiquitination leading to proteasome degradation.[17−24] (Figure 1).

In addition to this core clock regulation, several oscillators help to maintain the robustness and precision. The regulation through the retinoic acid-related orphan receptor response element (RORE) found in the *Bmal1* promoter represents another loop. Reverse-erb α (REV-ERBα)-repressor and retinoic acid-related orphan receptor α (RORα) activator bind to RORE. Because of an E-box element in their promoters, BMAL1 activates the expression of *Rev-erbα* and *Rorα*. After

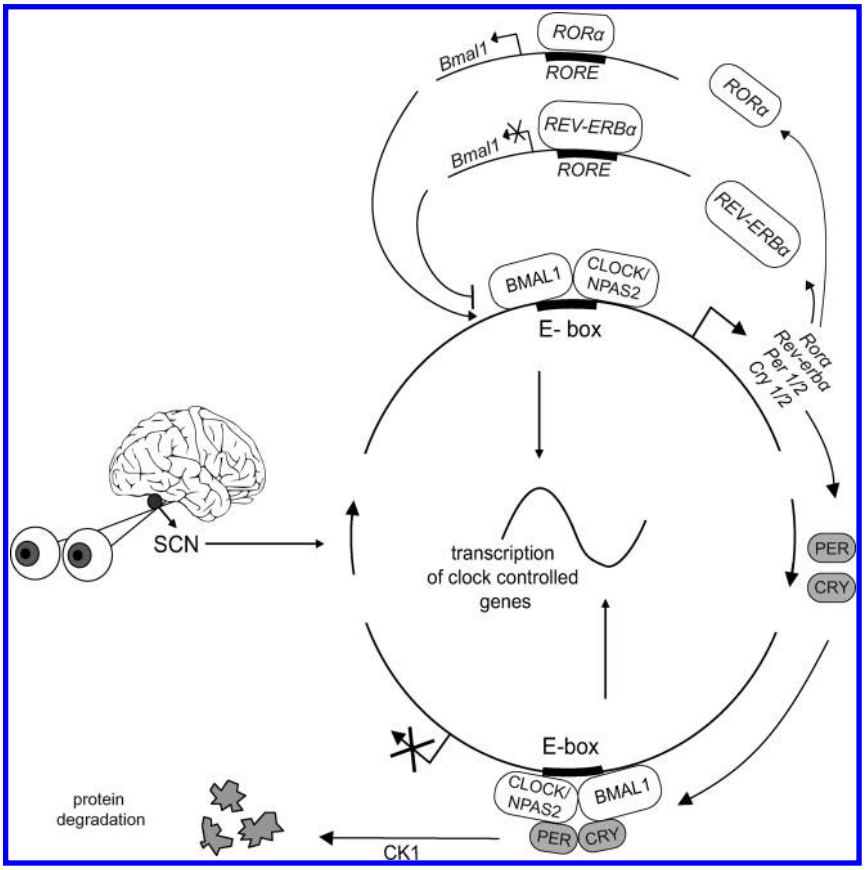

Figure 1. Molecular basics of the circadian clock. The master oscillator lies in the suprachiasmatic nucleus (SCN), which is positioned in the hypothalamus above the optic chiasm. The molecular clock is composed of transcriptional−translational and post-translational feedback loops: transcriptional activators BMAL1 and CLOCK/NPAS2 bind to E-box elements on DNA. They have binding partners PER1,2 and CRY1,2 that act as repressors. Precise expression amplitude of clock controlled genes is enabled because half-life of repressor proteins is precisely controlled with casein kinase1 (CK1) leading to degradation and because additional loops are present. One of them involves the binding of REV-ERBα (repressor) or RORα (activator) to retinoic acid-related orphan receptor response element (RORE) in the *Bmal1* promoter. *Rev-erbα* and *Rorα* expression is regulated through E-box in their promoters.

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REV-ERBα and RORα proteins are produced, they repress or activate the transcription of *Bmal1*[25−29] (Figure 1). CLOCK has an additional role as histone acetyltransferase, so it directly regulates the accessibility of chromatin for transcription.[30]

CENTRAL CLOCK ORGANIZATION AND COMMUNICATION WITH THE PERIPHERY

Most circadian studies were performed in animal models, and if not stated differently, the data in this review are from rodent studies (mice and rats). We are aware that extrapolation to humans is not straightforward since rodents are generally nocturnal animals. However, the basic circadian mechanisms are evolutionarily extremely well preserved, and it is assumed that regulatory mechanisms of the circadian clock are very similar in rodents and humans.

The oscillator in SCN is considered as central since it regulates basic physiological and behavioral control: activity/sleep, food consumption, and body temperature, all strongly oscillating.[31] The superior role of SCN was proven with the ablation and transplantation studies.[32] Initially surprising circadian clocks were found also in other organs: they are called peripheral oscillators. SCN controls them by hormonal and neural signals[3,33] by not yet completely understood mechanisms. Direct influence of the SCN on peripheral clocks is by the entrainable rhythm of glucocorticoids.[34] Metabolically important self-sustained oscillators are in the liver, adrenal, adipose tissue, muscle, intestine, and other organs.[35,36] The liver oscillator is most important for the metabolism of xenobiotics. Schibler's group prepared genetically modified mice in which they could switch on or off one of the core clock genes *Bmal1 via* the liver specific conditional overexpression of REV-ERBα. They could identify systemically driven components of the liver circadian clock. From the core clock genes, only *Per2* was affected. This indicates that the strong almost autonomic liver oscillator exists but is still under systemic control.[37] When liver innervation was disrupted, *Per1* response to light resetting in the liver was abolished.[38] This shows that by SCN mediated response to light stimuli is transmitted to the periphery manly via neural pathways. The liver oscillator is most powerfully entrained by food[39,40] followed by light signals,[34] so it can be speculated that also nutritional mechanisms regulate the core liver clock. These nutritional mechanisms are believed to be gated by hormones. In the absence of glucocorticoids or a glucocorticoid hormone receptor, feeding time can induce larger and faster phase shifts in the mouse liver compared to those in intact animals.[41] Restricted feeding can invert the circadian expression of metabolic genes, and sterol regulatory element-binding protein 1 (SREBP-1) is described as a possible candidate for immediate response that affects a set of coordinately regulated metabolic genes in the liver.[2,42,43]

