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Cannabinoids in Eating Disorders and Obesity

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Abstract Cannabinoid system is a crucial mechanism in regulating food intake and energy metabolism. It is involved in central and peripheral mechanisms regulating such behavior, interacting with many other signaling systems with a role in metabolic regulation. Cannabinoid agonists promote food intake, and soon a cannabinoid antagonist, rimonabant, will be marketed for the treatment of obesity. It not only causes weight loss, but also alleviates metabolic syndrome. We present a review of current knowledge on this subject, along with data from our own research: genetic studies on this system in eating disorders and obesity and studies locating cannabinoid receptors in areas related to food intake. Such studies suggest cannabinoid hyperactivity in obesity, and this excessive activity may have prognostic implications.

Keywords Cannabinoid system · Obesity · Eating disorders · Food intake · Energy metabolism

Abbreviations

AgRP	agouti-related protein
AEA	anandamide
2-AG	2-arachidonoyl-glycerol
ARC	arcuate hypothalamic nucleus
BBB	blood–brain barrier
BMI	body mass index
BDNF	brain-derived neurotrophic factor
CB1	cannabinoid receptor type 1
CCK	cholecystokinin
CART	cocaine- and amphetamine-regulated transcript
CRH	corticotropin-releasing hormone
DIO	diet-induced obesity
DMH	dorsomedial hypothalamic nucleus
ED	eating disorders
ECS	endocannabinoid system
FAAH	fatty-acid amide hydrolase
FAS	fatty-acid synthase
GHS-R	ghrelin receptor
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
HDL	high-density lipoprotein
HPA	hypothalamic–pituitary–adrenal axis
KO	knockout
LHN	lateral hypothalamic nucleus
MAP-kinase	mitogen-activated protein kinase
MCH	melanine concentrating hormone
α-MSH	melanocyte stimulating hormone
NPY	neuropeptide Y
Nac	nucleus accumbens
NTS	nucleus of the tractus solitarius
OEA	oleoyl-ethanolamide
PVN	paraventricular nucleus
PYY	peptide YY
POMC	pro-opiomelanocortin
RIO	Rimonabant in Obesity clinical trials
SREBP-1c	sterol response element-binding protein 1c
STRATUS	Studies with Rimonabant and Tobacco Use
THC	tetrahydrocannabinol
TRH	thyrotropin-releasing hormone
VTA	ventral tegmental area
VMH	ventromedial hypothalamic nucleus

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Introduction

The first evidence of the use of cannabis for medical purposes was found in China in the year 4000 BC. From this country, the plant spread through India and Southeast Asia, reaching the Greek and Roman civilization. In India, cannabis plant was used for its appetite-stimulating properties [1]. During the Middle Ages, the Arabs (Al-Badri, 1251 AD) recommended its use because of this effect. In 1842, O'Shaughnessy, an Irish surgeon returning from India, introduced cannabis in Britain as a medicinal remedy. He promoted the use of the so-called cannabis tincture for several diseases, describing its effects on appetite. [2]. In a paper published in *The Lancet* in 1889, Birch reported on the effects of cannabis on opiate dependence, and he mentioned the increase in appetite. In 1942, an editorial of the *JAMA* recognized the treatment of anorexia as a possible therapeutic application of cannabis [1].

Cannabis users describe persistent hunger, even if previously satiated. They often feel a craving for candies [3]. However, it seems a transient effect because no weight difference has been described between regular cannabis users and nonusers. Moreover, there is no increase in prevalence of cannabis use among overweight people.

The description of the endocannabinoid system (ECS) has prompted a surge of interest in this matter, and there are numerous animal research studies that establish the relevance of ECS to appetite regulation. However, it is too early to judge its clinical and therapeutic implications.

Anandamide (AEA) and other *N*-acylethanolamides, ligands of ECS, are found in chocolate and other foods. It has been proposed that these substances could mediate the reinforcing properties of some foods, although their concentration may be too low to have central effects on ECS [4].

Basic Neuroanatomy of Feeding Regulation

The dual hypothalamic hypothesis was introduced in the 1940s and 1950s based on research with animals that caused them localized brain lesions. It was valid until recently. According to this model, there would be a satiety center (ventromedial hypothalamic nucleus, VMH) and a hunger center (lateral hypothalamic nucleus, LHN) [5]. Nowadays, it is accepted that this regulation is more complex, involving other neural centers of similar relevance. In other words, a hierarchical structure has been replaced by neural centers of similar level, distributed throughout the brainstem, limbic system, and hypothalamus. Several hypothalamic structures should be mentioned: arcuate nucleus (ARC), VMH, LHN, paraventricular nucleus (PVN), dorsomedial nucleus (DMH); along with other nuclei such as nucleus accumbens (NAc), which is part of brain rewarding circuitry, nucleus tractus solitarius (NTS), and pontine parabrachial nucleus. Various structures of cerebral cortex, mainly frontal cortex, are also involved. Hypothalamic structures receive fairly complex input on the individual's metabolic status, such as viscerceptive information through the vagus nerve, information on energy stores levels, catabolic situations such as infections, immediate metabolic status through blood glucose levels, and sensory input. These centers process this information and send their output mainly through three pathways: endocrine system (pituitary gland), autonomic nervous system (sympathetic nervous system), and motor expression (promoting or inhibiting food intake) [6, 7].

ARC is a critical region. Located near the median eminence, where blood–brain barrier (BBB) is more permeable, it receives direct information from the bloodstream (for instance, the glycemic level). This nucleus receives information on energy stores through hormones such as leptin and insulin, which reflect adipose tissue stores. Ghrelin, through its receptors (GHS-R), conveys information about the gut. There are two main groups of neurons within this nucleus, and they release several neuropeptides relevant to regulation of eating behavior. One of these populations, which when activated leads to a decrease in food intake, expresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). The POMC precursor peptide is cleaved into melanocyte-stimulating hormones, ACTH and β-endorphin. Of these, α- and β-MSH reduce body weight and food intake by acting on melanocortin receptor subtypes 3 and 4 (MC3 and MC4) that are particularly abundant in the ARC, LH, DMH, and PVN. In contrast, cells in which an increased activity leads to orexigenic response contain neuropeptide Y (NPY) and the agouti-related protein (AgRP). NPY is high in concentration in the ARC. A distinguishing feature of ARC NPY neurons is that they also contain AgRP, a natural antagonist of MC3 and MC4 receptors, which reduces the anorectic effect of α-MSH. Both POMC and NPY neurons in the ARC express leptin and ghrelin receptors. Leptin increases the activity of POMC cells and inhibits that of NPY cells, whereas ghrelin does the opposite. Efferent pathways connect this nucleus with other hypothalamic nuclei: with VMH, in which brain-derived neurotrophic factor (BDNF), an anorexigenic peptide, prevails; DMH, the site of cells expressing NPY; lateral nucleus (LHN), in which orexigenic peptides such as melanin concentrating hormone (MCH) and orexins are expressed; and finally, with the PVN [8, 9].

