Impact on KCNMA1 Channelopathy on Sleep-Wake Behavior in Mouse Models

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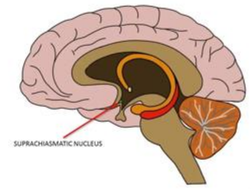
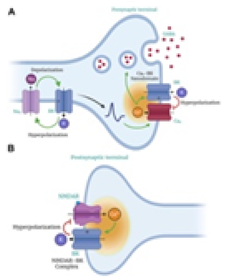
KCNMA1

KCNMA1 is a gene that regulates a voltage- and calcium activated K+ channel (BK) that varies over the circadian cycle, having lower expression during the day and higher expression during the night. The BK channel current has been shown to regulate firing in the Superchiasmatic nucleus (SCN).

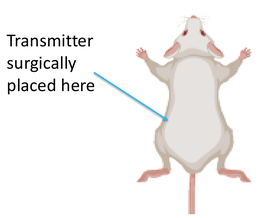


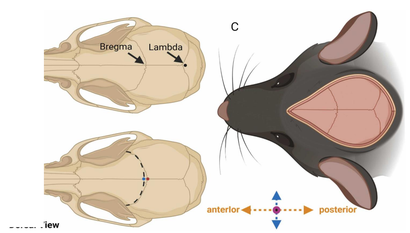


KCNMA1 is associated with epilepsy and/or dyskinesia, which is an abnormality or impairment of voluntary movement. It has been shown that it influences regulating the circadian rhythm in animals and associate with human neuromotor disease. There are three different genetic alterations in the KCNMA1 that can be classified as "Gain of function" (GOF) and "Loss of function" (LOF). In mice models where the gain of function mutation is induced, there is an increase in the BK channel current during the day, which would decrease the SCN excitability.

Methodology

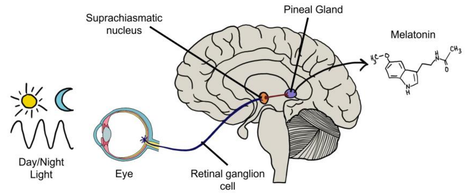
For our research, we are using D434G and N999S Mice models to study the changes in the circadian rhythm due to interactions between BK-Ca^{2+} channels.





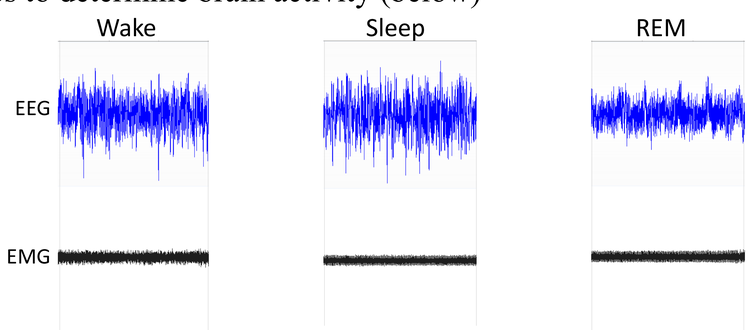
Circadian Rhythm

The circadian rhythm is the body's natural 24-hour clock that regulates many aspects of day-to-day life. This rhythm tells your body when to go to sleep and wake up. It is guided by the brain and is affected by outside factors, like light. The body has a biological need for sleep that would increase when being awake for a longer period. This is controlled by homeostasis; a process that helps self-regulate the body for conditions optimal for survival. Since the circadian rhythm is related with the light cycle, we have natural body responses that react to when it comes dark vs. light. Typically, the circadian rhythm is about 23 hours, causing a slight to offset every day.



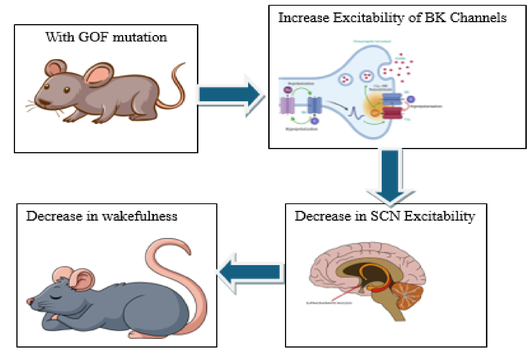
Sleep Wake Phases

There are 5 different stages of sleep that occurs, including Rapid eye movement (REM) and Non-rapid eye movement (NREM). Stage 1-3 is NREM and Stage 4 is REM. REM sleep is deep sleep and is defined by rapid eye movement and an almost complete paralysis of the body and tendency to dream. NREM sleep is marked by a reduction of physiological activity as the bodily functions slow down, during this the electrical activity in the brain slows down, and there is a decrease in muscle activity, heart rate, respiration, and oxygen consumption. Using EEG (electroencephalogram) we can record and see the brain waves to determine brain activity (below)



Hypothesis

When the circadian rhythm is disrupted; we anticipate that the sleep-wake cycle is disrupted – we expect a shift in the behavior of sleep, and we are testing if the homeostasis is disrupted. We are looking into how the sleep-wake cycle is affected through the GOF and LOF mutation to see if there is a shift in the phases of sleep.



Why is this important?

Disrupted circadian rhythms can lead to neurological disorders, mood disorders, and cancer. The circadian rhythm and seizure disorders have a crosstalk in several psychological processes such as the sleep-wake cycle, clock related genes, and hormone secretion. There has been reports that humans with the KCNMA1 mutation, suffer from sleep disturbances. Because of this, we want to look at how the sleep wake cycle is affected by the seizure related disorder. The mutation in KCNMA1 disrupts the circadian rhythm but we do not know if it influences the sleep-wake cycle.

Acknowledgements

This research was funded by two grants: STAR-PREP 5R25GM113262-09 and NGLBI R01HL102758

Reference

Ria L. Dinsdale, Cooper E. Roache, Andrea L. Meredith; Disease-associated *KCNMA1* variants decrease circadian clock robustness in channelopathy mouse models. *J Gen Physiol* 6 November 2023; 155 (11): e202313357