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Cannabinoid analgesia

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Abstract

During the last decade, rigorous scientific methods have been applied to determine the effects of cannabinoids on nociceptive neurotransmission. Cannabinoids have been observed to markedly decrease signalling in specific neural pathways that transmit messages about pain. These effects were found to be due to the suppression of spinal and thalamic nociceptive neurons, and independent of any actions on either the motor system or sensory neurons that transmit messages related to non-nociceptive stimulation. Spinal, supraspinal, and peripheral sites of cannabinoid analgesia have been identified. The discovery of endocannabinoids raised the question of their natural role in pain. Multiple lines of evidence indicate that endocannabinoids serve naturally to suppress pain. While it is now clear that cannabinoids suppress nociceptive neurotransmission, more work is needed to establish the clinical utility of these compounds. The few human studies conducted to date produced mixed results, with more promising findings coming from studies of clinical pain as compared with experimental pain. The therapeutic potential of cannabinoids remains an important topic for future investigations.

Keywords: Cannabinoid; Pain; Analgesia; Receptor; Anandamide; Endocannabinoid

Abbreviations: PAG, periaqueductal gray; RVM, rostral ventrolateral medulla; THC, tetrahydrocannabinol; WDR, wide-dynamic range.

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1. Introduction

Cannabinoids have been used to treat pain for many centuries (reviewed by Iversen, 2000). Early uses include surgical anesthesia in China; amelioration of childbirth pain in ancient Israel; as an analgesic in Asia throughout the middle ages; and in the West during the 1800s for a variety of painful ailments, with commercial preparations supplied by Lilly (Indianapolis, IN, USA) and Squibb (New York, NY, USA). For a variety of reasons, both political and pharmacological (e.g., the instability of cannabis extracts, unpredictable absorption, and insolubility in water), cannabinoids were discontinued as medical agents in the early 20th century.

1.1. Neurobehavioral studies of cannabinoid analgesia

Preclinical studies in animals revealed that cannabinoids block pain responses in every pain model tested. Perhaps the earliest study of this type was performed by Dixon (1899), one of the fathers of modern pharmacology, who demonstrated that cannabinoids suppress canine reactions to pinpricks. Early studies by Bicher and Mechoulam (1968) and Kosersky et al. (1973) paved the way for many subsequent studies, which verified the ability of cannabinoids to profoundly suppress behavioral reactions to noxious stimuli, inflammation, and nerve injury. In models of acute or physiological pain, cannabinoids are highly effective against thermal (Buxbaum, 1972; Bloom et al., 1977; Lichtman & Martin, 1991a, 1991b; Yaksh, 1981), mechanical (Sofia et al., 1973), and chemical pain (Sofia et al., 1973; Formukong et al., 1988). Typically, cannabinoids were comparable with opiates both in potency and efficacy (Bloom et al., 1977; Jacob et al., 1981). In models of tonic or chronic pain, both inflammatory (Tsou et al., 1995) and neuropathic (Herzberg et al., 1997), cannabinoids show even greater potency and efficacy.

Nevertheless, difficult issues related to the pharmacology of cannabinoids hampered the acceptance of cannabinoids as analgesics. The main drawbacks were (1) the lack of understanding of the molecular pharmacology of these compounds, (2) the possibility that cannabinoids produced behavioral suppression in pain models by effects on the motor system, and (3) issues associated with psychoactivity induced by cannabinoids. These concerns have been addressed in recent years. The following sections briefly review the rapid advances in these areas.

1.2. Molecular pharmacology of cannabinoids

Prior to the late 1980s, it was believed that cannabinoids affect the nervous system by perturbing neuronal membranes. These highly lipophilic compounds were presumed to dissolve in the cell membrane, altering its function in a nonspecific manner. Advances in the development of high specific activity radioligands that had permitted identification of neurotransmitter receptors for many classes of drugs proceeded slowly with cannabinoids. The main obstacle was that the traditional cannabis-derived compounds dissolve in neuronal membranes, making the identification of receptors almost impossible. This problem was overcome when Howlett's group at St. Louis University employed a labelled version of a new drug developed by Pfizer (New York, NY, USA), CP-55940, to demonstrate the existence of cannabinoid receptors on brain membranes (Devane et al., 1988). Matsuda and co-workers (1990) at the National Institutes of Health (Bethesda, MD, USA) cloned the receptor, which proved to be a G-protein-coupled receptor, now called CB_1, to differentiate from another subtype discovered later called CB_2 (Munro et al., 1993). The CB_1 subtype is found in the nervous system, spleen, and testes (Herkenham et al., 1991; Mailleux & Vanderhaeghen, 1992; Tsou et al., 1998; reviewed by Ameri, 1999), while the CB_2 is absent from neural tissues being located in immune tissues: the spleen, tonsils, monocytes, and B- and T-cells (Munro et al., 1993; Galiegue et al., 1995; Schatz et al., 1997; reviewed in Ameri, 1999).

