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The Endocannabinoid System: Role in Energy Regulation

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Abstract

Cannabis sativa has been used since antiquity to treat many ailments, including eating disorders. The primary psychoactive constituent of this plant, Δ^9 -tetrahydrocannabinol (THC) is an FDA approved medication to treat nausea and emesis caused by cancer chemotherapeutic agents as well as to stimulate appetite in AIDS patients suffering from cachexia. The effects of THC are mediated through the endocannabinoid system (ECS), which promotes a positive energy balance through stimulation of appetite as well as shifting homeostatic mechanisms toward energy storage. Here we discuss the physiological function of the ECS in energy balance and the therapeutic potential of targeting this system.

Keywords

anandamide; appetite; endogenous cannabinoid; lipogenesis; obesity; rimonabant

INTRODUCTION

While *Cannabis sativa* has a recorded history of medicinal use that dates back 5,000 years [1], the primary constituent responsible for most of the pharmacological effects of this drug, Δ^9 -tetrahydrocannabinol (THC), was determined almost 50 years ago [2]. Since that time, there have been many dramatic breakthroughs in understanding the molecular mechanisms underlying the pharmacological action of THC. Cannabis contains over 70 other chemicals that are structurally related to THC and are collectively known as cannabinoids [3]. Some of these compounds possess THC-like effects, though many act through different mechanisms of action and possess unknown pharmacology. THC acts upon an endogenous cannabinoid system (ECS) that modulates a variety of physiological systems, including pain, inflammation, feeding, energy balance, memory, attention, and reward processing.

Considering the robust nature of cannabinoid activity, it is no surprise then that it is an area of interest for a wide range of potential therapeutic applications. Chemotherapy-induced nausea and vomiting represents a major side effect in cancer patients undergoing treatment with implications for quality of life, adherence, and survival [4]. Cannabinoids show

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efficacy in treating these symptoms [5] and the biological systems upon which they act are currently being studied as a target for the treatment of these and other symptoms of disease such as anorexia and obesity. Marinol[®], which is synthesized THC in pill form, has been available since 1986 for the treatment of chemotherapy-induced nausea and vomiting as well as diminished appetite in patients with AIDS. Additionally, a synthetic cannabinoid, nabilone (Cesamet[®]), has also been approved by the FDA to treat nausea and vomiting related to cancer chemotherapy in patients who have failed to respond to conventional antiemetics. Recently, Sativex[®], an oromucosal spray containing THC and another phytocannabinoid, cannabidiol (CBD), was approved in Canada for the treatment of neuropathic and cancer pain as well as muscle spasticity in multiple sclerosis patients, further demonstrating the potential of drugs developed to target the endocannabinoid system. Finally, another area of interest has been the development of cannabinoid receptor antagonists, such as rimonabant (Acomplia[®]), for weight loss and the treatment of obesity-related disorders [6], though interest in the development of these compounds as therapeutic agents has waned because of concerns regarding the occurrence of serious psychiatric side effects.

While stimulating this system reduces chemotherapy-induced nausea and emesis, increases appetite, and may stimulate lipogenesis, the development of cannabinoid receptor antagonists for the treatment of obesity had been a very active area of research before the awareness of their untoward psychiatric side effects effectively ended the use of this type of drug in patients. Nonetheless, a considerable amount of interest remains in understanding the role of the ECS in energy regulation. In this review, we will provide an overview of the endocannabinoid system. In addition, we will summarize the literature regarding the effects of manipulating this system on feeding behavior and energy homeostasis in preclinical and clinical studies.

