Cannabinoids suppress inflammatory and neuropathic pain by targeting ?3 glycine receptors

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Certain types of nonpsychoactive cannabinoids can potentiate glycine receptors (GlyRs), an important target for nociceptive regulation at the spinal level. However, little is known about the potential and mechanism of glycinergic cannabinoids for chronic pain treatment. We report that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the ?3 GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors nor with their psychoactive side effects. NMR analysis reveals a direct interaction between CBD and S296 in the third transmembrane domain of purified ?3 GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking the ?3 GlyRs. Our findings suggest that the ?3 GlyRs mediate glycinergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction.