Mini-review

Cannabinoids and schizophrenia: where is the link?

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Abstract

Highlighting the association between schizophrenia and cannabis sativa and the endogenous cannabinoid receptor system, respectively, two opposite aspects are of major relevance. On the one hand, there is substantial evidence that cannabis has to be classified as an independent risk factor for psychosis that may lead to a worse outcome of the disease. This risk seems to be increased in genetically predisposed people and may depend on the amount of cannabis used. On the other hand, there are several lines of evidence suggesting that, at least in a subgroup of patients, alterations in the endocannabinoid system may contribute to the pathogenesis of schizophrenia, e.g., increased density of cannabinoid receptor type 1 (CB1) binding and increased levels of cerebrospinal fluid (CSF) anandamide. Accordingly, beside the „dopamine hypothesis“ of schizophrenia a „cannabinoid hypothesis“ has been suggested. Interestingly, there is a complex interaction between the dopaminergic and the cannabinoid receptor system. Thus, agents that interact with the cannabinoid receptor system such as the non-psychoactive cannabidiol (CBD) have been suggested for the treatment of psychosis.

Keywords: Cannabis, THC, tetrahydrocannabinol, schizophrenia, psychosis

Introduction

Schizophrenia is a common psychiatric disorder characterized by impairments in the perception or expression of reality. Schizophrenic symptoms are subclassified into positive (or productive) symptoms such as delusions, auditory hallucinations, and thought disorder, and negative (or deficit) symptoms such as blunted affect and emotion, poverty of speech, anhedonia, and lack of motivation. For many patients the prognosis is poor with incomplete recovery and significant illness. A multifactorial pathogenesis is assumed including genetic and environmental factors, neurobiological alterations, as well as psychological and social processes. Pathophysiologically there is evidence for an alteration in the dopaminergic system with increased dopaminergic activity in subcortical areas including the striatum, and decreased dopaminergic activity in cortical areas such as the prefrontal cortex. Dopamine receptor antagonists (neuroleptics) are the first choice treatment in schizophrenia.

Within the brain an endogenous cannabinoid system has been detected including different receptors (mainly the cannabinoid-1-receptor (CB1)) as well as a series of lipophilic endogenous ligands and enzymes for the biosynthesis and degradation of these endocannabinoids. CB1 receptors inhibit the release of several neurotransmitters and neuromodulators including dopamine, GABA, serotonin, glutamate, noradrenaline, and acetylcholine. The two most important endocannabinoids are anandamide (N-arachidonylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG). While 2-AG is a full agonist at the cannabinoid receptor, anandamide is a partial agonist. However, anandamide, in addition, is a full agonist at the vanilloid (VR1) receptor.

Cannabis as a risk factor for psychosis

The relationship between schizophrenia and the use of cannabinoids is complex and not completely understood. While it is well established that high doses of cannabis can cause a transient toxic psychosis, it is...
unclear whether cannabis use increases the risk of psychotic illness persisting after abstinence from the drug. However, there is substantial evidence that heavy cannabis abuse in healthy persons is a risk factor for the clinical manifestation of schizophrenia and triggers both the onset of psychotic episodes in predisposed individuals and the relapse in patients with schizophrenia. Since the vast majority of cannabis users do not develop psychosis, it can be hypothesized that some people are genetically vulnerable to these effects of cannabis.

