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THE ROLE OF MAJOR MARIJUANA CONSTITUENTS IN PSYCHOTIC DISORDERS

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S u m m a r y. Activation of the endocannabinoid system (ECS) in the brain leads to modulation of the excitatory and inhibitory neurotransmitters release, and has been strongly suggested to participate in neuropsychiatric disorders. Cannabis consumption is related to an increased risk of psychosis development due to psychomimetic compound, i.e. tetrahydrocannabinol (THC). Studies have found that another cannabis component, cannabidiol (CBD) might have antipsychotic effects in schizophrenia, mainly through enhancement of endocannabinoid signalling. The paper discusses the role of the ECS in developing psychotic disorders based on currently available results of animal and human experimental, epidemiological, imaging, and clinical studies. The authors review several research articles on the subject available from PubMed database.

K e y w o r d s: cannabis, schizophrenia, marijuana, psychosis, THC, CBD

INTRODUCTION

The endocannabinoid system (ECS) has heterogeneous regulatory functions in the central nervous system (CNS), and controls several physiological processes. The ECS is comprised of two G protein-coupled receptors, cannabinoid (CB) receptors CB1 and CB2, their endogenous small lipid ligands also known as endocannabinoids, and the enzymes for endocannabinoids biosynthesis and degradation. The ECS has been suggested as a pro-homeostatic and pleiotropic signalling system activated in physiopathological conditions. Activation of the ECS in the brain leads to modulation of the excitatory and inhibitory neurotransmitters release, and has been strongly suggested to participate in neuropsychiatric disorders, particularly in psychoses, e.g. schizophrenia or schizophreniform disorders, but also in depression and anxiety [33, 43]. The ECS has become a pharmacologically attractive target and opens new strategies for the treatment of psychoses or stress-related disorders. CB receptor ligands and non-psychotropic cannabinoids, such as cannabidiol (CBD) act via several parallel mechanisms including indirect interactions with ECS or via molecules which inhibit endocannabinoid degradation.

Schizophrenia is a serious psychiatric disorder characterized by the triad of symptoms: positive (psychotic, including hallucinations and delusions), negative (anhedonia and social withdrawal) and cognitive (impairment of memory and learning processes) [24]. Because of symptom diversity, different course of the disease and unclear pathology schizophrenia often defies effective treatment. Since the introduction of a new atypical generation of antipsychotics in the 1990s, few clinically meaningful new treatment options for schizophrenia have emerged. Schizophrenia remains a highly invalidating disorder, and different theories have attempted to clarify its aetiology but the exact reason for this complex and multifactorial disease remains

unexplained. The causes of schizophrenia involve dopaminergic and glutamatergic systems [8, 22] but recent evidence supports the statement that altered ECS might also contribute to the pathogenesis of the disease [16, 39]. According to the 'cannabinoid hypothesis' of schizophrenia pharmacological manipulation within the ECS might offer a promising tool for the alleviation of schizophrenia symptoms.

Cannabis use and schizophrenia

Human studies. Multiple lines of evidence have confirmed that cannabis consumption worsens the course of schizophrenia and might be a risk factor for the development of the illness. The psychomimetic effects of cannabis result from the action of the main psychotropic constituent, Δ-9-tetrahydrocannabinol (Δ-9-THC) for CB receptors, primarily CB1 receptor. Acute, intravenous administration of Δ-9-THC has been found to induce temporal (positive, negative and cognitive) schizophrenia symptoms in healthy individuals, or worsened psychotic symptoms and cognitive deficits in schizophrenia sufferers, which strongly sustains the association of cannabis consumption and schizophrenia and indicates cannabinoid signalling might be involved in the pathophysiology of the disease. [13]. This effect might be related to dopamine release in the striatum, nucleus accumbens and prefrontal cortex following THC exposure [6, 4, 48]. Moreover, the comorbidity of schizophrenia and cannabis has high prevalence. According to the self-medication hypothesis, the aim of taking cannabis is to alleviate schizophrenia-like symptoms and reduce unpleasant secondary effects. The consumption of cannabis is ten times higher among schizophrenia patients, suggesting that these patients could be differentially sensitive to its motivational effects [15]. It is generally accepted that there is a link between cannabis consumption and schizophrenia [47]. But this is still an outstanding issue whether cannabis use is an independent schizophrenia risk factor or high prevalence of cannabis use among schizophrenia patients results from self-medication for instance, amelioration of cognitive impairment, depression or anxiety symptoms [42].

Since the initial discovery of CB receptors and their endogenous ligands (endocannabinoids) such as anandamide (AEA) or 2-arachidonoylglycerol (2-AG) in the 1990s, huge progress has been made in understanding the contribution of endocannabinoid signalling at the molecular and behavioural level. This is vital in the study of pathophysiological mechanisms of the ECS effect on schizophrenia.

