Is cannabis an effective treatment for joint pain?

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ABSTRACT

Cannabis has been used to treat pain for thousands of years. However, since the early part of the 20th century, laws restricting cannabis use have limited its evaluation using modern scientific criteria. Over the last decade, the situation has started to change because of the increased availability of cannabis in the United States for either medical or recreational purposes, making it important to provide the public with accurate information as to the effectiveness of the drug for joint pain among other indications. The major psychotropic component of cannabis is Δ^9-tetrahydrocannabinol (THC), one of some 120 naturally occurring phytocannabinoids. Cannabidiol (CBD) is another molecule found in herbal cannabis in large amounts. Although CBD does not produce psychotropic effects, it has been shown to produce a variety of pharmacological effects. Hence, the overall effects of herbal cannabis represent the collective activity of THC, CBD and a number of minor components. The action of THC is mediated by two major G-protein coupled receptors, cannabinoid receptor type 1 (CB1) and CB2, and recent work has suggested that other targets may also exist. Arachidonic acid derived endocannabinoids are the normal physiological activators of the two cannabinoid receptors. Natural phytocannabinoids and synthetic derivatives have produced clear activity in a variety of models of joint pain in animals. These effects are the result of both inhibition of pain pathway signalling (mostly CB1) and anti-inflammatory effects (mostly CB2). There are also numerous anecdotal reports of the effectiveness of smoking cannabis for joint pain. Indeed, it is the largest medical request for the use of the drug. However, these reports generally do not extend to regulated clinical trials for rheumatic diseases. Nevertheless, the preclinical and human data that do exist indicate that the use of cannabis should be taken seriously as a potential treatment of joint pain.

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Introduction

Pain is one of the primary symptoms of joint disease and the major reason why patients seek medical advice. Unfortunately, at this point in time, we do not have a detailed understanding of how joint pain is generated under pathological conditions. When treating osteoarthritis (OA) pain, non-steroidal anti-inflammatory drugs (NSAIDs) are usually the initial drugs of choice in patients with mild to moderate pain (1, 2). However, the chronic use of NSAIDS is often problematic, particularly with elder patients owing to gastrointestinal and renal side effects. Opiates may be considered for patients who continue to have severe pain and who do not respond or cannot tolerate NSAIDs, and can provide relief in a subset of patients (1, 2), but tolerance, dependence and other adverse effects such as constipation often occur during continuous opioid use. Another serious problem is their abuse potential. Thus, even though long term use of opiates may sometimes produce pain relief, the current epidemic of opiate addiction in the United States clearly demonstrates the downside of using opiates as anodynes over extended periods of time. Although it is unlikely that the use of NSAIDS for the treatment of joint pain will be completely replaced in the near future, alternative treatments that are both effective and safe would be extremely welcome. One way these may be developed is through a better understanding of the physiology and pharmacology of the nerves that produce joint pain allowing the rational development of novel agents that selectively regulate their activity. However, there are also currently several possible avenues available that might produce new agents for the treatment of joint pain. One of the most obvious of these is cannabis.

Cannabis is anything but a new drug, having been used by humans for medical purposes for thousands of years. Some of the earliest evidence for

knowledge of the psychoactive properties of cannabis can be found in the *Shen-nung pen-ts'ao ching*, the world's oldest pharmacopeia, which describes Chinese practices from the time of Emperor Shen Nung (c. 2700 B.C.) (3). Later editions clearly describe the use of cannabis for a variety of conditions, including treating pain and inflammation (3). Indeed, cannabis has been continuously used for the treatment of pain in Asian countries from prehistory up until the present day (3). The drug was subsequently introduced into Europe and the United States in the 19th century and soon became widely used for its analgesic and other properties (4, 5).

So what happened? As the reader may be well aware, the highly restrictive legal status of cannabis in the United States and Europe beginning in the early part of the 20th century has made rigorous clinical evaluation of its effects using modern criteria virtually impossible. This situation has recently started to change. In spite of the fact that Federal laws still list cannabis as a Schedule I drug "having no medical utility", many individual states have moved to make the drug legal for "medical" purposes, or even for recreational use in some instances. It is therefore time to assess whether we might expect cannabis to be effective for joint pain and, ancient texts aside, what clear indications there are from the scientific point of view for believing that it might be useful.

This raises several questions. First of all, what is cannabis and what active molecules does it contain? Second, what is the evidence that any of these components might have beneficial effects on joint pain? Third, is there any evidence that these substances do actually ameliorate joint pain in animals and humans?

