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Minireview

Crosstalk between xenobiotics metabolism and circadian clock

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Abstract **Many aspects of physiology and behavior in organisms from bacteria to man are subjected to circadian regulation. Indeed, the major function of the circadian clock consists in the adaptation of physiology to daily environmental change and the accompanying stresses such as exposition to UV-light and food-contained toxic compounds. In this way, most aspects of xenobiotic detoxification are subjected to circadian regulation. These phenomena are now considered as the molecular basis for the time-dependence of drug toxicities and efficacy. However, there is now evidences that these toxic compounds can, in turn, regulate circadian gene expression and thus influence circadian rhythms. As food seems to be the major regulator of peripheral clock, the possibility that food-contained toxic compounds participate in the entrainment of the clock will be discussed.**

Keywords: Circadian rhythms; PARbZip transcription factors; Detoxification; Liver metabolism

1. Introduction

Virtually all light-sensitive organisms from cyanobacteria to humans show rhythmic regulation of many aspects of physiology and behavior. The cycles with a period of approximately 24 h are considered to be circadian, derived from the Latin words *circa diem* (meaning about a day). It has been recently suggested that the evolution of circadian clock in the early metazoan period was to avoid genotoxic UV-light [1]. Primitive marine organisms have used blue-light receptors (e.g., photolyase and cryptochromes) to avoid UV-rich sunlight by moving to deeper sea levels. These blue-light receptors later evolved to become coupled to a circadian oscillator that could anticipate this up-and-down migratory behavior. In mammals, this behavior has evolved to include the anticipation of daily food availability and predator threat.

At a physiological level, the main task of the circadian clock is the optimization of metabolism and energy utilization for sustaining life processes in the organism. In this context, many aspects of the physiological adaptation to daily food intake, metabolism and detoxification are regulated in an anticipatory fashion by the circadian clock [2]. For example, rest and activity cycles, heart rate, blood pressure, bile and urine production, drug metabolism and transport in liver and intestine as well as endocrine functions are all subjected to daily fluctuations. The mammalian timing system is organized in a hierarchical manner with a central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus which synchronizes in a coordinated fashion cellular circadian oscillators present in all peripheral organs by cyclic neuronal and humoral signals emanating directly or indirectly from the SCN [3]. At a molecular level, there is no difference in the circadian clock of SCN neurons and peripheral cells [4]. However, there is a major distinction in their synchronization: SCN neurons phase is engendered by light-dark cycles perceived by the retina [5], whereas peripheral oscillators phase is adjusted by chemical zeitgebers, like for example signals generated by feeding-fasting rhythms [6,7]. In this context, the time-dependent inactivation of food-contained toxic compounds is among the important function of the circadian clock. As a consequence, the circadian pharmacokinetics and pharmacodynamics that modulate drug effectiveness and toxicity are a manifestation of the circadian regulation of xenobiotic detoxification and could have important clinical applications since they allow treatment modification in order to increase drug effects or decrease side effects [8] (see Fig. 1).

In mammals, the xenobiotic defense system involved in drug metabolism is composed of three groups of proteins assuming distinct functions [9]. The phase I group contains the microsomal P450 cytochrome super-family enzymes with oxidase, reductase or hydroxylase activities. Phase II, or conjugating enzymes, comprises sulfotransferases (SULT), UDP-glucuronotransferases (UGT), NAD(P)H:quinine oxidoreductases (NQO), epoxide hydrolases (EPH), glutathione-*S*-transferases (GSH), and *N*-acetyltransferases (NAT). Conjugation help to make lipophilic compounds hydrophilic enough to subsequently control and facilitate their excretion into bile, faeces and/or urine by the transporters or phase III group, like multidrug resistance-associated proteins (MRP) or P-glycoprotein (P-gp), which serve as barriers to limit the penetration of xenobiotics. In addition, some other proteins like the Aminolevulinic acid synthase (ALAS1) and the P450 oxidoreductase (POR) regulate the activity of most of the phase I enzymes. ALAS1 is the rate-limiting enzyme in heme synthesis, the prosthetic group of all cytochrome P450 enzymes. Since monooxygenase reaction requires electrons that are extracted from NAD(P)H and transferred via