VMH inhibits feeding, the lesions to this region resulted in development of obesity, and it is one of a few key regions in the hypothalamus where the long-form leptin

receptors are highly expressed; therefore, it is the region that mediates leptin's effect on homeostasis. VMH contains MC4, NPY Y1, Y2, and Y5 receptors. A remarkable feature of VMH is that it highly expresses the BDNF. BDNF is a regulatory component controlled by leptin signaling; but anorectic effects of BDNF are not directly mediated by the melanocortin system [8, 9]. The LHN was identified as the hunger center. Two sets of neurons that contain either orexin or MCH, both potent stimulators of food, have been identified. Both types of neurons have a wide projection field to key cortical, limbic, and basal forebrain areas [9, 10]. DMH receives inputs from cells in the ARC and from brainstem centers. DMH has extensive connections with other hypothalamic nuclei. Lesions restricted to DMH typically result in hypophagia [8, 9]. PVN integrates signals of different brain regions and triggers endocrine responses through corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone, and autonomic responses [8, 9].

Hypothalamic nuclei have connections with NAc; through this link, the systems that regulate eating behavior interact with the brain reward systems. In turn, both centers receive input and send output to the NTS of the brainstem. This nucleus gathers important information that comes from the periphery through the vagus nerve and from the blood by means of its closeness to the area postrema, a location of increased permeability of the BBB [8].

Mesencephalic dopamine system has been implicated in the rewarding aspects of food. Hypothalamic peptides modulate the activity of dopaminergic neurons that target the NAc [6, 9].

Corticolimbic pathways are capable of integrating sensory inputs to produce cognitive representations that are stored and used for decision making. The insular cortex acts as a primary taste cortex where taste, appearance, smell, and texture are represented to establish which food is being ingested. Orbitofrontal cortex acts as a higher-order taste cortex, which determines how pleasant a particular food is [7].

Apart from central regulation, a complex mechanism of peripheral signals regulates food intake and metabolism both in the short- and in the long-term. Insulin and leptin, already mentioned, deserve emphasis because they convey information on fat stores and gut through two pathways, humoral and nervous. Leptin is a peptide secreted from adipose tissue. Restriction of food intake results in suppression of leptin levels. Production of leptin correlates positively with adipose tissue mass. Circulating leptin levels thus reflect both energy stores and food intake. Like leptin, levels of plasma insulin vary directly with changes in adiposity. Ghrelin is released by the stomach and the intestine in the fasting state and transmits humoral information to the nucleus ARC and through the vagus nerve. It is the first described gastrointestinal hormone that stimulates food intake. Increased ghrelin levels have been found in situations of anticipated eating and in diet treatments; it is suspected that such high levels could be responsible for rebound weight gain after low calorie diets [8, 11].

Cholecystokinin (CCK), released by the stomach, is one of the earliest short-term satiety signals. CCK exerts its effect via binding to CCK-A and CCK-B receptors. CCK-A receptors are found throughout the brain, including areas such as the NTS, and peripherally, in the pancreas, on vagal afferent, and enteric neurons. CCK-B receptors are also widely distributed in the brain. They are present in the afferent vagus nerve and within the stomach. CCK-A receptor subtype mediates the effect of the endogenous agonist on appetite [7, 8]. Peptide YY (PYY) also has satiating properties, being released by the ileum and colon. PYY acts as an important feedback signal from the gut to the hypothalamus. PYY is specifically stimulated by the presence of lipids and carbohydrates in ileum and colon [7].

Vagus nerve transmits information on physical (gastric distention) and chemical signals (CCK) to the vagus nuclei. Vagal afferents are broadly sensitive to gastrointestinal signals, including gastroduodenal distension, and to the presence of chemically distinct nutrients and to peptides produced by endocrine cells in the gut wall, such as CCK [7].

Adipose tissue was considered an inert organ for a long time, but now it is emerging as one important endocrine organ of the body, responsible for the secretion of many hormones. Apart from leptin, the significance of adiponectin is becoming clear: Secretion of this substance depends on fat store status and has a fundamental role in promoting lipolysis. The plasma concentration of adiponectin is inversely correlated with adiposity, and it is increased after food restriction. Plasma adiponectin levels correlate negatively with insulin resistance, and administration of adiponectin can reduce body weight gain, increase insulin sensitivity, and decrease lipid levels [8].

To give an idea of the complexity of this matter we can point out that, in 1999, at least 13 peptides with peripheral effects on food-intake regulation had been described, along with at least 26 peptides showing central effects [12]. Novel peptides are still being characterized; thus, obestatin has recently been described. It is encoded by the ghrelin gene, but has opposite effects and acts on a different receptor [13]. Moreover, classic neurotransmitters, such as dopamine, GABA and serotonin modulate this complex signaling system [14].

We increasingly have data which indicate that ECS plays a fundamental role in regulating food intake and energy metabolism. To review this role, we will focus on three aspects: animal research, human studies, and description of central and peripheral mechanisms.

Cannabinoid Agonists Increase Appetite and Weight in Experimental Animals

A series of investigations has focused on the role of ECS in regulating appetite, weight, and energy balance in animals. It supports an orexigenic effect of cannabinoid agonists and an anorexigenic one of the antagonists. The use of different experimental models has yielded some conflicting results. In some cases, animals were deprived of food from 1 to 24 h before the experimental substance administration. In other cases, they were satiated before the administration of the substance, whereas in some other, they were not (hyperphagic animal model in the latter case). In the same way, there could be simultaneous water deprivation or not. Other authors have used models of experimental animals that had free access to food, with high-carbohydrate, high-fat, or standard diets. On the other hand, animal models of obesity provide interesting data, both with diet-induced obesity (DIO) and with genetically manipulated animals *(ob/ob* or *db/db* mice leptin gene-deficient or leptin receptor-deficient mice, Zucker's obese rats, etc.). Other authorities use newborn animals to measure the influence of ECS on weight gain. Finally, CB1 receptor knockout (KO) animals are very useful. Administration routes have been diverse: whether systemic or intracerebral.

