

REVIEWS

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Cannabis sativa in the Light of Scientific Research

Cannabis sativa w świetle badań naukowych

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Abstract

Cannabis is one of the most controversial plants and it has been perceived by the world of science in many different ways over the years. At first it was proclaimed as a method of treatment, then as a remedy with side effects, and finally it was labeled harmful and became illegal in most countries. In the second half of the twentieth century, cannabis again became an object of interest among scientists. On the one hand it was seen as a cause of respiratory system dysfunction and mental and fertility aberrations, while on the other its enthusiasts perceived it as an alternative way of treating neurological disorders (e.g. multiple sclerosis, Parkinson's disease, Alzheimer's disease, epilepsy), vision disorders (glaucoma, diabetic retinopathy), and a supplementary therapy for cancer and HIV/AIDS (Adv Clin Exp Med 2007, 16, 6, 807–815).

Key words: cannabis, marijuana, cannabinoids, cannabinoid receptors.

Streszczenie

Konopie to jedna z najbardziej kontrowersyjnych roślin, która na przestrzeni wieków była bardzo różnie postrzegana. Początkowo została uznana za roślinę leczniczą, później stwierdzono, że nie jest całkiem bezpiecznym środkiem, następnie oceniono, że jest szkodliwa i w rezultacie zdelegalizowano w większości współczesnych państw. W drugiej połowie ubiegłego wieku stała się ponownie przedmiotem zainteresowań naukowców, którzy z jednej strony widzieli w niej przyczynę chorób dróg oddechowych, zaburzeń psychicznych i płodności, z drugiej zaś alternatywę w leczeniu bólu, chorób neurologicznych (stwardnienie rozsiane, choroba Parkinsona, choroba Alzheimera, epilepsja), zaburzeń widzenia (jaskra, retinopatia cukrzycowa) oraz w terapii pomocniczej w chorobach nowotworowych oraz w HIV/AIDS (Adv Clin Exp Med 2007, 16, 6, 807–815).

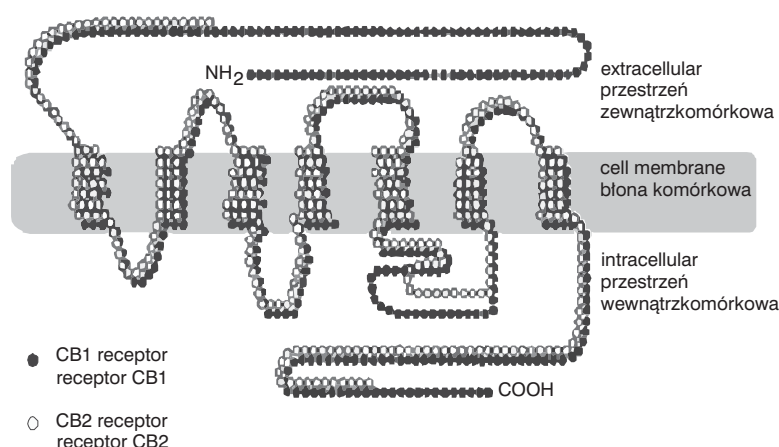
Słowa kluczowe: konopie, marihuana, kanabinoidy, receptory kanabinoidów.

Cannabis is one of the oldest plants in the world and has been used for different purposes for thousands of years. In most cases it was perceived as a stimulant; however, more recently it has been recognized as a potential medicine. Cannabis owes its properties to its main constituents, cannabinoids (CBs), with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most active. Both constituents can be found in the brown resin secreted by the hair which covers female plants [1]. In 1988 it was discovered that every human body naturally contains cannabinoid receptors (CB receptors). When combined with the cannabinoids from cannabis, these react with

each other and affect main functions of the human body [2].

