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A multicellular model for differential regulation of circadian signals in the core and shell regions of the suprachiasmatic nucleus

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ABSTRACT

We developed a multicellular model of the mammalian circadian clock characterized by a high degree of heterogeneity with respect to single cell periodicity and behavior (intrinsic and driven oscillators), neurotransmitter release (VIP, GABA and glutamate synthesis) and spatial organization (core and shell regions), mimicking structural patterns within the suprachiasmatic nucleus (SCN) associated with distinct circadian functions. We simulated the SCN core and shell separately utilizing experimentally derived connectivity schemes for the two subdivisions as observed within the rat SCN. The core was modeled via a small world network characterized by VIP and GABA co-localization, whereas the shell was simulated as a nearest neighbor network promoting local GABAergic connections. To study the function of the axonal plexus extending from the densely innervated ventrolateral region to distal areas across the dorsomedial SCN, directed long range links from the core to the shell were gradually introduced via a probability p_{cs} that ranged from 0 to 1. A probability value of 0 excluded core–shell interactions, whereas $p_{cs}=1$ achieved maximal connectivity between the two regions. Our model exhibited a threshold in the number of core-to-shell links required for sufficient cell-to-cell coordination to maintain periodicity and rhythmic behavior across the entire model network (including both shell and core populations) in constant darkness as well as 12:12 h light–dark cycles. By contrast, constant light was shown to increase phase synchronization across the shell while core populations remained poorly synchronized, suggesting differential light response across the two SCN compartments. We further simulated increasing percentages of intrinsic oscillators and demonstrated a negative correlation between the number of intrinsic oscillators distributed across the SCN and the ability of the system to produce synchronized signals. Simulations that differed with respect to the placement of intrinsic oscillators supported the hypothesis that improved synchronization is achieved with networks characterized by localized intrinsic oscillators placed exclusively within the shell versus networks containing uniformly distributed intrinsic oscillators in both SCN compartments. This study has successfully reproduced a number of spatiotemporal and behavioral attributes of the SCN, providing a useful computational tool to correlate observed circadian phenotypes with distinct chemoarchitectural properties of spatially localized neural populations.

1. Introduction

The suprachiasmatic nucleus (SCN) of the hypothalamus is the predominant circadian pacemaker in mammalian organisms. Circadian regulation of behavioral and physiological rhythms is principally dependent on the properties and the organization of cell populations within the SCN. Morphological studies in a variety of mammals (Abrahamson and Moore, 2001; Card and Moore, 1984; Moore, 1983) have demonstrated that the SCN is organized into two structurally and functionally distinct subdivisions. The two regions, differentiated based on their neuropeptide content and network architecture, have been designated as the "core" and the "shell" (Abrahamson and Moore, 2001; Robert, 1996). The core refers to the ventral region of the nucleus comprised of approximately 40% of all SCN neurons, which primarily produce vasoactive intestinal peptide (VIP) or gastrin-releasing peptide (GRP) co-localized with GABA (Moore et al., 2002). The core receives direct photic input, as retinohypothalamic tract (RHT) projections have been shown to terminate almost exclusively within the ventral region of the SCN overlapping the distribution of VIP and GRP synthesizing neurons (Abrahamson and Moore, 2001; Ibata et al., 1989; Moore et al., 2002; Morin, 2007).

The shell surrounds the core and contains approximately 60% of the SCN cell population. Shell neurons produce primarily arginine vasopressin (AVP) (Ibata et al., 1993; Kalamatianos et al., 2004)

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co-localized with GABA (Moore et al., 2002). Characterized by the lack of direct retinal innervations (Antle and Silver, 2005; Moore et al., 2002), the shell contains restricted dendritic arbors confined mostly between proximal neurons (Pennartz et al., 1998; Strecker et al., 1997; Vandenpol, 1980). By contrast, the axonal plexus originating from VIP and GRP synthesizing cells of the core extends densely over the entire SCN establishing synaptic connections between core neurons expressing VIP (Daikoku et al., 1992) as well as with shell neurons expressing AVP (Ibata et al., 1993; Kalamatianos et al., 2004). Functional axonal projections originating from the densely innervated core to distal areas across the shell are therefore postulated to have an active role in the synchronization of the circadian signal across the SCN and entrainment to various light schedules (Abrahamson and Moore, 2001; Jobst et al., 2004).

Contributing to heterogeneity of the circadian network, SCN neurons were further demonstrated to differ in their intrinsic rhythmic behavior in the absence of cell-to-cell communication. Treatments that desynchronize rhythms among SCN neurons have revealed that approximately 30% of the population behaves as intrinsic oscillators (Aton and Herzog, 2005). Data concerning the spatial organization of intrinsic oscillators across the SCN network remain controversial. A number of experimental studies have revealed the differential regulation of clock genes in the two distinct SCN compartments, suggesting the confinement of intrinsically rhythmic cells within the shell and arrhythmic cells within the core (Hamada et al., 2001, 2004; Maywood et al., 2006). By contrast, a more recent study argued against the concept of an anatomically localized class of cell-autonomous pacemakers, instead concluding that SCN neurons are intrinsic but unstable circadian oscillators which rely on network interactions to stabilize their rhythms (Webb et al., 2009).

