Introduction

Cancer and AIDS patients experience weight loss and tissue wasting due to increased metabolic demand and decreased nutritional intake (1). These complications are important indicators of patient prognosis and may directly result in death (1). To prevent adverse outcomes related to malnutrition, various treatments have been utilized including corticosteroids, metoclopramide, and progestational agents (2). Another appetite stimulant, medicinal marijuana, has been at the center of controversy regarding its therapeutic effect, route, dose, and side effects (3). Not only has medicinal marijuana been shown to relieve pain, anxiety, and depression, but also, studies among HIV patients reported appetite stimulation and weight gain as the primary reason for medicinal marijuana use (3,4).

Marijuana or *Cannabis Sativa* contains the active component delta-9-tetrahydrocannabinol (THC). The Food and Drug Administration approved the use of dronabinol, the oral form of THC, for the treatment of anorexia in AIDS patient, but since THC is not water soluble, smoking marijuana remains the most efficient delivery method for THC (5). Seconds after the first puff of a cannabis cigarette, THC is detectable in the plasma whereas oral administration of THC results in detectable plasma levels within one to two hours (6,7). THC may be taken orally in fat containing food or dissolved in suitable pharmaceutical oil, but the absorption remains delayed and variable because of gastric acid degradation and the first pass liver effect. (5,6).

Due to the potential benefits for cancer and AIDS patients and the recent discovery of the endocannabinoid system, medicinal marijuana's role in appetite stimulation has been an active area of research. In 1997, researchers initially found that THC did not produce acute appetite stimulation in the rat (8), but further studies disproved this previous hypothesis. Today, THC is known to bind to cannabinoid receptors located in the brain and may play a critical role in the leptin pathway, a critical system for appetite stimulation. This paper will explore the current knowledge of medicinal marijuana and its role in appetite stimulation.

Endocannabinoids and Appetite Stimulation

For many years, the effects of THC on the brain remained a mystery. The first major step in understanding the mechanism of THC was brought about by Matsuda et al (1990) with the discovery of cannabinoid receptors. Further research identified two cannabinoid receptors, CB1 and CB2, which are coupled to G inhibitory proteins (6). Activation of these G_i proteins inhibits adenylate cyclase with subsequent inhibition of AMP's conversion to cAMP. Due to their role as neuromodulators at axon terminals, cannabinoid receptors are hypothesized to be presynaptic rather than postsynaptic (5). CB1 receptors are located on neurons in the brain, spinal cord, peripheral nervous system, and some peripheral organs and tissue whereas CB2 receptors are located primarily in immune cells (6). More specifically, CB1 receptors are located in axons and nerve terminals (5). The frontal regions of the cerebral cortex, basal ganglia, cerebellum, hippocampus, hypothalamus, and anterior cingulated cortex of the limbic forebrain contain a high density of CB1 receptors (5).

After the identification of cannabinoid receptors, the endogenous ligands for these receptors known as endocannabinoids were discovered. (5,6). Of the three arachidonic acid derivatives known as endocannabinoids, *N*-archidonyl–ethanolamine or anandamide has been the most extensively studied thus far (5). These endocannabinoids are released locally on demand and are rapidly inactivated by an enzyme, fatty acid amide hydrolase, which provides a possible pharmaceutical target for the modification of cannabinoids and their effect on the brain (5).

Multiple studies have aimed to describe the role of cannabinoids in appetite stimulation. The endocannabinoid anandamide was proven to stimulate food intake in rats, and the CB1 antagonist rimonabant also known as SR141716 suppressed food intake, which resulted in decreased body weight in adult non-obese rats (10,11). In a related study, rimonabant was given to diet-induced obesity model mice, and the suppression of appetite and food intake was significant (12). Further research on mice demonstrated that CB1 (-/-) knockout mice were significantly leaner than CB1 (+/+) mice, which helped researchers conclude that endogenous cannabinoids are important in both feeding and peripheral metabolic controls (13). In an attempt to understand more precise mechanisms of CB1, one study discovered a relationship between ghrelin and CB1 antagonists. Ghrelin, a peptide hormone secreted by the fundus of the stomach, stimulates hunger. Rats that were treated with CB1 receptor antagonists, rimonabant and oleoylethanolamide, demonstrated a decreased level of ghrelin (14).

Research has revealed that endocannabinoids may play an integral role in the leptin pathway, which may be the key to understanding their role in appetite stimulation. Leptin is the main signal in which the hypothalamus senses nutritional state and modulates food intake. In one study, a defective leptin signaling pathway resulted in increased levels of hypothalamic endocannabinoids which points to a strong association between the leptin signaling pathway and the endocannabinoid system (15). One mechanism in which leptin decreases feeding is through the inhibition of neuropeptide Y production. Further, neuropeptide Y may be related to the endocannabinoid system. One study proved that the administration of SR141716, a CB1 antagonist, eliminated neuropeptide Y-induced overeating and reduced ethanol and sucrose intake in CB1 (+/+) wild type mice (16).