Cannabinoids: Their Receptors and Mechanism

The CB receptors belong to the superfamily of G protein-coupled receptors. There are currently two known subtypes: CB1, expressed in neurons, adipose tissue, lungs, liver, spleen, uterus, prostate, testis, sperm, placenta, stomach, kidneys, and skeletal muscles, and CB2, mainly present in the spleen, tonsils, and immune cells (lymphocytes



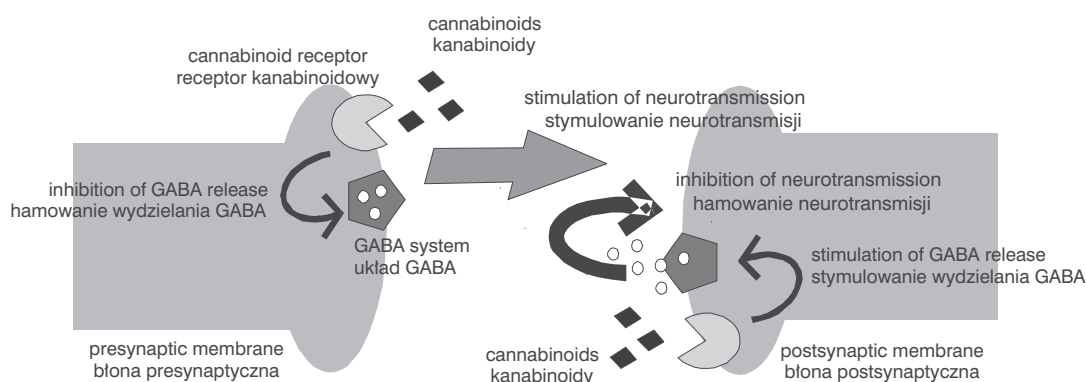
and macrophages) [2]. Both receptors are proteins and consist of seven transmembrane-spanning domains. The CB1 molecule is larger than CB2. However, both receptor molecules are alike in four of the seven regions embedded in the cell membrane (known as the transmembrane regions). The intracellular loops of the two receptor subtypes are quite different, which might affect the cellular response to the ligand (Fig. 1) [3].

Cannabinoids tend to inhibit neurotransmission, although the results are somewhat variable. In some cases, cannabinoids diminish the effects of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), while in other cases, cannabinoids can augment the effects of GABA. The effect of receptor activation depends on where it is located on the neuron: if the cannabinoid receptors are presynaptic and inhibit the release of GABA, cannabinoids diminish GABA's effects and the net effect is stimulation, but if the cannabinoid receptors are postsynaptic and on the same cell as the GABA receptors, they will probably mimic the effects of GABA and the net effect would be inhibition (Fig. 2) [3].

Mechanism of Toxic Action

Influence on the Respiratory System

The most common form of cannabinoid consumption is smoking a joint (a hand-rolled cannabis cigarette). Smoke from a joint is very similar to traditional cigarette smoke and exerts an adverse influence on the respiratory system. When scientists reported that approximately 25% of marijuana smokers have some symptoms of chronic bronchitis (chronic cough and excessive phlegm production), they proceeded to the visual bronchitis in order to examine the bronchial mucosa. The factors that were examined were the presence and extent of airway erythema, edema, and hypersecretion. It was found that smokers of marijuana had abnormal size and number of blood vessels (perceived erythema), slight edema, and decreased numbers of ciliated columnar cells, which were replaced by goblet cells. Histological examination of bronchial biopsy material confirmed abnormality in the structure of the bronchial mucosa of the smokers [4].



Scientists report that marijuana can also affect the respiratory system indirectly; smoke affects the functions of the main effectors of the immunological system, which is a very important component of the lung barrier:

- cannabinoids cause deactivation of macrophages; the organism thus has a limited ability to destroy disease-causing microorganisms, tumor cells, and foreign bodies,
- marijuana smoking decreases the production of proinflammatory cytokines,
- cannabinoids do not decrease the production of immunosuppressive cytokines (inflammatory reaction is disabled, while immunosuppression works properly) [5].

