

Sex-differences in acute Δ^9 -THC-induced antinociception are strain-specific

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Though cannabinoids are being increasingly used for their pain-relieving effects, tolerance to these effects, including those of delta-9-tetrahydrocannabinol (Δ^9 -THC), may limit their clinical efficacy. With more women than men now using medical cannabis for pain relief, it is crucial we understand how biological sex may influence cannabinoid-mediated antinociception and subsequent tolerance. Likewise, few studies have considered whether the efficacy of cannabinoids may vary as a function of genetics. Though studies in rats consistently find female rats to be more sensitive to the acute antinociceptive effects of cannabinoids than males, work in our lab consistently finds the converse. Studies in our lab primarily utilize mice on a C57BL6/J (B6) background. Consequently, not only is there is little genetic variation among our B6 mice, but it remains unknown whether the sex-specific effects we observe in B6 mice extend to other mouse strains. Therefore, the purpose of the present study is to examine whether our observed sex differences in Δ^9 -THC-induced antinociception and tolerance are strain-dependent. Male and female B6, DBA, AKR, and CBA mice were assessed for differences in acute Δ^9 -THC-induced antinociception and hypothermia prior to and following seven days of once-daily Δ^9 -THC administration. Consistent with our previous studies, male B6 mice were more sensitive to the acute antinociceptive effects of Δ^9 -THC than female B6 mice, an effect which correlated with differences in B6 CB₁ mRNA expression in the PAG and dissipated with age. While DBA and CBA female mice showed increased Δ^9 -THC-antinociception compared to male littermates at 30 and 10 mg/kg Δ^9 -THC, respectively, these effects dissipated at higher doses, revealing that dose of Δ^9 -THC may also be important. Overall, CBA mice were much more sensitive to Δ^9 -THC-induced antinociception while AKR mice were much less responsive. Despite the heterogeneity in Δ^9 -THC-induced antinociception, there was little variability in Δ^9 -THC-induced hypothermia as a function of either sex or mouse strain. Likewise, across all strains, female mice were faster to develop tolerance or developed tolerance at the same rate as male littermates. Taken together, these studies highlight the therapeutic potential of Δ^9 -THC in pain management and underscore the importance of considering not only Δ^9 -THC dose as a function of sex, but potentially genetic differences among various populations when evaluating their clinical utility.

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