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Emerging properties of cannabinoid medicines in management of multiple sclerosis

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Use of cannabis as a medicine for numerous conditions has a well-documented history stretching back thousands of years. With the identification of an endogenous system of receptors and ligands in recent years, abundant experimental data have reinforced the anecdotal claims of people who perceive medicinal benefit from the currently illegal consumption of cannabis. This, combined with data from recent clinical trials, points to the prospect of cannabis as a medication in the treatment of multiple sclerosis and numerous other medical conditions.

Introduction

Although there have been numerous anecdotal claims of the medical benefits of cannabis for a variety of medical conditions over the past few thousand years [1], there has recently been renewed interest, largely as a result of patient pressure, in the potential therapeutic value of this drug in several conditions. An estimated 15% of people with multiple sclerosis (MS) use cannabis for symptom relief [2]. Better understanding of the biological actions of cannabinoids now appears to support patient and clinical observations of the actions of cannabis in controlling symptoms such as muscle stiffness, spasms and pain [2–4], and raises the possibility of slowing neurodegenerative processes in diseases such as MS. Recent experimental advances in understanding the biological actions of cannabinoids have reinforced the widespread patient perceptions of their potential therapeutic benefit in symptom alleviation. However, clinical evidence remains equivocal and underlines the requirement for improved quantitative assessments of conditions such as spasticity.

Multiple sclerosis

Multiple sclerosis is an inflammatory, demyelinating disease of the CNS; it is the most common cause of non-traumatic neurological disability in young adults of northern European descent and it affects 2–3 million people worldwide [5,6]. The disease most commonly presents as a series of relapsing–remitting episodes of neurological deficit. This eventually develops into a chronic, progressive phase with no remission and with increasing disability over time [5,6]. The chronic axonal degeneration underlying active episodes and progression of MS has led to the realization that MS can be classified as a neurodegenerative disease. In MS, the time taken to convert to a secondary progressive neurodegenerative phenotype can vary widely between individuals [5]. However, once a threshold of disability has been reached, disease progression is remarkably uniform [7,8]. Although the relapsing–remitting nature of the disease might be accounted for by immune-mediated block of conduction and destruction of CNS myelin followed by lesion resolution and limited myelin repair, it is less clear which mechanisms account for conversion to the chronic neurodegenerative secondary phase and development of primary progressive MS, which usually exhibits less-inflammatory activity [7–10]. This conversion and progression are largely refractory to currently available MS therapies, which focus on immunomodulation; a shift of focus to neuroprotection is urgently needed [9–11]. Recently, axonal pathology during MS has been re-examined and it has been established that CNS atrophy and axonal loss coincides with inflammatory lesion formation, and is evident by the time of diagnosis. This might be accommodated initially by remodeling of neuronal circuits (neural plasticity). However, as disease continues, a threshold is reached beyond which permanent impairment and increasing disability are established [9–11]. This can lead to the development of additional distressing symptoms such as incontinence, limb tremor, nystagmus (uncontrollable eye tremor), pain, muscle spasms and spasticity, which have a major negative impact on quality-of-life indices [5]. Spasticity is a highly prevalent consequence of MS, leading to increased disability and reduced independence [12]. Treatment of spasticity can be suboptimal in a large proportion of the population and improved therapeutic agents are being sought [12]. During many neurodegenerative diseases, symptoms occur because homeostatic control of neurotransmission is lost, possibly owing to increased neurotransmission by excessive signaling of excitatory circuits, due to loss of inhibitory circuits [13]. Study of the endogenous cannabinoid system has revealed the importance of endocannabinoids in modulating neurotransmitter release by activating presynaptic CB_1 receptor expression [14]. This raises the possibility of therapeutic intervention in CNS events using cannabinoid drugs, for controls of symptoms and neurodegenerative processes. Greater

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understanding of the endogenous cannabinoid system has enabled a clearer understanding of how cannabinoid drugs act in the treatment of neuromuscular problems such as spasticity.

