Therapeutic Use of Cannabinoids in Eating Disorders

Walter Milano1, Uberia Padricelli2 and Anna Capasso3*

1Unità Operativa di Salute Mentale Distretto 24 ASL Napoli 1 Centro, Italy
2Farmacia Ospedale San Paolo ASL Napoli 1 Centro, Italy
3Dipartimento di Farmacia, Università di Salerno, Fisciano, Italy

*Correspondence to:
Anna Capasso, E-mail: annacap@unisa.it

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Introduction

Eating disorders (ED) are complex systemic pathologies, with evidence of a tendency to chronic symptomatology with exacerbations and/or relapses, frequently in graying with significant medical sequela and psychiatric comorbidity [1]. They are characterized by aberrant and pervasive food patterns linked to the body image, the interiorization of an unreachable ideal of beauty with extreme dissatisfaction for one’s own weight and body, low self-esteem, impulsiveness and, often, a structured perfectionism. In many cases, compensatory purging behaviors such as self-induced vomiting, laxative and diuretic abuse, excessive and unhealthy physical activity [2,3] are associated.

These disorders are diseases with a high social impact and affect mainly the younger sections of the population and represent an important public health problem because they are associated with discomfort, disability and increased risk of death [4]. In addition, eating disorders have a high comorbidity with mood, anxiety and substance abuse disorders. They are difficult to diagnose and even more complicated to treat. They are considered one of the most common health problems affecting adolescents and young adults in Western countries [5].

An eating disorder comes into the mind and becomes the biggest concern until it absorbs almost every energy. The flow of life is marked by fixations and phobias related to the weight, diet, or image that is believed to have the body. Everything is decoded according to those parameters, and it grows up and burns in function of the rages and desperations that those themes evoke. They alter; ruin lives, careers, marriages, families, parenting. Existential projects that blend and degrade. Personal stories that are abandoning [6].

Keywords
Endocannabinoids, Eating disorders, Neurobiology
The ED is fairly common diseases, especially in the female population; Men represent 5-10% of all AN cases, 10-15% of BN cases, and 30-40% of BED cases. In the general population aged 18 and older, lifetime prevalence rates of 0.9% for Anorexia Nervosa (AN), 1.5% for Bulimia Nervosa (BN) and 3.5% for the Binge Eating Disorder (BED). In women ages 18 to 24, rates are much higher: 2% for AN, 4.5% for BN and 6.2% for BED. The incidence of AN is estimated to be at least 8 new cases per 100,000 people per year and for BN 12 new cases per 100,000 people per year [7,8].

Both in AN and BN, the age range in which the debut is most common is between the ages of 15 and 19, with tendency to decrease in recent years, while for the BED it is distributed in a wider band with a peak in early adulthood [4,9]. There is, however, a significant difference between intercepted pathology and epidemiologically estimated disease, so many people with ED do not receive treatment; Additionally, those people with ED receive inappropriate care. They are among the most serious and less known psychiatric disorders by non-specialist doctors, with the highest mortality rates among psychiatric disorders; In fact, they have a death risk of 5 to 10 times greater than that found in healthy subjects comparable by age, with a Mortality Risk (MR) of 5.9 for AN and 1.9 for BN against the general population [5,10].

ED is classified as mental illnesses and fall within the area of psychopathology, psychiatry and psychotherapy. However, the physical pathogenesis of ED, or the use of the body as a means of extrinsic psychic suffering, can lead to significant, sometimes devastating, complications for the patient, which increase not only the mortality but also chronicity and disability rate [11,12].

The interactions between the psychopathologic and organic components mean that all mental illnesses are those that have multiple areas of intersection with other areas of medicine and place them in a land border that make it difficult not only nosographic framing but also therapeutic approach [13]. From the onset of the disease and throughout its course, the psychic and somatic processes interact synergistically and continuously with each other and contribute to determining, maintaining and complicating all the characteristic syndromic constellation of the ED. Nutrition and related behaviors have consistently multiple valves that find their sense in the history and shape of the person and his reference group [14].

