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Current Topics

## Synergistic interactions between cannabinoid and opioid analgesics

Diana L. Cichewicz\*

*Department of Pharmacology and Toxicology, Virginia Commonwealth University, PO Box 980524, Richmond, VA 23298, USA*

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### Abstract

Cannabinoids and opioids both produce analgesia through a G-protein-coupled mechanism that blocks the release of pain-propagating neurotransmitters in the brain and spinal cord. However, high doses of these drugs, which may be required to treat chronic, severe pain, are accompanied by undesirable side effects. Thus, a search for a better analgesic strategy led to the discovery that delta 9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, enhances the potency of opioids such as morphine in animal models. In addition, studies have determined that the analgesic effect of THC is, at least in part, mediated through delta and kappa opioid receptors, indicating an intimate connection between cannabinoid and opioid signaling pathways in the modulation of pain perception. A host of behavioral and molecular experiments have been performed to elucidate the role of opioid receptors in cannabinoid-induced analgesia, and some of these findings are presented below. The aim of such studies is to develop a novel analgesic regimen using low dose combinations of cannabinoids and opioids to effectively treat acute and chronic pain, especially pain that may be resistant to opioids alone.

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### Introduction

It is widely known that opioids and cannabinoids share several pharmacological effects, including antinociception, hypothermia, inhibition of locomotor activity, hypotension and sedation (Manzanes et al., 1999; Massi et al., 2001). Opioids such as morphine are commonly prescribed analgesics for chronic or persistent pain, but the analgesic benefits of cannabinoids such as delta 9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, have not been well explored in

\* Tel.: +1-804-828-3678; fax: +1-804-828-1532.

*E-mail address:* [dcichewi@hsc.vcu.edu](mailto:dcichewi@hsc.vcu.edu) (D.L. Cichewicz).

humans, aside from anecdotal reports. Early studies indicated that oral doses of THC were no more effective than codeine for pain, and produced a significant amount of dysphoric side effects (Noyes et al., 1975; Campbell et al., 2001). Thus it was believed that THC could only produce analgesia at doses that were high enough to cause other behavioral side effects. However, THC and other synthetic cannabinoid compounds have proven to demonstrate potent analgesic effects up to 10 times that of morphine in animal models of acute and neuropathic pain via parenteral or systemic administration (Johnson et al., 1981; Lichtman and Martin, 1997; Fuentes et al., 1999; Fox et al., 2001). The first evidence that the antinociceptive effects of THC could be separated from its adverse behavioral effects was published in 1994, when Smith and colleagues demonstrated that a kappa opioid receptor antagonist, nor-binaltorphimine (norBNI), blocked only the antinociceptive effect of THC in rodents with no effect on hypothermia, hypoactivity or catalepsy (Smith et al., 1994; Welch and Eades, 1999).

For many years, studies have indicated that cannabinoids can enhance the antinociceptive properties of opioids. The effects of morphine have been found to be enhanced by crude cannabis extract (Ghosh and Bhattacharya, 1979) and by orally administered  $\Delta^6$ -THC and  $\Delta^9$ -THC (Mechoulam et al., 1984). Evidence in recent years studying the synergy between opioids and cannabinoids has suggested that cross-talk between these two signaling pathways shows promise for combination pain therapy as well as novel treatments for opioid addiction and abuse. A combination of low dose analgesics devoid of undesirable side effects would be ideal to replace high dose analgesics that cause unnecessary sedation, respiratory depression and constipation.

