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Mechanisms underlying fragmented sleep in aging

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Aging has been associated with fragmented and poor sleep quality [1–3]. Chronic poor sleep has far-reaching implications, including decline in cognitive functioning [4,5]. Sleep disturbances have been observed across species but the underlying mechanisms remain elusive [1–5].

Li et al [6] recently reported in the journal *Science* that arousal-promoting hypocretin (Hcrt) neurons [7] in the

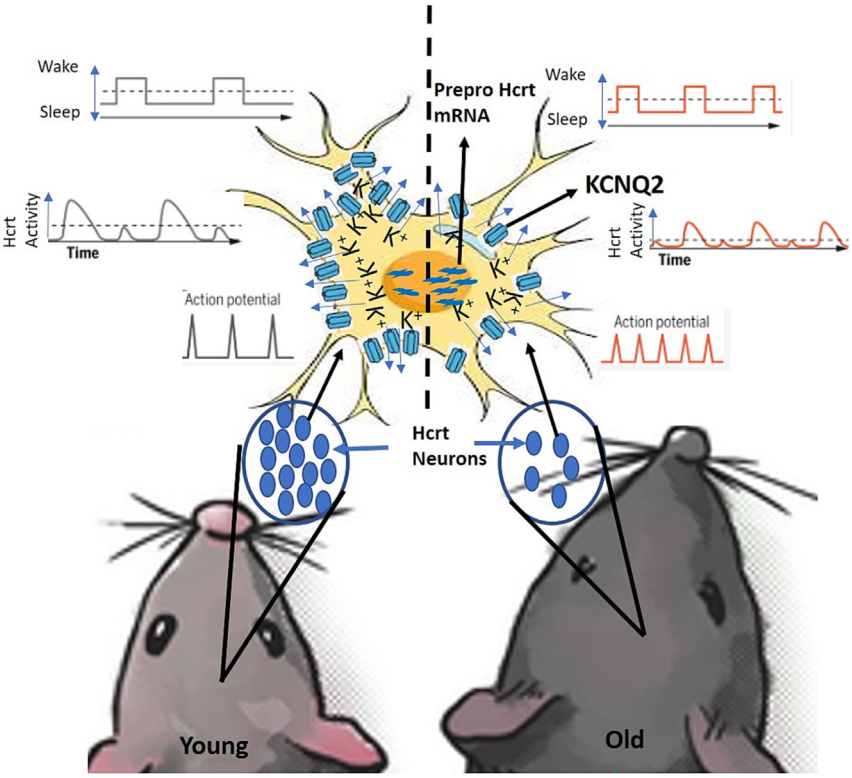

Fig. 1. Sleep fragmentation in old age is linked to hyperexcitability of Hcrt neurons in the brain and adaptive up-regulation of prepro-*Hcrt* mRNA expression with substantial Hcrt neuron loss. Functional impairment of KCNQ2/3 channel–mediated M-current and an anatomical loss of KCNQ2 is observed in hyperexcitable aged Hcrt neurons, compromising the neurons to repolarize.

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lateral hypothalamus of old laboratory rodents become hyperexcitable and drive sleep interruptions. The authors compared sleep-wake patterns of young [3,5–10] and old (18-to22-month-old) mice and found that, like in humans, sleep is disrupted in old mice; this is characterized by significantly shorter episodes of NREM and a significant reduction (38%) in the number of Hcrt-expressing neurons. Confirming the relationship between Hcrt and disturbed sleep, the authors showed that optogenetic stimulation [8] of Hcrt neurons results in prolonged bouts of wakefulness (See Fig. 1).

In addition, the authors observed that Hcrt neurons in aged mice show functional impairment of KCNQ2/3 channel-mediated repolarizing M−currents that could be attributed to a loss of KCNQ2 channels. Further, they showed that selective disruption of the KCNQ2/3 channels destabilized sleep in young mice; treatment of mice with flupirtine [9,10], a drug that activates the channels, prevents hypocretin neurons from becoming overly active, had the opposite effect.

Given that sleep disruption contributes to cognitive decline, pharmacological targeting of KCNQ2/3 channels may be potentially useful for improving sleep quality in aged individuals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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