However all these different clinical pictures, attributable to the DA, have found their own autonomy nosographic only in recent decades since the 70s of last century, with their entry in the DSM (Diagnostic and Statistical Manual of Mental Disorders) III to the present day our the fifth edition of the DSM. The recent DSM 5 [15], in attempting to reduce the many atypical forms falling into the diagnosis of “unhealthy eating disorder”, proposed a new classification for ED and modified some previous diagnostic criteria. There are six major diagnostic categories and two residual categories in adults and adolescents and, moreover, it has made the diagnostic criteria for the three major categories AN, BN and BED less restrictive.

The main nosogory categories are:

- Anorexia nervosa
- Bulimia nervosa
- Binge Eating Disorder
- Pica
- Mericity
- Avoidance/Restrictive Food Disturbance

However, this is not a complete picture; clinical and community studies indicate that it is not uncommon to detect an unrestricted eating disorder within these categories. In fact, there are two residual categories intended to accommodate partial or “subdominuous” syndromes and other forms of problematic relationship with food: 1) Other specified nutrition and nutritional disorders is the substantial absence of
binge eating and Night Eating Syndrome (NES). This ED includes forms for which the complete definitions of AN, BN or BED are not applicable as well as the elimination disorder (purging disorder: Food disorder in which recourse is recurring with elimination pipes, mainly in the form of self-induced vomiting or excessive use of laxatives or diuretics)

2) Nutrition and nutrition disorders not specified, in this category go for nutrition and nutrition that the clinician can not specify due to lack of information.

However, ED tend to persist over the years and symptomatology (weight, frequency/absence of compensatory phenomena, etc.) employed for nosographic classification often tends to change over time with high cross-over rates estimated at around 30% of cases. In fact, a current diagnosis is defined at the time of all the symptoms needed to diagnose a lifetime diagnosis with an assessment of all symptoms and disorders throughout the course of the disease [16].

The ED Etiopathogenesis

The ED etiopathogenesis is complex and multi-determined. The most accredited model is the biopsychosocial model in which more than one factor develops from genetic to family, social and cultural factors [17]. Several studies (on families, twins, DNA) [12,18-23] seem to suggest that about 50% of the risk is due to genetic factors. Environmental risk factors can be multiple and are divided into early and late; Early Risk Factors are all those conditions that interfere with the early stages of neuro-development and maturation of stress response systems and include intrauterine life conditions, perinatal complications and early alterations in relationship with figures of care [24]. Late environmental risk factors can be considered conditions of loss or trauma, abuse and neglect in childhood, psychosocial stress and strongly conflicting relationships between parents and children, psychoactive substance abuse and the exposure to pressures towards the thinness by members of the family group or the relational, affective, ethnic and cultural area in which the subject lives [4]. In fact, they engage in identification processes associated with canons of bodily perfection, the ideals of thinness as a synonym for beauty or towards an objectivation of the female body perceived, lived and shown in its sexual dimension, and thus treated as an object that must respond to an ideal of beauty and aesthetic perfection [16,17].

Being the ED of all mental illnesses involving and devastating more than the body and its biology, over the years, psychic and somatic processes interact with each other continually and contribute to the determination, maintenance and complication of symptoms. With the passing of time it becomes increasingly difficult to distinguish and address the primary factors that have triggered the pathological process from the side effects of malnutrition.

Genetic factors can significantly influence the regulation of neuronal circuits of brain areas used to control appetite and satiety.

Over the last decades it has been found that the appetite and hunger regulation system includes a large number of molecules that work from hormones, neurotransmitters and receptors. These molecules are produced in various organs, in the brain, in the adipose tissue, in the stomach, pancreas, intestines, and so on, and have multiple targets; The gut-brain axis expression refers to the bi-directional communication system that connects the digestive tract and the brain [25,26]. The network of signals that interact according to the state of the energy and energy requirements of the body and the energy reserves of the body is very complex and intricate. The energy-seeking and energy storage system seems to be more organized, articulate, efficient and redundant than the component used to consume any excess [27]. Such organization can best be explained in evolutionary terms, in fact, the push to look for and introduce energy and therefore food has been an essential condition of survival for organisms exposed to environments in which food availability was uncertain and inconsistent and energy expenditure to live was very high [28].
Several agents are involved in orexigenic circuits: They stimulate food research and ingestion, and the accumulation of energy reserves while others engage in anorexic circuits with the effect of reducing food ingestion. They have predominantly anorexic action on leptin, Uncoupling Protein UCP, Peptide YY (PYY), Pancreatic Polypeptide (PP polypeptide), β3-Adrenergic Receptors (β3 adrenergic receptor β3-AR), Proopiomelanocortin (POMC), Cholecystokinin (CCC), Melanocyte Stimulating Hormone (MCH), Melanocortin 4 receptor (MC 4-R), Release Hormone of Corticotropin (CRH), peptide 1 similar Glucagon (GLP 1), etc. However, there is a predominantly orexigenic action on the Neuropeptide Y (NPY), Agouti-related Protein (AGRP), orexine A and B, grelin (ghrelin), opiate peptides (endorphins) and endocannabinoids [27-34].