Influence on the Nervous System

The immediate response to cannabis, e.g. feelings of detachment and relaxation, cheerfulness, and talkativeness, are effects of the high expression of CB1 receptors in the brain and neuronal tissue, the main “target” for cannabinoids. The high number of receptors is also responsible for delayed effects, e.g. psychosis, depression-like condition, problems with memory, and addiction. For example, 16% of marijuana smokers in New Zealand suffered from a depression-like condition, 14% from depression, and 10.5% from dysthymia [6]. Approximately 15% of examined cannabis users were diagnosed with psychotic symptoms, such as hearing voices or having unwarranted feelings of persecution or risk of harm from others [6]. Reilly et al. described the adverse effects of feelings of anxiety, paranoia, or depression (21%) and tiredness and low motivation (21%) found among cannabis users who had taken the drug for at least 10 years [6].

Scientists conclude that cannabinoids also disrupt psychomotor behavior (probably caused by the high level of CB1 receptors in the basal ganglia and cerebellum), disable psychomotor functions, and cause a need for isolation and immobility [7]. Moreover, cannabinoids impede the abilities to drive a vehicle, fly an airplane, and dive (Fig. 3) [8]; marijuana smokers had poor results in tests evaluating hand steadiness, divided attention, sustained attention, and digit-symbol substitution [3].

Impaired memory is another side effect of cannabis consumption. It is believed to be a result of cannabinoids binding to CB1 receptors and inhibiting neurotransmission within the hippocampus, which is responsible for memory. Greek scientists were very successful in testing cannabis users. They focused on the mental abilities of three groups: long-term users (at least 4 joints a week for an average of 15 years), short-term users (an

average of 7 years of use), and nonusers (controls). It was found that long-term users scored low in memory tests, showing learning disabilities and weak capacity to recall information. They were asked to recall lists of 15 words that they had seen earlier. The long-term users averaged seven, short-term users nine, and controls twelve [9].

The addictive property of cannabis is still raising doubts and controversy. Although research results show that marijuana consumption is at first habitual, then desired, and eventually addictive, cannabis-withdrawal syndrome is not as severe as, for instance, heroine-withdrawal syndrome, and this factor may not classify cannabis as a hard narcotic. Jones and Benowitz administered oral THC in doses of 70–210 mg/day to subjects for 30 days and noted a progressive loss of the subjective “high” (feeling of happiness and euphoria). Withdrawal signs were found during the first week of abstinence, when the subjects became very irritable, uncooperative, resistant, and at times hostile. They also became hungry and experienced insomnia. The cannabis-withdrawal syndrome included autonomic effects: changes in heart rate, blood pressure, sweating, and diarrhea. These effects waned in the course of three weeks [6]. In another study, subjects were given oral THC doses of 180–210 mg/day for 10–20 days, roughly equivalent to smoking 9–10 2% THC cigarettes per day. The characteristics of the abstinence period were similar in both cases. The withdrawal symptoms, however, were short lived, as they abated within four days [3].

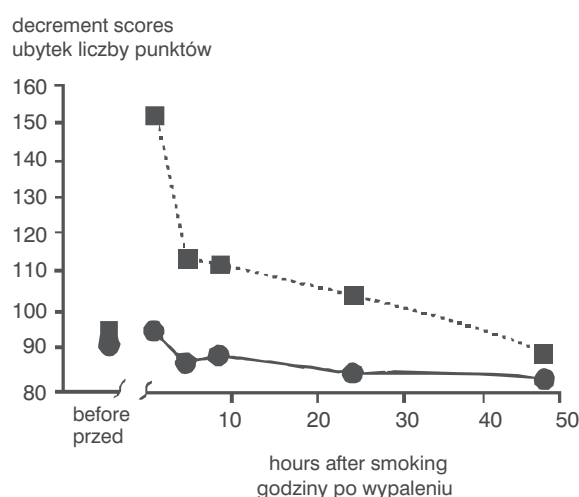


Fig. 3. Effect of smoking a cannabis cigarette containing 20 mg tetrahydrocannabinol (THC) on pilot performance in a flight simulator landing task; - - ■ - - 20 mg THC; - ● - placebo [8]

Ryc. 3. Wpływ wypalenia skręta zawierającego 20 mg tetrahydrokanabinolu (THC) na zdolność pilota do lądowania podczas symulacji lotu; - - ■ - - 20 mg THC; -●- placebo [8]

The above examples and information about the addiction mechanism allow classifying cannabis as a soft narcotic. However, addiction can be regulated by certain prerequisites: the frequency, quantity, and form of administration; genetic factors; the state of health; age and prior drug use; and gender (men are 1.6 times more likely to become drug dependent than women) [3].