Cannabinoids alter neurotransmission through CB_1 receptors by inhibition of P/Q-type Ca^{2+} channels (Mackie et al., 1993, 1995) and adenylyl cyclase (Howlett et al., 1988) and by activation of K^+ channels and mitogen-activated protein kinase (reviewed in Ameri, 1999). The overall effect is cellular inhibition. CB_2 receptors do not appear to modulate ion channels, but they inhibit adenylyl cyclase and activate mitogen-activated protein kinase.

The distribution of cannabinoid CB_1 receptors in the brain has been examined by receptor autoradiography, immunohistochemistry, and in situ hybridization histochemistry (Herkenham et al., 1991; Tsou et al., 1998; Mailleux & Vanderhaeghen, 1992). The papers revealed that cannabinoid receptors are frequently localized to nerve endings, suggesting that they function as presynaptic modulators of neurotransmitter release. Presynaptic inhibition is a particularly powerful mechanism of neural modulation, as it can have the final determinant influence on the output signal of a neuron and its subsequent communication to other neurons. The highest levels of cannabinoid receptors are found in the hippocampus, the basal ganglia, and the cerebellum, areas associated predominantly with memory and motor coordination. The low level found in brainstem cardiorespiratory centers probably accounts for the high therapeutic index of the compounds—to date, there are no deaths known to have resulted from overdose of marijuana.

Cannabinoid receptors also occur in high density in many areas related to pain. They densely populate the periaqueductal gray (PAG) and the rostral ventrolateral medulla, brain areas involved in descending pain modulation. They are concentrated in the superficial layers of the spinal dorsal horn, and they are found in the dorsal root ganglion, from which they are transported to both central and peripheral terminals of primary afferent neurons (Herkenham et al., 1991; Hohmann & Herkenham, 1998; Hohmann et al.,

1999; Hohmann & Herkenham, 1999; Sañudo-Peña et al., 1999). These areas provide peripheral, spinal, and central targets through which cannabinoids modulate pain.

The discovery of the cannabinoid receptors begged the question of whether the brain produces marijuana-like substances (termed nowadays, endocannabinoids). After the identification and cloning of the CB_1 receptor (Matsuda et al., 1990), Devane and co-workers (1992) identified *N*-arachidonyl ethanolamide as such an endogenous mediator, and named the compound anandamide, from the Sanskrit word ''ananda,'' which translates roughly as ''internal bliss.'' A second endocannabinoid, 2-arachidonylglycerol, was identified by Mechoulam and colleagues (1995) and Sugiura and colleagues (1995). Both compounds exhibit affinity for both CB_1 and CB_2 receptors. The subject of their roles in pain will be addressed in Section 2.2.1.

1.3. Motor effects of cannabinoids

Cannabinoid receptors densely populate the terminals of striatal output neurons that innervate the globus pallidus and the substantia nigra. By presynaptic inhibition, activation of these receptors blocks the communication between corticostriatal neurons and the output of the basal ganglia (reviewed in Sañudo-Peña & Walker, 1998). At high doses in animal studies, this produces an odd condition called catalepsy, a state characterized by frozen postures and immobility. Although the effects of cannabinoids on movement are complex (both inhibition and activation can occur, depending on dose), this hypoactivity produced at higher doses of cannabinoids raised the concern that even at doses where frank motor disability is not evident, the slowed reactions of animals in pain tests may have resulted from motor dysfunction rather than pain inhibition.

2. Cannabinoids and pain

2.1. Effects of cannabinoids on nociceptive neurons

As of 1990, virtually nothing was known about the effects of cannabinoids on the neural pathways that transmit pain messages from the spinal cord to the brain, and the determination of whether cannabinoids actually affect nociceptive neurotransmission was a crucial missing link in the developing story on cannabinoids and pain. Therefore, we undertook a series of studies that examined the effects of cannabinoids on noxious stimulation-evoked activity in nociceptive spinal and thalamic neurons (Hohmann et al., 1995, 1998, 1999; Hohmann & Walker, 1999; Martin et al., 1996; Strangman & Walker, 1999). In these studies, extracellular single neuron recordings were obtained from anesthetized rats, and the responses of both nociceptive neurons and non-nociceptive neurons to a variety of stimuli were studied. In these experiments (e.g., Fig. 1), cannabinoids produced profound suppression of cellular nociceptive responses. A summary of the findings of a series of experiments indicates that cannabinoids exhibit the following characteristics:

