Critical phase shifts slow down circadian clock recovery: Implications for jet lag

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HIGHLIGHTS

- We study circadian clock recovery after a phase shift of the light–dark cycle.
- Re-entrainment of the clock is either orthodromic or antidromic.
- A computational model reveals a threshold between the two types of re-entrainment.
- Phase shifts near the threshold markedly slow down circadian clock recovery.
- The threshold could be responsible for severe disturbances associated with jet lag.

ABSTRACT

Advancing or delaying the light–dark (LD) cycle perturbs the circadian clock, which eventually recovers its original phase with respect to the new LD cycle. Readjustment of the clock occurs by shifting its phase in the same (orthodromic re-entrainment) or opposite direction (antidromic re-entrainment) as the shift in the LD cycle. To investigate circadian clock recovery after phase shifts of the LD cycle we use a detailed computational model previously proposed for the cellular regulatory network underlying the mammalian circadian clock. The model predicts the existence of a sharp threshold separating orthodromic from antidromic re-entrainment. In the vicinity of this threshold, resynchronization of the clock after a phase shift markedly slows down. The type of re-entrainment, the position of the threshold and the time required for resynchronization depend on multiple factors such as the autonomous period of the clock, the direction and magnitude of the phase shift, the clock biochemical kinetic parameters, and light intensity. Partitioning the phase shift into a series of smaller phases shifts decreases the impact on the recovery of the circadian clock. We use the phase response curve to predict the location of the threshold separating orthodromic and antidromic re-entrainment after advanced or delayed phase shifts of the LD cycle. The marked increase in recovery times predicted near the threshold could be responsible for the most severe disturbances of the human circadian clock associated with jet lag.

1. Introduction

The circadian clock, characterized by an intrinsic period close to 24 h, is generally entrained by light–dark (LD) cycles, which correspond to the alternation of day and night. Circadian rhythms thus allow adaptation of most organisms to their periodically varying environment. In humans, flying across time zones disrupts circadian rhythms, which become re-entrained in a new LD system of reference after sufficient time. Advanced rhythms (corresponding to eastward flights) need generally more time to be re-entrained when compared with delayed rhythms (which correspond to westward flights). Re-entrainment rates are around 90 min per day for delayed phase shifts and 60 min per day for advanced phase shifts (Boulos et al., 1995; Aschoff et al., 1975). For small phase shifts of the LD cycle, the circadian clock resynchronizes in the same direction as the shift, while for larger shifts, the circadian clock sometimes resynchronizes in the opposite direction: the first type of resynchronization is called "orthodromic", and the second "antidromic" (Aschoff et al., 1975; Klein and Wegmann, 1980). Although orthodromic readjustment remains the most frequent, opposite cases are not rare (Burgess et al., 2003). Antidromic readjustment occurs mostly for long advanced phase shifts; thus it was observed for 1 out of 7, 4 out of 8, and 7 out of 8 people after an eastward flight of 8 h (Arendt et al., 1987), 9 h (Klein et al., 1977) and 11 h (Takahashi et al., 2001), respectively.

In view of the physiological disturbances, commonly referred to as "jet lag" (Waterhouse et al., 2007), that follow changes in the phase of the LD cycle, it is important to determine in a detailed

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manner the response of the circadian clock to such perturbations. This issue can be conveniently addressed by means of computational models for the mammalian circadian clock. Although Goodwin-type models (Leise and Siegelmann, 2006; Locke et al., 2008) and abstract models of the van der Pol type (Kostreva et al., 2002; Gundel and Spencer, 1999; Nakao et al., 2004; Dean et al., 2009) have been used to study the impact of jet lag on the circadian clock, the transition between orthodromic and antidromic re-entrainment after phase shifts of the LD cycle has not received much attention. Molecular models for the mammalian circadian clock (Leloup and Goldbeter, 2003, 2004; Forger and Peskin, 2003; Becker-Weimann et al., 2004; Mirsky et al., 2009) are available, but none of these has been used so far to address this issue. Here we resort to a detailed molecular model for the mammalian circadian clock (Leloup and Goldbeter, 2003) to investigate the conditions that result in either orthodromic or antidromic re-entrainment after a shift in the LD cycle. We examine the influence of several factors such as the autonomous period of the circadian clock in constant conditions, the magnitude of the phase shift achieved through changing the duration of a single light or dark phase of the LD cycle, and the effect of light intensity.

Numerical simulations of the circadian clock model show that when it exists the switch between orthodromic and antidromic resynchronization takes place beyond a threshold near which the circadian clock takes extremely long times to synchronize with the new LD cycle. Thus, such critical phase shifts can markedly slow down circadian recovery. The prolongation of the resynchronization process near the threshold could well underlie some of the most pronounced physiological manifestations of jet lag. We show that the time needed for the system to resynchronize after a phase shift in the LD cycle can be minimized when the phase-shift in the LD cycle is partitioned in several, successive shorter phase shifts, a strategy that has been proposed to alleviate the consequences of jet lag (Eastman et al., 1995). Finally we use the phase response curve (PRC) of the circadian clock to explain and characterize the threshold separating the orthodromic and antidromic modes of resynchronization after a phase shift of the environmental cycle.

