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FUTURE PROSPECTS FOR CANNABINOIDS AND ENDOGENOUS CANNABINOID SYSTEM IN THE EPILEPTIC BRAIN – A SHORT OVERVIEW OF THE LATEST SCIENTIFIC REPORTS

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CONTENTS

Summary	857
Cannabinoids - a new potential in medicine	857
Endogenous cannabinoid system in experimental epilepsy	858
Cannabinoids and epilepsy: evidence from in vitro studies	858
Cannabinoids in epilepsy: evidences from in vivo studies	860
Conclusions	861
References	861

SUMMARY

Effective treatment of epilepsy has been the main therapeutic challenge for the past several years. The biggest problem is refractory epilepsy. Despite the fact that the problem of seizure resistance to monotherapy affects approximately 30% of epileptic patients, clear algorithms of drug selection have not been yet fully developed. Considering the treatment with two or more antiepileptic drugs (AEDs), it is of particular importance that the AEDs should be selected based on their high anticonvulsant properties, as well as a high level of neuroprotection and minimal side effects. For the last several years many researchers focused their efforts on looking for new potent natural and synthetic anticonvulsants. Results from studies of some natural cannabinoid compounds as well as synthetic cannabinoids clearly prove the anticonvulsive properties of these substances in various in vitro and in vivo models of epilepsy. This review summarizes the latest experimental data concerning the potential significance of the endogenous cannabinoid system and cannabinoids in the treatment of epilepsy.

Key words: Endogenous cannabinoid system – Cannabinoids – Animal model of epilepsy

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CANNABINOIDS - A NEW POTENTIAL IN MEDICINE

The endogenous cannabinoid system consists of neuromodulatory lipids and their receptors (endogenous arachidonate-based lipids, enzymes metabolizing the endocannabinoids, cannabinoid CB₁/CB₂ receptors and G protein-coupled receptors) in the brain. They play a key role in a variety of physiological processes including appetite, pain sensation, mood and memory. On the basis of results obtained over the last several years, researchers have focused on all three main groups of cannabinoids: endocannabinoids, synthetic cannabinoids and phytocannabinoids.

Endocannabinoids are endogenously produced compounds that influence cannabinoid cell receptors, which repress neurotransmitter release in the brain. Phytocannabinoids are mainly found in cannabis. Synthetic cannabinoids are manufactured chemically. Endocannabinoids are natural messengers in the body that help regulate many biological functions. In their chemical structure they are similar to the active compounds in marijuana. The main endocannabinoids (endogenous cannabis-like substances) are small molecules derived from arachidonic acid, anandamide (AEA) and 2-arachidonoylglycerol (2-AG). They bind to a family of G protein-coupled receptors, of which the cannabinoid CB₁ receptor is densely distributed in areas of the brain related to motor control, cognition, emotional responses, motivated behavior and homeostasis (1). Additionally, the cannabinoid CB₁ receptors are found to be highly expressed at the terminals of central and peripheral neurons where they regulate neurotransmitter release and psychoactivity (2). It has been suggested that modulators of the cannabinoid system activity could be a therapeutic tool for the treatment of many neurodegenerative diseases (3). Results of recent studies strongly support therapeutic properties of cannabinoids in many diseases, including the treatment of pain, affective and neurodegenerative disorders, gastrointestinal inflammation, obesity and related metabolic dysfunctions, cardiovascular conditions and liver diseases (4, 5). Cannabinoid treatment alleviates the symptoms of multiple sclerosis by reducing pain and sleep disturbances, and improving the general wellbeing (6). In in vivo studies in rats, CB₁ receptor agonists pre-

vented cognitive impairment and microglial activation induced by intracerebroventricular injection of β -amyloid protein (7). Aso et al. (8) indicated that arachidonyl-2'-chloroethylamide (ACEA), a highly selective cannabinoid CB₁ receptor agonist, protects neurons and reduces cognitive impairment in transgenic mice. Moreover, the phytocannabinoid Δ^9 -tetrahydrocannabivarin (Δ^9 -THCV) treatment indicated neuroprotective effects in animal models of Parkinson's disease (9). In addition, cannabinoids were found to modulate brain reward systems closely involved in stimulants addiction. Oliere and collaborators (10) provided evidence that the cannabinoid system could be explored as a potential drug discovery target for treating addictions across different classes of stimulants. According to recent data, endocannabinoids regulate memory processes differentially, depending on the level of emotional arousal of the subject like a buffering system that shapes the effects of environmental context and stress on cognitive processes (11). Hence, all this evidence clearly confirms the tremendous therapeutic properties of endocannabinoids.