THE ENDOCANNABINOID SYSTEM

The endogenous cannabinoid system is comprised of two known G_{i/o}-protein coupled receptors, CB₁ [7] and CB₂ [8], which when activated lead to (1) inhibition adenylyl cyclase and L-, N-, and P/Q-type voltage-gated calcium channels, and (2) activation of inwardly rectifying potassium channels, mitogen-activated protein kinase, and focal adhesion kinase [9]. In regard to tissue distribution, CB₁ is heterogeneously expressed at high levels in the central nervous system (CNS) and in peripheral tissue (e.g., liver and adipocytes), while CB₂ is localized mainly on immune cells and microglia and is associated with immune function [10]. The wide distribution of CB₁ throughout the CNS explains the plethora of physiological processes that this system modulates, including cognition, pain, memory, attention, reward, motor behavior, and feeding. Drugs targeting the CB₁ subtype appear to possess more potential therapeutic actions as well as untoward side effects than the compounds targeting the CB₂ receptor [11]. Specifically, in terms of energy regulation and feeding behavior, CB₁ receptors can be found in the hypothalamus, nucleus accumbens, vagus nerve, nodose ganglion, myenteric neurons, epithelial cells of the gastrointestinal tract, adipocytes, and the liver [12,13].

There are two main endogenous ligands for these receptors, 2-arachidonoylglycerol (2-AG) [14,15] and *N*-arachidonylethanolamide (anandamide; AEA) [16], both of which are post-synaptically synthesized and released on demand via cleavage of phospholipids from the cellular membrane in response to Ca²⁺ [17]. These molecules are believed to serve as retrograde messengers, which travel to the presynaptic terminal where they modulate neurotransmitter release through activation of CB₁ receptors. Thus, endocannabinoids can either facilitate inhibitory or excitatory post-synaptic potentials depending upon the type of neurons on which their receptors are expressed.

Biosynthesis of endocannabinoids 2-AG and AEA is activity-dependent [18,19] and multiple enzymes are implicated in the formation of each from phospholipid precursors. 2-AG is primarily produced via a two-step process involving phospholipase C (PLC) hydrolysis of membrane phospholipids resulting in the release of an arachidonic acid-containing diacylglycerol which is then converted into 2-AG by diacylglycerol lipase (DAGL) [20–22]. The biosynthesis of AEA involves the hydrolysis of *N*-acylphosphatidylethanolamines (NAPEs), but the specific enzymes involved are less well characterized than those of 2-AG, and remains an open area of study. AEA biosynthesis was originally thought to be primarily mediated by NAPE-selective phospholipase D (NAPE-PLD) [23]. However, NAPE-PLD (–/–) mice possess wild-type AEA brain levels, which suggests alternate biosynthetic pathways for this endo-cannabinoid [24]. Proposed pathways include conversion of NAPE precursors by the serine α/β hydrolase 4 (ABHD4) into lyso-NAPE which is then converted into AEA either directly by lyso-phospholipase D or via a two-step process involving further hydrolysis of lyso-NAPE by ABHD4 into glycerophospho-NAE (GP-NAE) followed by glycerophosphodiesterase 1 (GDE1) cleavage of the glycerophosphate group [25,26]. However, GDE1 (–/–) mice displayed wild-type levels of anandamide, suggesting the involvement of additional enzymatic pathway(s) in AEA biosynthesis [27].

Termination of cannabinoid signaling involves reuptake, which may involve a putative endocannabinoid transporter that has yet to be cloned [28,29], and hydrolysis carried out primarily by two enzymes, the fatty acid amide hydrolase (FAAH) through which catalysis of AEA results in the release of arachidonic acid and ethanolamine [30], and monoacylglycerol lipase (MAGL) which breaks down 2-AG into arachidonic acid and glycerol [31]. Other enzymes that play a smaller role in the hydrolysis of 2-AG than MAGL include ABHD6 and ABHD12 [32], the former of which has been shown to be expressed post-synaptically and to be involved in 2-AG regulation [33]. As well, cyclooxygenase-2 and 12- and 15-lipoxygenases are known to oxidize both 2-AG and AEA [34].

