MINIREVIEW

Endocannabinoids and Food Intake: Newborn Suckling and Appetite Regulation in Adulthood

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The appetite-stimulating effects of the cannabis plant (*Cannabis sativa*) have been known since ancient times, and appear to be effected through the incentive and rewarding properties of foods. Investigations into the biological basis of the multiple effects of cannabis have yielded important breakthroughs in recent years: the discovery of two cannabinoid receptors in brain and peripheral organ systems, and endogenous ligands (endocannabinoids) for these receptors. These advances have greatly increased our understanding of how appetite is regulated through these endocannabinoid receptor systems. The presence of endocannabinoids in the developing brain and in maternal milk have led to evidence for a critical role for CB_1 receptors in oral motor control of suckling during neonatal development. The endocannabinoids appear to regulate energy balance and food intake at four functional levels within the brain and periphery: (i) limbic system (for hedonic evaluation of foods), (ii) hypothalamus and hindbrain (integrative functions), (iii) intestinal system, and (iv) adipose tissue. At each of these levels, the endocannabinoid system interacts with a number of better known molecules involved in appetite and weight regulation, including leptin, ghrelin, and the melanocortins. Therapeutically, appetite stimulation by cannabinoids has been studied for several decades, particularly in relation to cachexia and malnutrition associated with cancer, acquired immunodeficiency syndrome, or anorexia nervosa. The recent advances in cannabinoid pharmacology may lead to improved treatments for these conditions or, conversely, for combating excessive appetite and body weight, such as CB_1 receptor antagonists as antiobesity medications. In conclusion, the exciting progress in the understanding of how the endocannabinoid CB receptor systems influence appetite and body weight is stimulating the development of therapeutic orexigenic and anorectic agents. Furthermore, the role of cannabinoid CB_1 receptor activation for milk suckling in newborns may open new doors toward understanding nonorganic failure-to-thrive in infants, who display growth failure without known organic cause. Exp Biol Med 230:225–234, 2005

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Cannabinoid Stimulation of Eating: Basic Phenomena

The appetite stimulating effect of the cannabis plant (*Cannabis sativa*) has been known about since ancient times (1, 2). With more systematic observations of cannabis actions by physicians in the 19th century, potential clinical applications for treating loss of appetite or body weight, such as occur in cachexia, were proposed (2, 3).

Recent research has confirmed these observations, spurred by the identification of the psychoactive compounds contained in cannabis such as Δ^9-tetrahydrocannabinol (THC) and related cannabinoid molecules. More recently, a physiological basis for the actions of plant-derived cannabinoids has been explained by the discovery of two cannabinoid receptors and their endogenous ligands, the endocannabinoids. These substances include anandamide, 2-arachidonoyl glycerol (2-AG), noladin ether, NADA, and

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virodhamine (for reviews, see for example Refs. 4, 5). These discoveries have opened the door to the characterization of the mechanisms underlying a range of traditionally known medicinal effects of cannabis, including appetite stimulation (2, 6–8).

THC, or Δ^9-tetrahydrocannabinol, the major active component of the marijuana plant (9), stimulates eating in people (see Ref. 10). In an early study, Hollister (11) examined acute THC effects on the consumption of chocolate milkshakes. The drug significantly increased intake, elevated hunger ratings, and enhanced food appreciation (12). More systematic studies using marijuana cigarettes with varying THC content have been conducted by Foltin and colleagues (12–14). Substantial increases in daily caloric intake are routinely observed after cannabis smoke inhalation, primarily through an increase in the frequency and consumption of snack foods, such as candy bars, cookies, and cakes. The intake of sweet drinks (e.g., cola, fruit juice) or savory solid items (e.g., potato chips) were less affected. Similar effects of THC on snack intake were reported (15) using a variety of routes of administration. As discussed in a later section, the hyperphagic effects of the drug are currently being exploited clinically for the amelioration of appetite loss and weight loss in disease.

Recent work using animal models has begun to shed light on the mechanisms by which THC acts to exert its actions on feeding. In particular, the discovery of cannabinoid receptors within the central nervous system and their endogenous ligands has indicated that THC-induced effects reflect the modulation of key neural systems implicated in the normal control of appetite.