In the general population, it has been shown that cannabis negatively impact cognitive functioning, although it is unclear whether cognitive deficits even persist after abstinence for a longer period. Investigating the effects of cannabis on cognitive functions in patients with first episode psychosis, it has been demonstrated that cognitive functioning and performance is comparable or even better (i.e., higher scores for problem solving and reasoning and visual memory) in those patients using cannabis compared to non-using patients [1, 2, 3] suggesting a possible neuroprotective effect of cannabis among persons with schizophrenia [3]. More recently, several epidemiological studies have been performed investigating whether cannabis use acts as an independent risk factor in the onset of schizophrenia. A large cohort study with more than 50,000 subjects found that heavy cannabis use at age 18 increases the risk for later schizophrenia six-fold compared to non-users suggesting a causal relationship between cannabis use and an increased risk of developing schizophrenia [4, 5]. In addition, not only a dose-response relation between cumulative exposure to cannabis use and the psychosis outcome [4, 6] could be demonstrated, but also an age dependence with increased likelihood for adult-onset schizophrenia six-fold compared to non-users suggesting a causal relationship between cannabis use and an increased risk of developing schizophrenia [4, 5]. In addition, not only a dose-response relation between cumulative exposure to cannabis use and the psychosis outcome [4, 6] could be demonstrated, but also an age dependence with increased likelihood for adult-onset schizophrenia six-fold compared to non-users suggesting a causal relationship between cannabis use and an increased risk of developing schizophrenia [4, 5].

Interaction between the dopaminergic and the cannabinoid system

There is a large number of both animal and human studies available substantiating an interaction between the cannabinoid and the dopaminergic system. Since it has been suggested that psychosis is caused by an overactive dopaminergic system (the „dopamine hypothesis“ of schizophrenia) [12], it has been speculated that cannabinoids might cause or exacerbate psychoses by increasing the activity of the dopaminergic system. There are several lines of evidence suggesting that in patients with cannabis-induced psychosis a genetic vulnerability may lead to an increased dopaminergic activity [13]. In dopamine transporter (DAT) knockout (KO) mice, an animal model associated with hyper-dopaminergia that has been suggested to be relevant to schizophrenia, a significant decrease of striatal anandamide levels has been demonstrated further suggesting that hyperdopaminergia leads to alterations of the cannabinoid system [14].

The “cannabinoid hypothesis” of schizophrenia

The hypothesis that the consumption of exogenous cannabinoids may contribute to the pathophysiology of psychosis is further supported by observations in healthy volunteers because administration of intravenous delta-9-tetrahydrocannabinol (THC) to healthy individuals may produce transient schizophrenia-like positive and negative symptoms [15, 16, 17, 18]. The binocular depth inversion test (BDIT) can be used as a model of illusionary visual perception. Using the BDIT to investigate cognitive impairment in patients with schizophrenia, it could be demonstrated that patients with schizophrenia are more veridical in their judgments viewing inverted (concave) faces [19]. However, this impaired binocular depth inversion improved in parallel to clinically effective antipsychotic treatment [20]. In healthy volunteers, it can be assumed that cognitive factors override the binocular disparity cues of stereopsis and, thereby, correct an implausible perceptual hypothesis. Accordingly, it has been suggested that impairment of binocular depth inversion reflects a common final pathway, characterized by an impairment of adaptive systems regulating perception [21].

Investigating binocular depth inversion in THC-intoxicated normal volunteers compared to both healthy controls and patients suffering from productive psychoses, similar alterations were detected in THC-intoxicated normal volunteers and patients with schizophrenia [19]. Therefore, comparable disturbances in the internal regulation of perceptual processes in patients with schizophrenia and THC-intoxicated people can be assumed suggesting that a dysfunctional cannabinoid receptor system might underlie at least a subtype of endogenous psychoses [19]. An involvement of the cannabinoid receptor system in schizophrenia is further supported by findings in cerebrospinal fluid (CSF) in patients with schizophrenia. The CSF concentrations of the endocannabinoids anandamide and palmitylethanolamide (PEA) were found significantly increased in patients with schizophrenia compared to non-schizophrenic controls. Therefore, it has been suggested that changes in the endocannabinoid concentrations in schizophrenia might reflect either a homeostatic adaption of the cannabinoid system to a primary dopaminergic dysfunction or a primary „hypercannabinergic“ state [22]. In addition, CSF anandamide levels were found eight-fold higher in antipsychotic-naive patients with first-episode paranoid schizophrenia than in healthy controls [23]. Because in non-medicated patients with acute schizophrenia CSF anandamide levels were negatively correlated with psychotic symptoms, it has been hypothesized that anandamide elevation in acute paranoid schizophrenia may reflect a compensatory adaptation to the disease
state [23]. While frequent cannabis exposure may down-regulate anandamide signaling in the brain of patients with schizophrenia, but not of healthy individuals, it can be speculated that frequent cannabis use increases the risk for psychotic episodes only in those individuals who exhibit preexisting pathologically hyperactive anandamide levels, as demonstrated in patients with first episode schizophrenia [24]. There is only a limited number of investigations available measuring endocannabinoid levels in plasma in patients with schizophrenia demonstrating increased amounts of both anandamide and the mRNA for the anandamide degrading enzyme fatty acid amide hydrolase (FAAH) in patients with schizophrenia [25, 26]. Successful antipsychotic treatment led to a reduction of anandamide blood levels and of the mRNA transcripts for cannabinoid receptors type 2 (CB2) and FAAH [25]. 2-arachidonoyl glycerol (2-AG) levels were found significantly lower in neuroleptic-naïve patients with first-episode schizophrenia compared to patients with chronic schizophrenia after withdrawal from neuroleptic medication. Based on these findings it has been suggested that an increase in plasma anandamide levels might be related to the disease independent of the state, but 2-AG might be related to disease progression [26].