The components of cannabis

The term cannabis is used rather loosely to describe preparations of the plant *Cannabis Sativa* or its close relatives *Cannabis Indica* or *Cannabis Ruderalis* (6). Originally the plant grew as a tall gangling weed within the area around Northern India and the Himalayas but has been cultivated by man from ancient times (6). Cannabis is a valuable source of tough fibrous material, which is the basis of hemp cloth. Indeed, another term for cannabis is "hemp" or "Indian hemp." However, as discussed above, the plant has also always been used for its beneficial medicinal effects. Pharmacologically active parts of the plant include the leaves and flowering tops and particularly the resin (hashish, charas) that is secreted by glands (trichomes) in the stems, flowers and leaves of the plant (5). The drug can be smoked, eaten or extracted using alcohol to produce a tincture.

As organic chemistry developed in the early part of the 19th century, progress began to be made in isolating the molecules responsible for the pharmacological effects of natural products. Starting with morphine in 1805, numerous alkaloids were isolated from different natural sources, which helped to "explain" pharmacological activities associated with these materials. However, the identity of the substances responsible for the pharmacological effects of herbal cannabis remained elusive until well into the 20th century, and it was not until 1964 that Δ^9-tetrahydrocannabinol (THC) was shown to be the component of herbal cannabis responsible for producing its psychotropic effects (5). Interestingly, THC does not contain a nitrogen atom and so is not an alkaloid, distinguishing it from many of the natural products isolated from other plant sources. It also explains its lipid like properties that make it chemically difficult to work with. THC is the archetypal member of the family of cannabis derived molecules which are known as *cannabinoids* or, considering subsequent developments in the field of cannabis medicinal chemistry, *phytocannabinoids*, indicating that they are natural plant products (6). Currently, some 120 cannabinoids have been identified from crude cannabis, although many of these are minor components (6). Among these phytocannabinoids are THC, cannabidiol (CBD, the major phytocannabinoid apart from THC), cannabinol, cannabigerol, cannabichromene, cannabitriol, and cannabicyclol (6) (Fig. 1 – generated using PubChem Substance (7)).

As indicated, a very large number of beneficial effects have been attributed to the use of cannabis beside its psychotropic actions, including effects on appetite, pain, metabolism and inflammation, Alzheimer's disease, multiple sclerosis, stroke, traumatic brain injury, Parkinson's disease, epilepsy, and various aspects of cancer (pain, nausea, *etc*.). The list is endless. This raises an interesting question. Which phytocannabinoids are responsible for all of these therapeutic effects? Is THC responsible for all of them or are there contributions of the other molecules as well? Smoking or eating cannabis will obviously involve ingesting a large number of different phytocannabinoids. Moreover, the exact combination of molecules ingested will depend on the strain of cannabis used, growth conditions and numerous other factors. It is therefore essential to deconvolute the effects of all of the major phytocannabinoids on a particular endpoint such as pain if we wish to understand the potential effects of the drug. In particular, when considering the potential effects of cannabis, we should be interested in the actions of both THC and CBD, the two major phytocannabinoids, as well as any beneficial interactions between them, and whether cannabis is superior to either pure substance used by itself.

The endocannabinoid system

What is the signal transduction mechanism through which cannabinoids act? Two major observations "explain" the effects of THC. Two G-protein coupled receptors have been identified that mediate its cellular effects. These two receptors, known as cannabinoid receptor type 1 (CB1) (8) and CB2 (9), have closely related amino acid sequences. Their transmembrane regions are approximately 70% similar (9), and they have characteristic expression patterns throughout the body. The major receptor in the nervous system is the CB1 receptor (10), which is also present in other tissues such as the adrenal gland, adipose tissue, heart, liver, lung, prostate, uterus, ovary, testis, bone marrow, thymus, tonsils – but poorly expressed in the respiratory centres of the brainstem indicating that respiratory depression, one of the major problems associated with opiates, would not occur with

