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The Effects of Cannabinoid Compounds on the Endocrine System

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Abstract

Cannabinoids are chemical compounds that occur naturally in the cannabis plant. They have been known for thousands of years and have been used to treat conditions such as asthma, malaria, hypertension, and spasticity. The most common cannabinoids are tetrahydrocannabinol and cannabidiol. Due to their abundant type 1 and 2 cannabinoid receptors, they affect most systems in the human body. This review focuses on the effects of cannabis on the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axis, growth hormone, food intake, glycemia regulation, reproductive system, prolactin, and oxytocin.

Keywords

cannabinoids, cannabis, marijuana, endocrine system

1. Introduction

1.1 General information

One of the most commonly used stimulants in the world, alongside tobacco and alcohol, is marijuana. [1, 2, 3] The issue of legalizing the non-medical use of this substance remains a problem. When used in rational amounts and at optimal frequency, it is probably safer than alcohol or tobacco, but intensive use can have serious consequences. [4] Statistics indicate that the age group most likely to use marijuana preparations are people aged 15-34, with a male to female ratio of 2:1. [5] WHO estimates that it is used annually by about 2.5% of people worldwide, and this number is growing. [1, 6]

Cannabis plants originate from Central Asia. [1, 7] Its use in India and China is estimated to have begun around 2000 BC, and in Europe it began to gain popularity around the mid-19th century. [2] Its various forms such as flowers, seeds, leaves and stems have been used for religious, spiritual, recreational and therapeutic purposes. [1, 8] The active form is most often introduced into the body by smoking, but also by aerosol, rectal, transdermal, intravenous, oral or inhalation. [9, 10, 11] It is said to have anxiolytic, appetite-enhancing, antiemetic,

antiallergic, pain-reducing and fear-reducing effects. [2, 12, 13, 14] It has been traditionally used to treat rheumatic pain, spasticity, asthma, malaria, glaucoma, hypertension, diarrhea, cramps and constipation. [2, 9, 12, 14] Some studies indicate that the cannabis plant may also be used as an anticancer agent or have an effect reducing the risk of developing cancer. [15]

1.2 Cannabinoid compounds

A "cannabinoid" is a chemical compound found in the cannabis plant or its derivatives, while the word "marijuana" refers to the dried flower buds of this plant. [1, 2, 16] They are most often obtained from Cannabis sativa subsp. indica or Cannabis sativa subsp. sativa. Cannabis derivatives include synthetic cannabinoids, phytocannabinoids and endocannabinoids. [1, 2] There are over 100 phytocannabinoids, the most common of which are tetrahydrocannabinol (THC), mainly responsible for the psychoactive effect, and cannabidiol, mainly useful for medicinal purposes (CBD). [1, 2, 8, 11, 12, 17, 18, 19] The first one is a partial CB1 receptor agonist, and the second one is a CB1 receptor negative allosteric modulator [16, 20]. On this basis, cannabis can be divided according to the type of dominant substance: Type I (dominant substance is THC), Type II (similar percentage of CBD and THC) and Type III (dominant substance is CBD). [1]

Endogenic cannabinoids (eCB) are substances produced naturally in the body, which are ligands of cannabinoid receptors. [2, 5] They are most often derivatives of arachidonic acid, and are synthesized under the influence of certain enzymes, cytokines, hormones or nerve impulses. [5] The main lipophilic endocannabinoid neurotransmitters include arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), as well as 2-arachidonoylglyceryl ether (AG, noladin ether), virodamine and N-arachidonoylglycerol (NADA). [1, 2] Their main functions in the body are the regulation of food intake and energy balance by affecting the limbic systems, hypothalamus, gastrointestinal tract and adipose tissue. [2] ESC is also responsible for the regulation of mood, cognitive functions, pain sensation and cell growth and proliferation. [5]

Cannabinoid Compounds

Type	Examples
NATURAL (Phytocannabinoids)	Δ9-THC, cannabinol, cannabidiol
SYNTHETIC	CP-55940, synthetic analogue of Δ9THC, e.g. dronabinol, nabilone
ENDOCANNABINOIDS (Aminoalkylindoles)	AEA, 2-AG, AG, virodamine, NADA

Table 1. List of 3 groups of cannabinoid compounds and their examples. [2, 12]