ENDOCANNABINOID MODULATION OF FEEDING BEHAVIOR

A well-known property of cannabis, throughout history as well as in popular culture, is its orexigenic effects [35]. In the 1970s some of the first experimental studies investigating the effects of THC on food intake in humans reported significant increases in consumption of chocolate milk shakes and marshmallows [36,37], a finding which now underlines the two main aspects of the endocannabinoid system in modulating both appetite and the hedonics of highly palatable foods such as sweets and fats [38]. Oral THC (0.5 mg/kg) or smoked cannabis increased consumption of highly palatable foods as well as increased qualitative ratings of hunger [36,37]. Caloric intake and body weight as well increase with cannabis use, however following cessation of drug taking there is a marked decrease in both, suggesting the effects on weight are transient and dependent upon continued use [39]. THC appears to produce a selective increase in the consumption of sweet snack foods [40], further supporting current theories regarding the endocannabinoid system's role in modulation of feeding via reward pathways [41].

In addition, many clinical studies have demonstrated cannabinoids possess remarkable anti-emetic as well as orexigenic properties and in 1986 the FDA approved THC (Marinol®) for the treatment of nausea and vomiting in cancer patients undergoing chemotherapy [42]. Notably, THC also improved appetite and appeared to increase body weight in advanced cancer patients [43]. Furthermore, THC was found to increase appetite in anorexic Alzheimer's disease patients [44] and patients with AIDS [45], suggesting even greater therapeutic potential for these agents.

Animal studies were initially not as successful in demonstrating an orexigenic effect of cannabinoids and in fact many reported that these compounds produced anorexic effects [46]. It is now known that while higher doses reduce food intake, low doses are able to produce hyperphagia in rats [47,48], which has been explained by arousal decrements following high doses of THC [49]. Further studies have demonstrated increased food intake following THC administration in mice [50], sheep [51], and dogs [52]. Low doses of AEA have been reported to increase chow intake during a 2.5 hours limited access paradigm [53] and subsequently more detailed procedures have demonstrated that in addition to increasing food intake, AEA also reduces latency to eat as well as increases meal number and length [54]. These effects of cannabinoids on feeding are CB₁ mediated as the selective CB₂ antagonist, SR144528, has no effect on feeding [55], while the CB₁ antagonist, rimonabant, reduces AEA-induced hyperphagia [56] and sweet food consumption [57].

The hypothalamus, a brain area known to play an important role in homeostatic control, contains CB₁ receptors [13]. The finding that THC administration facilitates feeding induced by electrical stimulation of the hypothalamus is consistent with a functional role of these receptors in feeding [58]. Moreover, in-tracerebral injection of AEA into the ventromedial hypothalamus stimulates food intake in rats [59].

Complementary genetic and pharmacological approaches have been instrumental in making major breakthroughs in elucidating the role of the endogenous cannabinoid system in feeding. A seminal study conducted by Di Marzo et al. [60] found that food deprived rimonabant-treated mice or CB₁ (–/–) mice ate significantly less than control mice following food deprivation. They also found that ob/ob and db/db mice as well as Zucker rats, genetic rodent models of obesity, possessed elevated levels of endocannabinoids in the hypothalamus compared to non-obese control mice, while no differences were found in the cerebellum. Importantly, rimonabant decreased food intake in the obese animals, suggesting that endocannabinoids in the hypothalamus may play a role in hyperphagic responses. Finally, the observations that 2-AG levels in the hypothalamus and limbic forebrain decrease during feeding, while both 2-AG and AEA increase in the limbic forebrain during fasting [61], suggests that endogenous cannabinoids may play a role in a negative feedback system. These effects are likely due to CB₁ mediated disinhibition of neurons releasing the orexigenic neuropeptide, melanin-concentrating hormone, in the lateral hypothalamus and inhibition of anorectic neurons in the paraventricular nucleus [41].