THC has been shown to stimulate feeding in a variety of animal models since the 1970s, and this action has now been shown to be mediated by central-type CB_1 cannabinoid receptors, because THC-induced feeding is reversed by treatment with the selective CB_1 antagonist rimonabant (SR141716; Ref. 16). The hyperphagic effect of THC in rats is remarkably potent, causing animals to overconsume even when replete (16, 17). Importantly, the hyperphagic actions of THC have been replicated following administration of the endocannabinoids anandamide and 2-AG. These substances increase intake in rodents following systemic or central injection, and their actions are CB_1 receptor-mediated (8, 16, 18–21). Moreover, anandamide and 2-AG will promote feeding when administered into hypothalamic nuclei and into the shell region of the nucleus accumbens. Both the hypothalamus and the nucleus accumbens are brain regions that are firmly associated with eating motivation (22, 23), and their sensitivity to the hyperphagic actions of anandamide and 2-AG strongly supports an important role for endocannabinoids in the control of eating.

Complementing the feeding actions of CB_1 agonists is the ability of CB_1 receptor blockade to suppress eating (6). Thus, acute peripheral administration of rimonabant reduces food intake in laboratory species (24–26). More recently, reliable anorectic actions of rimonabant or its analog, AM281, have been reported following intracerebroventricular administration in satiated or food-deprived rats (27).

A common theme in hypotheses about how cannabinoids affect eating motivation reflects the kinds of effects described earlier: an increased sensitivity to the sensory properties of foods and apparently preferential effects on preferred, highly palatable foods. There is now a good deal of evidence to support involvement of endocannabinoids in appetitive and consummatory processes. In other words, endocannabinoids appear to be linked to the instigation of food seeking and eating initiation, and also to the orosensory or hedonic evaluation of food during eating (what Berridge [28] has described as "wanting" and "liking" processes; Ref. 31). Notably, researchers have found that rats will work harder to obtain palatable ingesta after administration of CB_1 receptor agonists, while antagonist treatments attenuate responding (29, 30). Moreover, observational analyses and monitoring of meal patterns reveals that THC, anandamide, or 2-AG will induce feeding almost as soon as food becomes available; even when animals have been fully satiated by overconsumption of a highly palatable food (8, 17, 31). Crucially, once initiated, the subsequent pattern of cannabinoid-induced feeding behavior is identical to that of untreated rats feeding spontaneously under home cage conditions. These findings imply that stimulation of CB_1 receptors enhances the salience or incentive value of food, and hence increases the motivation to approach food and begin eating.

Returning to the possibility of cannabinoid involvement in food "liking," evident in anecdotal reports of cannabis users, there are new data to support a specific interaction of endocannabinoids with food palatability. For example, CB_1 receptor blockade is reported to preferentially attenuate the intake of preferred, palatable diets (24, 25). Examination of the actions of CB_1 receptor ligands on the microstructure of sucrose drinking reveals that alterations to sucrose drinking induced by exogenous and endogenous agonists were reminiscent of those observed in drug-free animals when a dilute sucrose solution is substituted by a more concentrated, more palatable solution (32). Conversely, a selective CB_1 receptor antagonist alters drinking in a way that is consistent with a reduction in the palatability of the sucrose. These effects thus support the hypothesis that tonic release of endocannabinoids contributes significantly to the hedonic evaluation of ingesta, and suggest that stimulation of endocannabinoid systems renders food more pleasurable.

As is well known, the cannabinoids are far from the sole factors involved in the regulation of appetite and weight balance (33, 34). A number of reviews have recently been written on the complex interplay of factors involved in appetite and weight control, to which readers are referred. In the following sections we will address some of the recent evidence linking endocannabinoids with other neurotrans-

mitter and hormonal factors linked to eating and body weight control.

As will be outlined below, it seems that the endocannabinoid-cannabinoid receptor (ECBR) system influences energy balance and food intake at four different levels: hedonic evaluation at the limbic system level, modulation of integrative functions within the hypothalamus and hindbrain and, peripherally, in the intestinal system and adipose tissue.

