

Estrogen increases cannabis sensitivity

September 3 2014



Smoking today's concentrated pot might be risky business for women, according to new research from Washington State University. The study is the first to demonstrate sex differences in the development of tolerance to THC.

Psychology professor Rebecca Craft showed that, thanks to their estrogen levels, [female rats](#) are at least 30 percent more sensitive than males to the pain-relieving qualities of THC—the key active ingredient in cannabis. Females also develop tolerance to THC more quickly. These sensitivities could increase vulnerability to [negative side effects](#) like anxiety, paranoia and addiction.

The findings were recently published in the journal *Drug and Alcohol Dependence*.

The research was supported by a grant from the National Institute on Drug Abuse.

Many unknowns

Craft said other researchers, like Margaret Haney at the Columbia University Medical Center, have shown that women are more susceptible to cannabis abuse and dependence than men. Haney has documented a cannabis withdrawal syndrome of irritability, sleep disruption and decreased food intake that Craft said tends to be more severe in women. Women also have a greater tendency to relapse when trying to stop using the drug.

Despite the known differences in how [marijuana](#) affects the sexes, Craft said most THC tolerance studies have been done on males.

With recent legalization of recreational marijuana in Washington and Colorado—and many more states allowing medicinal use—Craft said there is greater burden on researchers to understand the effects of cannabis and ferret out differences between males and females.

She said the "munchie effect" appears to be the only THC reaction where males show more sensitivity than females. Studies in California found that THC stimulated the appetites of male animals more than those of females.

Cannabis complex

The marijuana plant contains more than 60 compounds known as cannabinoids. THC, or tetrahydrocannabinol, is the psychoactive ingredient behind the characteristic mental high. Cannabidiol and cannabitol occur in smaller amounts but may be useful for medical

purposes.

All three compounds are present in the most common species of marijuana, *Cannabis sativa* and *C. indica*, but in varying proportions.

Craft said most [medical marijuana](#) patients prefer a balance between the cannabinoids. But when it comes to recreational pot, selective breeding has resulted in THC concentrations double or triple those seen in the 1960s and 70s.

"Marijuana is very different than it was 40 years ago," she said. "It's much higher in THC and lower in cannabidiol, so a little bit goes a very long way.

"We're more likely to see negative side effects today like anxiety, confusion, panic attacks, hallucinations or extreme paranoia," she said. "And women are at higher risk."

One of the few female studies

Most clinical drug trials have been conducted on men due to their more stable hormonal profile. Despite the recommendation of the National Institutes of Health in 1993 to include more women in studies or give good reasons not to, many researchers still avoid dealing with the hormone swings inherent in a woman's biology.

But Craft has been studying drug sensitivities in females for years.

Working with rats in her laboratory, Craft said she and her team "routinely manipulate hormones and follow females across their cycles to see if their drug sensitivities change along with their hormones. And they do...very frequently." Estrogen is the culprit.

"What we're finding with THC is that you get a very clear spike in drug sensitivity right when the females are ovulating - right when their [estrogen levels](#) have peaked and are coming down," she said.

Surprise finding

In the current study, Craft and her team examined the pain relieving effects of THC in male and female rats. After 10 days of treatment, tolerance to THC was shown to be significantly greater in females than males.

Tolerance occurs when the rat "adapts" to THC so that larger doses are required to produce the same pain-relieving effects initially seen with the first dose.

Because Craft already knew that females were more sensitive to THC, she adjusted their doses to be 30 percent lower than doses for males. The [females](#) still developed more tolerance.

"This is the lowest dose anyone has ever used to induce tolerance," she said.

The team also found that a low dose of THC did not disrupt the reproductive cycle in female rats, something that has been under debate and, Craft said, needs more study.

Medical marijuana

Hoping to gain greater insights into marijuana's medical potential, Craft and her team are also studying the effects of cannabidiol, which can counter some of THC's negative side effects.

The THC and cannabidiol studies will be extended to include chronic types of pain typically seen in people who request medical marijuana—such as those with debilitating back or joint pain, cancer, Crohn's disease, multiple sclerosis, severe muscle spasms and more.

"These people have pain that lasts for months or years," Craft said. "Tolerance develops differently and sometimes you get a lot less tolerance to a drug when people are in chronic pain."

Craft uses a standard research formulation of delta-9-THC for her studies and is approved by the U.S. Drug Enforcement Administration to work with Schedule I drugs such as cannabis.

Provided by Washington State University

Citation: Estrogen increases cannabis sensitivity (2014, September 3) retrieved 18 April 2024 from <https://medicalxpress.com/news/2014-09-estrogen-cannabis-sensitivity.html>

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