The endocannabinoid system

The endocannabinoid system is a regulatory pathway identified following the study of plant-derived narcotics from *Cannabis sativa* (the psychoactive component of which is Δ^9-tetrahydrocannabinol, THC) [15] and is involved in homeostatic control of signaling between neurons. Since the cloning of the neuronal cannabinoid receptor CB_1 [16], which is agonized by THC, the past decade has seen a huge increase in research in this new field. The CB_1 receptor is the most abundant G-protein-coupled receptor in the CNS [17]. A second, peripheral cannabinoid receptor CB_2 has been cloned; this is predominantly expressed by cells of the immune system [18], and at least one additional cannabinoid receptor has been identified by pharmacological studies [17]. CB_1 and CB_2 receptors inhibit adenylyl cyclase activity via G_i signal transduction proteins and both stimulate mitogen-activated protein (MAP) kinase activity. The CB_1 receptor can also inhibit Ca^{2+} channels and D-type K^+ channels, and can stimulate A-type and inwardly rectifying K^+ channels [17,19]. Endogenous ligands for these receptors, such as the endogenous fatty-acid derivatives arachidonoylethananolamide (anandamide) [20] and 2-arachidonoyl glycerol (2-AG) [21], have been isolated. These endocannabinoids are formed 'on demand' by enzymatic cleavage of membrane precursors following postsynaptic neuronal activation by neurotransmitters. Once released, anandamide and 2-AG act retrogradely by binding to presynaptic CB_1 receptors, which inhibit further neurotransmitter release [14]. They are then degraded by cellular uptake by a putative transport system followed by enzymatic hydrolysis [22,23]. The elements of the endocannabinoid system are also affected by the consumption of cannabis.

Pharmacology of cannabis

There can be >60 cannabinoid compounds among ~500 other compounds present in extracts of *C. sativa*; chief among these is THC, which is responsible for the psychoactive effects of cannabis and for many or all of the potential medicinal effects [24,25]. Because CB_1 is widely expressed in the CNS, separation of beneficial from psychoactive effects of cannabis is essentially impossible, although the latter can be reduced by dose-titration. Marinol® (synthetic THC) is a licensed treatment for chemotherapy-associated nausea and appetite loss in AIDS wasting. There are numerous anecdotal reports of self-medication with cannabis by MS patients to treat symptoms, particularly neuromuscular problems [2–4]. The psychoactive effects of cannabis are mediated by the CB_1 receptor, producing a mildly euphoric 'high' with slight changes in motor and cognitive function. In some cases, unpleasant effects such as anxiety, panic and paranoia are experienced. Acute psychosis, hallucination and delusions are also experienced occasionally by a few individuals [26]. Although THC can exert suppressive effects on the immune system (with potential benefit in autoimmune syndromes) in experimental animals [27–29], this occurs at doses that probably are not achieved in humans and can be largely discounted as a potential side-effect of therapeutic use. The other main cannabinoid of current medical interest is the non-psychoactive cannabidiol (CBD). This might also inhibit the neuronal uptake and hydrolysis of anandamide, which could stimulate the disease-modifying potential of the endocannabinoid system [30], although such an effect was not evident in experimental spasticity [31,32]. CBD can also function as a neuroprotective antioxidant [33] and has been reported to modulate the release of inflammatory mediators from cells of the immune system in a model of rheumatoid arthritis [34,35]. However, CBD has also been reported to modulate some psychotropic effects of THC, such as anxiety [35] and potentially to enhance the bioavailability of THC by inhibition of THC metabolism [36]. An extract purified from defined mixtures of THC-rich and CBD-rich *C. sativa* varieties formulated for a sublingual spray (Sativex®) and an orally-administered extract of THC and CBD (Cannador®) are currently being used in clinical trials.

