The role of cannabinoids and endocannabinoid system in the treatment of epilepsy

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SUMMARY

Introduction. The treatment of epilepsy is still a major challenge. Despite the introduction of many new antiepileptic drugs, approximately 30% of patients still remain drug resistant. In the absence of a satisfactory therapy outcome, which is sometimes associated with numerous side effects, there is a need for new and effective drugs with low toxicity. Cannabinoids have been shown in preliminary animal model studies and in studies of patients with epilepsy to have antiepileptic activity.

Aim. The aim of this paper is to review current reports on the role of the endocannabinoid system and cannabinoids in the treatment of epilepsy.

Methods. Articles from PubMed and Scopus published up to 2015 concerning the role of cannabinoids and the endocannabinoid system in the treatment of epilepsy are reviewed.

Review and Discussion. Cannabis has been used for thousands of years in the treatment of various diseases. They contain cannabinoids, which act on the endocannabinoid system which regulates many biochemical and physiological processes. By affecting glutamate and gamma-aminobutyric acid (GABA) neurotransmission cannabinoids have the ability to affect seizure threshold. The best known cannabinoid is cannabidiol, which inhibits the occurrence of seizures without causing significant side effects in humans and animals. However, only a small number of double blind, randomized and placebo controlled studies have been published to date.

Conclusions. The role of cannabinoids in the treatment of epilepsy is not well defined because these substances have shown pro-convulsive actions in some animal studies and also there are not many randomized trials performed to date. The existing human data do not support the conclusion that cannabinoids are effective and safe in the treatment of epilepsy, but do encourage further studies on a larger group of patients.

Key words: cannabinoids • cannabidiol • tetrahydrocannabinol • marijuana • epilepsy

INTRODUCTION

Epilepsy is one of the most common neurological disorders which affects about 50 million people in the world (Goldenberg, 2010). According to the 2009 definition of Therapeutic Working Group of the International League Against (ILAE) epilepsy can be considered as drug-resistant in the event of failure of two successive properly selected patient regimens – based on the use of one or more preparation (Kwan et al., 2010). The resistance to treatment entails approximately 20–30% of patients with epilepsy. Its consequence can be worse quality of life and higher mortality. In the absence of satisfactory results of therapy, which is often associated with numerous side effects, there is a need for new, effective and safe drugs with different mechanisms of action.

Recently, cannabinoids arouse particular interest as substances that can modify the course of some neurological diseases in a positive way. Until now the efficacy of the formulations of cannabis in treating the neuropathic pain, nausea and vomiting in cancer, for the

treatment of spasticity in multiple sclerosis and spinal diseases has been demonstrated (Ożarowski et al., 2014). They probably have anti-inflammatory, anticonvulsant, neuroprotective, antipsychotic and sedative activities (Zhornitsky and Potvin, 2012; Gloss and Vickrey, 2014). Perhaps they could find application in the treatment of alcohol and nicotine addiction (Karabowicz et al., 2014). An interesting subject of many researches is the effect of cannabinoids on the proliferation, growth and apoptosis of cells. These properties can cause regression of brain tumors, especially gliomas. They inhibit neurodegeneration processes, which can produce a beneficial clinical effect in Parkinson's disease, Huntington's Chorea, or Tourette's syndrome (Benbadis et al., 2014). Some of the isolated cannabinoids showed anticonvulsant properties in animal models, in particular cannabidiol (CBD) and its propyl derivative – cannabidivarin (CBDV) (Jones et al., 2010; Rymanowski, 2014; Hill et al., 2012).

Sativex, a drug based on cannabis and comprising of a mixture of CBD/tetrahydrocannabinol (THC) at a ratio of approximately 1:1, is approved for the treatment of spasticity in multiple sclerosis in over 20 countries (http://www.gwpharm.com). Another preparation – Epidiolex, a highly purified cannabis extract at a concentration of CBD approximately 98%, is currently being evaluated for the treatment of Lennox-Gastaut and Dravet syndromes, that constitute the so-called catastrophic epilepsies (https://clinicaltrials.gov).