CIRCADIAN CLOCK AND ENDOGENOUS METABOLISM INTERTWINE IN A DELICATE PATTERN

Sensing the Metabolic Status with NAD(H) and NADP(H). In normally fed animals, metabolic status is repeatedly changing from fasting to fed state. These cycles are in normal conditions repeated several times a day and may differ between species. Cellular redox status is represented by nicotinamide adenine dinucleotide cofactors NAD(H) and NADP(H). They regulate the transcription activity of CLOCK or NPAS2/BMAL1:[44] the reduced forms increase DNA binding, while oxidized forms work in an opposite manner.[45,46] However, the rate limiting enzyme in NAD biosynthesis nicotinamide phosphoribosyletransferase (NAMPT) displays circadian rhythmicity in peripheral tissues. It is under the direct control of CLOCK/BMAL1, so NAD levels in the liver show a circadian pattern. Nutrient responsive deacetylase sirtuin 1 (SIRT 1) uses NAD+ and represses the activity of CLOCK and BMAL1 showing that metabolic state can directly influence the core circadian clock. An additional circadian loop was described where CLOCK/BMAL1 positively regulates NAD production and SIRT 1 activity but SIRT 1 negatively regulates the activity of CLOCK/BMAL1[47,48] (Figure 2). NAMPT and SIRT1 are regulated also by the nutritional status of the organism: *Nampt* is upregulated in response to glucose restriction,[49,50] and *Sirt1* is increased during fasting or caloric restriction.[51−54] Therefore, NAMPT and SIRT1 can more precisely regulate the peripheral core clock in response to daily feeding and fasting cycles. Furthermore, processes like glucose-stimulated insulin secretion, adipocyte differentiation, and gluconeogenesis are circadian and regulated by NAD and SIRT1.[55]

NAD+ is a donor of ADP ribose for the activity of poly-ADP ribose-polymerase-1 (PARP-1). PARP-1 binds to the CLOCK/BMAL1 heterodimer and poly(ADP ribosyl)ates CLOCK in a daily manner, at the beginning of the light phase (Figure 2). The loss of PARP-1 enhances the binding of CLOCK/BMAL1 to DNA and leads to phase shift of the interaction of CLOCK/BMAL1 with PER and CRY. *Parp-1*$^{-/-}$ mice respond differently to changes in feeding times: the entrainment of liver clocks is significantly delayed.[56]

The energetic state of the cell is measured through the ATP/AMP ratio, and adenosine monophosphate activated protein kinase (AMPK) is a sensor of this ratio. If the AMP/ATP ratio is increased, then the activity of AMPK is also increased. In the mouse liver, the AMPK activity and nuclear localization are rhythmic and inversely correlated with CRY1 nuclear abundance. Lamia et al. have determined AMPK phosphorylation sites on CRY1, which lead to CRY1 degradation (Figure 2). AMPK has a strong impact on the core clock rhythmicity. This was shown using mouse embryonic fibroblasts isolated from AMPK$^{-/-}$ animals where the rhythmicity of cells was altered.[57]

Nutrient Sensing with PPARγ and PPARα. Another nutrient sensor and circadian regulator is the peroxisome proliferator-activated receptor (PPAR) γ. PPARγ is a member of the steroid hormone nuclear receptor superfamily and contains a ligand sensing domain and a DNA-binding domain that mediates specific binding to PPAR response elements. PPAR is active in a heterodimeric complex with retinoid X receptor (RXR) and a list of small accessory molecules that act as corepressors or coactivators.[58] One of the coactivators PPARγ coactivator 1-α (PGC1α) is rhythmically expressed and directly regulates *Bmal1* transcription[59] (Figure 2) as well as the transcription of *Rev-erbα*. Mice lacking PGC1α have abnormal diurnal locomotor activity rhythms with altered expression of clock and metabolic genes,[60] so PGC1α seems to be involved as the input gene to the core clock and a part of the core clock itself. PGC1α is also regulated by SIRT1: it is deacetylated and activated by SIRT1.[54] SIRT1 promotes fat mobilization during fasting by repressing PPARγ.[61] PER2 dictates the specificity of PPARγ transcriptional activity and exerts its inhibitory function by blocking PPARγ recruitment to target promoters.[62] A high fat diet (HF) can influence the circadian rhythms in mice.[63,64] Increase in PPARγ expression in light and dark periods was shown. A HF diet did not affect the circadian phase of core clock genes, but the amplitude was severely