Influence on the Reproductive System, Reproduction, and Participation in Teratogenesis

The influence of cannabis on the reproductive system is connected with a reaction that occurs between the cannabinoid receptors and LH and FSH hormones. Both hormones are responsible for sex hormone synthesis (testosterone and estrogen) and the normal functioning of the reproductive organs. In females, the influence of cannabinoids depends on the phase of the ovulatory cycle. Among women who smoked a single marijuana cigarette, a decrease in LH was observed during the luteal phase, whereas no effect was seen on the same hormone in the follicular phase and in the postmenopausal state. Sustained use of marijuana (at least four times per week) may cause alterations in the menstrual cycle, such as oligomenorrhea. An excess of cannabinoids may also impair regular ovulation, acting not only at the LH level, but also directly affecting ovarian granulosa layers [10].

Cannabinoids affect male reproductive organs not only by decreasing sex hormone levels, but also by the presence of functional receptors for cannabinoids in human sperm which influence infertility. Rossato and co-workers from the University of Padua showed that cannabinoids reduce sperm motility by reducing sperm's mitochondrial activity [11]. In addition, Professor Burkman from the University of Buffalo asserts that cannabis causes premature hyperactivation and hypomobility of sperm in the cervix, the place where sperm should be activated. Consequently, sperm is deactivated before it gets close to an egg and is not able to fertilize it. Moreover, scientists noted that the volume and capacity of sperm among long-term smokers is lower than among nonusers [12]. Burkman's studies also revealed that cannabinoids consumed by women can influence men's infertility. When women smoke, the active ingredient of marijuana (THC) appears in their reproductive organs and vaginal fluids. In both experiments conducted by Burkman, sperm exposed to THC acted identically [12].

In 1984, scientists discovered that cannabinoids can cross the placental barrier. They there-

fore proceeded to analyze the consequences of cannabis administration during pregnancy. A few years later they showed that smoking marijuana during pregnancy has a negative influence on the child (fetal hypoxia and exposure to mutagenic factors present in the smoke) [13]. It has also been shown that other ways of cannabis administration (not only smoking) can impair the fetus and cause miscarriage. Normally, after fertilization the egg faces a perilous path from the place of conception in the fallopian tube down into the womb. Proper levels of an endogenous cannabinoid, anandamide, are required for this passage to be completed safely [14]. Cannabinoid administration disrupts the balance in the anandamide level; THC binds to the CB1 receptors, thereby displacing anandamide and boosting its levels present in the oviduct. Impaired oviductal transport, implantation, and ectopic pregnancy are the results of the high level of anandamide [15].

Influence on the Cardiovascular System

The cardiovascular effects of cannabis are largely related to its biphasic effect on the autonomic nervous system. At low or moderate doses, the cannabinoids lead to an increase in sympathetic activity and a reduction in parasympathetic activity, increasing cardiac output and producing tachycardia. These increase blood pressure. At high doses, sympathetic activity is inhibited and parasympathetic activity increased, leading to bradycardia and hypotension. Moreover, vagal stimulation reduces the action potential duration, shortens the atrial refractory period, and produces cellular hyperpolarization. The net result is a reduction in the wavelength of atrial activation, predisposing to the reentrant mechanism of atrial fibrillation [16]. All these effects increase the risk of cardiac infarction, which is as much as eight times higher 30 minutes after smoking marijuana than during periods with no exposure to cannabis (Fig. 4) [17].

