BIOCHEMICAL PHARMACOLOGY 77 (2009) 560–565

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Review

Crosstalk between the AHR signaling pathway and circadian rhythm

Shigeki Shimba *, *Yuichi Watabe*

Department of Health Science, College of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi, Chiba 274-8555, Japan

ARTICLE INFO

Article history:
Received 8 August 2008
Accepted 26 September 2008

Keywords:
Aryl hydrocarbon receptor
Brain Muscle ARNT-like protein 1
Circadian rhythm

ABSTRACT

In this chapter, we review the crosstalk between the AHR signaling pathway and molecular clock system in mammals.

In mammals, circadian rhythm is observed in most physiological functions including behavior, metabolism, cell growth, and immune responses. Circadian rhythm is regulated by a transcriptional feedback loop, and the transcription factor called "Brain Muscle ARNT-like protein 1 (BMAL1)" is a master regulator of this system. Because of its structural similarity to ARNT, a partner of AHR, BMAL1 is also referred as ARNT3. This structural feature of BMAL1 suggests that the activation of the AHR signaling pathway may influence the regulation of circadian rhythm. Several studies have shown that the expression levels of AHR display diurnal variation in many tissues. This circadian variation of AHR means that the pharmacological effects of AHR agonists vary according to the time of administration. AHR agonist administration results in a disruption of circadian rhythm with regard to behavior, immune cell proliferation, etc. As such, understanding the crosstalk between the AHR signaling and circadian rhythm may provide a new insight into TCDD actions.

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Contents

1. Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), a highly toxic compound that has attracted attention for several decades, elicits a variety of toxic and biochemical responses. These include induction of drug-metabolizing enzymes, tumor promotion, thymic involution, hydronephrosis, cleft palate, and wasting syndrome [1–4]. These toxic effects are thought to

* *Corresponding author*. Tel.: +81 474655838; fax: +81 474655637.
E-mail address: shimba.shigeki@nihon-u.ac.jp (S. Shimba).

0006-2952/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2008.09.040

be mediated by the aryl hydrocarbon receptor (AHR). The AHR contains a basic helix-loop-helix structure (bHLH)/PAS domain and function as a transcription factor [5,6]. The bHLH-PAS proteins are characterized by a PAS domain, which is composed of two imperfect 50 amino acid repeats and a basic helix-loop-helix (bHLH) domain. The term ''PAS'' is derived from the first three members of the family: the period gene, the aryl hydrocarbon receptor nuclear translocator gene (ARNT), and the single-minded (SIM) gene. Using the PAS domain and the bHLH domain, proteins of this family form heterodimers that bind to a target gene through the basic region and govern the functions of that gene. The PAS domain is found in a variety of proteins that play a role in development and adaptation to the environment, affecting neurogenesis [7], circadian rhythms [8], hypoxia [9], and xenobiotic metabolism [10]. Thus, members of the bHLH-PAS superfamily are thought to serve as sensors of environmental and developmental signals.

Among the PAS family members, the Brain Muscle ARNT-like protein 1 (BMAL1) is known as a master regulator of circadian rhythm [11], and its amino acids sequence shows high homology to that of ARNT [12,13]. Because of this structural feature, BMAL1 is also termed as ARNT3 [12], or Mop3 [13]. As it has been well-characterized, several toxic effects of TCDD are known to be mediated by the AHR/ARNT complex as described in this issue. Therefore, the high homology of BMAL1 to ARNT in its amino acid sequence allows us to speculate that the activated AHR may influence the control of circadian rhythm. Indeed, after administration of TCDD, the highest concentration of compound has been found in the hypothalamus where the master pacemaker of circadian rhythm resides [14]. Therefore, in this chapter, we wished to review the crosstalk between the AHR signaling pathway and the molecular clock system in mammals.

2. Circadian rhythm

The basic regulatory system of circadian rhythm is evolutionally conserved from cyanobacteria to mammals [15–22]. In mammals, circadian rhythm is observed in most, if not all, physiological functions, including metabolism, cell growth, and immune responses [23–28]. The master pacemaker of circadian rhythm resides in the suprachiasmatic nucleus (SCN) of the hypothalamus. The master clock in the SCN is stimulated by the light/dark cycle and, in turn, synchronizes the phases of multiple peripheral clocks located in different peripheral tissues [29]. However, even in the absence of the master signal (i.e., in SCN lesioned animals), the peripheral clocks still function [30]. These results indicate that peripheral tissues possess autonomous molecular clock machinery and that the regulation of the peripheral system can be uncoupled from the central clock systems. This autonomous system allows the molecular clock in peripheral systems to respond to other synchronizing stimuli. For example, energy metabolism can be entrained by the feeding schedule independent of the SCN [31–34]. The ubiquitous nature of the clock machinery and its ability to respond to a variety of exogenous stimuli means that the circadian system plays an important role in controlling numerous physiological processes.

