Neurobiological Functions of the Period Circadian Clock 2 Gene, Per2

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Abstract

Most organisms have adapted to a circadian rhythm that follows a roughly 24-hour cycle, which is modulated by both internal (clock-related genes) and external (environment) factors. In such organisms, the central nervous system (CNS) is influenced by the circadian rhythm of individual cells. Furthermore, the period circadian clock 2 (Per2) gene is an important component of the circadian clock, which modulates the circadian rhythm. Per2 is mainly expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus as well as other brain areas, including the midbrain and forebrain. This indicates that Per2 may affect various neurobiological activities such as sleeping, depression, and addiction. In this review, we focus on the neurobiological functions of Per2, which could help to better understand its roles in the CNS.

Key Words: Circadian rhythm, Per2 gene, Sleep, Depression, Addiction, Neurotransmitter

INTRODUCTION

A circadian rhythm is any physiological process that displays a roughly 24 hour cycle in living beings, such as mammals, plants, fungi and cyanobacteria (Albrecht, 2012). In organisms, most biological functions such as sleeping and feeding patterns are adapted to the circadian rhythm. Additionally, hormone production, brain wave activity, and other biological activities are associated with the circadian rhythm. The circadian rhythms are modulated endogenously by clock-related genes such as Per1, Per2, Cry1, and Cry2, and externally by external cues such as light, food, and temperature (Ripperger et al., 2011). The endogenously generated circadian rhythms can be adjusted to the environment by external cues called zeitgebers (a German word meaning “time giver”) that influence the timing of the circadian rhythm. The suprachiasmatic nucleus (SCN) of the hypothalamus is the primary circadian pacemaker driving circadian oscillations of clock-related gene expression (Welsh et al., 2010). Conversely, more independent circadian rhythms are found in other organs as well as the SCN. For example, the circadian rhythm was reported in most peripheral organs and tissues (Guo et al., 2006; Mohawk et al., 2012). Even individual cells contain a circadian rhythm (Nagoshi et al., 2004). Based on these reports, the circadian rhythm is important in maintaining the physiological balance and lives in organisms because it can impart effects from the level of cells to organs including the brain. Thus, it is necessary to understand clock-related genes that are controlling the circadian rhythm endogenously.

The Period2 (Per2) gene is a member of the Period family of genes consisting of Per1, Per2, and Per3, and is mainly expressed in the central nervous system (CNS) including the SCN and the peripheral nervous systems. The period (per) gene was first discovered in 1971 by Konopka and Benzer via a mutagenesis screen in Drosophila melanogaster (Konopka and Benzer, 1971). They found three per genes on the X chromosome consisting of a short-period mutant (19 h, pera) and long-period mutant (28 h, perb) when compared to the normal-period length (24 h), and the arrhythmic mutant (pero). The Per2 gene in mammals was identified by Albrecht et al. (1997) while searching for homologous cDNA sequences using the Per1 sequence that was discovered by Sun et al. (1997). Recently, researchers have attempted to identify the role of the Period genes using mutant mice (e.g., single knockout [KO] mice). They found that Per1 and Per2 play important roles in circadian rhythms, while the role of Per3 is lesser than those two genes in mice (Albrecht et al., 2001; Bae et al., 2001; Bae and Weaver, 2003; Lee et al., 2004). Interestingly, Per2 plays a more prominent role in the circadian clock than Per1 (Zheng et al., 1999; Ripperger and Albrecht, 2012). Per2 mutant mice
showed a shorter circadian period than wild type (WT) mice and reduced Per2 expression in the SCN, indicating that Per2 regulates Per1. Thus, Per2 is one of the core genes of the circadian clock and has a role in generating the circadian rhythms in the SCN and peripheral organs (Arjona and Sarkar, 2006; Sujino et al., 2007). However, the mechanism and function of Per2 are still unclear. In particular, the roles of Per2 and PER2 in the nervous systems are poorly known. Thus, in this review, we have tried to focus on and discuss the neurobiological functions of Per2 in the CNS.