Early studies with cannabinoid agonists described a hypophagic effect, but it has been ascribed to the predominantly sedating effect of high doses. More recent experiments confirm the orexigenic effect of agonists, even in satiated animals, and this effect is mediated by CB1 receptors. The most widely used cannabinoid agonists are Δ^9-tetrahydrocannabinol (THC) and an endogenous agonist such as AEA; they increase food intake in different experimental models [15–20]. Other agonists like 2-arachidonoyl-glycerol (2-AG) [21] and noladin ether [22] have a similar effect. It has recently been described that Δ^8-THC, a substance with less psychoactive effects than Δ^9-THC, may have a stronger orexigenic effect [23].

Orexigenic effect is noticed when this substance is administered in centers related to food intake regulation. It has been delivered to VMH [24], which has a higher density of CB1 receptor than other hypothalamic nuclei; NAc [21]; or the fourth ventricle, close in location to parabrachial nucleus [25].

Centrally and Peripherally Administered Cannabinoid Antagonists Reduce Food Intake and Weight in Animals

The administration of cannabinoid antagonist, such as rimonabant, at a dose of 1–10 mg/kg for 14–35 days, to animals with an unrestricted access to food decreases their food intake [26–28]. Starved animals show the same effect [29, 30]. Other centrally administered cannabinoid antagonists have identical results [31]. Weight loss amounts to approximately 20% of baseline weight [32].

Whether the anorexigenic effect predominates on some type of food is controversial. In a series of experiments, a preferential effect on intake of palatable food has been observed [28, 33, 34]. Other experiments indicate that antagonists reduce intake of carbohydrate-rich, fat-rich, and standard diets, both in food-deprived and non deprived animals [27, 30, 35–37].

Tolerance to Anorexigenic Effects of Cannabinoid Antagonists but Not to Metabolic Effects. Possibility of Appetite Rebound after Withdrawal

In animal experiments with cannabinoid antagonists, mainly rimonabant, tolerance to its anorexigenic effect was seen after 4–5 days of administration, although weight loss persisted throughout the experiment [26, 38–40]. Tolerance developed more rapidly in lean than in obese animals [40]. However, this tolerance has not been noticed when animals received a palatable diet for 21 days [41]. Persistent weight loss supports a metabolic role of cannabinoid antagonists, unrelated to their anorexigenic effects. After discontinuing of treatment, obese animals experienced rebound weight gain [40].

Endocannabinoid Levels Vary Depending on Food Intake Status

Endogenous cannabinoids seem part of the signaling system promoting the start of food intake. An animal experiment shows that starved animals have increased 2-AG hypothalamic and 2-AG and AEA limbic levels. After feeding, hypothalamic 2-AG levels drop. However, no such change has been detected in satiated animals or in brain centers unrelated to food intake. 2-AG Administration in NAc induces food intake [21].

Effect of Cannabinoid Antagonists in Animal Models of Obesity

Experiments with obese animals, both genetically manipulated and DIO, suggest hyperactivity of cannabinoid system in obesity. Cannabinoid antagonists are more effective in reducing food intake in obese than in lean animals [40] and diminish weight and adipose tissue [42]. Food intake reduction is prolonged, even with a single dose [36, 43], and it is useful in the long-term because it keeps its effect after a repeated antagonist administration [44]. Again, these animal models showed tolerance to anorexigenic effects but

maintained weight loss. Moreover, antagonist treatment elicits favorable metabolic changes, reducing leptin, insulin, free fatty acids, and cholesterol levels, and improving insulin resistance [39, 44]. Beneficial effect on weight is noticed in pair-feeding animals and is greater in the fasting state [39]. We would like to emphasize the clinical implications of this latter finding because rimonabant effect on weight would be enhanced in association with low calorie diet, possibly because ECS hyperactivity in the fasting state would increase rimonabant efficacy.

Animals Lacking CB1 Receptor Gene Are Leaner and More Resistant to Obesity

Experiments with CB1 receptor gene KO animals, i.e., lacking this receptor, confirm its prominent role in regulation of feeding and in the pathophysiology of obesity. These animals are leaner than controls (wild-type), have less adipose tissue despite the same food energy intake, have lower levels of plasma leptin and insulin, and show less insulin resistance. A most interesting feature is that they do not develop DIO, which indicates that CB1 receptor is crucial in this kind of obesity [45].

Studies in Humans: Marihuana Consumption Increases Appetite

It has been well-known for decades that cannabis consumption triggers voracious appetite, especially for sweet food. Tart [46] described that marihuana intoxication caused appreciation of new qualities in food. Hollister [47] noticed that oral administration of THC to 12 satiated and fasting volunteers increased food intake in 7 of them. Abel [48] suggested increased craving for marshmallows. Greenberg et al. [49] observed that smoked THC increased intake and produced a weight gain of more than 2 kg in 3 weeks as compared with a control group. Foltin et al. [50] also described higher consumption of snacks with smoked THC, without increasing meal size. In another experiment, they found an increase in the intake of sweets and greater then expected weight gain for the caloric intake [51]. Mattes et al. [52] point out that, under certain experimental conditions, THC enhances snacking behaviors.

However, increased weight has not been described in regular cannabis consumers. This suggests tolerance to these effects with time or that other important variables have an influence on the weight of regular consumers.

Clinical trials with cannabinoid agonists in several diseases support this orexigenic effect; dronabinol and THC increase weight and adipose tissue in AIDS [53–55], cancer [56], or Alzheimer's disease [57].

Cannabis Withdrawal Causes Anorexia

Several experiments with smoked and oral marihuana consumption in humans have documented anorexia upon withdrawal [58, 59]. A review on this subject stated that, in 15 out of 18 studies on cannabis withdrawal syndrome, a reduced appetite was observed. Therefore, it has been proposed as a diagnostic criterion for this syndrome [60].