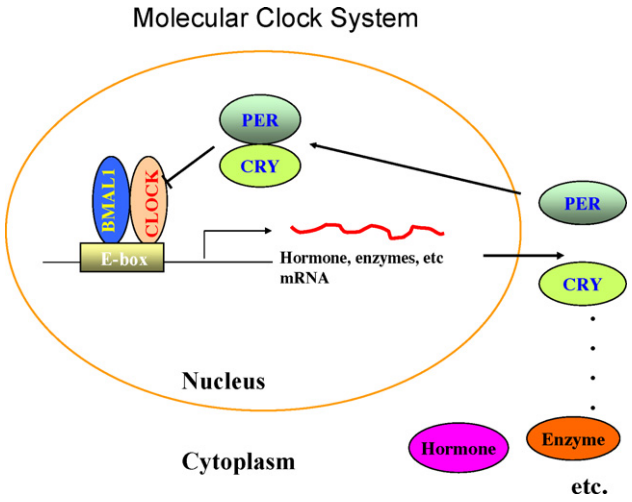

Fig. 1 – A simplified scheme of the molecular clock systems in mammals.
The bHLH-PAS type transcription factors BMAL1 and CLOCK form a heterodimer complex and bind to the E-box element on target genes, including hormones, and enzymes. The protein products of Periods (PER) and Cryptochromes (CRY) form various complexes, enter the nucleus and inhibit BMAL1/CLOCK-dependent transcription, including their own, thus completing the negative feedback loop.

The molecular clock is composed of several clock-controlled genes. These factors constitute the transcriptional feedback loops. Among the clock-controlled genes, two transcription factors, BMAL1 and CLOCK, play central roles in the regulation of circadian rhythms [11–13,35]. BMAL1 and CLOCK form a heterodimer and drive transcription from E-box elements found in the promoter of circadian-responsive genes, including period (Per)1 and cryptochrome (Cry). After translation of the Per and Cry proteins, the PER/CRY complex translocates to the nucleus, where it inhibits gene expression driven by BMAL1 and CLOCK (Fig. 1) [36–38]. In mouse liver and heart, approximately 10% of genes expressed display circadian rhythm in their expression [39], though the amplitude of expression varies for each gene. For example, the expression level of the clock-controlled genes such as BMAL1 changes more than 10-fold throughout the day, whereas there is less daily variation for general gene expressions (less than 5-fold) (Fig. 2).

3. Structural similarities and differences between AHR and BMAL1

The bHLH and PAS domains in the N-terminal half of the BMAL1 showed the highest similarity to those of ARNT and ARNT2 (44.3 and 41.6%, respectively), while the similarities to other PAS proteins were below 30% [12]. Thus BMAL1 is also designated as ARNT3, as described in Section 1. Other regions of BMAL1 showed essentially no similarity to any other PAS family members. Although BMAL1 is closely related to ARNT, BMAL1 failed to form a complex with AHR as judged by the two-hybrid experiments [13]. At present, only CLOCK [13] and

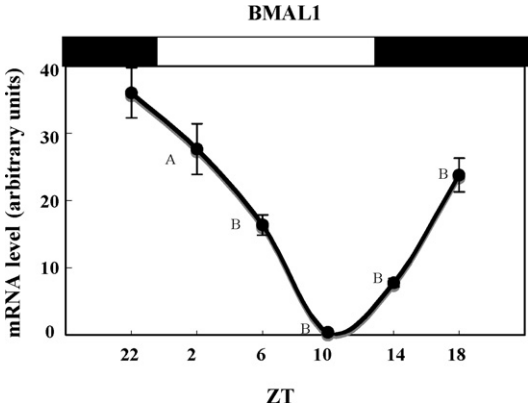

Fig. 2 – BMAL1 mRNA expression in mouse adipose tissue. Male C57BL/6J mice were maintained on a 12-h light/12-h dark cycle (light□: zeitgeber time ZT0–12 and dark■: ZT12–24). Epididymal white adipose tissues were obtained, total RNA was isolated, and the mRNA levels were determined by RT-qPCR using specific primers. Relative mRNA levels were normalized to the β-actin level. The values were plotted as arbitrary units. All data are represented as the mean standard deviation ($n = 4$). "A" indicates significant differences ($p < 0.05$) from the value at ZT22. "B" indicates significant differences ($p < 0.01$) from the value at ZT22.