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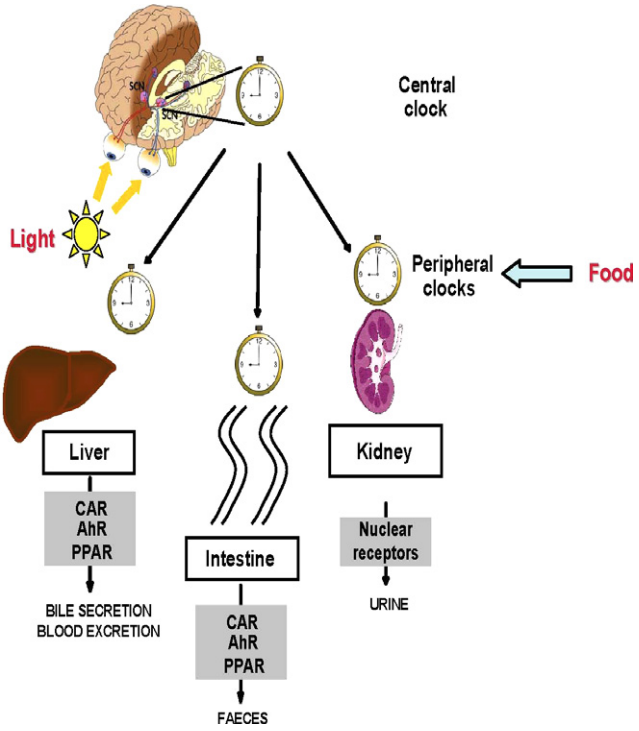

Fig. 1. Hierarchical organization of the circadian detoxification machinery. The light/dark cycle resets the activity of the master pacemaker located in the SCN via ganglionar cells of the retina. The SCN then provides timing cues that will synchronize other slave oscillators located in peripheral tissues. Peripheral oscillators can also be reset by changing the feeding rhythm. As a result, peripheral organs display synchronized orchestration of their individual detoxification processes which lead to circadian detoxification of the organism.

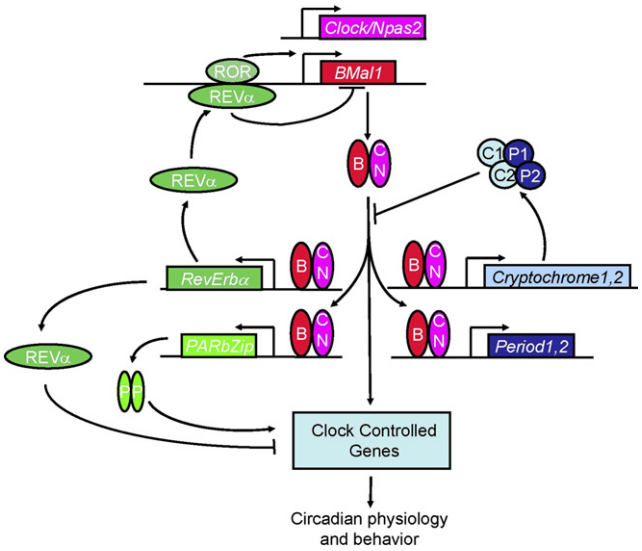

Fig. 2. Simplified model of the mammalian circadian oscillator. The molecular mammalian circadian clock is based on molecular feedback loops with a positive limb (BMAL1 heterodimer) and a negative limb (PER/CRY complex) that are interconnected via the nuclear orphan receptor REV-ERBα. This core oscillator, in addition to the core oscillator-regulated circadian transcription factors REV-ERBα and PARbZip, contribute to the generation of circadian clock controlled genes which participate in the generation of circadian physiology and behavior.

the flavin group of POR to the heme group of the cytochrome P450 enzymes, expression of cytochrome P450 enzymes, ALAS1 and POR are coordinated.

