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Relationship of the Endocannabinoid System with Hormonal Functions

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Abstract: Endogenous cannabinoids and the concomitant activation of their CB1 receptors cause a plethora of effects, including inhibition of prolactin and growth hormone secretion and increased ACTH44 secretion; anxiolytic effects, through actions on the hypothalamic-pituitary-adrenal axis; inhibition of testosterone secretion, anovulation, and uterine relaxation due to their effects on the release of hypothalamic peptides and hormones and their regulation by steroids. The manuscript aims to verify the relationship of the Endocannabinoid System with hormonal functions. This work is a literature review, based on scientific articles. The inclusion criteria for the articles that were part of this review were: articles published in the last 20 years and published in Portuguese and English on the subject, carefully selected in databases such as Scielo, PubMed (https://pubmed.ncbi.nlm .nih.gov/), Google Scholar (https://scholar.google.com.ec/schhp?hl=pt-br), Capes Portal (https://www.periodicos.capes.gov.br/), Latin American and Caribbean Literature in Health Sciences (http://www.bireme.br/), Scielo (http//www.scielo.org), (https://hal.archives-ouvertes.fr/ submit/index), SSRN (https://hq.ssrn.com/login/pubsigninjoin.cfm) and ResearchGate (https://www.researchgate.net) using the following keywords: Endocannabinoid system, *Cannabis sativa* L. (Cannabaceae), medicinal *Cannabis*, THC, phytocannabinoids, pharmacology of the endocannabinoid system, endogenous cannabinoid, cannabidiol, CB1, CB2 and hormones.

Keywords: Cannabinoids, Endocrine Glands, Hormones, Peptides, Receptors.

Research Paper

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1. INTRODUCTION

1.1. Hormones

Hormones are substances secreted by endocrine glands that act in specific locations. It is worth noting that some hormones, however, can reach their destination by passive diffusion. Hormones are released into the bloodstream and act as chemical signaling. Some hormones act very close to the site where they were produced; others, however, travel long distances to reach the organ in which they will exert their effect (Ferreira, 2023; Bunde, 2024; Santos, 2024; UOL, 2024).

The organs or tissues where the hormones act is called target tissues or target organs. These locations have receptors that recognize specific hormones, responding only to these substances. This characteristic is extremely important to prevent a hormone from affecting the action of another organ or tissue. The main regulator of the secretion of different hormones in the human body is the feedback mechanism, which can be positive or negative, with the latter being responsible for the secretion of most hormones (Figure 1) (Junqueira and Carneiro, 2005; Ferreira, 2023; Bunde, 2024; Santos, 2024; UOL, 2024).

The activities of the endocrine system are controlled by mechanisms called feedback. Feedback can be negative or positive. Negative feedback is the most common in the body and aims to limit excesses in the body. This means that if a hormone is in excess, its production will be interrupted; otherwise, its synthesis will be stimulated. This causes the hormones to remain at adequate levels. Positive feedback, on the other hand, is much less frequent and is characterized by having an initial stimulus that causes more stimulation of the same type. This means that the stimulus will cause more production of a given hormone (Figure 2) (Junqueira and Carneiro, 2005; Ferreira, 2023; Bunde, 2024; Santos, 2024; UOL, 2024).

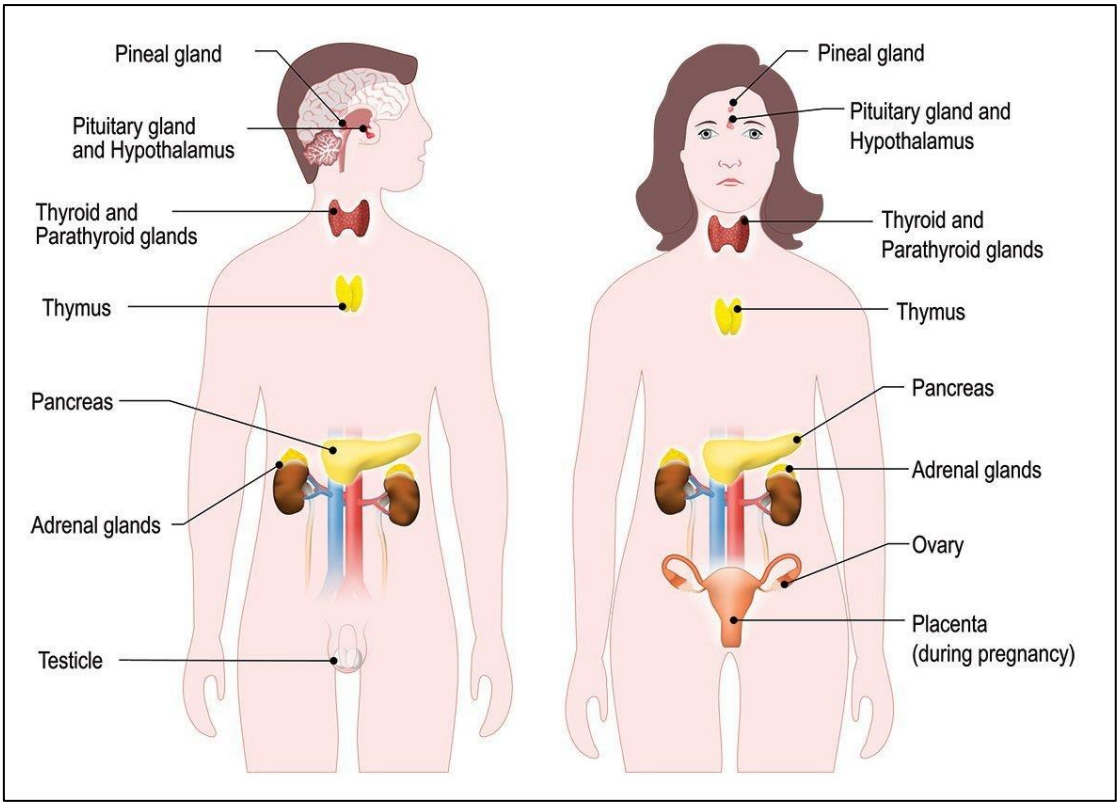

Figure 1: The Endocrine (or Hormonal) System - Hormones Australia. Endocrine glands are those parts of the body that make and release hormones in response to different situations and signals, that can come from both inside and outside the body

Source: https://www.hormones-australia.org.au/the-endocrine-system/

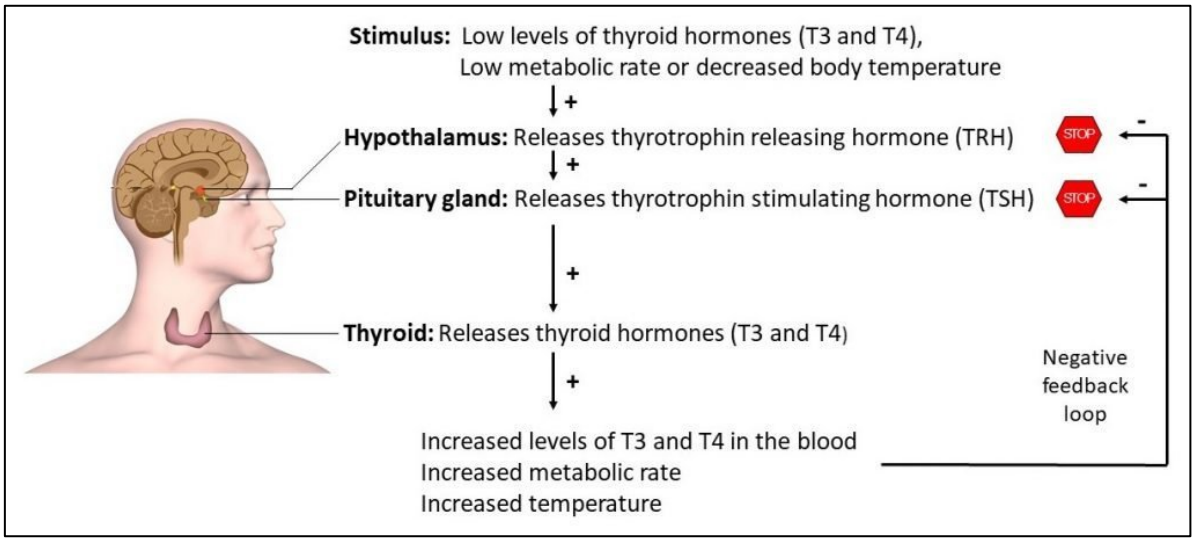

Figure 2: The activities of the endocrine system are controlled by mechanisms called feedback

Source: Source: https://www.hormones-australia.org.au/the-endocrine-system/

1.2. Endocannabinoid System

The physiology of the Endocannabinoid System consists of neuromodulation of the s through the binding of neurotransmitters to their respective receptors in the postsynaptic neuron, which stimulates cellular depolarization and consequently the increase in intracellular calcium. Given these conditions, this neuron is stimulated to produce endocannabinoids through enzymatic action, which will later be released into the synaptic cleft as retrograde messengers, that is, binding to the receptors in the presynaptic neuron (Figure 3) (Papagianni and Stevenson, 2019; Medeiros *et al.*, 2020; Baião *et al.*, 2021; Lu and Mackie, 2021; Dantas, 2022; Briques *et al.*, 2023; WeCann Team, 2024).