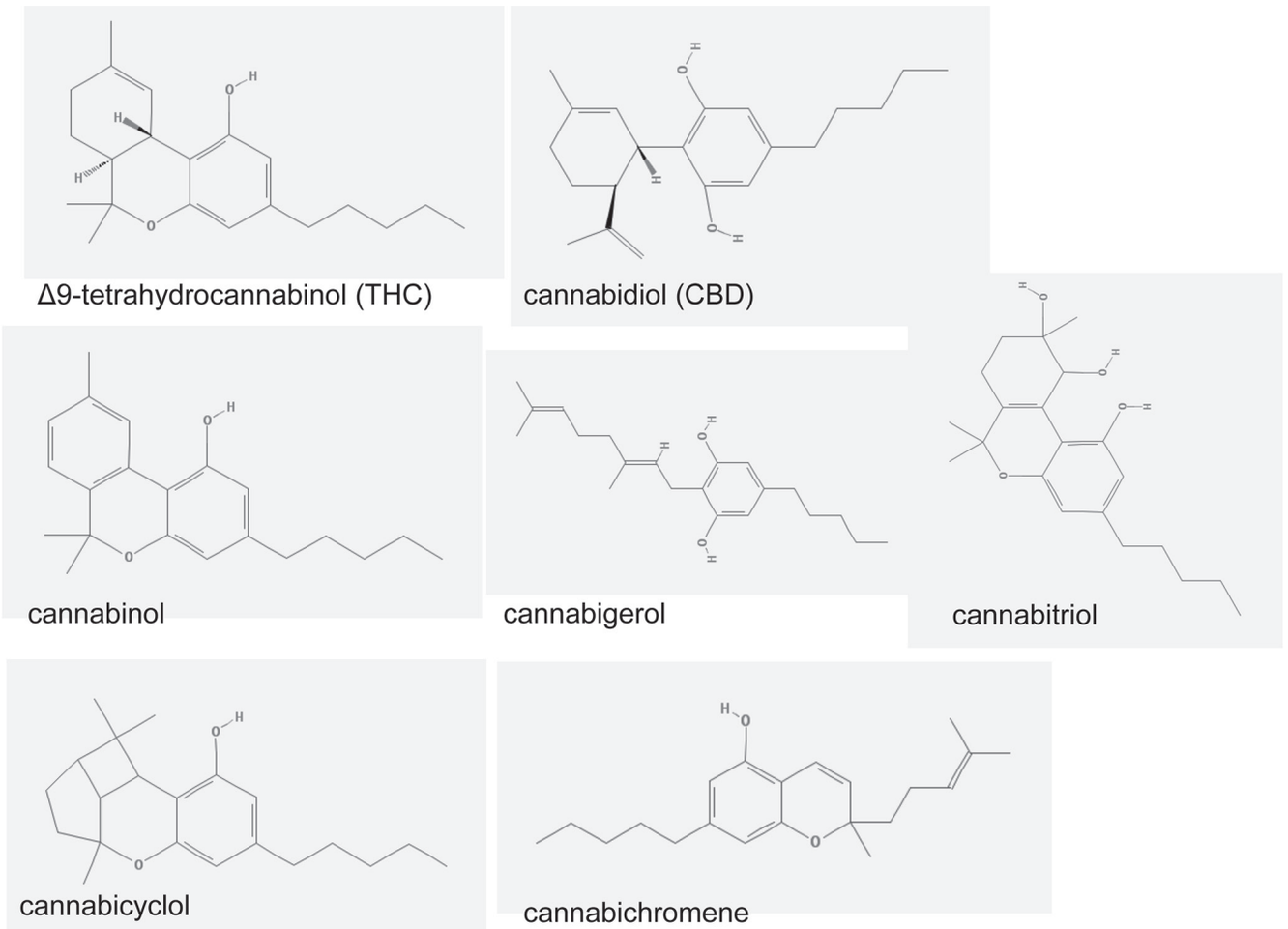

Fig. 1. Chemical structures of the major phytocannabinoids.

cannabinoid based analgesics. On the other hand, the CB2 receptor is rarely expressed in neurons, although there may be exceptions such as in the dorsal root ganglia (DRG, see below) (11). CB2 is widely expressed in the immune system, but can also be found in bone, the gastrointestinal system, and in activated microglia in the central nervous system under some circumstances (11).

The natural activators of CB1 and CB2 receptors are a family of arachidonic acid derived molecules known as *endocannabinoids*. Here again, there are many of these, but the major members of the family are anandamide (arachidonylethanolamide, AEA) and 2-arachidonylglycerol (2-AG) (6) (Fig. 2 – generated using PubChem Substance (7)). Biosynthetic and degradative pathways for these molecules have been clearly identified: fatty acid amide hydrolase (FAAH) normally degrades anandamide, and monoacylglycerol lipase (MGL) degrades 2-AG, arachidonic acid being produced in both instances. Moreover, a number of drugs that inhibit these enzymes have been produced, providing a mechanism for increasing the levels of either endocannabinoid *in vivo* (12, 13). It is interesting from the pharmacological point of view that both phytocannabinoids like THC and the major endocannabinoids act as partial agonists at the cannabinoid receptors (14).

In addition to the "classical" cannabinoid receptors, there are now several other receptors that have been suggested as possible mediators of some of the effects of phytocannabinoids. These include the recently deorphanised GPCRs: GPR18, GPR55 and GPR119 (15). GPR18 and GPR55 receptors do not share extensive sequence homologies with CB1 and CB2, which would presumably result in selectivity for a different set of ligands. Indeed, the normal endogenous ligand for GPR55 is probably lysophosphatidylinositol rather than an endocannabinoid (15). The cognate ligand for GPR18 on the other hand is reported to be the anandamide derivative N-arachidonylglycine. Interestingly, both GPR18 and 55 may also recognise the phytocannabinoid cannabidiol (CBD) (15), which has no agonist activity at CB1 or CB2 receptors. GPR55 has been shown to be antagonised by CBD in several studies (15). GPR18 expression has been mostly associated with immune cells. GPR55 is expressed in numerous brain regions as well as in the DRG where it is restricted to larger diameter neurons, hippocampus, frontal cortex, cerebellum, striatum and hypothalamus. There is also evidence of GPR55 expression in the immune system, and it is expressed in microglia and bone. However, the role of GPR55 in pain remains unknown, as GPR55 knock-out mice have recently

