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This section, edited by Michael C. Rowbotham, MD, and Annika Malmberg, PhD, presents timely topics in pain research and treatment.

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# Basic Mechanisms of Cannabinoid-Induced Analgesia

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The identification of cannabinoid receptors and the discovery of endogenous cannabinoids ushered in a new era of research on the biological effects of cannabis-like compounds. These advances, coupled with the ever-present need for safe, reliable pain-relieving compounds, have re-ignited interest in the cannabinoid receptor system as it relates to the transmission and modulation of pain. There is now unequivocal evidence that cannabinoids are antinociceptive in animal models of acute pain. Recent studies suggest that endogenous cannabinoids come into play under conditions of injury and contribute to the control of pain.

## Historical Notes on Cannabis and Pain

Cannabis has been used for recreational and medicinal purposes throughout the world for many centuries. The co-evolution of these two uses forms the basis for the current debates on the benefits of "marijuana as medicine." At the center of these debates is the notion that analgesia is a possible indication for cannabinoids, as recently reviewed in a report by the Institute of Medicine (Joy et al. 1999). In 1839, W.B. O'Shaughnessy introduced cannabis to the Western medical establishment in a detailed article on its medicinal applications. After extensive investigations of this drug in both humans and animals, he concluded that it was effective in relieving several clinical conditions including, but not limited to, pain. Some 50 years later, this sentiment was echoed by an American professor of medicine, Hobart Hare, who wrote in his textbook that "cannabis is very valuable for the relief of pain, particularly that depending on nerve disturbances" (Hare and Chrystie 1892). Horatio Wood, a contemporary of Hare, wrote in his *Treatise on Therapeutics* that "cannabis is used chiefly for the relief of pain; especially of neuralgic character, although it will palliate even pain of organic origin" (Wood 1886). Perhaps one of the most revealing testimonials on the clinical attributes of cannabis came from a British physician to the Queen, J. Russell Reynolds, who made note of its unique pain-relieving properties by saying: "In almost all of painful maladies I have found Indian hemp by far the most useful of drugs" (Reynolds 1890).

## Cannabinoid Pharmacology

While these and other testimonials on the analgesic effects of cannabis are of historical interest, they provide little insight into the actions of cannabinoids on the nervous system. Cannabinoid receptors belong to the superfamily of G-protein-coupled receptors and possess all of the characteristics typical for this class of receptors (Howlett 1995). Cannabinoid receptors are activated by endogenous agonists, by active constituents of *Cannabis sativa*, and by synthetic cannabinoid agonists. Activation of cannabinoid receptors leads to an inhibition of adenylate cyclase, decreased production of cyclic adenosine monophosphate (cAMP) (Childers and Deadwyler 1996), and the modulation of ion channel activity. At the cellular level, cannabinoids hyperpolarize neurons by closing voltage-dependent calcium channels (Twitchell et al. 1997) and by activating potassium channels (Mackie et al. 1995).

Two cannabinoid receptor subtypes, CB1 and CB2, have been identified (Matsuda et al. 1990; Munro et al. 1993). These receptors are distinct in their anatomical distribution as well as in their binding profile for both agonists (endogenous) and antagonists. CB1 receptors are primarily found in brain regions associated with the behavioral effects of cannabinoids, such as the hippocampus, amygdala, cortex, basal ganglia, and cerebellum (Herkenham et al. 1991; Tsou et al. 1998). This distribution pattern accounts for the effects of cannabinoids on memory, emotion, cognition, and movement. Furthermore, elevated levels of CB1 receptors, like opioid receptors, are found in areas that modulate nociceptive processing, including the periaqueductal gray (PAG) and the dorsal horn of the spinal cord (Tsou et al. 1998; Hohmann et al. 1999). However, unlike opioid receptors, CB1 receptors are relatively sparse in the brainstem, which may explain the lack of respiratory depression associated with these compounds. In contrast to CB1 receptors, CB2 receptors are not found in the central nervous system (CNS), but are primarily distributed in peripheral tissues (Pertwee 1997).

Thus far, research on endogenous cannabinoids has focused on three ligands. Anandamide, which was the first and most thoroughly studied ligand, displays modest selectivity for CB1 receptors. 2-Arachidonylglycerol (2-AG), originally identified in intestinal tissue, is found at 170-fold higher levels than anandamide in the brain (Mechoulam et al. 1998). Finally, palmitoylethanolamide (PEA) has been identified as a putative ligand for the CB2 receptor (Facci et al. 1995). Although this characterization remains somewhat preliminary, it does not appear that 2-AG signals via CB1 receptors. In general, cannabinoid agonists, both natural and synthetic, exhibit little receptor selectivity for CB1 versus CB2 receptors. Therefore, the strongest pharmacological distinction between the subtypes is by antagonist activity. The antagonist SR141716A is believed to be CB1 selective, whereas SR144528 shows greater selectivity for CB2 (see Table 1 for summary). Two recent reviews describe the pharmacology of cannabinoids in detail (Pertwee 1997; Ameri 1999).

