Disturbed sleep and circadian rhythm in mice with vitamin D deficiency

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Background

Vitamin D deficiency (VDD), prevalent worldwide, is associated with an increased risk of developing diseases and also be linked to sleep disturbances, such as reduced sleep duration and lower sleep quality, but the underlying mechanism is not yet understood. Vitamin D receptor is highly expressed in several subcortical nuclei, including, but not limited to, the bed nucleus of the stria terminalis, thalamic reticular nucleus, dorsal raphe nucleus, and central nucleus of the amygdala. Interestingly, these nuclei are also essential in controlling sleep-wake behavior. It is plausible that vitamin D may play a role in sleep-wake control, given that VDR is abundant in sleep-related brain regions. However, there is no biological evidence to support this theory.

Hypothesis

Vitamin D might play an essential role in controlling sleep-wake behavior and circadian rhythmicity.

Methods

We investigated sleep-wake behavior and circadian characteristics before and after the VDD induced by providing chows lacking vitamin D for six weeks. Electroencephalography (EEG) and electromyography (EMG) electrodes were implanted into C57BL/6J male mice. The vigilance states were recorded 24-hour baseline, 6-hour sleep deprivation, and 6-hour recovery sleep. Then data of the wheel-running activity were collected for one week in a 12:12 hour light-dark cycle followed by two weeks in the constant dark state.

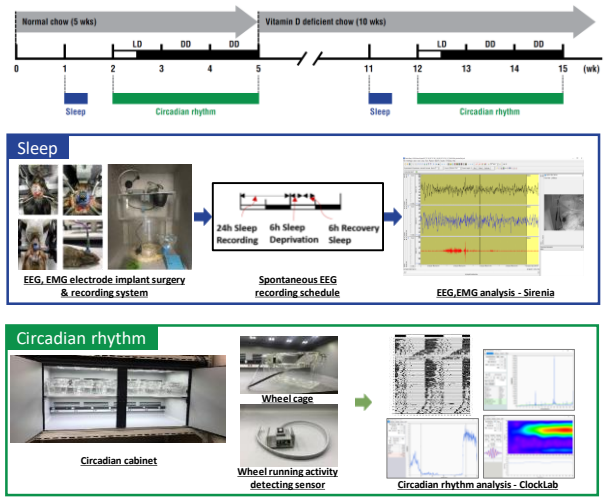

Figure 1. Experimental design and recording system

Results

Our data showed total sleep duration decreased in mice with VDD, the homeostatic sleep response to sleep deprivation was attenuated, and sleep bouts were more fragmented. In addition, circadian rhythm analysis showed similar actogram patterns in normal and VDD conditions, but the intensity of wheel running activity decreased.

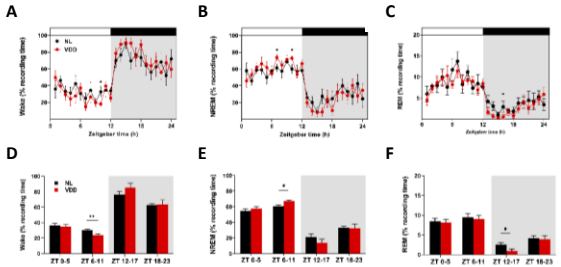

Figure 2. VDD mice showed decreased arousal and increased NREM sleep at the end of the light period. Circadian variation in wakefulness (A), NREM (B), and REM sleep (C) in the normal state and VDD state mice. The lighting condition was annotated by the bar above the graphs and the shade in the graphs; open bar means lights on, and closed bar means lights off. Percent time in wakefulness (D), and NREM (E), and REM sleep (F) are presented as means ± SEM for each state (n=8 animals each state; *P < 0.05, **P < 0.01, two-way RM ANOVA, Tukey test). All error bars denoted SEM.

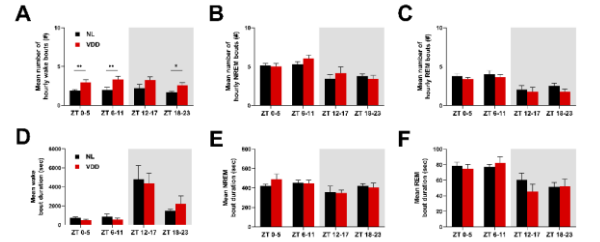

Figure 3. The wakefulness of VDD mice was significantly fragmented. The number of wakefulness bouts (A), NREM (B) and REM sleep (C). Averaged length per bout in each sleep stage in 6 hours bins. Bout length of wakefulness (D), NREM (E), and REM sleep (F). Data was expressed as mean ± SEM for each state (n=8 animals each state; *P < 0.05, **P < 0.01, two-way RM ANOVA, Tukey test). All error bars denoted SEM.