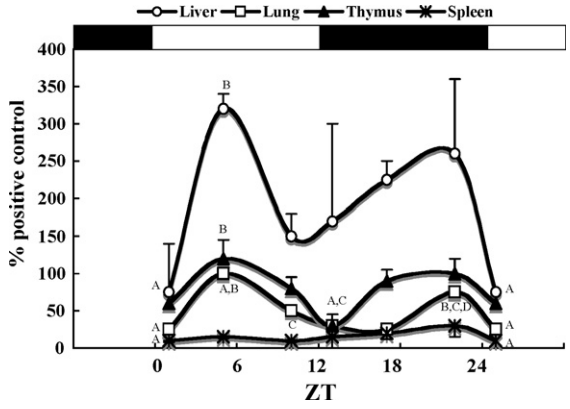

Fig. 3 – Daily cycle of AHR protein expression in multiple tissues obtained from female Sprague–Dawley rat [43]. Tissues were obtained at the indicated time, the whole tissue extract was prepared, and the AHR levels were determined by Western blotting. The band intensity was measured and the protein expression was quantified by a comparison to a thymus tissue homogenate sample. All data are represented as the mean standard deviation ($n = 3$).
"A" indicates significant differences ($p < 0.05$) from the value at ZT22. "B" indicates significant differences ($p < 0.05$) from the value ZT1. "C" indicates significant differences ($p < 0.05$) from the value ZT5. "D" indicates significant differences ($p < 0.05$) from the value ZT13.

NPAS2 [40] have been identified as physiological partners of BMAL1. Therefore, the functions of the bHLH/PAS domain of BMAL1 are distinct from those of ARNT, despite their similarities.

It has been proposed that the bHLH/PAS family can be divided into two classes that are represented by AHR and ARNT based on their amino acid sequences [41]. As described, because of its high homology to ARNT, BMAL1 belongs to the ARNT class. However, a comparison of the genomic organization of BMAL1 with other members of the bHLH/PAS gene family revealed that the intron/exon splice pattern around its bHLH/PAS domains in Bmal1 is closely related to that in Ahr [42]. All nine intron–exon junction sites around the bHLH/PAS domains are conserved between Bmal1 and Ahr. In the bHLH/PAS family, Bmal1 and Ahr are the only genes for which five exons comprise the PAS domain [42]. This high conservation of the genomic organization suggests that Bmal1 and Ahr belong to the same class, and it is possible to speculate that these genes are derived from a common ancient gene.

4. Circadian rhythm of AHR expression and activity

Richardson et al. have reported the diurnal changes of AHR and ARNT proteins in multiple tissues in female Sprague–Dawley rat [43]. In their study, the animals were housed under a 12 h of light/dark cycle. The tissues including those of the liver, lungs, thymus, and spleen, were excised, and the levels of AHR and ARNT protein were determined by Western blotting using specific antibodies. The daily cycle of AHR protein exhibits a similar oscillation pattern in the liver, lungs, and thymus (Fig. 3). In these tissues, the AHR levels display dual peaks. One peak is at ZT5 (5 h after light on) and the other peak is at ZT22 (10 h after light off) (Fig. 3). The lowest level of AHR is observed at ZT1 (1 h after light on) in the liver and at ZT13 (1 h after light off) in the lungs and thymus (Fig. 3). The degree of amplitude for one day is approximately 2–3-fold (Fig. 3). The daily cycle of AHR protein levels observed in the liver, thymus and lungs was not seen in the spleen (Fig. 3).

The daily cycle of hepatic ARNT protein levels is almost identical to that of AHR, i.e., there are two peaks of expression at ZT5 and ZT22. Daily expression of ARNT protein in the lung also displays two peaks at ZT5 and ZT17. In the thymus, the expression of ARNT protein oscillated throughout the day, showing a single peak at ZT1. The levels of ARNT protein in the spleen remained constant during the light phase and were elevated during the dark phase.

As described above, AHR protein expression oscillates throughout the day and, in some cases, the protein levels show dual peaks. However, studies of the expression levels of AHR transcripts have provided similar but slightly different results. While AHR protein expression exhibits a dual peak in the liver, the expression of hepatic AHR mRNA levels cycles throughout the day, with a single peak in both mice and rat [44,45]. In both cases, the degree of amplitude is approximately 2–3-fold, while the expression of clock-controlled genes such as BMAL1 mRNA displays robust oscillation during the day in both SCN and liver [45]. The mechanisms for the appearance of an additional peak at the protein level are unknown. One possibility is a circadian rhythm of translational activity.

Alternately, the stability of mRNA may vary throughout the day. Also, it could be possible that the additional peak of AHR protein is a part of experimental variations, since the results in Fig. 3 have large error bands in some points (Fig. 3).

Although the precise mechanisms of diurnal oscillation of the AHR levels are yet to be determined, it is likely that a molecular clock system regulates the oscillation of the AHR expression. It has recently been reported that disruption of Per1 and 2 genes, suppressive factors for the circadian system, alters the AHR signaling pathway in mammary gland [46]. In mice with disrupted Per genes, the TCDD-induced expression levels of Cyp1A1 and 1B1 are significantly higher than those found in WT animals [46]. Consequently, we might conclude that the quantity and quality of the AHR signaling is, at least in part, regulated by the molecular clock system.