1. Suppression of behavioral and neurophysiological responses to all types of nociceptive stimuli tested
2. High potency (effects observed at ~ 75 μg/kg, i.v.)
3. High efficacy (typically > 80% reduction in response to noxious stimulation)
4. Effects CB_1 receptor-mediated
5. Suppression of both wide-dynamic range (WDR) neurons (respond to touch and pain) and nociceptive specific neurons (respond to pain only)
6. No suppression of low-threshold mechanoreceptive neurons (respond to touch only)
7. Spinal and thalamic neurons affected similarly
8. Behavioral analgesic time course and potency highly correlated with neuronal suppression of nociceptive stimulus-evoked activity
9. Suppression of windup (a model of central sensitization that is observed in chronic pain)
10. Suppression of increased spontaneous firing following injection of complete Freund's adjuvant, an inflammatory agent

The reader will note that 1–8 reflect effects on nociceptive or physiological pain, whereas 9–10 employed chronic pain models. In windup, we studied the increasing response of neurons to trains of C-fiber strength electrical stimulation (Strangman & Walker, 1999), and the complete Freund's adjuvant experiments examined responses to an inflammatory stimulus. The results of these experiments are consistent with behavioral tests discussed above, which showed that cannabinoids are active in models of inflammatory and neuropathic pain. This is important because these models are better indicators of the therapeutic potential of cannabinoids than tests of physiological (acute) pain.

2.2. Sites of action of cannabinoids

Although the studies discussed in Section 2.1 demonstrated the ability of cannabinoids to suppress nociceptive neurotransmission, one must ask about the site of action of the drugs. Ostensibly, the cannabinoids could produce analgesia by an action in the brain via descending modulation, by a direct spinal action, and/or by an action on the peripheral nerve. The consensus from studies conducted in a number of different laboratories is that cannabinoids exert effects at all three locations.

2.2.1. Central nervous system actions

Early studies in our laboratory indicated that cannabinoids, administered intracerebroventricularly, suppress tail-flick responses (Martin et al., 1993) and spinal nociceptive responses in rats (Hohmann & Walker, 1999). This effect occurs at low doses, and further studies using direct brain