Cannabinoid System Is a Crucial Element in the Mechanisms of Food Intake Regulation

These studies indicate that ECS has an important role in the regulation of food intake and weight. There are emerging data on the mechanisms used by this system. Firstly, cannabinoids have an orexigenic central effect and modulate many peptides involved in the regulation of food intake; secondly, ECS contributes to the hedonic appraisal of intake, and finally, the role of ECS in peripheral metabolic regulation is increasingly appreciated. Some authors state that ECS could be the first retrograde signaling system involved in food intake regulation [61].

CB1 receptors are found in centers related to food intake, such as hypothalamic nuclei [62], NAc [10, 63], NTS, and dorsal motor nucleus of the vagus [64]. These receptors are expressed in peptidergic hypothalamic circuits regulating food intake, as neurons in the ARC secreting POMC/CART, neurons of the LHN releasing MCH and orexin, and PVN neurons secreting CRH [65].

ECS belongs to the complex mechanisms that regulate food intake. CB1 stimulation leads to modulation of the release of some hypothalamic anorexigenic and orexigenic mediators and of dopamine in the NAc shell. Recent evidence has proved that CB1 is also present in the peripheral organs, such as the adipose tissue and gastrointestinal system, key organs in the regulation of energy metabolism [66]. Interactions of this system with multiple peptides with a central or peripheral role in this regulation have been described, among others: leptin [67, 68], NPY [69, 70], CART [71], opioid system [72], ghrelin [73, 74], adiponectin [38, 75–78], CCK [79], oxytocin [80], MCH [81], orexins [82], glucocorticoids [83], and CRH [65, 84]. Its full description is beyond the scope of this review.

Regarding these interactions, it should be emphasized that food intake control circuit was regulated by leptin [68]. Thus, these authors demonstrated that leptin-deficient animals had increased hypothalamic endocannabinoid levels, and leptin treatment normalized them. Conversely, CB1−/− mice possess significantly decreased plasma levels of leptin, but exhibit enhanced sensitivity to exogenously administered leptin compared with that in wild-type mice [45, 65]. An electrophysiological analysis reveals that

perifornical LHN neurons are subject to CB1 receptor-mediated depolarization-induced suppression of inhibition (DSI), and that the effects of leptin involve the modulation of endocannabinoid-mediated DSI. Leptin inhibits voltage-gated calcium entry via janus kinase 2 and mitogen-activated protein kinase (MAP-kinase)-dependent signaling, thereby decreasing synthesis and release of endocannabinoids. These results are consistent with the hypothesis that the integration of endocannabinoid and leptin signaling regulates the excitability of neurons in appetite-related circuits [67].

Moreover, it has to be stressed that ECS interacts with opioid system to regulate the motivational aspects of food intake and hypothalamic satiety mechanisms [72, 85]. Distribution of CB1 and opioid receptors has been found to be very similar within brain areas of reward circuitry. Opioid and CB1 receptor agonists synergistically activate the mesolimbic dopaminergic system, and bidirectional interactions between cannabinoid and opioid circuits seem to be mandatory for the motivational effects of drugs and food. Although the specific mechanisms involved in the endocannabinoid and opioid interaction within the hypothalamus have still to be defined, a very probable site for functional interplay between both systems is represented by the PVN (see a review in [86]).

We should also mention a novel proposed aspect, based on the integration of the ECS in the physiology of stress, primarily through effects on the regulation of the hypothalamic–pituitary–adrenal (HPA) axis. Central modulation of the HPA axis by the endogenous cannabinoid ligands at the level of the hypothalamus is supported by the CB1 and CRH coexpression in the PVN [65]. On the other hand, the adrenal gland is a possible target for endocannabinoid regulatory effects on the HPA axis. This would be another putative mechanism involved in the central metabolic actions of the ECS [87].

Cannabinoid System Modulates Reinforcing Effects of Food

ECS belongs to the brain reward system and has a pervasive importance on addictive behavior. Regarding motivational aspects of food intake, ECS may be involved in its two phases. Berridge [88] distinguish the incentive, "wanting" or appetitive phase, in which dopaminergic circuits are relevant, from the consummatory phase, which they call "liking," in which opioid and GABAergic transmission are prominent.

CB1 receptors are presynaptic receptors found in dopamine releasing neurons originating in ventral tegmental area (VTA) and reaching NAc. This circuit is crucial to incentive processes of food intake. These dopaminergic neurons release 2-AG. In the shell portion of NAc—the most significant in incentive processes—there is a high density of CB1 receptor [89]. THC administration triggers dopamine release by the NAc [90], and dopamine D_1 receptor antagonists mitigate THC induced hyperphagia [91]. Thus, CB1 receptor modulates dopamine's ability to increase the motivational value of foods.

Several animal experiments suggest that cannabinoid agonists increase the rewarding value of foods, diminishing latency for intake and inducing food intake in satiated animals in which motivation to eat is very limited [20, 21, 85]. On the contrary, cannabinoid antagonists reduce the rewarding value of foods [92, 93].

But ECS also mediates orosensory aspects of food intake (see a review by Cooper [61]). Cannabinoid agonists enhance intake of more palatable foods [28, 33, 94, 95].

Some experiments in animals studying the effects on these two phases seem to confirm the involvement of ECS in both motivational components. Rimonabant increases latency for intake and reduces the number of intake episodes of palatable foods [93, 96].

Cannabinoid System Peripherally Regulates Energy Metabolism

Most recent findings highlight the increasing importance of ECS in peripheral regulation of food intake and energy metabolism. Some authors consider this peripheral role of CB1 receptor more relevant than its central effect [29]. Findings supporting this peripheral role are, among others: the anorexigenic effect of cannabinoid antagonists unable to cross BBB [97]; high levels of AEA in the small intestine during fasting [29]; and the anorexigenic effect of rimonabant through its interaction with CCK [98]; or the effect of oleyl-ethanolamine (OEA), an AEA analoge, on appetite, despite its lack of action on CB1 receptors [29]. Furthermore, cannabinoid receptors are being described in peripheral tissues related to energy metabolism (adipose tissue, gastrointestinal tract, liver, endocrine cells of the pancreas or muscle) [99, 100]. CB1 receptors are located in the enteric nervous system and in sensory terminals of vagal and spinal neurons [101].

It has been suggested that AEA could be a short-term peripheral signal of hunger because fasting increases its levels in the gut [29, 85].