Mechanism of Therapeutic Action

Analgesic Action

The perception of pain is controlled by a neurotransmitter system within the central nervous system as well as by endocannabinoids excreted by peripheral tissues. Different cannabinoid receptor subtypes act synergistically: anandamide acts primarily upon the CB1 receptor, whereas palmi-

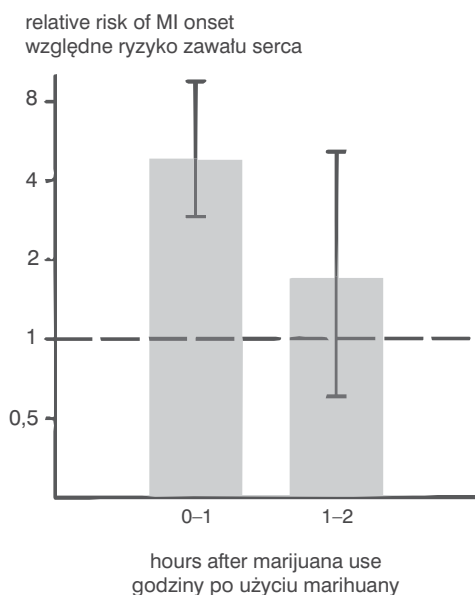


Fig. 4. Relative risk of myocardial infarction onset after smoking marijuana. The dotted line represents the baseline risk during periods of no exposure to marijuana [17]

Ryc. 4. Względne ryzyko zawału serca po wypaleniu marihuany. Linia przerywana oznacza normalne ryzyko zawału serca u osób nieeksponowanych na działanie marihuany [17]

tylethanolamide (PEA) is a CB2 agonist. They both inhibit pain stimulus [3]. The cannabinoids from cannabis act in the same manner.

The human brain contains a larger quantity of CB1 than CB2 receptors; scientists are therefore struggling to produce a medicine which would interact only with the CB2 receptors. They are looking for a formula with more selective biological actions, including analgesia, that would be devoid of psychotropic effects, making it more desirable for patients who wish to be pain-free instead of “high” [18]. There are other medicinal properties of CB2 receptor-selective agonists that make them promising candidates for the treatment of pain: activating the CB2 receptor inhibits acute, inflammatory, and neuropathic pain responses, but does not cause central nervous system (CNS) effects, consistent with the low level of CB2 receptors in the normal CNS. A chain reaction occurs: CB2 receptor activation stimulates the release of the endogenous opioid β -endorphin from keratinocytes, which then acts upon opioid receptors on primary afferent neurons to inhibit nociception [19]. Since cannabimol, isolated from cannabis, binds with much higher probability to the CB2 than the CB1 receptor, researchers see it as a potential remedy which does not demonstrate a psychoactive mode of action [3].

Relieving Neurological Disorder Syndromes

The successive discovery of endogenous cannabinoids and their neuroprotective properties led to a better understanding of the pathomechanism of some neurological disorders and facilitated the invention of effective medications for multiple sclerosis, Alzheimer’s disease, epilepsy, and Parkinson’s disease.

Even though the etiology of multiple sclerosis is still unclear, scientists suppose that disorders in the inflammatory reaction and unbalanced endogenous cannabinoid levels are causes of it [20]. In the opinion of these researchers, endogenous cannabinoids can moderate the inflammatory reaction: a pathological condition increases endogenous cannabinoids that activate neuronal CB1 receptors, modulate ion channels, and inhibit neurotransmission, whereas pathological conditions lead to much slower and sustained (hours to days) increases in endogenous cannabinoids. Specifically, an increase in endogenous cannabinoids activates immune CB2 receptors, which reduce the expression of proinflammatory cytokines and enzymes involved in the generation of free radicals [21, 22]. A chance for people suffering from multiple sclerosis is cannabis, a source of exogenous cannabinoids which can compensate endogenous cannabinoid deficiency. The results of animal tests and clinical trials are very promising: cannabis is able to inhibit the pathological transformation of nerve tissue, inhibit neurodegeneration [20], reduce spasticity [23], and relieve acute neuropathic central pain from sclerotic plaque lesions affecting pain pathways in the central nervous system [24].