Interestingly, genome-wide analysis of liver transcriptome revealed that proteins of the phase I–III groups of detoxification as well as ALAS1 and POR are expressed in a circadian fashion [10–13]. It is thus conceivable that the circadian expression of proteins involved in xenobiotic detoxification is responsible for the daytime-dependent drug metabolism that modulates drug effectiveness and toxicity.

2. Control of circadian genes expression

Studies in mice have shown that the circadian rhythm in gene expression is generated by a molecular oscillator, presents in all cells of the animal, driven by transcriptional and post-transcriptional feedback loop involving a positive and a negative limb. The positive limb consists of the bHLH-PAS transcription factor BMAL1 and its dimerization partners CLOCK or NPAS2. This heterodimer activates the transcription of the members of the negative limb cryptochrome (*Cry*) and period (*Per*). As a consequence, CRY and PER accumulate until they reach a treshold level that will allow them to form complexes to attenuate the transcriptional activity of the BMAL1 heterodimer and thereby autorepress their own genes. Subsequently, this leads to a decrease of the CRY-PER complex now unable to perform the autorepression and a new cycle of *Cry* and *Per* transcription can start. The same activators and repressors drive the circadian expression of the orphan nuclear receptor REV-ERBα which periodically represses *Bmal1* expression and then contributes to the circadian expression of *Bmal1* (see Fig. 2 and for more detailed reviews, see Ref. [14]).

In addition to the core oscillator genes, the circadian clock drives numerous output genes to translate circadian rhythm into physiological and behavioral events. These output genes comprise transcription factors directly controlled by the core oscillator [15,16] that repress (REV-ERBα) [17] or activate (PARbZip) [18,19] their target gene. This transcription factors cascade thus orchestrates the circadian genes expression involved in the daytime-dependent xenobiotic detoxifications. Transcriptome profiling in several tissues indicated that 2–10% of the genes are transcribed in a circadian manner [10–13]. The transcriptional circuitry leading to circadian detoxification is resumed in Fig. 3 and will be described in the next section.

3. Circadian transcription factors and detoxification

3.1. PARbZip transcription factors

Recent data suggests that the well-conserved transcription factors of the PARbZip family play an important role in xenobiotic detoxification. This family is composed of the three members DBP (albumin site *D*-*b*inding *p*rotein), TEF (*t*hyrotroph *e*mbryonic *f*actor) and HLF (*h*epatocyte *l*eukemia *f*actor). These proteins bind DNA elements of the consensus sequence 5′-VTTAYGTAAY-3′(where V is C, G or A, and Y is C or T) as homo- or heterodimer [20]. They are expressed under a robust circadian fashion in most organs, although the

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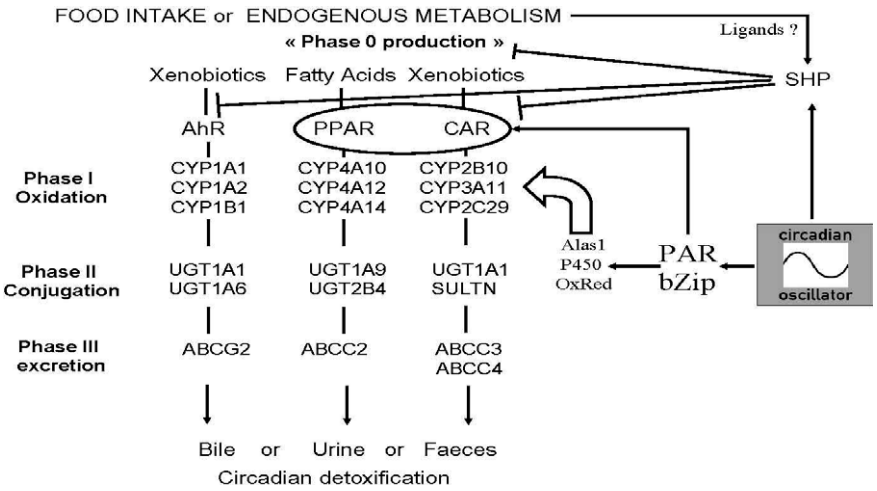