ECS Regulates Lipid Metabolism in Adipose Tissue

CB1 receptors are found in fat tissue of animals and humans, and its agonists enhance lipogenesis [65, 102]. Adipocytes of obese animals overexpress CB1 receptors [38]. Visceral fat from mice with DIO contain higher

endocannabinoid levels than lean mice, and CB1 receptor stimulation increases lipid droplets and decreases adiponectin expression in adipocytes [76]. Rimonabant diminishes adipose tissue independently of its anorexigenic effect. This antagonist promotes adiponectin release by fat tissue, by a direct effect on adipocytes and more so in obese than in lean animals [38]. Adiponectin is an adipocytokine exclusively expressed and secreted by adipose tissue, which regulates lipid and glucose metabolism. This protein stimulates free fatty acid oxidation and reduces hyperglycemia and hyperinsulinemia. Adiponectin messenger RNA (mRNA) expression in adipose tissue is decreased in obesity [103]. Rimonabant stimulates lipolysis-inducing enzymes that enhance lipid oxidation, restores adipocyte morphology of obese animals, and reverses gene expression changes by these cells [78]. Moreover, rimonabant inhibits preadipocyte cell proliferation and stimulates mRNA expression and increases protein levels of two late markers of adipocyte differentiation (adiponectin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The authors suggest that rimonabant-inhibition of MAP-kinase activity may be one of the mechanisms involved in both effects [75]. Lipid accumulation in adipocytes is also another marker of adipocyte maturation and final stage of differentiation. Results show that rimonabant does not induce lipid accumulation in cultured mouse preadipocytes. Inhibition of preadipocyte cell proliferation and induction of adipocyte late maturation without fat accumulation may participate in rimonabant-induced reduction of body fat mass [75]. Overall, this data support a most beneficial role of cannabinoid antagonists on lipid metabolism of obese individuals.

ECS Modulates Liver Lipid Metabolism

Recently, CB1 receptors have also been described in the liver [104]. The liver plays a major role in de novo lipogenesis. Cannabinoids promote hepatic lipogenesis and enhance steatosis through CB1 receptors [104, 105]. In DIO animals, there is an increase in fatty acid synthesis mediated through liver CB1 receptors. In these animals, high levels of liver AEA are produced, probably through a reduction of the activity of its catabolic enzyme, fatty-acid amide hydrolase (FAAH). To provide further evidence of the role of hepatic CB1 receptors, Osey Hyiaman et al. [104] stimulated mice with HU210, a specific CB1 agonist. HU210 upregulated the hepatic expression of genes that are known to be key regulators of fat metabolism in the liver, including the transcription factor sterol response element-binding protein 1c (SREBP-1c) and its targets, acetylcoenzyme-A carboxylase-1 (ACC1) and fatty acid synthase (FAS), and increased hepatic fatty synthesis. Cannabinoid antagonists prevent the increase in density of CB1 receptors and hepatic fatty acid synthesis. These changes are absent in CB1 KO animals that are resistant to the development of diet-induced hepatic steatosis. They conclude that AEA acting at hepatic CB1 receptors contributes to DIO and that regulation of FAS through CB1 is the final common pathway of central hypothalamic and hepatic effects of cannabinoids [104].

ECS Modulates Muscle Metabolism

CB1 receptor is expressed in striated muscle as well [99, 106]. In genetically obese mice, rimonabant increases energy consumption, glucose intake by muscle, and promotes thermogenesis, thus improving glucose levels [107]. Indeed, CB1 local expression is up-regulated in obesity [107].

CB1 Receptor and FAAH Are Found in Human Gastric Mucosa

Our hospital research team has described CB1 receptor in myenteric plexus (Auerbach's, related to motility) of human stomach, in submucous plexus (Meissner's, related to gastric secretion) and in parietal cells. FAAH has also been detected in the latter cells, which suggests CB1 receptor involvement in gastric secretion and motility (Pazos et al., unpublished data). The resemblance of CB1 receptor distribution with that of ghrelin and glucagon-like peptide 1 [108, 109], and the fact that SR141716 administration is able to reduce the levels of ghrelin [74], suggest that they are part of a gut–brain connection that regulates eating behavior.

Vagal afferents originating in the stomach and duodenum, which express CCK1 receptors, also express CB1 receptors. CB1 expression was increased by prolonged food deprivation and reduced on refeeding. These effects were blocked by a CCK1-receptor antagonist. It was concluded that CCK may inhibit the ability of peripheral AEA to stimulate feeding via vagal activity, and so fasting may release vagal cannabinoid signals from CCK inhibition [79]. More research is required to determine whether changing gut endocannabinoid levels reflect nutritional status directly or are related to their role in regulating gut motility and gastrointestinal enzyme secretion [85].

Cannabinoid System and Eating Disorders

Genetic and environmental factors are involved in the etiology of eating disorders (ED) [110]. Genes coding peptides involved in food intake regulation have been studied as possible candidate genes. Although genetic factors seem to explain 50–80% of variance in ED, on the

whole, candidate-gene studies have been negative (see a review in [111]). Therefore ECS, which is significant in this regulation, is another candidate for research. Nevertheless, the fact that cannabinoid agonists are effective in cachectic states does not mean that they are equally useful in anorexia nervosa because pathophysiologic mechanisms are different in these states. Changes in peptides regulating food intake have been documented in ED, but they seem mostly adaptive changes to the individual's nutritional status and not primary alterations [112–118].

To assess the role of ECS in ED, we will review three lines of research: genetic studies, cannabinoid levels in patients with ED, and use of cannabinoid agonists in ED.

Genetic Studies on ECS in ED

Genetic linkage studies have identified the significance of chromosome 1 in ED genetics [119]. The gene that codes FAAH, the main cannabinoid catabolic enzyme, has been mapped to the short arm of this chromosome. A polymorphism of this gene has been described (C385A). It implies substituting adenine for cytosine, which causes the appearance of a threonine residue instead of proline in the peptide chain of the enzyme: This mutation reduces catalytic activity [120]. This polymorphism has been associated with drug use [121]. It is worth pointing out that that the wild (non-mutated) type of this gene is fairly conserved in those animal species in which it has been cloned [122]. We investigated this polymorphism in a sample of 47 ED patients and 98 controls; no significant differences have been found [123].