Cannabinoids may have therapeutic potential in the treatment of many diseases, however, because of the actions of interest groups led by the environmentalists which support the legalization of marijuana, the subject entails a heated discussion not only in the world of medicine but also within the media.

AIM

The aim of this paper is to summarize data on the role of the endocannabinoid system and cannabinoids in the treatment of epilepsy.

METHODS

Articles from PubMed and Scopus published up to 2015, concerning the endocannabinoid system and treatment of epilepsy with cannabinoids were identified and reviewed. Keywords used: cannabinoids, cannabidiol, tetrahydrocannabinol, marijuana, epilepsy.

REVIEW OF LITERATURE AND DISCUSSION

Classification and properties of cannabinoids, history of cannabis use

Cannabinoids are organic compounds, which are divided into three groups:

1) phytocannabinoids, such as cannabidiol and Δ9-tetrahydrocannabinol,
2) endocannabinoids (e.g. anandamide and 2-arachidonylglycerol), and
3) synthetic cannabinoids (e.g. WIN55212-2, CP55940 or HU210).

Phytocannabinoids probably only occur naturally in plants of the species *Cannabis*. Endocannabinoids play a significant role in the human body, taking part in the regulation of many physiological phenomena, including immunological and hormonal phenomena (Karabowicz et al., 2014).

Hemp (*cannabis*) comes from Central Asia and is one of the oldest medicinal plants. Historical archives show that it has been used in the treatment of various diseases for approximately 5000 years (Mechoulam, 1986). Hemp was also used for the production of rope, fabric and paper. Emperor Shen Nong, the father of Chinese medicine (2700 BC), advocated marijuana in the treatment of rheumatism, malaria, constipation, menstrual disorders and beriberi. In India the use of cannabis for medicinal and probably religious purposes began approx. 1000 BC. These plants were used as analgesics, anticonvulsants, sedatives, hypnotics, antispasmodic, digestive and as appetizing aids (Zuardi et al., 2006). The tradition of using cannabis was transferred from India to Persia, Assyria and the whole Middle East and Africa. In Europe marijuana appeared most likely thanks to contemporary migration of peoples and trade. The precise time at which it appeared on this continent is not known (Jędrzejko, 2011).

The anticonvulsant properties of cannabis have been known for centuries. Between 9th and 10th century BC the Arabic scholar Al Mayusi described its anticonvulsant effect after nasal application of the juice from the leaves of *Cannabis sativa*. Persian physician Al-Badri, in the 15th century BC, described the efficacy of cannabis in the treatment of convulsions during its regular application (Lozano, 2001; Mechoulam, 1986). In the 19th century several articles on the efficacy of cannabis extract in controlling severe seizures were pub-

lished – e.g. O'Shaughnessy, 1842; Shaw, 1843 (Cunha et al., 1980). Irish physician William O'Shaughnessy in forty pages described the healing properties of cannabis, including the ability to inhibit seizures (O'Shaughnessy, 1842). In this way, hemp was introduced to the western pharmacopoeia (Mikuriya, 1969).

There are several varieties of *Cannabis* – *C. sativa*, *C. indica* and sometimes *C. ruderalis*. *Cannabis sativa* contains more than 500 different chemical compounds, of which approx. 100 are the cannabinols (Radwan et al., 2009; Hill et al., 2012; Szaflarski and Bebin, 2014). An important ingredient in cannabis is Δ9-tetrahydrocannabinol (Δ9-THC), which has psychoactive properties. This substance was first described in 1964 by a group of scientists from the Hebrew University in Jerusalem under the leadership of Gaoni and Mechoulam. Another important *Cannabis* compound is cannabidiol – isolated in the 1940's. Its structure was determined in 1963 (Gloss and Vickrey, 2014). The tetrahydrocannabinol content in a plant depends on genetic properties, age, growing conditions, the process of collection, the type of soil and the climate. The most common cannabis products include: 1) marijuana, which is drought leaves and inflorescence (approx. 0.5%–4% THC) and 2), hashish (15% THC), dried and compressed resin extracted from plants. Hashish oil (30% THC) is also available on the drug market. In specially genetically modified plants tetrahydrocannabinol content can be very high. In the Netherlands, a variety of cannabis called Netherweed is grown, containing approximately 20% THC (Jędrzejko, 2011; Szukalski, 2005).