2. Computational model for the mammalian circadian clock

To study the dynamics of circadian clock re-entrainment after a phase shift in the LD cycle we use a computational model previously proposed for the mammalian circadian clock (see Leloup and Goldbeter, 2003, 2004 for a detailed description). This model is based on the main positive and negative feedback loops involved in the regulatory mechanism of circadian rhythms in mammals (see Fig. 1 in Leloup and Goldbeter, 2003). The product of the *Clock* and *Bmal1* genes, the CLOCK and BMAL1 proteins, form a CLOCK–BMAL1 complex that activates the transcription of the *Per* and *Cry* genes and inhibits the transcription of the *Bmal1* gene. The PER and CRY proteins, products of the *Per* and *Cry* genes, form a PER–CRY complex that inhibits the activity of the CLOCK–BMAL1 complex, thus creating an indirect, negative feedback loop on transcription. The different proteins are phosphorylated and then targeted for proteasomal degradation. Light induces the transcription of the *Per* genes. For simplicity a single copy of the *Per* and *Cry* genes is considered. To describe the effect of light, we consider that parameter ν_{sP}, which measures the rate of expression of the *Per* gene, varies as a square wave from a constant low value in the dark phase to a constant high value in the light phase. The latter value increases by the quantity δ with light intensity.

For this study we consider the basal version of the model for the mammalian circadian clock, which contains 16 variables. We compared the results obtained with a 19-variable model

incorporating the regulation by REV-ERBα. The main conclusions obtained here hold for the two models both qualitatively and quantitatively; therefore, for the sake of clarity, we present only the results obtained for the 16-variable model. All figures are obtained by numerical integration of Eqs. (1)–(16) in Supporting Information in Leloup and Goldbeter (2003) for the parameter values listed there in Supporting Table 1 (see also Leloup and Goldbeter, 2004).

To investigate the effect of phase shifts in the LD cycle on the re-entrainment of the circadian clock, we define the phase of a variable in the model by the time at which this variable reaches its maximum value. Similar results could be obtained by choosing its minimum or half-maximum value (onset and offset). For all our numerical simulations, we focus on the phase of a single variable of the model, i.e. the maximum in *Per* mRNA (M_P). We consider that the system is fully resynchronized when it returns to ± 0.25 h of the final phase. Although this value was chosen arbitrarily, it falls within a reasonable range when compared to the precision of experimental data (Aschoff et al., 1975). Changing this cutoff value will also have an impact on the time for resynchronization: the system will need more time to be re-entrained for lower values and less time for higher values.

In laboratory conditions or *in silico*, phase shifts of the LD cycle can be induced through changing the duration of either the dark or the light phase. Either one of these phases can be shortened or lengthened to achieve advances or delays, respectively. We applied phase shifts in the model by changing only the duration of the light phase. Numerical simulations generally yield similar patterns of resynchronization after changing the duration of either the dark or the light phase, even when the duration of the phase shift is important (around 8 or 10 h). Some differences can nevertheless be observed for very large phase shifts, of the order of 10 h or more.

3. Patterns of re-entrainment of the circadian clock after phase shift

3.1. Influence of the autonomous period of the circadian clock

Circadian oscillations occur spontaneously in constant conditions, e.g., continuous darkness (DD), with an autonomous period τ. In human populations the value of τ ranges from 23.5 h to 24.6 h in men, and from 23.6 h to 24.5 h in women with a mean value close to 24.2 h and 24.1 h, respectively (Duffy et al., 2011). Such differences in τ could be responsible for the variability of 5–6 h observed in humans for the phase of the circadian clock with respect to the LD cycle (Kasukawa et al., 2012). To investigate the influence of τ on the resynchronization of the circadian system after a phase shift in the LD cycle, we first examine in Fig. 1 the effect of a delayed or advanced phase shift of 8 h in three cases that correspond either to an autonomous period of 24.2 h, close to the period observed in humans (Duffy et al., 2011), or to autonomous periods that are significantly shorter or longer than 24 h ($\tau = 22.7$ or 25.8 h). These large differences in τ allow us to highlight the effect of the autonomous period on the dynamics of re-entrainment of the clock.

When τ is close to 24 h (middle panels), an advanced or delayed phase shift of 8 h leads to orthodromic re-entrainment (Fig. 1c and d). When the autonomous period is significantly shorter than 24 h (left panels), an advanced phase shift of 8 h leads to orthodromic re-entrainment (Fig. 1a), while a delayed phase shift results in antidromic synchronization (Fig. 1b). Finally, when τ is significantly larger than 24 h (right panels), an advanced phase shift of 8 h leads to antidromic re-entrainment (Fig. 1e), while a delayed phase shift results in orthodromic resynchronization (Fig. 1f). A