In addition to possible modulation of homeostatic mechanisms in the hypothalamus, the endocannabinoid system also appears involved in reward-related functions. There are multiple levels at which these effects are thought to occur and include the nucleus accumbens where administration of endocannabinoids increases food intake [61] and consumption of a saccharin solution [62]. It is not yet clear whether cannabinoid modulation affects the hedonic aspect of or appetitive motivation for foods as rimonabant failed to affect sucrose consumption during a sham-feeding procedure [63], though some data support cannabinoid involvement in the sensory aspects of feeding. Injection of 2-AG into the pontine parabrachial nucleus, which gates gustatory information, increases consumption of sucrose pellets, but not regular chow, despite equal caloric densities of these two foods [64]. Moreover, CB₁ receptors have been found colocalized with the sweet taste receptor component, T1r3, where their activation by endo-cannabinoids selectively enhance sweet taste both electrophysio-logically and behaviorally [65].

ENDOCANNABINOID MODULATION OF LIPOGENESIS

It is clear that CB₁ receptor-compromised animals display reductions in consumption and work for palatable foods; however other research revealed that the endocannabinoid system

also plays a role in lipogenesis in peripheral tissues. Specifically, CB₁ (–/–) mice weighed less and had less body fat than control mice [66]. In young animals, these differences could be accounted by decreased food intake in the knockout mice. However, in adult animals, CB₁ (–/–) mice had decreased body fat and body weight compared to pair fed control mice. Moreover, the observation that energy expenditure was similar in both genotypes suggested a role of metabolic differences. Furthermore, the cannabinoid receptor agonist, WIN55,212-2, stimulated lipoprotein lipase activity in adipocytes, an effect that was blocked by rimonabant, suggesting that CB₁ activation stimulates lipogenesis [66]. Consistent with this idea, CB₁ was detected in epididymal mouse adipocytes and CB₁-specific activation in primary adipocyte cultures enhanced lipogenesis.

Other research identified the liver as a critical target for endocannabinoid-induced lipogenesis [67]. Mice maintained on a high-fat diet gained weight and developed fatty liver. Interestingly, these animals show significant increases in hepatic levels of CB₁ and AEA accompanied with decreases in FAAH activity. As well, CB₁ (–/–) mice were protected from weight gain and increased rate of hepatic fatty acid synthesis, increased levels of triglycerides, and the occurrence fatty liver caused by a high fat diet. The potent cannabinoid agonist HU210 produced a twofold increase in the rate of fatty acid synthesis in liver that did not occur in CB₁-compromised mice. HU210 increased expression of the lipogenic transcription factor SREBP-1c, as well as its target enzymes acetyl-CoA carboxylase-1 (ACC1) and fatty acid synthase (FAS), in liver. A similar pathway involving endocannabinoid modulation of SREBP-1c was identified in the hypothalamus. A high-carbohydrate diet as well as HU210 increased SREBP-1c and FAS in the hypothalamus. These effects were prevented by rimonabant treatment. Collectively, these results suggest that the endogenous cannabinoid system is an essential endogenous regulator of energy homeostasis via central orexigenic as well as peripheral lipogenic mechanisms. Consequently, CB₁ antagonists were developed as a novel pharmacological strategy to treat obesity.

CB₁ ANTAGONISM AND FEEDING: PRECLINICAL AND CLINICAL STUDIES

The intricate involvement of the endocannabinoid system with feeding behaviors and appetite and the availability of CB₁ receptor antagonists made it a promising target for the treatment of obesity. The CB₁ receptor antagonist rimonabant reliably decreases food consumption [50,57,68,69] as well as reduces motivation for regular [70] and highly palatable food [71], suggesting endocannabinoid involvement in both appetitive and consummatory processes [72]. CB₁ blockade also attenuated opioid-induced increases in food intake [73,74], suggesting interactions between these two systems. Indeed, co-administration of cannabinoid and opioid antagonists synergize to produce robust decreases in food intake [75]. Likewise, synergistic interactions between the endocannabinoid system and the melanocortin [76] and oxytocin [77] systems have been demonstrated following co-administration of sub-anorectic doses of respective agents. In addition to CNS effects of rimonabant, peripheral mechanisms have also been identified [55,78]. As previously discussed, rimonabant reduced body weight and adiposity in diet-induced obese mice, despite only transient effects on feeding, which exemplifies the ability of CB₁ antagonism to not only affect energy intake, but also energy regulation through alterations in lipid and glucose metabolism [69,70].

