

PPARG SIGNALING IN THE NUCLEUS ACCUMBENS REGULATES MESOLIMBIC DOPAMINE ACTIVITY

Background: The mesolimbic dopamine system consists of dopamine neuron projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). The NAc regulates VTA dopamine release through inhibitory GABA projections to the VTA. Hyperactive mesolimbic dopamine signaling is implicated in anxiety. Cannabidiol, a compound found in cannabis, demonstrates promising therapeutic potential for anxiety through the regulation of the mesolimbic dopamine system. Previous studies have revealed that cannabidiol infusions into the NAc decrease mesolimbic dopamine activity - potentially through the inhibitory GABA signaling to the VTA. However, the receptor mechanism in the NAc through which CBD produces its effects is unknown. Peroxisome proliferator-activated receptor gamma (PPARG) is a nuclear transcription factor that binds to CBD and colocalizes with GABA neurons. Recent evidence suggests that PPARG activation can decrease mesolimbic dopamine activity through inhibitory GABA signaling. Considering that the NAc expresses high levels of PPARG, intra-NAc CBD may regulate mesolimbic dopamine activity through PPARG activation.

Hypothesis: PPARG activation in the NAc regulates mesolimbic dopamine transmission through the modulation of the GABAergic inhibition of the VTA.

Methods: In-vivo electrophysiology was used to investigate the effects of intra-NAc PPARG activation on mesolimbic dopamine activity. The anxiolytic effects of intra-NAc PPARG activation was measured using the light-dark box and elevated plus maze behavioural tests.

Results: We report that PPARG activation in the NAc significantly decreases mesolimbic dopamine activity whereas PPARG antagonists block this effect. Additionally, we reveal that intra-NAc PPARG activation produces anxiolytic effects as measured in the light-dark box and elevated plus maze behavioural tests.