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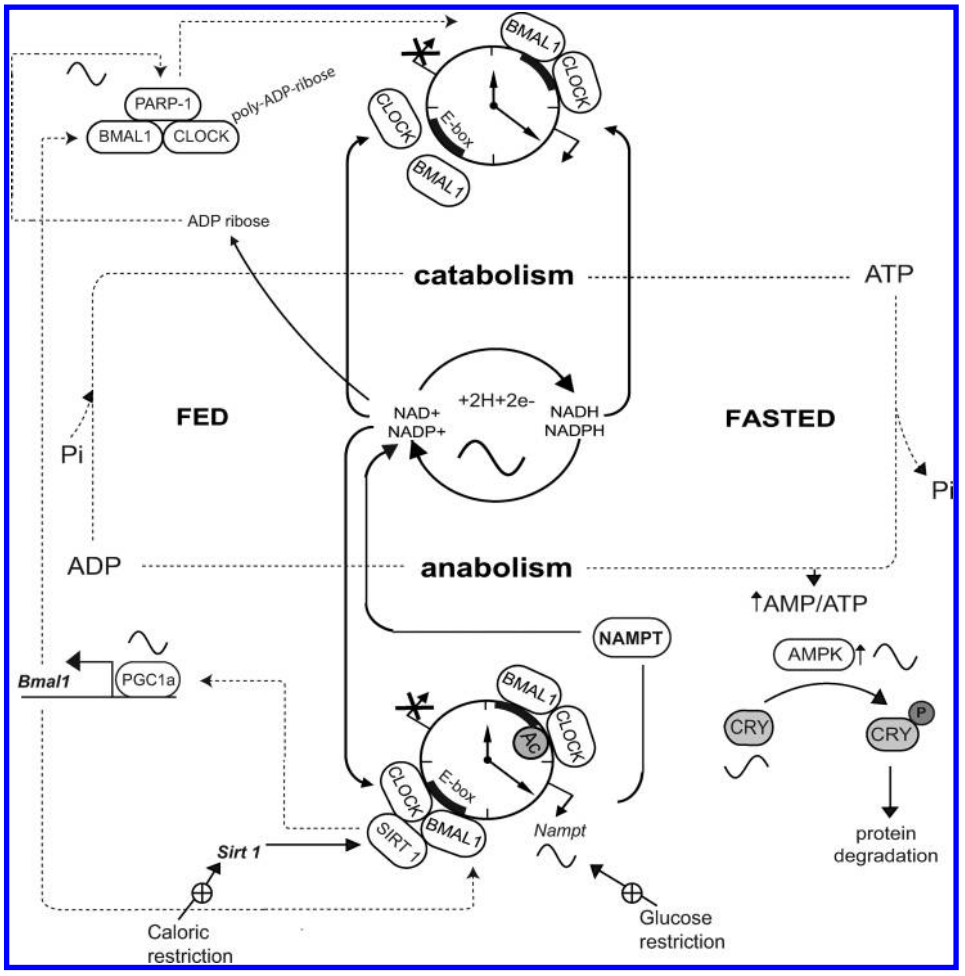

Figure 2. Communication between metabolism and the circadian clock in rodents. Cellular redox status (feeding status) is represented by nicotinamide adenine dinucleotide cofactors (NAD/H and NADP/H). Their synthesis and expenditure are circadian, but they also affect the circadian clock by promoting/preventing the DNA binding of core clock transcription factors. The core circadian clock regulates the expression of nicotinamide phosphoribosyletransferase (*Nampt*), the regulatory enzyme in NAD synthesis. NAD^+ is a cofactor for poly-ADP ribose-polymerase-1 (PARP-1) that adds ADP-riboses on the CLOCK protein. Adenosine monophosphate activated protein kinase (AMPK) senses the AMP/ATP ratio that defines the phosphorylation of CRY proteins, promoting their degradation. A part of the network where sirtuin 1 (*Sirt 1*) and PPARγ coactivator 1-α influence the expression/activity of the core clock is also shown.

attenuated. The amplitude of the corticosterone was also decreased,[63] which means that circadian synchronization of peripheral organs is deregulated and can lead to the development of metabolic syndrome.[65] PPARγ is mainly involved in adipocyte differentiation, lipid storage, and glucose homeostasis, while PPARα is included in fatty acid oxidation and lipoprotein metabolism.[58] PER2 can bind PPARα and REV-ERBα and in this combination binds to promoters of nuclear receptor target genes: hepatic nuclear factor 1α (*Hnf1α*), *Glucose-6-phosphatase*, and even *Bmal1*.[66] Metabolism is directly guided by one of the core clock components (PER2), but metabolism itself is feeding back to the clock since PER2 needs one of the nuclear receptor partners (PPARα, PPARγ, or REV-ERBα).

Circadian Disruption of Sleep and Hormones. Effects of circadian disruption in man can be observed as a disturbance of sleep pattern. Several studies describe different symptoms usually connected with glucose regulation, from diabetes, obesity, to metabolic syndrome. Short duration of sleep and poor quality of sleep predict the development of type 2 diabetes,[67] and sleep deprivation induces hunger through reduced levels of leptin and increased levels of ghrelin.[68] One of the first hormones related to the circadian cycle is melatonin. It is mainly produced in the pineal gland and released to the bloodstream during dark periods.[69] Its function is tumor-protective: if less melatonin is produced because of sleep deprivation or night-work, higher incidence of cancer is expected.[70−72] Melatonin also has an important function in glucose homeostasis.[73,74] At first, it was proposed that melatonin is responsive for night lowering of insulin.[75] More recently, it was shown that melatonin inhibits insulin release from pancreatic beta cells in response to glucose and is involved in the pathogenesis of type 2 diabetes.[76] Ablation of the pineal gland in rats leads to glucose intolerance and insulin resistance[77] (Figure 3).

Circadian Regulation of Glucose Levels. Glucose levels are variable during the day. One reason is the usual feeding pattern; the other is circadian regulation of insulin secretion and gluconeogenesis, which is especially important in fasting conditions. The rate limiting enzyme phosphoenolpyruvate carboxykinase (PCK) is regulated in a circadian manner through serine/threonine protein kinase Akt (AKT) mediated phosphorylation of transcription factor forkhead box O1 (FoxO1) that enhances its transcription[78] and with melatonin down-regulation of nocturnal hepatic PCK.[79] It is regulated also with kruppel-like factor (KLF10), which represses *Pck* in a time

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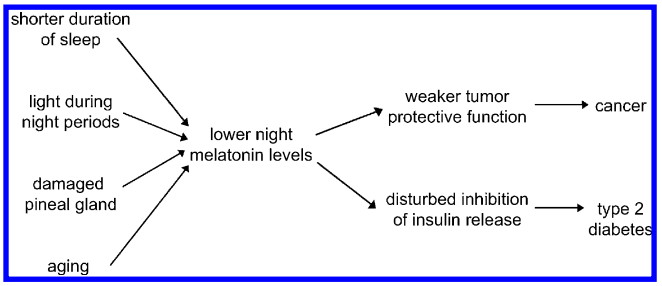

Figure 3. Melatonin importance in peripheral tissues and link to disease. If less melatonin is produced because of sleep deprivation or night-work, higher incidence of cancer is expected.[70−72] Melatonin also inhibits insulin release from beta cells in response to glucose and is involved in the pathogenesis of type 2 diabetes.[76]