Another candidate gene codes CB1 receptor, mapped to the long arm of chromosome 6. A polymorphism consisting of 7 to 15 repetitions of the base triplet AAT, with nine allelic forms, has been described. An initial study of 52 pedigrees of patients with ED found an association between binging/purging type of anorexia and one allelic form and of restricting anorexia with a different allele [124]. In our study, we observed a lack of allele 8 and overrepresentation of allele 7 in women with ED. This difference did not reach statistical significance, probably because of the small sample size (p=0.1) [123] (Table 1). Thus, consistent data demonstrating the involvement of genetic factors related to ECS in the etiology of ED are still lacking.

Endocannabinoid Levels in ED

One study analyzed AEA and 2-AG blood levels in ED patients. AEA levels were increased in anorexia nervosa and in binge ED, but not in bulimia. The authors suggested

Table 1 Allelic and genotypic frequencies of the AAT triplet repeats polymorphism of the *CNR1* gene and *FAAH* gene by group

	Control, n=98	ED, n=47		
		ANr, n=13	ANp, n=21	BNp, n=13
Allele A (*FAAH* gene)	37 (20.8)	6 (23.1)	7 (16.7)	4 (15.4)
Allele C (*FAAH* gene)	141 (79.2)	20 (76.9)	35 (83.3)	22 (84.6)
Genotype *FAAH*				
CC	56 (62.9)	7 (53.8)	14 (66.7)	9 (69.2)
AA	4 (4.5)	0	0	0
AC	29 (32.6)	6 (46.2)	7 (33.3)	4 (30.8)
Genotype *CNR1*				
<5 <5	8 (8.7)	0	2 (9.5)	3 (23.1)
≥5 ≥5	47 (51.1)	7 (53.8)	10 (47.6)	5 (38.5)
<5 ≥5	37 (40.2)	6 (46.2)	9 (42.9)	5 (38.5)
Allele 1 *CNR1*	4 (2.2)	1 (3.8)	0	1 (3.8)
Allele 2	0	0	1 (2.4)	0
Allele 3	0	0	0	0
Allele 4	49 (26.6)	5 (19.2)	12 (28.6)	10 (38.5)
Allele 5	5 (2.7)	0	2 (4.8)	0
Allele 6	36 (19.6)	8 (30.8)	6 (14.3)	5 (19.2)
Allele 7	40 (21.7)	6 (23.1)	13 (31.0)	5 (19.2)
Allele 8	46 (25.0)	6 (23.1)	8 (19.0)	3 (11.5)
Allele 9	4 (2.2)	0	0	2 (7.7)

For genotype: number of subjects with this genotype and within parenthesis is expressed in percentage. For alleles: number of alleles by group and within parenthesis is expressed in percentage. All comparisons are not significant (from the Pearson chi-square or Fisher's exact test when appropriate) comparing the whole sample of ED to control group

FAAH Fatty acid amide hydroxilase, *ED* eating disorders *ANr* anorexia nervosa restricting type, *ANp* anorexia nervosa purging type, *BNp* bulimia nervosa purging type

that AEA participates in reinforcing aspects of food intake behavior disturbances, but if this were true, these levels should also be altered in bulimia. The origin of the measured AEA should be established, and it would be necessary to know whether plasma AEA levels reflect central functioning of ECS. More interesting is the negative correlation between AEA and leptin levels, which suggests leptin deficiency in anorexia nervosa and leptin insensitivity in binge ED. This would explain high AEA levels in both [125].

Use of Cannabinoid Agonists in ED

As far as we know, there is only a single clinical trial on cannabinoid agonists in ED. In this randomized, double-blind, placebo-controlled trial, 11 patients with anorexia nervosa received THC. It concluded that THC was ineffective and had adverse psychological effects [126]. The THC dosage used (7.5–10 mg/day) was high, and it has been said that these doses may have anorexigenic effects, possibly through CRH release.

In summary, available information does not allow concluding that ECS is relevant in ED pathophysiology.

Cannabinoid System and Obesity

In Western countries, high prevalence of obesity makes it an important public health problem. Its diagnosis is made using a single piece of information, the body mass index (BMI). It is estimated that, in the USA, 30.5% of the population has a BMI >30 and 5% >40 [127].

Obesity is not considered an ED, although disturbances in eating behavior are frequent. Genetic and environmental factors are clearly involved in its etiology. Dietary factors, such as dietary fat content [128] or the consumption of palatable foods have a prominent role, along with sedentary lifestyle and food intake related to social and cultural factors [129]. Complex neurobiological mechanisms are involved in the regulation of food intake, and they are better suited for times of food shortage than for times of plenty, thus homeostatic control of food intake is felt to be asymmetric [7, 14].

Obesity has a strong heritable component [130], and genetic factors are relevant for BMI and for body fat percentage [131]. Monogenic forms of obesity have been described, but they are rare. Therefore obesity is considered a polygenic disorder [132]. Genes associated with obesity are numerous [133]. A set of “thrifty” genes is considered to confer an advantage in times of shortage but promote obesity in present environmental conditions [133].

Given the prominent role of ECS in the regulation of appetite and energy metabolism, it is a clear target of research in obesity, and available data demonstrate its pathophysiological significance. We are going to refer to three lines of research: genetic studies on ECS in obesity, endocannabinoid levels in obesity, and clinical trials with cannabinoid antagonists in obesity. As we will see, all of them suggest that obesity could be because of hyperactivity of cannabinoid system, as reported by other authors [100, 134]. In a recent review, the authors suggest that endocannabinoid overactivity seems to contribute to the development of abdominal obesity, dyslipidemia, and hyperglycemia [135].

Genetic Studies on ECS in Obesity

Chromosome 6 has been associated with obesity [136]; the gene coding CB1 has been mapped to this chromosome. An association between a polymorphism of the gene coding FAAH (C385A) and obesity has been described [137]. Mutated homozygotic AA form was more prevalent in obese patients than in controls. Possibly this mutated form causes a reduction in FAAH enzymatic activity, reduced inactivation of endocannabinoids and, therefore, cannabinoid hyperactivity in obese persons [137].