Cannabinoids and MS

What is the evidence for therapeutic benefits of cannabis in MS? Animal studies in experimental models of MS have demonstrated the efficacy of CB_1 receptor agonism in the treatment of pathological signs, notably spasticity and in some instances limb tremor [32,37,38]. Although THC appears to be the major agent in cannabis that controls experimental spasticity, CBD failed to demonstrate efficacy [32,39] via CB_1-dependent mechanisms [32,40]. Importantly, cannabinoid-mediated control of these disease processes involves inhibition of receptor function. Owing to inflammatory CNS insult and the development of progressive disability in experimental models of MS, endocannabinoid levels increase in mice that show spasticity due to spinal cord pathology [31]. Although blockade of cannabinoid receptors using Rimonabant® (a CB_1 receptor antagonist) transiently worsens signs, further increasing endocannabinoid levels by blocking uptake or inhibition of hydrolysis and direct CB_1 receptor agonism can ameliorate spasticity and tremor in these animals [31,32,37]. Cannabinoids might also reduce neuronal damage, through acute or chronic mechanisms, and thereby limit disease progression. This hypothesis is supported by the observations that CB_1-receptor-deficient animals have an increased incidence of axonal loss and poorer clinical outcome during experimental allergic encephalomyelitis (EAE; an experimental model of MS) and that CB_1 receptor agonism is neuroprotective [41]. There is also a recent report of previously undiagnosed MS being exacerbated by Rimonabant® in a person being treated for obesity, suggesting a protective role of the endogenous cannabinoid system in MS [42].

Clinical studies

Is this evidence replicated in clinical studies? Although studies in animals, where subtle dose-limiting effects are not detectable, clearly demonstrate quantitative

improvements in signs of disease, the picture from clinical trials is at best confusing, with both positive and negative results [43]. It is, however, important to note that in many of the previous investigations [43] and more recent controlled and blinded clinical studies [44–46], the delivery route of choice (or necessity, due to lack of an available or a suitable alternative) has been oral ingestion of THC or cannabis extract in capsule form, rather than smoking (which is obviously discouraged for medical reasons). Unfortunately, the pharmacokinetics of these two routes of delivery differ dramatically and appear not to have been adequately addressed in many clinical studies. Cannabinoids are extremely hydrophobic, which makes them difficult to formulate for drug use. A rapid (seconds) increase in plasma THC levels ($>100\ \mu g\ l^{-1}$) occurs when cannabis smoke is inhaled [47,48], which gives the possibility of dose-titration to limit psychoactive side-effects. By contrast, oral delivery produces a slow (hours), low ($<10\ \mu g\ l^{-1}$) and erratic increase in plasma THC levels [45,47–51], which limits the possibility of adequate dose-titration for side-effects, other than to reduce the initially administered dose. Extensive first-pass liver metabolism further reduces the oral bioavailability of THC, and variability of absorption and ability to tolerate the effects of cannabis between subjects is high, thus further limiting the possibility of demonstrating efficacy without significant side-effects complicating trial design and implementation. In addition, optimal plasma THC levels and correlation with symptom improvement is missing from many studies. Clinical investigations are also complicated by the difficulty of performing double-blinded studies, because cannabinoids need to be individually dose-titrated and both patient and observer are usually quickly aware that the patient has taken cannabis or THC [44,45].

Until recently, studies on the clinical utility of cannabis involved few subjects and largely failed to demonstrate significant improvements on outcome measures despite, in many cases, patient perceptions of improvement on pain and spasticity [43]. By 2002, in the largest blinded trial at that time, Killestein *et al.* [44] reported no positive effects on spasticity in 16 patients treated with oral Marinol® or the cannabis extract Cannador®. Adverse events were more common in patients taking the cannabis extract, and the patient perception of symptoms was worse. A randomized double-blind crossover study on spasticity performed by Vaney *et al.* [45] also used Cannador® delivered orally. In the patients who completed the study (35% withdrew), improvements in spasm frequency and mobility were reported. In the largest clinical study into use of cannabinoids for treating symptoms related to MS (CAMS) [46], 667 people orally administered capsules of THC (Marinol®), capsules of cannabis extract containing CBD and THC (Cannador®) or placebo capsules, over a 15 week period. No overall improvement in spasticity, the primary outcome measure, was reported [46], and no effect on tremor was demonstrated in the analysis of a subgroup of subjects [52]. Spasticity was clinically assessed using the visually qualitative Ashworth Scale (0=normal, 1=slight increase in plasticity, 2=more marked increase, 3=considerable increase, and 4=limb rigidity in flexion or extension) [53]. This scale has likewise been unresponsive to change in other spasticity trials, including one using the GABA receptor agonist Baclofen®, which is a licensed and major agent used for the treatment of this symptom [54]. Although patients were unblinded, they did report a subjective perception of improvement of specific symptoms (pain, spasticity and sleep disturbance), and a beneficial effect on walking time was evident in both cannabinoid-treated groups [46]. Improvements in pain were reported in an additional study [55]. More encouraging is the one-year follow-up of the CAMS study, in which two-thirds of the original patients opted to continue the trial, and overall objective improvements on both spasticity (Ashworth Scale) and general disability indices have been reported [56]. The improvements in the one-year follow-up were confined to patients taking THC and no improvements were seen in the cannabis-extract group. This indicates that the active principle is THC and fails to provide evidence that CBD has positive effects on disease. This follow-up data would suggest that, by contrast, CBD might limit the therapeutic potential of THC [56].