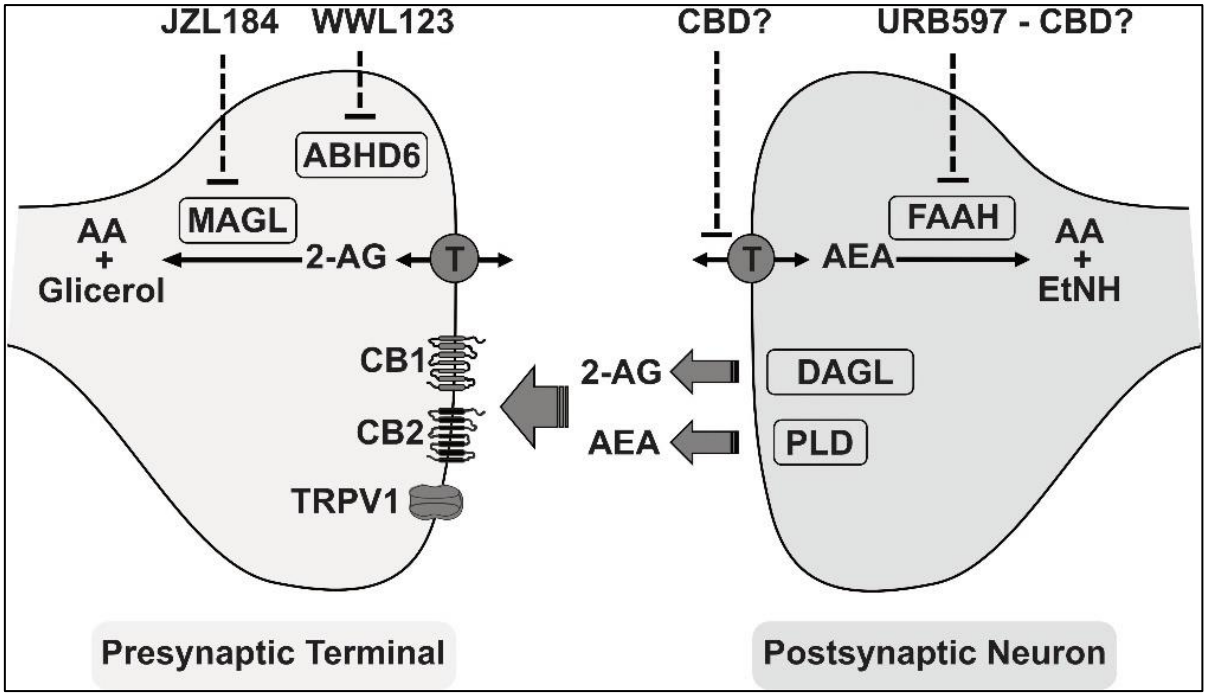

Figure 3: A simplified view of the endocannabinoid system and its main components. Endocannabinoids: Arachidonoylethanolamide (AEA, anandamide) and 2-arachidonoylglicerol (2-AG). Synthesizing enzymes: Diacylglycerol lipase (DAGL) and phospholipase-D (PLD). Membrane transporter (T). Cannabidiol (CBD) is an inhibitor of anandamide reuptake and hydrolysis. Hydrolyzing enzymes: Monoacylglycerol lipase (MAGL), alpha/beta-hydrolase domain containing 6 (ABHD6), and fatty acid amide hydrolase (FAAH). Enzymes inhibitors: JZL184 irreversible inhibitor for MAGL, URB597 selective inhibitor of FAAH, WWL123 inhibitor of ABHD6. Receptors: cannabinoid type-1 (CB1), cannabinoid type-2 (CB2), and transient receptor potential vanilloid-1 (TRPV1). AEA metabolites: arachidonic acid (AA) and ethanolamide (EtNH). 2-AG metabolites: arachidonic acid (AA) and glicerol

Source: Doi: 10.3389/fnbeh.2020.603245

The Endocannabinoid System is a set of receptors, ligands, and enzymes that act as signals between cells, contributing to the most diverse functions of the body. Endocannabinoid receptors and endocannabinoid substances are distributed throughout all organs and systems of the body, performing different tasks, always to maintain and restore the stability of our physiological functions, that is, establishing homeostasis in our organism. The balance of body systems is essential for health. Any imbalance in physiological functions can be decisive for the development of diseases (Godoy-Matos *et al.,* 2006; Viviane *et al.,* 2010; Papagianni and Stevenson, 2019; Baião *et al.,* 2021; Lu and Mackie, 2021; Dantas, 2022; Briques *et al.,* 2023; WeCann Team, 2024).

The Endocannabinoid System comprises the receptors, endogenous agonists, and the related biochemical apparatus responsible for synthesizing these substances and terminating their actions. The receptors have been named CB1 and CB2. The receptors are G-protein coupled. Within the central nervous system, CB1 is primarily located in presynaptic nerve terminals and is responsible for most of the neurobehavioral effects of cannabinoids. CB2, on the other hand, is the main cannabinoid receptor in the immune system, but can also be expressed in neurons. The main endogenous agonists of CB1 and CB2 are derivatives of arachidonic acid (Figure 4) (Matos *et al.,* 2006; Viviane *et al.,* 2010; Papagianni and Stevenson, 2019; Baião *et al.,* 2021; Boczek and Zylinska, 2021; Lu and Mackie, 2021; Dantas, 2022; Briques *et al.,* 2023; WeCann Team, 2024).

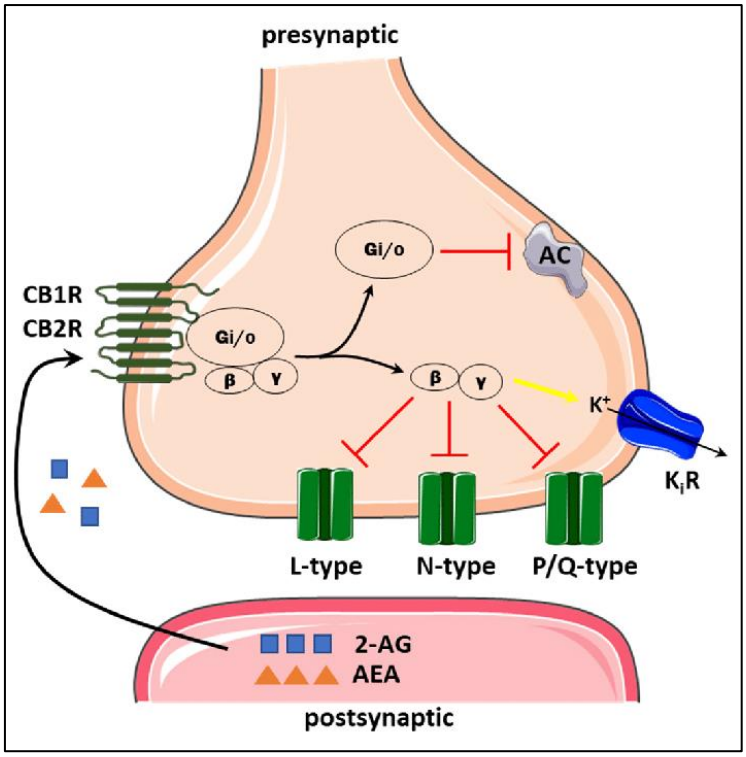

Figure 4: The schematic representation of endocannabinoid action on presynaptic Ca 2+ channels. Endocannabinoids synthesized postsynaptically act on presynaptic CB1/CB2 receptors coupled to Gi/o, which may decrease cAMP level by inhibiting adenylyl cyclase (AC). The βγ inhibits L, N, and P/Q-type calcium channels but activates inwardly, rectifying the potassium channel (KiR, yellow arrow). Inhibitory action is indicated by the red arrow

