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Research article

Dynamical analysis of the effects of circadian clock on the neurotransmitter dopamine

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Abstract: The circadian clock is an autonomous timing system that regulates the physiological and behavioral activities of organisms. Dopamine (DA) is an important neurotransmitter that is associated with many biological activities such as mood and movement. Experimental studies have shown that the circadian clock influences the DA system and disorders in the circadian clock lead to DA-related diseases. However, the regulatory mechanism of the circadian clock on DA is far from clear. In this paper, we apply an existing circadian-dopamine mathematical model to explore the effects of the circadian clock on DA. Based on numerical simulations, we find the disturbance of the circadian clock, including clock gene mutations, jet lag and light pulses, leads to abnormal DA levels. The effects of mutations in some clock genes on the mood and behavior of mice are closely related to DA disruptions. By sensitivity analysis of DA levels to parameter perturbation, we identify key reactions that affect DA levels, which provides insights into modulating DA disorders. Sudden changes in external light influence the circadian clock, bringing about effects on the DA system. Jet lag causes transient DA rhythm desynchronization with the environment and the influence of jet lag in different directions on DA level and phase varies. Light pulses affect the amplitude and phase shift of DA, which provides a promising method for treating DA disorders through light exposure. This study helps to better understand the impact of the circadian clock on the DA system and provides theoretical support for the treatment of DA disorders.

Keywords: circadian clock; dopamine; mathematical model; phase shift; jet lag; phase response curve; amplitude response curve

1. Introduction

DA is an important neurotransmitter that plays an important role in brain functions. DA's participation in learning and motivation transmits incentive value and promotes sports [1]. Numerous

biological behaviors affect the release and metabolism of DA, for example, drinking increases the release of DA [2], smoking leads to increased DA release in striatum [3] and aerobic exercise increases evoked DA release in the caudate nucleus [4]. DA dysfunction is associated with various disorders, such as schizophrenia, Parkinson's, addiction and mood disorders (mania and depression) [5].

The circadian clock is an intrinsically autonomous timing system with a period that is close to 24 hours (h). The mammalian circadian clock coordinates physiological and behavioral rhythms and synchronizes the organisms to daily environmental cycles, which are controlled by the suprachiasmatic nucleus (SCN) [6]. The circadian clock is composed of a core oscillator together with input and output pathways [7]. The core oscillator generates a basic rhythm. The input pathway senses environmental signals, such as the daily light-dark (LD) cycles, and adjusts the core oscillator to adapt to the external environment. The output pathway transmits information from the oscillator to downstream biochemical processes to control the physiology of the organism. In mammals, the circadian clock is based on interlocking transcription-translation feedback loops which are composed of clock genes and proteins [8].

Studies have found DA and the circadian clock interact with each other. On one hand, the disorder of the circadian clock leads to symptoms such as hyperactivity, learning and memory defects, impulsivity, and other symptoms, which are related to DA [5]. On the other hand, people with DA-related diseases also exhibit circadian rhythm disorders [9]. It has been found that the circadian clock directly regulates DA-related components, including monoamine oxidase (MAO) and dopamine hydroxylase (*dbh*) [10]. REV-ERBs and ROR of the circadian clock regulate the tyrosine hydrogenase (TH) and MAO, which are respectively involved in the synthesis and degradation of DA [11, 12]. DA signal regulates the expression of PER2 in the dorsal striatum of the rat [13]. Some agonists of the DA D2 receptor inhibit the expression of clock genes *Clock* and *Per*1 and some agonists of the D1 receptor stimulate the expression of *Per*1, *Clock* and *Bmal*1 [14]. Biological experiments found mutations in core clock genes cause abnormal DA levels, which led to some unusual reactions in biological behavior or physiology [10, 15].

The underlying regulatory mechanism of the circadian clock on the DA system and the methods for modulating DA disorder through the regulation of the circadian clock on DA are still far from clear. Mathematical modeling is a useful method to investigate the mechanism of circadian clocks [16–18] and DA synthesis and release [19]. In this paper, with an existing circadian-dopamine model [12], we analyze the dynamical effects of the circadian clock on DA. We mainly explore the effects of the disruption of the circadian clock caused by mutations in clock genes and changes in external environmental lighting on DA. Based on the analysis results, we provide some reasonable suggestions for treating DA disorders. The rest of this article is organized as follows. In Section 2, the detailed mathematical model is introduced. The numerical simulation results and analysis are presented in Section 3. The conclusion and discussion are given in Section 4.

2. Description of the mathematical model

The mathematical model used in this paper is developed by Kim et al [11, 12], and is composed of differential equations characterizing the core circadian clock, secondary feedback loop and downstream DA. The detailed schematic diagram of the mathematical model is shown in Figure 1. The model

describes the regulation of clock proteins on the transcription of clock genes, as well as the regulation of clock proteins on TH and MAO related to DA.