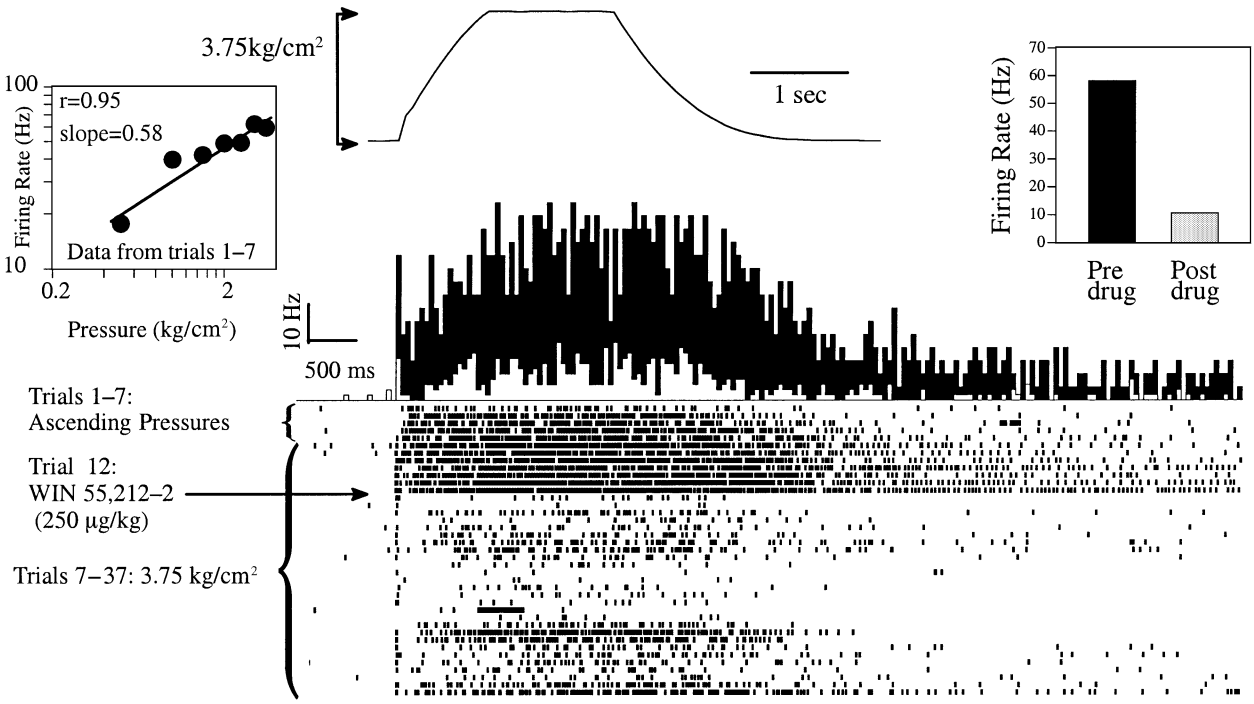

Fig. 1. Example of inhibition of evoked activity in a WDR neuron by the cannabinoid WIN-55,212-2. The responses of the neuron to mechanical pressure were examined during 37 trials corresponding to each row of dots in the raster plot (top row = trial 1). Each dot represents the time of occurrence of a single action potential relative to the stimulus onset. Trials 1–7 consisted of applications of increasingly strong mechanical stimulation, ranging from non-noxious to noxious levels (0.5, 1, 1.5, 2, 2.5, 3, and 3.75 kg/cm^2). The concomitant increases in density of dots under the stimulus in the first 7 rows are indicative of the increasingly strong response of the neuron. **Left** (inset): the mean firing rates of the neuron during a graded series of stimulations are plotted (log-log coordinates) against the applied pressure. The systematic change of the neuron in responsiveness was the basis for classifying this cell as a WDR neuron. **Center**: the noxious stimulus illustrated by the pressure waveform (top center) was administered every 2 min for trials 7–37. Trials 8–12 constituted baseline trials; after trial 12 (arrow), WIN-55,212-2 (250 mg/kg, i.v.) was administered. A marked decrease in the responsiveness of the neuron is indicated by the sharply decreased density of dots in subsequent rows of the raster plot. **Right** (inset): comparison of the mean firing rate during the stimulus for the 5 baseline trials to the firing rate during the stimulus for the first 10 post-injection trials illustrating, approximately, an 82% decrease in responsiveness. The black peristimulus time histogram between the raster plot and the pressure waveform represents the baseline firing rate prior to injection, whereas the gray peristimulus time histogram represents the firing rate for the first 10 postinjection trials. Adapted from Hohmann et al. (1995).

injections indicated that the antinociceptive effects can be elicited from at least seven different brain areas, which include the dorsal PAG in the midbrain, the rostral ventrolateral medulla (RVM), and the noradrenergic nucleus A5 in the medulla (Martin et al., 1995, 1998, 1999). All of these areas participate in descending inhibition of spinal nociceptive projection pathways (Proudfit, 1988). Work from Field's group confirmed the behavioral studies by showing that cannabinoids exert marked effects on neurons in the RVM, a site active in descending suppression of spinal nociceptive neurons (Meng et al., 1998). These sites of action of cannabinoids are further supported by work in Christie's group demonstrating modulation of postsynaptic currents in the RVM and the PAG in brain slices (Vaughan et al., 1999, 2000). It is clear, therefore, that cannabinoids produce antinociceptive effects by descending spinal inhibition.

Endocannabinoids appear to participate in endogenous pain modulation by actions in the PAG. Work from our laboratory showed that blocking the cannabinoid CB_1 receptor by the antagonist SR141716A produces hyperalgesia in the formalin test, and SR141716A blocks the analgesia produced by electrical stimulation of the dorsal PAG (Strangman et al., 1998). These findings confirmed those of Richardson et al. (1997, 1998a, 1998b), who found that this cannabinoid antagonist, injected intrathecally, produced hyperalgesia, and that the same effect occurs with spinal CB_1 receptor knockdown. Chapman (1999) found that spinal nociceptive neurons exhibit markedly greater C-fiber-mediated responses following low doses (0.1–1 ng in 50 µL applied to spinal cord) of SR141716A. The pro-nociceptive actions of the antagonist provide evidence that endocannabinoids serve naturally to suppress pain. Presumably, the pain enhancement by the antagonist occurs due to blockade of a tonic or evoked pain-inhibitory effect of endocannabinoids. However, the conclusions from these and other experiments that use SR141716A in this manner are limited by two factors. First, several reports have suggested that SR141716A acts as an inverse agonist, an effect that would mimic that of blocking endocannabinoids (reviewed by Walker et al., 2000). Second, these studies do not identify any particular endocannabinoid that might be involved in the proposed suppression of pain. Therefore, it became of increasing importance to directly demonstrate release of endocannabinoids in circuits that mediate pain suppression.