ENDOGENOUS CANNABINOID SYSTEM IN EXPERIMENTAL EPILEPSY

All types of cannabinoids (plant-derived, synthetic or endogenous cannabinoids) are known to act through two cannabinoid receptors, CB₁ and CB₂ (12, 13) (Table I). Additionally, some cannabinoids (AEA or the endocannabinoid/endovanilloid *N*-arachidonoyl dopamine) may interact with other receptors, such as the transient receptor potential TRPV1 channel (14), or the G protein-coupled receptor 55 (GPR55) (15).

Recent studies have advanced our understanding of the endogenous cannabinoid system and renewed interest in cannabinoids as a potential treatment for epilepsy. The endogenous cannabinoid system is rapidly activated after seizure activity, despite the fact that little is known about the molecular mechanisms underlying the role of the cannabinoid system in epilepsy.

Although *Cannabis sativa* is one of the highly promising plants, known to reduce seizures in patients suffering from epilepsy (16), it should be mentioned that preparations obtained from this herb possess addictive and psychoactive properties, which excludes them

from being used as an anticonvulsant treatment (17). Evidence accumulated over the last few years has proved that the cannabinoid system plays an important role in the protection against many central nervous system diseases, including epilepsy (18-24).

CANNABINOIDS AND EPILEPSY: EVIDENCE FROM IN VITRO STUDIES

Based on the results obtained over the last several years, researchers have focused on all three main groups of cannabinoids: endocannabinoids, synthetic cannabinoids and phytocannabinoids.

Endogenously occurring cannabinoids, like AEA, have already been proven to manifest pro- and anticonvulsant properties (Table II). Results obtained almost 10 years ago by Al-Hayani (25) indicate that in the presence of picrotoxin (that caused a small increase in the amplitude of the first population spike PS1, and caused epilepsy by introducing a second or multiple population spikes PS2), AEA reduced the amplitude of both the PS1 and the PS2, thus reducing the epilepsy in the rat hippocampal slices.

An interesting group with strong anticonvulsant properties is that containing synthetic cannabinoids. WIN-55212-2 mesylate, a non-selective cannabinoid CB₁ and CB₂ receptor agonist, was shown to produce a dose-dependent anticonvulsant effect against both spontaneous recurrent epileptiform discharges and status epilepticus in the hippocampal neuronal culture models of acquired epilepsy and status epilepticus (19). Desphande and coworkers (20) evaluated the role of CB₁ receptor-dependent endocannabinoid synaptic transmission towards preventing the development of status epilepticus-like activity in the well-characterized hippocampal neuronal culture model of acquired epilepsy using the CB₁ receptor antagonists: SR-141716A (rimonabant) and AM-251. According to the results, development of continuous epileptiform activity, resembling electrographic status epilepticus was observed, whereas the control neurons with CB₁ receptor antagonists did not produce status epilepticus or hyperexcitability. On the contrary, 2-AG and methanandamide clearly produced dose-dependent and CB₁ receptor-dependent inhibition of status epilepticus as produced by low magnesium in hippocampal neuronal culture (26). Moreover, it was found that prolonged exposure to WIN-55212-2 mesylate causes

Table I. Cannabinoid CB₁/CB₂ receptor mechanism of action for selected cannabinoids.