### Enhancement studies

Spinal administration of various cannabinoids with morphine produces a greater-than-additive effect with respect to antinociception in mice as measured by the tail–flick radiant heat test (Welch and Stevens, 1992; Smith and Martin, 1992; Smith et al., 1994). THC at i.t. doses that are marginally active in the tail–flick test significantly shift the dose–response curve of morphine to the left, indicating an increase in antinociceptive potency (a 4- to 12-fold shift). Similar shifts in morphine potency are also seen with 11-hydroxy-THC,  $\Delta^8$ -THC, and levonantradol (Welch and Stevens, 1992). The enhancement of morphine by cannabinoids is not universal; studies have shown that there are two categories of cannabinoid/opioid interactions—supraspinal and spinal components. Some cannabinoids have been found to enhance morphine in the brain while others act predominantly in the spinal cord, as seen from a comparison of i.t. and i.c.v. administration (Welch et al., 1995). THC enhances the effects of morphine in the spinal cord, whereas the synthetic cannabinoid CP 55,940 does not enhance spinally administered morphine but shifts the morphine dose–response curve nearly 10-fold after i.c.v. administration (Welch and Stevens, 1992; Welch et al., 1995). CP 55,940 also increases morphine antinociception by about 45% when administered i.p. (Massi et al., 2001). Anandamide, an endogenous cannabinoid, does not enhance opioid antinociception, most likely due to its rapid breakdown by lipid-hydrolyzing enzymes (Pugh et al., 1996; Welch, 1997; Fowler et al., 2001).

A synergy also exists in the opposite direction; that is, morphine can enhance the antinociception induced by THC. Reche and colleagues report that an ineffective dose of morphine i.p. shifted the dose–response curve of THC i.v. to the left in a significant fashion (Reche et al., 1996). Parenteral administration of morphine and THC also increases the efficacy of morphine (Smith et al., 1998).

Table 1

ED<sub>50</sub> values (mg/kg) and potency ratios for various opioids in combination with vehicle or THC (20 mg/kg) in the tail–flick test for antinociception

Drugs	ED <sub>50</sub>		Potency ratio
	vehicle	THC	
morphine	28.8 (20.2–41)	13.1 (8.8–19.5)	2.2
codeine	139.9 (75.2–260.5)	5.9 (1.4–24.9)	25.8
oxymorphone	2.6 (1.7–3.9)	0.5 (0.3–0.8)	5.0
hydromorphone	5.6 (3.2–9.7)	0.4 (0.2–0.8)	12.6
methadone	12.0 (8.1–17.9)	2.7 (1.4–5.2)	4.1
LAAM	8.0 (6.4–10.1)	2.6 (1.7–3.9)	2.5
heroin	26.1 (12.7–53.4)	5.4 (1.7–16.9)	4.1
meperidine	86.2 (52.8–140.6)	11.1 (4.2–29.4)	8.9
fentanyl	6.1 <sup>a</sup>	0.5 (0.3–0.8)	ND <sup>b</sup>
pentazocine	625.9 <sup>a</sup>	838.6 <sup>a</sup>	ND <sup>b</sup>

Mice were injected with vehicle (1:1:18; emulphor, ethanol, saline) or THC (20 mg/kg) p.o. 10–30 min prior to p.o. opioid treatment, and tested 10–30 min later in the tail–flick test. Dose–response curves were generated for each opioid, with at least 4 doses (n=6 for each dose) per curve. ED<sub>50</sub> values and 95% confidence limits were determined along with potency ratios between opioid plus vehicle and opioid plus THC.

Reprinted from Cichewicz et al., 1999.

<sup>a</sup> Estimated ED<sub>50</sub> from an extrapolated curve.

<sup>b</sup> ND = not determined; showed no % MPE above 50%.

Altogether, these data examining the behavioral interaction between THC and morphine suggest a greater-than-additive analgesic effect when given in combination.

THC and morphine administration by any combination of routes (i.t., i.c.v., s.c., p.o.) significantly enhances the potency of morphine in mice (Smith et al., 1998). Further studies confirm that a non-antinociceptive oral dose of THC (20 mg/kg) can enhance the potency of an acute oral dose of morphine, codeine, oxycodone and other opioid analgesics (Cichewicz et al., 1999; see Table 1). Most recently, a full isobolographic evaluation of the synergy between oral THC and morphine or codeine has been published (Cichewicz and McCarthy, 2003). Using this type of evaluation, a graph is constructed which compares the effects of actual experimental dose pairs with a *line of additivity*; i.e. the line which contains all points describing the effects predicted from a solely additive relationship. The combinations of THC and morphine or codeine tested all fell below this line and thus demonstrated synergy. Isobolographic analysis provides the best evidence that two drugs produce a greater-than-additive effect because the doses are varied in the combination. Oral synergy is particularly relevant to clinical settings because of the ease of administration to patients, and thus these combinations show promise as novel drug therapies for pain.

