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Molecular, Genetic and Pharmacological approaches to elucidate mechanisms underlying Cannabinoids-induced analgesia and analgesic tolerance.

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The results of this study can be summarized as follows-

1. We have generated transgenic mouse line (SNS-Cre) which expresses Cre recombinase selectively in sensory ganglia using promoter elements of the Nav1.8 gene. Cre mediated recombination is evident in all nociceptive and thermo-receptive neurons of the dorsal root ganglia and trigeminal ganglia, but only in a small proportion of proprioceptive neurons. Cre-mediated recombination was not detectable in the brain, spinal cord, or any non-neural tissues and began perinatally after invasion of primary afferents into the developing spinal cord. Thus, these mice enable selective deletion of pain-related genes in subsets of sensory neurons in DRG.

2. Using SNS-Cre mice we have conditionally deleted CB_1 specifically in primary nociceptive neurons. By performing behavioral, electrophysiological and pharmacological analyses in preclinical models of inflammatory pain and neuropathic pain, we observed that a nociceptor-specific loss of CB_1 precludes an unexpectedly large proportion of analgesia mediated by cannabinoids. Our data show that peripheral CB_1 functions as a key mediator of the physiological as well as therapeutic actions of cannabinoids.

3. CB_1 interacts physically with the lysosomal sorting protein, GASP at its C-terminus. Interfering with CB_1-GASP interaction in HEK cells using a dominant-

negative form of GASP (cGASP) promoted surface recycling of internalized CB_1 in HEK293 cells after agonist-induced internalization.