Other important compounds isolated from *Cannabis* are: cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabidivarin (CBDV) (Izzo et al., 2009; Russo, 2011; Jones et al., 2010).

Tetrahydrocannabinol, which has psychoactive properties, is a partial agonist of the CB1 and CB2 receptors (Pertwee, 2008; Szaflarski and Bebin, 2014). In the central nervous system it has the ability to both stimulate and inhibit the secretion of neurotransmitters. It can activate or block the CB1 receptors, which explains the anticonvulsant and proconvulsant properties in different models of epilepsy (Pertwee, 2008; Wallace et al., 2003).

The mechanism of the action of cannabidiol is not known (Wallace et al., 2003; Santos et al., 2015).This compound has a very weak affinity for the CB1 receptors, it affects other mechanisms – it is the antagonist of 5-hydroxtryptamine receptor (5HT1α), N-methyl-D-aspartate receptor (NMDA) and GABA receptors. It inhibits the reuptake of adenosine, serotonin, dopamine, GABA, norepinephrine (Szaflarski and Bebin, 2014; Maa and Figi, 2014; Agar, 2015). Other receptors associated with CBD that are putative endothelial cannabinoid receptors (Cbe), are paroxisome proliferator-activated receptors gamma (PPAR-γ), alpha adrenergic receptors and opioid (μ) receptors (Gloss and Vickrey, 2014; Stanley et al., 2015). Cannabidiol may act indirectly on CB1 receptors by inhibition of fatty acid amide hydrolase activity (Stanley, 2015). It is the enzyme responsible for the degradation and destruction of anandamide – endocannabinoid that through the affinity to the CB1 receptors compete with THC for binding sites. Therefore, cannabidiol causes an increase of N-arachidonylethanolamine (AEA), thereby reducing the psychoactive effect of THC in the preparations of the CBD, causing their better tolerability. These compounds may act synergistically in the treatment of pain, inflammation, epilepsy and cancer (Russo, 2011).

Endocannabinoid receptors, endocannabinoid system

Substantive research on the endocannabinoid system began in 1988, after the isolation of cannabinoid receptors from the rat's brain. They are a part of the endocannabinoid system that also includes endogenous ligands anandamide (AEA) and 2-arachidonylglycerol (2-AG), as well as transporters and enzymes involved in the biosynthesis and degradation (Pertwee et al., 2010). The endocannabinoid system is involved in many physiological processes (Pacher, et al., 2006; Karabowicz et al., 2014).

So far known cannabinoid receptors CB1 and CB2 close-coupled to G-proteins – are activated by endocannabinoids, which are emitted on the request in response to neuronal agitation (Lutz, 2004). This leads to inhibition of extracellular calcium influx into the cytoplasm, which in turn blocks the production of cyclic adenosine monophosphate (cAMP).

CB1 receptors, which are responsible for the psychotropic activity of THC, are mainly located at the ends of CNS neurons, and to a lesser extent in the peripheral system. Most are present in the hippocampus, cerebellum, striatum and basal ganglia (Ameri, 1999; Szaflarski and Bebin, 2014). They have also been identified in the internal organs, tonsils and skin (Karabowicz et al., 2015). Postsynaptic increase in intracellular calcium induced by neurotransmitters can cause the biosyn-

thesis and release of endocannabinoids in the synapse. Activation of CB1 receptors inhibits the release of, inter alia, glutamate and GABA – it is important in modulating the seizure threshold (Pertwee, 2008).

CB2 receptors were mainly found in immune cells, neurons of peripheral terminals, microglia and in the cerebral vascular endothelium. They have an effect on the cardiovascular system and processes of cellular immunity, also they regulate the secretion of cytokines and the migration of immune cells (Sugiura and Waku, 2002).

