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# Inhibitory and excitatory networks balance cell coupling in the suprachiasmatic nucleus: A modeling approach

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## HIGHLIGHTS

- Predicted how changes in VIP and GABA release rates influence circadian networks.
- A balance between inhibitory and excitatory networks was required for synchronization.
- Over-excitation increased the time required for adjustment to changing light schedules.
- Increased GABA network activity could assist with light shifts for high VIP levels.

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## ABSTRACT

Neuronal coupling contributes to circadian rhythms formation in the suprachiasmatic nucleus (SCN). While the neurotransmitter vasoactive intestinal polypeptide (VIP) is considered essential for synchronizing the oscillations of individual neurons, γ-aminobutyric acid (GABA) does not have a clear functional role despite being highly concentrated in the SCN. While most studies have examined the role of either GABA or VIP, our mathematical modeling approach explored their interplay on networks of SCN neurons. Tuning the parameters that control the release of GABA and VIP enabled us to optimize network synchrony, which was achieved at a peak firing rate during the subjective day of about 7 Hz. Furthermore, VIP and GABA modulation could adjust network rhythm amplitude and period without sacrificing synchrony. We also performed simulations of SCN networks to phase shifts during 12 h:12 h light-dark cycles and showed that GABA networks reduced the average time for the SCN model to re-synchronize. We hypothesized that VIP and GABA balance cell coupling in the SCN to promote synchronization of heterogeneous oscillators while allowing flexibility for adjustment to environmental changes.





## 1. Introduction

The way organisms anticipate the timing of daytime and nighttime, referred to as circadian rhythms, is essential for good health and optimal timing of metabolic processes and behavior (Kondratova and Kondratov, 2012; McClung, 2007; Xu et al., 2005). Circadian rhythms may be disrupted in otherwise healthy individuals by a variety of perturbations such as jet lag, social jet lag, rotating shift work and seasonal changes (Sack et al., 2007). Psychiatric disorders such as schizophrenia (Boivin, 2000; Wulff et al., 2012) and neurodegenerative disorders such as Alzheimer's disease (Satlin et al., 1995; Wu and Swaab, 2007) are also characterized by loss of circadian rhythms. Those afflicted with circadian disruption suffer from sleep loss and erratic wake times (Buysse et al., 2005). Reduced cognitive performance has also been exhibited by employees whose jobs require shift rotation or flight crew members with over eight hours of jet lag per week (Cho et al., 2000; Rouch et al., 2005; Viitasalo et al., 2014). Maladies such as obesity, diabetes, and heart attacks have also been correlated to human social jet lag (Roenneberg et al., 2012) and knockout mice lacking circadian rhythmicity (Shi et al., 2013; Turek et al., 2005). Therefore, circadian disruption represents a serious public health concern.

In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus generates these rhythms and responds to cues such as light and feeding (Klein et al., 1991). Mice with their SCN surgically ablated have their circadian rhythms abolished, while the SCN confers host rhythmic behavior to transplant recipients (Sujino et al., 2003). Remarkably, a coherent signal is produced by the SCN despite it being composed of 20,000 heterogeneous neural

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oscillators (Herzog et al., 2004; Webb et al., 2009; Welsh et al., 1995). In order for these cells to develop a consensus circadian rhythm, they form networks to exchange information about their individual and collective oscillatory patterns (Reppert and Weaver, 2002). Robust rhythms are necessary for ensuring that regular sleep and other behavioral schedules are followed even when external cues are absent; however networks must also be flexible so that organisms may adjust their schedule to seasonal changes or time shifts (Herzog, 2007; Meijer et al., 2010; Pfeuty et al., 2012).

The neurotransmitter vasoactive intestinal peptide (VIP) has been shown to be essential for synchronizing SCN neurons (Aton et al., 2005). VIP secretion follows a circadian pattern with peaks during the subjective day (Shinohara et al., 1995). Mice lacking genes for VIP or its receptor, $VPAC_2$, have highly disrupted circadian rhythms (Bechtold et al., 2008; Maywood et al., 2006), while doses of VIP have entrained or phase shifted SCN tissue oscillations in vitro (Reed et al., 2001; Watanabe et al., 2000). Furthermore, when the dorsolateral SCN shell, which lacks VIP secreting cells, is separated from the ventromedial SCN core, which contains many VIP secreting cells, the core remains synchronized while rhythms are not observed in the shell (Belenky et al., 2008; Yamaguchi et al., 2003). $VPAC_2$ activation, in conjunction with cytosolic calcium oscillations, stimulate Per1 and Per2 gene expression through the cAMP response element-binding protein (CREB) signaling cascade (Nielsen et al., 2002; Tischkau et al., 2003). Therefore, VIP is likely paramount among neurotransmitters for connecting SCN cells into a functional network.

