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The Role of Peroxiredoxin 6 (PRDX6) in Cannabinoid-Induced Antinociception

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Cannabinoid-based therapies potentially offer a safer, non-opioid alternative for the management of chronic pain, but tolerance to cannabinoids like delta-9-tetrahydrocannabinol (Δ^9-THC) may limit their therapeutic utility. Blocking peroxiredoxin 6 (PRDX6) activation has been shown to attenuate the development of morphine tolerance, and PRDX6 activation in morphine tolerance is at least partially mediated through phosphorylation by c-Jun N-terminal kinase (JNK). JNK signaling has also been shown to modulate tolerance to the antinociceptive effects of cannabinoids, including Δ^9-THC and CP55,940, in an agonist-specific manner. As such, the purpose of this study was to determine whether pharmacological inhibition or genetic disruption of PRDX6 would alter Δ^9-THC- and/or CP55,940-induced antinociception and/or tolerance. The acute antinociceptive dose response effects of Δ^9-THC (0 to 100 mg/kg) or CP55,940 (0 to 1.0 mg/kg) were tested across a range of doses using the tail-flick test. The dose response effects of these cannabinoids on hypothermia was also measured. Consistent with previous findings in our lab, male mice were, overall, more sensitive to the antinociceptive effects of Δ^9-THC than female mice. Across both sexes, KO mice exhibited a decreased acute antinociceptive response to Δ^9-THC (but not CP55,940) compared to their WT counterparts. Cannabinoid-induced hypothermia did not differ as a function of genotype. Male C57Bl/6 mice pretreated with the PRDX6 antagonist, MJ33 (1.25 mg/kg) and male PRDX6 KO mice were also assessed for tolerance to Δ^9-THC-mediated antinociception and hypothermia. In contrast to our hypothesis, inhibition of PRDX6 using genetic or pharmacological approaches blunts Δ^9-THC-mediated antinociception. However, no difference in tolerance to the effects of Δ^9-THC was detected in either PRDX6 KO or MJ33-treated WT mice compared to WT or vehicle-treated WT controls. These results suggest that PRDX6 likely plays a role in modulating Δ^9-THC-induced antinociception, and future studies should examine whether these changes are mediated through JNK-dependent pathways.

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