Following from the finding that SR141716A blocks the analgesic effect of PAG electrical stimulation, we hypothesized that electrical stimulation would release anandamide in the PAG. To examine this possibility, we set upon the task of measuring endocannabinoids in the PAG using microdialysis (Walker et al., 1999). This method permits collection of neurotransmitters/modulators from the extracellular space, and is, therefore, an indicator of the release of these modulators. Using liquid chromatography/mass spectrometry, we were able to establish that analgesia producing electrical stimulation of the PAG or injections of the chemical irritant formalin into the hind paws of anesthetized rats induced the release of anandamide in the PAG (Fig. 2). Thus, it appears that either pain itself, or electrical stimulation (which mimics neuronal excitation), leads to the release of anandamide, which acts on cannabinoid receptors in the PAG to inhibit nociception.

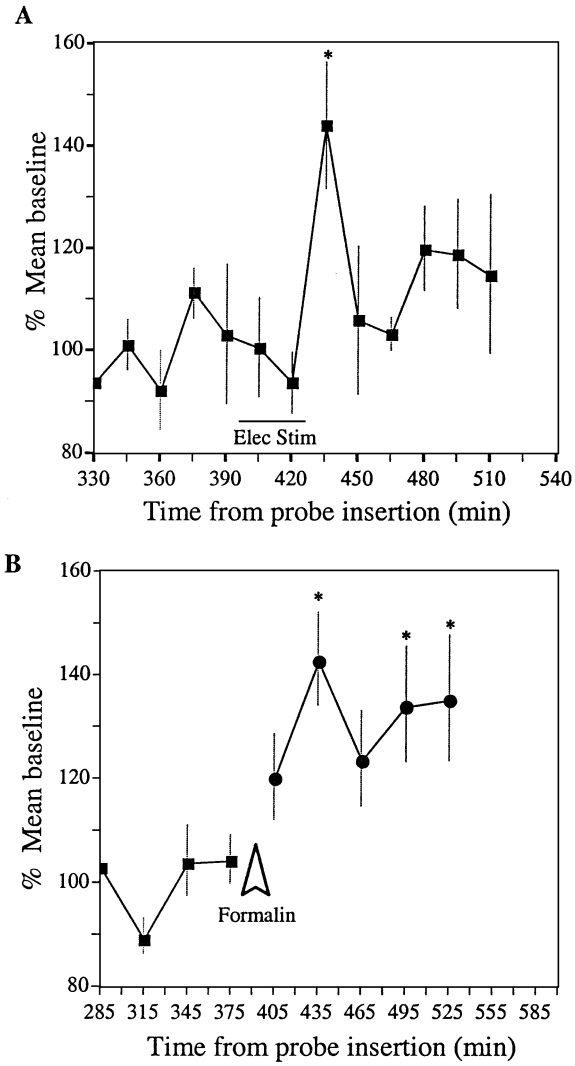

Fig. 2. Stimulation of the release of anandamide in the PAG of the rat using electrical depolarization or pain. **A**: Increased extracellular levels of anandamide following electrical stimulation of the PAG in urethane-anesthetized rats. Following the establishment of stable baseline values, electrical stimulation (Elec Stim) (monopolar 0.1 msec/1 mÅ, 60 Hz, 5 sec trains, 5 sec rest) was delivered for 30 min. Microdialysis samples were collected in 15-min intervals and analyzed using HPLC, with detection by atmospheric pressure chemical ionization mass spectrometry, selected ion monitoring mode at molecular weight 348.3 ($n = 5$, $P<0.05$, repeated measures analysis of variance). * Significantly different from baseline average via post-hoc test ($P<0.05$). The delay in the measurement presumably reflects the time needed to produce sufficient overflow of anandamide in the extracellular space to achieve recovery by microdialysis. **B**: Increased extracellular levels of anandamide in the PAG following induction of prolonged pain in urethane-anesthetized rats. Following establishment of a stable baseline, formalin solution was injected subcutaneously in both hind paws (4%, 150 μL). Samples shown span 30-min intervals ($n = 6$; $P<0.001$, repeated measures analysis of variance). * Significantly different from baseline average via post-hoc test ($P<0.05$). Adapted from Walker et al. (1999).