Several studies investigated the role of endocannabinoids in the neurobiology of the disease in schizophrenia patients. The researchers have found that the levels of endocannabinoids (AEA and palmitoylethanolamide - PAE) were markedly increased in the cerebrospinal fluid (CFS) [16, 28] and peripheral blood [10, 29] compared to healthy controls. Moreover, increased level of AEA was reversed in clinical remission obtained by antipsychotic therapy [10, 29]. The authors suggested that increased level of anandamide is a reactive inhibitory feedback to over-activation of dopamine receptors D2 [29]. Additionally, schizophrenia patients who regularly use cannabis have lower AEA levels than patients who do not take cannabis, which suggests that cannabis consumption leads to downregulation of AEA signalling in schizophrenia patients which may in turn enhance psychosis [16, 29].

Also several findings from genetic, neuroimaging and post-mortem studies imply that the ECS is significantly involved in the pathology of schizophrenia. Post-mortem examinations found an increase in cannabinoid receptor binding in the prefrontal area in schizophrenia patients by using *in vitro* autoradiography, and [^{3}H] CP-55940 as a ligand [11]. Another study reported the up-regulation of CB1 receptors in the anterior cingulate cortex in schizophrenia patients using more selective CB1 receptor ligand, [^{3}H]SR141716A [52]. Also, an increase in CB1 receptor binding density was found in the posterior cingulate cortex in schizophrenia patients with another CB1 receptor ligand [^{3}H] CP-55940 [39]. Inconsistent results were received from expression analysis by immunohistochemistry.

The researchers found no alteration of the expression of CB1 receptors at the protein level in the anterior cingulate cortex in schizophrenia patients [26]. Moreover, another scientific team reported even reduced CB1 receptors expression, both at the protein and messenger RNA level in the prefrontal cortex in schizophrenia patients using *in situ* hybridization and immunohistochemical analysis [14]. The discrepancy between data might be explained in the following way: the increase in CB1 receptors binding by autoradiography may result from the

conformational change of CB1 receptors which increases binding affinity of radioligands but might not influence the amount of CB1 receptor itself [14].

The results of magnetic resonance imaging (MRI) scans also confirmed the correlation between cannabis consumption and schizophrenia. The volume loss of certain brain regions, such as anterior and posterior cingulate cortex was observed in the patients with first episode of schizophrenia who use cannabis. The affected brain areas are also known to be rich in CB1 receptors [45]. Additionally, it has been demonstrated that cannabis use during adolescence results in higher volume loss of the entire brain than cannabis consumption in post-adolescence period [49].

Even though, there is much evidence indicating the correlation between cannabis consumption and psychotic symptoms, the majority of cannabis users do not develop schizophrenia. That suggests that cannabis usage is not sufficient to trigger full-blown disease onset, but may constitute an environmental risk factor in a specific population vulnerable to schizophrenia development, for example patients with co-occurrence of environmental or genetic risk factors.

An example of genetic risk factor may be the functional polymorphism of catechol-O-methyltransferase (COMT) gene which encodes main dopamine degradation enzyme, and is related to increased risk for psychosis after cannabis intake [7, 18]. A missense mutation of COMT found on valine to methionine substitution at codon 158 (Val158Met) changes enzymatic activity, and is genetically correlated to schizophrenia [46]. Individual homozygous for valine 158 but more plausible manifestation of psychotic symptoms occurs after cannabis use in adolescence.

Although several data indicate the relationship between cannabis consumption and schizophrenia, it cannot be stated conclusively that cannabis use itself is either essential or sufficient to develop the disease. Cannabis might be a significant risk factor for developing schizophrenia, but an influence of other co-occurring factors from before the onset of cannabis use should be considered, such as parental factors, familial risk, other psychiatric disorders, social background, socioeconomic status, trauma, IQ, educational background, addictive substance abuse, etc. [1].

Cannabis consumption in adolescence

Epidemiological evidence has confirmed that cannabis consumption during adolescence can enhance relative risk for psychotic disorders such as schizophrenia and schizophreniform disorders in comparison to non-cannabis users [21, 47, 51]. Furthermore, many longitudinal prospective studies have demonstrated a dose-response relationship between the frequency of cannabis intake and the risk for developing psychotic disorders, including schizophrenia [21]. Also, the risk for first psychosis symptoms and prodromal symptoms is much greater in individuals who use cannabis during adolescence [12].

The ECS plays an important role in early brain development, and adolescence is a critical period for the maturation of several neurotransmitter systems, including glutamatergic, dopaminergic, gamma-aminobutyric acid (GABA)-ergic projections and dynamic changes in the expression of their receptors and synaptic density [40]. The activation of CB1 receptors supresses the release of neurotransmitters, such as glutamate or GABA, and an abnormal CB1 receptor signalling (induced by using cannabis) might hinder full-maturation of the neuronal circuit network and impair proper neuronal communication during adolescence. This is consistent with the statement that cannabis use during adolescence is an environmental risk for disordered full-maturation of neuronal circuit which might facilitate subsequent development of schizophrenia.