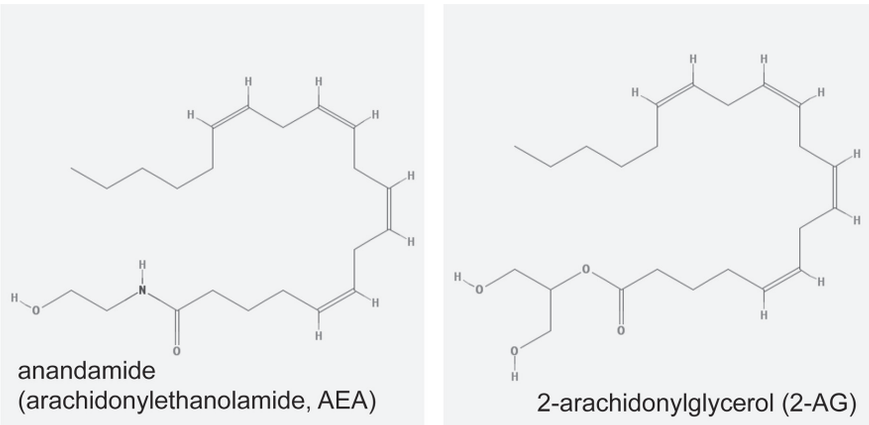

Fig. 2. Chemical structures of the major endocannabinoids.

been shown to behave similarly to control mice in a variety of inflammatory and neuropathic pain models (16).

There are also several possible sites of cannabinoid action which are not GPCRs. Transient receptor potential (TRP) channels are a widely expressed group of ligand activated ion channels. Some members of the TRP family play a central role in sensory physiology acting as chemical receptor/transducers expressed by sensory neurons or cells that act in close proximity to them. The role of TRP channels in the detection of painful stimuli is well established. One characteristic that is shared by many TRPs is their ability to be activated or "sensitised" by lipids, particularly products of the phosphatidylinositol 4,5-bisphosphate (PIP2) signalling pathway. Consistent with their lipid like characteristics, it has also been demonstrated that several endocannabinoids can activate several TRPs including TRPV1-4, TRPM8 and TRPA1 (17). In addition, several phytocannabinoids share this ability, leading to the suggestion that TRPs act as "ionotropic" cannabinoid receptors (6). Finally, THC has also been shown to activate peroxisome proliferator-activated receptor gamma (PPARγ), resulting in vasorelaxation, reduction of tumour growth rate, and other actions preclinically (6).

In summary, although the actions of cannabinoids have traditionally been thought to be mediated by CB1 and CB2 receptors, it is becoming clear that other signal transduction mechanisms may be involved in some of their actions.

Synthetic cannabinoids

In the same way that an increased understanding of the medicinal chemistry and pharmacology of morphine led to the development of numerous useful synthetic and semisynthetic opiate drugs, there have been similar developments in the field of cannabinoid pharmacology. As a result, there is now a complete range of small molecules that can act as agonists, partial agonists, antagonists, inverse agonists and biased agonists at the two cannabinoid receptors (18). Many of these molecules are actually much more potent than the phytocannabinoids and act as full agonists at CB1 and CB2 receptors (18).

Although most of the initial attempts to make cannabinoid like drugs did not stray too far from the structure of the phytocannabinoids, more recent developments have produced a number of structural types that bear no apparent chemical similarity to THC but have nevertheless been shown to strongly activate CB1 and/or CB2 receptors (18). Interestingly many of these molecules resulted from development programs that took place in large pharmaceutical companies such as Pfizer, Eli Lilly and Sterling-Winthrop in an attempt to produce non-opiate drugs for pain. Indeed, many of these substances proved to have potent analgesic effects in a variety of pain models. However, the fact that they also produced powerful psychotropic effects limited their ultimate attractiveness as drug development targets. Currently these advances have taken a somewhat ominous turn. Many of the most potent cannabinoid agonists have been taken up as illegally synthesised street drugs (19). The use of these extremely potent substances has often resulted in the incapacitation or even death of individual consumers. In spite of this unfortunate turn of events, one should be aware that some of these substances, used at appropriate doses and under the appropriate conditions might turn out to have useful therapeutic effects for several indications including pain. In addition to synthetic cannabinoids, other drugs are available that are based on the endocannabinoid system. Synthetic endocannabinoids have been produced that exhibit potent activity *in vivo* and selective FAAH and MGL inhibitors have been developed that can be used to raise levels of endocannabinoids *in vivo* (20).