It is these effects on adiposity which made rimonabant such an attractive candidate to treat obesity. Results from an early phase IIb clinical trial demonstrated remarkable decreases in body weight, from 3.5 kg (5 mg) to 4.4 kg (20 mg) as compared to 1.1 kg in the placebo group with no plateau in weight loss during the 16-week study [79]. Decreases in fat intake as well as hunger ratings were also observed in another study [79]. Improvements in waste

circumference, plasma triglycerides, HDL cholesterol, and blood pressure were found in the larger Rimonabant in Obesity (RIO) studies. The RIO North America study, for example, conducted over 2 years found 20 mg rimonabant caused significant decreases of body weight (-6.3 ± 0.2 kg vs. -1.6 ± 0.2 kg), waist circumference (-6.1 ± 0.2 cm vs. -2.5 ± 0.3 cm), triglycerides (percentage change, -5.2 ± 1.2 vs. 7.9 ± 2.0) as well as increases in HDL cholesterol (percentage change, 12.6 ± 0.5 vs. 5.4 ± 0.7) [80]. Participants switching to placebo following the first year regained weight, while those continuing the drug saw continued reductions in weight and improvement in cardio-metabolic risk factors and overall reported tolerating treatment fairly well, with study- and adverse-event participant withdrawals lower than in the first year. Adverse events reported during the first year in the 20 mg group were mostly due to psychiatric (e.g., 2.2% experiencing depression, 1% experiencing anxiety) and gastrointestinal (e.g., 0.9% experiencing nausea) effects [80].

Rimonabant was approved in 2006 as a weight loss medication in the European Union (EU); however, shortly thereafter a special FDA panel unanimously advised against approval in US and requested additional safety. Subsequently, rimonabant was removed from the market in the EU because of the occurrence of suicide ideation and other psychiatric side effects. Similarly, other CB₁ antagonists, such as taranabant, possessed significant efficacy for weight loss accompanied with psychiatric-related adverse events [81]. Because of concerns related to psychiatric side effects, the approach of targeting central CB₁ receptors for weight loss has been abandoned [82]. On the other hand, efforts are underway to develop neutral CB₁ antagonists that are largely restricted to the periphery, which would presumably lack psychiatric side effects [83,84].

CONCLUSION

Presently, two cannabinoid receptor agonists, THC and nabilone, are clinically available to treat nausea and emesis related to cancer chemotherapeutic agents as well as to stimulate appetite in patients with AIDS suffering from cachexia. These compounds are believed to produce their orexigenic effects through the stimulation of CB₁ receptors in the hypothalamus and other brain regions regulating feeding behavior. Similarly, administration of the endogenous cannabinoids, AEA and 2-AG, stimulates feeding behavior. CB₁ receptors are also present in peripheral tissue. Stimulation of these receptors on adipocytes and in liver leads to increases in lipogenesis. Thus, endocannabinoids promote anabolic processes, as they increase food intake, promote storage, and decrease energy expenditure. In preclinical models of diet-induced and genetic obesity, endocannabinoid levels are elevated and produce adverse effects on insulin-sensitive tissues and lead to fatty liver. These findings led to the proposal that over-activity of the endogenous cannabinoid system contributes to human obesity. Consistent with this notion, CB₁ receptor blockade promotes weight loss, reduces appetite, and elicits beneficial effects on dyslipidemia in preclinical models of obesity as well as in obese patients. Accordingly, CB₁ receptor antagonists showed great promise in reducing body weight and other risk factors related to cardiovascular disease. However, the occurrence of psychiatric side effects caused by these drugs raised serious safety concerns and essentially ended efforts to develop centrally acting CB₁ receptor antagonists for weight loss. Nonetheless, basic research continues to investigate the role of the endogenous cannabinoid system on energy expenditure and feeding behavior and the development of peripherally restricted CB₁ antagonists may hold promise an alternative pharmacological strategy to treat obesity.

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