Neurobiology

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A contributing gene for cannabis dependence

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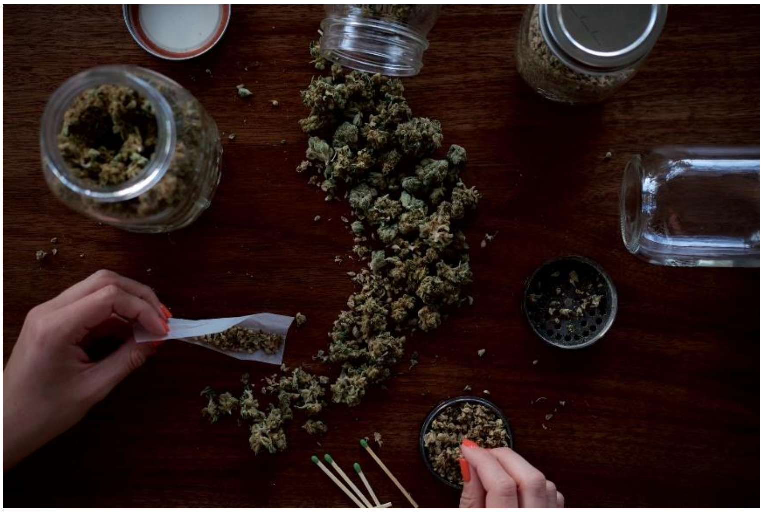
Individual variations in our genetic material contribute to more than we imagined and may combine with age and sex to influence how someone responds to drugs of abuse. Our results show that our genes might affect how much an individual likes marijuana due to underlying differences in reward regions of the brain.



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It's easy to see how certain traits can be linked back to your genetics, such as your hair color or height. It's also undeniable that some mental health disorders, such as schizophrenia, have a strong genetic link. More recently, substance use disorder - a category of mental health disorder - can also be linked to changes in a person's genetic background or variants in their DNA. These genetic variants can change how the brain functions, especially in regions known to be activated by rewarding items such as drugs of abuse. These differences can cause some people to return to the drug, leading down a path to addiction, whereas others remain unaffected. However, very few studies have looked at genetic variants that might impact an individual's response specifically to marijuana or cannabis. Marijuana is the most widely used illicit drug in the United States, with most dependent individuals beginning drug use in adolescence. We call cannabis a "rewarding substance" because it causes pleasure to the user and has been shown to affect areas of the brain that are triggered by other types of rewards.

After a rewarding substance such as cannabis enters the brain, the brain activates several processes, one of these being the endogenous cannabinoid system, or the endocannabinoid system. This system regulates the psychoactive ingredient Δ9-tetrahydrocannabinol (THC), found in cannabis. It's not hard to imagine that any changes in the endogenous cannabinoid system's activity might affect how the brain processes THC, hence how an individual perceives it.In our recent study, we attempted to understand the endocannabinoid system's role in cannabis-associated reward behavior by introducing a genetic variant found in a third of humans into a mouse. This variant causes fatty acid amide hydrolase (FAAH) to breakdown more easily. Since FAAH normally is responsible for breaking down endogenous cannabinoids, a variant that doesn't allow FAAH to work properly will lead to more cannabinoid circulating in the brain. We tested the effect of this variant on the mouse's cannabis-associated reward behavior and the underlying neurobiology.

Humans with cannabis dependence start using cannabis in adolescence, and a select population accelerates faster into heavy drug use. For this reason, we compared adolescent male mice to adolescent female mice with and without the variant. To test whether this variant impacted cannabis-associated reward behavior, we exposed mice to THC before placing them in a specific context. When given a choice during the testing period, some mice chose to spend more time in the THC-associated chamber, indicating a developed preference for THC.

Using this behavioral testing method, we discovered that adolescent female mice, but not male mice with the variant, preferred THC. This result indicates a specific vulnerability in female mice. Most significantly, this effect persisted into adulthood, as seen in humans. However, female mice exposed to THC only in adulthood did not show a preference for THC. This evidence emphasizes the specific vulnerability to the drug during adolescence.

When looking at the brains of adolescent male and female mice with and without the variant, we also found that the genetic variant led to increased neuronal connections and neural activity between two brain regions heavily implicated in reward behavior.

This study introduces new insights into cannabis dependence by providing evidence that this genetic variant in FAAH induces a preference for THC in adolescent females due to increased activity between reward-related brain regions.

Our research provides a circuit and molecular framework to explore the mechanisms of cannabis dependence further. Our results led us one step closer to understanding exactly how neurodevelopmental and genetic factors play interrelated roles. Together, these factors might increase susceptibility for substance use disorders such as cannabis dependence.

In the future, the presence of this genetic variant could potentially predict if an individual is more likely to be vulnerable to cannabis dependence. Eventually, our ability to predict risk for cannabis dependence by looking at one's genetic materials may be as easy as predicting hair color and height.