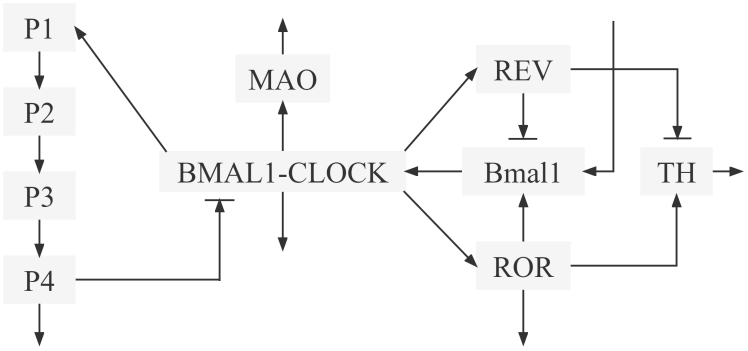

Figure 1. Schematic diagram of the circadian clock model [12]. The protein complex BMAL1-CLOCK promotes the production of PER and P_i ($i = 1, 2, 3, 4$) are phosphorylated PER, which inhibits the production of BMAL1-CLOCK. ROR and REV are activated by BMAL1-CLOCK, which modulates *Bmal1*. TH and MAO are downstream dopaminergic variables, modulated by BMAL1-CLOCK, ROR and REV. TH is the rate-limiting enzyme in DA synthesis and MAO is involved in DA degradation.

To simplify, Per_1, Per_2 and Per_3 genes are not distinguished here, which are represented by gene *Per*. P_i ($i = 1, 2, 3, 4$) represents phosphorylated PER proteins. The core circadian clock consists of BMAL1-CLOCK heterodimers and the successively phosphorylated PER proteins, not including biosynthesis of discussed proteins, especially transcription regulation of related genes. The model of the core circadian clock agrees with major known properties of the clock including a 24-hour period length for clock components [11], which can be used here to study the effects of the circadian clock on the DA system. P_4 sequestrates BMAL1-CLOCK, which promotes the production of P_1. *Bmal1* affects the production of BMAL1-CLOCK. In the following, *BC* is used to denote the concentration of the protein complex BMAL1-CLOCK. The equations for the core circadian clock are as follows.

$$\frac{dP_1}{dt} = g_1 l(t, x) f_0(BC, P_4) - g_2 P_1, \tag{2.1}$$

$$\frac{dP_2}{dt} = g_2 P_1 - g_3 P_2, \tag{2.2}$$

$$\frac{dP_3}{dt} = g_3 P_2 - g_4 P_3, \tag{2.3}$$

$$\frac{dP_4}{dt} = g_4 P_3 - d_p P_4, \tag{2.4}$$

$$\frac{dBC}{dt} = \beta_{bc} S - d_{bc} BC. \tag{2.5}$$

$l(t, x)$ denotes the 12:12 LD cycle. Light enhances the expression of *Per* gene [20], so light input is modeled by resetting the production rate of P_1 to vary diurnally.

$$l(t,x) = \begin{cases} 1+x & t \; mod \; 24<12, \\ 1-x & otherwise, \end{cases} \tag{2.6}$$

where $0 \leq x<1$. When $x = 0$, $L = 1$, which represents the free running condition without the LD cycle.

The secondary feedback loop and the core circadian clock are connected by the protein complex BMAL1-CLOCK, which activates the transcription of REV and ROR. REV is a nuclear receptor, which inhibits the transcription of *Bmal*1 [21]. ROR is a functional component of the cell-autonomous core biological clock, which promotes the transcription of *Bmal1* and maintains a stable circadian rhythm [22]. The equations for the secondary loop are as follows.

$$\frac{dBmal1}{dt} = \beta + \alpha f_0(Bmal1, REV)ROR - d_s Bmal1, \tag{2.7}$$

$$\frac{dREV}{dt} = r_{rev} f_0(BC, P_4)ROR - d_{rev} REV, \tag{2.8}$$

$$\frac{dROR}{dt} = r_{ror} f_0(BC, P_4)ROR - d_{ror} ROR. \tag{2.9}$$

TH and MAO form the downstream DA. REV and ROR play a connecting role in the circadian clock system and DA system. TH is the rate-limiting enzyme in DA synthesis, which is inhibited by REV and activated by ROR [23]. MAO is an enzyme necessary for DA degradation, which is promoted by BMAL1-CLOCK [15].