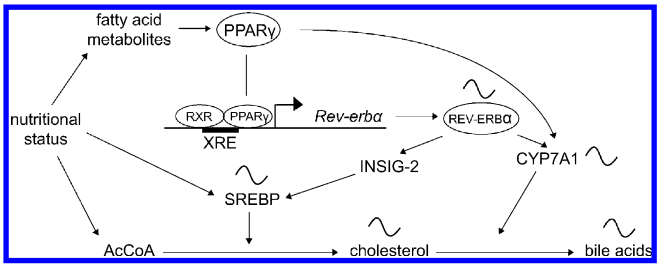

Figure 4. Circadian PPARγ regulation of cholesterol and bile acid synthesis. Peroxisome proliferator-activated receptor γ (PPAR γ) regulates the expression of REV-ERBα, which directly or indirectly regulates cholesterol and bile acid synthesis.

dependent manner. KLF10 was identified as a circadian output gene which is directly regulated with BMAL1/CLOCK.[80] Gluconeogenesis is regulated by cAMP in response to circulating hormones glucagon and epinephrine, but this same response is fine-tuned with *Cry1* expression. In night−day transition, CRY1 interacts with G protein coupled receptor (GPRC) and blocks this response to improve insulin sensitivity.[81] Most recent data show that CRY1 and 2 interact with the glucocorticoid receptor in a ligand-dependent fashion and globally alter the transcriptional response to glucocorticoids in mouse embryonic fibroblasts.[82] CRY deficiency doubles the number of dexamethasone-induced genes, suggesting that cryptochromes oppose glucocorticoid receptor activation. Genetic loss of *Cry1* and/or *2* results in glucose intolerance and constitutively high levels of circulating corticosterone. This is due to increased glucocorticoid transactivation in the liver. CRY1 and 2 associate with the glucocorticoid response element in the *Pck1* promoter in a hormone dependent manner, which couples the activity of clock and receptor target genes in regulating the normal metabolic homeostasis.

Circadian Aspect of Cholesterol and Fatty Acid Metabolism. Cholesterol diurnal variation is a consequence of dietary input and circadian transcription of hydroxymethylglutaryl CoA reductase (HMGCR). Cholesterol diurnal variation is demolished with dietary intake of cholesterol in a range of 1%, but the oscillation of low density lipoprotein (LDL) receptor and scavenger receptor (SR-B1) are maintained regardless of the diet.[83] Redundant cholesterol is transformed to bile acids with CYP7A1. CYP7A1 circadian nature was detected and explained through the D site of albumin promoter (albumin D-box) binding protein (DBP)[84,85] and REV-ERBα mediation.[43,86]

In the metabolic pathway of cholesterol and bile acids, nutrients are important as sources of acetyl-coenzyme A (AcCoA), as a mediators to SREBP inactivation, and as sources of fatty acid metabolites. They are important in the connection between *Rev-Erbα* and PPARγ. Fatty acid metabolites regulate PPARγ expression: at least in adipose tissue PPARγ dimerizes with RXR and regulates *Rev-Erbα* expression, so authors propose a feed-back loop of *Rev-Erbα* repressing PPARγ to induce adipogenic function.[87] REV-ERBα regulates cholesterol and bile acid synthesis also through modulation of SREBP activity. REV-ERBα controls the cyclic timing of SREBP accumulation in the nucleus[43] (Figure 4). Both cholesterol and bile acid synthesis have a circadian pattern. In rodents, the two processes are synchronous, while in man they are not.[88]

REV-ERBα is a nuclear receptor that binds heme as a prosthetic group. Heme synthesis itself is circadian, and many processes require heme for normal activity: NPAS2[89] and PER2[90] need heme as the prosthetic group. Aminolevulinic acid synthase 1 (ALAS1), the rate limiting enzyme of heme biosynthesis, requires succinyl CoA, a Krebs cycle intermediate. Gluconeogenesis competes with the Krebs cycle for metabolic intermediates whose depletion compromises heme biosynthesis as well.[91] It is believed that REV-ERBα acts as a receptor for heme which could provide a general mechanism for coordinating the circadian clock with glucose homeostasis and energy metabolism.[92]

The metabolism of fatty acids (FA) is composed of several processes which are daily oscillating: lipid digestion and absorption, lipoprotein metabolism, *de novo* FA synthesis, triglyceride turnover, phospholipid metabolism, and the oxidation of FA. These oscillations are a consequence of feeding pattern as well as circadian regulation. The latter is shown in the *Clock Δ19* mutant and BMAL1 null mice where most of these processes become asynchronous.[93] Lipid absorption peaks during the beginning of the active period. At this time also grater activity of digestive lipases as well as the enzymes involved in chylomicrometer synthesis occurs.[94,95] Oscillations of circulating triglycerides and lipoproteins persist during prolonged fasting, so it is under circadian control.[96] Lipoprotein lipase activity demonstrates time of day dependent oscillations which are in the opposite phase in muscle compared to adipose tissue.[97] Autonomous circadian clocks may therefore channel lipoprotein-derived triglyceride utilization into adipose and muscle at distinct times of the day.[98] Increased rates of lipolysis are during the less active phase and attenuation of lipolysis during the active phase.[99] Phospholipid metabolism generally peaks during the inactive phase.[100] Fatty acid oxidation can be measured by indirect calorimetry−respiratory exchange ratio (RER). Circadian oscillations were observed in constant darkness conditions with peaks during the periods of fasting.[93]

Nocturnin. Deadenylase nocturnin (NOC) is circadian in the liver but also has roles in bone-marrow stromal cells and adipocytes. NOC is activated with PPARγ and is in turn also involved in the regulation of PPARγ. NOC binds to PPARγ and enhances its activity by facilitating PPARγ2 transport to nucleus. Kawai et al. did not exclude the possibility of negative regulation of PPARγ by deadenylase activity of NOC. Therefore, a negative feedback loop could be generated.[101] Liver NOC transcription is partly regulated with the expression pattern of microRNA-122. If miR-122 was knocked down, the NOC rhythms increased in amplitude. Since both genes are important regulators of lipid metabolism and are also circadian

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output genes, they have important roles in the fine-tuning of both processes.[102]