The potential use of cannabis in the treatment of Parkinson’s disease has also been discussed recently. It was substantiated by the rich representation of cannabinoid receptors in basal ganglia. The globus pallidus and the substantia nigra pars reticulata contain the highest density of CB1 receptors in the body [25]. In Parkinson’s disease, neurodegeneration and decreased stimulation of the motor cortex by the basal ganglia, which is normally caused by the action of dopamine produced in the substantia nigra, are the main causes of Parkinson’s. Scientists showed that cannabinoids applied *in vivo* increase striatal dopaminergic transmission, probably by increasing neuronal firing in the ventral tegmental area and in the substantia nigra. However, they did not directly affect the release of dopamine *in vitro*, but only depressed both GABAergic and glutamatergic activation [26]. Thus this mechanism is still controversial. Nevertheless, some other properties of

cannabis seem to be much clearer. A scientist from Manchester discovered that cannabinoids can reduce levodopa-induced dyskinesia, a side effect of levodopa, the most frequently applied medication, which increases the level of dopamine in Parkinson's disease. Stimulation of cannabinoid receptors in the globus pallidus reduces GABA transmission and may alleviate dyskinesia [27].

The other neurodegenerative disorder which may be treated with cannabis is Alzheimer's disease. It is characterized by enhanced β -amyloid peptide deposition along with glial activation in senile plaques, selective neuronal loss, cognitive deficits, and decreased levels of CB1 and CB2 receptors, which are responsible for neuroprotection and control of the inflammatory reaction. Scientists from Madrid showed that the administration of exogenous cannabinoids prevents β -amyloid-induced microglial activation, cognitive impairment, and loss of neuronal markers. Cannabinoids also block β -amyloid-induced activation of cultured microglial cells, as assessed by mitochondrial activity, cell morphology, and tumor necrosis factor release [28]. The other cause of Alzheimer's disease is an excessive activity of acetylcholinesterase (AChE), an enzyme responsible for the degradation of acetylcholine and for the induction of aggregation of β -amyloid. Scientists from California demonstrated that delta-9-tetrahydrocannabinol competitively inhibits acetylcholinesterase and also prevents AChE-induced amyloid aggregation (THC binds to the peripheral anionic site of AChE, the critical region involved in amyloidogenesis) [29].

In the second half of the twentieth century, scientists decided to treat epilepsy with cannabis. They did not know about endogenous cannabinoids and their role in neuroprotection. Today, scientists who are knowledgeable in the field corroborate that cannabinoids have anticonvulsant properties. The medicinal properties are based on the activation of presynaptic cannabinoid receptors by cannabinoids, which causes the suppression of presynaptic voltage-gated calcium channels and blockage of calcium currents, the result of which is decreased Ca^{2+} -dependent release of glutamate, the primary excitatory neurotransmitter of the central nervous system [30]. Moreover, the activation of cannabinoid receptors increases K^+ -channel permeability, attenuates neuronal burst, and stabilizes the membrane potential and is an additional factor that contributes to a decreased epileptiform discharge [31].

Cannabis as a Treatment for Vision Disorders

The high level of cannabinoid receptors in the human eye is an implication for the antiglaucoma

properties of cannabis [32]. The main cause of glaucoma is high intraocular pressure, which impairs an optic nerve. Cannabinoids have been proposed to lower intraocular pressure by either central or peripheral effects, but a specific mechanism for this action has never been elucidated. Scientists suppose that cannabinoids may mediate vasodilation in the ciliary body or may reduce noradrenaline release in the eye and the production of aqueous humor [33]. The results of clinical trials are promising: an initial decrease in intraocular pressure was observed in all patients, and the investigators' therapeutic goal was met in four of the nine patients. However, the decreases in intraocular pressure were not sustained [33], and all the patients discontinued the treatment within one to nine months for various reasons (systemic toxicity appears to limit the usefulness of this potential treatment) [34].