Fig. 3. Transcriptional network controlling circadian detoxification. The core oscillator control circadian expression of PARbZip transcription factors which, in turn, control the expression of CAR and PPARα, but also Alas1 and P450 OxRed, to coordinate an important part of the circadian xenobiotic detoxification. In addition, this oscillator induces the circadian expression of AhR, contributing to another way of regulation of circadian drug metabolism. Finally, the BMAL1-controlled circadian expression of SHP negatively modulates different aspects of the xenobiotic response and amplifies the circadian regulation.

expression of HLF is more restricted to brain, liver, kidney and small intestine [21]. Mice devoid of one or two PARbZip genes show mild phenotypes. However, mice deficient of all three members suffer from a high juvenile mortality and a high adult morbidity. The high mortality within the first three months is due to spontaneous and sound-induced seizures probably caused by a defect in vitamin B6 metabolism. PARbZip-deficient mice have reduced level of pyridoxal phosphate (PLP), the active form of vitamin B6 and a required coenzyme involved in neurotransmitter synthesis. The gene coding for pyridoxal kinase (*Pdxk*), that controls PLP synthesis, is under the control of PARbZip transcription factors [19]. Despite the fact that after three months the seizures decreased, the mice continue to present an important mortality since less than 20% of them are still alive after one year. Moreover, PARbZip-deficient mice show signs of accelerated aging, such as cachexia, lordokyphosis, and an absence of vigor. Transcriptome profiling using DNA microarray technology revealed that PARbZip proteins control expression of many genes involved in xenobiotic detoxification in liver and kidney [18]. These include genes of the phase I (Cyp 2b, 2c and 2a), phase II (Ces3, Cml3,4,5, GSTt1, a3) and phase III (ABCG2) group of detoxification. In addition, these proteins control the expression of ALAS1 and POR, two enzymes required for the activity of cytochrome P450 enzymes.

Importantly, this study revealed that PARbZip transcription factor control the circadian expression of the constitutive androstane receptor (CAR), a key nuclear receptor involved in xenobiotic detoxification [22]. The consequence of the circadian expression of CAR is a strong daytime-dependent induction of *Cyp2b10* mRNA by phenobarbital in liver and small intestine of wild-type mice, whereas PARbZip-deficient mice have a very low induction throughout the day. Moreover, PARbZip-deficient mice are highly susceptible to toxicity induced by anticancer drugs. Therefore, it is possible that the downregulation of some detoxification genes in PARbZip triple knockout mice, including *Cyp2b10*, is a consequence of the decreased expression of CAR but not a consequence of the PARbZip deficiency per se. A recent study also revealed a role for clock genes in xenobiotic tolerability [23]. The authors of this study show that mice with a *Bmal1* null allele or a mutation of the *Clock* gene displayed increased sensibility to the toxic effect of the anticancer agent cyclophosphamide, whereas mice devoid of the two *Cry* genes were more resistant to this effect. As, at least for DBP, the expression of PARbZip transcription factor is obliterated in *Clock* and *Bmal1* knockout mice whereas this expression is constitutively high in *Cry*-deficient mice [16,24], it is conceivable that these effects reflect the level of PARbZip transcription factors, and of their target genes.

3.2. Peroxisome proliferator activated receptor α

Peroxisome proliferator activated receptor alpha (PPARα) is a nuclear receptor with a modular structure typical for steroid receptor that binds to its cognate DNA elements as heterodimers with the retinoid X receptor α (RXRα). PPARα is activated by compounds referred to as peroxisome proliferators, such as lipid lowering fibrates, phthalate-ester plasticizers, as well as endogenous fatty acids. In response to these xenobiotic toxic compounds, activated PPARα stimulates the expression of phase I and II proteins such as Cyp4a [25] and UGT [26,27]. If the major function of PPARα is to regulate lipid and glucose homeostasis [28], the requirement of the PPARα detoxification pathway has been shown recently in the case of toxic compounds contained in vegetal food such as sesame grains [29].

