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Commentary

Should they team up to make your brain clock?

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ABSTRACT

Large-conductance calcium-activated potassium channels (BK channels) are important regulators of neuronal excitability in the mammalian nervous system. BK channels are activated by changes in membrane electrical potential and intracellular calcium concentration and play a key role in shaping neuronal action potential. Indeed, under typical physiological conditions, opening of BK channels allows potassium ions to flow outside of the cell leading to membrane repolarization and fast afterhyperpolarization, thus controlling cellular excitability. These aspects are of direct relevance to a new study by Farajnia et al., 2015, reported in this issue of *Neurobiology of Aging*, on the role of BK channels in aging circadian clock neurons.

Large-conductance calcium (Ca^{2+})-activated potassium (K^+) channels (BK channels) are important regulators of neuronal excitability in the mammalian nervous system. BK channels are activated by changes in membrane electrical potential and intracellular Ca^{2+} concentration, and play a key role in shaping neuronal action potential. Indeed, under typical physiological conditions, opening of BK channels allows potassium ions to flow outside of the cell leading to membrane repolarization and fast afterhyperpolarization, thus controlling cellular excitability. These aspects are of direct relevance to a new study by Farajnia et al. (2015), reported in this issue of *Neurobiology of Aging*, on the role of BK channels in aging circadian clock neurons.

The suprachiasmatic nucleus (SCN) in the hypothalamus is responsible for generating electrical and hormonal activities in a 24-hour cycle, which in turn contribute to the control of mammalian circadian rhythms. It was postulated that age-related change of circadian rhythms might be caused by alteration of the ionic conductances and membrane excitability of SCN neurons. However, the molecular and cellular mechanisms by which aging affects circadian rhythms remain incompletely understood. Farajnia et al. used electrophysiological recordings from SCN slices to test the hypothesis that age-related changes in circadian rhythms may rely on the alteration of BK-channel activity. To make such studies possible, the authors had to examine electrical properties of SCN slices prepared from young (2–4 months of age) and old (23–33 months of age) mice either 1 hour after the start of the light phase ("day-like" condition) or at the end of the day ("night-like" condition). As previously reported, BK currents recorded from young neurons were found significantly increased during the night. In contrast, the authors found that circadian-dependent activity of BK channels is completely abolished in aged neurons, with a steady activity similar to what was observed in young neurons in "day-like" condition. Consistent with the role of BK channels in membrane repolarization, action potential duration and afterhyperpolarization were found increased and decreased, respectively, in old neurons at night compared with young neurons. Interestingly, pharmacological inhibition of BK channels at night in young neurons was sufficient to mimic an aged phenotype, suggesting that absence of circadian BK activity is the primary cause of altered neuronal excitability in aging cells at night. Finally, Farajnia et al. showed that alteration of circadian activity of BK channels resulted in an increased intracellular Ca^{2+} concentration in aged neurons at night, but stopped short of demonstrating the cellular mechanism underlying age-dependent alteration of circadian BK activity.

The novel and important findings of Farajnia et al. raise interesting questions about the role of BK channels in the establishment and maintenance of circadian rhythms and thus their contribution to age-related rhythm disturbance.

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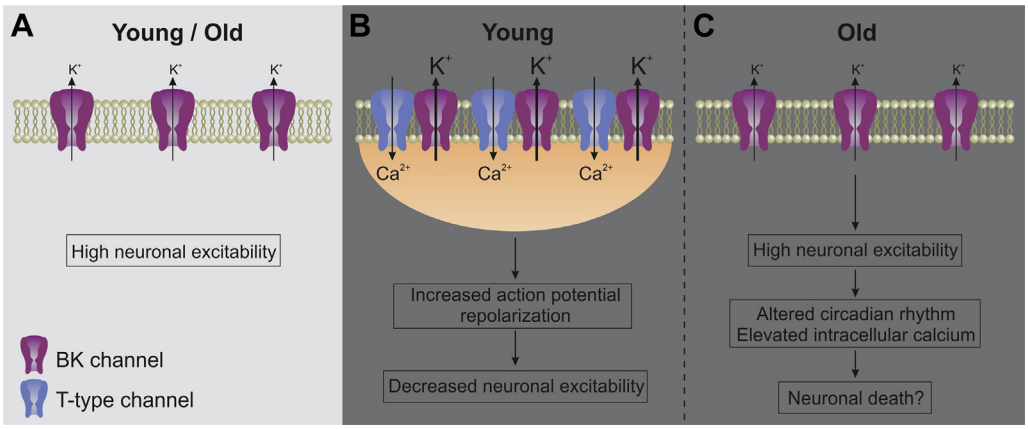

Fig. 1. A putative model of large-conductance calcium (Ca^{2+})-activated potassium (K^+) channels (BK) and/or T-type channel signaling complex in the control of circadian rhythms. (A) During daytime, expression of T-type Ca^{2+} channels at the plasma membrane is low and activity of BK channels reduced. (B) In contrast, during night-time, increased expression of T-type channels stimulates BK channels. The opening of BK channels allows potassium ions to exit the cell and accelerates repolarization and afterhyperpolarization of the cell membrane during neuronal activity, which in turn contributes to a decrease of neuronal excitability at night. (C) Alteration of T-type channel expression in aged neurons abolishes T-type–dependent stimulation of BK channels at night, contributing to age-related disturbance of circadian rhythms.

Previous studies have reported a circadian expression of low-voltage-activated T-type Ca^{2+} channels in mammalian SCN neurons (Nahm et al., 2005) and more recently in pinealocytes with an increased expression at night (Yu et al., 2015). In addition, T-type channels were shown to interact with BK channels in cerebellar Purkinje cells to support a transient Ca^{2+} nanodomain, which in turn triggers low-threshold activation of BK channels (Engbers et al., 2012; Rehak et al., 2013; Turner and Zamponi, 2014). We thus speculate that T-type channels may have similar regulatory effect over the activity of BK channels in SCN neurons, that is, stimulating BK activity during the night phase (Fig. 1). Considering that expression of T-type channels is altered during aging and in an animal model of Alzheimer's disease (Proft and Weiss, 2014; Rice et al., 2014), T-type channels may emerge as important contributors to rhythm disturbances associated with aging and possibly with neurodegenerative disorders. These new findings should also be taken into consideration when designing ion-channel modulators for human disorders, which may have non-negligible side effects on neuronal rhythmic activities.

Overall, the findings of Farajnia et al. provide novel insights into the physiology of the SCN and establish BK channels as key protagonists in age-related alteration of circadian rhythms.

Disclosure statement

The authors have no conflicts of interest to disclose.

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