One should also remember that although cannabis is a Schedule I drug, strangely this is not the case for pure THC, known as Dronabinol, which is marketed under the name Marinol. This is a Schedule III drug and can therefore be prescribed for a number of disorders (5). It is most commonly employed to treat nausea in connection with chemotherapy. In addition, Nabilone, a close semisynthetic derivative of THC, is also available for the same purposes (5). Nabilone is marketed under the name Cesamet. In many countries, Nabiximols, which is sold under the name Sativex, is also available. This is an oral spray containing approximately equal amounts of THC and CBD and therefore better mimics the effects of actually taking herbal cannabis, which contains both of these molecules. Nabiximols in most countries is sold for a number of purposes including the treatment of neuropathic pain, particularly in the context of multiple sclerosis (phase 3 clinical trials in the US are ongoing) (5). A limited, but ever increasing amount of data, has been obtained assessing the effectiveness of different types of cannabinoid molecules for the control of pain in both pre clinical and clinical situations.

Preclinical studies on cannabinoids and pain

Based on the ancient literature, informal reports and the results of drug

development programs, one might anticipate that cannabinoids would have a beneficial effect on pain of different types. Given the current problems with drug abuse encountered by people using opiates for long term pain relief, there is a pressing need for non opiate analgesics, and the effects of cannabinoids have been examined with great interest. Generally speaking, cannabinoid agonists have been repeatedly shown to produce antinociceptive effects in numerous animal pain models. Moreover, considerable evidence also exists demonstrating that mobilisation of the endocannabinoid signalling pathway represents an important factor in the body's response to pain. The distribution of cannabinoid receptors is consistent with this idea. CB1 receptors are expressed by neurons in many parts of the neuraxis, and CB1 mediated modulation of neural pathways in the cortex, amygdala, rostroventral medulla, periaqueductal gray and the spinal cord can inhibit nociceptive processing. Injection of CB1 agonists into many of these brain regions or intrathecally elicits an antinociceptive response (21). Moreover, analgesia evoked by electrical stimulation of brain regions such as the periaqueductal grey is blocked by CB1 antagonists, indicating a role for endocannabinoid signalling in this response (22). In the peripheral nervous system, CB1 receptors are also expressed in many DRG neurons, including nociceptors (21).

Consistent with these data, several papers demonstrate the ability of systemic CB1 agonists or inhibitors of FAAH and MGL to elicit antinociceptive effects in different rodent models of pain (21). Interestingly, CB2 agonists also have many positive effects in rodent pain models, presumably due to their anti inflammatory effects, including their ability to reduce the activation of microglia in the central nervous system. As THC activates both of these receptors, one would predict that smoked herbal cannabis might reduce pain through both of these mechanisms. It should be noted that there are a couple of older reports suggesting that CB2 receptors are also expressed in DRG neurons, including nerves innervating human osteoarthritic synovium, raising the possibility that activation of CB2 receptors might also directly regulate the excitability of nociceptors (11). Indeed, this possibility has been confirmed in one study of OA related pain in rats (23).

One potential problem, however, is that drugs like THC that work by activating CB1 receptors in the central nervous system are likely to produce psychotropic effects. However, it is now believed that many of the potentially beneficial effects of cannabinoids such as pain relief, amelioration of certain intestinal and cardiovascular disorders, and inhibition of cell proliferation and spread of many cancers can be produced by selectively activating CB1 and/or CB2 receptors expressed outside the central nervous system (24). This raises the possibility that developing peripherally restricted molecules that selectively activate cannabinoid receptors located outside the blood-brain barrier may be useful for some purposes. Attention has focused particularly on the possibility of developing such medicines for pain relief. The relative roles of central and peripheral CB1 receptors in the antinociceptive effects of a mixed CB1/2 agonist were therefore assessed in mice in which the CB1 receptor had been selectively deleted from nociceptors expressing the sodium channel $Na_V1.8$ (25). Under such circumstances mice showed an enhanced response to both inflammatory stimuli and in the spared nerve injury model of neuropathic pain. Moreover, the analgesic effects of systemically administered mixed CB1/2 agonist were reduced, although not entirely absent. These results indicate that there is an important role for the peripheral endocannabinoid system in the regulation of pain and of peripheral CB1 receptors in the antinociceptive actions of cannabinoids. In keeping with this conclusion, several studies have tested the effectiveness of peripherally restricted cannabinoid receptor agonists or FAAH/MGL inhibitors in pain models and have found them to be effective (26, 27), suggesting that drugs that target CB1 receptors expressed in joint tissue rather than centrally might be effective is the treatment of joint pain. However, thus far, peripherally restricted CB1 agonists have failed in clinical trials of pain due to cardiovascular and metabolic side effects (27).

