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Time course of the enhancement and restoration of the analgesic efficacy of codeine and morphine by Δ^9-tetrahydrocannabinol

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Abstract

Δ^9-tetrahydrocannabinol (Δ^9-THC) synergizes with morphine and codeine by releasing endogenous opioids. These studies determined 1) the duration of enhancement of morphine and codeine by Δ^9-THC, 2) the effect of (Δ^9-THC on the time course of fully efficacious doses of the opioids, 3) restoration of efficacy of morphine and codeine by Δ^9-THC, and 4) duration of restoration. Sub-active combination doses of Δ^9-THC/morphine or Δ^9-THC/codeine are equivalent in duration of action and efficacy to high-dose opioids alone. Δ^9-THC (20 mg/kg p.o.) significantly restores the antinociceptive effects of both high-dose morphine and codeine (100 and 200 mg/kg p.o., respectively) at later time points at which morphine or codeine was no longer active (360- and 120-min post-administration, respectively). Thus, the cannabinoid/opioid combination might be useful in therapeutics to enhance opioid activity, as well as to restore the efficacy of opioids.

Keywords: Cannabinoid; Opioid; Synergy; Enhanced antinociception

1. Introduction

The interaction of cannabinoids with opioids has been extensively reviewed (Manzaneres et al., 1999; Massi et al., 2001; Cichewicz, 2004; Vigano et al., 2005). We have shown that THC and morphine synergize in the production of antinociception (Smith et al., 1998; Cichewicz and McCarthy, 2003). Anatomical studies have reported a similar distribution of CB_1 cannabinoid and mu opioid receptors in the dorsal horn of the spinal cord (Hohmann et al., 1999; Salio et al., 2001) and in several structures within the central nervous system (CNS) (Kuhar et al., 1973). The kappa opioid receptor antagonist, nor-binaltorphimine (nor-BNI), and dynorphin antisera block Δ^9-THC-induced (i.t.) antinociception, but do not block catalepsy, hypothermia, or hypoactivity (Smith et al., 1994; Pugh et al., 1995). These findings suggest that we can enhance antinociception by opioid/Δ^9-THC interactions, but not enhance other effects of Δ^9-THC. In addition, the discovery of the bi-directional cross-tolerance of Δ^9-THC to kappa agonists in the tail-flick test (Smith et al., 1994) indicates that cannabinoids release endogenous kappa opioids. We have found that dynorphins (i.t.) are also cross-tolerant to Δ^9-THC (Welch, 1997). We have reported that Δ^9-THC releases dynorphin-A-(1–17), as well as leucine enkephalin, in the spinal cord (Mason et al., 1999a,b). The attenuation of the antinociceptive effects of Δ^9-THC by antisense to the kappa-1 receptor (Rowen et al., 1998), by the kappa opioid receptor antagonist, nor-BNI, and by dynorphin antibodies implicates dynorphins in the spinal mechanism of action of the cannabinoids (Pugh et al., 1996). In addition, as animals are rendered tolerant to Δ^9-THC, dynorphin A release is only elicited by very high doses of Δ^9-THC. Thus, the acute antinociceptive effects of Δ^9-THC are due in a large part to dynorphin release. Given that the Δ^9-THC/morphine and Δ^9-THC/codeine interactions are synergistic in the tail-flick test for antinociception (Cichewicz and McCarthy, 2003), we hypothesized that the administration of Δ^9-THC would restore the efficacy of morphine and codeine at a point when the opioids were no longer active. We further hypothesized that the low dose Δ^9-THC/morphine and Δ^9-THC/codeine antinociceptive synergy would have a similar

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duration of action to equiefficacious high doses of morphine or codeine, respectively, and that Δ^9-THC might in fact extend the duration of action of highly efficacious doses of either morphine or codeine.

2. Materials and methods

2.1. Animals

Male ICR mice (Harlan Laboratories, Indianapolis, IN) weighing 25–30 g were housed 6 per cage in an animal care facility maintained at 22±2 °C on a 12-h light/dark cycle. Food and water were available ad libitum. The mice were transported to the testing laboratory 24 h prior to the test day to allow acclimation and recovery from transport and handling. All procedures were conducted in accordance with the regulations of the Institutional Animal Care and Use Committee at Virginia Commonwealth University.

