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SYNAPTIC MECHANISMS

COMMENTARY
Excitation by GABA in the SCN reaches its time and place (Commentary on Irwin & Allen)

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The mammalian circadian clock resides within the suprachiasmatic nucleus (SCN). This relatively small group of neurons controls most aspects of our daily lives by dictating our 'internal time' and keeping us synchronized with the environment. Intensive research in the past 20 years has revealed that a complex intracellular molecular mechanism enables each of the SCN neurons to function as a stand-alone circadian oscillator (Hastings *et al.*, 2008). The firing rate of these neurons alternates between high and low levels that correspond to the light and dark phases of the circadian rhythm. However, for efficient function of the circadian clock, these individual oscillators must be synchronized. Since the SCN is comprised of interconnected GABAergic neurons, it is tempting to assume that this GABAergic network serves as a synchronizing device. Over a decade ago we reported (Wagner *et al.*, 1997) that in the SCN GABA can operate either as an excitatory or inhibitory neurotransmitter. We further demonstrated the prevalence of excitation in response to GABA during the light phase and predominance of inhibition during the dark phase. We suggested that the duality of GABAergic effect on SCN neurons, which reflects circadian oscillations in intracellular chloride concentrations, serves to amplify the circadian rhythmicity in firing rate. This original report was immediately followed by a joint publication by three groups reporting that GABA has only an inhibitory effect in the SCN (Gribkoff *et al.*, 1999). Since then, however, a steady stream of publications confirmed the dual effect of GABA (De Jeu & Pennartz, 2002; Colwell, 2003; Ikeda *et al.*, 2003; Choi *et al.*, 2008). The groundbreaking study of Albus *et al.* (2005) has ascribed the duality of GABA effect with a physiological role by demonstrating that the SCN is composed of two well-defined compartments, termed 'core' and 'shell'. It is the GABA-mediated interaction between these two compartments that enable the SCN to respond to light resetting signals. They also found that excitation by GABA is more common in the shell compartment whereas inhibition is more frequently found within the core neurons, probably due to differential expression of the chloride transporter KCC1 (Belenky *et al.*, 2008).

The study by Irwin & Allen (2009) published in this issue of *EJN* adds an important contribution to the duality of the GABA effect in the SCN. They loaded SCN neurons with a calcium indicator that enables simultaneous recordings of calcium concentrations in a large portion of the SCN neuronal network, thus allowing for an accurate description of the distribution of the GABAergic effect in time and space. Their results clearly show that most SCN neurons (50–70%) respond to GABA application with an increase in intracellular calcium concentrations, which is associated with neuronal excitation. A careful analysis of the contribution of $GABA_A$ and $GABA_B$ receptors confirms that the excitatory effect is mediated solely by the $GABA_A$ receptor, which is a chloride channel. Using specific blockers Irwin & Allen (2009) further demonstrate that the change in calcium concentration is caused by voltage-sensitive calcium channels, responding to the GABA-mediated shift in membrane potential. Analysis of the spatial and temporal distribution of the responses to GABA shows that that the excitatory responses prevail, and that they are most abundant in the shell region. Moreover, in both shell and core compartments excitation predominates during the night phase. In order to demonstrate that the duality of the GABA effect occurs within physiological conditions, one must show that it can be induced by endogenous GABA. Irwin & Allen (2009) confirm this by blocking $GABA_A$ receptors and by stimulating the optical nerve input to the SCN. Whereas stimulating the optical nerve induces changes in calcium concentration that are similar to those induced by GABA, blocking $GABA_A$ receptors induces the opposite effect.

Overall these results demonstrate that GABA excitation is far from an anecdotal observation, and that it in fact dominates the network activity of the SCN. Beyond alternating between excitation and inhibition, GABA also imposes a dual effect on the intracellular calcium concentrations. Given the prominent role played by intracellular calcium in numerous cellular processes, this finding opens new avenues for research and interpretations. The most exciting possibility is that the GABA-mediated changes in calcium concentration directly affect gene expression, thus providing the elusive link between neuronal activity and the molecular clock of SCN neurons.

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