## Endogenous opioids and opioid receptors

THC administered i.t. has been shown to release endogenous opioids which stimulate both delta and kappa opioid receptors (Welch, 1993; Smith et al., 1994; Pugh et al., 1996). This has been substantiated by the findings that dynorphin antisera and nor-BNI block THC-induced antinociception (Welch, 1993; Smith et al., 1994; Pugh et al., 1996; Reche et al., 1996). Furthermore, the discovery of a bi-directional

cross-tolerance of THC and CP 55,940 to kappa agonists in the tail–flick test (Smith et al., 1994) confirms that cannabinoids interact with kappa opioids. It is believed that the synergistic effect with THC and morphine results from the initial release of dynorphin A by THC and the subsequent breakdown of dynorphin A to smaller dynorphin fragments and leucine–enkephalin metabolites (Pugh et al., 1996; Mason et al., 1999). A time correlation between antinociception and increased dynorphin levels suggest that these endogenous opioids interact with the delta and kappa opioid receptors to mediate the antinociceptive effect of THC (Mason et al., 1999; Welch and Eades, 1999). In fact, Corchero and colleagues report that five-day treatment with THC produces increases in both prodynorphin and proenkephalin gene expression in rat spinal cord (Corchero et al., 1997), while other studies demonstrate that THC-induced analgesia is reduced in prodynorphin knockout animals (Zimmer et al., 2001). Simultaneous stimulation of the mu receptor by morphine with these other opioid receptors may account for the greater-than-additive antinociceptive effect seen with THC and morphine. Leucine–enkephalin and DPDPE, a specific delta opioid receptor agonist, both increase the analgesic potency of mu opioid receptor agonists (Vaught et al., 1982; Horan et al., 1992). In addition, others have shown a functional relationship between kappa and mu, and heterodimerization between delta and mu, suggesting a link between opioid receptors (Pan et al., 1997; Gutstein et al., 1998; Gomes et al., 2000).

Antagonist studies with cannabinoid receptors implicate the CB1 and mu receptors in the enhancement of morphine by THC. SR141716A, the CB1-specific receptor antagonist, blocks active doses of THC but has no effect on morphine alone (Smith et al., 1998), demonstrating that SR141716A selectively antagonizes THC. Furthermore, the enhanced antinociception due to a combination of a low oral dose of THC and a low oral dose of morphine is blocked by SR141716A (Smith et al., 1998). Naloxone also blocks the synergistic antinociception produced by low oral doses of THC and morphine or codeine, indicating the involvement of the mu receptor. However, oral synergy is not blocked by norBNI, contrary to what was seen in the spinal cord (Cichewicz et al., 1999). Taken together with the above spinal findings, it seems that all three of the major opioid receptor subtypes are involved in some part in the enhancement of opioids by THC, depending on route of administration.

Cannabinoid and opioid receptors are both members of the G-protein-coupled receptor family, activating pertussis toxin-sensitive  $G_i/G_o$  proteins. Recent work has examined agonist-stimulated GTP binding in both of these receptor systems, using cellular and molecular paradigms. In COS-7 cells transfected with cannabinoid and opioid receptors, a combination of these drugs failed to induce an additive increase in [ $^{35}$ S]GTP $\gamma$ S binding, suggesting that these receptors share a common pool of  $G_i/G_o$  proteins (Shapira et al., 2000). However, in neuroblastoma cells that endogenously express delta opioid and cannabinoid receptors, etorphine and desacetyllevonantradol (DALN) produce an additive stimulation of binding, indicating that the receptors draw from separate G protein pools (Shapira et al., 2000). Thus, cells which typically contain these receptors likely contain different mechanisms than those into which foreign receptors are introduced, pointing to the importance of models that accurately depict human systems. The enhancement of opioid analgesic effect by cannabinoids in rodent models suggests that the receptors involved do not share the same pool of G proteins.

