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SYSTEMATIC REVIEW OF OBESITY CONTROL WITH CANNABIDIOL USE: MAJOR CURRENT ASPECTS

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ABSTRACT

Introduction: There are 2.0 billion overweight and obese people in the world, and Brazil is in fifth place in the world ranking. In this context, a factor associated with an eating disorder is anxiety. In this sense, cannabidiol (CBD) showed anxiolytic, antipsychotic, neuroprotective symptoms, anti-inflammatory, and antiemetic properties. **Objective:**Wasto analyze through a systematic review the main considerations and results in animal and human models of cannabidiol use in obesity control. **Methods:** The model followed for the systematic review was PRISMA. The search strategy was performed in the PubMed, Embase, Ovid and Cochrane Library, Web Of Science, Science Direct Journals and Scopus. **Main findings:** In the context of increase in the incidence of obese people, activation of CB1 receptors improves diet by modulating the activity of hypothalamic neurons and, subsequently, the release of orexigenic and anorectic neuropeptides. Thus, in obesity, the endocannabinoid system (ECS) is usually down-regulated in central and peripheral tissues, as indicated by high and/or overexpression of the CB1 receptor. Therefore, CBD has been shown to be beneficial for anxiety-related disorders. Thus, CBD has been shown to have anxiolytic, antipsychotic and neuroprotective properties. **Final Considerations:** Increasing evidence indicates that CBD acts as antipsychotic and anxiolytic, and several reports suggest neuroprotective effects. In addition, CBD attenuates the detrimental effects of trans-Δ9-tetrahydrocannabinol, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects.

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INTRODUCTION

Obesity represents a multifactorial disease that causes serious public health problems (WHO, 2019). There are 2.0 billion overweight and obese people in the world (WHO, 2019), and Brazil is in fifth place in the world ranking. The prevalence of disordered eating behaviors increases during adolescence and young adulthood, and estimates of involvement in at least one pathological eating behavior reach 60% for adolescents and adults (IBGE, 2019). In this context, a factor associated with an eating disorder is anxiety, which affects 33.7% of the general population, the high level of negative affect and, in particular, the difficulty in managing anxiety (Becker, 2017). Thus, anxiety disorders usually precede the onset of the eating disorder and clinically significant anxiety persists after treatment of the eating disorder.

In addition, higher anxiety levels are associated with higher body mass index (BMI), longer symptom duration and increased rates of compensatory behaviors, binge eating and body dissatisfaction (Santos-Veloso, 1992 and Guerdjikova, 2019). In this sense, cannabidiol (CBD) was identified 50 years ago and its effects can change mood, sensation, perception, tension, appetite, and pain (Mandolini, 2018). Also, CBD showed anxiolytic, antipsychotic, neuroprotective symptoms, anti-inflammatory and antiemetic properties (Crippa, 2009 and Premoli, 2019). However, growing interest in the substance as a medicine was renewed in the 1990s, with the discovery of cannabinoid receptors 1 and 2 (CB1 and CB2, respectively), endogenous ligands (endocannabinoids, N-arachidonoyl ethanolamine (anandamide/SAA) and 2 - arquidonoyl glycerol (2-AG)) and enzymes as part of the endocannabinoid system (ECS) in the brain (Elms, 2019).