The ECBR System and Feeding Regulation in the Newborn

In a recent report, weanling offspring of undernourished dams displayed lower body weights and levels of anandamide compared with controls, whereas 2-AG concentrations were not influenced (35). Given the dependence of pups on maternal fatty acid precursor supply for their production of long-chain polyunsaturated fatty acids, together with a previous observation that dietary supplementation with essential fatty acids increased concentrations of anandamide but not of 2-AG in piglets (36), the authors estimated that the influence of maternal undernutrition on hypothalamic anandamide concentrations in their offspring may have resulted from a disruption in the essential fatty acids supplies from the maternal blood supply, or from her milk, or both (35).

The detection of endocannabinoids in bovine as well as human milk—2AG in at least 100-fold to 1,000-fold and higher concentrations than anandamide (37, 38)—suggest a role for 2-AG in newborn milk intake.

The high levels of CB_1 receptor mRNA and 2-AG that have been observed on the first day of life in structures such as the hypothalamic ventromedial nucleus (39), which is associated with feeding behavior, further supported our hypothesis that 2-AG in the newborn pup's brain comprises a major stimulus for the newborn to initiate milk intake.

Indeed, in a series of studies performed in neonatal mice, we have demonstrated that CB_1 receptors are critically important for the initiation of the suckling response. Thus when the CB_1 receptor antagonist rimonabant was injected in newborn mice, milk ingestion and subsequent growth was completely inhibited in most pups (75%–100%) and death followed within days after antagonist administration (37). The antagonist must be administered within 24 hr after birth to obtain the full effect: injections on Day 2 result in a 50% death rate; rimonabant administration on Day 5 has no effect at all on pup growth and survival (40, 41).

Subsequent studies indicated that the dramatic effect of CB_1 receptor blockade is dose-dependent and specifically mediated by CB_1 receptors. Thus, coapplication of Δ^9-THC with rimonabant almost completely reversed the rimonabant-induced growth failure (37). We have replicated this phenomenon in three different strains of mice (Sabra, C57BL/6, and ICR).

In agreement with these observations, CB_1 receptor-deficient mice (42, 43) displayed deficient milk suckling on the first days of life, while by Day 3 of life they had developed normal suckling behavior. Their weight gain, however, remained significantly reduced compared with that of the C57BL/6 background strain. Further, as expected, the growth curve of CB_1 receptor knockout mice was not affected by neonatal injections of the CB_1 antagonist. On the other hand, survival rate and the initiation of the suckling response were significantly inhibited by the CB_1 receptor blocker, suggesting the existence of an additional CB_3 receptor, possibly up-regulated in $CB_1^{-/-}$ knockout mice (41).

Recent experiments in our laboratory were designed to further analyze potential physiological/behavioral mediators by which the neonatally administered CB_1 receptor antagonist prevents the development of milk ingestion. Based on the complex relationship between thermoregulation, ultrasonic vocalization (44–47), suckling (46, 47), and maternal behavior (44, 45), we decided to study body temperature and ultrasonic vocalizations in rimonabant-treated pups throughout postnatal development. Thus we have observed now that rimonabant-treated pups are hypothermic, while their ultrasonic vocalizations are inhibited (a preliminary report of these data were reported in Ref. 48).

In a further set of experiments, 2- to 11-day-old pups that had been injected with rimonabant or with vehicle within 24 hr after birth were exposed to anesthetized nursing dams. While vehicle-injected pups all located the nipples and nursed from the dam on every testing day, none of the rimonabant-injected pups did so on the day after injection. Further experiments suggest that the rimonabant-treated pups have a severe oral-motor impairment (Fride and Ezra, unpublished observations).

The sequence of events induced by the blockade of the CB_1 receptor immediately after birth is difficult to determine. Is a hypothermic pup unable to call his mother to stimulate the suckling response? Or perhaps, does the pup who fails to call his mother become hypothermic and thus does not have the motor capability to suckle?

Based on data gathered thus far (37, 39, 41), we propose the following model for the initiation of the milk suckling process during the first days postnatally in the mouse (see Ref. 49). At birth, the 2-AG content in the brain is sufficiently high to stimulate the suckling response (appetite). Upon milk intake, 2-AG from the maternal milk elevates the levels of 2-AG in the pup's brain so that by the second day of life and further on, the milk-derived 2-AG stimulates suckling. If endogenous 2-AG cannot stimulate the first bouts of milk sucking (as in CB_1 receptor antagonist-treated pups), milk-derived 2-AG is not present to stimulate milk sucking on Day 2 of life, and the window to develop a pattern of milk suckling behavior has closed.

