Up all night: BK channels' circadian dance with different calcium sources

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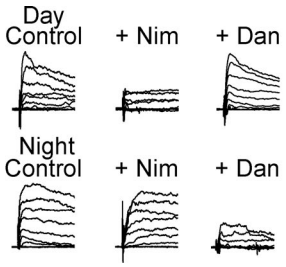
JGP study explores diurnal changes in calcium sources governing BK activity in the SCN.



First author Joshua Whitt (right), senior author Andrea Meredith (left), and Beth McNally (not depicted) show that daytime BK currents require L-type calcium channels (sensitive to blockade by nimodipine, +Nim), whereas nighttime BK currents respond to calcium release from intracellular stores (blocked by dantrolene, +Dan).

The suprachiasmatic nucleus (SCN) is the brain's central timekeeper, responsible for entraining diurnal rhythms for everything from locomotor activity to hormone levels, body temperature, and sleep. This activity is generated by the molecular circadian clock via the cyclic production and destruction of certain proteins. In the SCN, the circadian clock also produces rhythmic action potentials whose frequency is greatest during the day—a phenomenon that's created through changes in the expression and activity of ion channels, including large-conductance potassium (BK) channels (1), L type calcium channels (LTCC; 2), and others. In this issue of JGP, Joshua Whitt, Andrea Meredith, and Beth McNally explore circadian variations in the calcium sources that regulate BK channel activity in SCN neurons (3).

BK channels are voltage-gated potassium channels whose opening is potentiated by binding of calcium ions at four sites on the cytoplasmic portion of the protein (4); in the absence of calcium, BK channels generally do not pass current because their opening would require membrane voltages outside what neurons can normally achieve. In the SCN, BK channel currents and expression are highest at night (1), when it helps suppress SCN action potential frequency by hyperpolarizing the neuronal membrane. But in an apparent paradox, cytoplasmic calcium levels are highest in daytime (5).

"This didn't really bother us because we knew that intracellular cytosolic calcium oscillations were likely to be of little relevance to BK activation. BK basically has to be sitting next to its calcium source, and tightly spatially localized calcium release is what's relevant for gating the channel," says Andrea Meredith, Associate Professor at the University of Maryland School of Medicine. Several calcium sources could potentially regulate BK channel activity. These include plasma membrane calcium channels such as LTCC, N/P/Q-type, and R-type channels, plus intracellular stores released through ryanodine receptors (RyR). Which of these calcium sources governs BK activity in the SCN was unknown.

Meredith's graduate student Joshua Whitt probed this question using pharmacological agents to specifically inhibit or activate the different candidate channels in SCN tissue slices from rodents. When LTCC, N/P/Q, and RyR channels were simultaneously inhibited, BK currents disappeared, indicating that these calcium sources were collectively responsible for BK activity in the SCN. Then, inhibitors were applied individually, during the day or at night, to determine whether any of these sources was more important at different times of day.

> "We have dynamic switching of calcium sources"

"During the day, the majority of the current was [dependent on L-type channels, but] when we recorded BK currents at night, when the L type current becomes somewhat reduced, it looked like BK current activation became more dependent on calcium release from intracellular stores," explains Meredith. Inhibition of the different channels also impacted SCN action potential frequency, with LTCC inhibition affecting the frequency during the daytime but not at night. Interestingly, RyR inhibition increased nighttime action potential frequency, but RyR activation also altered frequencies during the day, suggesting BK could remain in proximity to these channels all day long.

Reliance on different calcium sources at different times of day may have its roots in other features of the circadian cycle. For example, earlier work by Meredith's group demonstrated increased daytime inactivation of BK current, mediated by the BK β2 subunit (6). The new data indicates that LTCC currents are also required for daytime β2-mediated BK channel inactivation, possibly because β2 adjusts BK calcium sensitivity, or somehow promotes BK association with LTCC. In contrast, the more sustained nighttime BK currents may require steadier release of calcium available from intracellular stores.

"We have dynamic switching of calcium sources occurring as a function of circadian rhythmicity," notes Meredith. This has implications for understanding SCN activity, particularly the regulation of SCN action potential shape and frequency, which Meredith's group is already investigating. Keep your eyes open for new data in the coming months.

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Journal of General Physiology