Cannabinoids and Cystic Fibrosis: A Novel Approach to Etiology and Therapy

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ABSTRACT. Cannabis stimulates appetite and food intake. This property has been exploited to benefit AIDS and cancer patients suffering from wasting disease, by administering the whole plant or its major active ingredient Δ^9-tetrahydrocannabinol (THC).

Endogenous cannabinoids ("endocannabinoids") are found in maternal milk. We have recently shown that endocannabinoids are critical for milk ingestion and survival of newborns because blocking CB_1 receptors resulted in death from malnutrition.

Lack of appetite resulting in malnutrition is a contributing factor to mortality in many Cystic Fibrosis (CF) patients. It is proposed here for the first time, to administer THC to CF patients. It is hoped that the cannabinoid will alleviate malnutrition and thus help prevent wasting in CF patients.

Recent findings suggest that a lipid imbalance (high arachidonic acid/low DHA) is a primary factor in the etiology of CF and that defective CFTR (CF transmembrane conductor regulator) that characterizes the CF condition is responsible for the dysregulation. Endocannabinoids are all fatty acid derivatives. Therefore, it is further proposed here that the CFTR gene product also modulates endocannabinoid synthesis, through regulation of fatty acid biosynthesis. According to this hypothesis, CF patients display decreased levels of endocannabinoids and by elevating these levels, symptoms may improve. Indeed, a number of physiological mechanisms of cannabinoids and endocannabinoids coincide with the pathology of CF. Thus it is suggested that potential benefits from THC treatment, in addition to appetite stimulation, will include

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This paper is dedicated to Ies Fride (1952-2000) who fought to better the life of all CF patients

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antiemetic, bronchodilating, anti-inflammatory, anti-diarrheal and hypoalgesic effects.

KEYWORDS. Cannabis, cannabinoids, endocannabinoids, cystic fibrosis, appetite, wasting disease, fatty acids, medical marijuana

INTRODUCTION

Δ^9-tetrahydrocannabinol (THC) is the major psychotropic constituent of the cannabis (*Cannabis sativa*) plant. Since 1988, two specific receptors for Δ^9-THC have been discovered: CB_1, located in brain and other organs including lungs, blood vessels and spleen, and CB_2, located mainly in the periphery, notable the immune system (Ameri 1999). In 1992 the first endogenous ligand for the CB receptors was isolated from porcine brain and denoted "anandamide" (Devane et al. 1992). In 1995 and 2001, two additional major ligands were isolated from mammalian tissue, 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995) and "noladine" (Hanus et al. 2001). Collectively, the natural ligands of the CB receptors are called "endocannabinoids" and these three prototypes are derivatives of arachidonic acid (anandamide is an amide, 2-AG is an ester and noladine is an ether of arachidonic acid). Other ethanol amides of fatty acids with pharmacological activity, including docosatetraenyl ethanol amide and homo-g-linolenyl ethanol amide have been reported since the discovery of anandamide (Barg et al. 1993; Pertwee et al. 1994).

Appetite

Cannabis has been known for many years to enhance appetite and weight gain (Fride and Sanudo-Pena 2001; Fride and Mechoulam 2001). Anandamide has similar effects (Williams et al. 1998; 1999). Recent research in the medicinal aspects of marijuana has indicated that the plant may be used beneficially to combat wasting disease in AIDS and cancer patients (Mechoulam et al. 1998b). Indeed THC is used clinically for this purpose, particularly in AIDS patients (Beal et al. 1997).

We have reported previously that endocannabinoids are present in milk, with 2-arachidonylglycerol (2-AG) found in human milk in

