

Activating cannabinoid CB1 receptors in a newly identified neural circuit ameliorates depressive-like behaviors in mice

With the support by the National Natural Science Foundation of China, the research team led by Prof. Li XiaoMing (李晓明) at the Center for Neuroscience, NHC and CAMS Key Laboratory of Medical Neurobiology, Zhejiang University School of Medicine, uncovered the new circuit and molecular mechanisms of depression, which was published in *Nature Medicine* (2019, 25(2): 337—349).

Major depressive disorder (MDD) is a devastating psychiatric disease that afflicts up to 17% of the world's population. The lifetime prevalence ($\sim 17\%$) and economic burden (\$100 billion annually) associated with MDD make it one of the most common and debilitating neurobiological illnesses worldwide. In a five-year study, Li's group focused on a brain area called the basal lateral amygdala (BLA). Postmortem brain analyses and imaging studies from human studies have implicated BLA dysfunction in the depressive patients. However, the circuit and molecular mechanisms through which BLA neurons modulate depressive behavior are largely uncharacterized.



Figure CB1 in the BLA CCK^{BLA}-D2^{NAc} glutamatergic circuit regulates depression-like behavior.

Here, in mice, they identified that BLA cholecystokinin (CCK) glutamatergic neurons mediated negative reinforcement via D2 medium spiny neurons (MSNs) in the nucleus accumbens (NAc) and that chronic social defeat selectively potentiated excitatory transmission of the CCK^{BLA}-D2^{NAc} circuit in susceptible mice via reduction of presynaptic cannabinoid type-1 receptor (CB1R). Knockdown of CB1R in the CCK^{BLA}-D2^{NAc} circuit elevated synaptic activity and promoted stress susceptibility. Notably, selective inhibition of the CCK^{BLA}-D2^{NAc} circuit or administration of synthetic cannabinoids in the NAc was sufficient to produce antidepressant-like effects. These results suggest, for the first time, that downregulation of CB1R in a CCK^{BLA}-D2^{NAc} circuit represents an endophenotype for stress-induced depression and points to an essential role of CB1R within this circuit in promoting stress resilience.

Medical cannabis is still a long way to go for the treatment of depression because of its addiction. However, their research suggests that CB1R in the NAc can be used as a potential biomarker for the diagnosis of depression.