$$\frac{dTH}{dt} = b_{th} + \frac{\rho_{th}}{(1 + k_{th}(1 - \frac{f(TH,REV,\epsilon_{th})}{TH}))^{n_{th}}} + \alpha \frac{f(TH, REV, \epsilon_{th})}{TH} \frac{ROR}{ROR + \kappa_{th}} - d_{th} TH, \tag{2.10}$$

$$\frac{dMAO}{dt} = r_m f_0(BC, P_4) - d_m MAO. \tag{2.11}$$

In the above equations, the expressions of functions f and f_0 are shown in the following [12].

$$f(A,B,C) = 1/2(A - B - C + \sqrt{(A - B - C)^2 + 4AC}), \tag{2.12}$$

$$f_0(A,B) = \frac{A - B + |A - B|}{2} = \begin{cases} A - B & A > B \\ 0 & A \leq B \, . \end{cases} \tag{2.13}$$

As described in [12], the above model is connected to the DA synthesis and release model developed by Best et al. and full details of the DA model can be found in [19]. TH is converted into l-dopa, decarboxylated into cytoplasmic DA and then transported and released by vesicles outside the cell. MAO decomposes cytoplasmic DA and extracellular DA. Referring to Kim's method [12], we multiply the time series of TH and MAO in the model by the reaction speeds of TH and MAO in Best's model to get the time evolution of DA.

$$\frac{dDA}{dt} = TH \cdot V_{TH} - MAO \cdot V_{CATAB}, \tag{2.14}$$

where V_{TH} and V_{CATAB} are the reaction speeds of TH and MAO respectively, which can be found in [19].

The calculation in this paper is solved by MATLAB.

3. Results

3.1. Effects of mutations in clock genes on DA

Studies have found that mutations of clock genes or proteins bring about the disorder of the circadian clock and then affect the physiological or behavioral behaviors of organisms [24, 25]. Here, we use the mathematical model to verify the impact of mutations in several key clock genes on DA.

Clock gene encodes an important part of the master clock driving circadian rhythm. CLOCK protein, as a key member of the biological clock core, promotes the expression of *Per* and *Cry* genes by binding to BMAL1 [26]. Knockout of *Clock* gene leads to the deletion of CLOCK protein, which in turn affects the synthesis of BMAL1-CLOCK. Here, we simulate *Clock* gene knockout by silencing BMAL1-CLOCK. Figure 2(a) shows the effect of *Clock* knockout on the time course of DA. After *Clock* gene is knocked out, the concentration of DA remains at a high level with a small amplitude. Experiments found the response of mice with *Clock* gene knocked out to the environment shows a significant increase in exercise activity [27] and the circadian rhythm of dopaminergic cells almost disappeares [28]. The numerical results are consistent with experimental findings. The reason is that the inability to synthesize BMAL1-CLOCK after *Clock* gene knockout leads to increased levels of TH and decreased synthesis of MAO, resulting in increased DA synthesis.

Per is also a core gene of the circadian clock. We simulate *Per1* knockout by significantly reducing the basic production of PER protein in the model. Figure 2(b) shows that the concentration of DA remains at a reduced level with a small amplitude with *Per1* knockout. This may lead to the decline of the daily transport capacity of mice, showing an inactive state, which is consistent with the reduced levels of DA and attention deficit disorders observed in experiments [10]. From Figure 1, one knows PER inhibits the synthesis of BMAL1-CLOCK, so the knockout of *Per1* leads to an increase in BMAL1-CLOCK level, which in turn increases the synthesis of MAO. The increase in MAO as a DA catabolic enzyme is followed by an increase in the rate of DA catabolism, which leads to a decrease in DA level as shown in Figure 2(b).

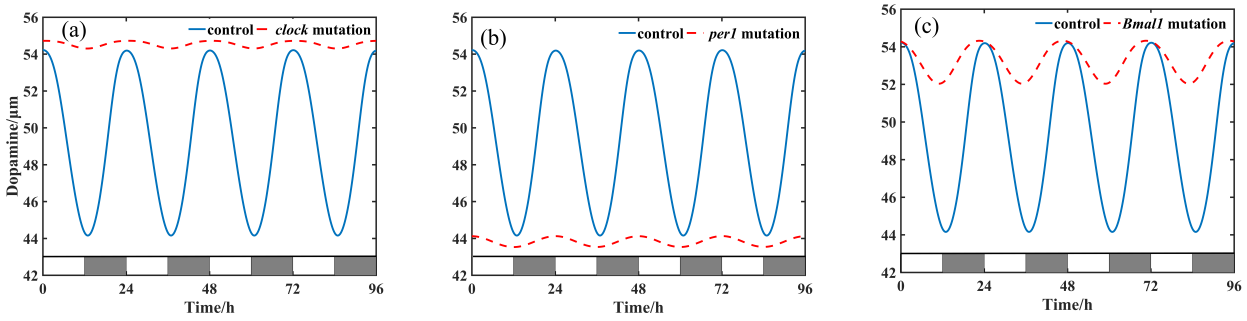

Figure 2. Simulations of the DA oscillators. The blue solid line indicates the DA oscillator in the situation of the normal circadian clock. The red dotted line indicates the DA oscillator in the situation of a disordered circadian clock with gene mutations in *Clock* (a), *Per1* (b) and *Bmal1* (c).