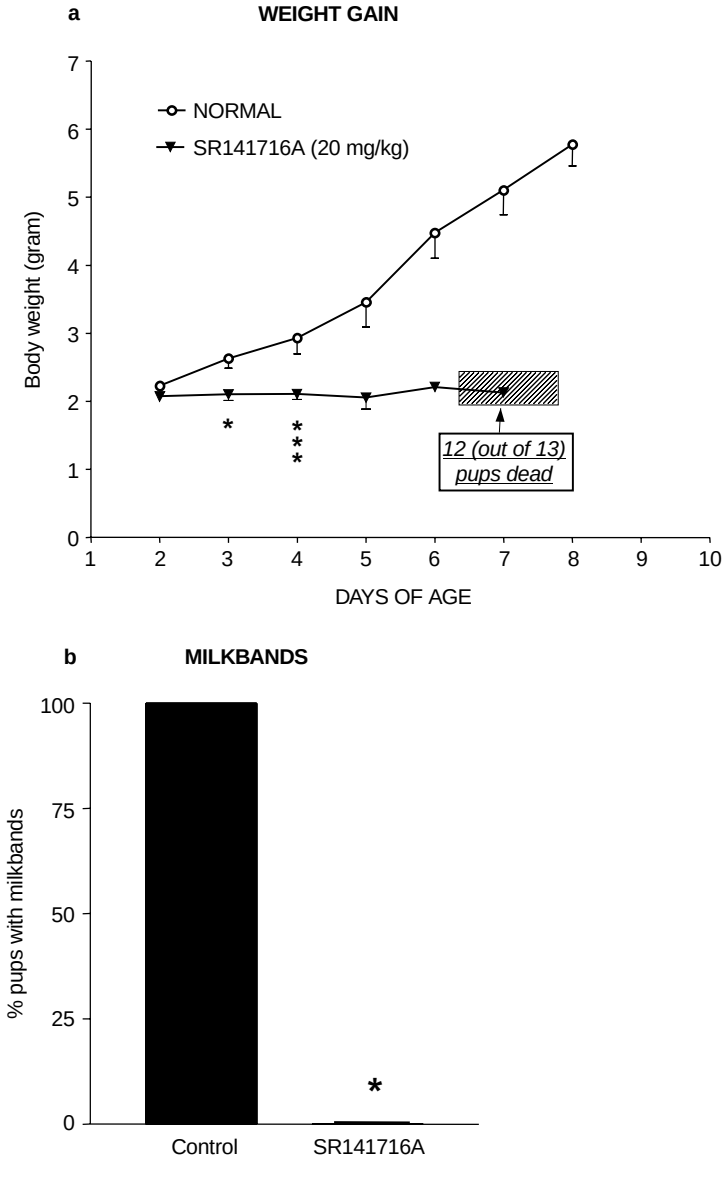
higher concentrations (8.7 ± 2.8 µg/g extracted lipids) than anandamide (0.0015 ± 0.003 µg/g) (Fride et al., 2001). We (Di Marzo et al. 1998) have also shown that 2-AG when administered orally, albeit in high doses, is active in the mouse 'tetrad,' a battery of tests that is used to assess central cannabimimetic activity (Martin et al. 1991; Fride and Mechoulam 1993). These findings suggest that 2-AG in maternal milk may reach, in part at least, the sucklings' central nervous system, thus possibly affecting appetite regulation, brain development and behavior.

Specific blockade of the cannabinoid (CB_1) receptor within the first 24 hr after birth completely abolishes the ability of newborn mice to ingest milk, as expressed in a complete failure to gain weight and an absence of "milkbands." (As the stomach area in mouse pups is transparent, due to lack of hair and the thinness of the skin, the amount of milk consumed can be observed as a "milk band.") Hence neonates exposed to a CB_1 receptor antagonist (SR141716A) did not survive the first week of life (Fride et al. 2001) (Figure 1).

This finding is compatible with the observation that the levels of the 2-AG in rodent pup brain, peak immediately after birth (Berrendero et al. 1999) and suggests a critical role for endocannnabinoids in milk intake and survival of newborns.

Cystic Fibrosis (CF) is the most prevalent lethal autosomal recessive disorder in the Caucasian population, affecting 1 in 2500 newborns (Collins 1992). A mutated form of the CFTR (CF transmembrane conductance regulator) gene is found CF patients (Zeitlin 2000). The disease is expressed as the formation of viscous secretions affecting several organs, mainly the lungs and the digestive system (Quinton 1999). Usually, a gradual decline in physiological functions is seen, eventually leading to death. Due to major strides over the years in palliative care, survival is expected to exceed 30 years (Resnikoff and Conrad 1998). Pulmonary dysfunction has long been considered the primary cause for morbidity and mortality in CF (Pilewski and Frizell 1999), with malnutrition appearing as a compounding detrimental factor (Borowitz 1996). More recently however, malnutrition is being recognized as playing a primary role in disease progression (Borowitz 1996; Schoni and Casaulta-Aebischer 2000) possibly even being responsible for lung pathology and infections (Yu et al., 2000). Thus in many CF patients, appetite reduction greatly accelerates the aggravation of the condition in its final stages (Anthony et al. 1999; Schoni and Casaulta-Aebischer 2000). Moreover, there is now evidence that im-