One of the most important attributes of the SCN is its ability to perceive photic input and adapt its periodicity to various light and dark schedules. Entrainment of the SCN is primarily achieved via glutamate and pituitary adenylate cyclase activating peptide (PACAP) neurotransmitters released within nerve terminals located predominantly in the ventrolateral, retinorecipient core region (Hannibal et al., 2000). Glutamate release initially activates AMPA receptors on retinorecipient cells, depolarizing them and further potentiating the effects of NMDA receptors (Colwell, 2001; Mintz and Albers, 1997). Stimulation of these iontropic glutamate receptors is associated with increased calcium influx (Ghosh and Greenberg, 1995; Gillette and Mitchell, 2002), which has been shown to activate a number of protein kinases which ultimately induce core-clock gene transcription (Paul et al., 2005; Schurov et al., 1999) via activation of the cAMP response element binding protein (CREB) (Ginty et al., 1991). PACAP exerts its function within the SCN via two G-protein coupled receptors, PAC1 (Cagampang et al., 1998a; Hannibal et al., 1997) and VPAC2 (Cagampang et al., 1998b). Upon bindings its receptors, PACAP has been shown to instigate a signaling cascade involving a cAMP/protein kinase dependent pathway (Hannibal et al., 1997), which in turn stimulates the phosphorylation of CREB ultimately inducing core-clock gene expression (von Gall et al., 1998).

Previously developed mathematical models (Bernard et al., 2007; Li et al., 2009) have also focused on structural and functional heterogeneities observed within the SCN. In these studies non-identical oscillators expressing a range of intrinsic periods were distributed across the model SCN network. Distinct coupling schemes were utilized to capture the network topology of each SCN compartment. Although the precise network architectures adopted differed, in both studies the ventrolateral region (core) was assumed to contain light-inducible neurons which projected their signal to the non-retinorecipient dorsomedial region (shell). Although computationally efficient, these models utilized phenomenological coupling mechanisms and omitted a number of signaling pathways important for circadian regulation. The purpose of the present study was to capture the molecular events responsible for circadian rhythm generation to investigate the interplay between SCN spatiotemporal organization and behavioral attributes on a mechanistic level.

For the purpose of this study a previously developed model comprised of molecular descriptions of gene expression, neural firing and intracellular signaling pathways was utilized (Vasalou and Henson, 2010). To mimic known SCN network topology, we utilized distinct connectivity schemes for each SCN subdivision. Although the compartmentalization of core and shell regions is specific to the organization of the rat SCN, the analysis of neural groups distinct with respect to their neurochemical content and topological features can generally advance understanding of how individual groups affect circadian behavior and rhythm generation. The densely innervated core was simulated via a small world network that promoted both VIP and GABA signaling (Vasalou et al., 2009), whereas the shell was simulated as a locally connected network promoting GABAergic coupling between nearest neighbors. Our main objective was to evaluate the functional importance of long range connections extending from the retinorecipient core to the sparsely connected shell and to investigate the effects of network organization on cell-to-cell coordination, system periodicity and rhythmic behavior as various light schedules were imposed. We simulated different percentages of intrinsic oscillators to establish a relationship between the size of the number of intrinsic oscillators distributed across the SCN and the ability of the system to produce phase synchronized signals. We further compared networks of intrinsic oscillators evenly distributed across the SCN shell and core regions with networks where intrinsic oscillators were confined exclusively within the shell to investigate the relationship between specific cell types and their spatial localization on circadian rhythmicity and behavioral phenotypes.

2. Materials and methods

2.1. Intracellular oscillator model

The gene expression model utilized in our simulations originated from a previously published core oscillator model (Leloup and Goldbeter, 2003) modified to include intercellular communication between multiple cells. Each model neuron was defined by 16 ordinary differential equations that described negative and positive transcriptional feedback loops involving key genes of the circadian clock. The model included *Per* and *Cry* gene transcription activated by a dimer formed from the CLOCK and BMAL1 proteins and subsequently suppressed by a PER–CRY protein complex. Circadian rhythmicity resulted from the accumulation and degradation of these two protein complexes over the course of the day. Our model did not include a positive feedback loop involving *Rev-Erb*$_\alpha$ as it is not required for rhythm generation.

2.2. Electrophysiology model

The firing rate-code model obtained from our previous study (Vasalou and Henson, 2010) described electrical events on the SCN neuron membrane responsible for the generation of action potentials. Our model took into account contributions of relevant ion channels as well as extracellular synaptic stimuli involving VIP, GABA and glutamate that influenced membrane excitability and neural firing. The glutamate pathway was modified from our original model (Vasalou and Henson, 2010) to include direct activation of NMDA/AMPA receptors (Colwell, 2001; Mintz and Albers, 1997) as well as increased Ca^{2+} influx (Ghosh and