Celastrol alleviates comorbid obesity and depression by directly binding amygdala hnRNPA1 in a mouse model

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June 8, 2021

Abstract

Background and Purpose: Obesity and depression are highly comorbid and far from effective treating. Celastrol was reported useful for obesity, but its role in the obesity-depression comorbidity remains unknown. This study aims to investigate the efficacy and associated mechanism of celastrol in this comorbidity.

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Experimental Approach: A comorbidity mice model of obesity and depression was constructed. Bodyweight, adipose tissue rate, blood glucose, and blood lipids were used to assess obesity. Forced swimming test and tail suspension test were investigated to evaluate depression. In microglial cells, direct targets of celastrol were screened and determined by chemical proteomics, pull-down experiment, cellular thermal shift assay, competitive binding test, and surface plasmon resonance test. In the mice model, the target gene's mediating effect was investigated by stereotactic injection of AAV9 virus. The expression level of target molecules was detected by immunofluorescence.

Key Results: Celastrol relieved the comorbid symptoms, inhibited the mal-activated Neuropeptide Y, and activated the mal-inhibited 5-HT neurons in the amygdala. The efficacy was associated with the inhibition of the mal-activated microglia. chemical proteomics, pull-down experiment, cellular thermal shift assay, competitive binding test, and surface plasmon resonance test results indicated celastrol's directly binding with hnRNPA1. In the animal model, downregulation of hnRNPA1 in the amygdala relived symptoms, and NPY and 5-HT neurons' changes. Meanwhile, overexpression of hnRNPA1 aggravated the comorbidity and antagonized the effect of celastrol.

Conclusion and Implications: Celastrol alleviated comorbid obesity and depression in a mouse model by directly binding hnRNPA1 in the amygdala. Celastrol may become a potential drug, and hnRNPA1 in the amygdala could be a useful target to combat the comorbidity.