Endocannabinoids are synthesized in neurons of both GABA and glutamate; by the stimulation or inhibition of transmission of the transmitters they can cause a pro- and anti-convulsant effect (Maa and Figi, 2014).

The high density of CB1 receptors in the cerebral cortex, basal ganglia, hippocampus and cerebellum is associated with the impact of cannabinoids on the seizure threshold and adverse effects on memory processes and cognitive and motor skills. A small number of CB1 receptors are located in the brainstem, medulla and thalamus and is the reason that relatively high doses of Δ9-THC are associated with low toxicity (Herkerham et al., 1990; Szukalski, 2005).

The existence of other cannabinoid receptors cannot be excluded. The GPR 55 receptor associated with G protein is considered by some researchers to be the third cannabinoid receptor (Brown, 2007; Ryberg et al., 2007). However, for many researchers, it is not classified to any family of receptors and is called the orphan receptor. GPR 55 has similar structure to the cannabinoid receptors, it can interact with agonists of CB1/CB2, as well as other ligands (Shore and Reggio, 2015).

Cannabinoids in animal models

Except for cannabidiol and THC, other ingredients of cannabis (cannabinol, kannabidivarin and tetrahydrocannabidivarin) have also shown anticonvulsant properties in animal models (Gloss and Vickrey, 2014; Jones et al., 2012). Wilkinson et al. (2003) reported that THC-free extract, although devoid of antispastic properties, still had anticonvulsant characteristics. Cannabidiol inhibited the occurrence of tonic-clonic seizures in mice in models of acute seizures induced by the maximal electroshock (MES). It was also active in models based on the inhibition of GABA, with picrotoxin, isoniazid, bicuculline, pentylentetrazol (PTZ) and 3-mercaptopropionic acid (Hill et al., 2012). CBD has shown anticonvulsant properties in the pilocarpine model of temporal lobe epilepsy, the penicillin model of partial seizures in rats (Jones et al., 2010), electrical kindling (Turkanis et al., 1979) and the audiogenic model (Consroe and Wolkin, 1977). There was no inhibition of seizures induced by strychnine (Consroe et al., 1982) and secondarily generalized seizures induced by cortical implantation of cobalt in the model of chronic epilepsy (Colasanti et al., 1982). Tetrahydrocannabinol was effective inter alia in models with MES, PTZ, strychnine, nicotine and in the model of temporal lobe epilepsy (Devinsky et al., 2014).

Preclinical studies show that the CBD and other cannabinoids are effective in models of acute seizures, but there are little data on their effectiveness in chronic epilepsy models that are most useful in testing drugs (Loscher, 2002).

Studies with the use of cannabinoids in human epilepsy

To date only a small number of clinical trials of cannabinoids in the treatment of epilepsy have been published. In the "Cochrane Systematic Review" (Gloss and Vickrey, 2014) only four studies with blinded, randomized, placebo-controlled study design were identified: Mechoulam (1978), Cunha et al. (1980), Ames and Cridland (1985), Trembly and Sherman (1990). They are summarized in table 1.

Summarizing the above trials, it must be concluded that the study group was small (up to 15 people). Two studies were presented in an incomplete form (abstract and letter to the editor). There was no toxicity or significant side effects at doses of 200–300 mg of CBD for up to several months. The most common side effect was somnolence.

The American Academy of Neurology analyzed the existing publications (1948–2013) on the use of cannabis preparations in treating various neurological disorders. The results indicate a likely effectiveness in reducing spasticity in multiple sclerosis and inefficiencies in the treatment of dyskinesias induced by levodopa. The role of cannabis preparations in the treatment of epilepsy, chorea and tics remains unclear (AAN Subcommittee Koppel et al., 2014).