Correct interaction between all these ESS elements plays an important role in central nervous system (CNS) development, synaptic plasticity, motor control, memory, cognition, stress, emotional responses, reward and motivated behavior, appetite, pain, development, and homeostasis (Gruden, 2015). Outside the brain, the ECS system is one of the crucial modulating factors of the autonomic nervous system, the endocrine immune system, the gastrointestinal tract, the reproductive and microcirculatory system (Gruden, 2016). Endocannabinoids are one of the most important excitatory and inhibitory neurotransmission control systems, as well as neuroplasticity (Gruden, 2015). They serve as retrograde signaling messengers in GABAnergic and glutamatergic synapses, as well as modulators of postsynaptic transmission, interacting with other neurotransmitters, including dopamine. Endocannabinoids also participate in the hypothalamus-pituitary-adrenal axis (HPA) modulation and stress regulation. The synthesis of cannabinoid receptor agonists and antagonists, anandamide uptake blockers and anandamide endocannabinoid degradation inhibitors have opened new treatment strategies (Kaur, 2016). Despite some setbacks in ECS drug-related clinical trials, much research is still underway to explore and establish therapeutic targets for cannabinoid receptor agonists and antagonists. One challenge is to develop drugs that target only cannabinoid receptors in a specific tissue and another to invent drugs that selectively act on cannabinoid receptors located outside the blood-brain barrier. In addition, the development of suitable dosage forms with maximum efficacy and minimal adverse effects is also required.

To successfully exploit the therapeutic potential of ESA, it is imperative to further characterize the endocannabinoid system in terms of identifying the exact cellular location of cannabinoid receptors and their role as a "protective" and "disease-inducing" substance, time-dependent changes in expression. of cannabinoid receptors (Kaur, 2016). In this sense, CBD can relieve hyperphagia without the side effects of rimonabant (eg, depression and reduced insulin sensitivity). Thus, CBD is similar to peroxisome proliferator-activated gamma receptor agonists, helping to reduce adipocyte differentiation. In addition, CBD has an immunomodulatory effect that helps slow the progression of atherosclerosis induced by high glucose levels. It can also be effective in combating ischemic disease, the most harmful complications of metabolic syndrome. However, it can only be given as adjuvant therapy because of its low binding potency, and its inhibitory effect on cytochrome P450 enzymes should also be considered. However, it can be beneficially used in adjunctive therapy due to its few side effects (Kleiner, 2012). Therefore, the present study aimed to analyze through a systematic review of the main considerations and results of the use of cannabidiol in the control of obesity.

MATERIALS AND METHODS

Study Design: Following literary search criteria using the MeSH terms, a total of 45 studies were collated and submitted to eligibility analysis, and after that 21 studies were selected divided into clinical studies, systematic review and meta-analysis, preclinical and simple review following the rules of systematic review – PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http: //www.prisma-statement.org/).

Search Strategy and Information Sources: The search strategy was performed on PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) databases followed the following steps: - search by MeSH Terms: Cannabidiol. Obesity. Obesity control. Clinical studies, and use of booleans “and” between MeSH Terms and “or” among historical findings.

Development: In the context of obesity, CB1 receptor activation improves diet by modulating the activity of hypothalamic neurons and, subsequently, the release of orexigenic and anorectic neuropeptides (Hales, 2017). In addition, CB1 receptor signaling affects reward and reinforcement circuits in the mesolimbic system, leading to a preference for highly palatable foods (Hahn, 2018). Furthermore, the CB1 receptor is also present in peripheral organs important in the control of metabolism and activates anabolic pathways, favoring energy storage (Hoch, 2019). In white adipocytes, CB1 receptor activation increases fatty acid synthesis, improves triglyceride accumulation and reduces lipolysis, while in brown adipose tissue, CB1 receptor neutralizes respiration decoupling of ATP production. In addition, the CB1 receptor increases hepatic lipogenesis and leads to defective oxidative metabolism through impaired mitochondrial oxidative phosphorylation in skeletal muscle (Hoch, 2019). Thus, in obesity, the ECS is generally down-regulated in central and peripheral tissues, as indicated by CB1 receptor overexpression and/or overexpression (Gruden, 2015). The exact underlying mechanisms are unclear, however, ECS are lipid mediators and their biosynthesis maybe directly influenced by dietary fat intake, contributing to higher fat accumulation, increasing food intake and favoring lipogenesis and reducing energy expenditure. in peripheral organs. Thus, both pharmacological and CB1 receptor genetic blockade reduces body weight in animal models of obesity (Hoch, 2019).