Sources: https://www.researchgate.net/figure/The-schematic-representation-of-endocannabinoid-action-on-presynaptic-Ca-2-channels_fig4_353576042 and Doi.org/10.3390/ijms22158168

Endocannabinoid System allows adequate communication and coordination at the intersections of various systems in the body. When endocannabinoid receptors are stimulated, physiological mechanisms are triggered that regulate a series of functions, such as inflammatory processes and neuronal signaling. The main chemical elements of *Cannabis* L. (Cannabaceae) phytocannabinoids, and terpenes, are capable of stimulating endocannabinoid receptors and interacting with endocannabinoid substances, interfering in aspects such as appetite regulation, metabolic expenditure, sleep quality, learning processes, and memory (Tabach *et al.*, 2019; Lowe *et al.*, 2021; Briques *et al.*, 2023; WeCann Team, 2024). Below, we list some disorders that have shown positive results with cannabinoid therapy:

A. Anxiety

Anxiety and trauma-related disorders are the most common psychiatric diseases and are associated with inadequate treatment options and thus high social and economic costs. Psychological treatments are often limited or temporary in their effectiveness, while medications can lack efficacy or have unwanted side effects in a considerable number of patients. Psychological therapies can also be combined with medications to enhance treatment synergistically, but some medications can interfere with these therapies. Better options are therefore urgently needed for treating these disorders (Maccarrone *et al.*, 2015; Fisher *et al.*, 2016; Rock *et al.*, 2017; ASPC, 2024).

B. Parkinson's disease

Studies have shown the beneficial effects of *Cannabis chemovariants* L. (Cannabaceae), for people with Parkinson's disease. The main result is an improvement in the quality of life and well-being of the patients evaluated, in the reduction of motor and non-motor symptoms, such as pain, sleep disorders, and mood disorders (Fisher *et al.*, 2016; Rock *et al.*, 2017; ASPC, 2024).

C. Autism Spectrum Disorder

Recent studies have shown that phytocannabinoids can also be effective in the adjuvant treatment of symptoms common to people with Autism Spectrum Disorder, such as sleep disorders, anxiety, psychomotor agitation, and seizures. Mechanisms of action are beginning to be explained and the therapeutic potential for treatment in the following areas is growing metabolism, neurology, psychiatry, autoimmune diseases, and oncology. In this context, countless patients suffering from serious illnesses now have a concrete alternative to find relief from their suffering. On the other hand, despite the widespread international prohibition,

the long history of medical, religious, and recreational use, and current scientific knowledge, have shown that the therapeutic potential of cannabis is safe, effective, and economical, with fewer side effects than many widely used medications (Ofek *et al.*, 2006; Weisset *et al.*, 2008; Maccarrone *et al.*, 2015; Fisher *et al.*, 2016; Rock *et al.*, 2017; ASPC, 2024).

1.3. Objective

The manuscript aims to verify the relationship of the Endocannabinoid System with hormonal functions.

2. METHODS

This work is a literature review, based on scientific articles. The inclusion criteria for the articles that were part of this review were: articles published in the last 15 years and published in Portuguese and English on the subject, carefully selected in databases such as Scielo, PubMed (https://pubmed.ncbi.nlm .nih.gov/), Google Scholar (https://scholar.google.com.ec/schhp?hl=pt-br), Capes Portal (https://www.periodicos.capes.gov.br/), Latin American and Caribbean Literature in Health Sciences (http://www.bireme.br/), Scielo (http//www.scielo.org), (https://hal.archives-ouvertes.fr/ submit/index), SSRN (https://hq.ssrn.com/login/pubsigninjoin.cfm) and ResearchGate (https://www.researchgate.net/signup.SignUp.html) using the following keywords: Endocannabinoid system, Cannabis sativa, medicinal Cannabis, THC, phytocannabinoids, pharmacology of the endocannabinoid system, endogenous cannabinoid, cannabidiol, CB1, CB2 and hormones.

3.0. SELECTED STUDIES

3.1. Endocannabinoid

Promising results have been observed, but prospective and double-blind clinical studies are still lacking for the widespread acceptance of the use of cannabis and its derivatives as a therapeutic alternative. Understanding how the Endocannabinoid System works in all its complexity is the first step for those who wish to incorporate cannabinoid-derived medicines into their clinical practice and offer patients safe and effective therapeutic alternatives, always based on scientific evidence (Ofek *et al.*, 2006; Weisset *et al.*, 2008; Maccarrone *et al.*, 2015; Fisher *et al.*, 2016; Rock *et al.*, 2017; ASPC, 2024).

The cannabinoid arachidonoyl ethanolamine anandamide, 2-arachidonoyl glycerol (2-AG) has also been identified, followed by N-arachidonoyl dopamine (NADA), 2-arachidonoyl glycerol ether (noladin), and O-arachidonoyl ethanolamine, also known as virodamine. Endocannabinoids can bind to receptors other than CB1 and CB2, including transient receptor potential vanilloid type-1 (TRPV1) (Figure 5) (Scherma *et al.*, 2019; Baião *et al.*, 2021; Lu and Mackie, 2021; Briques *et al.*, 2023).

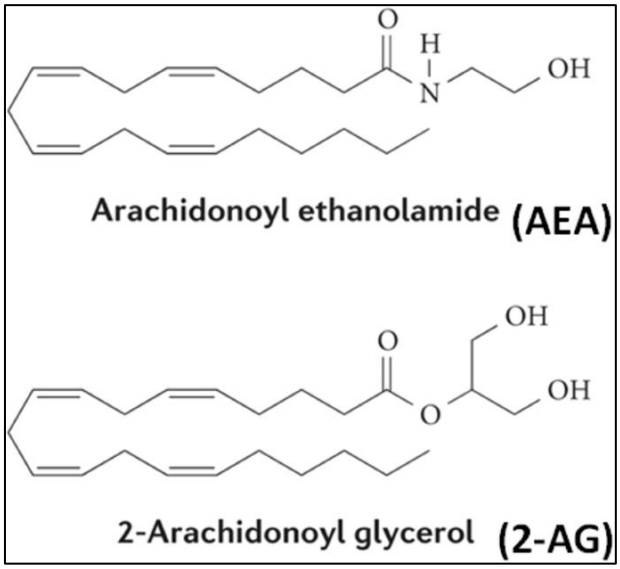

Figure 5: Structures of endocannabinoids AEA and 2-AG
Source: Doi.org/10.1038/s41401-018-0075-x

In the peripheral nervous system, TRPV1 is activated by heat, low pH, and the chili pepper compound capsaicin. Within the central nervous system, TRPV1 is expressed on postsynaptic nerve terminals and may be activated intracellularly by anandamide. Other endocannabinoid receptors include the G-protein-linked receptor and the peroxisome proliferator-activated receptor (PPAR) (Matos *et al.*, 2006; Viviane *et al.*, 2010; Papagianni and Stevenson, 2019; Dantas, 2022; WeCann Team, 2024).