Of course, cannabis doesn't only contain THC but a large number of other related phytocannabinoids as well. There is a widely held view that natural cannabis may have advantages over pure THC in a number of cases owing to the "added value" of the beneficial effects produced by these other molecules. It is certainly clear that the psychotropic effects of cannabis are related to activation of CB1 in the brain. As other major phytocannabinoids such as CBD don't produce such effects, it is argued that their therapeutic benefits would be free of what is considered by many to be an undesirable side effect. It has even been suggested that CBD may antagonise the psychotropic effects of THC (28), and so preparations that contain both of them, such as herbal cannabis or preparations like Nabiximols, might actually be better than either agent alone. There has been quite a lot of effort put into investigating the pharmacology and mechanism of action of CBD, including its effects in pain models. While there is now considerable evidence that CBD does produce interesting effects on pain and other disease syndromes, it has been difficult to pin down its precise mechanism of action, which makes the entire enterprise somewhat unsatisfactory. Indeed, a recent review of the effects of CBD listed 65 potential molecular targets for this molecule (29). According to one line of reasoning, although CBD doesn't seem to bind to CB1/2 receptors as a conventional orthosteric agonist it has been shown to antagonise the effects of the synthetic CB1/CB2 agonists CP55940 and WIN55212 at both the mouse CB1 and at the human CB2 receptors and has therefore been proposed as having some type of allosteric activity at these targets (30). CBD may also have effects at other GPCRs. For example, it has been reported to act on the two novel cannabinoid receptors GPR18 and GPR55 (15). CBD has been reported to act as a GPR55 antagonist, as well as a weak partial agonist

of GPR18 (15). Moreover, CBD acts as a full 5-HT1A agonist, 5-HT2A weak partial agonist, and non-competitive 5HT3A antagonist (6). The ability of CBD to activate the A1A adenosine receptor has also been proposed (29). In addition, the many potential effects of CBD extend well beyond the sphere of GPCRs (29).

Although CBD has been shown to have a large number of effects, generally speaking these occur at relatively high concentrations. CBD administration has been shown to have beneficial effects in some pain models (*e.g.* paclitaxel chemotherapy associated pain (31)) but it isn't really clear whether CBD actually reaches high enough concentrations *in vivo* to produce such effects through any of the numerous molecular mechanisms suggested in the literature (29). Hence, although it does appear that CBD can be of benefit for treating pain under some circumstances, the molecular/cellular basis for such effects are still far from clear.

The cannabinoid system in animal models of joint pain

The above discussion indicates that there are clear indications that cannabinoids can reduce pain in several animal models using a variety of signal transduction mechanisms, but are they effective in models of joint pain in particular? Although the number of studies relating to the function of the cannabinoid system in arthritic joints is somewhat limited, they do suggest that cannabis might well be effective in treating arthritic pain either through direct effects on nociceptive neurons or through a reduction in painful joint inflammation.

Given the fact that CB1 and CB2 receptors and a variety of "non classical" cannabinoid receptors are expressed in different joint tissues including neurons, chondrocytes, synovium and bone (32), it is not surprising that cannabinoids would exhibit activity in joint disease. We should note that this is not just the case in animal models. The main components of the endocannabinoid signalling system, including CB1 and CB2 receptors, have been found in synovial biopsies taken from patients undergoing total knee arthroplasty for both advanced osteoarthritis and rheumatoid arthritis (33). The endocannabinoids AEA and 2-AG were also detected in the synovial fluid of these patients at levels that were much higher than in normal control patients, providing further evidence for a functional endocannabinoid system in osteoarthritic joints (33). Spinal cord levels of AEA, 2-AG and their synthesising enzymes were also increased in the rat monosodium iodoacetate (MIA) model of OA (34). Endocannabinoids have been shown to limit the excitability of spinal neurons and DRG nociceptors in osteoarthritic animal models (34-37), suggesting that endocannabinoid signalling may function as a feedback system for the limitation of pain in patients with joint disease. Interestingly, overexpression of CB2 receptor attenuated mechanical allodynia associated with MIA induced OA in mice (38), further suggesting a role for endocannabinoid signalling in this model.

Local peripheral administration of a CB1 agonist arachidonyl-2-chloroethylamide (ACEA) reduced the firing of mechanosensitive knee afferents in both control rats and those with MIA associated knee pathology, consistent with a direct inhibitory action on CB1 expressing joint nociceptors under these circumstances (35). The effects of ACEA were inhibited by antagonists of both CB1 receptors and TRPV1 channels. In contrast, the CB1 receptor antagonist AM251 significantly increased mechanosensitivity in OA afflicted joints but not in controls, indicating a role for endocannabinoid activation of CB1 receptors under pathological circumstances. These results clearly suggest that in MIA induced OA there is activation of CB1 receptors expressed by the knee that in turn decrease the excitability of afferent nociceptors.