2.2. Drugs

Morphine sulfate, codeine phosphate, and Δ^9-THC were obtained from the National Institute on Drug Abuse. Morphine and codeine were dissolved in distilled water, and Δ^9-THC was prepared in 1:1:18 (emulphor:ethanol:saline).

2.3. Tail-flick for antinociception

Baseline tail-flick latencies were determined prior to drug administration using the tail-flick latency test for antinociception as designed by D'Amour and Smith (1941). Baseline values were between 2 and 4 s. During testing, the cut-off time of 10 s was employed to prevent damage to the tail. Antinociception was quantified using the percent maximal effect (%MPE) calculated as developed by Harris and Pierson (1964): $\%MPE = [(test - baseline)/(10 - baseline)] \times 100$. Percent MPE and standard error of the mean (S.E.M.) were recorded for the respective time points in each group.

2.4. Time course studies

Route of administration for all drugs was by oral gavage (p.o.). Separate groups of six male ICR mice were used for each time point (0–360 min) and for each treatment group. Mice were given one injection of vehicle or Δ^9-THC 30 min prior to a dose of morphine or codeine and tested for antinociception via the tail-flick test at time points after opioid dose until no significant antinociception was observed. Values for %MPE are an average (±standard error of the mean, S.E.M.) of six mice per time point. Four comparative treatments were established. Treatment 1 consisted of oral vehicle (1:1:18 emulphor:ethanol:saline) 30 min prior to an oral dose of morphine (80 or 20 mg/kg). Treatment 2 consisted of oral Δ^9-THC (20 mg/kg) 30 min prior to an oral dose of morphine (80 or 20 mg/kg). Doses of morphine used represent the sub-active dose of morphine (20 mg/kg, p.o.) and the fully efficacious, ED_{80} (effective dose 80%), dose of morphine (80 mg/kg, p.o.). Treatment 3 consisted of oral vehicle (1:1:18 emulphor:ethanol:saline) 30 min prior to an oral dose of codeine (30 mg/kg or 100 mg/kg). Treatment 4 consisted of oral Δ^9-THC (20 mg/kg) 30 min prior to an oral dose of codeine (30 or 100 mg/kg). Doses of codeine used represent the sub-active dose of codeine (30 mg/kg, p.o.) and the fully efficacious, ED_{80}, dose of codeine (100 mg/kg, p.o.). Data were collected incrementally across a 360-min time course post-morphine and a 120-min time course post-codeine. No animals were repeatedly tested. Each treatment group and time point represents a separate group of 6 mice. Analysis of variance (ANOVA) was used to determine significant differences between control and treatment groups followed by Dunnett's *t*-test post hoc analysis. Statistical analysis was performed using StatView, version 5.0 (SAS Institute, Cary, NC). Significance is defined as a p value of less than 0.05.

2.5. Restoration of antinociceptive efficacy

The time course of morphine- and codeine-induced antinociception was first identified following administration of morphine (100 mg/kg) or codeine (200 mg/kg) alone as in Section 2.4 above. Morphine and codeine were inactive by 360- and 120-min post-administration, respectively. Using separate groups of mice, morphine and codeine (or vehicle controls) were then injected at 330 or 90 min prior to Δ^9-THC (20 mg/kg, p.o.) or vehicle (1:1:18; emulphor:ethanol:saline, p.o.) and the animals were retested for antinociception 30 min later, and data were analyzed statistically as in Section 2.4 above for restoration of antinociception of morphine or codeine by Δ^9-THC.

2.6. Duration of restoration of antinociceptive efficacy

The duration of restoration of morphine-induced (100 mg/kg) or codeine-induced (200 mg/kg) antinociception by Δ^9-THC (20 mg/kg, p.o.) was similarly evaluated using the same subjects from Section 2.5 (a separate group of mice for each drug/vehicle combination and time point as indicated above). Morphine (100 mg/kg), codeine (200 mg/kg) or vehicle (dH_2O) was administered followed by Δ^9-THC (20 mg/kg, p.o.) as in the studies in Section 2.5 above. The mice were then tested for antinociception at 30, 75 and 105 min after administration of Δ^9-THC, time points that correspond to morphine pretreatment times of 360, 405 and 435 min prior to testing. The mice previously injected with codeine (200 mg/kg) or vehicle (dH_2O) were injected with Δ^9-THC and were then tested for antinociception at 20, 60 and 90 min after administration of Δ^9-THC, time points that correspond to codeine pretreatment times of 150, 180 and 210 min.

