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PO-091 - (23841) - OREXIN-MEDIATED LATERAL HYPOTHALAMUS-ANTERIOR CINGULATE CORTEX CIRCUIT ALLEVIATES CHRONIC STRESS-INDUCED ANXIETY-LIKE BEHAVIORS

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The authors declare no conflicts of interest

Stress-induced anxiety is one of the most prevalent psychiatric disorders worldwide. The orexin system is known to be associated with both stress and anxiety, however, the neural mechanism of the orexin system in stress-induced anxiety remains to be elucidated. Our work identifies a specific neural circuit that mediates anxiety, providing new insights into the mechanisms of chronic stress-induced anxiety.
This study investigated the role of orexinergic neurons in the lateral hypothalamus (LH) and their projections to the anterior cingulate cortex (ACC) in mediating anxiety-like behaviors induced by chronic unpredictable mild stress (CUMS). Animal behavior tests were crucial in demonstrating the mitigating effects of the LH-ACC pathway on CUMS-induced anxiety-like behaviors. Immunofluorescence and virus tracing confirmed the functional connectivity between the LH and ACC. Optogenetics, fiber photometry, and electrophysiology further elucidated this pathway's role in mediating anxiety-like behaviors induced by CUMS.
We found that LH^{Orx} neurons specifically inhibited in stress-induced anxiety-like behaviors. Chemogenetic activation of LH^{Orx} neurons ameliorated anxiety-like behaviors in CUMS mice. Furthermore, LH^{Orx} neurons projected to the ACC^{Glu} neurons which were found to be inhibited after CUMS. In addition, activation of the LH^{Orx}-ACC pathway or exogenous application of orexin to the ACC significantly alleviated CUMS-induced anxiety-like behaviors, whereas pharmacologically blocking orexin 2 receptor (OX2R) but not orexin 1 receptor (OX1R) in the ACC blocked the anxiolytic effects of LH^{Orx}-ACC activation.
Taken together, our study revealed the critical role of orexin-mediated LH-ACC circuit in chronic stress-induced anxiety-like behaviors, providing potential therapeutic target for anxiety and stress-related disorders.

Palavras-chave : Anxiety, Lateral hypothalamus, Anterior cingulate cortex