With regard to a cannabinoid hypothesis of schizophrenia, it is of importance that highest densities of cannabinoid receptors type 1 (CB1) in the brain are found in those regions that have been implicated in schizophrenia, including the prefrontal cortex, basal ganglia, hippocampus, and the anterior cingulate cortex (ACC). In postmortem studies CB1 receptor binding density was found to be increased in the dorsolateral prefrontal cortex and in the posterior cingulate cortex (PCC) in patients with schizophrenia. At present results regarding the ACC remain contradictory [27, 28]. These data, however, demonstrated for the first time alterations in CB1 receptor binding in patients with schizophrenia.

**Neuroimaging studies of the CB1 receptor**

In vivo neuroimaging using positron emission tomography (PET) and single photon emission computed tomography (SPECT) to investigate different aspects of the cannabinoid CB1 receptor system is in a very preliminary state. To date, there is only one single case study available investigating a patient with schizophrenia that demonstrates a high cannabinoid CB1 receptor binding in the striatum and the pallidum, and a moderately high binding in the frontal cortex, the temporal cortex and the cerebellum. These findings reflect results from in vitro studies regarding receptor distribution [29]. From several magnetic resonance imaging (MRI) studies it is known that patients with schizophrenia have progressive brain reductions [30, 31]. By contrast, volumetric MRI studies in (“healthy”) cannabis users resulted in inconsistent findings with reduced [32] or normal [33] brain volumes. From recent MRI studies it is suggested that in patients with schizophrenia cannabis use might amplify a pre-existent vulnerability to brain volume changes [34], in particular in regions rich in CB1 receptors such as the PCC [35].

**Genetic predisposition for cannabis-induced schizophreniform disorders**

Because variants within the cannabinoid receptor gene (CNR1) (AAT repeat polymorphism) were found to be associated with schizophrenia, it has been supposed that the cannabinoid CB1 receptor system is overactivated in patients with some types of schizophrenia [36, 37]. Recent studies, in addition, demonstrated that specific genetic variations (the valine158 allele of the catechol-O-methyltransferase, COMT) may lead to an increased risk not only to exhibit psychotic symptoms but also to develop cannabis-induced schizophreniform disorders [38]. This effect, however, was observed only for people using cannabis before the age of 18 for the first time. From these data a gene x environment interaction between COMT genotype and cannabis use on risk of schizophrenia has been deduced [38].

**CBD improves psychotic symptoms**

Cannabidiol (CBD) is a major non-psychotropic constituent of cannabis. Case studies [39] as well as a double-blind controlled study [40] suggested that CBD may be effective in the treatment of patients suffering from acute schizophrenia. The endogenous cannabinoid system, therefore, has been proposed as a possible novel therapeutic target for the treatment of acute schizophrenia [40]. However, the underlying pathophysiological mechanisms of CBD in schizophrenia remain unclear.

**References**

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