FIGURE 1. Effects on weight gain and milk ingestion of a single administration of SR141716A on the first day after birth. Mouse pup (Sabra, Harlan, Israel) littermates were injected sc within the first 24 hr after birth with SR141716A (20 mg/kg) or with vehicle (ethanol:emulphor:saline = 1:1:18) using 30G needles.



provement of the nutritional status *per se* may counteract the progression of lung disease (Shepherd et al. 1986; Dalzell et al. 1992).

Therefore, administration of cannabinoids may promote appetite, thus combating malnutrition and increasing chances for survival.

Side Effects of Cannabinoids During Development?

It is especially important to maintain growth in CF patients during the first years of life, because early malnutrition is associated with impaired cognitive development (Blecker et al., 2000). On the other hand, potential side effects of an appetite stimulant would be of particular concern at that stage. Interestingly, there is evidence from animal studies indicating that the developing organism does not display a central (psychotropic) response to THC administration (Fride and Mechoulam 1996), possibly because CB_1 receptors do not appear in high enough concentrations until adulthood (Rodriguez de Fonseca et al. 1993). Yet, Δ^8-THC (a stable metabolite of Δ^9-THC with similar activities) was a very effective antiemetic, while causing only minimal side effects in a clinical trial assessing the antiemetic effects of THC in children with hematological cancers (Abrahamov et al. 1995). These observations suggest that in the developing organism, while the psychotropic effects are not yet apparent, certain activities of cannabinoids are present including their antiemetic effects. In view of the critical role of endocannabinoids in feeding in the newborn (Fride et al. 2001), appetite enhancement is also likely to be present.

Fatty Acid Balance

A fatty acid imbalance is observed in CF patients, including elevated levels of arachidonic acid and reduced levels of docosahexanoic acid (DHA) (Gibson et al., 1986; Roulet et al., 1997), as well as in a knockout mouse model for CF ($cftr^{-/-}$ mice) (Freedman et al. 1999). The implications of this observation are far reaching. Heeckeren et al. (1997) have demonstrated that, in the absence of *a priori* lung disease, the lungs of $cftr^{-/-}$ mice displayed an excessive inflammatory response to *Pseudomonas aeruginosa*, resulting in increased pathology and mortality. Possibly, the increased levels of arachidonic acid are responsible for the excessive response (Freedman et al. 1999; Greener 2000). Furthermore, the low DHA levels have been shown to play a fundamental role in the pathogenesis in the organs affected by the CF disease: lungs, pan-

creas and ileum (Freedman et al. 1999). Thus, further decreasing DHA levels in $cftr^{-/-}$ mice worsened pathological manifestations, while elevating DHA levels by oral supplementation corrected the lipid imbalance and reversed the pathology of the affected organs. As a consequence it has been postulated that the mutated CFTR gene product is responsible for the lipid imbalance and the ensuing pathogenesis (Greener 2000).

Endocannabinoids and Cystic Fibrosis

Is it possible that the synthesis of endocannabinoids, being fatty acid derivatives, is also modulated by CFTR proteins? There are a number of striking parallels between the clinical manifestations of CF and the domains of cannabinoid and endocannabinoid influence, including lack of appetite, nausea, diarrhea, and lung disease. Low endocannabinoid levels could explain the appearance of these symptoms. However, even in the absence of a causative role, it is proposed here that by stimulating the cannabinoid system, some of the CF pathology symptoms may be alleviated. The potential for cannabinoids to enhance appetite, thereby possibly preventing malnutrition in CF has been described above. Below, a number of additional manifestations of CF and a possible therapeutic role for cannabinoids are described (Figure 2).