XENOBIOTICS INFLUENCE THE HORMONAL ACTIVITY AND AFFECT OUR CLOCKS AND SLEEP

Several chemical compounds can affect the circadian rhythmicity of core clock genes. The application of large concentrations of serum in the media of cultured cells reset their circadian clock with activation of *Per1* and *Per2*.[103] Serum contains a large number of potential signals, such as growth factors and hormones. When Balsalobre et al. tried to determine which signaling pathway is included in the resetting, various chemicals were used: forskolin, which activates protein kinase A (PKA); phorbol-12-myristate-13-acetate (PMA), which activates protein kinase C (PKC); calcimycin which is a calcium ionophore; and epidermal growth factor[104] and a glucocorticoid analogue dexamethasone.[105] Since the listed compounds provoked the immediate early response of *Per1*, it can be concluded that several pathways are able to disturb the central circadian clock and affect its phase.[104]

The core circadian proteins can modulate response to genotoxic stress. Circadian mutant mice were tested for the sensitivity to anticancer drug cyclophosphamide. *Clock/clock* (the homozygous Clock mutant mice) and *Bmal1*$^{-/-}$ mice are extremely sensitive to the drug but *Cry1*$^{-/-}$*Cry2*$^{-/-}$ double knockout mice demonstrate high resistance. This suggests that the CLOCK/BMAL1 complex may directly control the molecular determinants of drug sensitivity at the transcriptional level.[106] Therefore, the CLOCK/BMAL1 complex is a promising target for pharmacological modulation of the circadian clock. The idea is to reset the clock in a drug sensitive tissue to the time when the toxicity is the lowest, therefore minimizing the damage effects of genotoxic treatments.[107]

Glucocorticoid hormones and their analogues induce circadian gene expression and transiently change the phase of expression in the liver, kidney, and heart,[105] so clinical use can lead to reinforcement of circadian rhythmicity. Alternatively, at other times dosing may serve as a rhythm disrupter.[108] Sleep onset is associated with an acute inhibition of cortisol secretion,[109,110] again influencing circadian expression on the periphery.

As explained previously, melatonin shows an endogenous rhythm generated by SCN and it peaks at night (1 a.m. to 5 a.m. in humans[111]). Among other functions, melatonin is connected with the onset of sleep. Light during the night can lower the peak of melatonin secretion, so disturbances of sleep as a result of jet-lag or night shift work are connected with lowered or altered melatonin secretion.[112,113] The main neurotransmitter regulating melatonin secretion is norepinephrine, which is released at night in response to SCN signals.[114,115] β1-Adrenergic blockers athenolol and propanolol and α2 blocker clonidine suppress nocturnal melatonin in a dose dependent manner. Activation of GABA-receptors by benzodiaepines reduces melatonin at night.[116,117] However, melatonin secretion is increased by medications that increase synaptic cateholamine availability, such as tricyclic antidepressants.[118] Many agents can alter the cycle of melatonin and can affect the tissues that express melatonin receptors. The effects of exogenous melatonin dosage are time dependent: when administered in the morning, it results in phase delay while in the evening, they phase advance the endogenous rhythm.[119]

Prolactin is excreted as a series of daily pulses occurring every 2−3 h, but the amplitude of released hormone is time dependent. The highest plasma prolactin concentrations occur late during the night.[120] Sleep onset is associated with an increase in prolactin secretion: if we take a nap during the day the secretion is less intense compared to night time sleep onset. Since prolactin plasma concentration is regulated by the circadian clock, the maximal secretion can be measured when sleep and circadian rhythmicity are in phase.[121] Prolactin secretion is restrained by dopamine, and a variety of stimulatory compounds were identified: estrogen, tyrotropin releasing hormone, vasoactive intestinal peptid (VIP), oxytocin, and growth factors (EGF and EGF-2).[122] Chronic use of neuroactive drugs like antidepressants, antimetics, and narcotics can mask the physiologic rhythmicity of prolactin.[123,124]

Interferons (IFN) have been widely used as antiviral and antitumor agents but can cause neuropsychiatric effects like depression and neurosis.[125] When IFNs are administered during the early morning, we can detect changes in the rhythm of cortisol and lymphocyte counts.[126] In animal studies, it was shown that IFNα disrupts the rhythm of *Per1* expression in SCN and affects locomotor activity and body temperature. The photic induction of the *Per1* in SCN is also completely disturbed by daily administration of IFNα at the early acute phase, which may have caused a functional disorder in the resetting and entrainment of SCN.[127] It seems that IFNα influences some input genes or genes of the core circadian clock.

CIRCADIAN CONTROL OF DETOXIFICATION PATHWAYS

Xenobiotic Sensors: Nuclear Receptors. Cell membrane is a barrier for protection of the cell from toxic water-soluble xenobiotics, but lipophilic substances can cross the membrane and accumulate until toxicity levels are reached. Therefore, biotransformation mechanisms evolved which enable the organism to convert xenobiotics into water-soluble metabolites and excrete them from the body.

Sensitive and specific sensors are required for induction of proper enzymes. This role is achieved by nuclear receptors. Xenobiotics are ligands that after binding to nuclear receptors translocate receptors to promoter regions of several drug processing genes.[128] The promoter sequence where nuclear receptors bind is named XRE, xenobiotic response element. Different nuclear receptors bind that response element, either as homodimers, heterodimers with retinoid X receptor (RXR), or as monomers.[129] Nuclear receptors expressed in the liver and white and brown adipose tissue display rhythmic patterns of expression.[130−132] The NURSA (Nuclear Receptor Signaling Atlas) consortium scanned circadian expression of nuclear receptors in different tissues. In the group of rhythmically expressed receptors, we find the aforementioned receptors that are involved in the core circadian clock: *RevErbα*, *RevErbβ*, and *Rorγ* and nutrient sensing nuclear receptors such as *Pparα*, *Pparδ*, and *Ppary*. From the group of nuclear receptors involved in xenobiotic metabolism RXR, the constitutive androstane receptor (CAR) and small heterodimer partner (SHP) are strongly oscillating in the liver (Figure 5). Another important receptor involved in xenobiotic metabolism is pregnane x receptor (PXR); however, it is not rhythmic.[132] PXR is mainly expressed in the liver and intestine. Its distribution is similar to CYP3A's distribution pattern.[133−136] CAR is expressed in the liver and also in the intestine. After induction with compounds like statins[137] or phenobarbital-like CYP2B inducers, CAR is translocated from cytoplasm to the nucleus.[138] It is not known which circadian factors contribute to the CAR circadian profile