A compromise between the oral and inhaled route of delivery is the sub-lingual spray, where an alcoholic extract of cannabis is sprayed under the tongue. The potential advantage of this route is that delivery directly to the blood is increased, thus reducing first-pass effects associated with the oral route and allowing for much greater dose-titration [57]. Because this is an alcoholic extract, even if the majority of the dose is swallowed it will still enter the bloodstream more quickly than an orally delivered capsule. A recent placebo-controlled study by Wade *et al.*, using Sativex® in 160 MS patients, reported an improvement in patient-assessed scores (visual analogue scale) but again no improvement as measured by the Ashworth scale [58]. However, 96% of patients completed the study, indicating a good side-effect profile with this delivery method. Other studies are ongoing and once they are published we will be better able to assess efficacy via this route and the value of the mixture of THC and CBD. The more definitive CAMS study and current biology indicate that THC will be required for efficacy in MS and, on available information from cannabis trials, CBD might limit efficacy of THC to control some signs of MS [56]. A small-scale open-label study of cannabis extracts (THC and Sativex®) in MS patients reported improvements in bladder dysfunction, most notably with THC-rich cannabis [59]. This might reflect the particular nature of the neurological deficit in lower urinary tract symptoms or that another ratio of CBD is required in these patients, but it also suggests that THC could be responsible for the positive effects of cannabis on neurological symptoms, as is indicated in the long-term CAMS study. Although these data should be interpreted cautiously and CBD does seem to be inert clinically, it might have benefit for certain signs such as pain [60].

Concluding remarks

The conclusion from these clinical studies is still frustratingly unclear compared with experimental data, which indicate clear efficacy. Nevertheless, there is a general trend in groups receiving cannabis through either oral or

sublingual routes: at doses of cannabis aimed at limiting psychoactive side-effects, there is none-to-marginal efficacy according to clinically assessed scales. It is consistent with the biology of cannabis that beneficial and psychoactive effects will invariably be linked. However, there are consistent improvements in certain signs (spasticity, pain and sleep) from the patient perspectives. These appear to validate claims made in earlier surveys [2,3]. Improvements in trial design and outcome measurements are likely to be important in clarifying the situation; these could include introduction of quantitative assessment of symptoms such as spasticity, because the Ashworth scale might not be sufficiently sensitive to measure small but clinically beneficial effects [54]. It might be necessary to address problems in the oral delivery of cannabinoids, because this is unsatisfactory for short-term studies of symptom relief (owing to poor pharmacokinetics) and because other routes such as an aerosol inhaler [61,62] might produce better efficacy by enabling patients to dose-titrate to minimize side-effects. There is much potential for researchers to develop weaker agonists of the CB_1 receptor that can have therapeutic benefit and also widen the therapeutic window, because the current window between symptom relief and psychoactivity of THC or cannabis is narrow. In addition, targeting endocannabinoid degradation by inhibiting uptake or degradative enzymes could locally target sites of damage where endocannabinoids are upregulated, while sparing cognitive sites and reducing unwanted psychoactive effects.

The long-term CAMS study is particularly encouraging because the results indicate that cannabis not only relieves symptoms but also is potentially neuroprotective and involved in synaptic plasticity; this should be investigated further. It is clear, however, that cannabinoids present a novel target for symptom relief in many neurological conditions, not just in MS, and that they might also have an important neuroprotective role in slowing progression of CNS disease. The difficult task for the future will be to determine whether these emerging biological effects can be better identified in clinical trials.

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