Neuropharmacology. 2011 Sep;61(4):778-88. doi: 10.1016/j.neuropharm.2011.05.024. E[illegible]

Cannabinoid receptor antagonists AM251 and AM630 activate TRPA1 in sensory neurons.

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Author information

Abstract

Cannabinoid receptor antagonists have been utilized extensively in vivo as well as in vitro, but their selectivity has not been fully examined. We investigated activation of sensory neurons by two cannabinoid antagonists - AM251 and AM630. AM251 and AM630 activated trigeminal (TG) sensory neurons in a concentration-dependent fashion (threshold 1 μM). AM251 and AM630 responses are mediated by the TRPA1 channel in a majority (90-95%) of small-to-medium TG sensory neurons. AM630 (1-100 μM), but not AM251, was a significantly more potent agonist in cells co-expressing both TRPA1 and TRPV1 channels. We next evaluated AM630 and AM251 effects on TRPV1- and TRPA1-mediated responses in TG neurons. Capsaicin (CAP) effects were inhibited by pre-treatment with AM630, but not AM251. Mustard oil (MO) and WIN55,212-2 (WIN) TRPA1 mediated responses were also inhibited by pre-treatment with AM630, but not AM251 (25 uM each). Co-treatment of neurons with WIN and either AM630 or AM251 had opposite effects: AM630 sensitized WIN responses, whereas AM251 inhibited WIN responses. WIN-induced inhibition of CAP responses in sensory neurons was reversed by AM630 pre-treatment and AM251 co-treatment (25 μM each), as these conditions inhibit WIN responses. Hindpaw injections of AM630 and AM251 did not produce nocifensive behaviors. However, both compounds modulated CAP-induced thermal hyperalgesia in wild-type mice and rats, but not TRPA1 null-mutant mice. AMs also partially regulate WIN inhibition of CAP-induced thermal hyperalgesia in a TRPA1-dependent fashion. In summary, these findings demonstrate alternative targets for the cannabinoid antagonists, AM251 and AM630, in peripheral antihyperalgesia which involve certain TRP channels.

PMID: 21645531 PMCID: PMC3130079 DOI: 10.1016/j.neuropharm.2011.05.024

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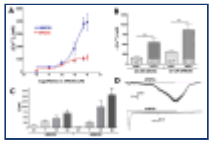
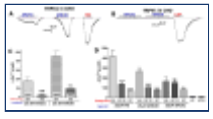
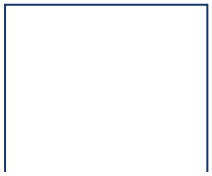
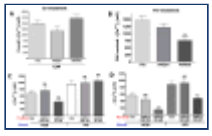
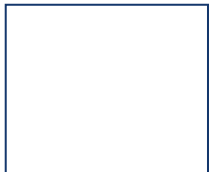

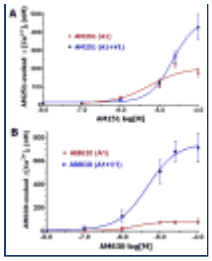

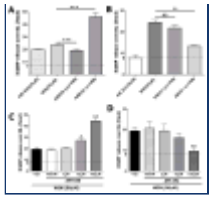

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