BMAL1 is a transcriptional regulator in SCN [29]. It plays a role in regulating biological learning

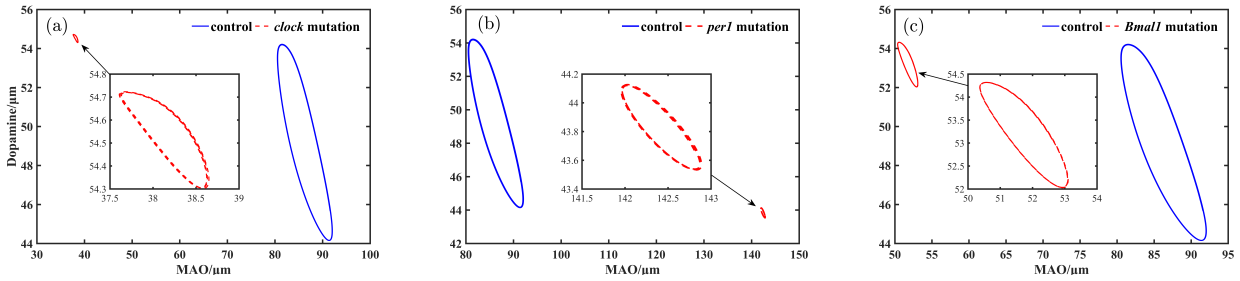

Figure 3. The phase plane diagram projected onto the MAO-DA plane. The blue solid line indicates the orbit in the situation of the normal circadian clock. The red dotted line indicates the orbit in the situation of a disordered circadian clock with gene mutations in *Clock* (a), *Per1* (b) and *Bmal1* (c).

and memory [30]. We simulate *Bmal1* mutation by reducing the basic transcription rate of *Bmal1* in the model, shown in Figure 2(c). We can see that *Bmal1* gene mutation makes the level of DA oscillate at a high level with a small amplitude and decreased rhythmicity of DA. The DA level increases significantly near dawn leading to abnormally active behavior in mice, which is consistent with the experimental results [31]. With the mutation of *Bmal1*, the concentration of protein BMAL1 decreases, which leads to a reduction of protein complex BMAL1-CLOCK dimer. Furthermore, the decrease in BMAL1-CLOCK results in increased levels of TH and decreased synthesis of MAO, making for increased DA synthesis.

In order to explore the dynamical mechanisms of gene mutations, we present the phase plane diagram in Figure 3. As mentioned in Section 2, MAO is an intermediate substance that connects the circadian rhythm and the DA system. Mutations in clock genes first cause changes in MAO concentration, which in turn affects DA levels. The mutations of gene *Clock* and *Bmal1* both bring the decrease of MAO, which leads to the increase of DA level. From Figure 3(a),(c), we can see the limit cycle is smaller with gene mutation than that in the normal situation. Therefore the amplitude of the DA oscillator decreases with gene mutations in Figure 2(a),(c). Similarly, *Per1* mutation increases the concentration of MAO, which results in the decrease of DA level. The small limit cycle shows the small amplitude of the DA oscillator in Figure 2(b).

In summary, mutations in the core clock genes cause DA to oscillate at abnormally high or low levels, leading to an overly active or inactive physiological state in the organisms. Mutations in all three genes result in a decrease in the amplitude of the DA oscillator, which means a decrease in the rhythmicity of DA. The mutation of core clock genes leads to a decrease in the amplitude of the circadian clock, which in turn reduces the regulatory rhythmicity of the DA system, resulting in a decrease in DA amplitude. This also indicates that the regulation of the circadian clock plays a decisive role in the DA system. By comparing the effects of three key gene mutations on DA, we find that on the one hand, mutations in clock genes lead to abnormal DA expression levels. On the other hand, this also provides us with an idea to use clock genes to regulate DA levels.

3.2. Sensitivity analysis of parameters

Robustness describes the ability to maintain performance facing up to the perturbation of system parameters, which is an essential characteristic of a system. To study the robustness of the DA system, we present the sensitivity analysis, which shows an inverse correlation with that of robustness. Through sensitivity analysis, one can study how alters of a parameter lead to changes in the dynamic behavior of the system, and then find the most critical parameters that affect the whole system.

The level of DA is closely related to the behavior and mood of organisms [5], which determines the health status of the body. Therefore, we investigate the peak value of DA sensitivity, which describes the variations of peak values coming from the perturbations of system parameters. The peak value sensitivity is described as follows

$$S(P; p_i) = \frac{\partial \ln P}{\partial \ln p_i} = \frac{p_i}{P} \cdot \frac{\partial P}{\partial p_i}, \tag{3.1}$$

where P is the peak value of DA and p_i is the parameter with index i.