Endocannabinoid degradation occurs through hydrolysis, in which anandamide is degraded by the enzyme fatty acid amide hydrolase (FAAH), forming

arachidonic acid and ethanolamine, while 2-AG is hydrolyzed by monoacylglycerol lipase (MAGL), resulting in arachidonic acid and glycerol. These binding molecules have distinct affinities for cannabinoid receptors, which provide different physiological and pathological activities. In this sense, anandamide has a greater affinity for CB receptors, while 2-AG acts on both receptors, but has a low affinity (Figure 6) (Scherma *et al.*, 2019; Márquez, 2020; Pereira, 2020; Baião *et al.*, 2021; BIP-FARMACIA, 2021; Lu and Mackie, 2021; Briques *et al.*, 2023).

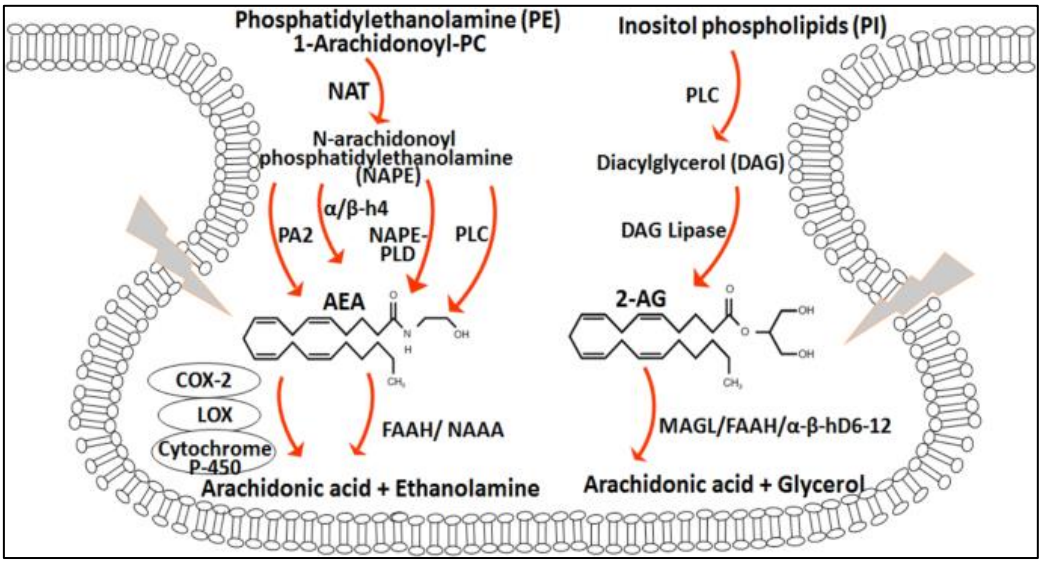

Figure 6: Schematic representation of AEA and 2-AG biosynthesis and degradation
Source: Doi.org/10.1038/s41401-018-0075-x

Location of endocannabinoid receptors: CB1: Cortex and pituitary, basal ganglia, hypothalamus, cerebellum, spinal cord, dorsal medulla ganglia, enteric nervous system, adipocytes, endothelial cells, muscle and gastrointestinal tract. CB2: Immune system, T cells, B cells, spleen, tonsils, and activated microglial cells (Márquez, 2020; Pereira, 2020; Lu and Mackie, 2021).

3.2. *Cannabis sativa*, L. (Cannabaceae)

In addition to acting on local mediators of peripheral tissues, with action in physiological processes of memory, anxiety, and nociception. This system is composed of enzymes, lipid signaling molecules called cannabinoids, and their receptors. Cannabinoids can be of endogenous origin endocannabinoids or exogenous phytocannabinoids which are obtained from *C. sativa* (Vieira, 2019; Baião *et al.*, 2021; Croeq, 2020; Lu and Mackie, 2021; Briques *et al.*, 2023).

Cannabis sativa is a plant belonging to this plant has subspecies that differ in terms of morphological aspects and the number of phytocannabinoids present in each species, the main ones being *C. sativa* subspecies *indica* and *C. sativa* subspecies ruderalis. *Cannabis sativa* is already used for medicinal purposes, providing treatment options for diseases such as refractory epilepsy, multiple sclerosis, anxiety, depression, Alzheimer's disease, sleep and appetite disorders, autism spectrum disorders, and schizophrenia, among others (Baião *et al.*, 2021; Lu and Mackie, 2021; Briques *et al.*, 2023).

The main substances produced by *C. sativa* are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which act in the treatment of the pathologies addressed (Rock *et al.*, 2017; ASPC, 2024). This plant has subspecies that differ in terms of morphological aspects and the number of phytocannabinoids present in each species, the main ones being *C. sativa* subspecies indica and *C. sativa* subspecies ruderalis. This plant has a variety of phytoconstituents, among which flavonoids, monoterpenes, sesquiterpenes, steroids, and nitrogen compounds stand out. However, of the more than 500 existing compounds, only 164 are characterized as cannabinoids, which in turn are the main biologically active constituents (Morais, 2018; Tabach *et al.*, 2019; Baião *et al.*, 2021; Lu and Mackie, 2021; Briques *et al.*, 2023).

The topics reviewed in this study open up possibilities from the point of view of neurobiology, pharmacology, and a new, unusual therapeutic perspective that could not only maintain the quality of life of its users but also generate a possible curative effect for certain pathologies. Therefore, the diversity of effects generated by *C. sativa* and its cannabinoids will continue to arouse great interest, prejudice, and controversy (Baião *et al.*, 2021; Lu and Mackie, 2021; Briques *et al.*, 2023).

3.3. Cannabinoids

Endogenous cannabinoids also act in response to cellular damage, modulating the functions of neuronal, glial, and endothelial cells, and providing anti-

inflammatory effects. Furthermore, because their receptors are present in cells of the immune system, the inhibitory action of the protein (Gi/o) modulates the production of pro-inflammatory cytokines and blocks microglial activation, which reduces antioxidant activity and protects the Nervous System from damage. Cannabidiol (CBD) is one of the most abundant phytocannabinoids in *C. sativa* and has several pharmacological activities in the body, but without presenting psychoactive action (Figure 7) (Vieira *et al.*, 2020; Belgo *et al.*, 2021; Sechat Academy. (2024).