Like other nuclear receptor, PPARα expression follows a circadian rhythm at the mRNA and protein level [30]. It has been suggested that this circadian expression is controlled directly by BMAL1 and the molecular oscillator [31]. However, recent data suggests that lipid metabolism regulated by PARbZip proteins seems to be also involved in the regulation of PPARα expression (F. Gachon and Ueli Schibler, unpublished results).

3.3. Aryl hydrocarbon receptor

The aryl hydrocarbon receptor (AhR), and its dimerization partner AhR nuclear translocator (Arnt), belong to the

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basic-helix-loop-helix (bHLH)-PAS family of transcription factors. AhR/Arnt is activated by halogenated and polycyclic aromatic hydrocarbons such as dioxin [32]. Once activated, the AhR/Arnt heterodimer binds to its cognate DNA elements and activate phase I and II enzymes such as Cyp1a and 1b, UGT and NAD(P)H dehydrogenase [33,34]. AhR is known to be modulated by a variety of dietary plant constituents present in vegetables and fruits and is also one of the major effectors of the elimination of food-contained toxic compounds [35]. Finally, and not surprisingly, AhR and Arnt show both a diurnal expression in many organs including liver [36]. Interestingly, Cyp1a1, the major AhR target gene, displays a circadian expression suggesting a daily activation of the receptor by food-contained toxic compounds [37].

3.4. Small heterodimer partner

The small heterodimer partner (SHP) is an atypical orphan nuclear receptor containing the ligand-binding and dimerization domains but lacking a DNA-binding domain. However, SHP is located in the cell nucleus where it can interact with many nuclear receptors and repress their transcriptional activity [38,39]. Interestingly, it has been shown that SHP is able to interact and inhibit CAR [38,40], and also the related pregnane X receptor (PXR) [41], two nuclear receptors that play a fundamental role in xenobiotic detoxification. Importantly, these two proteins are involved in the detoxification of more than 60% of the drugs currently available and which display considerable overlap in their action [42–44]. In addition, an interaction between SHP and Arnt has been also described, despite the fact that Arnt is not a nuclear receptor. This interaction leads to the repression of the activated AhR/Arnt heterodimer by SHP [45].

Since CAR, PXR and AhR constitute the major part of the response to xenobiotics, the ability of SHP to interact and thus subsequently inactivate them, identify SHP as a major repressor of the xenobiotic detoxification. Interestingly, it has been shown that *SHP* mRNA showed a circadian expression pattern in mouse liver, with a maximum of expression at the end of the night which corresponds to the mouse active period [46]. The authors speculate that this circadian expression is directly controlled by the positive branch of the oscillator via an interaction with the nuclear receptor LRH-1 (liver receptor homolog-1), whereas the phase of *SHP* expression did not correspond to the one of a classical BMAL1 target gene. In addition, this maximum time of expression correspond to the time where CAR and AhR/Arnt start to show decreased expression and also less transcriptional response to their normal activators. It seems that circadian SHP expression acts as a negative modulator of the xenobiotic response and could play potentially an important role in liver metabolism of toxic drugs by amplifying the time-dependent response to toxic compounds. Since SHP does still have the ability to bind a ligand, it will be of interest to determine whether xenobiotics and/or their metabolites can modulate SHP activity and therefore the end of the xenobiotic response. Moreover, the recent characterization of small molecules those are able to activate LRH-1 open the possibility to study detoxification modulation by nuclear receptors in a circadian manner [47]. Intriguingly, SHP was originally described as a CYP7A1 repressor, the limiting step of the bile acid synthesis [48,49]. Bile acids are toxic compounds detoxified by CAR among other nuclear receptors and are involved in cholesterol metabolism [50]. Enzymes generating endogenous toxics are often call "Phase 0 enzymes" by analogy with the phase I–III detoxification systems (see above). Based on the hopeful role of SHP, it was anticipated that SHP and CYP7A1 rhythms will be strictly antiphasic. However, SHP regulation by BMAL1/CLOCK and LRH-1 on one hand and CYP7A1 promoter *trans*-activation by LRH-1 on the other hand seem to exclude a major role for SHP in CYP7A1 bile acid-mediated negative feedback and makes more likely that SHP will control CYP8B1 a downstream enzyme of the pathway. This can explain why SHP transgenic mice that over express SHP do not have a smaller bile pool as assessed by the bile acid content of the blood [51]. It explains also why CYP7A1 expression does not always negatively correlate with SHP expression [52]. More research will be required to elucidate the interactions between production and inactivation of toxics.