Side Effects

Although marijuana may prevent cachexia associated with AIDS and cancer, health care providers must consider the side effects associated with smoking marijuana. Similar to the toxicities associated with cigarettes, smoking marijuana leads to cellular dysplasia and subsequent increase risk for the development of pulmonary malignancy (9,17). A different inhalation pattern of marijuana smokers results in a 50% increase exposure to procarcinogen benz-alpha-pyrene and carboxyhemoglobin compared to cigarette smokers (17,18). In addition, researchers have identified alveolar macrophage damage as a result of marijuana use (19).

Since a large proportion of CB1 receptors are located in the brain, marijuana users have been thought to experience neurologic side effects. Unfortunately, many studies have yielded conflicting results of both neuroprotective and neural damaging actions (5). One systematic review found that marijuana use was associated with lower education attainment and increased utilization of illicit drugs, but a relationship with psychological health problems could not be proven (5,20). Although statistics did not prove or disprove this relationship, the evidence points in the direction of marijuana's negative impact on psychosocial functioning and psychopathology (21). Marijuana may adversely affect learning, memory, and psychomotor and cognitive performance (6). In addition, marijuana may influence various forms of impulsivity (22), driving ability (23), and flying ability (24). One phenomenon associated with increased marijuana intake is "cannabis psychosis" which can present with delusions, grandiose identity, persecution, auditory hallucinations, and blunting of emotion (5,25). In addition, marijuana use may exacerbate existing psychotic illness (25).

Smoking marijuana may be detrimental to AIDS and cancer patients. First, smoking marijuana may cause hypotension and tachycardia, a stressful response on the body (6,18,26). In

addition, these immunocompromised patients may be exposed to life threatening microbes such as Klebsiella, Enterobacter, Group D Streptococcous, Salmonella, and Shigella, which have been cultured from marijuana (18). Since AIDS patients are treated with anti-retroviral therapies, researchers explored the potential impact of cannabinoids on indinavir and nelfinavir and found no significant impact of marijuana on the efficacy of these drugs (27,28).

Discussion

The first written account of medicinal marijuana took place in China in the 5th century BC (26), and with ongoing research of cannabinoid receptors and endocannabinoids, the therapeutic actions of marijuana are becoming clearer. Medicinal marijuana has been a controversial topic for many years which is characterized by the petition in the 1970s to convert marijuana from a schedule I drug to a schedule II drug and the support of rescheduling and appeal by the Drug Enforcement agency in the 1980s (18). In 1996, California proposition 215, the Compassionate Use Act, passed and stated "Patients and caregivers may possess or cultivate medical marijuana for medical treatment" (29). This vague statement that legalized marijuana enraged the government and health care providers because of the new stereotypes regarding the safety of marijuana and the lack of regulation. As a result, the federal government attempted to eliminate medicinal marijuana indirectly by prohibiting physicians to discuss medicinal marijuana with the consequence of losing prescription writing privileges (30). In addition, the definition of pharmaceutical grade marijuana and its production has been an area of active debate. The heterogeneous population of medicinal marijuana fails to meet a consistent standard of composition and quality (31). Solving this problem would require pharmaceutical companies to successfully develop a synthetic cannabinoid derivative (7).

In the modern patient-centered health care system, health care providers must acknowledge the current research and make evidence based decisions on the benefits of medicinal marijuana as a treatment for cancer and AIDS related weight loss. Fifteen years ago, the existence of cannabinoid receptors was unknown, but research has painted a clearer picture of the hypothalamic CB1 receptors' role in appetite stimulation. Despite the controversy of medicinal marijuana, continued research in this field has opened new avenues for treatment and prevention of the nation's biggest health care problem, obesity. Understanding the cannabinoid receptors' role in appetite suppression and its link in the leptin pathway may allow future physicians to treat and prevent obesity (32). Obesity is a significant risk factor for deadly diseases such as atherosclerosis, hypertension, and diabetes, and further research in medicinal marijuana's role in appetite stimulation may be the key to curing an obese nation.

Although the amount of information regarding medicinal marijuana is vast, there are many areas that need further research for more effective use among patients. First, double blind randomized control trials in humans are needed to truly assess the effectiveness of marijuana in appetite stimulation. Many studies on rats and mice have produced a working scientific basis for medicinal marijuana, but human trials are necessary to assess potential benefits and adverse effects in patients. Further, a risk/benefit analysis of medicinal marijuana is needed. Medicinal marijuana is often disputed as a treatment based on its side effect profile, but terminally ill cancer and AIDS patients might be willing to increase their risk for lung cancer in the long term to achieve an immediate improvement in quality of life. With a target population of immunocompromised patients, research on alternative delivery methods need to be employed to decrease the risk of infection associated with marijuana smoking. Finally, a logistical study on the most effective and safest mechanism for distribution of marijuana in the population must be

conducted. With this information, marijuana can be utilized safely to allow sick patients to engage in one of the most essential actions in life, eating.

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