In this sense, weight loss occurs predominantly by blocking CB1 receptors. However, recent data suggest that the ECS also controls peripheral energy metabolism. Because visceral adiposity is a major determinant of insulin resistance, it is not surprising that ECS hyperactivity favors the development of obesity-associated metabolites (Gruden, 2015). Emerging data suggest that a deregulated ECS also has direct deleterious effects on insulin sensitivity and glucose metabolism regardless of weight gain. In adipose tissue, activation of ECS increases glucose uptake to increase energy storage in the form of newly synthesized lipids, downregulates adiponectin, affecting insulin sensitivity in distant organs and may favor local inflammation. In skeletal muscle, the CB1 receptor interferes with glucose uptake by inhibiting insulin-activated signaling pathways, including those necessary for translocation of glucose by plasma membrane transporters (Kaur, 2016). In the liver, activation of CB1 liver receptors may reduce systemic insulin sensitivity regardless of body weight. In fact, mice expressing exclusively hepatocyte CB1 receptors remain thin when fed a high-fat diet, but they develop resistance to hepatic and systemic insulin, whereas mice with hepatocyte-specific CB1 receptor deletion become obese but remain obese. sensitive to insulin (Kaur, 2016). Thus, several mechanisms may underlie these findings, such as CB1 receptor activation may reduce insulin clearance, reducing hepatic expression of the insulin-degrading enzyme, resulting in increased hepatic glucose production mainly due to increased

glycogenolysis (Kaur, 2016). In addition, CB1 receptor activation induces stress in the endoplasmic reticulum, resulting in elevated hepatic long-chain ceramide levels, which in turn inhibit insulin signaling. These data provide strong evidence that an ESA disturbed by conditions that lead to obesity, such as a high-fat diet, may contribute to increased fat accumulation and insulin resistance due to CB1 receptor overactivity and thus be a trigger. for the development of type 2 diabetes mellitus (T2DM) (Gruden, 2015). Regarding the role of CB2 receptors in controlling metabolic processes, recent studies suggest that CB2 receptors may affect inflammatory aspects of obesity and T2DM (Teitelbaum, 2019 and Van Dis, 2019). In addition, overexpression of the CB2 receptor in the brain induces hyperglycemia and a decreased phenotype in adult mice. However, these studies need further confirmation with improved CB2 selective ligands, particularly due to the potent anti-inflammatory role of CB2 agonists reported in numerous pathological disease models (Gruden, 2016). In addition, G 3, 6 and 12 protein-coupled receptors (GPR3, GPR6, and GPR12) comprise a family of closely related orphan receptors with no confirmed endogenous ligands. These receptors are constitutively active and capable of signaling through protein G-mediated mechanisms or not. It has been previously reported that these orphan receptors play important roles in many normal physiological functions and are involved in a variety of pathological conditions. Although orphaned, GPR3, GPR6, and GPR12 are phylogenetically more closely related to cannabinoid receptors. Using β-arrestin2 recruitment assays and cAMP accumulation, it has recently been found that CBD is an inverse agonist of GPR3, GPR6, and GPR12. This finding highlights these orphan receptors as potential new molecular targets for CBD, providing new mechanisms of action, and suggests new therapeutic uses of CBD for diseases such as Alzheimer's disease, Parkinson's disease, cancer, and infertility. Furthermore, the identification of CBD as a new inverse agonist for GPR3, GPR6, and GPR12 provides the initial chemical supports on which potent and effective agents acting on these receptors can be developed (Laun, 2018). Despite these findings, a recent study in 2019 conducted a systematic review of randomized controlled trials to analyze the efficacy and safety of CBD-based drugs in patients with mental disorders. Five databases were systematically searched (2006 to August 2018); A total of 1629 participants were included in all studies analyzed. A narrative synthesis method was applied. Study quality was assessed using the bias risk tool and the SIGN checklists. CBD-based medications have been associated with improvements in various symptoms of mental disorders, but not remission. Side effects occurred, but serious adverse effects were mentioned only in single cases. To provide reliable treatment recommendations, more and more are needed with follow-up assessments, consistent outcome measures, and active comparisons (Hoch, 2019).