ROLES OF Per2 IN THE CIRCADIAN CLOCK

In a mammalian circadian clock, several genes (e.g., Clock, Bmal1, Per1, Per2, Cry1, and Cry2) cooperate to function through positive and negative transcriptional-translational feedback loops (Shearman et al., 2000; Ko and Takahashi, 2006; Ripperger et al., 2011). In the positive translational feedback loop, CLOCK (or Npas2) forms heterodimers with BMAL1 in the cytoplasm (Gekakis et al., 1998; Reick et al., 2001; Albrecht, 2012). The CLOCK-BMAL1 heterodimer activates transcription of Per1, Per2, Cry1, and Cry2 by binding to the E-box enhancers of their target genes after translocation to the nucleus. In the negative feedback loop, PER and CRY accumulate in the cytoplasm form a complex which translocates to the nucleus to inhibit transcription of Clock and Bmal1 (Jin et al., 1999; Kume et al., 1999; Shearman et al., 2000; Lowrey et al., 2004). During the translocation of the PER-CRY complexes from the cytoplasm to nucleus, PER2 plays a role in interacting with nuclear receptors such as REV-ERBs and PPARα (Schmutz et al., 2010). This study reported that Per2 regulates nuclear receptor-mediated transcription of Rev-Erba and Bmal1. In addition, Per2 is associated with the degradation of the CLOCK-BMAL1 heterodimer (Kwon et al., 2006). CLOCK was not detected in BMAL1-deficient mouse embryo fibroblasts, which indicates that expression of CLOCK is BMAL1-dependent (Kondratov et al., 2003), and that the BMAL1 loop is regulated by PER2 (Shearman et al., 2000). Therefore, Per2 has dominant roles in the circadian rhythm that affects the central and peripheral nervous systems.

SLEEP AND Per2

Sleep is an important part of life, and the sleep cycle is under the control of the circadian rhythms. Among the circadian clock genes, Per2 plays critical roles in sleep, especially in familial advanced sleep phase syndrome (FASPS), which is a kind of inherited abnormal sleep patterns where one sleeps very early and rises very early. In humans, PER2 is the first gene found to be associated with FASPS (Zhang et al., 2013). Furthermore, it was demonstrated that per2 S662 (a human homolog of the period gene in Drosophila) is located in the casein kinase (CK) Iε-binding region (Toh et al., 2001). The per2 S662G mutation causes hypo-phosphorylation by CKε in vitro. This mutation shortened the circadian rhythm and caused sleep defects as well as the development of FASPS (Toh et al., 2001; Ebisawa, 2007; Xu et al., 2007). In addition, PER2 in FASPS showed reduced stability in vitro because it was more sensitive to degradation by CKε than that in wild type (Vanselow et al., 2006). The per2 S662G mutant could lead to a decrease in PER2 transcription in FASPS through phosphorylation and degradation (Mignot and Takahashi, 2007). Per2 is associated with general sleep problems as well as FASPS. Per2 mutant mice showed a different daily distribution of sleep (e.g., earlier waking episode than WT) and reduced total sleep time compared to WT mice (Kopp et al., 2002; Miyazaki et al., 2007). The level of Per2 expression is also influenced by sleep deprivation (SD) (Franken et al., 2007; Curie et al., 2015; Zhang et al., 2016). SD for 6 h increased the levels of Per2 and PER2 expressions when compared to controls. Sustaining high levels of Per2 expression may have a negative impact on the sleep recovery. In contrast, Curie et al. (2013) found that SD-induced changes in Per2 expression varied with the time of day. Interestingly, a PER2 polymorphism was associated with diurnal preference in healthy people (Lee et al., 2011b). However, patients with attention-deficit hyperactivity disorder (ADHD) who have sleep problems did not show circadian rhythms of PER2 expression, whereas the control healthy group did (Baird et al., 2012). Based on these findings, Per2 may be deeply associated with the sleep cycle.

NEURODEGENERATIVE DISEASES AND Per2

Many studies have reported that circadian rhythm disruption may be associated with neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s diseases (HD) (Witting et al., 1990; Wulff et al., 2010). A few studies reported that the level of Per2 expression was attenuated in the SCN of APP-PS1 transgenic mice, AD mouse model (Duncan et al., 2012), or disrupted through the degradation of BMAL1 in another AD mouse model, 5XFAD (Song et al., 2015). Conversely, some studies failed to find the effect of Per2 on the neurodegenerative diseases. For example, in humans, PER2 polymorphisms were not associated with AD (Yesavage et al., 2011; Pereira et al., 2016). PER2 expression rhythm was not different in healthy controls and patients with AD (Cermakian et al., 2011). In addition, the level of PER2 expression showed similar rhythms in controls and patients with PD, but BMAL1 expression rhythm was altered in the patients with PD (Breen et al., 2014). In animals, Per2 expression was normal in the SCN of the PD mouse model, ASO (alpha-synuclein overexpressing transgenic mouse) (Kudo et al., 2011b). The level of Per2 expression was not altered in the SCN of HD mouse models, BACHD (Kudo et al., 2011a) and Q175 (Loh et al., 2013). Based on those findings, it is inconclusive that Per2 may influence the neurodegenerative diseases.

