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ABSTRACT OF DISSERTATION

Title	Pain sensitivity increases with sleep disturbance under predictable chronic mild stress in mice (軽度な慢性ストレスはマウスの睡眠を障害し疼痛感受性を増大させる)
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【Background】

The effects of stress have been studied since the early 1980s using the chronic mild stress (CMS) model. Majority of these studies used a variety of unpredictable chronic mild stresses (UCMS). In contrast, only a few have ventured into predictable chronic mild stress (PCMS) to understand neurogenesis of the hippocampus, fear memory extinction, depression, and resilience. The relationship of stress to either sleep disturbance and pain threshold has been done. However, no longitudinal experiments have been done to elucidate the relationship between sleep and pain using PCMS. This study determined the changes in sleep amount, mechanical and thermal pain thresholds, and neurobiological changes in mice under PCMS.

【Methodology】

Animals. Eight-week-old, male, C57BL6/J mice were used in all experiments.

Stereotactic implantation of electrodes for sleep recording. Cranial electroencephalograph (EEG) and electromyograph (EMG) electrodes were stereotactically embedded for EEG/EMG recording and analysis.

Peritoneal attachment of telemetry device for locomotion and core body temperature measurement. Intraperitoneal implantation of a telemetry device was also performed to record locomotor activity and core body temperature.

Predictable chronic mild stress rearing conditions. Mice were reared under PCMS using mesh wire (MW) or through the use of water (W) for 21 days.

Polysomnographic recording of sleep-wake stages and data analysis. The vigilance states of wake, NREM sleep, and REM sleep were determined through spectrum and pattern analysis using a fast Fourier transform (FFT)

algorithm.

Quantitative sensory testing for pain threshold. Tail clip, tail immersion, hot plate, and orofacial pain assessment device were used to ascertain the pain threshold.

Real-time RT-PCR and plasma corticosterone analysis. Brain regions were assayed for TNF-α and IL-6 through RT-PCR, and blood plasma for corticosterone levels through ELISA.

【Results】

This data shows that PCMS decreased slow-wave activity (SWA) during NREM sleep. Mechanical pain in the W group, thermal pain and orofacial pain in both PCMS groups were also heightened. In terms of cytokine expression, TNF-α was significantly increased in hypothalamus of the W group and trigeminal ganglion in the MW group. While IL-6 expression increased in the thalamus of the W group. On day 21 of PCMS, significant upsurges in plasma corticosterone of the PCMS groups were reported. Lastly, this study found significant correlation between SWA during non-rapid eye movement sleep and pain sensations.

【Conclusion】

The PCMS is a variant of the CMS paradigm that has grown its reputation as a model that is milder than the UCMS and elicits resilience in rodents. However, the current data suggests that chronic rearing to predictable stress can also lead to sleep disturbance and pain sensations. Furthermore, it can also lead to overexpression of cytokines like TNF-α and IL-6 in various brain regions. In relation to this, stress can be confirmed by the increase of corticosterone levels in blood plasma.