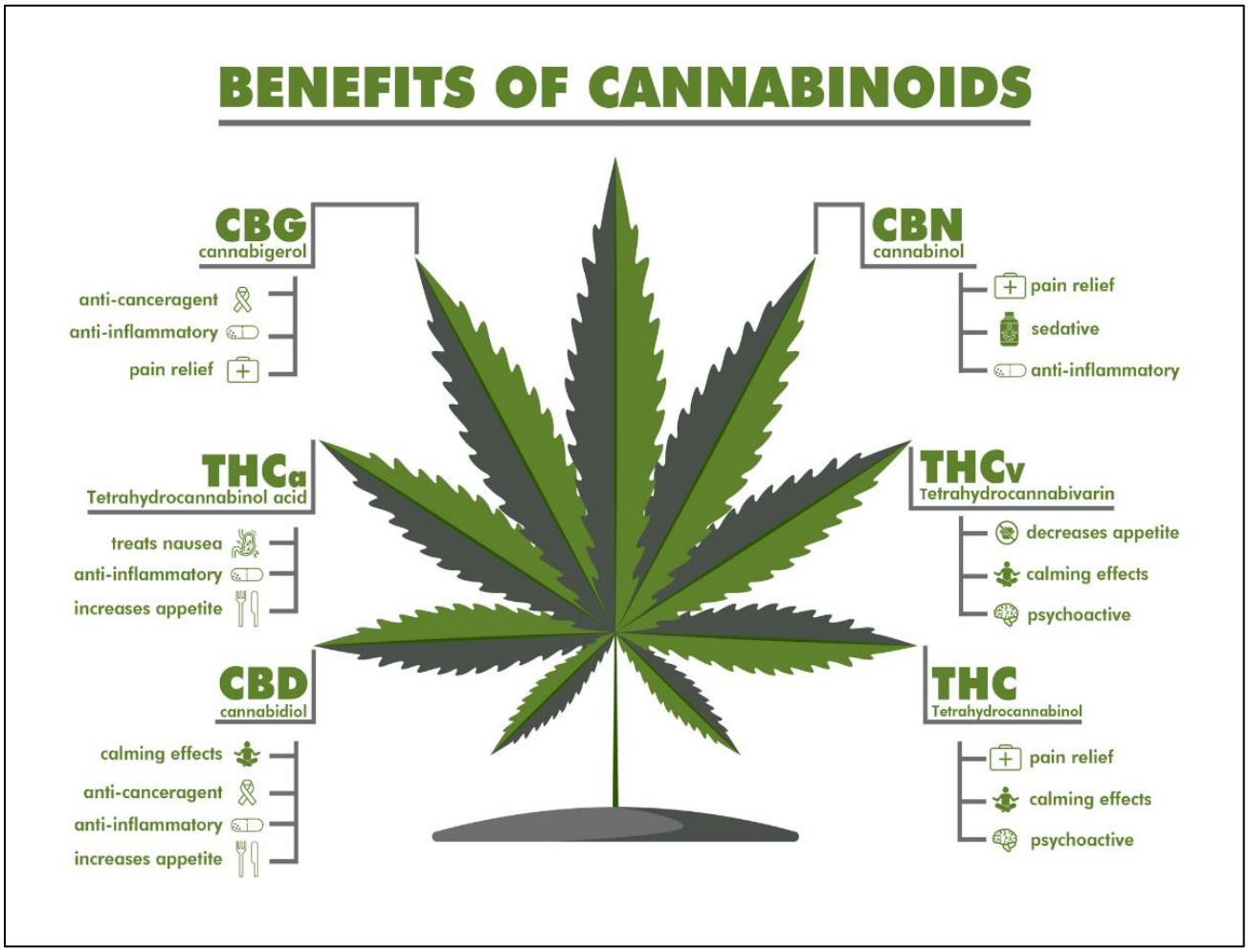

Figure 7: CBG – Cannabigerol – Anticancer agent, anti-inflammatory, pain relief.
CBN – Cannabinol – Pain relief, sedative, anti-inflammatory.
THCa – Tetrahydrocannabinolic acid – Treats nausea and inflammation; increases appetite.
THCv – Tetrahydrocannabivarin – Calming effect, psychoactive, decreases appetite.
CBD – Cannabidiol – Calming effect, anticancer agent, anti-inflammatory, increases appetite.
THC – Tetrahydrocannabinol – Pain relief, calming effect, psychoactive
Source: https://www.pharmabinoid.eu/pt/pages/beneficios-dos-canabinoides

Considering the various targets of CBD in different systems of the body, it is possible to list some of its therapeutic potential. Among them is the anticonvulsant action, useful in cases of epilepsy and Dravet syndrome; anti-inflammatory activity, suitable for cases of menstrual cramps; reduction in intraocular pressure associated with glaucoma and in the side effects of chemotherapy, as well as antitumor activity (Seltzer *et al.*, 2020; Belgo *et al*, 2021).

3.4. Cannabidiol

Associated with this, cannabidiol is attributed to the action on anxiety, depression, and insomnia; neurodegenerative diseases such as Alzheimer's and Parkinson's; analgesia and decreased perception and tolerance to pain, including neuropathic pain. In addition, CBD contributes to muscle relaxation to relieve spasticity in cases of multiple sclerosis, has antiemetic action, and promotes appetite stimulation in cases of anorexia (Figure 8) (Camargo *et al.*, 2019; Marques, 2020; Vieira *et al.*, 2020; Seltzer *et al.*, 2020; Belgo *et al.*, 2021).

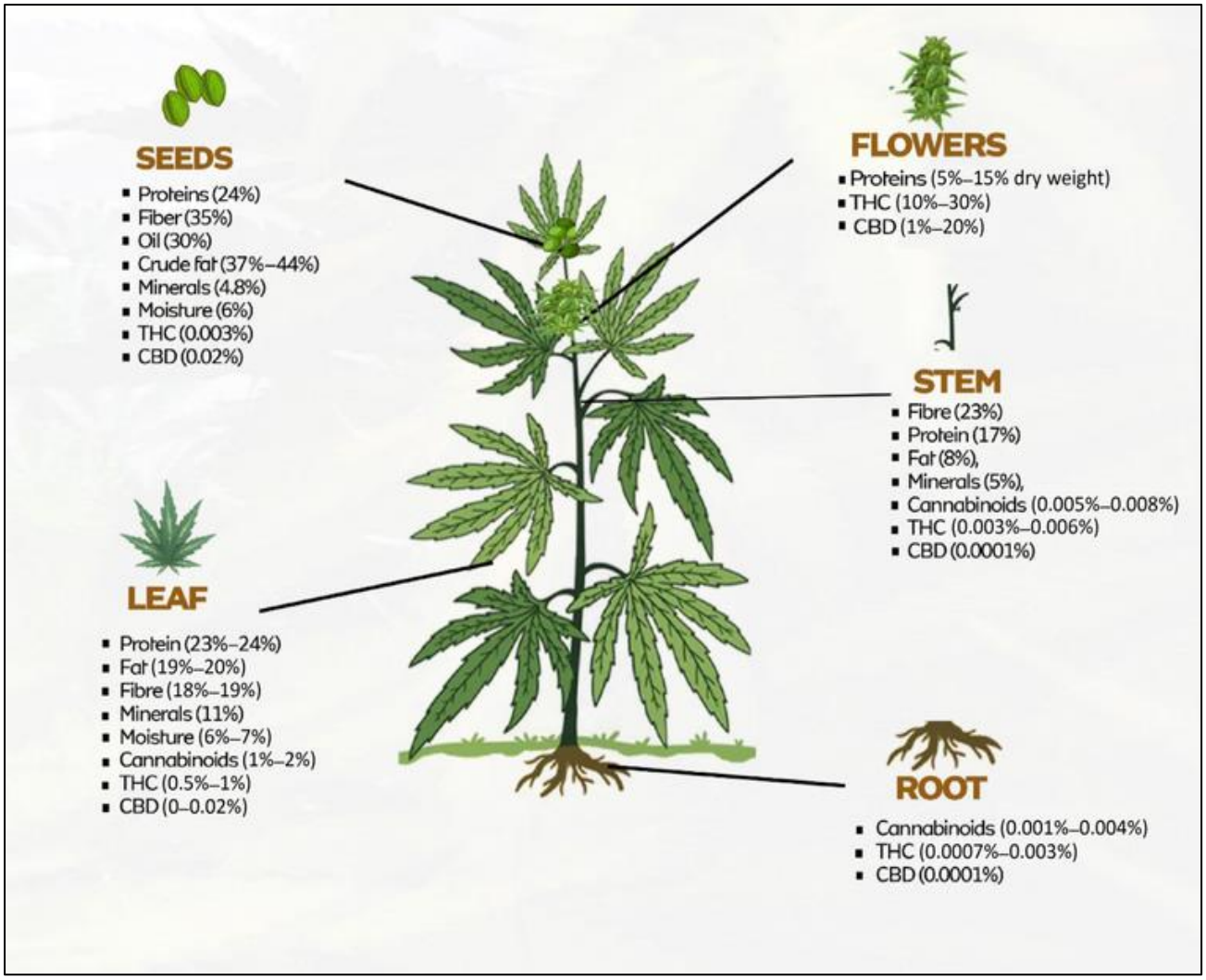

Figure 8: Dietary and bioactive constituents of cannabis. CBD, cannabidiol; THC, tetrahydrocannabinol
Source: Edited from Xu *et al*., (2022)

3.5. Endocannabinoid System and Hormones

3.5.1. Cortisol

Cortisol is a vital hormone produced by the adrenal glands, which are located above the kidneys. It is known as the "stress hormone" because it has several actions in response to stressful situations, but it also has other essential functions such as regulating metabolism, reducing inflammation, and contributing to the functioning of the immune system. Cortisol levels in the blood vary throughout the day, starting to rise around 3 to 4 a.m. and reaching their highest levels around 9 a.m. From there, cortisol levels decrease until they reach their lowest levels around 11 p.m. (Araújo, 2008; Bueno, 2011; Faria, 2023; Ferreira, 2023; Olivia, 2023).

With increasing pressure from work, family responsibilities, and everyday challenges, many people face elevated levels of stress on an ongoing basis. This prolonged state of stress can lead to many health complications, including high blood pressure, heart disease, digestive problems, and sleep disorders. At the heart of the stress response is cortisol, a vital hormone produced by the adrenal glands (Figure 9) (Araújo, 2008; Bueno, 2011, Ferreira, 2023; Olivia, 2023).