This is still a highly speculative statement, that cannabis consumption during adolescence might be a ‘second hit’ factor for the onset of schizophrenia in people with genetic predispositions, but based on that, an intervention in endocannabinoid signalling during adolescence might be a potentially useful strategy for the prevention of schizophrenia.

Animal studies

Expression of CB1 receptor is particularly abundant in nerve terminals in the cerebellum, hippocampus, basal ganglia, frontal cortex, basolateral amygdala, hypothalamus, and midbrain [17]. CB1 receptor is found to play a significant role in mediating acute psychotic experiences associated with cannabis use [44]. Blockade of CB1 receptor results in the inhibition of acute psychological effects associated with

cannabis use, suggesting key role for CB1 receptor in mediating psychotic symptoms [23]. In fact, CB1 receptor antagonists have been tested for anti-psychotic properties substantial to treating schizophrenia in preclinical studies. The administration of AVE1625, a CB1 receptor antagonist in a co-treatment setting with antipsychotics improved cognitive function and reduced side effects typical for antipsychotics usage in rodents [5]. An amnestic effect or hyperactivity induced by acute MK-801 (NMDA receptor antagonist) was attenuated by acute administration of AM 251, a CB1 receptor antagonist in mice [27]. The administration of AM-251 also reversed schizophrenia-like symptoms in neurodevelopmental animal model based on social isolation procedure in rats. Isolation-reared rats showed hyperlocomotion in a novel environment, cognitive impairment in the novel object recognition (NOR) test, and a significant increase in the number of aggressive behaviours in the social interaction test. The behavioural picture presented reduced CB1 receptor coupling in specific brain areas, and reduced c-Fos immunoreactivity in the prefrontal cortex and caudate putamen.

The chronic administration of AM-251 inversed these effects, the behavioural recovery was accompanied by regained CB1 receptor function and c-Fos level in all brain regions which were altered in isolation-reared rats, including the nucleus accumbens, as it was demonstrated for antipsychotic drugs. Moreover, this behavioural recovery effect persisted until 10 days after discontinuing AM-251 administration, indicating long-lasting effect of CB1 receptor antagonist on psychotic-like symptoms [50].

The experimental findings concerning the effects of CB receptor ligands on schizophrenia-like symptoms are still controversial and often produced different effects depending on the drug, dose, species and the animal model of induced schizophrenia. However, in some patients, for instance with glutamate hypofunction, CB1 receptor antagonist could provide a potential new therapeutic strategy in the future treatment of schizophrenia.

Cannabidiol as an antipsychotic drug

Although cannabis use is associated with an increased risk of developing schizophrenia, its main non-psychotropic constituent, CBD has potentially antipsychotic properties. In contrast to the main psychoactive phytocannabinoid, THC in a dose-dependent manner induced psychiatric symptoms such as psychosis [34, 44] CBD was reported to interfere with psychomimetic actions of THC [25] providing the first indication of its antipsychotic potential.

CBD has a complicated mechanism of action, exhibits low affinity for CB1 and CB2 receptors, and is capable of altering the functions of CB receptors by antagonizing CB1 and CB2 receptor agonists such as AEA or 2-AG [41], and therefore it is able to interfere with THC effects, which suggests that the THC/CBD ratio in cannabis might moderate the adverse effects after its consumption.

Additionally, CBD increases the level of AEA by reducing cellular uptake and inhibiting hydrolytic degradation of AEA [29], which supports the hypothesized counteracting role of AEA in overactivity of dopamine receptor D2. Antipsychotic properties of CBD might be due to enhanced AEA synaptic level to rebalance D2 receptor overactivation [43].

Evidence from animal studies

THC and CBD have demonstrated very different effects in several murine psychosis models. CBD not only causes different effects than THC, but also is capable to inverse THC-induced psychosis phenotypes, such as reduction in social interaction [32] and CBD-inversed apomorphine-induced stereotyped behaviour in rats [56], and dexamphetamine-induced hyperlocomotion in mice [31], or ketamine-induced hyperlocomotion in mice with efficiency similar to clozapine [35].

The antipsychotic effect of CBD was similar to haloperidol, a reference antipsychotic drug, however CBD was devoid of catalepsy side effect and increased prolactin levels only at doses higher than those needed to block typical behaviour [53].

CBD effect on glutamate hypofunction was confirmed in later studies in rats, investigating MK-801-induced hyperactivity, deficits in prepulse inhibition and social withdrawal [19]. In a sensory gating mouse model, CBD reversed MK-801-induced prolonged prepulse inhibition similarly to clozapine [31].