Scientists decided to use cannabis in the therapy of diabetic retinopathy, a disease characterized by neurotoxicity and blood-retinal barrier damage. The researchers associated these pathologies with oxidative stress and proinflammatory cytokines, which may operate by activating their downstream target, p38 MAP kinase. El Remessy and co-workers showed that treatment with cannabidiol, a non-psychoactive constituent of cannabis, significantly reduced oxidative stress, decreased the levels of tumor necrosis factor α (TNF- α), vascular endothelial growth factor, and intercellular adhesion molecule-1 and prevented retinal cell death and vascular hyperpermeability in the diabetic retina. The mechanism of cannabidiol's action is based on the inhibition of p38 MAP kinase in the diabetic retina (Fig. 5), without producing psychotropic effects [35].

Cannabis and Supplementary Therapy of Cancer and HIV/AIDS

Cancer and HIV require patients to undergo endless therapies which induce severe side effects such as nausea and vomiting, leading to malnutrition and devastation of the organism. Scientists suppose that emesis is caused by the stimulation of receptors in the central nervous system or the gastrointestinal tract. This stimulation appears to be caused by the drug used in treatment itself or a metabolite of the drug. The mechanism for cannabis's antiemetic action is still unclear. However, the high concentration of cannabinoid receptors in the nucleus of the solitary tract, a brain center important in the control of emesis, suggests that exogenous cannabinoids bind to

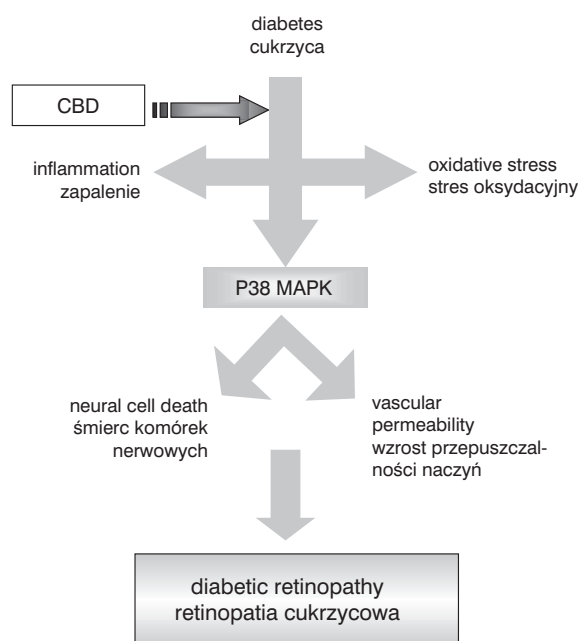


Fig. 5. Influence of diabetes on both oxidative stress and inflammatory mediators [35]

Ryc. 5. Wpływ cukrzycy na stres oksydacyjny i uwalnianie mediatorów zapalnych [35]

receptors and prevent them from binding with drugs and metabolites [3].

THC is an appetite stimulant as well. This property is connected with the presence of cannabinoid receptors in the digestive system, especially in the liver. Hepatocytes express CB1 receptors, the activation of which increases the expression of lipogenic genes and *de novo* fatty acid synthesis, which contributes to the development of diet-induced obesity [36]. Moreover, the hypothalamus, the main organ responsible for the regulation of appetite, is also a molecular target for cannabinoids (the hypothalamus expresses CB1 receptors). Scientists showed that cannabinoids can activate fatty acid synthase (FAS), whereas the inhibition of FAS is a result of profound anorexia. These findings thus suggest that the same molecular pathway is involved in both the central appetitive (CB1 receptor activation stimulates appetite) and the peripheral anabolic effects of cannabinoids (CB1 receptor activation promotes lipogenesis and energy storage) [37].