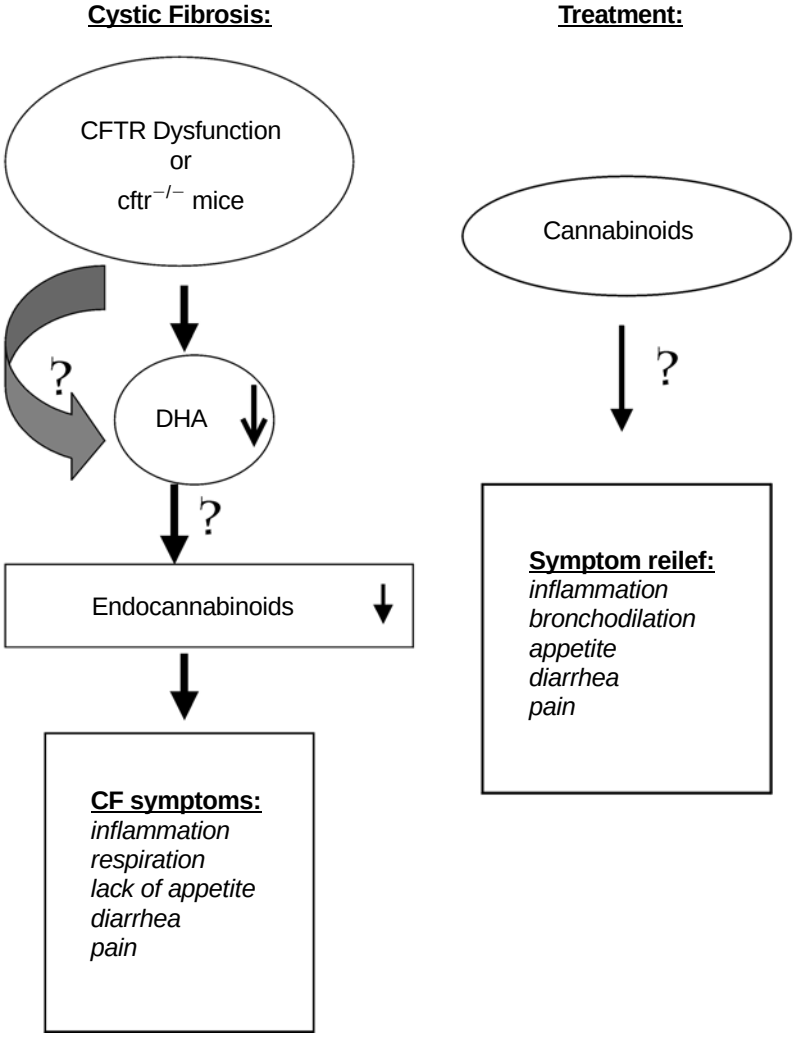
Antiemetic Effects

Vomiting induced by coughing (Blecker et al. 2000) often exacerbates the development of malnutrition in cystic fibrosis. Antiemetic benefits of THC have been demonstrated in its effective relief of chemotherapy-induced nausea and vomiting (Mechoulam et al., 1998b; Abrahamov et al. 1995). Therefore the antiemetic potential of cannabinoids would be expected to contribute to appetite enhancement induced by cannabinoids in CF patients.

Diarrhea

Diarrhea appears in CF as a result of inadequate digestion due to pancreatic insufficiency (Rolles 1998). Cannabinoids inhibit intestinal motility via local CB_1 (Colombo et al. 1998; Tyler et al. 2000) and/or via CB_2 (Fride 1995; Hanus et al. 1999) receptors. Therefore administration of cannabinoids to CF patients may counteract diarrhea and thereby help prevent loss of nutrients.

FIGURE 2. Hypothesis for pathogenesis and therapeutic approach to cystic fibrosis. Mutated CFTR gene products result in a lipid imbalance: high arachidonic acid/low docosahexanoic acid (DHA) and consequently in low endocannabinoid levels. Alternatively, the mutated CFTR results in low endocannabinoid levels in parallel to the lipid imbalance. The ensuing manifestations of CF are relieved by endocannabinoid treatment



Inflammation

Most destruction of lung tissue in CF is now thought to be secondary to a very aggressive neutrophilic inflammatory response (Konstan & Berger 1997; Wagener et al. 1997). This ultimately leads to respiratory failure. The antiinflammatory potential of cannabinoids is well documented (Klein et al. 2000; Straus 2001) and is thought to occur by interference with the arachidonic acid-eicosanoid synthetic pathways (McPartland 2001). We have demonstrated in a mouse model of arachidonic acid-induced ear inflammation that cannabinoids and endocannabinoids are effective antiinflammatory agents acting via CB receptors (Hanus et al. 1999; Fride et al. unpublished observations). Since cannabinoid receptors are present in lungs (Calignano et al. 2000), THC may be of additional benefit for CF patients, by reducing inflammatory processes in the lungs.