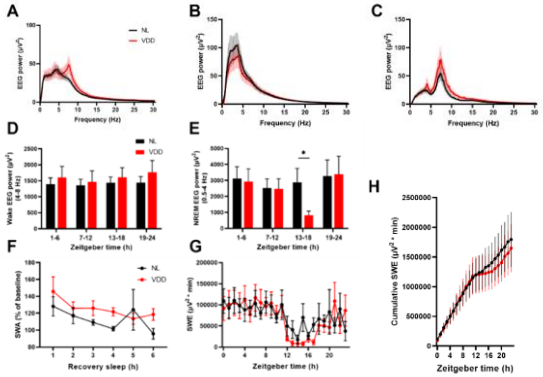

Figure 4. NREM delta power tended to decrease in VDD state mice. EEG spectral profiles during wakefulness (A), NREM (B), and REM sleep (C). Theta frequency band (4-8 Hz) during wakefulness (D) and the delta frequency band (0.5-4 Hz) during NREM sleep. Slow-wave activity (SWA) in recovery sleep (F), slow wave energy (SWE) and accumulation SWE. Data were expressed as mean ± SEM for the normal (n=5) and VDD (n=8) animals; *P < 0.05, two-way RM ANOVA, Tukey test). All error bars denoted SEM.

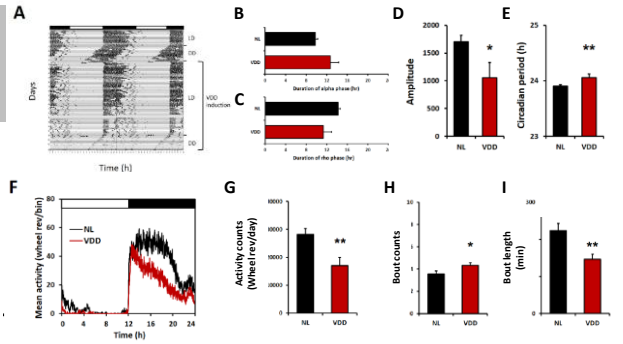

Figure 5. Characteristics of circadian behavior rhythm in NL and VDD state mice. Representative actogram (A). The black and white bars above the actogram indicate light-on and off periods, respectively. The black vertical bar in each row represents the number of wheel resolutions of the mouse. Average duration of the alpha phase (B) and rho phase (C) in NL and VDD states. The amplitudes (D) and the circadian period (E). Activity profiles (F) generated from 7 days in 12 L:12D. Daily activity counts (G), daily activity bouts (H), average length of the bout (I). All error bars denoted SEM.

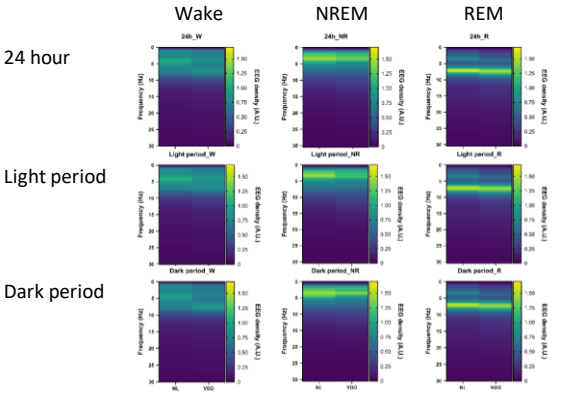

Figure 6. Heatmap of EEG density in each state of sleep. Averaged EEG density ranging from 0 to 30 Hz are presented in the wake and sleep states, respectively. (n=8, each state)

Conclusion We found that VDD might cause disturbances in regulating sleep, wakefulness, and circadian rhythmicity. To our best knowledge, this is the first study to investigate sleep-wake behavior and circadian rhythmicity in an animal model of VDD. Further research is warranted to elucidate the neurobiological link between vitamin D and sleep-controlling nuclei.

Funding source

Ministry of Science & ICT (NRF-2017R1A5A1014708)

Gwangju Institute of Science and Technology