1.3 Cannabinoid receptors

The endocannabinoid system consists of endogenous cannabinoid receptor ligands, the cannabinoid receptor system, a set of enzymes involved in the synthesis and degradation of material, and their transmembrane transporters. There are 2 main types of cannabinoid receptors - CB1 receptors and CB2 receptors, which were discovered in 1990 and 1993, respectively. [2, 5, 21] They are metabotropic transmembrane receptors coupled to the Gi/o protein. [2, 16, 18, 19, 20, 21] They inhibit the formation of cAMP and stimulate mitogen-activated protein kinase. [2, 7] CB1 receptors are common in many structures of the human body. In the endocrine system, they can be found mainly in such structures as corticotropic, somatotropic and prolactin cells of the pituitary gland, parafollicular and follicular cells of the thyroid, vagus nerve endings, adrenal glands, placenta, sperm plasma membrane, Leydig cells, testes, granulosa cells of the ovaries, uterus, and stomach fundus. CB2 receptors are found primarily in peripheral nerve endings, on the surface of immune cells, including monocytes, NK cells, macrophages and B lymphocytes; hematopoietic cells, keratocytes, tonsils and spleen. [2]

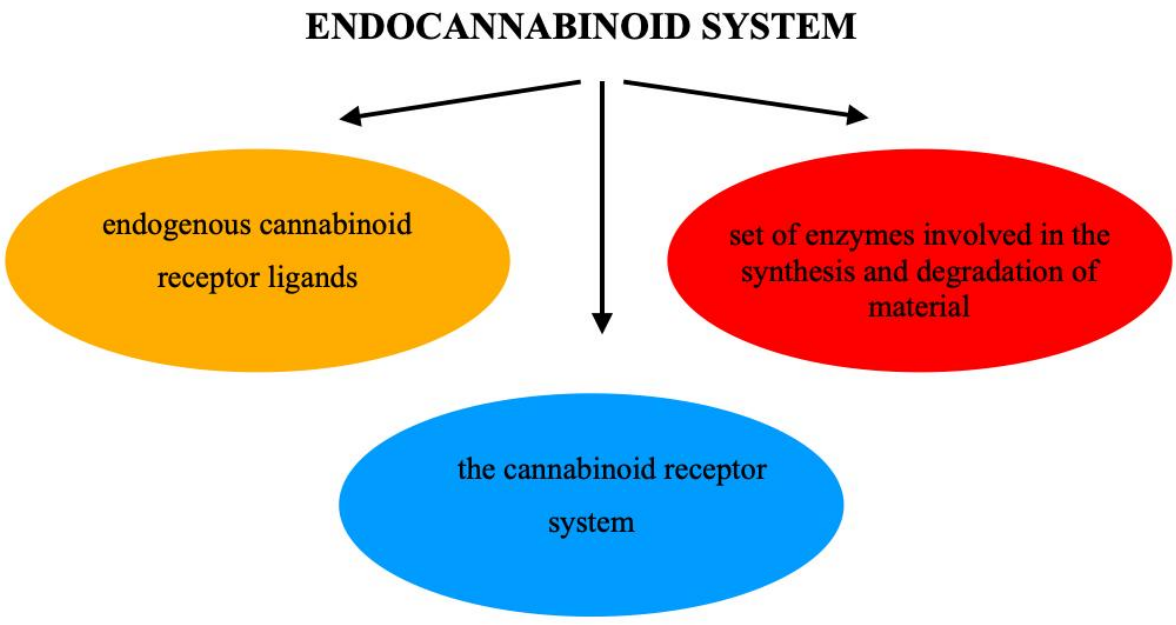

Figure 1. Components of the endocannabinoid system [2, 5, 21]

2. Methods

This review paper analyzed 27 scientific articles from 2014. The articles were sourced from PubMed, Google Scholar, Frontiers and Science Direct.

3. Review of results

3.1 Effects on the hypothalamic-pituitary-adrenal axis

The ECS inhibits the basal, pulsatile and circadian activity of the hypothalamic-pituitary-adrenal axis in a manner that varies with sex and time of day. [2] CB1 receptors are present in each element of this axis, with differences in their distribution depending on sex. [13] The action of cannabinoids at the hypothalamic level is associated with the activation of CB1 receptors, which results in the inhibition of glutamate influx to CRH neurons. Additionally, the lack or deficiency of ESC components is associated with excessive activation of the hypothalamic-pituitary-adrenal axis, including during the stress response. [12] It has been observed that low doses of cannabinoids reduce the activity of the hypothalamic-pituitary-adrenal axis, while high doses increase it. Interestingly, THC, unlike other cannabinoids, only has a dose-dependent stimulating effect on this axis, probably by activating monoaminergic hindbrain nuclei, increasing cortisol concentration. [13] In individuals who took cannabis once, the effect was more pronounced than in individuals who took THC preparations chronically, which suggests the development of tolerance. However, in heavy users, there was deregulation of the hypothalamic-pituitary-adrenal axis in terms of circadian, basal and stress-stimulated secretion. Activation of CB1 receptors is also responsible for reducing the secretion of adrenaline directly from the adrenal medulla and glucocorticoids from the adrenal cortex, which is supported by the fact that ACTH expression remains unchanged. [12, 13]