Clinical Implications of the ECBR System Role in the Newborn. The apparent selective oral-motor deficiency in mouse pups with blocked CB_1 receptors is reminiscent of a syndrome identified in human babies and

designated nonorganic failure-to-thrive (NOFTT). Failure-to-thrive (FTT) is commonly defined as an abnormally low weight, height, or both for age (50, 51). NOFTT is defined as FTT without a known organic cause. Traditionally, NOFTT was believed to be associated with parental psychopathology (52–54). However, recent research points to NOFTT as a mild neurodevelopmental disorder or pathophysiology (55) in which an oral-motor defect apparently plays a central role, resulting in deficient sucking or milk ingestion (or both) by the infant (51, 56, 57).

Thus, in the opinion of most authors, to denote this FTT entity as *nonorganic* has become inappropriate. NOFTT is generally considered now as a biological vulnerability (51), the underlying mechanism of which is, however, unknown. Based on the oral-motor deficiency, which is associated with the severe nursing and growth failure observed in CB_1 receptor-blocked neonatal mice, we propose that a deficient endocanabinoid-CB_1 receptor system comprises the enigmatic biological vulnerability in NOFTT.

Mechanisms by Which the Endocannabinoid-CB_1 Receptor System Affects Feeding and Appetite

Central Mechanisms: Hypothalamus and Hindbrain. The hypothalamus and its discrete subregions have long been considered to play a key role in integrating the multiple biochemical and behavioral components of feeding and weight regulation. It is not surprising, then, to find evidence that endocannabinoids modulate these integrative processes. Administration of cannabinoids into hypothalamic nuclei will induce eating (8, 18), and cannabinoid activity in the hypothalamus varies according to changes in nutritional status and the expression of feeding behaviors. For example, levels of 2-AG are increased in the hypothalamus after 24 hrs of food deprivation in rats (19) and mice (58), and decline as animals eat, returning to control levels with the onset of satiety (19). These changes are compatible with the behavioral actions of cannabinoids: the enhanced motivation to eat after CB_1 agonist treatments reflects that observed after fasting (35). However, Hanus *et al.* (58) also reported that hypothalamic 2-AG decreased after 12 days of food restriction. These findings were elegantly explained by the authors to reflect adaptive behavioral strategies in response to acute or chronic food deprivation. Thus, during short-term starvation it is beneficial for high levels of the appetite-inducing 2-AG to compel the animal to actively seek food. Conversely, during long-term deprivation, when apparently no food is to be found, it may aid survival to conserve energy by reducing the motivation to engage in food seeking—perhaps by reducing the conscious experience of hunger (58).

The hormone leptin, which originates in adipose tissue and affects a number of appetite-related factors in the hypothalamus, has been proposed to be a core component in the regulation of food intake and weight control (34, 59). It is therefore of great interest that functional relationships between cannabinoids and leptin have been demonstrated (60; also see Ref. 33), and that endocannabinoid synthesis may be regulated by leptin. Thus, leptin administration, which exerts an anorectic action, suppresses hypothalamic endocannabinoid levels in normal rats, while genetically obese, chronically hyperphagic rats and mice express elevated, leptin-reversible, hypothalamic anandamide or 2-AG levels (60).

Careful studies of food intake, appetite, and fat mass of CB_1 knockout mice showed these animals to display a lean phenotype throughout their lifetime. This is very different from the effects of simultaneous deletion of neuropeptide Y (NPY) and Agouti-related protein, transmitters heavily implicated in intake control, which do not result in a lean phenotype (61). This comparison may indicate that the ECBR system is more critical for the regulation of energy balance than either of these orexigenic neuropeptides (62). In the absence of a change in hypothalamic CB_1 receptors as well as a lack of correlation between receptor density and plasma leptin under conditions of dietary-induced obesity (63), Harrold and Williams suggest that hypothalamic CB_1 receptors do not play a role in driving appetite during dietary obesity, but may stimulate hunger under different conditions such as starvation (64). This interpretation is compatible with the reported increase in 2-AG concentration in response to short-term food deprivation (21, 39), but not with the decline in 2-AG levels in the hypothalamus after long-term starvation (39) (also see the previous section).