3. Results

3.1. Enhancement of antinociception

As expected there was no significant difference in antinociception produced by the high-dose morphine (80 mg/kg)/Δ^9-THC combination in comparison to morphine (80 mg/kg)/

vehicle. One injection of Δ^9-THC prior to the maximally efficacious dose of morphine (80 mg/kg) did not extend the duration of action of morphine alone. Morphine/vehicle or morphine/Δ^9-THC groups retained significant activity for 240 min (Fig. 1). However, as expected, we observed a significant enhancement of a low inactive dose of morphine (20 mg/kg) following administration of one dose of Δ^9-THC (20 mg/kg) versus the antinociception of morphine (20 mg/kg)/vehicle (Fig. 2). In codeine groups, we observed results slightly different from that of morphine. The duration of action of high-dose codeine (100 mg/kg)/Δ^9-THC (20 mg/kg) [120 m min] was significantly longer than that of codeine/vehicle [90 min] (Fig. 3). We also observed significant enhancement of antinociception of low-dose codeine (30 mg/kg) by Δ^9-THC compared to codeine (30 mg/kg)/vehicle out to 120-min post-administration of codeine (Fig. 4). In summary, a combination of a low (inactive) dose of morphine (20 mg/kg) or codeine (30 mg/kg) with a single pretreatment of an inactive dose of Δ^9-THC produced the same efficacy (ED_{80}) as the high doses of each opioid alone. In the case of codeine, Δ^9-THC pretreatment also increased the duration of action of the ED_{80} dose of codeine.

3.2. Restoration of antinociception

Δ^9-THC (20 mg/kg), administered at those time points when morphine or codeine ED_{80} doses had lost significant efficacy, restored the efficacy of both high-dose morphine and codeine to levels observed upon initial administration (Figs. 5 and 6). We observed the time point of marginal activity of high-dose morphine (80 mg/kg) to be 360 min. Δ^9-THC (20 mg/kg) 30 min prior to this time point significantly restored antinociception of morphine at this time point to 66.2±16.5 %MPE (Fig. 5). Similarly, when the point of marginal activity of high-dose codeine (100 mg/kg) was identified as 120 min, a 30-min pretreatment with Δ^9-THC (20 mg/kg) significantly restored the antinociceptive effects of codeine to 88.1±11.9 % MPE (Fig. 6).

3.3. Duration of restoration of efficacy

Studies of the duration of restored efficacy of morphine (80 mg/kg) and codeine (100 mg/kg) by Δ^9-THC (20 mg/kg) indicated the following: morphine/Δ^9-THC produced 66.2±16.5, 45.8±17.9 and 24.1±9.3 %MPE for time points 360-, 405- and 435-min post-morphine administration, respectively, compared to morphine/vehicle of 18.3±10.3, 0.6±0.3 and 2.0±1.3 %MPE for the same time points (Fig. 5). Codeine/Δ^9-THC produced 88.1±11.9, 73.8±12.9 and 33.8±13.5 %MPE for time points 150-, 180- and 210-min post-codeine administration, respectively, compared to codeine/vehicle of 60.6±14.9, 25.3±10.5 and 17.5±4.0 %MPE for the same time points (Fig. 6). Thus, the duration of the restoration of morphine-induced

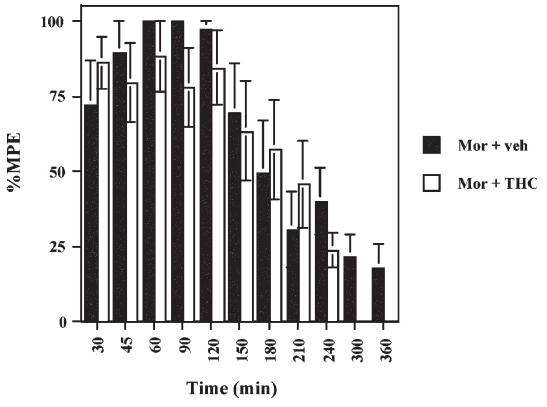

Fig. 1. Time course of high-dose morphine (80 mg/kg, p.o.) with Δ^9-THC (20 mg/kg, p.o.). Vehicle or Δ^9-THC was administered 30 min prior to morphine, and tail-flick was performed 30 min after morphine administration. One oral dose of THC did not extend the duration of action of morphine. Both groups retained significant activity for 240 min. Mor = morphine p.o.; veh = vehicle, 1:1:18; THC = Δ^9-THC p.o.; Cod = codeine p.o.; %MPE = percent maximal effect.