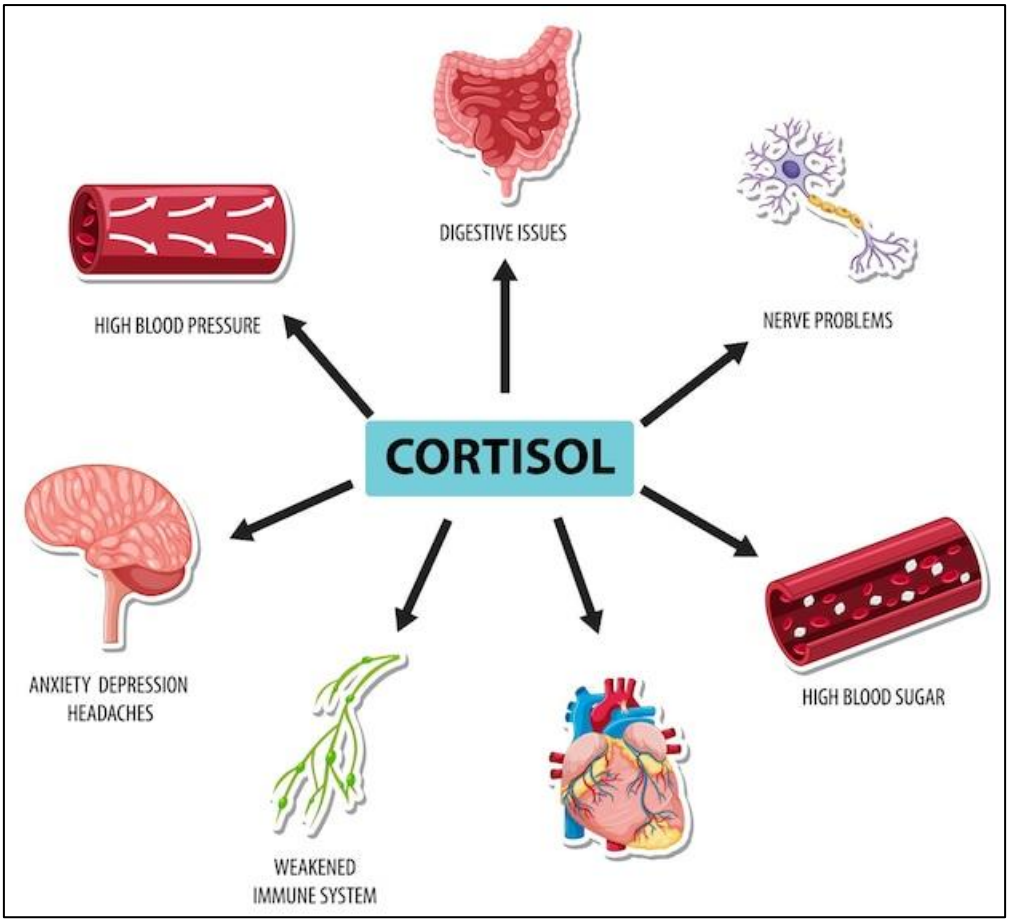

Figure 9: Cortisol hormone with common symptoms diagram

Source: https://br.freepik.com/vetores-gratis/hormonio-cortisol-com-diagrama-de-sintomas-comuns_39207814.htm

It is released in response to situations of threat or challenge. It prepares the body for the "fight or flight" response by increasing the availability of glucose in the blood, enhancing the use of fats and proteins as energy sources, and suppressing functions that are not essential for immediate survival, such as digestion and reproduction. While this response is crucial in emergencies, chronically elevated cortisol levels can lead to many health problems, including anxiety, depression, weight gain, and compromised immune systems (Araújo, 2008; Bueno, 2011, Ferreira, 2023; Olivia, 2023).

This study suggests that CBD may help stabilize cortisol levels, and influence other hormones involved in metabolism and inflammatory response. In a typical daily cycle, cortisol levels are highest in the morning and gradually decline throughout the day. With the effect of CBD: The study found that CBD administration blunted this normal drop in cortisol levels, resulting in more stable levels throughout the day (Araújo, 2008; Bueno, 2011; Ferreira, 2023; Olivia, 2023).

3.5.2. Insulin

Insulin is a hormone produced naturally by the pancreas, after meals, and is responsible for transporting glucose from the blood into cells so that it can be used as a source of energy. In addition, at the same time that insulin acts to reduce the amount of circulating sugar, there is an increase in the production of another hormone, glucagon, which acts to increase blood glucose, in situations of fasting, for example. Insulin serves to: Reduce the amount of sugar circulating in the blood; Allow glucose to enter cells to be used as an energy source; Promote the storage of glucose in the liver, muscles, and adipose tissue; Regulate the metabolism of carbohydrates, fats, and proteins (Haber *et al.*, 2001; Cavalheira, *et al.*, 2002; Ferreira, 2023; Grossi, 2024).

Insulin is a vital hormone produced by the pancreas that plays a crucial role in regulating blood glucose levels. It enables the body's cells to absorb glucose from the bloodstream to be used as energy or stored as fat. Insulin resistance, a condition in which the body's cells do not respond adequately to insulin, is a key factor in the development of type 2 diabetes. Understanding how cannabis influences insulin sensitivity and metabolism is essential to assessing its therapeutic potential and risks (Figure 10) (Haber *et al.*, 2001; Cavalheira, *et al.*, 2002; Ferreira, 2023).

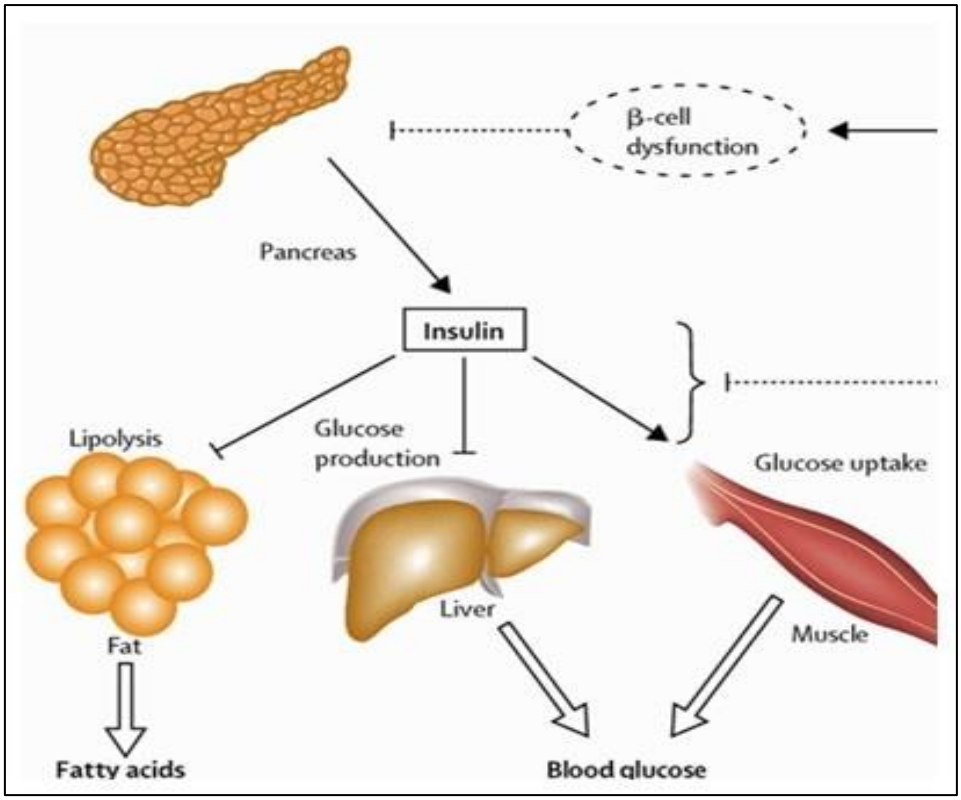

Figure 10: Insulin is synthesized in significant quantities only in beta cells in the pancreas. It is secreted primarily in response to elevated blood concentrations of glucose. Insulin thus can regulate blood glucose and the body senses and responds to a rise in blood glucose by secreting insulin
Source: https://www.news-medical.net/health/What-is-Insulin.aspx

The interaction between cannabinoids and the endocannabinoid system (ECS) may explain these effects. The ECS, which includes CB1 and CB2 receptors, regulates energy metabolism and glucose homeostasis. CB1 receptors, which are widely distributed in the brain and peripheral tissues, are particularly involved in appetite control and the regulation of energy storage. Activation of CB1 receptors by THC may increase appetite, an effect often referred to as "the munchies," and influence lipid metabolism (Haber *et al.,* 2001; Cavalheira, *et al.,* 2002; Ferreira, 2023).