We have studied this polymorphism of FAAH and the repetition polymorphism AATn of the CNR1 gene in a sample of 79 morbidly obese patients (mean BMI=46) and 98 normal-weight controls. We did not find differences in AA, AC, and CC genotypes of FAAH enzyme between obese patients and controls, possibly because of a very low prevalence of allele A. Neither were there differences among various allelic forms of the AATn polymorphism of CNR1 gene. But when these allelic forms were classified in short/short, short/long, and long/long genotypes, as suggested by Comings et al. [138], the short/short genotype was found twice as frequent among obese patients (15.2% vs. 8.7% in controls; $p=0.18$; Fig. 1). There is evidence that the short genotype entails improved function of CB1 receptor [139]. Moreover, we documented a putative interaction of both polymorphisms: The presence of two short alleles of CNR1 and at least one allele A of FAAH gene was associated with an increased risk of morbid obesity. Among individuals with AA or AC genotype, 23.3% of obese patients had a short/short polymorphism of CNR1 gene, versus 6.1% in controls (OR=4.7, 95% CI 1–25; $p=0.05$). This suggests the presence of hyperactivity of ECS in morbid obesity because of increased functional activity of CB1 receptor and reduced activity of FAAH enzyme (Gorgojo et al., unpublished data). Interactions between genes have previously been described in the etiology of morbid obesity [140].

A different CB1 polymorphism was associated with BMI. Two hundred ten healthy subjects from a population survey carried out in Italy were divided into quintiles by BMI. Genotyping for the CB1 1359G/A polymorphism was

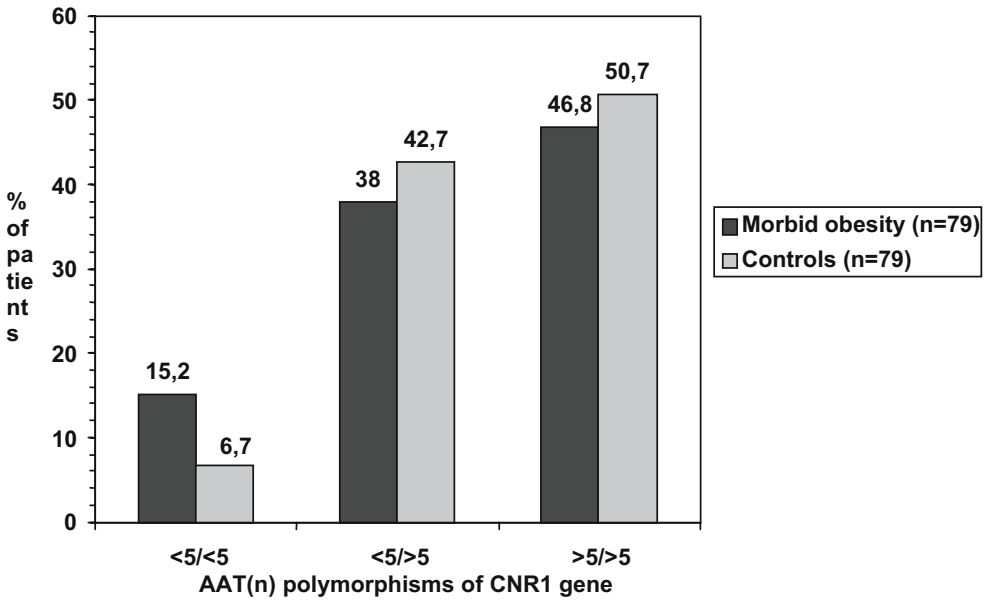

Fig. 1 Distribution of short (<5) and long (≥5) alleles of the AAT (n) polymorphisms in morbidly obese (MO) patients and controls. <5: 7 to 10 repeats; >5: >11 repeats. No significant differences in the single allele frequencies were found when comparing the MO patients with the control group. After grouping the allelic types into three genotypes (short/short, short/long, and long/long), the prevalence of the short/short genotype was 15.2% in MO patients versus 6.7% in controls (p=0.092)

performed. A clear trend of increasing relative frequency of the CB1 wild-type genotype with the increase of BMI was found [141].

Peripheral Tissue Endocannabinoid Levels in Obesity

One study measured plasma endocannabinoid levels and expression of CB1 receptor and FAAH in adipose tissue of obese postmenopausal women. Obese women had increased plasma levels of AEA and 2-AG and lower expression of CB1 receptor and FAAH enzyme in adipose tissue than controls. Weight loss had no influence on endocannabinoid levels nor on CB1 and FAAH expression, which suggests that ECS hyperactivity may be a cause and not a consequence of weight gain and that this hyperactivity might be the result of diminished peripheral FAAH activity [142].

The same group determined whether circulating endocannabinoids are related to visceral adipose tissue mass in lean, subcutaneous obese, and visceral obese subjects. They measured expression of the CB1 receptor and FAAH genes in subcutaneous and visceral adipose tissue. Circulating 2-AG was significantly correlated with body fat and visceral fat mass. In visceral adipose tissue, CB1 and FAAH expression were negatively correlated with visceral fat mass. These findings suggest that abdominal fat accumulation is a critical correlate of dysregulation of the peripheral ECS in human obesity [143].

In a similar way, another group found that patients with obesity (BMI≥30 kg/m^2) exhibit higher concentrations of endocannabinoids in visceral fat than controls. The authors concluded that peripheral endocannabinoid overactivity might explain why CB1 blockers cause weight-loss independent reduction of lipogenesis, of hypoadiponectinemia, and of hyperinsulinemia in obesity [76].

In another study by the same group, fasting plasma levels of AEA and 2-AG were measured in a sample of men with BMI from 18.7 to 35.2 kg/m^2. Plasma 2-AG, but not AEA, levels correlated positively with BMI and intra-abdominal adiposity and negatively with adiponectin levels. Obese men with similar BMI values but who markedly differed in their amount of intra-abdominal adiposity exhibited higher 2-AG levels in the presence of high intra-abdominal adiposity. These findings suggest a relationship between endocannabinoid and cardiometabolic risk factors, including intra-abdominal adiposity [144].

Cannabinoid System and Course of Obesity

It has been suggested that cannabinoid hyperactivity could explain relapses of weight gain [142]. We studied the aforementioned genetic polymorphisms of ECS as predictors of response to medical and surgical treatment of obesity. After adjusting for other relevant variables, obese patient homozygous for the short polymorphism of CNR1 gene lost less weight (5% lower weight loss, 95% CI 1.3–8.9) after medical treatment (diet and drugs) than patients with long polymorphisms. This suggests that cannabinoid system hyperactivity could result in a less favorable outcome (Gorgojo et al., unpublished data).

