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Cannabis induced increase in striatal glutamate associated with loss of functional corticostriatal connectivity

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Abstract

Cannabis is the most commonly used illicit drug and is known to alter state of consciousness and impair neurocognitive function. However, the mechanisms underlying these effects have yet to be fully elucidated. Rodent studies suggest that Δ9-tetrahydrocannabinol (THC) activates dopaminergic neurons in the limbic system, subsequently enhancing dopamine, which is implicated in the rewarding effects of cannabis. Additional evidence suggests that THC may act indirectly on dopamine firing by modulating GABA and glutamate release. This double-blind, placebo-controlled study assessed the acute influence of two doses of THC on brain kinetics of glutamate, GABA, and dopamine, in relation to behavioral outcomes, by using magnetic resonance spectroscopy and functional magnetic resonance imaging. Twenty occasional cannabis users received acute doses of cannabis (300 µg/kg THC) and placebo, in one of two dose regimes (full dose and divided dose), during two separate testing days. Administration of THC increased striatal glutamate concentrations, and dopamine as indicated by a reduction in functional connectivity (FC) between the nucleus accumbens (NAc) and cortical areas. Alterations in glutamate and FC were dose dependent and evident in the full dose group where THC serum concentrations exceeded 2 ng/ml at T-max. Average glutamate changes correlated strongly with FC alterations. Additionally, THC induced changes in FC correlated with feelings of subjective high and decreased performance on an attention task. Taken together, this suggests that THC elicits subjective and cognitive alterations via increased striatal dopaminergic activity and loss of corticostriatal connectivity, which is associated with an increase in striatal glutamate.

Keywords: Cannabis; Dopamine; Functional connectivity; Glutamate; Proton magnetic resonance spectroscopy; THC.

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