4. Perturbation of the circadian clock by xenobiotics

If the impact of circadian rhythm on drug metabolism and xenobiotic detoxification start to be described, there is also now evidences showing perturbations of circadian rhythm by xenobiotics [33,53–57]. Indeed, at a molecular level, xenobiotic exposure can significantly alter the expression of circadian clock genes by different pathways; mostly AhR and PPARα (see Table 1). By disturbing the circadian clock, and hence circadian expression of xenobiotic metabolism and transport genes, some drugs might modify their own metabolism, and consequently their toxicity. Hence, WY14643, a synthetic PPARα ligand, could entrain the circadian clock by activation of the *Bmal1* promoter [53], whereas TCDD, an activator of AhR, disrupts the circadian clock by downregulation of *Per1* and *Per2* expression [55].

Various other compounds that target known signaling pathways, such as PMA (phorbol 12-myristate 13-acetate) or forskolin, and are sometimes used as medical drugs can also perturb or entrain the circadian clock [58]. In the same context, drugs that mimic natural hormones like glucocorticoid or

Table 1
Transcriptional regulation of circadian clock genes by xenobiotics

Circadian gene	Drug	Receptor	Reference
BMal1	WY14643	PPARα	Canaple et al. [53]
	TCDD	AhR	Miller et al. [56]
Per1	FICZ	AhR	Mukai and Tischkau [57]
	TCDD	AhR	Garrett and Gasiewicz [55]
			Miller et al. [56]
Per2	TCDD	AhR	Garrett and Gasiewicz [55]
			Fletcher et al. [33]
Per3	DEHP	PPARα	Currie et al. [54]
Cry1	FICZ	AhR	Mukai and Tischkau [57]
	DEHP	PPARα	Currie et al. [54]
Cry2	FICZ	AhR	Mukai and Tischkau [57]
Dbp	DEHP	PPARα	Currie et al. [54]

FICZ: 6-Formylindolo[3,2-b]carbazole.
TCDD: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin.
DEHP: Diethylhexylphtalate.

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steroid can also have strong effects on circadian gene expression [59,60]. It is also interesting to mention the possible effect of retinoic acid in circadian regulation of detoxification. Like other drugs or hormones cited above, retinoic acid can also interfere with the circadian clock by inactivating the BMAL1/CLOCK or NPAS2 heterodimers after the ligand-dependent interaction of its receptors RAR and RXR with CLOCK or NPAS2 [61]. In addition, RXR, as heterodimerization partner of the nuclear receptor PPARα, CAR, and PXR, can synergically reinforced the transcriptional activity of the heterodimer after binding of its ligand, 9-*cis*-retinoic acid [62], but not always [63]. Interestingly, the concentrations of retinoic acid and of some of its metabolites are increased after retinoic acid administration [64] and have been found to follow a moderate circadian rhythm in serum [65]. RXR seems thus to play a role in the circadian rhythm of detoxification and administration of retinoic acid during medical treatment, particularly of cancer [66], can both perturb circadian rhythms and the nuclear receptor-dependent detoxification pathways.

In all cases, if circadian rhythms have an important impact on drug toxicity and effectiveness, the impact of drugs on circadian rhythm should be not neglected and on the other hand can also have an influence on drug metabolism and drug/drug deleterious interactions. By giving a rational reason to study the interactions between circadian rhythm, administration timing of a drug and drug metabolism, studies deciphering xenobiotic influence on clock systems will help to define a molecular clock-controlled pharmacology.

