

High time for cannabinoids. Dr Mike Lee (Cambridge)

The medicinal use of cannabis has endured over millennia. Clinical interest in cannabis-based medicines is renewed by the recent discovery of cannabinoid receptors, and pain is a key therapeutic target. The cannabinoid-1 (CB-1) receptor is mainly expressed in neurons. CB-1 receptors have a characteristic distribution within the central nervous system that accounts for the pharmacology of cannabis. Numerous studies in other species demonstrate that CB-1 receptor agonism produces analgesia. CB-1 agonists appear to be more potent in inflammatory or neuropathic pain models, and unlike opioids, tolerance to cannabinoid analgesia does not seem to occur. Nonetheless, the psycho-trophic effects of CB-1 agonists on the brain limit their clinical efficacy in humans. Long-term cannabis use is associated with schizophrenia. As such, the use of cannabis-based drugs for chronic pain remains controversial. Pharmaceuticals now turn to the development of cannabinoids that target cannabinoid-2 (CB-2) receptors. CB-2 receptors are expressed by non-neural tissue, primarily in epithelial and immune cells. Preclinical data suggest that selective CB-2 receptor agonists may produce relief from neuropathic pain by suppressing neuro-inflammation.

While targeting CB-2 receptors for chronic pain is promising, the impact of prolonged exposure of the immune system to potent CB-2 receptor agonists is unknown in humans. Furthermore, the central effects of cannabis may be important to the relief of otherwise intractable pain. Cannabis is particularly efficacious for the relief of pain associated with incurable disease, for example in patients with multiple sclerosis and HIV neuropathy. The analgesic efficacy of cannabis in these patients is remarkable when one considers how refractory their pain can be to conventional analgesics. The neural bases for such analgesia are unclear, though converging evidence suggests that cannabis may target the affective aspects of pain. As yet unpublished data from neuro-imaging in humans, suggest that cannabinoid analgesia can be explained by central activity, and may involve a functional uncoupling of sensory-limbic systems that mediate the experience of pain. However, there is considerable inter-individual variation in analgesic response. The fear of pain trait and amygdala reactivity may be predictors of cannabinoid analgesia, which merit further investigation.