In parallel, a recent increase in scientific publications has found clinical and preclinical evidence documenting the value of CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points to a calming effect of CBD on the central nervous system. Interest in CBD as a treatment for a wide variety of disorders has exploded, although there are few clinical studies of CBD in the psychiatric literature. Thus, one study looked at a large series of retrospective cases in a psychiatric clinic involving the clinical application of CBD for anxiety and sleep complaints as a complement to usual treatment. A retrospective review of medical records included monthly documentation of anxiety and sleep quality in 103 adult patients. Sleep and anxiety scores using validated instruments at baseline and after CBD treatment. The final sample consisted of 72 adults who had primary concerns of anxiety (n = 47) or lack of sleep (n = 25). Anxiety scores decreased in the first month in 57 patients (79.2%) and remained decreased for the duration of the study. Sleep scores improved in the first month in 48 patients (66.7%) but fluctuated over time. In this review of medical records, CBD was well tolerated in all patients. Therefore, CBD has been shown to be beneficial for anxiety-related disorders (Shannon, 2019). Another review study described major advances in the development of experimental and clinical use of CBD in neuropsychiatry. As a result, CBD has been shown to have anxiolytic, antipsychotic and neuroprotective properties. In addition, basic and clinical investigations into the effects of CBD have been conducted in the context of many other health conditions, including its potential use in epilepsy, substance abuse, and dependence, schizophrenia, social phobia, posttraumatic stress disorder, depression, bipolarity, sleep disorders and Parkinson's. Therefore, CBD is a useful and promising molecule that can help patients with various clinical conditions. Controlled clinical trials with different neuropsychiatric populations currently under investigation should bring important answers in the near future and support the translation of research findings into clinical contexts (Crippa, 2018). Despite these previous results, immersion in a controlled 3D virtual reality scenario was used to test anxiety in a sample of pre-selected non-clinical volunteers (n = 32) for high paranoid traits. Participants were randomized to receive oral cannabidiol (600 mg) or placebo 130 min before entering virtual reality. Well validated rating scales were used to assess persecutory thinking and anxiety. Salivary cortisol concentration, heart rate, and blood pressure were measured throughout the experimental session. As a result, immersion in the virtual reality session caused anxiety, indexed by Beck's anxiety inventory ($p < 0.005$), and increased cortisol concentration ($p = 0.05$), heart rate ($p < 0.05$) and systolic blood pressure ($p < 0.05$). However, CBD had no impact on any of these effects. Therefore, in contrast to previous studies, there was no evidence of any benefits of CBD on anxiety or persecutory ideation in healthy volunteers with high characteristic paranoia. However, a larger sample will be required for a definitive study (Hundal, 2018). However, increasing evidence indicates that CBD acts as antipsychotic and anxiolytic, and several reports suggest neuroprotective effects. In addition, CBD attenuates the detrimental effects of THC, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects. This suggests that CBD may improve the disease trajectory of individuals with early psychosis and misuse of comorbid cannabis in particular (Hahn, 2018). Thus, studies show that CBD reduces 5-HT1A anxiety and cannabinoid receptor activation. In this sense, a literature review study demonstrated the anxiolytic effects of CBD before focusing on studies that investigate its effects on various fear and memory drug processes. Understanding how CBD regulates emotion and emotional memory processing can lead to its use as a treatment for anxiety disorders and substance abuse (Lee, 2017).

Conclusion

Increasing evidence indicates that cannabidiol acts as antipsychotic, anxiolytic and neuroprotective. There are

studies that show weight reduction in people with anxiety and binge eating because of the CB1 receptor blockade. Alternative strategies to counter ECS overactivity would be to develop drugs that reduce endocannabinoid levels by modulating biosynthesis and/or degradation or to develop dietary interventions that reduce the abundance of endocannabinoid precursors.

Declaration of Conflicts of Interest: The authors declare nothing.

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