Very little is presently known about the interaction of the ECBR system with other hormones involved in energy control and food intake. However, Cota and colleagues (62) have shown colocalization of CB_1 receptor with the appetite regulating hormones cocaine amphetamine regulated transcript (CART), melanin concentrating hormone (MCH), and corticotropin releasing hormone (CRH) in the paraventricular nucleus of the hypothalamus, while no colocalization was found with NPY in the arcuate nucleus. These findings suggest a direct interaction of endocannabinoids with CART but not with NPY. There is also evidence for functional interactions between endocannabinoids and orexin A, an orexigenic peptide that is selectively expressed in the lateral hypothalamus and which has been linked to the stimulation of feeding (65, 66). More specifically, evidence was obtained for cross-talk between CB_1 receptors and the orexin OX1R receptor (67). Additionally, CB_1 receptor knockout mice (which are characterized by hypophagia, reduced body weight, and reduced fat mass compared with their wild-type littermates) show higher levels of mRNA for the anorexigen CRH (62). Synergistic interactions between cannabinoids and melanocortin systems have also been detected in relation to feeding with, for example, rimonabant facilitating the anorectic actions of alpha-MSH (68). Recently, evidence has been obtained for significant interactions between the stomach-derived, orexigenic peptide ghrelin and endocannabinoids. Specifically, feeding

stimulated by intrahypothalamic ghrelin injection is blocked by pretreatment with rimonabant (69).

In addition to the hypothalamus, CB_1 receptors located in feeding-relevant hindbrain areas such as the dorsal motor nucleus of the vagus (DMV) and the nucleus tractus solitarius (NTS; Ref. 70) may also be subject to cannabinoid regulation. Thus, the cannabinoid receptor agonist CP 55,940 injected into the fourth ventricle enhances milk intake with greater potency than when injected into the third ventricle (71).

Central Mechanisms: Limbic System. As mentioned earlier, cannabinoids appear to partly influence food intake by modifying the hedonic response to foods. Key components of the neural mechanisms underlying food palatability lie within the limbic forebrain, including the nucleus accumbens (18, 19). It is notable, therefore, that the shell subregion of the accumbens (AcbSh) is a highly sensitive site of action for cannabinoid-induced eating: 2-AG administered into this site produces the most profound hyperphagic response so far observed after central cannabinoid treatment (19). Importantly, the AcbSh is involved in the generation of emotional arousal and behavioral activation in response to potentially rewarding stimuli, including the stimulation of eating. Furthermore, fasting (which would be expected to elevate the incentive and reward value of food) increases levels of anandamide and 2-AG in the limbic forebrain. Moreover, Harrold and colleagues have shown that nucleus accumbens CB_1 receptors are down-regulated in rats that overconsume palatable food supplements. This effect is consistent with increased activation of these receptors by endocannabinoids, and suggests they mediate the hedonic evaluation of palatable foods (63). By contrast, in the same model of diet-induced obesity, CB_1 receptor density was unaltered in the hypothalamus (64).

Endocannabinoids may also have important functional relationships with the endogenous opioid systems that mediate the rewarding properties of food (72). Thus, in rats, the hyperphagic action of THC is reversed by the general opioid receptor antagonist, naloxone (73). Importantly, the facilitatory effects of a CB_1 agonist on responding for palatable solutions were reversed by both a CB_1 antagonist and naloxone (30). Moreover, low doses of rimonabant and naloxone that are behaviorally inactive when administered singly, combine synergistically to produce a profound anorectic action when coadministered (74–76). Given the established ability of opioid antagonists to reduce the hedonic evaluation of foods and to reverse CB_1 agonist-stimulated ingestion, the potentiation of anorexia by combined CB_1 and opioid receptor blockade strengthens the proposition that endocannabinoids contribute to orosensory reward processes. There is also evidence for interactions between these neuromodulators within the hypothalamus, and particularly the paraventricular nucleus (PVN). Crucially, the PVN is a focus of converging orexigenic and anorexigenic neuropeptide pathways that integrate metabolic, hormonal, and neural factors in energy homeostasis. Importantly, the PVN is a sensitive site for the hyperphagic actions of cannabinoid receptor agonists. Moreover, in addition to CB_1 receptors, opioid receptors are also expressed within the PVN (77), and feeding induced by injection of morphine into this site can be reversed by rimonabant (68).