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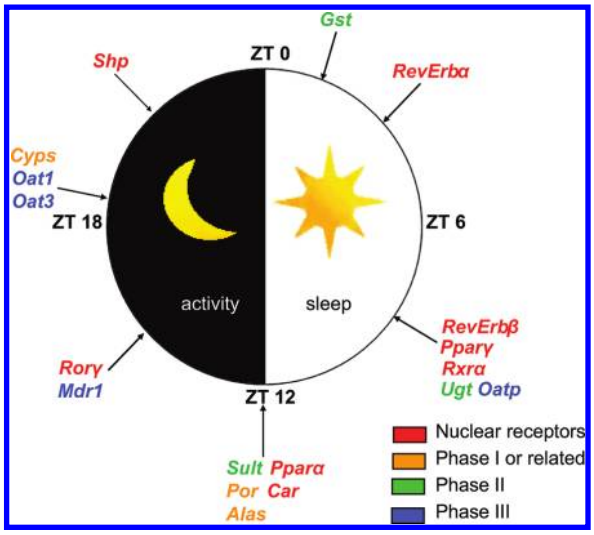

Figure 5. Clock of the mouse xenobiotic metabolism. A majority of circadian xenobiotic metabolism studies were done on rodents (mice and rats). They are nocturnal animals, acting and feeding during the night when the majority of phase I enzymes are expressed. Nuclear receptors, phase II and III enzymes are expressed around the clock. ZT means zeitgeber, a signal that synhcronises the internal circadian clock. The strongest zeitgeber is light. In standardized circadian experiments, light onset is at 7 a.m. (ZT 0) and dark onset is at 7 p.m. (ZT 12).

in the liver, but it is believed that PAR bZIP proteins control its transcription. Three proline and acidic amino acid-rich basic leucine zipper (PAR bZIP) proteins DBP, thyrotroph embryonic factor (TEF), and hepatic leukemia factor (HLF) are direct output mediators of the core circadian clock. All are expressed in the liver and regulate various genes involved in detoxification and drug metabolism. When triple knockout of PAR bZIP proteins was generated, mice showed high morbidity rate and hypersensitivity to xenobiotic compounds. In these mice also the CAR circadian expression profile was absent. So far, it is not possible to conclude whether this is a direct or indirect effect of the absence of PAR bZIP proteins.[139]

3,3′,5,5′-Tetrachloro-1,4-bis(pyridyloxy)benzene (TCOBOP) is a CAR ligand and activator. Mice fed with TCOBOP or in combination with cholesterol exhibit down-regulated expression of *Cry*1 and *Bmal1*.[140] Dietary aldehydes can induce dyslipidemia, and this state results in differentially regulated core circadian genes (*Clock* and *Cry1*) and genes involved in their regulation (*Sirt1*, cAMP-responsive element modulator *Crem* and *Foxo1*).[141] Therefore, xenobiotics can influence core circadian genes that regulate the expression of nuclear receptors and lead to disturbed metabolism overall.

SHP is an atypical orphan nuclear receptor containing the ligand binding and dimerization domains but lacks a DNA binding domain.[142] It interacts with many nuclear receptors and represses their transcriptional activity. It interacts also with CAR[143] and PXR[144] and inhibits them and is thus identified as a major repressor of xenobiotic detoxification. Mouse *Shp* mRNA shows circadian expression with a maximum at the end of the night,[145] which corresponds to the time where CAR starts to decline (Figure 5). It seems that SHP acts as a negative regulator of circadian expression of CAR.[146]

Phase I Drug Metabolizing Enzymes. When nuclear receptors enter the nucleus, they up-regulate the system of enzymes which metabolize xenobiotics. First are phase I drug metabolizing enzymes, which are mainly microsomal CYPs but also alcohol dehydrogenases, aldehyde dehydrogenases (*Aldhs*), carboxylesterases (*Cess*), and paraoxonases (*Pons*). They have oxidase, reductase, or hydroxylase activities[147] that are regulated with ALAS1 and P450 oxidoreductase (POR). All CYPs require heme as the prosthetic group, and ALAS1 is the rate limiting enzyme in heme biosynthesis.[148] As described above, the availability of heme is strongly circadian,[90] and expression of *Alas1* is regulated by the CLOCK paralogue NPAS2.[90] Therefore, functionality of CYPs is gated with the availability of heme. POR is a membrane-bound enzyme required for electron transfer to cytochromes P450.[148] The transcription of both *ALAS1* and *POR* is regulated by CAR, and their expression pattern in PAR bZIP triple knockout mice is decreased.[139] In these mice, the expression pattern of phase I enzymes (*Cyp2b*, *Cyp2c*, *Cyp2a*, and *Cyp3a*) is also changed. For some of them, direct binding of DBP was shown: in the case of *Cyp3a4*, activation by binding to the element near the transcription start site was confirmed.[149] Also *Cyp2a4* and *Cyp2a5* are under the direct control of DBP.[150] Since many CYPs are regulated by CAR, the altered expression pattern can result from an indirect effect of PAR bZIP knockout. However, some of the CYPs are directly regulated by the core circadian clock: in the case of CYP2E1, it was shown that induction of expression with hepatic nuclear factor 1α (HNF-1α) was decreased upon the addition of CRY1.[151] Phase I enzymes and transporters that help in uptake and clearance of xenobiotics are expressed in a coordinate fashion and reach maximal expression during the night when animals are active and feeding (Figure 5).[147] Thus, enzymes that eliminate xenobiotics from the body are expressed maximally at times when ingestion is most probable.