Opioid and cannabinoid receptors are co-distributed in areas of the dorsal horn of the spinal cord (Welch and Stevens, 1992; Hohmann et al., 1999; Salio et al., 2001) as well as areas of the brain controlling nociceptive responses, such as the periaqueductal gray (PAG), raphe nuclei and central-medial thalamic nuclei (Mansour et al., 1988; Herkenham et al., 1991; Lichtman et al., 1996). Studies show that cannabinoids exhibit a similar binding distribution in the brain to that of morphine (Kuhar et al., 1973; Mailleux and Vanderhaeghen, 1992). Furthermore, the blockade of THC-induced Fos

immunoreactivity by naloxone in the ventral tegmental area, hypothalamus and PAG suggests that these areas are important in cannabinoid-opioid interactions (Allen et al., 2003). In fact, Meng and colleagues demonstrate that analgesia produced by cannabinoids and opioids involve similar brainstem circuitry through modulation of rostral ventromedial medulla neuronal activity (Meng et al., 1998). Thus the spinal blockade of pain transmission becomes greater-than-additive as both opioid and cannabinoid receptor types are activated in the dorsal horn. Simultaneous activation of brain receptors could then disinhibit interneurons regulating endogenous opioid release, further contributing to the antinociceptive effect.

Cannabinoid-opioid interactions not only underlie synergy in acute analgesia, but persist after chronic drug administration. Up-regulation of opioid receptor protein in the spinal cord that we observe in chronic combination-treated animals (Cichewicz et al., 2001) may underlie the retention of efficacy of the drug combination. In addition, the CB1 receptor and mu opioid receptor have been found to be co-localized in areas important for the expression of morphine abstinence—nucleus accumbens, septum, striatum, PAG and amygdaloid nucleus (Navarro et al., 2001). Thus, THC might alter the expression of morphine antinociceptive tolerance and/or dependence. After short-term treatment in mice with low doses of THC and morphine in combination, there is an avoidance of tolerance to the opioid without compromising the antinociceptive effect (Cichewicz and Welch, 2003). Chronic interactions between opioids and cannabinoids have also been examined at the cellular level. Prolonged exposure to DALN failed to result in a downregulation of delta opioid receptors in HEK-293 cells co-transfected with CB1 and delta receptors (Shapira et al., 2003). These results support behavioral data which suggest that cannabinoids like THC can alter the expression of morphine tolerance. Thus, not only does THC increase the acute analgesic effect of morphine, but may also be useful long-term to provide pain relief in opioid-tolerant subjects.

## Clinical implications

In conclusion, the research presented here marks a potential use for low doses of THC to enhance the potency of opioid drugs. The wealth of research examining endogenous opioid tone and receptor function points to the involvement of the opioid system in the analgesic effects produced by THC. THC is a schedule II drug currently marketed for oral administration as dronabinol (Marinol®), and is primarily used as an appetite stimulant in AIDS-wasting patients and as an anti-emetic for cancer chemotherapy (Nelson et al., 1994; Timpone et al., 1997; Beal et al., 1997); however, THC has not been approved for analgesic use due to lack of consistent data. Recent clinical reports support the use of cannabinoids and opioids for peripheral inflammatory pain (Sawynok, 2003) but debate the effectiveness of cannabinoids for chronic cancer-related pain due to adverse side effects (Campbell et al., 2001). However, other studies emphasize the frequency of cannabis use among chronic pain patients and provide statistics that support analgesic benefits of marijuana (Ware et al., 2003). While high doses of THC are analgesic, they can be accompanied by anxiety, headache, dry mouth, euphoria, and tachycardia. Low doses of oral THC have no analgesic effects, and in mice, no behavioral changes such as ataxia, aggressiveness or loss of righting reflex have been observed. Thus, these low doses could safely be administered in combination with opioids such as morphine without increasing detrimental side effects. Since continued administration of morphine can lead to tolerance and morphine-resistant pain, an adjunct to morphine may be the key to prolong appropriate treatment. The administration of low doses of

THC in conjunction with low doses of morphine seems to be an alternative regimen that reduces the need to escalate opioid dose while increasing opioid potency.

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