Regarding the anatomical level, much of the cerebral formations involved in the governance of eating behaviors fall into the limbic system and includes many phylogenetically older structures than the neocortex and has been found quite similar in the various species of mammals. It includes the hippocampus, the amygdaloid complex, and the dorsal complex of the vague, the nucleus accumbens, the orbitofrontal cortex and the hypothalamus occupying a key position in the limbic system. Ultimately, the limbic system more than a well-defined anatomic area can be termed as a physiological and neuropsychological continuum. All of its components, interconnected by neuronal interconnection, are involved in emotional, motivational processes and hence in the organization of behaviors, in particular those related to the conservation of the individual and species, and therefore the reproductive, defensive functions, the access of children, breastfeeding and of course to eating behaviors and are associated with experiences of immediate satisfaction and pleasure. The limbic system and the neurotransmitters involved are therefore also connected to the reward system, especially in the connections involving two major neuronal groups: The ventral tegmental area and the accumbens nucleus, with dopamine as a neurotransmitter. The tegmental, stimulated, free dopamine that invests accumbens, prefrontal cortex, pale ventral, amygdala, septum. In addition to dopamine, endogenous opioids and endogenous cannabinoids also come into play [35-40].

Regarding the food control, at today, the predominantly accepted model indicates that homeostatic nutrition-related signals are linked to the reward system and thus to the experiences, feelings, emotions, memories that relate to the pleasure experience associated with satisfying the nutritional needs and motivating the subject to repeat the actions that give pleasure and satisfaction [39]. Disorder of the reward system, sometimes present in patients with ED, produces abnormal activation and alterations in the release of dopamine, serotonin and endogenous opioids [37,41,42].

Cannabinoids and Eating Disorders

The hypothalamic endocannabinoids has been shown to control food intake in both animals and humans, modulating eating behavior thus indicating that alterations of the endocannabinoid system could be involved in the pathophysiology of eating disorders [43,44].

Hypothalamic areas such as ventromedial, dorsomedial and lateral hypothalamus, arcuate and Paraventricular nuclei are involved in food intake control and feeding behavior [45]. These area are interconnected with the neuronal pathways regulating the so-called ‘reward’ system [46-48].

CB1 receptors are highly expressed in the above areas involved in reward thus indicating that the cannabinoid system is directly involved in feeding behavior [49-54].

Given the strong link between cannabinoids and reward circuitry, the role of endocannabinoids in the processes underlying the motivation to eat is an attractive hypothesis.

The mesolimbic dopaminergic system is one of the most important reward path-
way [46] and a functional link between endocannabinoids and dopaminergic activity has been reported [55-58]. Therefore, a correlation between limbic endocannabinoid/dopamine levels and craving for tasty food is supposed to occur [55-59].

The interaction of the endogenous cannabinoid system with the serotonergic system has been also studied according to the involvement of serotonin in the control of feeding behavior [60]. However, the administration of cannabinoid antagonist in rats combined with dexfenfluramine, a drug stimulating the release of serotonin, let to additive but not synergistic effects on reducing food intake, which is consistent with the hypothesis that the two pathways are working via independent mechanisms of action [61].

Also, the endogenous opioid peptides are linked to central reward processes and there is increasing evidence supporting an important functional crosstalk between the opioid and the endocannabinoid system [62-69].

Finally, CB1 are present in the enteric nervous system. This area of CB1 expression might suggest the existence of a putative crosstalk between central and peripheral sites in the context of the roles of the cannabinoid system [70]. Therefore the endocannabinoids are also involved in the peripheral regulation of feeding.