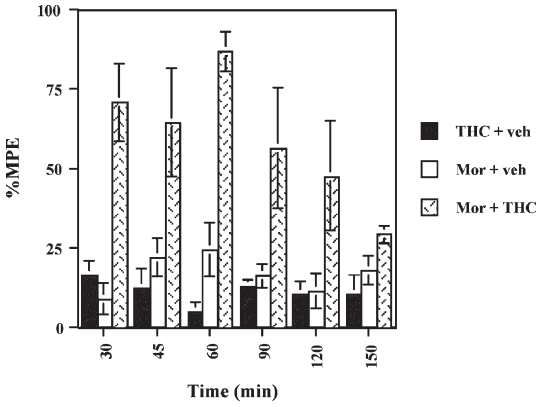

Fig. 2. Time course of low-dose morphine (20 mg/kg, p.o.) with Δ^9-THC 20 mg/kg. Vehicle or Δ^9-THC was administered 30 min prior to morphine, and tail-flick was performed 30 min after morphine administration. THC significantly enhanced the antinociceptive activity of low-dose morphine at 30, 45, 60, 90 and 120-min time points. Mor = morphine p.o.; veh = vehicle, 1:1:18; THC = Δ^9-THC p.o.; Cod = codeine p.o.; %MPE = percent maximal effect.

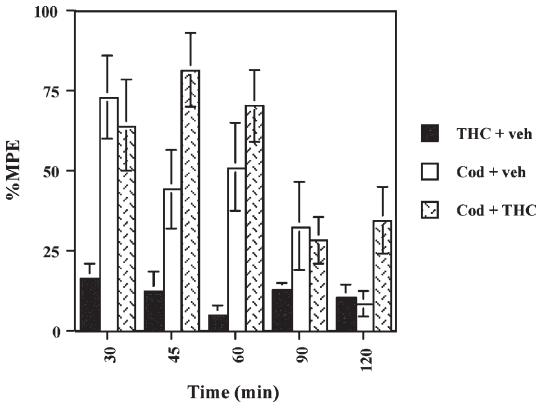

Fig. 3. Time course of high-dose codeine (100 mg/kg, p.o.) with Δ^9-THC 20 mg/kg. Vehicle or Δ^9-THC was administered 30 min prior to codeine, and tail-flick was performed 30 min after codeine administration. THC extended the duration of action of high-dose codeine out to 90 min ($p<0.05$). Mor = morphine p.o.; veh = vehicle, 1:1:18; THC = Δ^9-THC p.o.; Cod = codeine p.o.; %MPE = percent maximal effect.

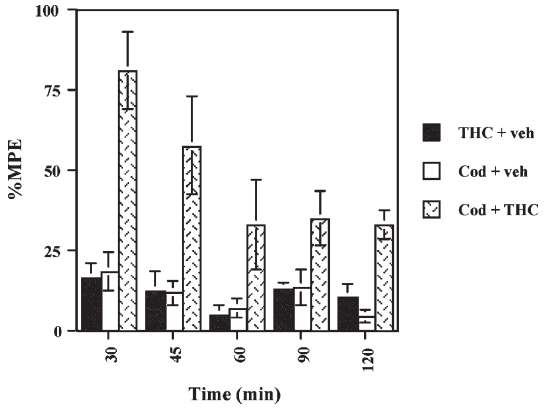

Fig. 4. Time course of low-dose codeine (30 mg/kg, p.o.) with Δ^9-THC 20 mg/kg. Vehicle or Δ^9-THC was administered 30 min prior to codeine, and tail-flick was performed 30 min after codeine administration. Significant enhancement of antinociception of low-dose codeine (30 mg/kg) by THC compared to codeine (30 mg/kg)/vehicle was observed out to 120-min post-administration of codeine. Mor = morphine p.o.; veh = vehicle, 1:1:18; THC = Δ^9-THC p.o.; Cod = codeine p.o.; %MPE = percent maximal effect.

antinociception by Δ^9-THC was significant out to 435-min post-morphine administration (Fig. 5), and the duration of the restoration of codeine-induced antinociception was significant out to 210-min post-codeine administration (Fig. 6).