In animal studies, CBD may reduce inflammation and oxidative stress, which contribute to insulin resistance. CBD, along with another lesser-known cannabinoid, THCV (tetrahydrocannabivarin), has been shown to improve pancreatic beta cell function and reduce fasting blood glucose in patients with type 2 diabetes. In populations where cannabis use is legal, a lower prevalence of obesity has been observed, despite the increased appetite caused by THC. This suggests that the metabolic effects of cannabis are complex and may vary according to dose, frequency of use, and cannabinoid composition (Haber *et al.,* 2001; Cavalheira, *et al.,* 2002; Ferreira, 2023).

3.5.3. Thyroid

The thyroid is a gland that regulates the function of important organs such as the heart, brain, liver, and kidneys. It produces the hormones T3 triiodothyronine and T4 thyroxine. In this way, it ensures the body's balance. The gland is butterfly-shaped with two lobes) and is located in the front of the neck, just below the Adam's apple. About other organs in the human body, the thyroid is small, but it is one of the largest glands, as it can reach up to 25 grams in an adult. It directly affects the growth and development of children and adolescents and regulates menstrual cycles, fertility, weight, memory, concentration, mood, and emotional control (Bollerslev, 2022; Ferreira, 2023; Persani *et al.,* 2024).

The thyroid is a key gland in the endocrine system, responsible for producing the hormones T3 and T4 which regulate metabolism, growth, and development. Thyroid hormones influence every tissue in the body, controlling how quickly cells use energy. Any imbalance in the production of these hormones can lead to conditions such as hypothyroidism (underproduction of hormones) or hyperthyroidism (overproduction of hormones), each with its health challenges (Figure 11) (Bollerslev, 2022; Ferreira, 2023; Persani *et al.* 2024).

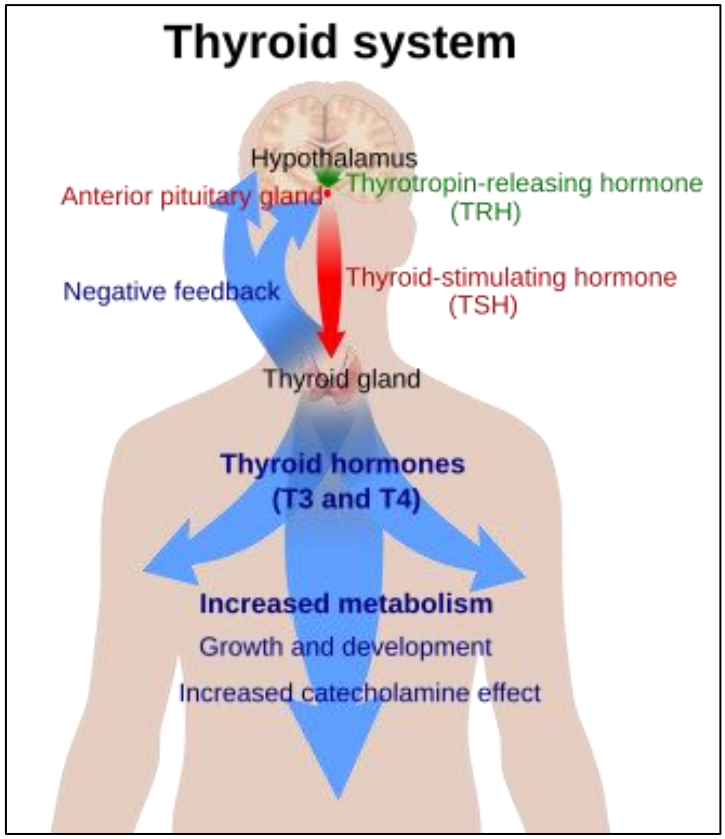

Figure 11: The thyroid system of the thyroid hormones T3 and T4
Source: https://en.wikipedia.org/wiki/Thyroid_hormones

The interaction of cannabis with thyroid function is an emerging and complex area of research. Cannabinoids, such as THC and CBD, interact with the endocannabinoid system (ECS), which is involved in regulating several physiological functions, including thyroid function. While there are still many gaps in knowledge, some preliminary studies offer valuable insights into how cannabis may affect the thyroid. In the case of thyroid problems, it helps to rebalance hormone production or, if necessary, TSH hormone production (Keith *et al.,* 2021; Bollerslev, 2022; Ferreira, 2023; Persani *et al.,* 2024).

CBD has a modulating effect on thyroid function. Studies suggest that CBD may help to stabilize thyroid hormone levels, offering therapeutic potential for conditions such as hypothyroidism. CBD has been shown to not only influence thyroid hormone levels but also have a positive impact on reducing thyroid inflammation. Inflammation is a contributing factor in many thyroid disorders, and CBD's ability to modulate the inflammatory response may be particularly beneficial for patients with autoimmune thyroid diseases such as Hashimoto's disease (Keith *et al.,* 2021; Bollerslev, 2022; Ferreira, 2023; Persani *et al.,* 2024).

The cannabis in the treatment of thyroid disorders comes from anecdotal reports of hypothyroid patients using CBD as an adjunct to conventional treatment. Some patients have reported improvements in symptoms such as sleep quality, anxiety, depression, fatigue, and weight gain after introducing CBD into their treatment regimen (Keith *et al.,* 2021; Bollerslev, 2022; Ferreira, 2023; Persani *et al.,* 2024).

3.5.4. Melatonin

Melatonin is a hormone produced by the pineal gland, located in the brain. The function of this substance is to regulate the body's biological rhythm according to the circadian cycle, stimulating sleep at night. The circadian cycle is the rhythm in which the body performs its functions throughout the day. This cycle is related to the division between day and night, with light being its main influence. Based on lighting, the body releases the correct hormones and conducts the necessary processes for different activities, such as waking up, eating, exercising, and sleeping (Figure 12) (LaMotteda, 2022; Ahmad *et al.,* 2023; Ferreira, 2023; Paulino *et al.,* 2024; Waad *et al.,* 2024).

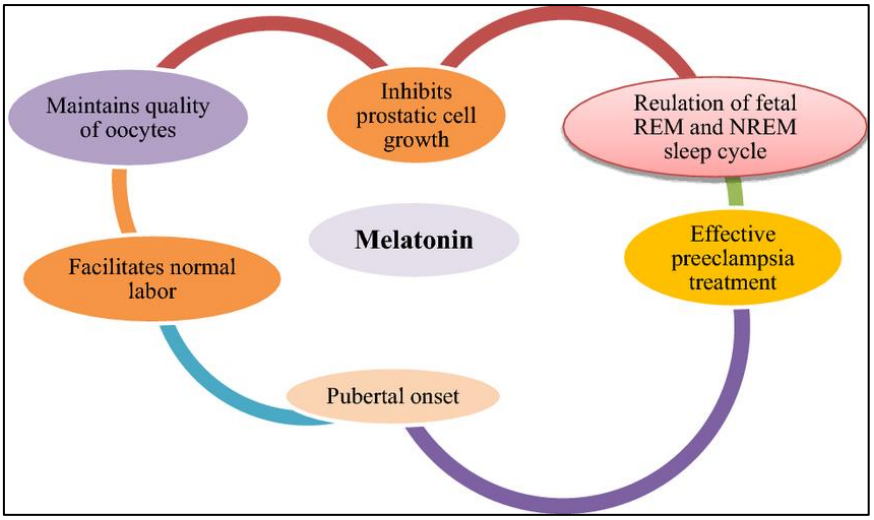

Figure 12: Melatonin and its effects on reproductive status
Sources: https://www.researchgate.net/figure/Melatonin-and-its-effects-on-reproductive-status_fig5_368361735 and Doi.org/10.1007/s10571-023-01324-w

Regulating the sleep-wake cycle and promoting healthy sleep. Its production is influenced by exposure to light: elevated levels of melatonin are produced at night, facilitating the onset and maintenance of sleep, while daylight suppresses its production, helping to maintain wakefulness. Adequate quality and quantity of sleep are vital for several bodily functions, including memory, mood, immune function, and general health (LaMotteda, 2022; Ferreira, 2023; Paulino *et al.*, 2024; Waad *et al.*, 2024).