DEPRESSION AND Per2

Depression is a very common but serious mood disorder that causes a variety of emotional and physical problems such as thinking, sleeping, or eating. Depression is affected by genetic and environmental factors (Lesch, 2004). Circadian rhythms and circadian-related genes have some roles in depression (Johansson et al., 2003; McClung, 2007a; Turek, 2007; Soria et al., 2010). In a gene-wise logistical regression analysis, winter depression was associated with three circadian clock genes Per2, Arnt, and Npas2 (Partonen et al., 2007). Another study in humans also reported that PER2 ge-
nentic variants were associated with vulnerability to depression (Lavebratt et al., 2010). Blocking PER2 conferred a protective effect against depression in the Swedish population (Lavebratt et al., 2010). In animals, Hampp et al. (2008) found that Per2 mutant (KO) mice showed less immobility than WT mice in the forced swimming test (FST), which are usually used to screen levels of depression. This may be due to the high levels of dopamine (DA) because treatment with alpha-methyl-p-tyrosine (AMPT), a potent inhibitor of tyrosine hydroxylase (TH, the rate-limiting enzyme of DA synthesis), increased immobility of the mutant mice in the FST (Hampp et al., 2008). Thus, Per2 may regulate depression through DA activities. Similarly, another study suggested that Per2 influences DA metabolism and mood-related behaviors through MAO activities (Hampp and Albrecht, 2008). Based on these findings, the researchers assumed that increased levels of Per2 may lead to reduced DA levels and a more depressed mood. Conversely, mice exposed to unpredictable chronic stress showed depressive-like behaviors and decreased Per2 expression (Jiang et al., 2011; Logan et al., 2015). All these findings support the idea that Per2 may be associated with depression, although the mechanism of Per2 function in depression is still not clear.

**DRUG ADDICTION AND Per2**

Drug addiction is a chronic and relapsing brain disease that is characterized by compulsive drug seeking and use despite adverse consequences. According to World Drug Report 2016, approximately 247 million people worldwide have used an illicit drug (United Nations Office on Drugs and Crime, 2016). It is estimated that 1 out of 20 adults have used illicit drugs, and the number of drug users is continuously increasing. Recently, many studies have indicated that drug addiction is associated with some genes. Particularly, Per2 has been implicated to have some role in drug addiction. The length of PER2 alleles was different between cocaine users when compared to the healthy control group (Shumay et al., 2012). The PER2 alleles of the cocaine users were shorter than those of the healthy group. In addition, mutant mice lacking Per2 tend to be more vulnerable to drug addiction (Abarca et al., 2002; Spanel et al., 2005). Per2 mutant (KO) mice exhibited higher cocaine sensitization and cocaine-induced place preference when compared to WT mice (Abarca et al., 2002). Per2 mutant mice also showed higher non-photic and photic phase-resetting responses to cocaine when compared to WT mice (Brager et al., 2013). These findings suggest that the level of Per2 expression negatively modulates the responses to cocaine.

Per2 is also associated with responses to methamphetamine (METH) (Pendergast et al., 2012; Yamamoto et al., 2005). Per1^+/−/Per2^+/−/Per3^−/− mutant mice showed shorter circadian oscillators (~21 h) after METH injections when compared to WT mice (>24 h) (Pendergast et al., 2012). The levels of PER2 increased in the hippocampus after administration of METH (Yamamoto et al., 2005). The studies concluded that the long-lasting alterations of the period gene expressions including Per2 may play important roles in METH addiction. In addition, Per2 modulates alcohol consumption both in animals and in humans (Spanel et al., 2005; Comasco et al., 2010; Brager et al., 2011b; Blomeyer et al., 2013; Gamsby et al., 2013). In humans, haplotypes of PER2 influenced the amount of alcohol consumption (Spanel et al., 2005). In animals, Per2 mutant (KO) mice consumed more alcohol than WT mice (Spanel et al., 2005). This study reported that higher consumption of alcohol in Per2 mutant mice was associated with higher glutamate levels in the brain by reducing the expression of excitatory amino acid transporter 1 (EAAT1), a glutamate transporter. The hypothesis that alcohol consumption was associated with glutamate levels was supported by studies using Acamprosate, a glutamate antagonist. Acamprosate suppressed alcohol intake and preference in Per2 mutant mice showing greater alcohol intake than WT mice (Brager et al., 2011a, 2011b). Per2 mutant mice also displayed a strong alcohol-induced place preference compared to WT mice (Gamsby et al., 2013). Taken together, Per2 influenced alcohol intake and reinforcement.

