

Sex-specific behavioural, metabolic and immunohistochemical changes after repeated administration of the synthetic cannabinoid AKB48 in mice

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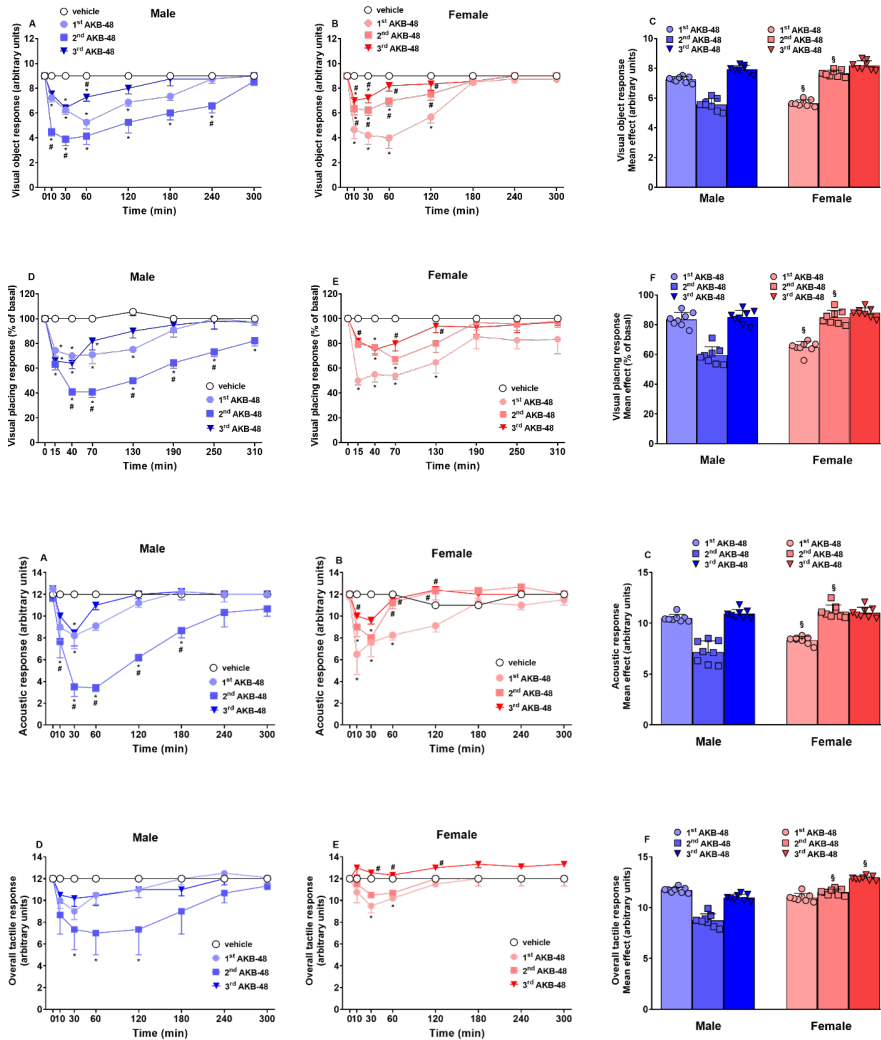
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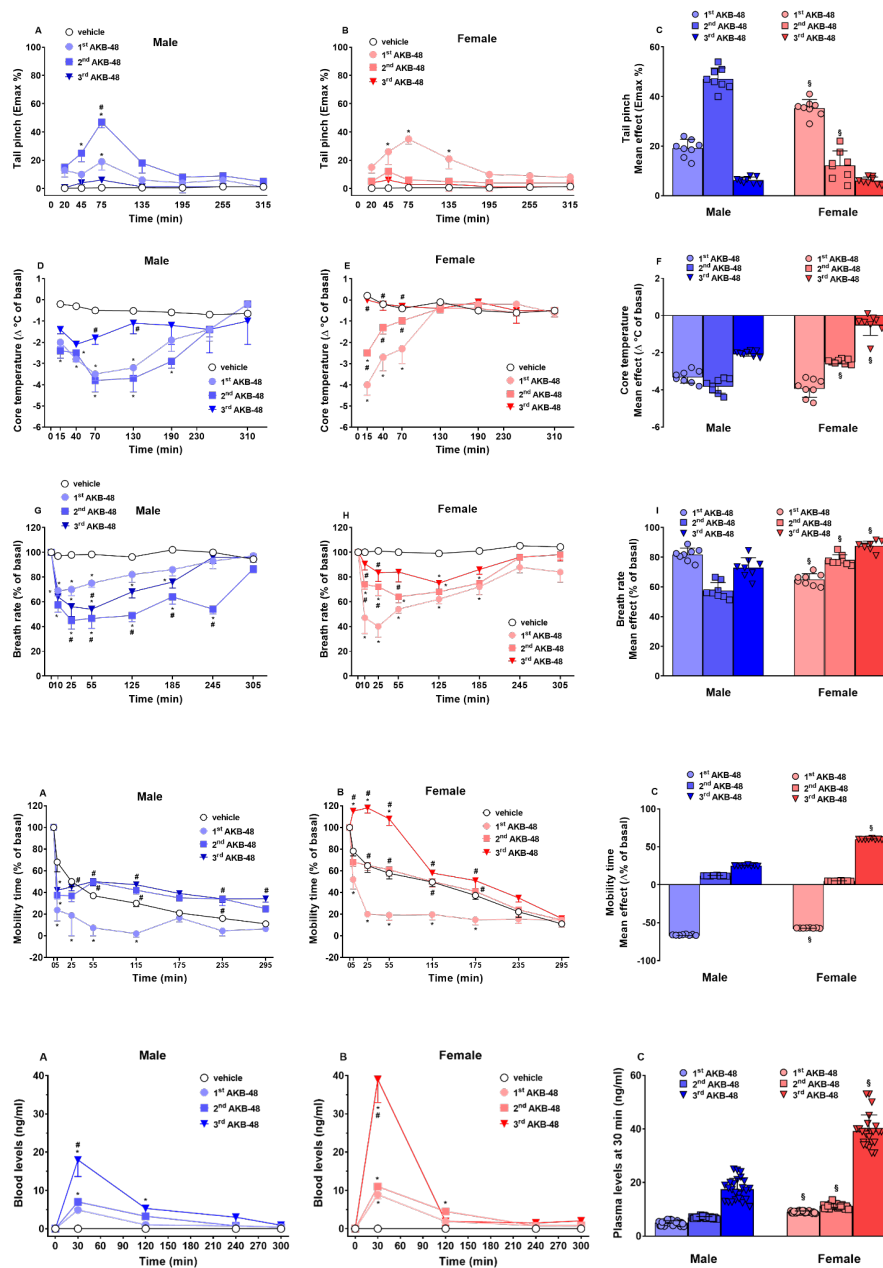
Abstract

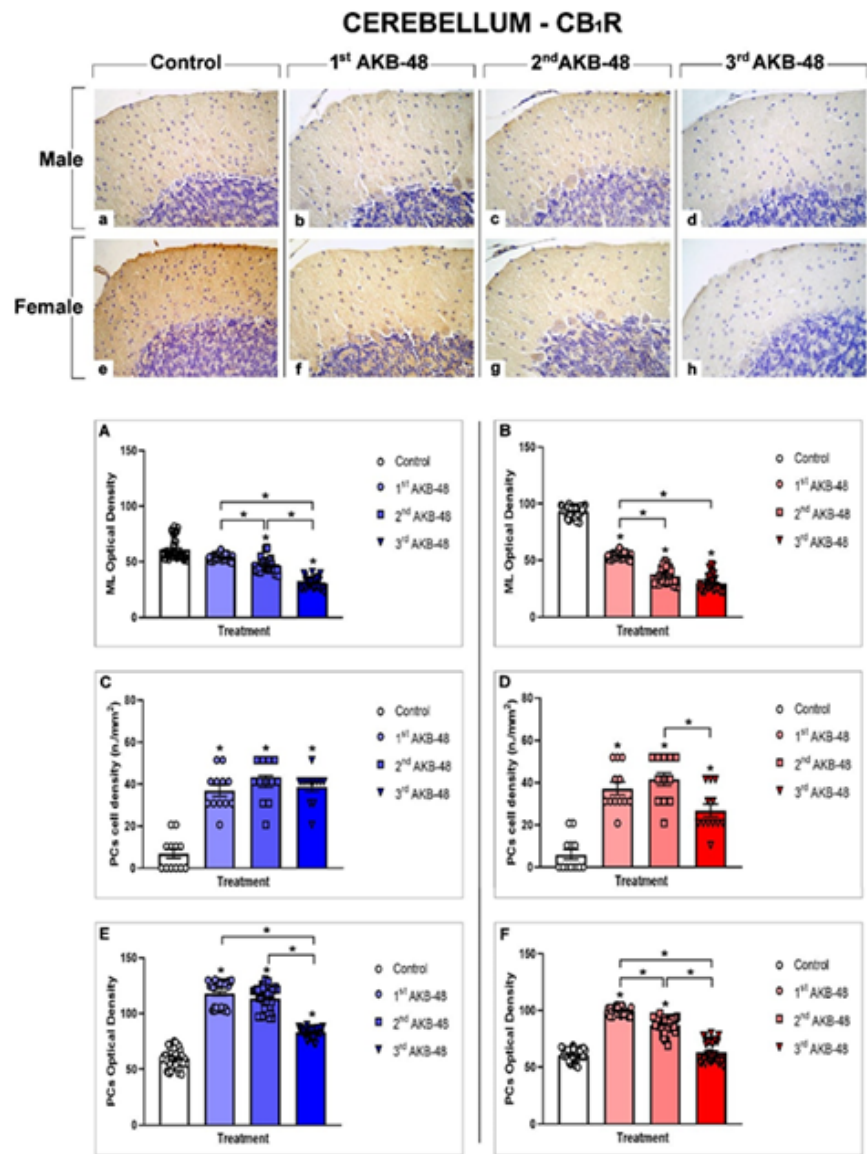
AKB48 is a synthetic cannabinoid illegally sold for its psychoactive cannabis-like effects that has been associated to several acute intoxications and which effects are poorly known. Using a behavioural, neurochemical and immunohistochemical approach we investigated