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Coupling mechanism in the gate and oscillator model of the SCN

Ying Li [a,b,*], Zengrong Liu [c]

[a] College of Information Technology, Shanghai Ocean University, Shanghai, 201306, China
[b] Department of Neurology, University of Massachusetts Medical School, Worcester, MA, 01655, United States
[c] School of Science, Hangzhou Dianzi University, Hangzhou 310018, China

HIGHLIGHTS

- According to the heterogeneity of the SCN, a gate and oscillator model is proposed based on the Goodwin oscillator.
- Interior coupling among the oscillator cells and exterior coupling from the gate cells to the oscillator cells are considered.
- The combined effects of two kinds of coupling on the entrainment of the oscillator cells in the DM part are analyzed.
- The interior coupling is conducive to entrainment, but a stronger coupling is not beneficial to entrainment.
- The gate mechanism in exterior coupling is more propitious to entrainment than continuous coupling.

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ABSTRACT

In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus is considered as the master circadian pacemaker. The SCN is divided into two subgroups of gate and oscillator cells: the ventrolateral (VL) neurons, which receive the periodic light-dark (LD) signal, and the dorsomedial (DM) neurons, which are coupled to the VL cells. The fundamental question is how the individual cellular oscillators, expressing a wide range of periods, interact and assemble to create an integrated pacemaker that can govern behavioral and physiological rhythmicity and be reset by environmental light. The key is that the heterogeneous network formed by the cellular clocks within the SCN must synchronize to maintain timekeeping activity. Based on the structural and functional heterogeneity of the SCN, the authors bring forward a mathematical model including gate cells and oscillator cells with a wide range of periods. The gate neurons offer daily injection to oscillator neurons and the activation of gate is determined by the output of the oscillator neurons. In this model, the authors consider two kinds of coupling: interior coupling among the oscillator cells and exterior coupling from the gate cells to the oscillator cells. The authors mainly analyze the combined effects of these two kinds of coupling on the entrainment of the oscillator cells in the DM part. It is found that the interior coupling is conducive to entrainment, but a stronger coupling is not beneficial to entrainment. The gate mechanism in exterior coupling is more propitious to entrainment than continuous coupling. This study helps to understand collective circadian rhythm in the mammals.

* Corresponding author at: College of Information Technology, Shanghai Ocean University, Shanghai, 201306, China.
E-mail address: leeliying@163.com (Y. Li).

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1. Introduction

Mammals have endogenous circadian clocks that coordinate physiological and behavioral rhythms and synchronize the organisms to daily environmental cycles. The circadian oscillations are controlled by the suprachiasmatic nuclei (SCN) [1,2]. The rhythmicity of the SCN is a product of multiple individual cellular circadian oscillators that are coupled together in a tissue network. It is now known that the circadian oscillations in individual cells, with periods ranging from 20 to 28 h [3,4], are based on interlocked transcription–translation feedback loops [5,6]. Because free-running periods of isolated neurons are broadly distributed, a coupling mechanism is operating among the neurons to produce a coherent circadian oscillation at the tissue level. The coupling between cells in the SCN is achieved partly by neurotransmitters which are released by each cell [7,8]. The multiple synchronized single-cell circadian oscillators produce coordinated circadian outputs, which ultimately regulate overt rhythms.

The SCN cells and regions have functional and structural heterogeneity [9]. It is well known that the SCN is anatomically organized into a dorsomedial (DM) region and a ventrolateral (VL) region [10]. The VL is composed by cells containing vasoactive intestinal polypeptide (VIP), substance P, and gastrin-releasing peptide, while the DM is composed by cells containing vasopressin (VP) [11]. In addition, there are also a dense population of cells that contain calbindin D28K (CalB) in VL [12]. Expression of rhythmic and light-induced *Per* mRNA is regionally specific [13]. Endogenous rhythmicity in *Per* mRNAs expression is primarily restricted to the VP region of the SCN, whereas light-induced *Per* mRNAs expression occurred primarily in the CalB region, where rhythmic *Per* mRNAs expression was not detectable. Additionally, CalB-containing cells in this subregion, which receives direct photic input, do not express a circadian rhythm in their firing rate [14].

Destruction of the CalB region, but that spare other parts of the SCN (marked by VP cells), leads to elimination of overt behavioral and physiological rhythms. Moreover, the shell SCN becomes arrhythmic because of lacking synchrony [15,16]. Hence, the CalB region cells serve as a gate which relays photic resetting information to oscillator cells in VP region, thereby providing the daily signal that synchronizes the oscillators in the rhythmic region of the SCN. The gate has 2 states, either open or closed. Activation of the gate is possible only while it is in an open state.

Based on the heterogeneity of SCN, many mathematical models have been proposed, with which the production mechanism of circadian rhythm together with the synchronization and entrainment of circadian oscillators have been researched widely [17–20]. The coupling between two parts of the SCN has also been studied [21–25]. Especially, Gu et al. also found that there is a critical value for the coupling strength with which the entrainment ability is maximal [21]. However, most of the model did not consider the gate effect. That is to say the CalB region incessantly relays light information to the VP region. However, biological experiments have found there actually exists gated light induced gene expression in VP region and a light pulse during different time region induces different effects on the VP cells gene expression [13]. Therefore, it is necessary to consider the gate effect in mathematical model. A few years ago, Antle et al. brought forward the gate and oscillator model [26,27], which has successfully accounted for many biological phenomena and could explain the complex behavior of SCN in many aspects [28], some of which are difficult to be explained by uniform coupling only [29].

In the gate and oscillator model of Antle et al., they used van der Pol oscillator to describe the single oscillator neuron [26,27]. The gate has 2 states, either open or closed, and they proposed that the output of the ensemble of oscillators determines these states. When the gate is activated, the phase of individual oscillator cells are adjusted to a common phase by a resetting function. Inspired by their work, we wonder what will happen if we consider the gate effect from molecular level. That is to say, use the molecular model to describe the gate and oscillator model. Goodwin oscillator is the simplest molecular model including a basic negative feedback loop to describe the circadian oscillator [30], which has been used widely [18–20,31]. In this paper, we propose a gate and oscillator model based on the Goodwin oscillator to explore the mechanism of entrainment. In the previous work, Antle et al. did not require nor exclude interior coupling among oscillators [26,27]. Since coupling plays crucial role in the emergence of coherent rhythm and entrainment [18–20], we wonder what will happen if we consider the interior coupling among oscillators in the DM. Our goal is to explore the combined effects of interior coupling and the exterior coupling from the gate cells to the oscillator cells on the entrainment of the oscillator cells in the DM part.

2. Model of the SCN

Based on the functional and structural heterogeneity of the SCN cells and regions mentioned above, we propose a model to describe the dynamics of the neurons in two compartments. One compartment has intrinsically rhythmic oscillator cells that are not directly retinorecipient. The other compartment consists of gate cells that are sensitive to photic zeitgebers. The state of gate is also sensitive to the state of the circadian oscillators. Thus, it regulates the clocks own sensitivity to external signals.

2.1. Single gate cells

The models of single gate and oscillator cells are both based on the Goodwin oscillator [31] which is still widely used to describe fundamental properties of the core circadian oscillator [32], or the synchronization or entrainment of an ensemble of coupled circadian oscillators [31,33]. The Goodwin model describes circadian oscillations in single mammalian cells by means of three variables. A clock gene mRNA (X) produces a clock protein (Y) which activates a transcriptional inhibitor (Z)