2.2.2. Spinal actions

Yaksh (1981) and later Welch's group and others (Welch & Stevens, 1992; Lichtman & Martin, 1991a, 1991b; Hohmann et al., 1998; Richardson et al., 1997, 1998a, 1998b; Drew et al., 2000; Chapman, 1999) have shown that cannabinoids inhibit pain in part by a direct spinal action. These observations are consistent with the dense labelling by CB_1 receptor antibodies or CB_1 receptor radioligands of cannabinoid receptors in the superficial and deep layers of the dorsal horn. Direct spinal application of cannabinoids inhibits the nociceptive responses of spinal nociceptive neurons.

2.2.3. Peripheral actions

Recent work also indicates an action of cannabinoids in the periphery. Injections of low doses of anandamide into an area of inflammation in the paw produced by carageenan reduced the ensuing hyperalgesia (Richardson et al., 1998c). This finding is consistent with the presence of cannabinoid receptors in the peripheral nerve and their transport to the distal endings (Hohmann & Herkenham, 1999). Subsequent work by Calignano et al. (1998) showed that endocannabinoids acting in the periphery may modulate pain responses.

3. Studies of the effects of cannabinoids on pain in humans

The human trials of cannabinoids are few in number and typically small in subject size. These studies differ in important ways. There are marked differences in dose and dose regimens, and the drug preparations differ, with some using smoked marijuana and some using Δ^9-tetrahydrocannabinol (THC) by the oral or intravenous routes. Some studies used healthy volunteers, whereas others used patients with clinical pain of various origins. Therefore, in reviewing this literature, it is important to note that some negative results may have arisen from doses that were too low; that the oral route would add variability due to the unpredictable absorption of THC; that smoked marijuana contains additional constituents which may contribute to any observed

effects; and that clinical pain is very different from experimental pain, owing to plasticity in the neuronal circuits that mediate pain. In light of the fact that the extant materials do not permit one to come to solid conclusions about the utility of direct-acting full-cannabinoid agonists as therapeutic agents in pain, it seems best to examine this literature with an eye toward findings that may uncover whatever therapeutic potential exits.

3.1. Experimental pain

One approach in studying the effects of cannabinoids on pain perception in humans is through paradigms that involve administering controlled painful stimuli to healthy volunteers. An interesting approach used in two studies (Zeidenberg et al., 1973; Clark et al., 1981) aimed at distinguishing between response bias (often referred to as B, β, or L_x) and sensitivity (often referred to as P(A) or d′) to painful stimuli, involved methods from the sensory decision theory. In this approach, response bias refers to the tendency of a particular subject to rate events in a more positive or negative direction. This variable is related to higher brain processes reflecting factors such as a person's temperament. Sensitivity refers to the detectability of a stimulus and the subject's ability to distinguish stimuli that are similar, but of slightly different intensities. It is important to note that this method requires a variety of statistical assumptions, which makes interpretation of the results more difficult.

Zeidenberg et al. (1973) administered 5 mg (p.o.) of Δ^9-THC to healthy male volunteers between the ages of 25 and 29, and tested them for thermal pain perception to a radiant heat source before and after administration of the drug. They found that d′ or the ability to distinguish between stimuli of different intensities dropped, and this drop occurred both during the period of subjective effects of the drug and, in 3 of 4 subjects, for the subsequent testing period. Response bias exhibited more intersubject variability. The authors noted that the analgesic effects of the drug remained at a time when effects on memory and psycholinguistic parameters were returning to normal levels, suggesting a longer time course for the effect of the drug on pain sensitivity.

A second study that used sensory decision theory reached opposite conclusions (Clark et al., 1981). However, in this study, tolerance to cannabinoids is confounded with the pain tests. Healthy volunteers were permitted to smoke increasing quantities of National Institute of Drug Abuse-supplied marijuana cigarettes (2%, 20-mg THC content per cigarette). The total number of cigarettes consumed were very high for both the moderate- and high-consumption groups (average 19.4 cigarettes/day for high consumption, 13.1 cigarettes/day for moderate users), which undoubtedly induced tolerance in the subjects. This confound is so deeply embedded in the experimental design that it is difficult to interpret the data from this experiment.

