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RESEARCH NEWS

Kv12 channels flick the switch

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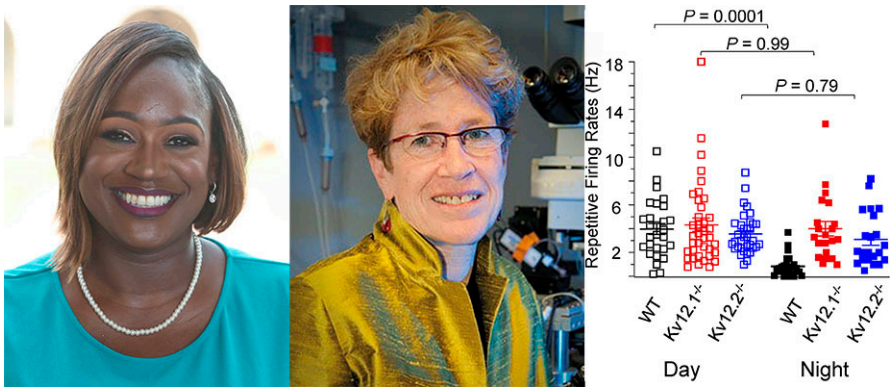
JGP study (Hermanstyne et al. 2023. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202213310) shows that Kv12-encoded K^+ currents reduce the repetitive firing rates of SCN neurons at night, thereby regulating daily oscillations in the master circadian pacemaker.

The suprachiasmatic nucleus (SCN) is a region of the hypothalamus considered to be the master circadian pacemaker in mammals. Neurons in the SCN show daily oscillations in spontaneous activity, displaying high repetitive firing rates during the day and low repetitive firing rates at night (1). This, in turn, is thought to control circadian rhythms in numerous aspects of animal physiology and behavior, including physical activity (2). In this issue of *JGP*, Hermanstyne et al. (3) reveal that, in most SCN neurons, this day–night switch in activity is regulated by Kv12 K^+ channels (3).

The daily oscillations in neuronal activity in the SCN are thought to be regulated by subthreshold K^+ currents. During the day, these currents are low, input resistances are relatively high, membrane potentials are more depolarized, and firing rates are high, averaging ~5 Hz. At night, subthreshold K^+ currents are increased, input resistances drop, membrane potentials become more hyperpolarized, and firing rates decline to ~1 Hz (4).

Although K^+ currents mediated by several different types of K^+ channels have been identified in SCN neurons and shown to influence the repetitive firing rates of SCN neurons, none of them have been shown to control the day–night switch in repetitive firing rates. Tracey Hermanstyne, Jeanne Nerbonne, and colleagues at Washington University School of Medicine in St. Louis wondered whether Kv12.1 and/or Kv12.2, members of the *Elk* subfamily of voltage-gated K^+ channels, might control the daily oscillations in SCN neuronal activity.



Tracey Hermanstyne (left), Jeanne Nerbonne (center), and colleagues reveal that Kv12-mediated K^+ currents regulate the day–night switch in firing rates of neurons in the SCN, the master circadian pacemaker in mammals. Compared with wild-type mouse SCN neurons (black), loss of Kv12.1 (red) or Kv12.2 (blue) has no effect on daytime firing rates but increases nighttime rates to eliminate the normal day–night difference in neuronal activity.

To test this idea, they prepared brain slices from the SCN of adult Kv12.1- and Kv12.2-knockout mice during the day or night, and compared the activity of neurons in these slices to neurons in slices from wild-type animals (3). Remarkably, they found that deletion of the genes encoding Kv12.1 or Kv12.2 significantly increased firing rates in nighttime SCN neurons but had no effect on daytime firing rates. "In nighttime slices, the neurons, on average, were firing close to daytime rates, so there was no longer a switch between the day and night," Hermanstyne says. Similarly, deletion of the Kv12.1 or Kv12.2 genes selectively altered the membrane properties of SCN neurons at night, eliminating the day–night differences in input resistances and membrane potentials.

"We saw the same phenotypes when we injected shRNA-expressing viruses into the SCN to knockdown Kv12 expression acutely in adult animals," explains Nerbonne, "demonstrating that the loss of the day–night switch in the firing rates of SCN neurons is a direct effect of Kv12 depletion, rather than an indirect consequence of the absence of Kv12 channels during development."

To explore the effects of Kv12-mediated currents in real time, Hermanstyne et al. (3) developed a mathematical model of Kv12.1 currents, and used dynamic-clamp to add or subtract these simulated currents from

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daytime and nighttime wild-type SCN neurons. They found that subtracting Kv12.1 currents immediately increased the firing rate of nighttime SCN neurons, but had no effect on daytime neurons.

Inhibiting Kv12 channels with the small molecule blocker CX4 also increased the nighttime firing rates of SCN neurons. Moreover, Hermanstyne et al. (3) found that CX4-sensitive (i.e., Kv12-mediated) currents were higher at night than during the day, in keeping with a selective role for Kv12 currents in regulating nighttime firing rates. The expression levels of the mRNAs encoding the Kv12.1 and Kv12.2 subunits don't oscillate over the course of the day, so the reason for this day–night difference in Kv12-encoded currents remains unclear. But it could involve any number of posttranscriptional mechanisms that control Kv12 channel protein expression, stability, and/or trafficking to the cell surface.

A further mystery is why, despite the loss of day–night differences in SCN firing rates, Kv12.1$^{-/-}$ and Kv12.2$^{-/-}$ mice show no alterations in circadian locomotor activity patterns. "Approximately 30% of SCN neurons were not affected by the loss of Kv12," Hermanstyne says. "Is that enough cells to keep circadian rhythms going? Or is there a population of cells that is particularly important? We need to start teasing apart the functional roles of cellular differences within the SCN."

"There could also be a role for plasticity in vivo, where changes in synaptic activity compensate for the changes in intrinsic properties to maintain rhythms in firing patterns and locomotor activity," Nerbonne adds. "It's a really important question."

References

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