Here, we consider two kinds of parameters. The first kind is closely related to the synthesis of DA, which includes the maximum rate of TH reaction indicated by V_{TH}, the maximum rate of conversion between bh4 and bh2 indicated by V_{DRR}, the maximum rate of btyr to tyr denoted by V_{Tyrin}, the maximum rate of levodopa to intracellular dopamine (cda) indicated by V_{AADC}, the maximum rate of cda to vesicular dopamine (vda) indicated by V_{Mat}, and the maximum rate of extracellular dopamine (eda) to hva indicated by V_{Catab}. As mentioned earlier, the DA synthesis and release model developed by Best et al. is not displayed here, so the parameters V_{TH}, V_{DRR}, V_{Tyrin}, V_{AADC}, V_{Mat} and V_{Catab} can be referenced in [19]. The second kind is related to the circadian clock, which concerns the rates of the PER phosphorylation process, indicated by parameters g_2, g_3 and g_4, as well as the synthesis and degradation rate of REV and ROR, denoted by parameters r_{rev}, d_{rev}, r_{ror} and d_{ror} respectively.

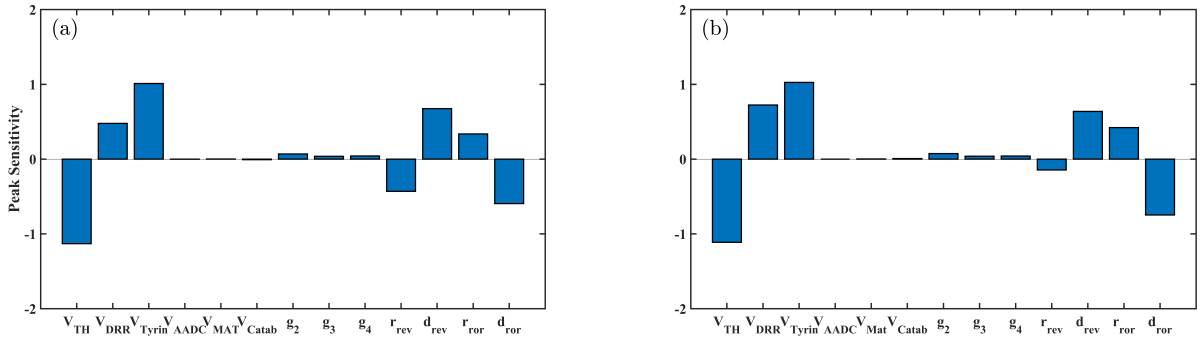

Figure 4. Peak sensitivity related to the system parameters. (a) and (b) indicate the conditions of +5% perturbation and -5% perturbation to each parameter, respectively. V_{TH}, V_{DRR}, V_{Tyrin}, V_{AADC}, V_{Mat} and V_{Catab} relate to the DA synthesis and release model in Ref. [19] and g_2, g_3, g_4,r_{rev}, d_{rev}, r_{ror} and d_{ror} related to the circadian clock model Eqs (2.1)–(2.9).

Figure 4 shows the resulting peak value sensitivity to the parameter perturbations. In Figure 4(a),(b), +5% perturbation and −5% perturbation to each parameter are introduced respectively.

Based on Figure 4, we obtain some interesting findings. The peak value of DA is most sensitive to the perturbation of parameters closely related to the synthesis of DA, followed by that of parameters related to the synthesis and degradation of PER and ROR.

Among them, TH is involved in the synthesis of DA predecessor l-dopa, converting tyrosine to l-dopa. V_{Tyrin} and V_{DRR} are both related to this process. In addition, REV and ROR are connections between the circadian clock and DA, which directly affect the synthesis of TH. Accordingly, the disturbance of parameters related to the synthesis and degradation of PER and ROR leads to fluctuations in TH, which in turn affects fluctuations in DA levels. This finding indicates that TH as the key enzyme of DA synthesis plays a core role in deciding the level of DA. Therefore, it is more effective to modulate the level of DA by adjusting the parameters directly or indirectly involved in TH reactions.

3.3. Effects of Jet Lag on DA

Circadian rhythms are endogenous oscillations with periods close to 24 h, but seldom exactly 24 h, which can be entrained to 24 h by the natural LD cycle. A sudden shift in the phase of the LD cycle may disrupt the entrainment. Then, the circadian oscillator has to adjust its phase until the oscillator is reentrainmented or locked to the new LD cycle [32]. For example, long-distance flight across several time zones may result in jet lag, which causes physical discomfort for a while, including insomnia, decreased attention, irritability, etc., which is caused by the temporary non-entrainment of the circadian clock with the new LD cycle [33]. The degree of jet lag depends on the number of time zones crossed and the direction of flight, i.e., east or west [34]. In the following, we study the influence of circadian clock disturbance caused by jet lag on the DA system.