Peripheral Mechanisms: Intestinal Factors. In addition to the central nervous system, cannabinoids and CB_1 receptors are also present in intestinal tissues (78, 79). A role for peripheral endocannabinoids in the control of feeding has been indicated by observations that anandamide is synthesized within gut tissues, with intestinal concentrations increasing in 24-hr fasted rats (20). Moreover, the respective hyperphagic or anorectic actions of intraperitoneal anandamide and rimonabant were attenuated by capsaicin-induced deafferentiation of peripheral sensory nerves. These findings suggest that stimulation or blockade of peripheral CB_1 receptors may influence central motivational processes, and have been interpreted as indicating a possible role for peripheral anandamide as a "hunger signal." It is noteworthy that gastric and intestinal vagal afferents that express receptors for the anorexigenic peptide cholecystokinin (CCK) also express CB_1 receptors. Expression of vagal CB_1 receptors is increased by fasting and reduced by refeeding. Additionally, CCK, which is released from the gut by food and believed to act as a satiety signal, also decreases CB_1 receptor expression in vagal afferent neurons. Thus it is possible that appetite may be modulated by interactions between peptide and cannabinoid signals originating in the periphery (80).

Of interest, a natural analog of anandamide, oleoylethanolamide (OEA), which is synthesized within the gut, may also play a role in appetite (20). Although OEA does not activate cannabinoid receptors, Rodriguez de Fonseca and colleagues have proposed that intestinal OEA may play a role in peripheral components of satiation processes (81). Thus, OEA synthesis in the small intestine is stimulated by feeding and inhibited by food deprivation, and OEA reduces food intake in free-feeding and starved animals, primarily by delaying the onset of meals. Additionally, OEA can respectively attenuate the feeding actions of cannabinoids or enhance rimonabant-induced anorexia (81). Further research is necessary to confirm the role of OEA in satiety, and some caution in interpretation of its reported anorectic properties is necessary. For example, selective actions of the compound to reduce feeding motivation need to be definitively separated from marked, nonspecific behavioral effects that occur after peripheral administration. These latter effects are clearly incompatible with normal feeding, and might account for OEA-induced intake suppression (82).

Peripheral Mechanisms: Adipose Tissue. We have already noted the possible relationship between the adipokinin leptin and endocannabinoids. There is evidence for a reciprocal relationship between circulating, fat-derived

leptin and hypothalamic endocannabinoids in the regulation of eating. Importantly, adipocytes express CB_1 receptors in normal, but not in CB_1 receptor-deficient mice (62). Moreover, agonist stimulation of these receptors will dose-dependently stimulate lipogenesis (62). These facts raise the possibility of important cannabinoid influences on adiposity/body weight that are distinct from their direct actions on appetite. Indeed, the CB_1 receptor antagonist rimonabant and analogues have been shown to reduce adiposity in diet-induced obese mice and genetically obese rodents independently of their primary anorectic actions (83, 84). Thus, while chronic CB_1 blockade initially suppresses food intake, this action is seen to gradually wane. In contrast, weight loss persists even after the marked anorectic effects of the antagonists have subsided. Antagonist treatments may therefore cause direct interference with cannabinoid-mediated processes that regulate fat deposition in adipose tissues. Another possibility is that CB_1 antagonists may enhance fatty acid oxidation, because rimonabant was found to lower plasma free fatty acid levels in dietary obese mice (84). Similarly, rimonabant has been reported to correct hyperglycemia, reduce plasma insulin levels, and counter insulin resistance, suggesting that the drug may also improve glucose homeostasis. Additionally, this class of antagonists may act via hypothalamic mechanisms to increase sympathetic nervous system activity that stimulates lipolysis (84).