M. Hamerle et al. conducted an interesting study on people suffering from epilepsy who had experienced the use of illicit drugs; both cannabis and non-cannabis drugs. Cannabis was used by the group consisting of 310 patients with epilepsy, from whom 13 were active cannabis users and 297 were non active cannabis

Table 1. Controlled study evaluating the anticonvulsant effects of cannabinoids in humans

Study	Number of patients	Type of study	Product and dosage	Efficacy	Adverse effects
Mechoulam and Carlini (1978)	9 adults treatment-resistant epilepsy	Randomized and blinded study	CBD 200mg/day for 3 months	3/4 CBD and 0/5 placebo improved	No toxicity
Cunha et al. (1980)	15 adults treatment-resistant temporal lobe epilepsy	Double-blind, placebo-controlled trial	CBD 200–300 mg/day for 3–18 weeks	4/8 CBD full seizure control, 3/8 CBD partial improvement 1/8 placebo improved	Somnolence
Ames and Cridland (1986)	12 adults group CBD: 6 group placebo: 6	Randomized and blinded. This was a letter to the editor, limited information	CBD 200–300 mg/day	No significant change to seizure incidence	Somnolence
Trembly and Sherman (1990)	10 or 12 adults	Randomized and blinded. Results presented at conference, limited information	CBD 300 mg/day	Significant improvement	No toxicity

Data based on articles (Mechoulam and Carlini, 1978; Cunha et al., 1980; Trembly and Sherman, 1990), letter to the editor (Ames and Cridland, 1986) and complemented with the publication Gloss and Vickrey, 2014.

users. The results show that in the vast majority of cases of cannabis consumption there was no affect significant effect on epilepsy (Hamerle et al., 2014).

Currently, there is too little research proving that cannabinoids are effective in the treatment of epilepsy. Only performing double-blind, placebo-controlled, randomized clinical trials with one or several cannabinoids can provide reliable information on their safety and efficacy (Friedman and Devinsky, 2015).

Anecdotal reports

Among the Facebook community of parents of children suffering from severe epilepsy syndromes (such as Dravet, Doose and Lennox-Gastaut), a survey consisting of 24 questions concerning the clinical picture of epilepsy and the use of cannabis preparations rich in CBD (without precisely defining the product composition, dosage) was conducted. Inclusion criteria (diagnosis of epilepsy and current use of cannabis) entailed 19 people. In the survey, 84% of respondents (16/19) stated that was a reduction in number of seizures in their children, 42% (8/19) reported a reduction in the frequency of attacks by more than 80% and in 2 patients (11%) seizures did not appear. Some parents reported improved attention, mood, and sleep in children, some experienced minor side effects such as fatigue and sleepiness (Porter and Jacobson, 2013).

Marijuana addiction and epilepsy

A separate theme is the dependence of severity of epilepsy patients who smoke marijuana. The data are inconclusive and sometimes contradictory. In a study (Ng et al., 1990) smoking marijuana reduced propensity to first seizure in men. Other findings may be based on the results of the interview carried out among 215 patients with epilepsy who smoked marijuana (Gordon and Devinsky, 2001). Among this group of respondents, 90% stated no association between the use of cannabis, and the impact on the frequency or severity of seizures. In some patients, with primary generalized epilepsy, marijuana exacerbated the illness. Unfortunately, both of these studies do not include reliable data on the regular use of anti-epileptic drugs and patient compliance.

A single publications describe the possible proconvulsive effects of marijuana after withdrawal. In the case of two patients treated for refractory epilepsy with chronic useing of marijuana, smoking cessation resulted in the numerous seizures occurring within 24 hours (Hegde et al., 2012).