The interaction of cannabis with melatonin and the sleep cycle is an area of great interest, especially in light of the increasing rates of sleep disorders in the modern population. Studies suggest that the main cannabinoids in the cannabis plant, THC and CBD, influence sleep in distinct and complementary ways. THC (tetrahydrocannabinol) is a potent sleep inducer and has been associated with a reduction in sleep latency, or the time it takes to fall asleep. This may be particularly helpful for people who suffer from onset insomnia, a condition where there is difficulty initiating sleep (LaMotteda, 2022; Ferreira, 2023; Paulino *et al.*, 2024; Waad *et al.*, 2024).

However, long-term use of THC may have adverse effects on sleep quality. Research suggests that while THC may help users fall asleep faster, it may reduce the amount of Rapid Eye Movement sleep, a critical phase of sleep associated with dreaming and memory consolidation. Cannabidiol (CBD) has shown a more promising profile for improving sleep quality (LaMotteda, 2022; Ferreira, 2023; Paulino *et al.*, 2024; Waad *et al.*, 2024).

Research has shown that CBD may help reduce anxiety and stress, which are often contributing factors to insomnia. Additionally, CBD helps regulate sleep and promote relaxation without interfering with the normal sleep cycle, including REM sleep, so when combined with THC, it may encourage restful, relaxing, and long-lasting sleep. This study shows that cannabis oil with THC and CBD is effective in improving sleep quality and duration, midnight melatonin levels, quality of life, and mood in adults with insomnia in just 2 weeks. CBD and the reduction of nightmares in patients with post-traumatic stress disorder (PTSD). Preliminary studies suggest that CBD may help reduce the frequency and intensity of nightmares, which are a common symptom in patients with PTSD, thereby improving sleep quality and overall well-being (LaMotteda, 2022; Ferreira, 2023; Paulino *et al.*, 2024; Waad *et al.*, 2024).

3.6. Participation of the endocannabinoid system in hormonal responses induced by saline overload

Hypophagia is a term used to describe decreased appetite or reduced food intake. It is a condition that can occur in different contexts, such as in cases of illness, eating disorders, and stress, among others. Hypophagia can be temporary or chronic and can vary in intensity and duration. A variety of factors can cause Hypophagia. In some cases, it can be the body's natural response to certain situations, such as illness, infection, or injury. In other cases, it can be a symptom of eating disorders, such as anorexia nervosa or bulimia. In addition, stress, anxiety, and depression can also lead to decreased appetite (Figure 13) (Nutritionists RJ., 2022).

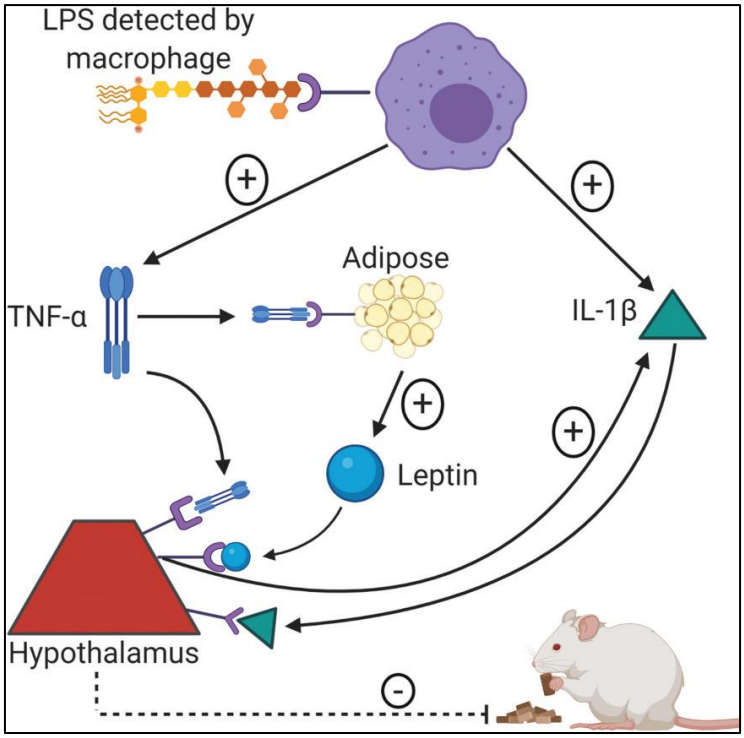

Figure 13: Putative mechanisms of action of IL-1β and tumor necrosis factor-α (TNF-α) on feed intake. Macrophages produce cytokines when activated, which then bind receptors on glucose-responsive neurons in the hypothalamus to trigger a reduction in feed intake. Peripheral TNF-α also induces adipose tissue leptin production, which further stimulates the central production of IL-1β in a unique endocrine-immune crosstalk mechanism

Source: Figure Created using BioRender (https://biorender.com/)

Hypophagia resulting from hyperosmolality or cellular dehydration is characterized by reduced food intake observed in animals subjected to chronic situations of dehydration, such as salt overload for prolonged periods, as well as water deprivation. Hypophagia induced by dehydration may be due to the observed hormonal changes, such as increased secretion of Oxytocin, which is known to inhibit salt intake. Animals in hypophagia induced by hyperosmolality have elevated levels of corticosterone and reduced mRNA for corticotropin-releasing hormone (Vechiato, 2014).

Animals in hypophagia due to dehydration present hormonal responses appropriate to the negative energy balance in which they find themselves, such as increased plasma levels of corticosterone and ghrelin, as well as decreased plasma leptin and insulin. These coordinated responses thus enable the maintenance of adequate serum glucose levels. Glucocorticoids can mobilize energy from energy stores, particularly by promoting hepatic glycogenolysis and gluconeogenesis (Vechiato, 2014).

3.7. How cannabis affects hormones that control appetite and stress

3.7.1. Ghrelin.

Growing evidence also suggests a collaborative interaction between the endocannabinoid system and ghrelin. Both drive feeding and experts believe that the two work synergistically to stimulate hunger and eating. Endocannabinoid and ghrelin receptors are also similarly distributed in areas of the brain associated with feeding and in organs involved in metabolism (Sechat Academy, 2024).

3.7.2. Leptin

Leptin is a protein hormone released by adipocytes and its quantity is strongly related to the amount of fat present in the human body. It is one of the main hormones regulating food intake, with anorectic action, that is, it induces a state of satiety (Sechat Academy, 2024).

Cannabis also influences the body's levels of the hormone leptin. "Leptin is secreted by fat cells and sends signals to the hypothalamus, regulating food intake and energy expenditure, helping to maintain a normal or set-point body weight," [Patricia Frye, director of the Society of Cannabis Clinicians]. Research has shown that cannabis smokers have lower levels of leptin than non-smokers. This finding may explain why cannabis smokers tend to have lower body fat percentages and rates of obesity (Sechat Academy, 2024).

4.0. CONCLUSION

Endogenous cannabinoids and the concomitant activation of their CB1 receptors cause a plethora of effects, including inhibition of prolactin and growth

hormone secretion and increased ACTH44 secretion; anxiolytic effects, through actions on the hypothalamic-pituitary-adrenal axis; inhibition of testosterone secretion, anovulation, and uterine relaxation due to their effects on the release of hypothalamic peptides and hormones, and their regulation by steroids.

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