**Table 1. Characteristics of cannabinoid receptors**

| Characteristic | CB1 | CB2 |
|---|---|---|
| Cloned and G-protein coupled | Yes | Yes |
| Location | CNS/periphery | Periphery |
| Cell type | Neuronal | Non-neuronal |
| Adenylate cyclase | Inhibit | Inhibit |
| MAP* kinase | Activate | ?? |

| | | |
|---|---|---|
| Voltage-sensitive calcium channel conductance | Inhibit | No/?? |
| Potassium channel conductance | Enhance | No/?? |
| Endogenous agonists | Anandamide, 2-AG | Palmitoylethanolamide (PEA), 2-AG? |
| Agonists | WIN55,212-2, D -9-THC, CP55,940, HU210 | WIN55,212-2, D-9-THC, CP55,940, HU210 (modest) |
| Antagonists | SR141716A | SR144528 |
| * MAP = mitogen-activated protein kinase.<br><br>*Note:* See Pertwee (1997), Hirst et al. (1998), and Ameri (1999) and references therein for detailed discussion. | | |

### Acute Pain

For many years, cannabinoids have been shown to inhibit behavioral responses to noxious stimuli pain (reviewed by Martin and Lichtman 1998; Walker et al. 1999). However, the effects of cannabinoids on motor systems have called into question whether or not the decreased behavioral responses in tail-flick and hot-plate tests were attributable to the antinociceptive actions of these compounds or were merely the result of motor impairment. Anatomical specificity of cannabinoid-induced antinociception at spinal (Lichtman and Martin 1991a) and supraspinal levels (Lichtman and Martin 1991b; Martin et al. 1993, 1999) suggests that the analgesic effects of these compounds are distinct from their motor effects. For example, direct injections of cannabinoid agonists into specific brain regions, including the PAG (Martin et al. 1995; Lichtman et al. 1996) and rostral ventromedial medulla (RVM) (Martin et al. 1998), inhibit the tail-flick reflex, whereas injections outside pain-modulatory areas do not (Martin et al. 1995; Lichtman et al. 1996).

Electrophysiological studies confirm that the antinociceptive actions of cannabinoids are produced by the specific modulation of nociresponsive neurons. For example, WIN55,212-2, a potent synthetic cannabinoid agonist (62.5–250 mg/kg, i.v.), inhibits activity evoked by noxious stimuli in wide-dynamic-range (WDR) neurons in the spinal dorsal horn (Hohmann et al. 1995, 1998) and in the ventroposterolateral (VPL) nucleus of the thalamus (Martin et al. 1996), but has no effect on mechanoreceptive neurons. Furthermore, the absence of stimulus intensity encoding by WDR neurons in the VPL is highly correlated with behavioral measures of analgesia, but not with motor impairment. In addition, WIN55,212-2 modulates neuronal activity of nociresponsive neurons in the RVM, and these effects correlate with cannabinoid-induced analgesia (Meng et al. 1998). Moreover, inactivation of the RVM abolishes the analgesia (but not the motor impairment) produced by systemic WIN55,212-2. Importantly, the effects of cannabinoids within this important pain-modulatory brainstem circuit are similar to, but distinct, from those of morphine. First, the effects of WIN55,212-2 on RVM neurons are not antagonized by naloxone (Meng et al. 1998). Second, cannabinoids inhibit only presynaptic GABAergic neurotransmission in the RVM, whereas opioids exhibit both pre- and postsynaptic inhibitory actions (Vaughan et al. 1999). These findings indicate that cannabinoids inhibit acute pain processing through actions on nociresponsive neurons within distinct pain transmission and modulatory circuits.