In contrast, in tail-immersion and hot-plate experiments to assess analgesic effects of morphine in Per2 mutant (KO) mice, the mutant mice showed more analgesic responses to the chronic morphine injections, which suggests less tolerance than WT mice (Perreau-Lenz et al., 2010). This study also reported that the Per2 mutant mice had decreased withdrawal symptoms when compared to WT mice, which was contrary to the expectations that the mutant mice would have enhanced withdrawal signs because of the higher glutamate levels in Per2 mutant (KO) mice. The researchers postulated that the reduced withdrawal symptoms in the Per2 KO mice may be due to “ceiling effect.” Thus, the differences in glutamate levels before and after administration of morphine in Per2 mutant mice were less compared to that in WT mice, resulting in fewer withdrawal symptoms. Other studies reporting the increased level of Per2 expression after drug treatment also support the hypothesis that Per2 plays an important role in drug addiction. For examples, cocaine treatment increased Per2 expression in the striatum, hippocampus, and nucleus accumbens (McCung and Nestler, 2003; Yuferov et al., 2003; Uz et al., 2005). Consistent with these findings, the levels of Per2 expression increased in the striatum after amphetamine administration in spontaneously hypertensive rats that exhibited less rewarding effects after chronic methylphenidate treatment than Wistar rats (dela Peña et al., 2012a, 2012b, 2015). Based on these findings, the levels of Per2 expression may be associated with drug addiction.

**FOOD ANTICIPATION AND Per2**

Food-seeking behaviors share neurobiological mechanisms (e.g., DA levels) with drug addiction (Salamone et al., 2003; Simery, 2006). The food-entrained oscillator (FEO) in Per1^+/−/Per2^+/−/Per3^−/− mutant mice during restricted feeding was changed compared to WT mice that maintained the usual FEO (24 h) (Pendergast et al., 2012). The FEO in the mutant mice showed a shorter period (21 h) similar to the shorter circadian rhythms (21 h) in the mutant mice treated with METH. Almost all animals usually exhibit food anticipatory activity (FAA), such as increased locomotor activity to daily mealtime under circadian schedules (Mistlberger, 1994). However, Per2 mutant (KO) mice did not exhibit FAA (Feillet et al., 2006; Mendoza et al., 2010). Additionally, double-mutant mice (e.g., Per1^+/− Per2^−/− Cry1^−/−) did not show FAA in constant darkness or under a light-dark cycle (Mendoza et al., 2010). The relationship between Per2 and food anticipation is also
supported in other studies reporting that the restricted feeding changed the rhythm of Per2 expression in the brain (Wakamatsu et al., 2001; Lamont et al., 2005; Mieda et al., 2006; Verwey et al., 2007). The levels of Per2 expression peaked at mealtime. However, food consumption was identical in Per2 mutant mice when compared to WT mice (Grimaldi et al., 2010). These findings suggest that Per2 plays some roles in food anticipation, although the mechanism of Per2 in FAA is still unknown.

**NEUROTRANSMITTERS AND Per2**

Neurotransmitters are endogenous chemicals that transmit signals across synapses in the brain. The release of neurotransmitters, such as dopamine, glutamate, and γ-aminobutyric acid (GABA) have been shown to be modulated by circadian rhythms (Castaneda et al., 2004). Per2 is associated with the generation of the circadian rhythms (Arjona and Sarkar, 2006; Sujino et al., 2007), and is expressed in the brain including the SCN of the hypothalamus, midbrain, and forebrain (Albrecht et al., 1997; Hood et al., 2010). Thus, Per2 may be associated with modulating the release of the neurotransmitters in the brain.

