#36: Effects of differential cannabinoid agonists on development of antinociceptive tolerance

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A major barrier to the clinical utility of cannabinoid agonists is the potential for rapid development of tolerance at therapeutic doses. Tolerance to G protein-coupled receptor (GPCR) agonists, including cannabinoids, has classically been thought to occur through GPCR kinases (GRK) and arrestin-mediated receptor desensitization and down-regulation. We have previously shown that tolerance to Δ9-THC occurs in part via desensitization of the cannabinoid receptor 1 (CB1). Mice expressing a desensitization-resistant form of the CB1 receptor (S426A/S430A) exhibit delayed tolerance to the antinociceptive effects of Δ9-THC. However, in contrast with many synthetic cannabinoid agonists, Δ9-THC is a strongly desensitizing, weakly internalizing, partial agonist for CB1. Therefore, the purpose of this study was to investigate the extent to which tolerance for strongly internalizing full CB1 agonists CP55,940 and WIN55,212-2 were also mediated by this mechanism. Tolerance to the antinociceptive, cataleptic, and hypothermic effects of daily 30 mg/kg Δ9-THC, 0.3 mg/kg CP55,940, and 10 mg/kg WIN55,212-2 was assessed in wild type and S426A/S430A desensitization-resistant mutant mice. Mice were also assessed for tolerance to Δ9-THC, CP55,940, and WIN55,212-2 via shifts in the cumulative dose responses curves following seven days of once daily treatment with each agonist. Antinociceptive tolerance to CP55,940 was modest in both wild type and S426A/S430A mice, while tolerance to 10 mg/kg WIN55,212-2 was partially prevented in desensitization-resistant mice. Although S426A/S430A mice demonstrated significant tolerance to the antinociceptive effects of 30 mg/kg Δ9-THC, this tolerance was reduced compared to wild type mice. Our results demonstrate that different mechanisms may mediate tolerance to various cannabinoid agonists acting at CB1. In particular, our results suggest that while GRK and arrestin-mediated signaling may be partially involved in tolerance to the antinociceptive effects of all three agonists it is the most crucial for tolerance to WIN55,212-2. These studies explore the differences in agonist-specific effects in cannabinoid tolerance and offer potential avenues to better understand development of tolerance to their antinociceptive effects on acute pain.