5. Circadian clock, detoxification and aging

It is known for decades that circadian rhythms change with aging: absent in the newborn, they start three months after birth, undergo changes during adolescence, stabilize in adulthood and deteriorated with advanced age [67,68]. As shown in rodent, this perturbation of the circadian clock during aging is characterized by a general alteration of the circadian expression of the circadian clock genes in the SCN and in peripheral organs [69,70]. Interestingly, the aging-linked changes are also described for the detoxification capacity in both rodents and humans [71]. This decrease in detoxification efficiency seems to be linked to a decrease in the expression of genes coding for detoxification enzymes and their regulators [72,73]. Whereas it has not been clearly demonstrated, some evidence suggest that this age-dependent decrease in detoxification is related to the deterioration of circadian rhythms in aged people, as circadian-regulated transcription factors play an important role in xenobiotic detoxification. Moreover, it has been shown that the life span of the nematode *Caenorhabditis elegans* is dependent of the DAF-2/Insulin growth factor receptor pathway that was recently described to control the expression of genes involved in many aspects of detoxification [74]. Accordingly, a reduced activity of detoxification genes would be expected to promote premature aging and reduced life span, two features shared by the PARbZip and *BMal1* deficient mice [18,75]. It is likely, therefore, that age-dependent perturbations of the circadian rhythms could be linked to the detoxification capacity and thus contribute to acceleration of the aging process.

6. Conclusion

Recent discoveries start to reveal the molecular mechanisms of circadian drug metabolism. Not surprisingly, this highlights the fact that the mechanisms involved are the same as the one implied in the metabolism of food-contained toxic compound. As this function is one of the major functions of circadian rhythm in living organisms, we now start to understand the time-dependent drug toxicity and effectiveness in rodent and human. In addition, it has been shown that xenobiotics can perturb normal circadian rhythm by acting on circadian gene expression. As food seems to be the major zeitgebber for most peripheral organs [6,7], it is conceivable that food-contained toxic compounds modulate expression of circadian clock genes via xenobiotic-sensible transcription factors and, in turn, plays a role in the food entrainment of the circadian oscillator. Interestingly, it has been recently shown that an oscillator-independent circadian transcription could exist, with a Heat Shock factor 1 (HSF1)-dependent transcriptional regulation of the mouse *Per2* gene [76]. As HSF1 is known to be activated by a wide range of stimuli including toxic compounds contained in food [77], this possibility will have to be taken into account.

Finally, the biological consequence of xenobiotics exposure depends on interactions between the timing of exposure and the xenobiotic effect on circadian clock machinery. The final goal of chronobiology is to find the optimal time to administer drugs in order to obtain maximum efficiency with minimum doses and side-effects. However, to reach this goal, we have to better understand human circadian clock. Unfortunately, determination of period length of circadian behavior and physiology in human is costly and time consuming, and cannot be realize by simple clinical test. Nevertheless, recent *in vitro* results show the relative easy recording of period length on cultured primary fibroblasts obtained from skin punch biopsies, using lentiviral vectors encompassing a circadian luciferase reporter gene [78]. These experiments revealed a high variability in the circadian period length between human individuals which can possibly reflect genetic variations in genes controlling the human circadian clock. In the same time, to personalize chronotherapy and obtain better adapted treatments, knowledge of pharmacogenomics profile of the patient will be required. Genomic data acquired through the international HapMap project will help in this attempt [79]. Interestingly, this study revealed that the genes involved in detoxification are under positive and negative selection in populations with different diets and lifestyle, and showed that some phase I–III drug-metabolizing enzymes are highly polymorphismic [80]. Integration of genomic informations concerning circadian rhythm and drug metabolism may lead to the understanding of circadian xenobiotic detoxification in each individual and thus to the formulation of novel therapeutic regimens. It will be important to take into account the perturbations of circadian gene expression induced by xenobiotics since they can have harmful effects like increased predisposition to breast cancer among women [81], or atherosclerosis in male-shift workers [82], who together represent 10% of the working force across the European Union.

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