Raft et al. (1977) used 2 doses of THC administered intravenously (0.022 and 0.044 mg/kg) in 10 males (18–28 years of age), and measured pain induced by two types of noxious stimuli, pressure and electrical. These investigators examined the pain threshold (the lowest intensity, that of stimulation, that gives rise to pain) and pain tolerance (the intensity at which the pain becomes unbearable). At both doses and for both stimuli, the threshold for pain was increased, whereas pain tolerance was not affected. In this and other studies conducted around the same time, the use of threshold and tolerance measures is unfortunate. Clinical pain is normally somewhere in between the two, and it is difficult to assess from the present data what happens in this middle range. Modern approaches would likely use a range of noxious stimuli coupled with ratings of pain intensity, which would provide stimulus response functions. What is clear from the results of the study by Raft et al. (1977) is that at some levels of noxious stimulation, the sensation of pain was entirely absent, but whether this would extend to the clinically relevant levels cannot be assessed from these data. An interesting result from this paper stems from patient reports on pain severity overall. Although the largest decrease in pain threshold occurred with the pressure stimulus at the 0.44 mg/kg dose, most patients rated this condition as the least desirable. It appears that the dysphoric effects of THC heightened the overall negativity of the pain. Thus, there is a dissociation between the sensory phenomena and the overall pain experience, such that the negative overall psychotropic effects of THC at the higher dose range overrides the positive effects of the drug on sensory threshold.

Hill et al. (1974) also measured pain thresholds and tolerance. In this single-dose study, healthy male volunteers (21–30 years of age, $n = 26$) inhaled marijuana smoke using an apparatus that caused nearly complete combustion of the plant while the subject practiced inhalation in a timed manner. Subjects experienced ascending intensities of electrical stimulation, and were asked to report when the stimulation became painful and when it became intolerable. The strength of stimulation was then reversed, and the subjects were asked to report when the pain disappeared. The authors found that marijuana smoking lowered the pain threshold and pain tolerance. A drawback of this study is the inability to state the dose with any accuracy, which is a possible basis for the fact that this study is at variance with the results of Raft et al. (1977).

3.2. Clinical pain

The studies discussed in this section are undoubtedly the most telling because the subject population was drawn from patients suffering from significant chronic clinical pain. Chronic pain takes on features that distinguish it from acute pain due to neural plasticity. Changes in sensory processes that take place during periods of prolonged pain serve mainly to amplify the pain. Ongoing painful stimulation

leads to peripheral and central sensitization, a process in which the responses to stimulation are enhanced. This leads to allodynia (a painful sensation pursuant to mild tactile stimulation), hyperalgesia (a greater than normal pain sensation to a noxious stimulus), and spontaneous pain. The peripheral mechanisms for different classes of pain (e.g., inflammatory pain versus neuropathic or nerve injury pain) differ. Consequently, different analgesics exhibit different degrees of efficacy in chronic pain of different etiologies. For example, morphine is an excellent analgesic for inflammatory pain, whereas it frequently lacks efficacy in neuropathic pain. Therefore, studies of clinical pain of different types are necessary precursors to drawing sound conclusions about the possible role of cannabinoids in the pharmacotherapy for pain.

Positive results of cannabinoids have been found in studies of cancer pain conducted by Noyes et al. (1975a, 1975b). The larger of the two studies used 36 subjects (26 women and 10 men, mean age 51). These patients reported continuous pain of moderate intensity. In a double-blind random pattern, patients received on successive days placebo, 10 and 20 mg of THC, and 60 and 120 mg of codeine. Pain ratings by the patients were used to estimate pain relief and pain reduction scores. As shown in Fig. 3, 20-mg THC was roughly equivalent to 120-mg codeine. Five of the 36 patients experienced adverse reactions to THC, 1 following 10-mg THC, 4 following 20-mg THC. These side effects undoubtedly limit the amount of analgesia that can be produced by Δ^9-THC. Another report by Noyes et al. (1975b) reached similar conclusions with a smaller sample.

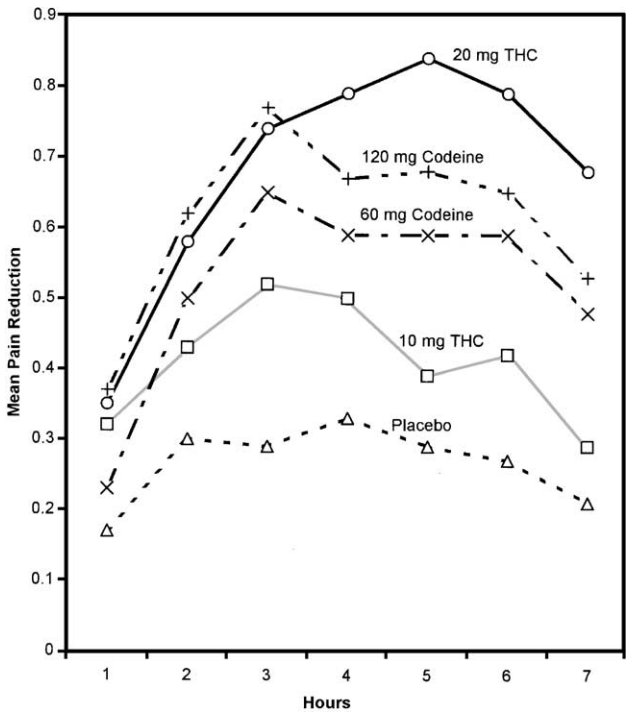

Fig. 3. Mean hourly pain reduction following THC, codeine, and placebo. Adapted from Noyes et al. (1975a).