Phase II Drug Metabolizing Enzymes. The phase II group are conjugating enzymes. They also contribute to the conversion of lipophilic compounds to soluble forms which facilitates their excretion into the bile, feces, or urine. The phase II group consists of many superfamilies of enzymes: sulfotransferases (SULT), UDP-glucuronosyltransferases (UGT), NAD(P)H-quinine oxidoreductases (NQO), epoxide hydrolases (EPH), glutation *S*-transferases (GST), and *N*-acetyltranferses (NAT).[152] Most phase II enzymes also show diurnal expression, but their pattern is not the same for the entire group. mRNA levels of *Ugts* (*Ugt1a1*, *1a6*, *1a9*, *2a3*, *2b35*, and *2b36*) are maximal during the light time of the day, when the animals are fasting (Figure 5). *Gsts* (*Gst1/2*, *1a4*, *m2*, and *p1*) are maximally expressed during the early light phase. *Sults* have higher expression during light to dark transition. Taken together, in rodents phase II conjugation of xenobiotics in the liver has a circadian rhythm with more glutathione conjugation in the early light phase, glucuronidation in the late light phase, and sulfation in the early dark phase[147] (Figure 5). In PAR bZIP deficient mice, many of the phase II transcripts were down-regulated (*Ces3*, *GSTτ1*, and *GSTτ3*). This may be again due to direct or indirect (CAR mediated) influence on transcription.[139]

Phase III Drug Metabolizing Enzymes. In the group of phase III metabolizing genes, we find transporters that help in the uptake of xenobiotics from blood to the liver or eliminate the metabolized xenobiotics. Their expression is limited to the organs where the excretion occurs: in the liver (excretion via bile), intestine (via feces), and kidney (via urine). In the liver, transporters reside on the sinusoidal membrane. For the uptake, several proteins are included: Na^+-taurocholate-cotransporting polypeptide (*Ntpc*), organic anion-transporting polypeptide (*Oatp*) 1a1, 1a4, 1b2, and 2b1, organic anion

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transporter 2 (*Oat2*), organic cation transporter 1 (*Oct1*), and equilibrative nucleoside transporter 1.[153] Murine hepatic *Oatp* transporters (*1a1*, *1a4*, and *1b2*) show maximal expression at approximately 2 p.m. (second half of light day); *Oct1* shows a similar expression. No significant daily fluctuations were observed in the expression of the bile acid transporter *Ntpc* or the bidirectional nucleoside transporter equilibrative nucleoside transporter 1.[147] For the transport of xenobiotic metabolites out of hepatocytes into the bile, the canalicular transporters are used. These include multidrug resistance-associated protein 2 (*Mrp2*), breast cancer resistance protein (*Bcrp*), multidrug resistance protein 1 (*Mdr1*), multidrug and toxin extrusion 1 (*Mate1*), and the bile salt export pump. mRNA expression of these show mild or none circadian rhythmicity with the exception of *Mdr1* that peaks in rodents at 10 p.m.[147] (Figure 5). If the excretion is directed to kidneys and urine, the processed xenobiotics must be transported back to the blood. Transporters *Mrp3*, *4*, and *6* are responsible for this alternative efflux. These transporters do not show a circadian profile.[147] The vast majority of water-soluble drugs or drug metabolites are eliminated by the kidney. The rate of drug elimination in urine depends on renal blood flow, the glomerular filtration rate, the capacity of the kidney to reabsorb or to secrete drug molecules across the tubular epithelium, the urine flow, and the degree of urine alkalinization/acidification by the kidney. These functional variables have been shown to follow circadian rhythms.[154] Most of renal transporters that are responsible for reabsorption and secretion of drugs belong to the ATP-binding cassette (ABC) superfamily and solute cariers (*Slc*). Many of these show strong circadian pattern in the distal nephron and the collecting duct.[155] OAT1 and OAT3, two transporters that mediate the basolateral secretion of a wide variety of drugs, exhibit circadian expression patterns with a maximum during the night. Expression of *Abcc4* and OAT2 is significantly reduced in the kidney of PAR bZIP knockout mice. This is the evidence for the control of tubular reabsorbtion/secretion by the circadian clock.[139] In the jujenum, more precisely intestinal mucosa enterocytes, many members of the ABC superfamily of transporters can be found.[156] Their role in drug pharmacokinetics remains unclear, but there is increasing evidence that they mediate the absorption of enterally delivered drugs and contribute to intestinal clearance of systemic drugs.[157] In experiments where they screened jujenum transporters in rats, 6 out of 10 studied transporters showed circadian rhythmicity: *Bcrp*, monocarboxylate tetransporter (*Mct1*), *Mdr1*, *Mrp2*, peptide transporter 1 (*Pept1*), and organic cation transporter (*Octn2*). Their peak level of expression is between ZT0 and ZT12, the daylight fasting period. Most of these were initially described as chemoresistance proteins overexpressed in cancer cell lines. It may be interesting to investigate whether these transporters display a diurnal rhythmicity in visceral cancers in vivo, as this would have strong therapeutic implications.[158]

GOOD PRACTICE OF DRUG ADMINISTRATION: THE TIME MATTERS

Chronotherapy is a new interdisciplinary science aimed at delivering drugs in synchrony with endogenous biological rhythms. As discussed earlier, many crucial physiological facts, i.e., the body temperature, plasma concentration of hormones, and other metabolites, quantity of receptors, enzymes, transporters, etc., change over the 24 h time in a circadian manner. Consequently, a precisely timed drug delivery is required to provide maximum therapeutic efficacy. Diseases that benefit from the time dependent delivery of drugs are called chronotherapeutic diseases. These include asthma, cardiovascular disorders, rheumatoid arthritis, and several types of cancer and in a minor scale also diabetes, pain, and others.[159] Additionally, myocardial infarction and thrombosis occur early in the morning, and the absence of normal nocturnal variation of blood pressure is a predictor for cardiovascular risk. Such phenotypes are affected by the circadian clock function that can benefit greatly from chronotherapy.[160] However, despite clear scientific evidence, appreciation of chronotherapy in cardiovascular events including hypertension still lags behind. The clinical trials Syst-Eur (Systolic Hypertension in Europe) and HOPE (Heart Outcomes Prevention Evaluation) showed that administration of hypertension drugs in the evening decreases cardiovascular risk, as reviewed in ref 161. The recent prospective MAPEC (Monitorización Ambulatoria de la Presión Arterial y Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring and Cardiovascular Events) study clearly established the benefit of dosing hypertension medication at bedtime since this regime maintains the normal diurnal blood pressure. Even more important is the finding that bedtime chronotherapy significantly reduced cardiovascular risk.[162,163]