4. Discussion

The interaction of cannabinoids with opioids has been extensively reviewed (Manzaneres et al., 1999; Massi et al., 2001; Cichewicz, 2004; Vigano et al., 2005). We have shown that Δ^9-THC and morphine synergize in the production of antinociception (Cichewicz and McCarthy, 2003). The clinical benefits of such an enhancement can be easily imagined, as it would allow for the prescription of much lower drug doses, which would still yield high analgesic effect yet induce fewer side effects (e.g., morphine-induced respiratory depression and constipation) that would normally accompany high drug doses. This study investigated the time course of enhancement of the analgesic efficacy of morphine and codeine by Δ^9-THC. No significant difference in antinociception or duration of action of morphine was observed with Δ^9-THC (20 mg/kg) in combination with high-dose morphine (80 mg/kg). At 80 mg/kg morphine is maximally active and Δ^9-THC would not be expected to produce any additional antinociception. Co-administration of Δ^9-THC and high-dose codeine (100 mg/kg) extended the duration of action of codeine. We hypothesize that since codeine is a shorter-acting opioid than morphine, the effects of Δ^9-THC may be sustained throughout the codeine time course. Our findings using low doses of morphine or codeine in combination with Δ^9-THC are consistent with isobolographic analyses from studies in which morphine and codeine produce synergistic antinociception with low-dose Δ^9-THC (20 mg/kg) (Cichewicz and McCarthy, 2003). Our studies on the restoration of opioid efficacy are also consistent with the interaction of low remaining amounts of morphine or codeine at the end of their time course of action being enhanced by Δ^9-THC. Other investigators have shown that Δ^9-THC enhances the antinociceptive effects of morphine (Fuentes et al., 1999; Reche et al., 1996). However, the mechanism underlying the enhancement or restoration of opioid action remains to be determined.

We have reported that Δ^9-THC releases dynorphin-A-(1–17), as well as leucine enkephalin, in the spinal cord (Welch, 1993; Mason et al., 1999a). Δ^9-THC releases dynorphin-A-(1–17) only at the onset of THC-induced antinociception, yet Δ^9-THC retains nor-BNI-sensitive antinociceptive activity 30-min post-administration (Mason et al., 1999a) indicating a kappa opioid-mediated antinociceptive effect. Thus, the dynorphin-A levels peak at the point of antinociception induced by Δ^9-THC, but clearly do not maintain Δ^9-THC's antinociceptive effects. Evidence suggests involvement of dynorphin-A-(1–8), a metabolite of dynorphin-A-(1–17), in Δ^9-THC-induced antinociception. However, Mason et al. (1999a) found that dynorphin-A-(1–8) levels remained constant throughout the 20 min period of evaluation following Δ^9-THC. The attenuation of the antinociceptive effects of Δ^9-THC by antisense to the kappa-1 receptor (Rowen et al., 1998) further implicates the release of endogenous kappa opioids in the mechanism of action of the cannabinoids (Pugh et al., 1995). Our findings of the blockade of cannabinoids by nor-BNI and dynorphin antibodies in the spinal cord but not the brain, implicate dynorphins in the spinal mechanism of action of the cannabinoids (Pugh et al., 1996). Δ^9-THC is cross-tolerant to the dynorphins of the "A" type (Welch, 1997). In addition, as animals are rendered tolerant to Δ^9-THC, dynorphin-A release is only elicited by very high doses of Δ^9-THC. Thus, tolerance to Δ^9-THC involves a decrease in the release of dynorphin-A (Mason et al., 1999b). Dynorphin antibodies block Δ^9-THC-induced antinociception, and prevention of the metabolism of dynorphin-A-(1–17) to dynorphin-A-(1–8) or to leucine enkephalin, which prevents the enhancement of morphine-induced antinociception by Δ^9-THC (Pugh et al., 1996). In cannabinoid CB_1 knockout mice, the