The effects of CB2 agonists in OA are less clear cut. Schuelert *et al*. examined the effects of GW405833, a CB2 agonist, in the rat MIA model (23). These authors confirmed the older reports that DRG neurons express CB2 receptors even under normal conditions. They also demonstrated CB2 expression in the synovium. Interestingly, in both small DRG neurons and the synovium, TRPV1 was always coexpressed with CB2. Local administration of GW405833 to control animals inhibited the electrical response of joint nociceptors to a painful knee twist. On the other hand, the same drug sensitised nociceptors in MIA treated rats. According to the authors, this "paradoxical" effect appeared to be due to the fact that in MIA animals the primary effect of the drug was to directly activate TRPV1 channels on nociceptors leading to an enhanced release of CGRP. In contrast to these results, systemic administration of the CB2 agonists A-796260 and JWH133 were reported to produce analgesia in MIA rats (37, 39). Of course, following systemic administration, these drugs would also have access to sites outside the knee such as the central nervous system, which could represent their major site of action under these circumstances. Examination of the role of endocannabinoids in OA was further investigated through local administration of the FAAH inhibitor ULRB597 which would produce increases in anandamide. This had the effect of inhibiting the activity of joint afferents in MIA treated or Dunkin-Hartley guinea pigs, but the drug had no effect on normal controls (36). As such, effects were blocked by a CB1 but not a CB2 agonist, supporting the idea that activation of joint CB1 receptors may be a useful strategy for inhibiting OA associated joint pain. Also in the MIA rat model, a potent and selective MGL inhibitor (MJN110) was able to acutely reverse both weight-bearing asymmetry and mechanical allodynia of the hind paw via both CB1 and CB2 (40).

There are few preclinical studies on the effects of CBD in joint disease. Malfait *et al*. demonstrated that i.p. or oral delivery of CBD after onset of symptoms in the collagen-induced arthritis mouse model (rheumatoid arthritis model) blocked progression of arthritis via an immunosuppressive pathway (41). Interestingly, a bell-shaped dose dependency was observed, which has been observed for other cannabinoids as well. Hammell *et al*. examined the effects of transdermally administered

CBD in a model of inflammatory joint disease (complete Freund's adjuvant) in rats (42). CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. CBD also produced a reduction in CGRP expression in the dorsal horn, a reduction in the number of activated microglia and a reduction of TNF-α production by DRG neurons. Unfortunately, in spite of the fact that the drug produced such clear cut effects, no further studies were performed to assess its mechanism of action. Studies have also been carried out using O-1602, a semisynthetic analogue of CBD, in an acute inflammatory model of joint pain induced in rats using intra-articular kaolin/carrageenan (43). The drug produced a clear reduction in mechanically evoked discharges of joint nociceptors. This effect was not inhibited by CB1 or CB2 antagonists, consistent with the well established observation that CBD does not activate these receptors. On the other hand, the effects of O-1602 were inhibited by a blocker of GPR55, suggesting that activation of such receptors might also represent a route for inhibiting joint pain.

It should also be pointed out that the benefits of cannabinoids for treating OA may extend beyond their effects in pain and inflammation. In particular, several papers have now demonstrated that chondrocytes express cannabinoid receptors, including human osteoarthritic chondrocytes (44), and activation of these receptors has a protective effect on cartilage, particularly CB2 (45). Chondrocytes express both CB1 and CB2 receptors and synthetic cannabinoid agonists such as WIN-55,212-2 and HU-210 produce a variety of effects on these cells (46). For example, cannabinoid agonists reduced both basal and IL-1 stimulated gene and protein expression of MMP-3, MMP-13 and ADAMTS-4 and inhibited IL-1 stimulated proteoglycan and collagen degradation. Bone may also be another target for cannabinoid action. CB1 knock-out mice are more susceptible to developing age-related osteoporosis (47), suggesting that some non-psychoactive cannabinoids may be a useful therapy for diseases such as osteoporosis in which bone resorption is a central feature.

Overall, there is strong support for the idea that the endocannabinoid system operates to limit pain in joint disease and that activation of this system with the appropriate cannabinoids is effective in limiting joint pain at both central and peripheral sites.

Effects of cannabinoids on human joint disease

Considering what is now known about the distribution of the endocannabinoid system and the generally positive results from preclinical studies, it would be reasonable to expect that the use of cannabis would have a beneficial effect on pain, including joint pain in human subjects. Whether this is actually the case is of considerable importance given the increasing availability of medical or recreational cannabis in the USA and elsewhere. Although much of the present interest is centered on the use of herbal cannabis, this is also a good time to reconsider the use of currently available cannabis related products such as Dronabinol, Nabilone and Nabiximols.