**Persistent Pain**

Recent electrophysiological and behavioral evidence suggests that in addition to their effects on acute pain, cannabinoids may be important in modulating persistent pain. WIN55,212-2 inhibits the activity-dependent facilitation ("wind-up") of nociresponsive neurons in the spinal cord at doses (250 mg/kg, i.v.) that have no effect on baseline C-fiber responses (Strangman and Walker 1999). This effect on spinal cord excitability contrasts with that of morphine, which only inhibits wind-up at doses that reduce the initial C-fiber response (Dickenson and Sullivan 1987). Consistent with these effects, cannabinoids block capsaicin-induced nocifensive behaviors and inhibit thermal and mechanical hyperalgesia in rats. Low doses of WIN55,212-2 (10–200 mg, i.v.) significantly reduce the time spent guarding and lifting the injected paw, and eliminate these behaviors at the highest dose. Moreover, WIN55,212-2 blocks the development of thermal and mechanical hyperalgesia in the capsaicin-injected paw, but does not affect responses in the contralateral paw (Li et al. 1999).

Cannabinoids are also efficacious in other persistent pain models. Delta-9-tetrahydrocannabinol (THC), the primary active component of marijuana, inhibits behavioral responses to formalin injection (Moss and Johnson 1980). Moreover, systemic administration of WIN55,212-2 (5 and 10 mg/kg, i.p.) reduces formalin-induced nociresponsive behavior and selectively inhibits immediate early gene (c-*fos*) expression in the superficial (I, II) and deep (V, VI) laminae of the spinal cord dorsal horn (Tsou et al. 1996). In addition to the analgesic effects of natural and synthetic cannabinoid agonists, the endogenous agonists anandamide (5–25 mg/kg, i.p.) and PEA (5–10 mg/kg, i.p.) significantly reduced second-phase pain behavior in the formalin test (Jaggar et al. 1998a).

Cannabinoids also attenuate inflammation-induced behavioral hypersensitivity. In the carrageenan model of inflammation, anandamide dose-dependently reversed thermal hyperalgesia at doses that lack antinociceptive activity (Richardson et al. 1998a). In rats treated with complete Freund's adjuvant (CFA), THC and anandamide raised mechanical thresholds in a paw-pressure test (Smith et al. 1998), and WIN55,212-2 reversed mechanical allodynia without producing analgesia (Martin et al. 1999). In a model of neuropathic pain, WIN55,212-2 (2.14 mg/kg, i.p.) reversed mechanical allodynia as well as pinprick, cold, and thermal hyperalgesia associated with chronic constriction of the sciatic nerve (Herzberg et al. 1997). The cannabinoid agonist normalizes nociceptive thresholds on the injured side without altering thresholds contralateral to the injury. Also, administration of a CB1-receptor antagonist exacerbated the hyperalgesia and mechanical allodynia by lowering response thresholds on the injured, but not the contralateral side. Finally, both anandamide and PEA blocked the hyperalgesia associated with inflammation of the rat urinary bladder (Jaggar et al. 1998a, 1998b). In summary, cannabinoids demonstrate anti-hyperalgesia and/or anti-allodynia in formalin, capsaicin, carrageenan, adjuvant, nerve injury, and visceral models of persistent pain.

**Sites/Mechanisms of Action**

The mechanisms by which cannabinoids produce their anti-hyperalgesic and anti-allodynic effects are not fully known. Cannabinoid receptors have been localized in the spinal cord (Herkenham et al. 1991; Tsou et al. 1998; Hohmann et al. 1999). In addition, there is evidence that CB1 receptors are present in small neurons that express TrkA (Friedel et al. 1997) and in neurons that express substance P or calcitonin gene-related peptide (CGRP) in the dorsal root ganglia (Hohmann and Herkenham 1999b), from where they are transported to central and peripheral terminals (Hohmann and

Herkenham 1999a). The bidirectional transport of CB1 receptors raises the question as to whether the modulation of persistent pain by cannabinoids is centrally or peripherally mediated.

Spinal administration of anandamide reverses carrageenan-induced thermal hyperalgesia and also inhibits capsaicin-evoked, but not basal, release of CGRP from isolated rat spinal cord (Richardson et al. 1998a). In addition, WIN55,212-2 (10 mg, i.t.) restores mechanical thresholds in the CFA-inflamed paw to pre-inflammation levels (i.e., normalized nociceptive thresholds), without altering the response to mechanical stimuli in the non-inflamed paw or in control animals (Martin et al. 1999). These anti-hyperalgesic and anti-allodynic effects are blocked by spinal co-administration of the CB1-preferring antagonist, SR141716A. Thus, cannabinoids may influence nociceptive thresholds after injury by acting through spinal CB1 receptors to modulate neuropeptide release from capsaicin-sensitive primary afferent terminals. However, since dorsal rhizotomy does not completely eliminate binding to CB1 receptors in the dorsal horn (Hohmann et al. 1999), is also likely that cannabinoids act postsynaptically to modulate spinal cord activity.