Cannabis has been considered more frequently in cancer therapy with regard to its proapoptotic properties. It has been found that signal transmission for programmed cell death takes place via cannabinoids receptors, which are a very important link in the induction and transmission of that signal. Cannabinoids, by binding to CB1 and/or CB2 receptors, cause enhanced activity of serine palmitoyltransferase, which

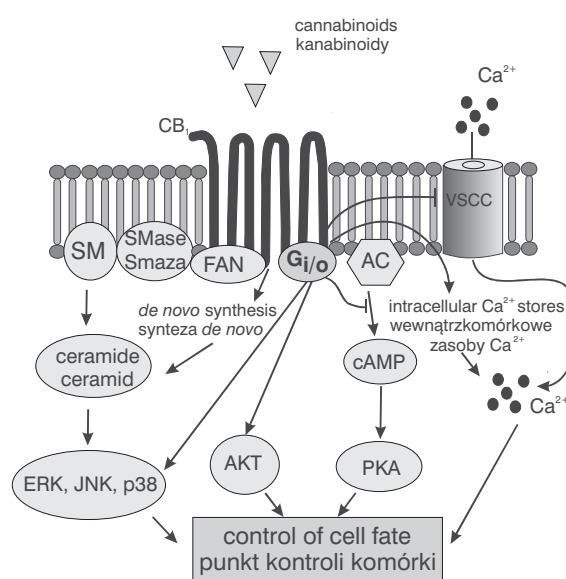


Fig. 6. Signaling pathways involved in the control of cell fate by cannabinoids [39]:

SM – sphingomyelin, SMase – sphingomyelinase, FAN – factor associated with neutral sphingomyelinase activation, ERK – extracellular signal-regulated kinase, JNK – JUN amino-terminal kinase, $G_{i/o}$ – G-protein-coupled receptor, AKT – protein kinase B, AC – adenylyl cyclase, VSCC – voltage-sensitive Ca^{2+} channels, PKA – protein kinase A

Ryc. 6. Ścieżka sygnałowa obejmująca wpływ kanabinoideń na punkt kontroli komórki [39]:

SM – sfingomielina, SMaza – sfingomielinaza, FAN – czynnik związany z aktywacją sfingomielinazy, ERK – kinaza regulująca sygnały zewnątrzkomórkowe, JNK – kinaza amino-końcowego odcinka JUN, $G_{i/o}$ – białko G związane z receptorem, AKT – kinaza proteinowa B, AC – cyklaza adenylova, VSCC – kanał wapniowy zależny od napięcia, PKA – proteinowa kinaza A

catalyses the rate-limiting step in *de novo* ceramide synthesis, a molecule responsible for apoptosis [38]. Moreover, cannabinoids induce the inhibition of adenylate cyclase (cAMP) and modulate the activity of Ca^{2+} and K^{+} channels. Cannabinoids have also been found to modulate several signaling pathways that are more directly involved in the control of cell fate: they stimulate mitogen-activated protein kinases (MAPKs), i.e. the extracellular signal-regulated kinase (ERK) and the stress-activated kinases JUN amino-terminal kinase (JNK) and p38 MAP (Fig. 6.), which have prominent roles in the control of cell growth and differentiation. Cannabinoid receptors are also coupled to the stimulation of the phosphatidylinositol 3-kinase-AKT survival pathway. Activated AKT can phosphorylate and inhibit the nuclear translocation of Forkhead transcription factors, thereby preventing the expression of pro-apoptotic proteins [39].

The antiproliferative and proapoptotic properties of cannabinoids are so far the best researched antitumor qualities with regard to gliomas (a high expression of cannabinoid receptors in glial tissue) and skin cancers (the presence of CB1 and CB2 receptors in the skin and skin tumors). Scientists are considering using cannabinoids especially in the therapy of skin cancers due to the fact that at least two mechanisms may be involved in this action: direct apoptosis of tumor cells and inhibition of tumor angiogenesis. It has been observed that after administration of cannabinoids, the expressions of proangiogenetic factors (VEGF, placental growth factor, and angiopoietin 2) were decreased, which led to impairment of tumor vas-

cularization, reduction of tumor volume, and death of tumoral cells [40].

The authors conclude that there is constant debate whether cannabis should be considered toxic or therapeutic. Perhaps the numerous experiments and studies that are being conducted worldwide to investigate this controversial plant and its influence on the human organism will give the public a better understanding of and information about cannabis. In the opinion of the present authors, popularizing scientifically validated facts about cannabis should be the main focus of the scientific world to avoid misconceptions about cannabis, which seem to be its most common threat.

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