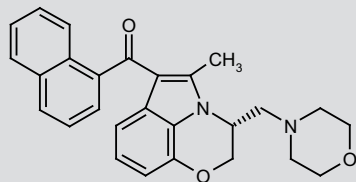
Type of cannabinoid	Name of cannabinoids	Mechanism of action	Source
Endocannabinoids	AEA	CB ₁ /CB ₂ receptor agonist	(24, 25)
	AM-251	CB ₁ receptor antagonist	(20)
	2-AG	CB ₁ receptor agonist	(20, 31)
	Methanandamide	CB ₁ receptor agonist	(20)
Phytocannabinoids	CBD	CB ₁ receptor agonist/CB ₂ receptor antagonist	(45)
	CBDV	CB ₂ receptor agonist	(31)
	Δ^9 -THCV	CB ₁ receptor agonist	(30, 43)
Synthetic cannabinoids	WIN-55212-2	CB ₁ /CB ₂ receptor agonist	(24, 35)
	ACEA	CB ₁ receptor antagonist	(23, 36)
	Rimonabant	CB ₁ receptor antagonist	(24)

AEA, anandamide; 2-AG, 2-arachidonoylglycerol; ACEA, arachidonyl-2'-chloroethylamide; CBD, cannabidiol; CBDV, cannabidivarin; Δ^9 -THCV, Δ^9 -tetrahydrocannabivarin.

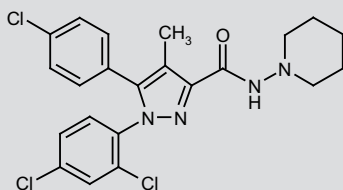
Table II. Anticonvulsant effect of cannabinoids: *in vitro* and *in vivo* studies.

Specimen or cell culture	Study	Endocannabinoids	Synthetic cannabinoids	Phytocannabinoids
Rat hippocampal slices	Model of epileptiform activity	AEA (25)	HU-210 (27)	CBD (28, 31) CBDV (30, 31) Δ^9 -THCV (29)
Rat hippocampal neurons	Neuronal model of acquired epilepsy/ status epilepticus	AM-251 2-AG Methanandamide (20)	WIN-55212-2 (19, 26)	
Mice	Maximal electroshock- induced seizure model (MES)		ACEA (21, 32) WIN-55212-2 (22)	CBDV (30) CBD (41)
Mice	Audiogenic seizures			CBDV (29)
Rats	Pentylenetetrazole-induced seizure model		ACEA (38)	Δ^9 -THCV (29) CBDV (30) CBD (28)
Rats	Amygdala kindling		WIN-55212-2 (38)	
Rats	Pilocarpine model of epilepsy			CBDV (29) CBD (40)
Mice	Pentylenetetrazole-induced seizure model		WIN-55212-2 (33) ACEA (23)	CBD (41)
Mice	6Hz psychomotor seizure model		WIN-55212-2 (36)	
WAG/Rij rats	Genetic model of absence epilepsy	AEA (24)	WIN-55212-2, SR-141716A (24)	
Rats	Penicillin-induced seizures	AM-251 (37)	ACEA (37)	CBD (40)

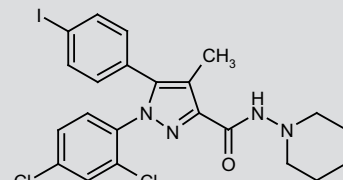
See Table I for abbreviations.



WIN-55212-2



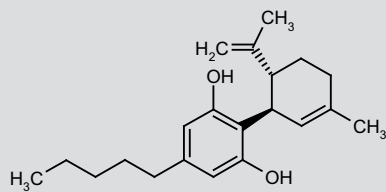
Rimonabant



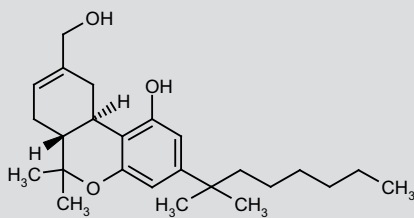
AM-251

downregulation of the CB₁ receptor and the development of tolerance to its anticonvulsant effects in the hippocampal neuronal culture model of acquired epilepsy (27). Another synthetic cannabinoid, HU-210, was proved to reduce kainate-induced synchronized population burst firing in rat hippocampus (28).