Therefore, genetic variants that involve higher level of function of cannabinoid system may be relevant in obesity etiology and, in turn, have an influence on the weight course of these patients.

Use of Cannabinoid Antagonists in Obesity

There are four clinical trials on rimonabant use in obesity, the RIO studies (rimonabant in obesity): RIO-Lipids, RIO-

North America, RIO-Europe and RIO-Diabetes, and three clinical trials on its use in nicotine dependence, STRATUS (Studies with Rimonabant and Tobacco Use) [145]. Data suggest that rimonabant achieves weight loss in obese individuals. In addition, it improves lipid profile and metabolic syndrome.

RIO-Europe was a 2-year trial, enrolled 1,507 individuals with a BMI >27. Doses of 5 and 20 mg rimonabant once daily, along with a low calorie diet, were compared with placebo. In the analysis carried out at 1 year of follow-up, patients receiving 20 mg/day showed greater weight reduction than patients treated with placebo, with an improvement in lipid profile which could not be explained by the amount of weight loss, according to the researchers. Of the patients treated with 20 mg rimonabant a day, 27.4% achieved a weight reduction of more than 10% from baseline, a loss considered clinically relevant, versus 7.3% in the placebo group. The number of patients diagnosed as having metabolic syndrome was reduced by 65% in those on a 20-mg daily dose of rimonabant compared to 34% in the placebo group after completing 1 year of treatment. Depression was the most frequent cause of dropout in all groups. The 20-mg rimonabant dosage was associated with more dropouts because of gastrointestinal complaints, headache, and dizziness. Publication of the 2-year results is awaited [146].

RIO-Lipids study [147] enrolled 1,036 subjects with a BMI >27, comparing 5 and 20 mg rimonabant once a day versus placebo, along with low calorie diet, with a follow-up of 12 months. Patients who received rimonabant at a dosage of 20 mg/day lost more weight—6.7 kg—than individuals receiving placebo. In addition, they showed improved levels of adiponectin, leptin, HDL, and triglycerides. Of the individuals treated with 20 mg/day of rimonabant, 32.6% experienced a weight loss greater than 10% of baseline, as compared with 7% in the placebo group. Most frequent dropouts were caused by gastrointestinal complaints and psychiatric disturbances (anxiety and depression).

The clinical trial RIO-North America enrolled 3,045 patients. The study design was similar, but after a 1-year follow-up, patients were re-randomized for an additional year of follow-up. Results are consistent with the earlier studies, with similar size of effect versus placebo (6.3 kg weight loss vs. 1.6 kg) and much the same changes on lipid and glucose metabolism, unexplained by the amount of weight loss achieved. After re-randomization, individuals taking 20 mg rimonabant maintained their weight loss, whereas those assigned to placebo regained weight. In general, there was a dropout rate of 12.8% (20-mg group) versus 7.2% (placebo group). Respectively, 6.2% versus 2.3% of the dropouts were because of psychiatric disturbances [148].

The Rimonabant-in-Obesity (RIO)-Diabetes trial studied the safety and efficacy of rimonabant in overweight and obese patients with type 2 diabetes who were treated with metformin or sulfonylureas. RIO-Diabetes was a 1-year, randomized, double-blind, placebo-controlled, parallel-group study of 1,047 overweight/obese patients with type 2 diabetes. The BMI of participants ranged from 27 to 40. All patients received either metformin or sulfonylurea therapy and were asked to follow a hypocaloric diet for the duration of the trial. After a 4-week placebo plus diet run-in period, patients were randomized to receive placebo or rimonabant 5 or 20 mg once daily. At 1 year, absolute change in weight from baseline in the intention-to-treat analysis of the rimonabant 5- and 20-mg groups, respectively, was loss of 2.3 and 5.3 kg compared with 1.4 kg in the placebo group. Waist circumference and glycosylated hemoglobin were significantly decreased in the rimonabant 5- and 20-mg groups. Some of the improvements in metabolic parameters could not be attributed to observed weight loss. Compared with placebo, rimonabant 20 mg also demonstrated significant improvements in the prevalence of metabolic syndrome. The incidence of adverse events that led to discontinuation was slightly greater in the 20 mg/day rimonabant group, mainly because of depressed mood disorders, nausea, and dizziness [149].

Therefore, one may conclude that rimonabant use achieves moderate weight loss in obese individuals, similar in size to that showed by other antiobesity drugs [150] but with an additional improvement of lipid profile. Treatment with 20 mg/day of rimonabant produced clinical meaningful weight loss, reduction in waist circumference, and associated improvements in several metabolic and cardiovascular risk factors, including insulin levels, insulin resistance index, HDL cholesterol and triglyceride concentrations, and adiponectin levels. In addition, the prevalence of metabolic syndrome was significantly reduced.

The need of long-term administration to avoid relapse emerges from these trials. Main adverse effects are gastrointestinal complaints and psychopathological disturbances. Probably, the latter would be the main obstacle for use of rimonabant in obesity, considering the high prevalence of psychiatric disorders in obese individuals [151]. In obesity, rimonabant has central and peripheral mechanisms of action: anorexigenic central effect, reduction in motivation for food intake, stimulus of satiety signals in the gut, increase in lipolysis and release of adiponectin by adipose tissue, along with increase glucose uptake by muscle [152]. Other authors suggest that cannabinoid antagonists would normalize deficient leptin signaling present in hyperphagic states [67]. However, an aversive mechanism through nausea induction, mediated by its effects on gastric motility, cannot be ruled out [153, 154].

The obese patient profile that would benefit most from cannabinoid antagonist therapy remains to be defined. It is not known whether it is more effective in patients who

snack between meals, if it has preferential effect on sweets intake, or if its efficacy increases when associated with a low calorie diet. This is a most interesting field for clinical research.

Conclusions

ECS is a crucial part of regulation of food intake and energy metabolism. Cannabinoid agonists increase appetite, whereas antagonists have an opposite effect, both in animals and in humans. No single mechanism explains this; centrally acting mechanisms are involved, and peripheral mechanisms seem increasingly significant. There is no evidence that cannabinoid system is involved in the etiology of ED, but there are data that suggest its hyperactivity in obesity. Such hyperactivity may be an important prognostic factor. Thus, clinical trials with rimonabant, a cannabinoid antagonist, suggest that a novel therapeutic weapon will be available for treating obesity, with a new interesting profile.

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