

Investigate how Orexin system regulates the medial-prefrontal cortex-mediated extinction of conditioned-fear memory

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INTRODUCTION: People with Post-traumatic stress disorder (PTSD) have impaired ability to distinguish trauma-associated fear memories and suffer from REM sleep disturbances. Previous studies have shown that orexin antagonists not only promote REM sleep but also impair the recall of fear memories after extinction learning. Interestingly, the medial prefrontal cortex (mPFC), which is downstream of the lateral hypothalamus (LH) and receives projections from orexinergic input, is also necessary for recalling extinction memories. It appears that mPFC-projecting hypocretin neurons in the LH might play a role in the extinction of conditioned fear memories and be involved in mediating REM sleep.

OBJECTIVES: Using cue-fear conditioning assay as the PTSD-like animal model to study the extinction learning process, then evaluate the anxiety level and sleep quality under the manipulation, addressing whether the LH-IL pathway is critical.

METHODS: Using chemogenetic techniques to specifically target the LH-IL pathway, artificially activate, or inhibit extinction learning, and combine electrocorticography to quantify sleep states under manipulation.

RESULTS: The mPFC and LH are highly active in the process of extinction acquisition. And the activation of the LH-to-mPFC pathway can maintain a high freezing level during the CS trials. In contrast, when the LH-to-mPFC pathway is silenced, mice initially exhibit a lower freezing level, which decreases rapidly. Moreover, the effects of this manipulation not only directly affect the expression of freezing but may also impact the formation of the extinction engram. This is evident from the similar patterns observed during fear memory retrieval and anxiety evaluation tasks compared to extinction acquisition. These findings indicate that the LH-to-mPFC pathway plays a crucial role during the extinction acquisition process. Additionally, the boosting of LH-to-mPFC resulted in insomnia-like features during the light period.

CONCLUSION: These findings support the hypothesis that boosting orexinergic projection from the LH to the mPFC is sufficient to induce impairment of extinction fear memory and disrupt REM sleep.

中文題目：探討食慾素在內側前額葉皮質調節之恐懼記憶消退中的角色

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