One thing that is already abundantly clear is that patients like to self medicate themselves using herbal cannabis for joint pain. Indeed, it is the most commonly requested use of the drug (48). Many individuals report that they do benefit from its use. For example, a recent survey of users in Arizona reported a very high frequency of satisfaction with the results-77% of fibromyalgia patients, 63% of patients with arthritis, and 51% of patients suffering from neuropathic pain reported experiencing "a lot or almost complete overall pain relief" (4). Most patients suffering from these conditions (94% of patients with fibromyalgia, 81% of arthritic patients, and 61% of patients with neuropathy) also found that they were able to lower their use of other medications such as opioids. Of course, one also has to consider the beneficial effects of cannabis on conditions such as insomnia, anxiety, and depression, which are frequently comorbid with pain in patients with joint disease, may have influenced these informal reports that do not differentiate between benefits to overall quality of life from specific indications such as pain.

Indeed, informal reports are not the same as controlled clinical trials. When these are considered, the evidence is much less clear cut. Although significant preclinical data have highlighted the potential therapeutic benefits of smoked cannabis for pain relief in patients suffering from osteoarthritis, rheumatoid arthritis, fibromyalgia, and cancer, no randomised controlled trials (RCTs) for smoked herbal cannabis have been carried out for these conditions.

The situation is complicated. For example, there are numerous ways that people can take herbal cannabis – smoking, vaping or ingesting brownies or candies. Secondly, not all strains of cannabis are the same and may differ substantially in terms of their overall content of THC and CBD or even other naturally occurring cannabinoids. Then there is also data on individual products such as Dronabinol, Nabilone and Nabiximols to be considered. In order to begin getting to grips with the problem the US National Academy of Sciences commissioned a report on all the data on cannabis use since 1999. The report was issued in Jan 2017 (5). The committee did come out with some specific recommendations encapsulated in the following statement, "In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics. In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms. In adults with multiple sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient reported spasticity symptoms. For these conditions, the effects of cannabinoids are modest; for all other conditions evaluated, there is inadequate information to assess their effects." The report did not consider joint pain as a separate modality, but it is clear that the "chronic pain" population likely contained numerous patients suffering from these complaints.

Individual RCTs examining the effects of cannabinoids on neuropathic pain

have produced some positive results. Individual cannabinoids (Dronabinol, Nabilone, Nabiximols) have been tested as adjunct analgesics in conditions such as multiple sclerosis, avulsion injuries to the brachial plexus, and painful diabetic neuropathy (49). Although the data from such studies suffer from deficiencies (low numbers, bias etc), meta-analyses of these trials have reported small positive effects, particularly for Nabiximols, which because it contains both THC and CBD most resembles the chemical composition of smoked cannabis (50).

There has also been a limited examination of the effects of individual cannabinoids in patients with rheumatic diseases, including inflammatory arthritis, OA, rheumatoid arthritis, and fibromyalgia. A meta-analysis of Canadian data concluded that no positive effect could be detected, but the authors also pointed out that the quality of the data was not very good (small numbers, limited durations, bias *etc*.) and recommended more extensive trials in the light of positive preclinical data and reports from non controlled human trials (51). Another meta-analysis originating in Germany also found little effect in patients with rheumatoid arthritis or fibromyalgia, but again commented on the inadequacy of the data and also how their findings were at odds with self reporting of patients who took the drug (52). They pointed out, for example, that in the UK a survey of 2969 patients, 155 (16%) had obtained herbal cannabis specifically for the control of their "arthritis" symptoms. Similarly, in a recent online patient survey, the US National Pain Foundation and National Pain Report reported that 1300 fibromyalgia patients rated cannabis as more effective than two SNRI's (duloxetine, milnacipran) or pregabalin (53). Moreover, whereas the vast majority of patients rated these three drugs as "unhelpful," 62% rated cannabis as "very effective".

Conclusions

So, is herbal cannabis likely to be helpful for treating joint pain? In spite of the fact that it has been used for this purpose for thousands of years, it has to be concluded that rigorous clinical evidence is really not available supporting this claim at this point in time. On the other hand, there are numerous surveys suggesting that patients themselves are convinced that they do benefit from using it. Moreover, cannabis does seem to be helpful in other chronic pain syndromes (neuropathic pain, cancer pain *etc*.). Furthermore, preclinical data has clearly demonstrated that the different elements of the endocannabinoid signalling system are expressed in the appropriate tissues in humans and animals and that cannabinoids do produce beneficial effects in animal models of joint pain. So, the situation should certainly be viewed as promising. Another thing that is not clear is whether CB1 active cannabinoids such as THC are essential for producing analgesic effects or whether non psychotropic substances such as CBD are also helpful. Clearly it would be advantageous to have peripherally active cannabinoids, or non psychotropic molecules that really benefited patients. Given the fact that 22.2 million Americans over the age of 12 use cannabis or related products every month (54), an accurate assessment of what the drug is actually good (or bad) for is a pressing matter. It is clearly important for there to be a relaxation of restrictions on cannabis so that large scale clinical trials can be conducted in the near future. The availability of medical cannabis is rapidly becoming a reality throughout the world, and its effects on the human population need to be accurately assessed.

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