Meanwhile, GABA is the principal inhibitory neurotransmitter in the brain and is also pervasive throughout the SCN where its functionality is controversial (Castel and Morris, 2000; Moore and Speh, 1993). GABA has been reported to synchronize (Liu and Reppert, 2000) or desynchronize (Freeman et al., 2013) SCN neurons. A potential link between VIP and GABA is also strongly suggested by the increase in GABA secretion from SCN neurons administered exogenous VIP (Itri and Colwell, 2003). One study has shown that while GABA opposes VIP-mediated synchrony during steady-state conditions, it facilitates resynchronization from antiphase conditions induced by long days (Evans et al., 2013). Although GABA, unlike VIP, has no known mechanism for directly influencing the molecular core clock of SCN neurons (Aton et al., 2006), it does open GABAA chloride ion channels (Itri et al., 2004) and its concentration oscillates throughout the day in phase with VIP. Whether GABA networks are excitatory or inhibitory has been shown experimentally (Wagner et al., 1997) and in models (Vasalou et al., 2011) to depend on the intracellular chloride concentration, but in the SCN core GABA networks seem to only be inhibitory (Albus et al., 2005). The aim of our modeling study was therefore to explore new ways of how GABA-induced inhibitory post-synaptic currents (IPSCs) could modulate network properties in conjunction with VIP signaling.

To discover new relationships between VIP and GABA networks in the SCN, we performed computational analyses with a modified version of a heterogeneous multicellular model previously developed by our group (Vasalou et al., 2011). Heterogeneous cell populations were of particular interest because of the wide phenotypic behavior that exists, even within classically defined regions such as the core or the shell. Our network population consisted of neurons that in the absence of neurotransmitter signaling exhibited either sustained, damped, or no oscillations (Vasalou and Henson, 2010). Neurons with different intrinsic properties have different requirements for entrainment (Abraham et al., 2010), and so a network of heterogeneous oscillators would ideally include local differences in neurotransmitter concentrations that are responsive to receptor cell feedback (Fig. 1). This responsiveness is similar to what was observed by Itri and Colwell

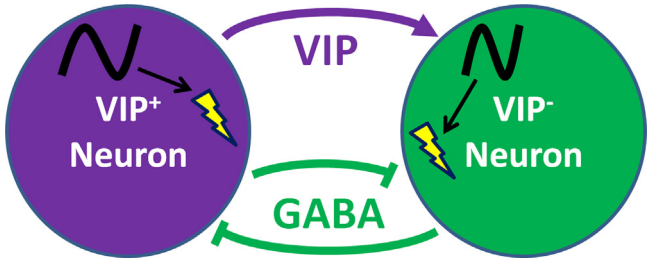


**Fig. 1.** Diagram of model neurotransmitter signaling. The connections between two cells in the multicellular model of the SCN core are depicted, one of which secretes VIP and one of which does not secrete VIP. The model was based on the assumption that 20% of cells are VIP producers while all cells secrete GABA. VIP is a key driver of molecular core clock oscillations (waves), making this neurotransmitter essential for synchronization. The neurons are heterogeneous, so the intrinsic period and amplitude of their molecular core clocks will vary. The molecular clock oscillations drive firing rates (lightning bolts) which in turn drive neurotransmitter release. Firing rates are inhibited by GABA reception for all SCN core neurons. Therefore, the GABA network can be conceptualized as a negative feedback mechanism. The overlapping VIP and GABA feedback mechanisms across networked heterogeneous cells influence each other's concentrations and local cellular dynamics and as such form the basis of the hypothesis of coordination tested in these studies.

when they found that GABA was released by neurons in the presence of high levels of exogenous VIP (Itri and Colwell, 2003). When entraining to periods different from their intrinsic periods, we expected weak oscillators to require excitatory positive feedback networks for generating robust rhythms. Meanwhile we expected inhibitory negative feedback networks to weaken strong oscillators, having the effect of increasing their range of entrainment (Abraham et al., 2010). So while VIP is ultimately necessary for rhythmic coupling, we hypothesized that too strong of an excitatory signal could push a cell into circadian disruption whereas a subtler influence would more effectively shift the neuron to the consensus periodicity. Therefore, we expected that a system where the strongest oscillators also released the highest levels of inhibitory GABA (thus slowing VIP and GABA release from cells in its local network) would achieve this neuroexcitatory balance locally and confer improved synchronization globally.

Our model was particularly useful for testing these hypotheses because it included not only the effect of VIP on the core molecular clock (Leloup and Goldbeter, 2003) but also an electrophysiological component that captured the effect of GABA on the resting membrane potential and firing rate (Vasalou and Henson, 2010). Since the two neurotransmitters influenced different components of the model, their combined action would be indirectly rather than directly antagonistic for a coupled network of heterogeneous SCN neurons. Our modeling studies were therefore designed to determine if GABA signaling could counterbalance high concentrations of secreted VIP to improve network performance. We used two scenarios to test this hypothesis, one where the network synchronized in the dark and another where the network resynchronized to an imposed light shift.

## 2. Results

### 2.1. GABA and VIP coordinate to change network properties

By modulating the maximum rates of release of VIP and GABA ($\nu_{VIP}$ and $\nu_{GABA}$, respectively), the model predicted that VIP and GABA had differential roles in determining network properties. The heat maps in Fig. 2 show the effects of these modulations on network synchrony, mean peak firing rate, amplitude, and period, with the values of $\nu_{VIP}$ and $\nu_{GABA}$ centered on previously published values (Vasalou et al., 2011). We also reported variability of these values across five simulations performed with different network



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