4. Clinical implications

It is notable that the debate surrounding medical marijuana is not whether cannabinoids can be marketed as therapeutic agents; two approved drugs are currently available by prescription: Marinol (Δ^9-THC) and Nabilone (a Δ^9-THC analog). Rather, the debate is whether we should permit smoking of our medicines and whether the crude plant material may have some effects that differ from synthetic Δ^9-THC.

Since smoking is associated with grave health risks, it is an undesirable drug delivery system. Recognizing this fact, the United States National Academy of Sciences Institute of Medicine recommended that therapeutic use of smoked marijuana be highly regulated and reserved for dire circumstances (Joy et al., 1999). Because it is readily available and may be useful against pain, why not simply prescribe Marinol? While in some cases this may be a reasonable strategy, the utility of Marinol is hindered by its slow and unpredictable pharmacokinetics. This is a serious drawback because although an overdose of Marinol would almost certainly not be lethal, it does produce dysphoria at sufficiently high doses. Indeed, this characteristic of cannabinoids is the main limiting factor in dosing, so that the prototypic compounds may well produce unwanted side effects in humans at doses lower than those that produce maximal analgesic effects. These factors have led some medical marijuana users to prefer smoking, which allows the consumption of relatively small titratable amounts. One could imagine cases (e.g., terminal illness) in which health risks associated with inhalation of marijuana smoke are outweighed by the adverse effects of uncontrolled pain or nausea.

Another feature of cannabinoid pharmacology that should be noted is the possibility that the unwanted side effects can be dissociated from the therapeutic effects. One example of this may be found in the experimental compound ajulemic acid (1′,1′ dimethylheptyl-Δ^8-THC-11-oic acid). This compound, which is under development by Atlantic Technology Ventures (New York, NY, USA) produces analgesia, but it is almost entirely lacking side effects in animals (Burstein et al., 1998). This analgesic effect is blocked by the CB_1 receptor antagonist SR141716A. Yet, this compound exerts only modest inhibition of adenylyl cyclase via the CB_1 receptor (Rhee et al., 1997). This finding coincides with emerging reports that cannabinoid agonists are capable of differential stimulation of different G-proteins, resulting in different alterations in cell physiology. It is conceivable that the neurons that mediate pain inhibition may require one signal transduction pathway, while those that mediate dysphoria require another. Many questions about this and similar compounds are awaiting further research, but this appears to be a line of inquiry that may bear fruit.

It should also be noted that stimulation of CB_2 receptors may inhibit pain initiation (Calignano et al., 1998). Since

there are very few CB_2 receptors in the brain, it would appear that their activation would not produce any unwanted psychoactive side effects. The recent development of selective CB_2 agonists (Huffman et al., 1999) suggests that suitable compounds could be developed.

Another direction worthy of more research lies in the potential therapeutic value of drugs that would enhance the activity of endocannabinoids. We once envisioned pain therapies that operated by mobilization of endogenous opioid peptides. The disappointing results of much work in this area stemmed largely from the fact that the synthesis and inactivation processes are so similar amongst all peptides that selective agents for these neuromodulators never became available. In contrast, the known endocannabinoids are synthesized and degraded by what now appear to be relatively specific enzymes, and a selective transporter for the reuptake of anandamide has been identified (reviewed in Ameri, 1999; Childers & Breivogel, 1998; Ueda & Yamamoto, 2000). These findings raise the possibility that new drugs that block the reuptake, enhance the synthesis, or inhibit the breakdown of endocannabinoids may be effective therapeutic agents. In the same manner that levodopa exhibits a markedly improved therapeutic profile compared with apomorphine for treating Parkinson's disease, drugs that would modify endocannabinoid action may likewise be observed to produce pain relief with fewer side effects.

In summary, there remains little doubt that cannabinoids inhibit nociceptive neurotransmission. Mounting evidence further implicates endocannabinoids in pain regulatory circuitry in the CNS and the periphery. Further work in this area offers hope for new pharmacotherapies for pain, especially in instances where opiates either lack efficacy or produce intolerable side effects, such as in neuropathic and cancer pain.

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