**Dopamine (DA)**

Recently, increasing evidence has suggested a relationship between dopaminergic-system and Per2 (Besharse et al., 2004; Hood et al., 2010; Gravotta et al., 2011; Shumay et al., 2012). In addition to DA release, dopaminergic gene expression, such as the dopamine transporter (DAT), DA receptors (e.g., DRD2 and DRD3), and TH have been shown to be modulated by circadian rhythms (Akhisaroglu et al., 2005; McClung, 2007b; Sleipness et al., 2007; Chung et al., 2014). DA receptor responsiveness was modulated by per genes in Drosophila (Andretic and Hirsh, 2000). Per2 plays critical roles in regulating DA levels in the mesolimbic DA circuit including the striatum through TH and monoamine oxidase A (MAOa) activity (Hampp et al., 2008; Bussi et al., 2014; Agostino and Cheng, 2016). Per2 mutant (KO) mice had decreased expression and activity of MAOa and showed increased DA levels in the striatum (Hampp et al., 2008). As a compensatory response to the elevated DA levels, the expression of DRD1 that act as an excitatory receptor decreased, and the expression of DRD2 that acts as an inhibitory receptor increased in Per2 mutant mice. Similarly, the levels of PER2 was high during the late night in the substantia nigra, and then the DA levels were low in the early morning in the striatum (Bussi et al., 2014). Bussi et al. (2014) reported that high PER2 levels late at night lead to decreased DA levels. In addition, PER2 also regulated DRD2 availability in the human brain (Shumay et al., 2012). They found that the availability of striatal DRD2 changed according to the PER2 polymorphisms. For example, humans with short alleles of PER2 showed decreased levels of DRD2. Based on these facts, some researchers assumed that the increased levels of Per2 expression may lead to less DA levels especially through MAOa degradation mechanisms (Hampp and Albrecht, 2008).

Conversely, DA levels also regulate Per2 expression level. The levels of Per2 expression decreased in the striatum of DRD1 mutant (KO) mice (Gallardo et al., 2014) and DRD2 KO mice (Sahar et al., 2010). Rats housed in constant light showed increased levels of Per2 and DRD1 in the striatum and prefrontal cortex (Garmabi et al., 2016). When DRD1 was blocked in the inner mouse retina, Per2 was reduced (Ruan et al., 2008). In addition, when DA was depleted by 6-hydroxydopamine or AMPT, or DRD2 was blocked, the levels of the Per2 expression was reduced, which indicates that the levels of DA may regulate the transcription of Per2 expression (Amir and Stewart, 2009; Hood et al., 2010; Gravotta et al., 2011). Based on these findings, Per2 may be closely related to the dopaminergic-system.

**Glutamate**

The release of glutamate exhibits a circadian pattern but is not influenced by light (Castaneda et al., 2004; Kalsbeek et al., 2008). Beaulé et al. (2009) found that glutamate levels were regulated by Clock, Npas2, and Per2. Glutamate transporter expression and reuptake decreased in Per2-deficient astocytes. Per2 mutant (KO) mice showed low expression levels of EAAT1 in the brain (Spanagel et al., 2005). Low expression of EAAT1 would result in reduced uptake of glutamate by astrocytes. As a result, glutamate levels increased in the synaptic cleft of Per2 mutant mice. Another glutamate transporter, vesicular glutamate transporter 1 (vGLUT1) was also modulated by Per2 (Yelamanchili et al., 2006). They also reported that Per2 mutant mice did not show circadian rhythms in vGLUT1 levels, although it led to alterations in the glutamate content of synaptic vesicles. Conversely, glutamate administration can induce Per2 expression in vivo and in vitro (Nielsen et al., 2001). The N-methyl-D-aspartate (NMDA) receptor, another type of glutamate receptor, is associated with Per2 expression. For examples, NMDA receptor antagonists inhibited Per2 expression in vivo and in vitro, while NMDA administration can induce Per2 expression (Moriya et al., 2000; Paul et al., 2005; Bellet et al., 2011; Zunszain et al., 2013). Antagonist of AMPA/kainite receptors, another glutamate receptor, reduced Per2 expression levels in the SCN (Paul et al., 2005). Interestingly, mice null for type 1 equilibrative nucleoside transporter (ENT1), an adenosine transporter, showed increased levels of extracellular glutamate and decreased levels of Per2 expression in NAC (Hinton, 2016). Altogether, glutamate levels may be positively related to Per2 expression.

