Schizophrenia

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Contents

Abstract Since the discovery of the endocannabinoid system, a growing body of psychiatric research has emerged focusing on the potential role of this system in schizophrenia. On the basis of earlier epidemiological studies and results from animal models, endocannabinoids and their relation to symptoms are considered in clinical studies as well as in *post-mortem* analyses of cannabinoid CB_1 receptor densities. A possible neurobiological mechanism for the deleterious influence of cannabis use in schizophrenia is discussed, involving the disruption of endogenous cannabinoid signalling and function.

Keywords Schizophrenia • Endocannabinoids • Δ^9-THC • Animal modes • CSF

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Abbreviations

ACC Anterior cingulate cortex
CSF Cerebrospinal fluid
PCC Posterior cingulate cortex

1 Introduction

Investigations of the psychotomimetic properties of herbal cannabis preparations and certain purified phytocannabinoid compounds – and thus, indirectly, of manipulating the endogenous cannabinoid system – started as early as 1845, when Moreau de Tours observed the effects of cannabis in an experimental setting and described the occurrence of psychotic symptoms in healthy individuals after cannabis administration. In 1932, Beringer et al. described specific thought disturbances, perceptual alterations and delusions in healthy subjects after administration of a standardised extract from *Cannabis sativa*. These psychopathological findings were quite similar to the acute symptoms of schizophrenia. After more than 60 years of declining interest in this issue, further studies in healthy volunteers were initiated. It was now possible to use synthetic Δ^9-tetrahydrocannabinol (Δ^9-THC) instead of a natural preparation of *C. sativa* with its abundance of different cannabinoid compounds. These studies have observed psychotic symptoms and alterations of perception (Leweke et al. 1999b) and emotional processing (Leweke et al. 1998) after oral administration of Δ^9-THC. Furthermore, transient schizophreniform symptoms and cognitive disturbances were caused by both orally and intravenously administered Δ^9-THC (D'Souza et al. 2004; Koethe et al. 2006).

These findings were in agreement with the impressions of clinicians, over many decades, that frequent cannabis use increases the risk of schizophrenia and that schizophrenic patients are more likely than healthy individuals to abuse cannabis. Both observations have been verified over recent years. First, it has been demonstrated in a number of epidemiological studies that frequent cannabis use is associated with a greater risk of suffering psychotic symptoms or developing schizophrenia (Arseneault et al. 2002; Henquet et al. 2005; van Os et al. 2002; Zammit et al. 2002). This was first described by Andreasson and colleagues (1987), who reported an increased risk of developing schizophrenia correlated with a higher frequency of cannabis use in a cohort of Swedish conscripts. Even after correction for certain confounding variables, a twofold increased risk for schizophrenia was estimated following more than twenty episodes of cannabis use (Andreasson et al. 1989). These findings have been a source of controversy for more than a decade, but a number of more recent epidemiological studies applying different strategies also suggest an overall twofold increased risk of suffering schizophrenia in the wake of frequent cannabis use (for review see Arseneault et al. 2004), confirming the initial Swedish results. Additionally, cannabis users tend to be significantly younger when

developing schizophrenia and to suffer earlier from negative symptoms of the disease, both representing negative prognostic factors in schizophrenia (Veen et al. 2004). Second, schizophrenic patients are more likely than healthy individuals to abuse cannabis (Kovasznay et al. 1997). Several models have been proposed to explain the etiological relationship between substance abuse and psychosis, but no single model is able to explain all co-morbidity adequately. However, there is no substantial epidemiological evidence that cannabis abuse serves as a kind of self-medication for schizophrenic patients, while greater support has been found in self-reporting studies for an "alleviation of dysphoria" model, in which patients see substance misuse as a means of alleviating unpleasant affective states (Gregg et al. 2007). Furthermore, in schizophrenic patients, the abuse of cannabis seems to trigger psychotic symptoms and may worsen the outcome of the disease (e.g. Linszen et al. 1994). Whereas cannabis use may precipitate the development of psychosis in vulnerable people, the hypothesis that cannabis use causes schizophrenia is not supported (Leweke et al. 2007a).

Taken together, there exists a large body of evidence that there is a relevant association between acute and chronic cannabis, or more specifically Δ^9-THC, intake and behavioural, cognitive and psychotic symptoms or the development of schizophrenia. It is known that Δ^9-THC, the main psychoactive compound of herbal cannabis preparations, binds to and activates CB_1 receptors and has been suggested to disrupt the physiological role of endogenous cannabinoids, its primary target system. While, over the last decade, the endogenous cannabinoid system has become a major theme of interest in a variety of fields such as pain modulation, neurotransmitter systems, energy metabolism and immune functions, the system has also been hypothesised to be involved in the pathophysiology of schizophrenia (Emrich et al. 1997).