Taken together, the preclinical data suggest that CBD possess antipsychotic properties and exhibits activity profile compatible with atypical antipsychotics.

Evidence from human studies

Before clinical trials in humans, it is required to establish a safety profile of CBD. Reported *in vivo* and *in vitro* CBD administration in a wide range of concentrations did not induce serious or toxic side effects [2]. Even chronic administration of CBD (for one month) to healthy volunteers at daily doses from 10 to 400 mg did not cause any significant neurological or psychiatric abnormalities [9]. Also chronic use of high doses (up to 1500 mg/day) was well-tolerated in humans, but some studies observed that CBD may cause some minor side effects, such as the inhibition of hepatic drug metabolism [2]. The available clinical data support the statement that CBD could be safely administered in a wide range of doses, which seems to confirm the results from animal studies.

In the first human study, the co-administration of CBD and THC to healthy subjects induced less psychomimetic symptoms than THC alone [55], which was confirmed in later studies where positive psychotic symptoms caused by THC were reduced by CBD [3], also CBD attenuated the impairment effects induced by nabilone (synthetic THC) [30]. In the studies investigating THC/CBD ratios in hair samples in the volunteers who smoked cannabis in naturalistic settings, the subjects with THC only showed higher positive psychotic symptom level compared to the groups on THC and CBD, or non-cannabinoids in hair samples [36].

Additionally, the subjects who smoked CBD-rich cannabis showed no memory impairment, whereas the ones who smoked cannabis with low CBD content showed significant impairment in prose abilities. However, CBD did not influence psychomimetic symptoms which were elevated in both groups when intoxicated [38]. Investigating THC/CBD ratios in hair samples in acute administration of cannabis found CBD had a protective effect on positive psychotic symptoms and in the recognition memory impairment related to THC daily use in subjects with high levels of THC [37]. In ketamine model of psychosis, oral administration of 600 mg CBD caused increased psychomotor activation and reduced depersonalization symptoms [20].

In clinical trials CBD decreased psychotic scores on the Brief Psychiatric Rating Scales (BPRS) in a 19-year old female schizophrenia patient who was treated for four weeks with increasing doses (up to 1,500 mg/day) of CBD [55].

In the next open-labelled study in three treatment-resistant schizophrenia patients after for weeks of CBD administration at the oral dose up to 1,280 mg one patient showed partial improvement, another one improved slightly, and the third one did not respond to CBD treatment. Worsening of the symptoms was observed with CBD interruption in all three patients. Additionally, the third patient was also resistant to clozapine [54]. In open trial in patients suffering from Parkinson's disease with psychotic symptoms after dopaminergic drugs administration after four week of CBD oral administration at the dose from 150 to 400 mg/day in addition to their usual antiparkinsonian treatment, a reduced score in BPRS and Parkinson Psychosis Questionnaire (PPQ) was observed. Moreover, no decrease in motor function or other adverse effects were observed during CBD treatment [53].

In the first double-blind clinical trial of CBD compared to amisulpride in psychotic patients (acute paranoid schizophrenia or schizophreniform psychosis) during four-week treatment, there was no significant difference in the scores between both CBD and amisulpride on BPRS and Positive And Negative Syndrome Scale (PANSS). What is more, CBD caused less side effects. Another clinical trial in antipsychotic-naïve first-episode schizophrenic patients compared CBD and placebo effect. 18 patients out of 29 completed a 28-day treatment with a significant reduction in psychotic symptoms after CBD treatment compared to baseline model [29].

Although CBD mechanism of action is still unclear, multiple lines of preclinical or clinical evidence strongly support the statement that CBD causes therapeutic effects in psychotic symptoms similar to atypical antipsychotics and demonstrates safety therapeutic profile at the same time. The presented results must be considered in the light of some limitations, such as few randomised placebo-controlled clinical trials, small sample size, various CBD dosage and administration time, co-administration with other drugs which might have conditioned the results. Nonetheless, taken together preliminary findings suggest that CBD might be a very effective pharmacological tool in the treatment of psychiatric disorders. However, further and larger clinical trials are required.

CONCLUSIONS

The ECS is involved in multiple neuromodulation processes, including neurogenesis and neurotransmitters release. At the same time, the neuronal circuits are impaired in schizophrenia patients. Several evidence shows that CB receptors density and the level of endocannabinoids is altered in schizophrenia patients which suggests that the ECS is engaged in the pathophysiology of this psychiatric disorder. Many preclinical and clinical findings stand for strong correlation between cannabinoids and schizophrenia development. The data suggest the ECS is a very significant and exciting area for the search of novel treatments for schizophrenia via different pharmacological targets, such as cannabinoid receptors ligands or indirect alteration of endocannabinoids levels by CBD. Novel pharmacological prospects for the treatment of schizophrenia strongly emphasize the role of ECS modulation, however they need to be tested in further well-controlled pre- and clinical trials.

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