**GABA**

GABA is an inhibitory neurotransmitter in the CNS, and the release of GABA is associated with circadian rhythms (Ralph and Menaker, 1989; Castaneda et al., 2004). There are few studies directly demonstrating that Per2 regulates GABA levels. Straub and Cutoio (2007) reviewed that Per2 induced neuron activation in the SCN with neurotransmitters including GABA. Other studies have shown that GABA regulates Per2 expression through GABAA receptor activation in the SCN (Ehlen et al., 2006; Novak et al., 2006; Challet, 2007; Matsuo et al., 2016). Treatment with muscimol, a GABAA receptor agonist in the SCN, decreased Per2 expression (Ehlen et al., 2006; Novak et al., 2006), while treatment of a GABA antagonist increased Per2 expression (Aton et al., 2006). Those negative regulations were induced by GABA-induced membrane hyperpolarization and casein kinase activation (Ruan et al., 2008; DeWoskin et al., 2015).

**Serotonin (5-HT)**

Serotonin (5-HT) is also regulated by circadian rhythms
However, only a few studies have been conducted to show a relationship between 5-HT and Per2. Some studies reported that levels of 5-HT regulated Per2 expression. Treatment with the 5-HT\textsubscript{1A} receptor agonist during daytime decreased Per2 expression in the SCN (Horikawa et al., 2000; Yokota et al., 2000; Caldelas et al., 2005; Mendoza et al., 2008), while during early night, administration of the 5-HT\textsubscript{1A} agonist induced Per2 expression (Varcoe, 2008). There is also a report demonstrating that high 5-HT levels induced by 5-HT reuptake inhibitors during nighttime induced Per2 expression (Cuesta et al., 2009). However, further studies are needed to prove directly that Per2 may be associated with 5-HT.

Table 1. Neurobiological effects of Per2 in mutant (KO/deficient) animals

| Category                          | Effects in mutant animals | Reference                                      |
|-----------------------------------|---------------------------|------------------------------------------------|
| 1 Dopamine (DA)                   | Increased                 | Hampp et al., 2008                             |
| 2 MAOa                            | Decreased                 | Hampp et al., 2008                             |
| 3 DA receptor D1                  | Decreased                 | Hampp et al., 2008                             |
| 4 DA receptors D2                 | Increased                 | Hampp et al., 2008                             |
| 5 Glu transporter (Eaat1, vGLU1)   | Decreased                 | Hampp et al., 2008                             |
| 6 Glu reuptake                    | Decreased                 | Hampp et al., 2008                             |
| 7 Glu level                       | Increased                 | Hampp et al., 2008                             |
| 8 Cocaine sensitization           | Higher*                   | Abarca et al., 2002                           |
| 9 Cocaine CPP                     | Higher*                   | Brager et al., 2013                           |
| 10 Responses to Cocaine           | Higher                    | Brager et al., 2013                           |
| 11 Responses to METH**            | Higher                    | Pendergast et al., 2012                       |
| 12 Alcohol consumption*           | Higher                    | Spanagel et al., 2005; Brager et al., 2011b |
| 13 Alcohol CPP                    | Higher                    | Gamsby et al., 2013                           |
| 14 Food anticipatory              | No                        | Feillet et al., 2006; Mendoza et al., 2010    |
| 15 Analgesic effect of morphine   | Increased                 | Perreau-Lenz et al., 2010                     |
| 16 FST                            | Less immobility           | Hampp et al., 2008                             |
| 17 Total sleep time               | Decreased                 | Kopp et al., 2002; Miyazaki et al., 2007     |

*It was not significant, only trend. **In the Per\textsuperscript{1}/Per2\textsuperscript{2}/Per3\textsuperscript{3} mice. DA: dopamine, MAOa: monoamine oxidase A, Glu: glutamate, METH: methamphetamine, CPP: conditioned place preference, FST: forced swimming test.