The circadian rhythm oscillator runs for 19 days in the normal LD cycle. Then, six hours light delay (i.e. traveling west) is added on the 20th day. The solid and dotted lines in Figure 5(a) show DA levels in the control case and the case of light delay, respectively. Six-hour delay of light leads to phase delay and a significant increase in the amplitude of DA during the first two days after the light delay. As mentioned earlier, DA plays a role in regulating emotion and behavior, so the typical manifestations of jet lag, such as irritability and mild depression, may be related to the transient asynchronies in DA rhythms. Reentrainment with the new LD cycle is therefore very important for people who experience jet lag disorder. To see the adjustment speed more clearly, taking the peak of DA as the phase of the circadian oscillator, we calculate the phase shifts between the circadian oscillator under the new LD cycle and that of the normal LD cycle, as shown in Figure 5(b). It takes about three days for DA to adapt to the new LD cycle after the occurrence of light delay.

Now let's consider the phase shift in the opposite direction, which means traveling east with 6 h of advance light on the 20th day. A six-hour advance of light leads to a phase advance of DA. There is a significant decrease in the amplitude of DA during the first two days after the light advance as shown in Figure 5(c). The decrease in DA amplitude may lead to emotional distress as found in experiments. Studies have found that jet-lagged travelers mostly complain of lack of sleep and daytime sleepiness, low mood, reduced productivity and early awakenings [35]. It takes about five days for DA to adapt to the new LD cycle after the occurrence of light delay, as shown in Figure 5(d).

In summary, traveling across time zones in different directions has distinct impacts on DA and thus the human body's response to jet lag also varies. Different approaches should be adopted to adjust jet lag based on performance. For people traveling west, certain treatment measures need to be taken to

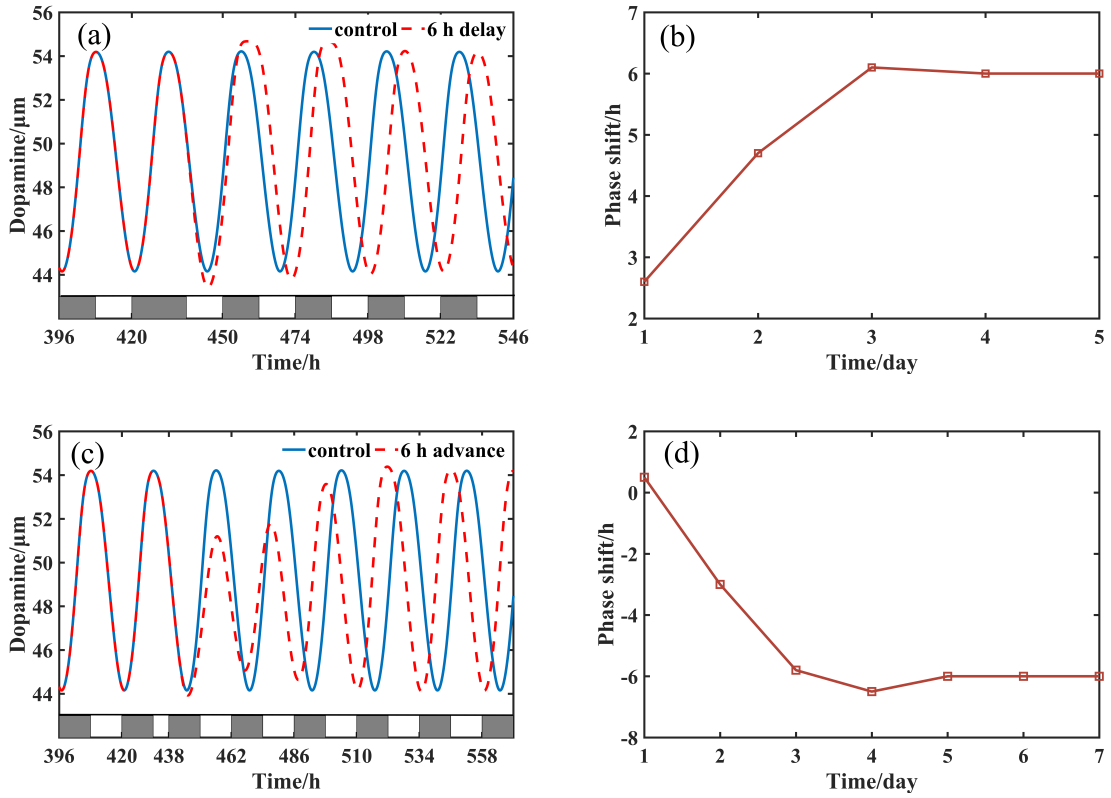

Figure 5. Effects of jet lag on DA. Reentrainment of DA where the LD cycle is disturbed by 6 h delay (a) and 6 h advance (c), respectively. White represents light and gray represents darkness. The solid blue and dotted red lines indicate the DA oscillator in the normal LD cycle and the disturbed LD cycle respectively. Phase shifts between the DA oscillator in the normal LD cycle and that in the disturbed LD cycle with 6 h delay (b) and 6 h advance (d), respectively.

reduce their DA levels, while those traveling east need to use treatment to increase their DA levels.

