Endocannabinoid-based drugs for pain control

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The major psychoactive constituent of cannabis, D^9-tetrahydrocannabinol, influences pain in laboratory animals and humans by activating cannabinoid receptors in the brain and peripheral tissues. The two primary endogenous ligands for these receptors are the lipid-derived transmitters, anandamide and 2-arachidonoylglycerol (2-AG). Anandamide and 2-AG are released in select regions of the brain and throughout the periphery of the body, and are deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. Anandamide hydrolysis is catalyzed by fatty-acid amide hydrolase (FAAH), while 2-AG hydrolysis is primarily mediated by monoacylglycerol lipase (MGL). In my talk, I will describe the pharmacological properties of a new drug class that selectively interferes with anandamide deactivation in peripheral tissues. Despite their inability to access brain and spinal cord, these compounds attenuate behavioral responses indicative of persistent pain in rodent models of peripheral nerve injury and inflammation, and prevent noxious stimulus-evoked neuronal activation in spinal cord regions implicated in nociceptive processing. CB_1 cannabinoid receptor blockade prevents these effects. The results suggest that anandamide-mediated signaling at peripheral CB_1 receptors controls the access of pain-related inputs to the CNS. Brain-impenetrant FAAH inhibitors, which strengthen this gating mechanism, might offer a new approach to pain therapy.