Therapeutic Effects of Cannabinoids in Relation to Appetite and Body Weight

Appetite Stimulation. THC (dronabinol) has been clinically used for a number of years to combat a reduction in appetite and consequent weight reduction and wasting, as observed in conditions such as acquired immunodeficiency syndrome (AIDS) and cancer (31, 85). Wasting, or cachexia, is a common feature of the later stages of diseases such as AIDS and metastatic cancer, and contributes significantly to their morbidity (86, 87). The clinical application of THC predates the current knowledge of endocannabinoids and their likely behavioral and metabolic functions, so it is probable that our growing understanding of these processes may produce enhanced treatments in the future. Additionally, few controlled clinical studies have been performed (88), so that cannabinoid actions in these conditions remain to be fully explored. In open pilot studies, dronabinol (Δ^9-THC) caused weight gain in the majority of subjects (89). A relatively low dose of dronabinol, 2.5 mg twice daily, enhanced appetite and stabilized body weight in patients with AIDS suffering from anorexia (90) for at least 7 months. In another study of patients with AIDS, no weight gain was reported over the course of 12 weeks of dronabinol administration (2.5 mg twice a day), whereas a dose of 750 mg/day of megestrol acetate (a synthetic progestational drug), effected significant weight gain (91). In that study, a high dose of megestrol (with potential adverse effects including dyspnea and hypertension), and a low dose of dronabinol were used. Higher doses of dronabinol may be more effective, although side effects such as weakness, confusion, memory impairment, and anxiety are a concern. However, recent experience in the treatment of neuropathic pain and multiple sclerosis suggests that cocktails of THC and a nonpsychoactive cannabinoid, cannabidiol, may minimize the impact of these side effects (92).

Optimized cannabinoid treatments may have additional benefits beyond stimulation of appetite. Cachexia involves abnormalities in lipid and glucose metabolism (enhanced lipid mobilization, reduced lipogenesis, and energy-inefficient hepatic gluconeogenesis), which together with an increased resting metabolic rate, result in a negative energy imbalance (93). Most importantly, patients with cachexia fail to respond to these metabolic challenges in the way that starved individuals might: there is no compensatory increase in motivation to eat (94). Given the links between endocannabinoids and these metabolic processes described above, new therapeutic avenues may soon be realized.

Appetite enhancement and reduction of wasting may improve the well-being of patients with other conditions too. Thus we have proposed (5, 95) that patients with cystic fibrosis may profit from treatment with cannabinoid in multiple ways, due to their wide range of therapeutic effects, including anti-inflammatory, bronchodilating, antidiarrheal, antiemetic, appetite-stimulating, and bone-forming (96) properties. Cannabinoids may also be useful in treating the wasting and appetite loss occurring with aging and associated conditions such as Alzheimer disease (97). A variety of factors contribute to anorexia and weight loss in the elderly, including decreased taste and smell acuity. In people with dementia, these factors are compounded by an inability of patients to feed themselves, or even by food refusal.

Anorexia nervosa has also been viewed as a possible target for the application of cannabinoids to overcome self-starvation. So far, only a single, ineffective study with THC has been reported (98), and more carefully designed studies may be more successful. For example, it is possible that the dose used in that study was too high (99), because very low doses of THC (0.001 mg/kg) have been found to exert potent hyperphagic effects in animal models of food restriction (21). However, the psychopathology of anorexia nervosa is very complex: care must be taken in stimulating involuntary eating in individuals for whom control over food intake, rather than loss of appetite, is a principal feature of their disorder. Additionally, patients with anorexia nervosa are often severely medically compromised, so that pharmacological treatments may be contraindicated.

The endocannabinoids anandamide and 2-AG are degraded by the enzyme fatty acid amide hydrolase (FAAH; Ref. 100). An entourage effect of FAAH inhibitors, which indirectly stimulate CB_1 receptor activation by inhibiting the enzymatic breakdown of anandamide or 2-AG, has been proposed (101, 102). Thus, indirect enhancement of

endocannabinoid function, rather than direct CB_1 receptor activation, may be a valid and more selective alternative in the treatment of malnutrition and cachexia, (64).