3.4. Phase shifts caused by a light pulse

The natural LD cycle information is transmitted to the DA system through the circadian clock. Light affects emotion and social behavior and proper light adjustment may improve health [37]. At present, light therapy has been proven to be a promising treatment for circadian rhythm disorder, sleep disorders, and cognitive status of patients [38, 39]. The DA energy transmission of persons with seasonal affective disorder (SAD) is abnormal and bright light therapy is one of the main treatments for SAD [40]. Daily specific light can improve and normalize the DA rhythm disorder in a time-dependent manner.

In order to seek better phototherapy effects, we explore the effect of light pulses on the DA system. We simulate phototherapy by adding strong light pulses at certain times. Figure 6 shows the phase shifts when a light pulse is added for 3 h at different circadian times (CTs). CT0 is the trough of the

DA oscillator. The control group is conducted in constant darkness. Figure 6(a)–(c) shows the effect of adding light pulses on the phase shift at CT6, CT9 and CT16. When a light pulse is added at CT6, the amplitude fluctuates in the first period after that and the phase is slightly advanced, then tends to be stable. Adding a pulse at CT9, the phase is approximately 0.7 h ahead of schedule. Adding a pulse at CT16, in the first period after that, the amplitude fluctuates obviously. When it is stable later, the phase is delayed for about 1.2 h. Therefore, light pluses added at different times bring about different effects on the phase and amplitude of DA. Therefore, the efficacy of phototherapy varies at different times.

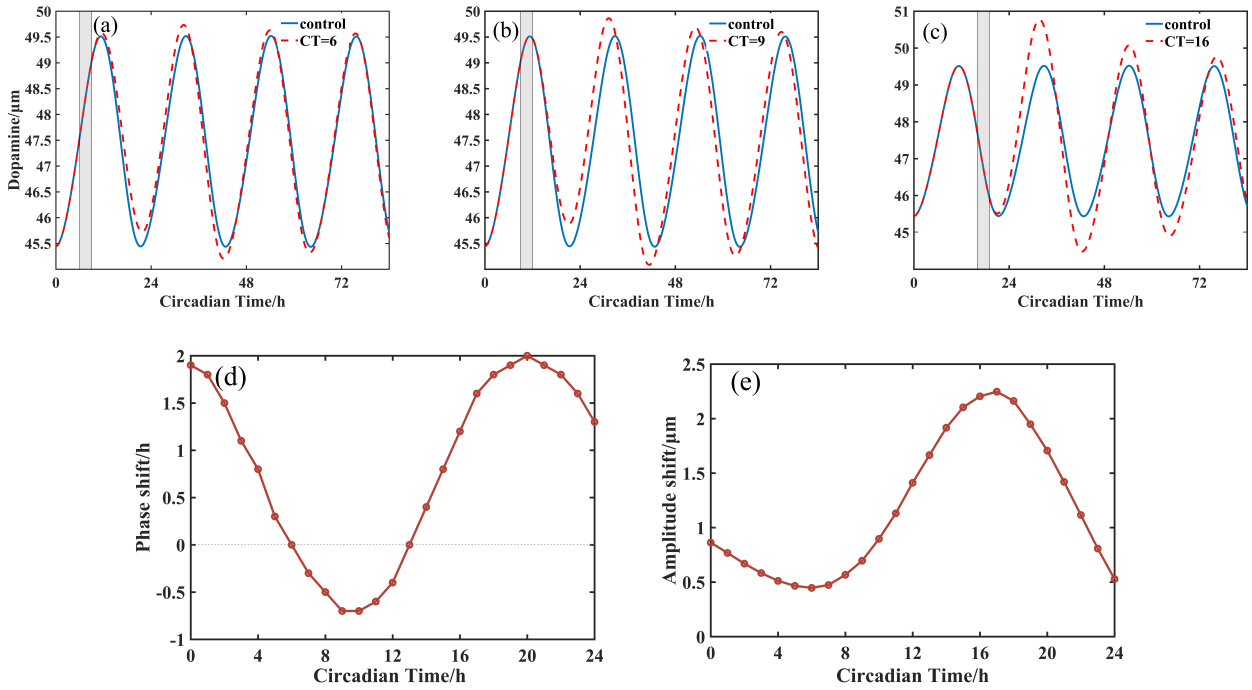

Figure 6. Effects of light pulse on DA. A 3 h light pulse is added at CT6 (a), CT9 (b) and CT16 (c). (d) Phase response curve(PRC) of the DA oscillator. (e) The amplitude response curve (ARC) of the DA oscillator.