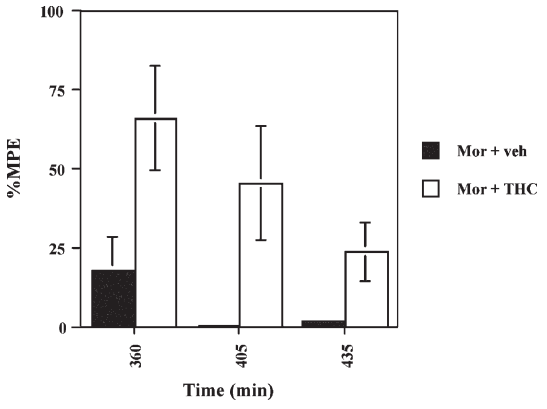

Fig. 5. Time course of restoration of antinociception of high-dose morphine (100 mg/kg, p.o.) with Δ^9-THC (20 mg/kg, p.o.). Oral morphine was administered 330 min prior to oral Δ^9-THC and restoration of efficacy observed. Δ^9-THC significantly restored antinociception of morphine at this time point to 66.2±16.5 %MPE. Duration of significant restoration was 75 min ($p<0.05$). Mor = morphine p.o.; veh = vehicle, 1:1:18; THC = Δ^9-THC p.o.; Cod = codeine p.o.; %MPE = percent maximal effect.

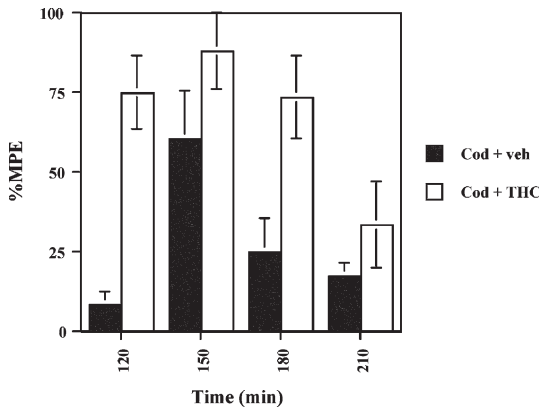

Fig. 6. Time course of restoration of antinociception of high-dose codeine (200 mg/kg, p.o.) with Δ^9-THC 20 mg/kg. Oral codeine was administered 90 min prior to oral Δ^9-THC and restoration of efficacy observed. Δ^9-THC significantly restored the antinociceptive effects of codeine to 88.1±11.9 % MPE. Duration of significant restoration was 90 min ($p<0.05$). Mor = morphine p.o.; veh = vehicle, 1:1:18; THC = Δ^9-THC p.o.; Cod = codeine p.o.; %MPE = percent maximal effect.

reinforcing effects of opioids are decreased (Ledent et al., 1999). Increases in prodynorphin and proenkephalin mRNA have been shown following exposure to Δ^9-THC (Cochero et al., 1997). We hypothesize that the functional coupling of the mu/delta and mu/kappa opioid receptors leads to enhanced antinociceptive effects of opioids by the cannabinoids. We envision cannabinoid-induced release of dynorphins as an indirect process due to the disinhibition of yet unknown neuronal processes. The events that precede and follow the release of dynorphin remain unclear.

Alternatively, Δ^9-THC and morphine may interact via the modulation of Substance P. Substance P and related neurokinins are major mediators of nociceptive transmission in the spinal cord (Nishiyama et al., 1995). Calcitonin gene related peptide (CGRP) co-localizes and is co-released with Substance P in spinal afferents (Ju et al., 1987; Lee et al., 1985). CGRP also enhances Substance P concentrations spinally, possibly by enhancing release (Oku et al., 1987) and decreasing degradation of Substance P (Le Greves et al., 1985). Morphine and other opioids, as well as endogenous opioids, have been demonstrated to decrease the release of Substance P (for reviews see Gao and Peet, 1999; Dray and Rang, 1998). CGRP enhances the nociceptive effects of intrathecally administered Substance P (Cridland and Henry, 1988; Wiesenfeld-Hallin et al., 1984) and modulates the acute effects of morphine (Welch et al., 1988). Δ^9-THC-induced dynorphin release may produce antinociception by decreasing the release of Substance P. Zachariou and Goldstein (1997) demonstrated that Substance P release following noxious stimuli could be attenuated by kappa opioid receptor stimulation. They demonstrated that intrathecal administration of dynorphin-A-(1–8) attenuated Substance P release, an effect blocked by nor-BNI (Zachariou and Goldstein, 1996). In addition, it has been shown that chronic Δ^9-THC treatment increases Substance P and enkephalin mRNAs concurrently in the same neurons in the caudate. Cannabinoid receptors co-localize with Substance P receptors in the striatum (Mailleux and Vanderhaeghen, 1992a,b, 1994), additional evidence for the interactions of the two systems. Thus, dynorphin release following cannabinoid receptor activation could elicit an antinociceptive effect by way of long-term suppression of Substance P release. The result of such dynorphinergic activity would be a Δ^9-THC-induced increase in tail-flick latency sensitive to nor-BNI attenuation. CGRP also co-localizes with dynorphin in spinal neurons (Gibbins et al., 1987). It has been demonstrated that in cannabinoid CB_1 knockout mice, brain levels of Substance P, dynorphin and enkephalin are significantly increased. Thus, it is likely that the cannabinoid CB_1 receptor plays a role in the tonic regulation of these peptides (Steiner et al., 1999).