3.2. Effects on the hypothalamic-pituitary-thyroid axis

The ECS inhibits the secretion of thyrotropin-releasing hormone in the hypothalamus, thyroid-stimulating hormone in the pituitary, and also directly affects thyroid cells by blocking the release of FT3 and FT4. [12, 13] However, some studies show that chronic exposure to cannabis does not cause significant deviations from the norm in laboratory tests for TSH, fT3, and fT4, which suggests the development of tolerance in the mechanism of reduced expression of CB1 receptors in the central nervous system. In the studies conducted, a small proportion of patients developed thyroid disorders in the form of euthyroid sick syndrome (15%), subclinical hypothyroidism (5%) or subclinical hyperthyroidism (10%). [17] However, in contrast to the above group of subjects, fetal exposure to cannabinoid compounds

led to serious cognitive deficits throughout life. It is likely that THC use during pregnancy results in reduced expression of the thyroid receptor β1, and consequently, a reduced effect of thyroid hormones on the fetus. [12] Some studies indicate that cannabinoid receptors in the thyroid may be associated with the development of the neoplastic process of this organ. It was noted that in malignant lesions, the expression of cannabinoid receptors was higher than in benign lesions. The level of CB2 receptor expression was not associated with the degree of follicular cell proliferation or tumor size, but correlated with the risk of malignant tumor recurrence and the presence of lymph node metastases. On the other hand, studies on mice have shown that increased expression of the CB2 receptor through IL-12 stimulation may be helpful in achieving regression of anaplastic thyroid cancer. [2, 22] Additionally, it is believed that cannabinoids, by reducing the level of IL-2, IL-3, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor alpha, interferon gamma and consequently increasing the level of IL-10, may have a beneficial effect on the course of autoimmune thyroid diseases, such as Graves-Basedow's disease or Hashimoto's disease. [2]

3.3. Effect on growth hormone

The ECS inhibits both basal and pulsatile secretion of growth hormone, depending on the dose. [2, 12] This occurs by affecting both CB1 receptors and by stimulating the release of somatostatin, which negatively regulates the secretion of growth hormone. [12]

3.4. Effect on glycemia regulation

The ECS affects many metabolic processes, including glucose metabolism, skeletal muscle and adipose tissue. [2] Stimulation of the CB1 receptor in adipose tissue is associated with increased secretion of visfatin and decreased secretion of adiponectin, which can be attributed to anti-inflammatory and insulin-sensitivity-increasing effects. [2, 23] Studies suggest that blockade of the CD1 receptor is associated with a reduction in body mass and adipose tissue, a transient decrease in appetite, improved insulin resistance, a decrease in leptin and free fatty acids, and their stimulation with an increase in the production of glucagon, somatostatin and insulin. In turn, CD2 receptors inhibit insulin production. Insulin resistance is associated with an increased level of some endocannabinoids in adipose tissue, primarily 2-AG. High levels of 2-AG combined with increased expression of the CB1 receptor result in the development of insulin resistance through obesity, reduced glucose utilization in skeletal muscles or transfer of free fatty acids from adipose tissue to the liver. [2]

3.5. Effects on food intake

Cannabinoids, especially 9-THC, AEA and 2-AG, have appetite-stimulating effects through activation of the CB1 receptor. It is believed that this effect is achieved mainly by reduced activity of corticotropin-releasing hormone and increased production and expression of neuropeptide Y, as well as by stimulating the secretion of food intake modulators such as preproorexin, melanin-increasing hormone, corticoliberin, cocaine-amphetamine regulated transcript peptides. Additionally, cannabinoids have a stimulating effect on lipogenesis [2]

3.6 Effects on the hypothalamic-pituitary-gonadal axis

Cannabinoids have a negative effect on both the female and male reproductive systems. Animal studies have shown that long-term administration of cannabinoids to females can reduce the pulsatile, but not basal, secretion of gonadotropin-releasing hormone (GnRH), stimulated by dopamine and noradrenaline. This results in the inhibition of LH secretion, induced by high-frequency pulses, and FSH, the release of which is stimulated by low-frequency pulses. [1, 2, 5, 12, 19] Long-term administration of cannabinoids to females was associated with impaired maturation of the Graafian follicle, ovulation, and decreased estrogen concentration in the follicular phase, as well as decreased progesterone concentration in the luteal phase. In males, THC administration resulted in decreased sperm motility, and CBD inhibited the enzyme 7α-hydroxylase, which is involved in the production of testosterone in the Leydig cells of the testes. [1, 2] Additionally, the administration of AEA and THC caused a reduction in the dimensions of the seminiferous tubules and testicular atrophy.