Making phase response curves (PRCs) is an effective way to study the phase shifts induced by environmental signals added at different CTs. To see the effect of light pulses on DA phase shift more clearly, we draw the PRC shown in Figure 6(d). Light pulse added from about CT6 to CT13 brings phase advance and light pulse added at other circadian times leads to phase delay. From Figure 5, we know that to adjust the jet lag as soon as possible, traveling east needs to accelerate the speed of phase advance while traveling west needs to accelerate the speed of phase delay. Therefore, increasing lighting during CT6 and CT13 for people traveling westward and increasing lighting at other times for those traveling eastward helps to adjust the jet lag faster. Furthermore, the intrinsic period of the circadian clock in the free condition is 21.5 h. Adding a light pulse near the trough of the oscillator CT0 results in maximum phase advance, while adding a light pulse near the peak of the oscillator around CT11 brings maximum phase delay.

In addition to period, amplitude also plays a very important role, which can respond to external

stimuli. As mentioned above the level of DA affects the behavior and emotions of organisms. To make clear the DA amplitude changes induced by environmental signals added at different CTs, we draw the amplitude response curve (ARC), shown in Figure 6(e). The amplitude shift is the difference between the amplitude of the first cycle after adding a light pulse and that of the controlled oscillator. It can be seen that adding light pulses at different times results in varying degrees of amplitude variation. Especially, adding a light pulse near CT17 causes the greatest amplitude change. So, the effect of phototherapy varies at different times. For patients who need to increase DA levels, such as those with reduced DA amplitude caused by *Per* gene mutation, phototherapy can be selected near CT17. However, for people with relatively high DA levels, the light near CT17 should be reduced.

In a word, the phase shifts caused by light pulses added at different times are different. The appropriate phototherapy time should be chosen based on different symptoms. In addition, a longer light pulse brings greater phase shift, which is not shown here. Therefore, appropriate light pulses should be selected for different circadian rhythm DA disorders to bring the DA rhythm back to normal levels. It is also important to choose the right time to perform phototherapy for different diseases, otherwise, it may be counterproductive.

4. Conclusions and discussion

DA is an important transmitter involved with many brain functions and associated with some neurological conditions, modulated by the circadian clock. The underlying mechanisms are not much known. In this study, using an existing mathematical model, we explore the effects of the circadian clock on the level of DA. First, we investigated the impacts of the disruption of the circadian clock i.e., mutations in the clock genes on DA. Then, the sensitivity of the DA level to system parameters is studied. Last, we analyze the effects of sudden changes in daily light, which indirectly regulates the DA system through the circadian clock, on the phase and level of DA. We get some meaningful results that concur with biological experiments.

Disorders in the circadian clock caused by gene mutations all cause abnormalities in DA levels and rhythms, indicating the regulatory role of the circadian clock in the AD system. Different gene mutations bring different effects, which also provides us with a way to adjust DA levels through the circadian clock.

Through sensitivity analysis of DA levels to parameter perturbation, we found that TH plays a crucial role in the DA system. DA level is most sensitive to reaction parameters directly or indirectly related to TH, which means adjusting DA levels by changing the rate of chemical reactions related to TH is an effective method.

The illumination information of the external environment is transmitted to the DA system through the circadian clock. Sudden changes in external light influence the circadian clock, leading to changes in the DA system. Jet lag caused by traveling across time zones in different directions has distinct effects on the DA level and phase shift. Different measures need to be taken to alleviate the impact of jet lag on DA according to the situation. By drawing the PRC and ARC, we find that adding light pulses at different times also has distinct effects on DA level and phase. This provides a theoretical basis for adjusting DA levels through light exposure.

As a key factor in coordinating our behavior and physiological activities, the circadian clock plays an important role in regulating daily biological processes. In particular, it regulates the DA system,

which is closely related to daily emotions and mental illness. Light, diet and temperature are all important external factors that affect the circadian clock. In the future, we can use this model to study the impact of external factors on DA, which can be used for the treatment or relief of diseases caused by DA disorders. In this paper, we only explore the regulation of the circadian clock on the DA system. As we know, abnormal DA can also cause disturbances in the circadian clock. The regulatory mechanism of DA on the circadian clock is far from clear. So, a complete model including the regulation of DA on the circadian clock needs to be developed, which may provide new insights into the link between the circadian clock and the DA system.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflict of interest.

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