Animal models have represented an ideal tool to get further insights into the mechanism(s) involved in the cannabinoid-mediated stimulation of food intake. However, the magnitude of the effect of exogenous cannabinoids on food intake strictly depends on the dose used and do not increases linearly with the dose considering that low doses of cannabinoids appear to increase food intake whereas high doses seem to decrease it [71-77]. Furthermore, the route of administration of cannabinoid compounds represents another source of confusion [78-80].

Several investigations indicate that defects in endocannabinoid signaling may underlie eating disorders [81-83]. The endocannabinoid system and leptin interact functionally at the molecular level [84]; therefore, the role played by both systems in the eating disorder as well as their therapeutic potential role was also studied [85].

Oleoylthanolamide, has been reported to promote satiety and lipolysis through the activation of the PPARα [86]. This molecule has an anorexigenic action by inducing oxytocin expression in the paraventricular nucleus of the hypothalamus and, interestingly, preliminary clinical results have shown altered levels of oleoylthanolamide in the cerebrospinal fluid and plasma of subjects recovered from eating disorders [87]. These preliminary observations could extend the findings of altered levels of eCBs in eating disorders to a more general involvement of acylethanolamides.

However, a genetic component in the eating disorder was also considered by performing studies to identify genes belonging to the endocannabinoid system genes involved in this pathology. In this respect, have been studied CNR1 and CNR2 (the genes encoding cannabinoid CB1Rs and CB2Rs, respectively), as well as the genes encoding the main enzyme responsible in the degradation of AEA (FAAH), NAAA (N-Acylethanolamine-hydrolyzing acid amidase [88-93].

The first family based study involved 52 families (parents with one or two affected siblings) that were genotyped for the (AAT) trinucleotide repeat of CNR1 gene. The distribution of alleles transmitted to the patients was not found to be significantly different from the non-transmitted parental alleles. However, upon dividing the samples to restricting and binging/purging subtypes of AN, the data analysis revealed a preferential transmission of different alleles in each of the subtypes, suggesting restricting AN and binging/purging AN may be associated with different alleles of the CNR1 gene [88]. However, a subsequent study involving up to 91 German AN trios (patient with AN and both biological parents) was unable to confirm these results, nor did it show an association for any of 15 single nucleotide polymorphisms representative of regions with restricted haplotype diversity in FAAH, NAAA, and MAGL genes [89].
Another study in 115 overweight/obese subjects with binge-eating disorder, 74 non-binge-eating disorder patients with obesity and 110 normal weight healthy controls investigated one of these FAAH polymorphisms, previously implicated in obesity in binge-eating disorder, and reporting a lack of association [90] and in a more recent article these authors studied the association of this FAAH polymorphism and the CNR1 polymorphism in both AN and BN, in 134 patients with AN, 180 patients with BN and 148 normal weight healthy controls [91]. The authors found a significant increase in the frequency of both polymorphisms in AN and BN patients, a result in sharp contrast with the previous findings by Muller, et al. [89] that showed a lack of association of these polymorphisms with AN. Additionally, Monteleone, et al. [91] found a synergistic effect of the two polymorphisms in AN but not in BN.

Finally, a recent article has detected an association of a CNR2 polymorphism with both AN and BN [92] in a study comprising in 204 subjects with eating disorders and 1876 healthy volunteers in Japanese population. Taken together, the human genetic association studies show evidence of association between eCB system genes and eating disorders, but further studies are necessary to definitively confirm these findings.