In addition to their central effects, cannabinoids also inhibit pain at the site of injury. In non-human primates, THC reverses the thermal allodynia produced by injection of capsaicin into the tail (Ko and Woods 1999). Local administration of anandamide (or a more stable analog) into the paw reduces carrageenan-induced thermal hyperalgesia, edema, and capsaicin-induced plasma extravasation (Richardson et al. 1998c) as well as formalin-induced behavior (Calignano et al. 1998). These effects are reversed by local injection of SR141716A (Richardson et al. 1998c). Thus, both natural and endogenous cannabinoids can inhibit hyperalgesia and neurogenic inflammation via actions at CB1 receptors in the periphery.

Interestingly, the anti-inflammatory and anti-hyperalgesic actions of cannabinoids in the periphery may not be limited to actions at CB1 receptors. There is also evidence that cannabinoids act on CB2 receptors located on mast cells (Facci et al. 1995) to directly attenuate the release of inflammatory agents (i.e., histamine and serotonin). In support of this notion, Mazzari and colleagues (1996) have shown that PEA attenuates carrageenan-induced mechanical hyperalgesia and edema by down-modulating mast cell formation induced by tissue injury.

**Endogenous Cannabinoids and Pain Modulation**

The localization of endogenous cannabinoids in brain and peripheral tissues as well as the identification of mechanisms for their synthesis, transport, release, and re-uptake/degradation provide strong evidence that these molecules signal through cannabinoid receptors to modulate biological activity. The analgesic effects produced by endogenous cannabinoids suggest that these compounds contribute to the modulation of pain (Fride and Mechoulam 1993; Smith et al. 1994; Calignano et al. 1998; Jaggar et al. 1998a,b). But perhaps more intriguing are the studies in which blockade, or downregulation, of cannabinoid receptors enhances behavioral responses to either acute or persistent noxious stimuli. For example, administration of CB1 or CB2 antagonists enhances formalin-induced pain behavior (Strangman et al. 1998; Calignano et al. 1998). Furthermore, spinal administration of SR141716A (Richardson et al. 1997) or reduction of the number of CB1 receptors by antisense treatment (Richardson et al. 1998b) can lower nociceptive thresholds to noxious thermal stimuli.

Consistent with the pain-modulatory effects of endogenous cannabinoids, anandamide modulates thermal nociceptive thresholds more effectively in the presence of carrageenan-induced inflammation (Richardson et al. 1998a). In addition, spinal

administration of SR141716A, which does not affect mechanical thresholds of non-inflamed animals, significantly reduced mechanical thresholds in the paw contralateral to the inflammation. Finally, blockade of spinal CB1 receptors evokes a different pattern of c-*fos* expression in the presence versus the absence of peripheral inflammation. In normal animals, spinal administration of the CB1-receptor antagonist significantly increased c-*fos* expression in laminae V–VI in the dorsal horn and in the ventral horn. This differential effect of the CB1 antagonist suggests that tissue injury modifies cannabinoid activity in the spinal cord. Taken together, these results indicate (1) that endogenous cannabinoids modulate acute nociceptive processing, (2) that this system is tonically active, and (3) that the activity of the cannabinoid receptor system increases after injury. If this is indeed the case, then the decreased nociceptive threshold that occurs in the setting of injury may partly be due to *loss* of a tonic cannabinoid activity. Thus, administration of exogenous cannabinoids could restore the tone of the system and presumably could alleviate the allodynia and pain that are triggered by injury.

## Conclusion

While the antinociceptive actions of cannabinoids are well established, their potential therapeutic use continues to be limited by their side-effect profile. Clearly, the development and use of novel cannabinoid compounds for the relief of pain in humans will hinge on the ability to dissociate psychotropic effects from therapeutic ones. One strategy to meet this need is the development of potent CB2-selective agonists whose actions would be limited to the periphery; such compounds would be devoid of psychoactive properties. While the inhibition of some forms of pain by CB2 agonists remains a distinct possibility, actions at the CB1 receptor will be required to demonstrate efficacy across a broad range of pain conditions. Toward this end, the anti-allodynic and anti-hyperalgesic actions of cannabinoids at non-analgesic doses is encouraging. If cannabinoids can restore nociceptive thresholds to pre-injury levels at low doses, then therapeutic efficacy could be attained within a dose range in which undesirable side-effects are absent. Ultimately, the development of clinically effective cannabinoids will rely as much as on the overturning of sociopolitical biases as it will on scientific advances in our understanding of this receptor system.

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