Commentary on "Cannabinoids Modulate Pain by Multiple Mechanisms of Action"

Susan J. Ward

Richardson provides a delightfully comprehensive review of the literature addressing the putative role(s) of cannabinoid systems in modulating pain. She argues crisply and convincingly that cannabinoids can affect nociceptive responding, at least to some stimuli, via distinct peripheral, spinal, and supraspinal mechanisms, and her foray into the relative roles of peripheral CB_1 and CB_2 receptors in modulating different types of nociceptive thresholds is laudable. The breadth of Dr. Richardson's review on a complex topic is very valuable, but given such scope, a graphic representation of the principle mechanisms would be a helpful enhancement.

Importantly, Dr. Richardson's bottom line is focused on the patient and the benefits that cannabinoid drugs could potentially bring to patients in pain. Three distinct types of drugs interacting with the cannabinoid system are implied: (1) A peripherally selective cannabinoid agonist, (2) an inhibitor of endogenous cannabinoid clearance mechanism(s), and (3) a low-dose CNS/PNS cannabinoid agonist administered in combination with morphine.

Discovery and development of new drugs is an expensive proposition, with costs averaging up to $300 million to bring a New Chemical Entity (NCE) to the marketplace.[1] Data that validate the importance of a molecular target in mediating the clinical condition to be treated are typically key to the decision to invest in a new program and are at the heart of Dr. Richardson's review. The following points may be made:

Peripheral Analgesia

Although the relative importance of CB_1 and CB_2 receptors is less clear, Dr. Richardson makes a compelling case that activation of cannabinoid system(s) in the periphery can attenuate nociceptive responding. To project potential benefits to patients, Dr. Richardson might have compared efficacy of cannabinoid agonists in models assessing activity in the periphery with the efficacy of opioids acting at peripheral sites. Like cannabinoids, μ and κ receptors are located on primary afferent neurones and are antihyperalgesic.[2-4] Although the comparisons are not direct, the data suggest a similar profile of action of opioids and cannabinoid in the periphery, with both types of agents demonstrating a high level of efficacy against inflammatory stimuli.[3-7] Local administration of morphine into the joint has shown efficacy against postoperative and osteoarthritis pain in the clinic,[8,9] and ADL-2-1294, a peripherally acting opioid, is effective against inflammatory hyperalgesia.[10] Dr. Richardson could speculate on whether the clinical analgesic benefits of a peripherally acting cannabinoid may be similar or different from those of a peripherally acting opioid.

Endogenous Cannabinoid Tone

Dr. Richardson proposes that drugs that enhance endogenous cannabinoid activity by preventing uptake or metabolism of endogenous cannabinoids would be analgesic. This approach is attractive, especially if cannabinoid tone is selectively enhanced in pain states because, in principle, such drugs should have a wider therapeutic index versus typical cannabinoid side effects than would a cannabinoid receptor agonist.

The proposal is predicated entirely on the existence of a tonic modulation of nociceptive thresholds by cannabinoids. Dr. Richardson's conclusion that there is a tonic modulation of nociceptive thresholds by endogenous cannabinoids is muddied by the pharmacological tools used in the studies cited. Although Dr. Richardson points out that SR 141716 and SR 144528 have been shown to have inverse agonist actions,[11,12] "for

From Wyeth-Ayerst Research, Radnor, PA.

Address reprint requests to Susan J. Ward, PhD, Wyeth-Ayerst Research, 145 King of Prussia Rd, Radnor, PA 19087.

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the sake of simplicity" the importance of these observations to interpretation of data using these tools is glossed over by referring to these agents simply as "antagonists." The importance of understanding the precise mechanism of action of the SR compounds should not be underestimated. One cannot conclude that the actions of various agonists are mediated by a specific receptor, if the "antagonist" on which the conclusions are based is in fact acting as an inverse agonist. Unlike a competitive receptor antagonist, an inverse agonist can theoretically provide "physiological" antagonism.[13]

Corroborative data, perhaps using imaging techniques, that show endogenous activation of cannabinoid systems during pain states, especially in humans, will be key to predicting the viability of drugs that could potentiate the cannabinoid system.

Potentiation of Opioid Analgesia

Dr. Richardson observes that the ability of subantinociceptive doses of Δ^9-THC to potentiate the antinociceptive actions of morphine could lead to new treatment in which side effects of both cannabinoids and opioids are avoided without sacrificing analgesic benefit to the patient. Given the differences in the spectra of side effects of cannabinoids and μ opioids, such a conclusion seems reasonable, with one important exception. Morphine-dependent mice have shown cross-tolerance to Δ^9-THC[14] and, although the acute effects of morphine and the development of morphine tolerance was unaffected in CB_1 knockout mice, the reinforcing properties of morphine and the severity of the morphine withdrawal syndrome were significantly reduced in these animals.[15] In light of these observations, and the proposed interaction of cannabinoids and opioids in reward systems associated with the development of opioid dependence,[16,17] it is not obvious that it would be feasible to dissociate abuse potential from analgesic benefit of morphine through the introduction of subanalgesic doses of a cannabinoid. Because patients in pain do not typically abuse opioid medication,[18-21] the potential inability to dissociate analgesic and dependence potential may pose more of a political than a medical problem in treating patients in pain.

Summary

Dr. Richardson's stimulating review should help spur investigations to address remaining unanswered questions and promote the much-needed political debate on the medicinal value of cannabinoids, without which pharmaceutical development of cannabinoid drugs will continue to be hampered.

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