Therapeutic Use of Cannabinoid Drugs in Eating Disorders

Cannabis preparations have been used for both medicinal and recreational purposes for centuries. Its ancient medicinal use has been primarily related to ameliorate pain and increase appetite in disease states. However, because of their psychostimulant properties and the lack of an adequate body of knowledge, their use in western medicine has been excluded until recently. During the last 20 years this picture has dramatically changed. There has been an exponential increase in the knowledge of the molecular mechanisms underlying cannabinoid effects, and morphological, physiological and pathophysiological studies have shown that the molecular system supporting these effects (i.e., the eCB system), is ubiquitous and has a highly relevant role in maintaining whole body homeostasis and, especially, energy homeostasis [93]. This fact has led to an increased interest in the medical use of cannabinoid-related drugs. Thus, in 1985 the Food and Drug Administration approved Marinol® (dronabinol), a synthetically derived THC preparation, to relieve nausea, and vomiting associated with chemotherapy in cancer patients who have failed to respond adequately to other antiemetics, and in 1992 this compound was also approved for inducing appetite in AIDS patients suffering from cachexia [94,95]. Similarly, Nabilone® (a synthetic cannabinoid that mimics THC) was also approved in 1985 for ameliorating the nausea of cancer chemotherapy. A more controversial step forward was the use of a cannabinoid CB1R antagonist/inverse agonist (rimonabant) for management of complicated obesity. Although the Food and Drug Administration never approved this drug, the European Medicine Agency did and Acomplia® (the commercial name of rimonabant) was in the market for approximately 2 years. Despite the weight loss and improved cardiometabolic profile observed in obese patients, the drug had to be removed from the market due to its undesirable central side effects [96]. More recently, Sativex® (the combination of THC and CBD) has been marketed in Canada and European countries like the United Kingdom and Spain for the treatment of spasticity due to multiple sclerosis, and it is currently in phase III clinical development for the treatment of cancer pain.

Taken into account the good therapeutic management of cannabinoids in cachexia and malnutrition associated with cancer and AIDS, it looks feasible that this kind of pharmacotherapy could be also useful in the treatment of eating disorders. Unfortunately, there are only two small trials assessing cannabinoid treatment in AN [85]. The former involved 11 AN patients in a 4-week crossover trial and THC treatment resulted in increased sleep disturbances and interpersonal sensitivity, whereas there was no significant effect on weight gain [97]. Unfortunately, this study raised several concerns given it was an in-patient study and the occasional tube feeding was used. In addition, THC was compared to diazepam instead of placebo, which could be a
confounding factor given diazepam has also been reported to increase food intake per se [98]. The latter involved nine AN out-patients treated with THC. The results showed a significant improvement of depression and perfectionism scores without improving weight gain [99].

Currently, there is an ongoing phase III clinical trial involving 22 subjects to reveal if severe chronic AN patients treated with Marinol® have significant improvement on weight, with secondary objectives of the study being evaluation of eating disorder inventory scale, motor and inner restlessness and endocrine parameters (EudraCT Number: 2007-005631-29). With this very limited number of performed trials (the last one being still not finished) it seems clear that no conclusions can be drawn out regarding the therapeutic validity of a cannabinoid-based approach in eating disorders. However, the satisfactory clinical use of cannabinoid agonists in other pathologies demands and encourages the development of further clinical trials on eating disorders patients. Interestingly, a very recent preclinical study in rodent have shown that the main active constituent of cannabis, THC, is able of reducing the weight loss associated with the development of AN via a mechanism involving reduced energy expenditure [100], thus providing encouraging preclinical data on the validity of a eCB-based therapy in AN.

Novel Therapeutic Applications of Cannabinoids in Eating Disorders

Novel compounds as antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the CB1 receptor. The compounds of the present study are useful as centrally acting drugs in the treatment of obesity or eating disorders [101]. The present study is also concerned with treatment of these conditions, and the use of compounds of the present invention for manufacture of a medicament useful in treating these conditions. The present study is also concerned with treatment of these conditions through a combination of compounds of formula I and other currently available pharmaceuticals. This study is also concerned with pharmaceutical formulations comprising one of the compounds as an active ingredient. The invention is further concerned with processes for preparing the compounds of this invention. While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable [101].

Another study relates to novel heterocyclic derivatives which are allosteric modulators of cannabinoid receptor 1 (CB1) and which are useful for the treatment or prevention of neurological and psychiatric disorders associated with endocannabinoid dysfunction and diseases in which the CB1 subtype of cannabinoid receptor is involved; to processes for their preparation; to pharmaceutical compositions comprising them; and to methods of using them [102]. The present study is directed to compositions and methods that can be used for the treatment of these disorders while minimizing or eliminating abuse potential and providing higher specificity with reduced side effects [102]. This study relates to heterocyclic derivatives which are
allosteric modulators of Cannabinoid Receptor 1 (CB1) and which are useful for the treatment or prevention of eating disorders associated with endocannabinoid dysfunction and diseases in which the CB1 subtype of cannabinoid receptor is involved [102]. This study is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of eating disorders [102]. The authors also relate to a method for the prevention and/or treatment of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of compound according to the invention to a patient in need thereof. The new CB1 allosteric modulators can be used alone, in combination or in combination with other pharmaceutical agents such as other agents used in the treatment of the conditions described herein. In such combinations, the new compounds may be utilized in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which the compounds disclosed herein may have utility, where the combination of the drugs together are safer or more effective than either drug alone [102].