Table 2. Various factors influencing Per2 gene expression

| Factors                          | Per2 gene expression | Reference                                      |
|----------------------------------|----------------------|------------------------------------------------|
| 1 DA receptor D1 (KO/blocked)    | Decreased            | Ruan et al., 2008; Gallardo et al., 2014       |
| 2 DA receptor D2 (KO/blocked)    | Decreased            | Hood et al., 2010; Sahar et al., 2010          |
| 3 Removed DA                     | Decreased            | Amir and Stewart, 2009; Hood et al., 2010; Gravotta et al., 2011 |
| 4 Glu (NMDA, AMPA) antagonists    | Decreased            | Moriya et al., 2000; Paul et al., 2005; Bellet et al., 2011 |
| 5 ENT1 KO                         | Decreased            | Hinton, 2016                                   |
| 6 GABAa agonist                  | Decreased            | Ehlen et al., 2006; Novak et al., 2006; Ruan et al., 2008; DeWoskin et al., 2015 |
| 7 5-HT\textsubscript{1A} agonist during daytime | Decreased | Horikawa et al., 2000; Yokota et al., 2000; Caldelas et al., 2005; Mendoza et al., 2008 |
| 8 Chronic unpredictable stress   | Decreased            | Jiang et al., 2011; Logan et al., 2015         |
| 9 Constant light                 | Increased            | Garmabi et al., 2016                          |
| 10 Glu                            | Increased            | Nielsen et al., 2001                          |
| 11 NMDA                           | Increased            | Paul et al., 2005                             |
| 12 GABA antagonist                | Increased            | Aton et al., 2006; Ruan et al., 2008; DeWoskin et al., 2015 |
| 13 High serotonin during nighttime| Increased            | Cuesta et al., 2009                           |
| 14 METH                           | Increased            | Yamamoto et al., 2005                         |
| 15 Cocaine                        | Increased            | McClung and Nestler, 2003; Yuferov et al., 2003; Uz et al., 2005 |
| 16 Sleep deprivation              | Increased            | Franken et al., 2007; Curie et al., 2015; Zhang et al., 2016 |

DA: dopamine, Glu: glutamate, ENT1: type 1 equilibrative nucleoside transporter-adenosine transporter, METH: methamphetamine.
CONCLUSIONS

The neurobiological effects of Per2 in mutant animals are summarized in Table 1, 2 shows various factors influencing Per2 gene expression.

In the past two decades, many roles of Per2 have been identified in mammals. Per2 affects range from the peripheral organs to the CNS as one of the key components of circadian clock. Per2 interacts with neurotransmitters to regulate neurobiological activities in the CNS. Alterations in the levels of Per2 expression and neurotransmitters affected the responses to drugs and emotional behaviors. For example, rewarding and reinforcing effects of cocaine or alcohol increased in Per2 mutant (KO) mice showing high levels of DA and Glu and low levels of MAO activities.

However, the mechanism of Per2 in neurobiological activities is still poorly understood. Further studies are needed to reveal the mechanism of Per2 in the CNS. First, the interaction of neurotransmitters and Per2 in the mesolimbic pathway and in the limbic system that regulate reward and primitive emotions would be good targets for understanding the mechanism of Per2 in the CNS because Per2 mutant mice showed alterations in neurotransmitters levels (Spanagel et al., 2005; Hampel et al., 2008). Next, PER2 could be another good target because PER2 is the final product of Per2 expression and acts in the target areas. Recently, increasing evidence suggests that the level of circadian clock-related proteins such as CLOCK, BMAL1, CRY, and PER affect circadian disorders (Hirota and Kay, 2009; Lee et al., 2011; Solt et al., 2012; Chun et al., 2014). In particular, the level of PER2 plays an important role in the circadian clock and sleep disorders such as FASPS in humans. A few studies have identified that the level of PER2 is regulated by phosphorylation, and many protein kinases such as CKI/δβ are involved in the mechanism of PER2 phosphorylation and degradation (Eide et al., 2005; Lee et al., 2011a). In addition, histone methylation affects the level of PER2 and the circadian rhythm (Brown et al., 2005). However, the exact molecular mechanism of PER2 functions in the circadian clock remains unclear. Thus, further studies need to focus on the function of PER2.

In the present study, we reviewed the effects of Per2 mutation on behavioral and emotional characteristics such as sleep rhythms and depression. However, it is not clear that the effect of Per2 mutation is direct or indirect as manifested by the feedback of molecular circadian clock network or a dysfunctional circadian rhythm. Per2 interacts with a variety of other genes, proteins, and regulators. Although it is not trivial to understand the interactions between Per2 and other factors, increasing knowledge of Per2 would be beneficial for understanding and treating neurobiological diseases.

CONFLICT OF INTEREST

The authors confirm that they have no conflicts of interest.

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