International Agency for Research in Cancer (World Health Organization, WHO) on December 5, 2007 concluded that shift work that involves circadian disruption is probably carcinogenic in humans (http://www.iarc.fr/en/media-centre/pr/2007/pr180.html). Most prone to circadian deregulation are the hormone dependent cancers, such as breast, prostate, and ovarian cancer. The estimated risk level is 2A, which is close to full evidence.[164] The basis for the WHO conclusions are epidemiological studies involving mainly nurses and flight attendants. Studies established that long-term nightworkers have a higher risk of breast cancer risk compared to those who did not work at night. These human studies were consistent with animal studies that demonstrated that light at night or simulated chronic jet lag can substantially increase tumor development. Other experimental studies show that reducing melatonin levels at night increases the incidence or growth of tumors. Thus, also in cancer management, prevention of circadian disruption might represent a novel and challenging objective of therapeutics.

The typical human medicine is carefully administered at the appropriate timing to result in targeted blood levels and predictable clearance based on rigorous ADME (Absorption, Distribution, Metabolism, and Excretion) data, irrespective of circadian regulation alone. Anticancer drugs appear to be a special subclass. The tolerability of anticancer drugs differs significantly between males and females. If chemotherapeutics are administered at their most toxic time, which can differ between the genders, this can disrupt the patient's clock, contributing to morbidity. Levi et al.[164] reviewed in detail the anticancer drugs with documented relevance of circadian timing in experimental animals and in clinical trials. In animals, circadian timing modified the toxicity of tens of anticancer drugs, including cytostatics, cytokines, and biological agents. A potentially lethal dose leads to increased incidence of deaths if drug administration was not appropriate by time: the change in incidence of morbidity rose from 2-fold to over 10-fold. The animal studies concluded that even if chemotherapeutics are combined, they display less toxicity close to times of their best tolerability. Examples of such combinations were doxorubicin-cisplatin, gemcitabine-cisplatin, etc.

The clinical and translational data show differences in the circadian rhythms of individual cancer patients, but currently there are no biochemical markers that would allow an efficient and noninvasive determination of an individual's endogenous clock. The individualization of pharmacotherapy is mainly by monitoring drug concentrations, in rare cases including also the genetic diagnosis.[165] Thus, experimental animals and in vitro models are still required to pave the way toward personalized cancer chronotherapies. With the aid of computational methods including mathematical modeling one would be able to predict a number of situations, where each situation would represent an individual patient. These are the current steps toward the future goal: personalized chronotherapies where the timing of drugs will be adjusted to an individual's circadian rhythm.

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ABBREVIATIONS

SCN, suprachiasmatic nucleus; CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle Arnt-like protein-1; NPAS2, neuronal PAS domain protein 2; CRY, cryptochorme (photolyase-like); PER, period homologue (*Drosophila*); CK1, casein kinase 1; RORE, retinoic acid-related orphan receptor response element; REV-ERB, Reverse-erb; ROR, retinoic acid-related orphan receptor; SREBP, sterol regulatory element-binding protein; NAD(H) and NADP(H), nicotinamide adenine dinucleotide cofactors; NAMPT, nicotinamide phosphoribosyletransferase; SIRT1, nutrient responsive deacetylase sirtuin 1; PARP-1, poly-ADP ribose-polymerase-1; AMPK, adenosine monophosphate activated protein kinase; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; PGC1α, PPARγ coactivator 1-α; HF, high-fat diet; HNF1α, hepatic nuclear factor 1α; PCK, phosphoenolpyruvate carboxykinase; AKT, serine/threonine protein kinase Akt; KLF, Kruppel-like factor; GPRC, G protein coupled receptor; HMGCR, hydroxymethylglutaryl CoA reductase; LDL, low density lipoproteins; SR-B1, scavenger receptor; CYP, cytochrome P450; DBP, D site of albumin promoter (albumin D-box) binding protein; AcCoA, acetyl-coenzyme A; ALAS1, aminolevulinic acid synthase 1; FA, fatty acid; RER, respiratory exchange ratio; NOC, noctrunin; PK, protein kinase; PMA, phorbol-12-myristate-13-acetate; VIP, vasoactive intestinal peptid; EGF, epidermal growth factor; IFN, interferon; XRE, xenobiotic response element; NURSA, nuclear receptor signaling atlas; CAR, constitutive androstane receptor; SHP, small heterodimer partner; PXR, pregnane x receptor; PAR bZIP, proline and acidic amino acid-rich basic leucine zipper; TEF, thyrotroph embryonic factor; HLF, hepatic leukemia factor; TCPOBOP, 3,3′,5,5′-tetrachloro-1,4-bis-(pyridyloxy)benzene; CREM, cAMP-responsive element modulator; FOXO1, forkhead box O1; ALDH, aldehyide dehydrogenase; CES, carboxylesterase; PON, paraoxonase; POR, P450 oxidoreductase; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase; NQO, NAD(P)H-quinine oxidoreductase; EPH, epoxide hydrolase; NAT, *N*-acetyltranferse; GST, glutation *S*-transferases; NTPC, Na^+-taurocholate-cotransporting polypeptide; OATP, organic anion-transporting polypeptide; OAT, organic anion transporter 2; OCT, organic cation transporter; MRP, multidrug resistance-associated protein; MDR, multidrug resistance protein; BCRP, Breast cancer resistance protein; MATE, multidrug and toxin extrusion; ABC, ATP-binding cassette superfamily; SLC, solute cariers; MCT, monocarboxylate tetransporter; PEPT1, peptide transporter 1; WHO, World Health Organization; Syst-Eur, systolic hypertension in Europe; HOPE, Heart Outcomes Prevention Evaluation, clinical study; MAPEC, Monitorización Ambulatoria de la Presión Arterial y Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring and Cardiovascular Events, clinical study; ADME, Absorption Distribution Metabolism and Excretion

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