Another study relates to new compounds which are modulators of cannabinoid receptor CB1 and which suppress the normal signalling activity of such receptors. The study further relates to compositions and methods using said compounds for the treatment of diseases or conditions which are mediated by CB1 receptor signalling activity, such as eating disorders as well as the use of the compounds in combination with other treatments for such disorders [103]. The study makes available a class of pyrazole compounds which modulate the activity of the cannabinoid receptor CB1. They are useful for modulating body weight and energy consumption in mammals [103] and for displaying varying physicochemical properties due to modulation peripheral CB1 receptors and to varying degree central CB1 receptors. Those new compounds associated with a lowered central action on CB1 receptors may have a reduced propensity to induce eating disorders and nervous system side-effects [103].

γ-Hydroxybutyric acid and its physiologically equivalent forms are also useful in the treatment of eating disorders [104]. The present study relates to pharmaceutical compositions having therapeutic effects on eating disorders (in particular bulimia, obesity and anorexia), such compositions being characterised in that they contain, as the active principle, γ-hydroxybutyric acid (GHB), or salts thereof with pharmaceutically acceptable cations, or the corresponding lactone [104]. The use of γ-hydroxybutyric acid or of its physiologically equivalent forms for the preparation of a medicament which is useful in the treatment of eating disorders [104]. The relevant salts of GHB include, for example, alkali metal (e.g. sodium or potassium) salts, alkaline earth metal (e.g. calcium or magnesium) salts, ammonium salts, salts of pharmaceutically acceptable bases (ethanolamine, diethanolamine, piperidine, piperazine and the like), salts of basic amino acids (lysine, ornithine, citrulline) etc. GHB, various salts thereof and its lactone have been known for decades. The acid is a normal constituent of the central nervous system (CNS) of mammals, with the highest concentration in the hypothalamus and in the basal ganglia ([\% 1.78 nM/g and 4.1 nM/g in rats and in guinea pigs, respectively] [104]. The almost universal prevalence of binding sites for GHB in the CNS makes it probable that such a compound acts as a neurotransmitter and as neuromodulator, rather than as incidental metabolite of γ-aminobutyric acid (GABA) [104]. It has been found that γ-hydroxybutyric acid and physiologically equivalent forms can advantageously be utilised for the treatment of eating disorders [104]. The withdrawal syndromes, dependences on drugs, drugs of abuse, psychotropics, stupefacent and/or psychoactive substances and nutritional disorders have as their common denominator the manifestation of so-called “craving” which can be defined as an intense and compulsive desire for a given substance or a given food. γ-Hydroxybutyric acid has proved to be particularly active in inhibiting the onset of such-symptoms, as it has been possible to demonstrate on the basis of clinical experiments on 23 subjects meeting the diagnostic criteria of opiate dependence and on 3 patients affected by nutritional disorders (one case of anorexia, one of bulimia and one of obesity) [104].
Conclusions

The present paper indicated that the endocannabinoid system plays an important role in the control of eating behavior by acting via central (brain) and peripheral (gut, liver, muscle and fat) mechanisms. The CB1 receptor is believed to be responsible for most of the central and peripheral effects of cannabinoids on the eating behavior. While some studies have clearly demonstrated that dysregulation of cannabinoid physiology can have detrimental effects on eating behavior, conversely, optimizing endocannabinoid tone appears to have beneficial effects on eating behavior regulation. Additional research is now needed to establish whether the observed changes are caused by the disease or whether these are neurochemical alterations that serve as risk factors for developing an eating disorder. Furthermore, these data indicate that the endocannabinoid system may be a potential new target for developing drugs to treat eating disorders.

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