Recent data from *in vitro* studies also indicate a pronounced effect of phytocannabinoids in seizures. Jones and coworkers (29) examined the antiepileptiform and antiseizure potential of cannabidiol (CBD) using *in vitro* Mg²⁺-free and 4-aminopyridine (4-AP) models of epileptiform activity in hippocampal brain slices. It was observed that CBD decreased local field potentials, burst amplitude, burst



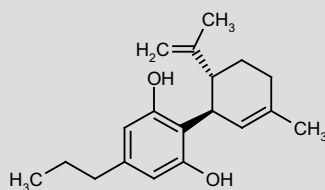
Cannabidiol



HU-210

duration and increased burst frequency. Subsequent psycho-active component of *Cannabis*, Δ^9 -THCV was shown to significantly reduce burst complex incidence and the amplitude and frequency of paroxysmal depolarizing shifts in an in vitro piriform cortex brain slice model of epileptiform activity. Furthermore, slices pretreated with Δ^9 -THCV prior to induction of epileptiform activity exhibited significantly reduced burst complex incidence and paroxysmal depolarizing shift peak amplitude (30).

Cannabidiol (CBD), a non-psychoactive phytocannabinoid, was shown to significantly attenuate status epilepticus-like epileptiform local field potentials induced by 4-aminopyridine and Mg^{2+} -free con-



Cannabidiol

ditions in rat hippocampal brain slices (31). Furthermore, results obtained by Iannotti and coworkers (32), studying the evaluation of the CBDV and CBD on the TRPV1 channels in vitro clearly showed that both substances activate and desensitize the TRPV1 channels, which could be a potential for the treatment of neuronal hyperexcitability.

CANNABINOIDS IN EPILEPSY: EVIDENCES FROM IN VIVO STUDIES

Similar to the results presented from in vitro studies, experimental data from different animal models of epilepsy clearly indicate anticonvulsant properties of all three groups of cannabinoids.

Synthetic cannabinoids and phytocannabinoids are the subject of interest for many researchers. WIN-55212-2 mesylate and ACEA seem to manifest strong anticonvulsant properties in various animal models of epilepsy either injected alone or in combination with antiepileptic drugs (AEDs) (21-23, 33-35). WIN-55212-2 mesylate was shown to reduce the frequency of spontaneous and tetrodotoxin-resistant excitatory postsynaptic currents in mice with temporal lobe epilepsy (35). Additionally, in the same study, two endocannabinoids (AEA and 2-AG) were proved to have anticonvulsant properties (35). Antiepileptic activity of WIN-55212-2 mesylate in combination with several classical AEDs was presented in the mouse maximal electroshock seizure (MES) and pentylenetetrazole (PTZ)-induced seizure models; however, these combinations proved to be toxic in behavioral tests, which precludes them from being used in the therapeutic protocols for resistant epilepsy treatment (22, 34). Results from subsequent studies with WIN-55212-2 mesylate combined with several selected second-generation AEDs (lamotrigine, pregabalin and topiramate) indicate beneficial anticonvulsant pharmacodynamic interactions in the MES-induced tonic seizure test (36). Moreover, WIN-55212-2 mesylate in combination with clonazepam, phenobarbital and valproate was shown to be synergistic in the mouse 6 Hz-induced psychomotor seizure test (37).

Kozan and coworkers (38) proved that intracerebrovascular injection of the synthetic cannabinoid ACEA, at a dose of 7.5 μ g, significantly decreased the frequency of penicillin-induced epileptiform in rats, whereas the CB₁ receptor antagonist AM-251 reversed the anticonvulsant action of ACEA. Similarly, a synthetic cannabinoid ACEA administered either alone or with phenobarbital enhanced the anticonvulsant action of phenobarbital with a lack of pharmacokinetic interaction and no acute adverse effects in the mouse MES-induced seizure model (21). In a different study, ACEA significantly increased the anticonvulsant activity of several classic AEDs, such as phenobarbital, ethosuximide and valproate in PTZ-induced seizure test in mice, although only the interaction of phenobarbital with ACEA proved to be pharmacodynamic in nature (23).