Circadian rhythm in the levels of AHR and ARNT proteins in multiple tissues suggests that the pharmacological effects of AHR agonists may vary according to the time of administration. To test this hypothesis, TCDD was administered to mice at different time points and the expression of Cyp1A1 and 1B1 in mammary glands was determined [46]. Irrespective of treatment time, Cyp1A1 mRNA levels were low in control mice [46]. Administration of TCDD triggered significant induction of Cyp1A1 mRNA in both light-phase (ZT6) and dark-phase administration (ZT18) [46]. However, the -fold differences in the TCDD-mediated Cyp1A1 induction depended on the time of administration, i.e., induction of Cyp1A1 mRNA in mice treated with TCDD at ZT18 was 8.6-fold higher than that at ZT6 [46]. Also, the -fold differences in TCDD-induced Cyp1B1 expression at ZT18 were significantly higher than those observed at ZT6 [46]. These results indicate that the sensitivity to AHR agonists varies according to the time of treatment.

5. Effects of AHR agonists on clock gene

There are no apparent abnormalities in the circadian rhythm of Ahr KO mice under a light/dark cycle [45]. The circadian period of the Ahr KO male was not significantly different from that of WT males under both constant dark and constant light conditions [45]. These results indicate that the AHR has no effects on circadian rhythm in the absence of exogenous agonist. Then, to study whether exposure to an AHR agonist affects the response to nocturnal light exposure, mice were housed under a constant dark condition after administration of TCDD [45]. Once mice were adapted to the dark environment, light was flashed to the mice for a short period. This light-pulse induced a phase shift in mouse activity, as judged by wheel-running activity. TCDD treatment resulted in a significant reduction in the amplitude of phase delay in mice [45]. These results suggest that activation of AHR may affect the ability of the circadian timekeeping system to adjust to alterations in environmental lighting by affecting canonical clock genes.

In addition to behavioral circadian rhythmicity, another example of disruption of circadian rhythm by TCDD has been reported in immune systems [47]. The immunoreactions and onset of inflammatory diseases exhibit circadian variation [47–55]. For example, the number of hematopoietic stem cells and hematopoietic progenitor cells is known to display circadian variation [47]. Activation of the AHR by TCDD results in disruption of diurnal changes of cell number of Lin(−) Sca-1(+) cKit(+) (LSK) bone marrow cells and myeloid and erythroid precursors [47]. TCDD treatment alters the expression of Per1 and Per2 mRNA in these cells, suggesting a direct effect on the molecular machinery responsible for these alternations of rhythm [47]. Therefore, disruption of circadian rhythm could be one of the mechanisms by which TCDD treatment suppresses immune systems.

Disruption of circadian rhythm by TCDD is, at least in part, associated with the alternation of the expression levels of clock-control genes. In control mice, expression of hepatic BMAL1 mRNA levels at CT 20 is several fold higher than that at CT8 [45]. However, in TCDD-treated mice liver, the level of BMAL1 mRNA expression at CT20 is significantly lower than that at CT8 [45]. Similar to BMAL1 mRNA, the hepatic Per1 mRNA expression pattern was found to be altered by TCDD in a time-dependent manner, i.e., Per1 mRNA levels decreased at CT8, but substantially increased at CT20 [45]. These results suggest that TCDD treatment induces a phase shift of clock gene expression, leading to a loss of circadian rhythm.

6. Conclusions

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), a very potent AHR agonist, induces a variety of toxic and biochemical responses including induction of drug-metabolizing enzymes, tumor promotion, thymic involution, hydronephrosis, cleft palate, wasting syndrome, etc. Although these AHR-mediated toxicities of TCDD have been extensively studied, the mechanisms remain ambiguous. As described, several studies have showed that the expression levels of the AHR vary throughout the day, although the physiological significance and precise mechanism by which the AHR levels oscillate during the day are currently unknown. This daily oscillation of AHR levels generates a diurnal difference in the sensitivity to the AHR agonist. Therefore, understanding the crosstalk between the AHR signaling and circadian rhythm may provide a new insight into the physiological roles of AHR as well as the novel mechanisms of action of the AHR agonists.

Acknowledgement

Work in our lab is supported in part by a grant from the Ministry of Education, Sciences, Sports, and Culture of Japan (to S.S); a General Individual Research grant from Nihon University (to S.S.); a grant from Ono Medical Research Foundation (to S.S.); an Interdisciplinary General Joint Research grant from Nihon University (to S.S.); and the ''High-Tech Research Center'' Project for Private Universities, a matching fund subsidy from the Ministry of Education, Culture, Sports, Science, and Technology 2007.

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