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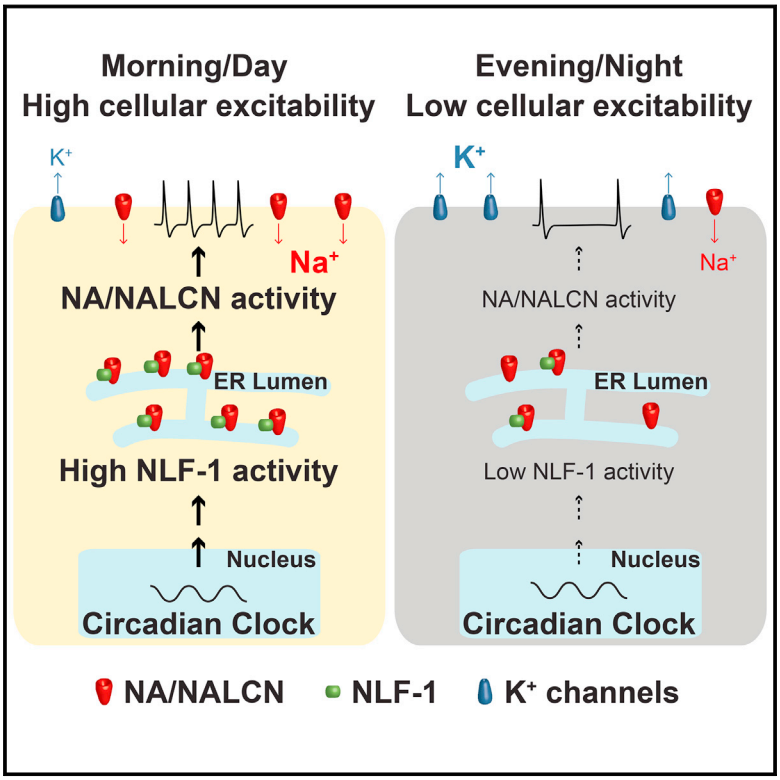
A Conserved Bicycle Model for Circadian Clock Control of Membrane Excitability

Graphical Abstract



Highlights

- Rhythmic sodium leak conductance depolarizes *Drosophila* circadian pacemaker neurons
- NCA localization factor 1 links the molecular clock to sodium leak channel activity
- Antiphase cycles in resting K^+ and Na^+ conductances drive membrane potential rhythms
- This "bicycle" mechanism is conserved in master clock neurons between flies and mice

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In Brief

Two distinctly timed sodium and potassium electrical drives collaborate to directly control membrane excitability and neuronal function in a circadian manner.

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A Conserved Bicycle Model for Circadian Clock Control of Membrane Excitability

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SUMMARY

Circadian clocks regulate membrane excitability in master pacemaker neurons to control daily rhythms of sleep and wake. Here, we find that two distinctly timed electrical drives collaborate to impose rhythmicity on *Drosophila* clock neurons. In the morning, a voltage-independent sodium conductance via the NA/NALCN ion channel depolarizes these neurons. This current is driven by the rhythmic expression of NCA localization factor-1, linking the molecular clock to ion channel function. In the evening, basal potassium currents peak to silence clock neurons. Remarkably, daily antiphase cycles of sodium and potassium currents also drive mouse clock neuron rhythms. Thus, we reveal an evolutionarily ancient strategy for the neural mechanisms that govern daily sleep and wake.

INTRODUCTION

Circadian clocks have evolved to align organismal biochemistry, physiology, and behavior to daily environmental oscillations. At the core of these clocks in all multicellular organisms are conserved transcriptional feedback loops (Allada and Chung, 2010; Hardin, 2011). In *Drosophila*, the bHLH-PAS transcription factor heterodimer CLOCK (CLK) and CYCLE (CYC) directly binds E boxes (CACGTG) in target promoters of the clock genes, *period* (*per*) and *timeless* (*tim*), and activates their transcription. PER and TIM proteins feed back to repress CLK/CYC activity. The temporal separation of transcriptional activation and repression and/or mRNA and protein oscillations, in some cases by many hours (Lee et al., 1998), results in robust daily oscillations of *per*, *tim*, and other rhythmic transcripts. These molecular clocks, in turn, control a broad range of cellular and physiological responses likely via the rhythmic transcription of clock output genes.

While molecular clocks are expressed in a variety of cell types, those in specific circadian clock neurons in the brain exhibit special properties. These so-called "master" circadian pacemakers, such as the mammalian suprachiasmatic nucleus (SCN) and the *Drosophila* lateral and dorsal neurons, drive robust 24 hr rhythms of sleep and wake behavior (Helfrich-Förster, 2005; Mohawk and Takahashi, 2011). Unlike generic clock cells, these clock neurons are interconnected via neural networks and, as a result, produce coherent and sustained free running molecular and behavioral rhythmicity under constant conditions (Flourakis and Allada, 2015; Guo et al., 2014; Peng et al., 2003; Seluzicki et al., 2014; Shafer et al., 2002; Yang and Sehgal, 2001; Yao and Shafer, 2014). Although the anatomical features of brain pacemaker networks are highly divergent between mammals and invertebrates such as *Drosophila*, their ability to control sleep and wake cycles uniformly depends on daily rhythms of membrane excitability (Cao and Nitabach, 2008; Colwell, 2011; de Jeu et al., 1998; Kuhlman and McMahon, 2004; Sheeba et al., 2008). However, the mechanistic links between the molecular clock and the machinery controlling cellular excitability are not well understood.

Using patch-clamp analysis of the *Drosophila* DN1p, we show for the first time that circadian clock control of membrane excitability operates via resting sodium leak conductance through the narrow abdomen (NA) channel, providing timed depolarizing drive to circadian pacemaker neurons. We demonstrate that the sodium leak rhythm depends on rhythmic expression of NCA localization factor 1, linking the molecular clock and membrane excitability. We reveal that both flies and mice, separated by hundreds of millions of years in evolution, utilize antiphase oscillations of sodium and potassium conductances to drive clock control of membrane potential. Thus, the conservation of clock mechanisms between invertebrates and vertebrates extends from core timing mechanisms to the control of membrane excitability in the master clock neurons governing sleep and wake.

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