Results obtained by Naderi and coworkers (39) showed a relationship between L-type Ca^{2+} channels and anticonvulsant effect of ACEA. It was found that ACEA significantly increased an acute PTZ-induced seizure threshold in rats, whereas ACEA in combination with L-type Ca^{2+} channel blocker (verapamil) attenuated the protective effect of the cannabinoid against PTZ-induced seizure. Moreover, in the same study, WIN-55212-2 administered alone exhibited an anticonvulsant effect in amygdala-kindled rats. Similarly as the combination of ACEA and verapamil, co-administration of WIN-55212-2

mesylate and verapamil attenuated the protective properties of WIN-55212-2. Interesting results were obtained in the following studies using ACEA, WIN-55212-2 mesylate and URB-597 (a fatty acid amide hydrolase [FAAH] inhibitor enzyme inhibitor) in PTZ-induced seizures in rats. WIN-55212-2 (in a dose of 1 mg) and ACEA (in doses of 1-4 mg) reduced the threshold for myoclonic seizures and enhanced epileptiform EEG activity-typical pro-convulsive effects, whereas URB-597 (1 mg/kg) had an anticonvulsive effect, as it increased the threshold for the occurrence of minimal seizures and reduced EEG epileptiform activity, which suggests that effects of CB₁ signaling upon seizure activity may depend on how this receptor is activated (40).

Citraro et al. (24) found that AEA and WIN-55212-2 mesylate reduced absence seizures independently from the brain focal site of infusion, while conversely, SR-141716A increased absence seizures, but only when focally administered to the ventroposteromedial thalamic nucleus in a genetic animal model of absence epilepsy in the WAG/Rij rat. These results support therapeutic potential for endocannabinoid system modulators in absence epilepsy, and highlight that attenuated endocannabinergic function may contribute to the generation and maintenance of seizures.

Among the phytocannabinoids intensively studied, Δ^9 -THCV, CBD and CBDV can be distinguished. Δ^9 -THCV was proved to suppress seizure activity in adult rats (30). Jones et al. (29) examined CBD in vivo using the PTZ model of generalized seizures in male Wistar Kyoto rats. CBD (100 mg/kg) exerted clear anticonvulsant effects with significant decrease in incidence of severe seizures and mortality compared with vehicle-treated animals. Additionally, in further studies, they confirmed the anticonvulsant effect of CBD in two rodent seizure models: the acute pilocarpine model of temporal lobe seizure and the penicillin model of partial seizure in rats. In the pilocarpine-induced seizure model, CBD significantly reduced the percentage of animals experiencing the most severe seizures. In the penicillin model, CBD significantly decreased the percentage mortality as a result of seizures; CBD decreased the percentage of animals experiencing the most severe tonic-clonic seizures (41). Furthermore, CBD administered intracerebroventricularly showed a protective effect in the mouse PTZ and MES-induced seizure models, involving big potassium (BK) channels only in PTZ-induced seizure model (42). Data from clinical studies also indicate that CBD appears to be an excellent candidate among phytocannabinoids to apply in

patients with treatment-resistant epilepsy (43, 44). Although results from the online survey seeking opinions about the use of medical marijuana and CBD for people with epilepsy indicated that there is a wide disparity in opinion on the use of medical marijuana and CBD in the treatment of people with epilepsy, which varied substantially, with fewer medical specialists supporting its use compared with general medical personal, patients and the public (45).

Hill and coworkers (31) characterized the anticonvulsant profile of CBDV in four rodent seizure models: MES and audiogenic seizures in mice, and PTZ and pilocarpine-induced seizures in rats. CBDV had significant anticonvulsant effects in the MES, audiogenic and PTZ-induced seizures, but no effect against pilocarpine-induced seizures.

CONCLUSIONS

Every day, new data are published from the world of science about the uniqueness of the human brain. This uniqueness is even greater when dealing with brain disorders. The endocannabinoid system as a central regulatory system affects a wide range of biological processes and is known to emerge as a key regulator of many neuronal systems relevant to neurodegenerative disorders including epilepsy. Since all available published information about anticonvulsant properties of various cannabinoids and possible strategies of treatment come mainly from preclinical studies, researchers are constantly looking for a substance, which would have strong anticonvulsant and neuroprotective properties and no side effects. Thus, the problem concerning the effect of cannabinoids as potential anticonvulsant and neuroprotective substances in the process of neurogenesis in epilepsy is very interesting, and certainly requires more advanced and intensive research.

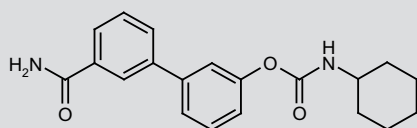
DISCLOSURES

The authors state no conflicts of interest.

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