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Review
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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 *Drosophilla melanogaster* (Konopka and Benzer, 1971). They found three per genes on the X chromosome consisting of a short-period mutant (19 h, per^s) and long-period mutant (28 h, per^l) when compared to the normal-period length (24 h), and the arrhythmic mutant (per^o). 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

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showed a shorter circadian period than wild type (WT) mice and reduced *Per1* expression in the SCN, indicating that *Per2* regulates *Per1*. Thus, *Per2* is one of the cores 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 accumulated 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 nucleus receptors such as REV-ERBa and PPARa (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 BMALl-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 CKIε *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 CKIε 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*, *Arntl*, and *Npas2* (Partonen *et al*., 2007). Another study in humans also reported that *PER2* ge-

netic 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; Spanagel *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 (Spanagel *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 (Spanagel *et al*., 2005). In animals, *Per2* mutant (KO) mice consumed more alcohol than WT mice (Spanagel *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 (McClung 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; Simerly, 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*^{Brdm1} and *Per2*^{Brdm1}/*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 astrocytes. *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 Cutolo (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

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
		Decreased by increased PER2	Bussi *et al*., 2014
2	MAOa	Decreased	Hampp *et al*., 2008
3	DA receptor D1	Decreased	
4	DA receptors D2	Increased	
5	Glu transporter (Eaat1, vGLU1)	Decreased	Spanagel *et al*., 2005; Yelamanchili *et al*., 2006; Beaulé *et al*., 2009;
6	Glu reuptake	Decreased	
7	Glu level	Increased	
8	Cocaine sensitization	Higher	Abarca *et al*., 2002
9	Cocaine CPP	Higher*	
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 *Per1*$^{-/-}$/*Per2*$^{-/-}$/*Per3*$^{-/-}$ 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$_{1A/7}$ 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.

(Quay, 1963; Snyder *et al*., 1965; Phillips, 2004; Cuesta *et al*., 2009). 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$_{1A/7}$ 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$_{2a/2c}$ 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.

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; Hampp *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 CKIε/δ 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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