Nausea and Emesis. Wasting in disease is compounded by the effects of drug or radiation treatments that can significantly affect appetite and alter psychological responses to food and eating (103, 104). Patients may lose enjoyment of, or interest in food, due to changes in taste perception produced by chemotherapy or through the acquisition of conditioned taste aversions following the nausea or vomiting accompanying many radical treatments.

Cannabinoid treatments that stimulate appetite by enhancing the attractiveness and enjoyment of food may be expected to be beneficial in these circumstances. Moreover, the apparent involvement of the ECBR system in the neural mechanisms controlling nausea and emesis supports the specific application of cannabinoids to overcome therapy-induced sickness and food aversion.

Cannabis has long been known to possess antiemetic properties (105, 106), and THC was demonstrated to exert antinausea and antiemetic effects in the 1970s. Both synthetic and endogenous cannabinoid CB_1 receptor agonists have been found to attenuate vomiting in a wide range of emetic species. It has been proposed that endocannabinoids may play an important role in the control of emesis, because CB_1 receptors are widely expressed in the brain stem dorsal vagal complex associated with triggering emetic responses (77, 107, 108). Cannabinoids may also be useful as pretreatments to avoid the establishment of conditioned nausea and anticipatory emesis associated with chemotherapy (109, 110). Patients who experience nausea or vomiting with chemotherapy treatments often experience anticipatory, conditioned retching or nausea that makes it difficult for them to tolerate subsequent medication. In animal models, Δ^9-THC and the potent CB_1 receptor agonist HU210 can prevent conditioned rejection (disgust) responses to flavors associated with illness-inducing drug treatments (111, 112).

A complicating issue is the association of cannabinoid therapy with side effects; most commonly, euphoria, sedation, dizziness, and ataxia. It is likely that these unwanted effects may be attenuated by improved formulations, or modes of administration that allow for self-titration of dose. Of course, euphoric effects of cannabinoids are not necessarily an obstacle to their effective administration. Mood elevation, or even actual antidepressant actions of chronic THC, may be an important component of its effectiveness in patients with cancer or AIDS. Alternatively, it may be possible to use cannabinoids that lack the psychotropic potency of Δ^9-THC. For example, Abrahamov et al. (113) reported that Δ^8-THC abolished vomiting in child patients receiving anticancer drugs. Similarly, a nonpsychotropic, synthetic cannabinoid, HU211, has been found to provide almost complete protection against emesis produced by one of the most emetogenic cytotoxins, cisplatin (114). Additionally, cannabidiol prevents nausea induced by lithium chloride or conditioned nausea elicited by a flavor paired with the toxin in rats (115). As noted above, coadministration of cannabidiol can inhibit some of the unwanted psychotropic actions of Δ^9-THC.

Obesity. An obvious target for intervention in cannabinoid systems is the treatment of overweight and obesity. There is now a large body of evidence from animal studies to indicate the effectiveness of rimonabant and its sister compounds to reduce intake and to effect beneficial changes in the metabolic correlates of obesity (6–8, 69, 70, 85). Moreover, recent clinical trials with rimonabant have indicated that the drug can effectively reduce food intake and adiposity. Mean weight reductions of 9.5 kg have been reported in volunteers maintained on the drug for 1 year; a weight loss that matches or exceeds those obtained with earlier classes of appetite suppressant. The drug also appears to significantly lower plasma free fatty acid levels, correct hyperglycaemia, reduce plasma insulin levels, and counter insulin resistance (116).

Clinical Implications and Conclusions

In conclusion, the preceding overview, although necessarily restricted in detail, clearly indicates the potential importance of endocannabinoid systems to the normal controls of appetite and body weight at many levels. The past few years have seen a remarkable expansion in our knowledge of these systems, and the rate of progress is accelerating at an exciting pace.

An antiobestity drug (rimonabant, under the trade name Acomplia) may be expected in the clinic within the next few years (116), while anorexic and cachexic conditions are being extensively analyzed for their responsiveness to cannabinoids. Further, the apparently major role for the endocannabinoids and their receptors during early development, putatively underlying the enigmatic syndrome nonorganic failure-to-thrive (4), together with the development nonpsychoactive cannabinoid drugs (117), may open doors to treat appetite-related conditions across the lifespan.

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