During studies conducted on women, a shortened luteal phase, hypoestrogenism, fertility disorders, ovulation disorders, prolonged menstrual cycles, increased testosterone concentration in the blood and, as a consequence, hirsutism, orgasmic disorders, decreased libido, oligomenorrhea, impaired implantation and development of the embryo were observed. [1, 2, 5, 14] Additionally, THC used during pregnancy can cross the placenta, resulting in the birth of a child with low birth weight, congenital anomalies, premature birth, increased pregnancy loss, neurological disorders of the fetus or sudden infant death syndrome. [1, 5, 6, 14] Disorders of the ECS system may also be associated with conditions such as gynecological cancers, endometriosis, polycystic ovary syndrome, preeclampsia, miscarriages or ectopic pregnancy. [2, 5, 19]

Some studies have shown that the use of cannabinoid compounds by men results in the inhibition of LH secretion, reduced sperm motility, their number and concentration, shortened

sperm viability, changes in the sperm epigenome, erectile dysfunction, orgasmic dysfunction, premature or delayed ejaculation, difficulty in inducing capacitation as a result of the acrosomal reaction and, consequently, reduced fertilization capacity. [1, 2, 6, 14, 24] However, other studies have not supported these conclusions, suggesting that cannabis use was not associated with impaired semen quality, with changes in testosterone or LH concentration, but did not demonstrate their safety. [25] It can be also associated with an increased risk of testicular cancer. [1, 2] Due to the fact that stress increases the secretion of endocannabinoids by stimulating the glucocorticoid receptor, it is believed that the ECS additionally negatively affects the hypothalamic-pituitary-gonadal axis, mediating the body's response to stress. [2]

3.7 Effects on prolactin

The ECS affects prolactin secretion in several ways, including directly affecting CB1 receptors in the pituitary gland and by stimulating dopaminergic neurons that have an inhibitory effect on prolactin. The effect is initially a decrease in prolactin concentration and an increase in dopamine release in the hypothalamus, and over time hyperprolactinemia, as a "rebound phenomenon". [12, 26, 27] It should be noted, however, that cannabinoid compounds have a variable effect on prolactin depending on sex, time of day and fertility phase in females. The use of THC in females in the morning produced the same effects as in males, in the form of inhibition of prolactin secretion and an increase in dopamine secretion, whereas exposure to THC in the afternoon during estrus or during the off-estrus period had no effect on prolactin concentration and a non-specific effect on dopamine concentration. Other studies, however, show that CB1 receptor agonists inhibit prolactin secretion by influencing the structures of the pituitary axis, i.e. the central nervous system and hypothalamus. This is supported by the fact that changes in prolactin secretion were not observed when isolated pituitary cells were exposed to THC or the pituitary gland was not under the influence of the hypothalamus. [12] Furthermore, the use of cannabinoids during lactation was associated with its shortening. [2]

3.8 Effect on oxytocin

Studies show that cannabinoids have an inhibitory effect on oxytocin secretion, maternal behavior, and lactation. [12, 27] Activation of CB1 receptors inhibits the secretion of glutamate to magnocellular neurons in the hypothalamus, which are responsible for the synthesis of, among others, oxytocin. In addition, it is suggested that AEA reduces oxytocin release via CB2 receptors, not CB1, and also by increasing the activity of nitric oxide

synthase. In turn, in the case of low oxytocin concentration in the area of magnocellular neurons of the ECS, it inhibits the release of gamma-aminobutyric acid, which results in an increase in oxytocin concentration. [12]

4. Conclusions

Cannabinoid compounds undoubtedly have an effect on the endocrine system. This article focuses on the effect of cannabis on the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axis, growth hormone, glycemia regulation, food intake, reproductive system, prolactin and oxytocin. The main effects exerted by this type of stimulant in both an acute and chronic manner depending on gender are presented.

5. List of abbreviations

2-AG - 2-arachidonoylglycerol
AEA - arachidonoylethanolamine, anandamide
AG - 2-arachidonoylglyceryl ether, noladin ether
CBD - cannabidiol
eCB - endogenous cannabinoids
ECS - endocannabinoid system
FT3 - free triiodothyronine
FT4 - free thyroxine
IL - interleukin
LH - luteinizing hormone
NADA - N-arachidonoylglycerol
THC - tetrahydrocannabinol
TSH - thyroid stimulating hormone

6. Author's contribution

Conceptualization and methodology, Julia Inglot; check Jadwiga Inglot; formal analysis Damian Sowa; investigation Dominik Feret; resources Michał Szczepański; data curation Maciej Mamczur; writing - rough preparation Julia Słowik; writing - review and editing Mateusz Bajak; visualization Marcin Kuliga; supervision Daniel Zapasek. All authors have read and agreed with the published version of the manuscript.

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The authors declare that they have no conflict of interest.

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