the pharmacotoxicological effects, plasma pharmacokinetic and neuroplasticity at cannabinoid CB1 receptor (CB1R) in the cerebellum and cortex induced by repeated AKB48 administration in male and female mice. The effects of AKB48 varied significantly depending on sex and length of treatment. The 1st injection impaired sensorimotor responses and reduced body temperature, analgesia, and breath rate at a greater extent in females than in males, the 2nd injection induced stronger effects in males while the 3rd injection of AKB48 induced weaker responses in both sexes, suggesting the emergence of tolerance. The CB1R antagonist NESS-0327 prevented the effects induced by repeated AKB48, confirming a CB1R-mediated action of the drug. Blood AKB48 levels were higher in females than in males and repeated administration caused a progressive rise of AKB48 content in blood samples of both sexes, suggesting an inhibitory effect on cytochrome activity. Finally, immunohistochemical analysis revealed higher expression of CB1Rs in the cerebellum and cortex of females, and a rapid CB1R downregulation in cerebellar and cortical areas following repeated AKB48 injections, with neuroadaptation occurring generally more rapidly in females than in males. We showed for the first time that AKB48 effects significantly vary with prolonged use and that sex affects the pharmacodynamic/pharmacokinetic responses to its repeated administration, suggesting a sex-tailored approach in managing AKB48-induced intoxication.

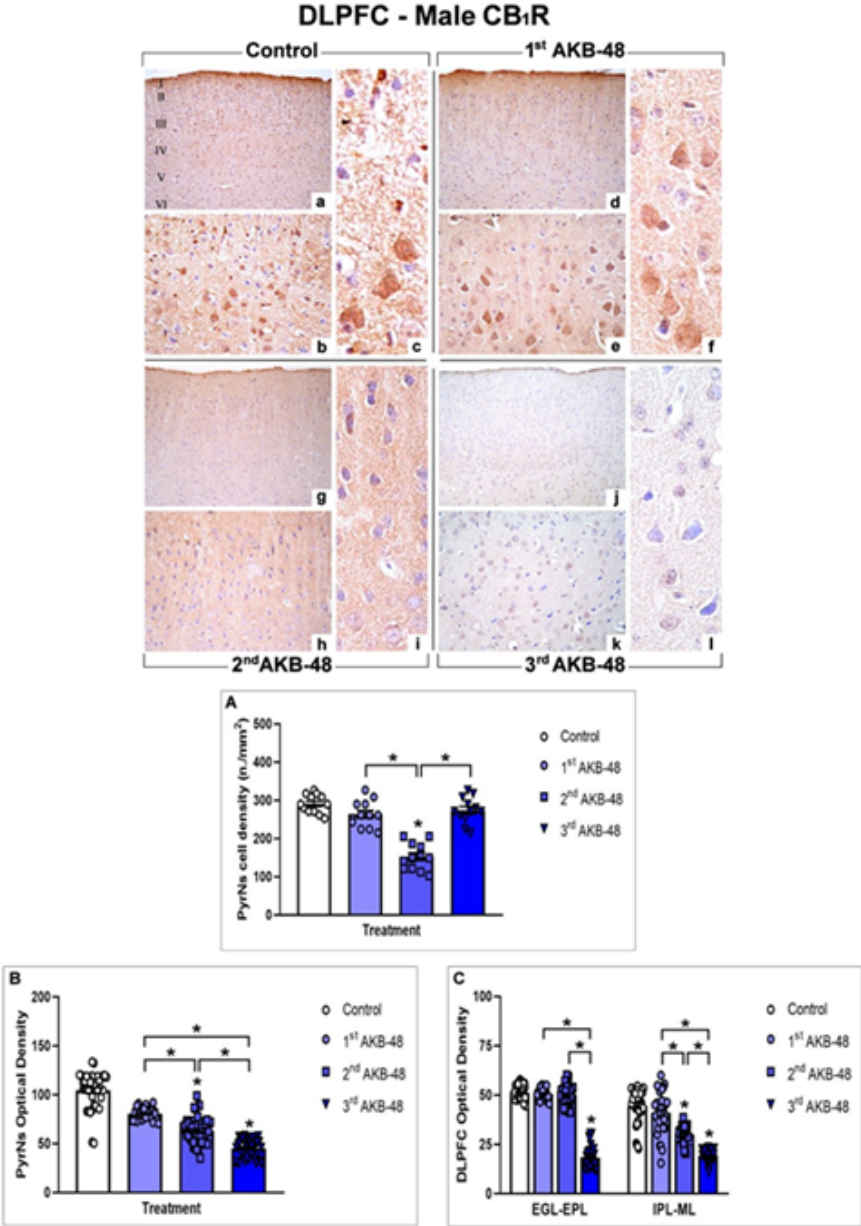
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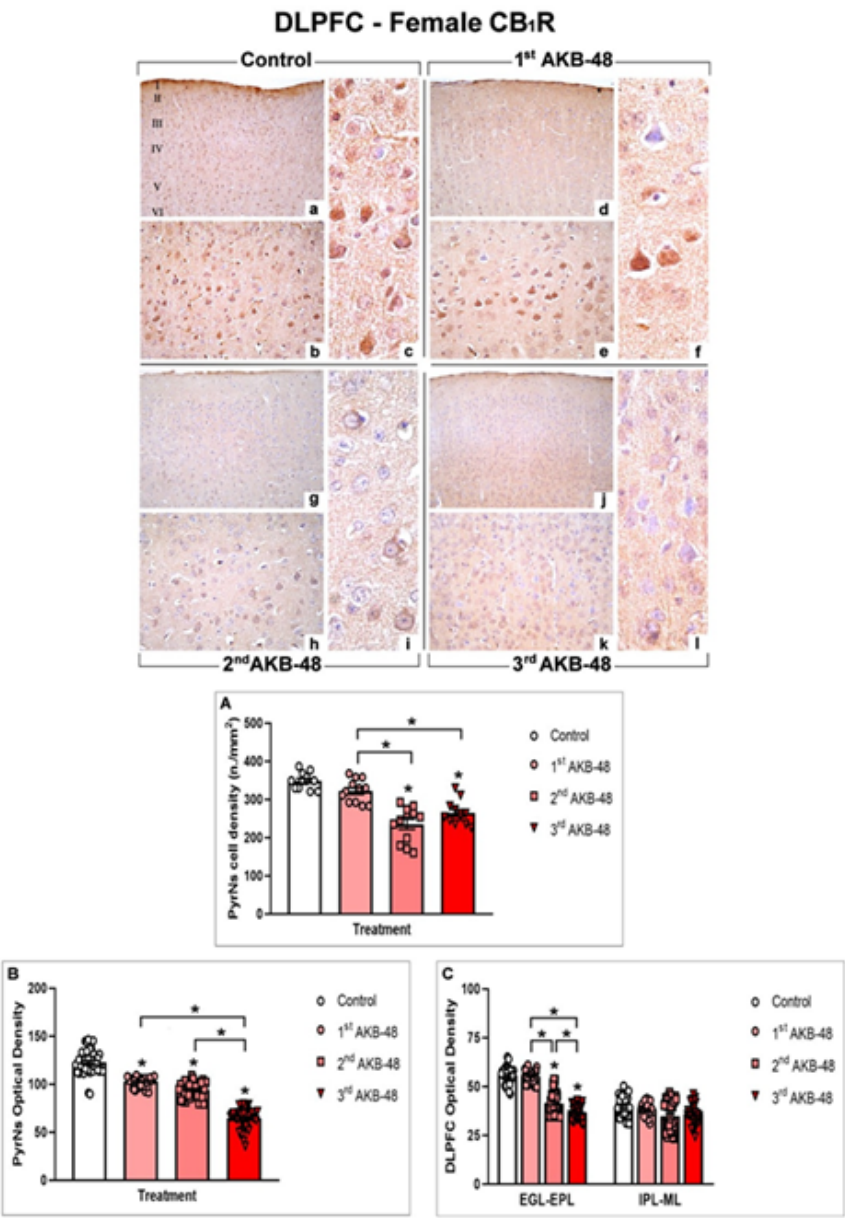
Corli et al. 2023 - 07.09.2023.docx available at <https://authorea.com/users/660826/articles/664172-sex-specific-behavioural-metabolic-and-immunohistochemical-changes-after-repeated-administration-of-the-synthetic-cannabinoid-akb48-in-mice>











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