Lungs

It has been demonstrated recently that bronchodilating and cough-reducing activity of endocannabinoids in irritated lungs are mediated by local CB_1 receptors (Calignano et al. 2000). Therefore cannabinoids may also benefit CF patients by their bronchodilating and cough suppressing effects.

Pain

CF patients suffer pain from a variety of sources (Ravilly et al. 1996) including abdominal pain related to steatorrhea and malabsorption (Zeltzer et al. 1996), chest pain due to impacted sputum, pleuritic involvement with lung inflammation and infection, or chest wall pain associated with developing kyphoscoliosis and decreased chest wall mobility (Massie et al. 1998). Pain may also occur from gall bladder or kidney stones or from osteoporosis (Haworth et al. 1999; Lambert 2000; Ravilly et al. 1996). Cannabinoids are analgesics effective in a variety of conditions (Mechoulam et al. 1998b; Martin and Lichtman 1998), acting via cannabinoid receptors within as well as outside the brain and spinal cord and suppressing both acute and chronic pain (Pertwee 2001).

Route of Administration

Due to the severe lung pathology that develops in CF patients (Pilewski and Frizell 1999), cannabis smoking is contraindicated, de-

spite it being a preferred route in conditions such as multiple sclerosis (Iversen 2000; Mechoulam et al. 1998b). However, THC administered orally has been shown to effectively reduce vomiting and nausea in children undergoing chemotherapy for hematological cancers (Abrahamov et al. 1995). Additional routes are available and/or are being explored at this time (Gieringer 2001), which may be applicable to CF patients in the future. These include rectal suppositories (Mattes et al. 1994), transdermal patches (Gieringer 2001; Hu 2000) and smoke-free inhalation systems (Iversen 2000). The latter method may be of particular relevance when bronchodilating and local antiinflammatory effects in the lungs are primary therapeutic aims. Novel, effective vaporizers are currently under investigation.

CONCLUSIONS

In this paper a novel therapeutic target for cannabis is proposed, based on recent developments in research on cannabis on one hand, and on research on cystic fibrosis on the other. Recent findings suggest that the primary factors in the pathogenesis of CF includes fatty acid imbalance, possibly leading to such major manifestations of CF as chronic inflammation of the lungs and pancreatic disease (Greener 2000; Freedman et al. 1999). In the final stages of the disease malnutrition accompanied by a lack of appetite is frequently seen (Anthony et al. 1999; Schoni and Casaulta-Aebischer 2000). Additional symptoms of the disease may include pain due to a variety of sources (Ravilly et al. 1996), diarrhea (Rolles 1998) and nausea (Blecker et al. 2000).

Intriguingly, the therapeutic effects of cannabinoids include the potential to counteract each of these conditions. Thus appetite enhancement (Beal et al. 1997) and a critical role in food ingestion (Fride et al. 2001), analgesic, antiemetic, antiinflammatory, inhibition of intestinal motility and bronchodilating effects have been demonstrated (Calignano et al. 2001; Colombo et al. 1998; Fride 1995; Mechoulam et al. 1998b; Hanus et al. 1999; Tyler et al. 2000).

The major endocannnabinoids are structurally similar to arachidonic acid (Mechoulam et al. 1998a; Hanus et al. 2001) and dietary supplementation of essential fatty acids is associated with increased levels of endocannabinoids in piglets (Berger et al., 2001). Thus a more fundamental role of endocannabinoids in CF disease progression should be investigated. It has been proposed previously that a lipid imbalance

(high arachidonic acid/low DHA) is a major step in the pathogenesis of CF.

Therefore supplementing DHA in the diet should improve disease manifestations (Freedman et al. 1999; Greener 2000). However, dietary supplementation of DHA to improve the imbalance has proven difficult. Bioavailability is impeded by pancreatic insufficiency in CF patients and by adverse effects of additional fatty acids present in the formulation (Greener 2000).

It is proposed here, that CFTR not only regulates fatty acid balance but also endocannabinoid biosynthesis. Such mechanism predicts that low levels of endocannabioids in CF patients and in $cftr^{-/-}$ mice will be found, which could be responsible for many symptoms. It is hoped that affirmative data will eventually lead to the use of cannabinoids at more initial stages of cystic fibrosis (Figure 2).

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