The above-mentioned studies highlight how ambiguous the role of cannabinoids in epilepsy is. We do not know their interactions potential with other drugs. Enhancing the anticonvulsant effects by the CBD for older antiepileptic drugs, such as phenobarbital and phenytoin, while decreasing the efficacy of clonazepam and ethosuximide has been observed (Consroe, 1977)

ADVERSE EVENTS OF CANNABINOIDS

There is little published data on the adverse effects caused by medical preparations of cannabis. However,

numerous references highlight the negative health effects of smoking cannabis, especially with chronic use. These effects are probably related with the action of THC, which causes mood disorders, depression, anxiety and psychosis. There are also reports of psychotic episodes after a single use of marijuana (Dąbrowska et al., 2012). Cases of psychological and physical addiction during chronic use have been described (Hall and Dagenhardt, 2009). Smoking cannabis can cause: dry mouth, conjunctivitis, mood disorders, dizziness, dysphoria, impaired memory, hallucinations, psychomotor retardation, amotivational syndrome, tachycardia and hypotension (Gordon and Devinsky, 2001). Cardiovascular effect can be particularly troublesome among those who have an earlier diagnosed of heart problems (Dąbrowska et al., 2012).

Reports of a potential association of the use of cannabis with cerebrovascular incidents are disturbing. Dozens of cases of stroke in people addicted to marijuana have been described. However, risk factors for cerebrovascular diseases have not been identified. The possible pathogenic effects of cannabis include an antihypertensive effect and pro-arrhythmia, which could trigger toxic and immunological mechanisms of damaging within the brain. The consequence of these processes may be multifocal cerebral vasospasm. In 2013 Wolff and colleagues published a prospective study conducted among 48 people smoking marijuana. Study patients underwent magnetic resonance angiography (MRA), which revealed the existence of the characteristic highlighted above, the pattern of multifocal cerebral artery stenosis – *multifocal intracranial stenosis* (MIS). A feature of this angiopathy is the location of many cerebral changes are reversible after discontinuation of cannabis. In the case of young people with stroke, smoking marijuana, without the identification of other risk factors, – MRA studies should be considered.

SUBJECTIVE OPINIONS ON THE USE OF CANNABIS IN EPILEPSY

An interesting result of a survey conducted among 776 people was published by Mathern et al. in 2014. They presented the differences in expectations in relation to the preparations of cannabis therapy in patients with refractory epilepsy. Nearly all patients and the public were of the opinion that there was sufficient evidence of the efficacy and safety of this therapy and would recommend its use. Clearly less trust in this form of therapy occurs among general physicians, basic researchers, nurses, and other medical personnel – about 83% would recommend treatment with cannabinoids.

In the group of epileptologists and neurologists only 50% would advise using this therapy for severe cases of refractory epilepsy. These results, in the face of the current lack of substantial evidence on the safety and efficacy of cannabis, show how large an impact of the environmental and media lobbying for the legalization of marijuana for the public review is.

CONCLUSIONS

Cannabinoids, substances naturally present in cannabis, probably regulate many biochemical and physiological processes. By stimulating or inhibiting the synthesis of GABA, glutamate and other neurotransmitter, they may affect the seizure threshold and the occurrence of seizures. Several of these compounds showed anticonvulsant properties in experimental animal models. Cannabidiol inhibited seizures in models of acute seizures, there is less data concerning the use in chronic epilepsy models. Tetrahydrocannabinol in preclinical animal studies was associated with both pro- and anticonvulsant effects.

Unfortunately, not many randomized, blinded and controlled studies of cannabinoids in the treatment of epilepsy have been undertaken. Cannabidiol was mainly used to provide data on small groups of patients in a short period of observation. It cannot be ruled out that to achieve a good clinical effect, apart from the CBD, the presence of the other ingredients of cannabis is necessary. An important issue is therefore the precise optimal composition, standardization and certification of medicinal preparations. Significant issues are also bioavailability, pharmacokinetics of tested substance and interactions with other drugs.

In conclusion, it can be said that there is little evidence regarding the safety and efficacy of cannabinoids in the treatment of epilepsy. Perhaps, they constitute a new therapeutic path, but it requires an execution of properly designed studies over a long period of time and on a larger group of patients.

CONFLICT OF INTEREST

Doctor Jacek Gawłowicz and doctor Monika Pędracka are involved in planning randomized controlled trials of CBD supplied by GW Pharmaceuticals: The study to investigate the efficasy and safety of Cannabidiol as adjunctive treatment for seizure associated with Lennox-Gastaut Syndrome in Children and Adults.

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