Morphine and codeine produce antinociception through G protein-coupled opioid receptors in the brain and spinal cord (Neil, 1984; Pasternak, 1993; Cichewicz et al., 1999). We have previously hypothesized that the antinociceptive effects of morphine, which are primarily mediated through mu opioid receptors, are enhanced by Δ^9-THC through the activation of kappa and delta receptors (Pugh et al., 1996). Δ^9-THC can act through opioid receptors to produce antinociception by releasing or increasing the transcription of endogenous opioids (Smith et al., 1994; Pugh et al., 1996; Cochero et al., 1997). It is possible that the enhancement of opioid-induced antinociception by Δ^9-THC requires a physical or functional coupling between mu and delta opioid receptors, or mu and kappa opioid receptors. Knockout studies show that not only delta but also mu opioid receptors are required for delta ligand-mediated antinociception (Sora et al., 1997). Other investigators suggest that the formation of mu/delta heterodimers may play a role in enhancement of mu receptor-mediated antinociception by delta-specific ligands (Traynor and Elliott, 1993; Gomes et al., 2000). Rothman and Westfall (1982) have shown evidence of an allosteric coupling between morphine and enkephalin receptors in vitro. Mu, delta and kappa opioid receptors have been shown to associate with each other in a homotypic or heterotypic fashion when expressed in heterologous cells (Jordan and Devi, 1999; George et al., 2000; Gomes et al., 2000), and heterotypic interactions appear to alter the ligand-binding and signaling properties of these receptors (Rios et al., 2001). Delta opioid receptor agonists, antagonists and inverse agonists have been shown to modulate mu opioid receptors by increasing the number of binding sites and enhancing the extent of receptor signaling (Gomes et al., 2004). Gomes et al. (2004) have also shown that low-dose delta opioid receptor antagonists may enhance the potency and efficacy of clinically relevant mu-opioid drugs. Thus, the enhancement of morphine antinociception by Δ^9-THC may be occurring not only through release of endogenous opioids interacting with proximal opioid receptors, but also through a direct stimulation of receptor coupling (Cichewicz and McCarthy, 2003).

In summary, we have previously demonstrated that a low dose of morphine or codeine in combination with a low dose of Δ^9-THC produces an effect equivalent in efficacy to a high dose of either opioid alone. The mechanism of such an interaction is hypothesized to involve Δ^9-THC-induced release of endogenous opioids, followed by a yet-to-be-determined cascade of

cellular events culminating in synergism in antinociceptive tests. In this study we have extended our previous work to include a demonstration that the low-dose combination of opioid/Δ^9-THC has a duration of action similar to that of the high-dose opioid alone for a short-acting opioid like codeine and somewhat shorter than that of a longer duration opioid like morphine. We have also demonstrated that a single injection of Δ^9-THC will lengthen the duration of action of a short-acting opioid like codeine, but not alter the duration of action of a longer-acting opioid like morphine. These data indicate that the interaction of Δ^9-THC and morphine or codeine is unlikely to be due to pharmacokinetic interactions. We have also demonstrated for the first time that Δ^9-THC can restore the efficacy of opioids at the end of opioid duration of action. It is important to note that the restoration of efficacy is complete. That is, efficacy of the opioid returns to initial levels after Δ^9-THC administration and is sustained for the duration of action of Δ^9-THC. Taken together and if extrapolated to humans, these data indicate that an oral Δ^9-THC administration may reduce the need for higher doses of an opioid to control pain and may in addition be used to restore analgesia in patients taking opioids. Thus, patients might require a lower dose of opioid and need fewer administrations of the opioid in order to control pain and subsequently have fewer side effects observed following opioid administration.

Acknowledgments

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