2 Neurobiology of the Endocannabinoid System in Schizophrenia

2.1 Animal Studies

Hypotheses concerning a disturbance of endocannabinoid functions in schizophrenia have been developed on the basis of valid animal models of cannabinoid-associated schizophrenia-like symptoms in rodents, and researchers have tested various cannabinoid compounds on a variety of animal models for schizophrenia. For example, animal models reflecting certain aspects of schizophreniform symptoms have been developed using acute or chronic treatment of rodents with the cannabinoid receptor agonist WIN55212-2 (Schneider and Koch 2003, 2005; Schneider et al. 2005). It is noteworthy that most of these models target the developing brain, suggesting its heightened susceptibility to the effects of exogenous cannabinoids both during the perinatal period through maternal cannabis use and in young

adolescent users (Schneider 2008). A number of studies have demonstrated a subtle rather than gross effect of cannabis upon later brain function, including the development of schizophreniform psychotic symptoms (for review see Sundram 2006).

Animal experiments suggested improvement of psychotic symptoms by CB receptor antagonism: rimonabant (SR141716A), a selective CB_1 receptor antagonist, was able to reduce the hyperactivity induced in gerbils by various stimulant drugs known to produce schizophrenic-like symptoms (Poncelet et al. 1999). Interestingly, in a clinical study with acute schizophrenic patients, the blockade of the CB_1 receptor by rimonabant did not show corresponding effects and the psychotic symptoms did not improve (Meltzer et al. 2004). To date, however, there are insufficient clinical data to support the hypothesis that CB_1 receptor antagonists could work as antipsychotic drugs, although there is evidence from basic research involving animal studies. Further animal studies showed that administration of Δ^9-THC increased dopaminergic activity in the mesolimbic dopaminergic system, and (indirectly) acetylcholine release in the hippocampus and prefrontal cortex, whereas Δ^9-THC (twice daily for 7 or 14 days) caused a persistent and selective reduction in medial prefrontal cortical dopamine turnover (Pisanu et al. 2006; Verrico et al. 2003). Interestingly cannabidiol, the non-psychotropic main compound in *C. sativa*, revealed antipsychotic properties in a study with rats (Zuardi et al. 1991). Cannabidiol is now being tested in clinical trials with promising preliminary results concerning both psychopathology and cognitive improvement (Leweke et al. 2005).

2.2 Human Post-Mortem Studies

With regard to endocannabinoid receptors, Dean et al. (2001) reported increased binding of the cannabinoid receptor agonist [^{3}H]-CP55940 to CB_1 receptors in the dorsolateral prefrontal cortex of schizophrenic patients as compared to controls using quantitative autoradiography, but showed no relationship with recent cannabis use. Zavitsanou et al. (2004) examined the distribution and density of CB_1 receptors in post-mortem anterior cingulate cortex (ACC) from schizophrenic patients by radioligand binding of the antagonist radioligand [^{3}H]-rimonabant. The CB_1 receptors displayed a homogeneous distribution among the layers of the ACC, and a significant increase of 64% in [^{3}H]-rimonabant-specific binding to CB_1 receptors was found in schizophrenic patients compared to controls. Recently, Newell et al. (2006) reported elevated binding of [^{3}H]-CP55940 to CB_1 receptors in the posterior cingulate cortex (PCC) in schizophrenic patients compared to controls. A 25% increase in CB_1 receptor binding was found in the superficial layers (I, II), which was not related to cannabis use. No difference was found in the deeper layers of the PCC. In addition, Koethe et al. (2007) analysed the expression of the CB_1 receptors in ACC at the protein level using immunohistochemistry. Five patients suffering from schizophrenia and fifteen controls were included in aquantitative post-mortem study. Densities of neurons and glial cells immunopositive

for CB_1 receptors were quantified. No evidence of an increased or decreased density of CB_1 receptor-immunopositive cells in schizophrenia was found. In this study, confounding variables such as post-mortem time, fixation time, use of illicit drugs, alcohol abuse or sex did not significantly influence the parameters measured. Such post-mortem studies do suffer from the limitation that the patients are mainly chronic cases treated with various medications over decades, which might have an impact on the expression of CB_1 receptors. These findings suggest some, albeit not particularly dominant, role of endocannabinoid receptors in the pathophysiology of schizophrenia.

Most recently, a post-mortem study was able to show that, in the dorsolateral prefrontal cortex, levels of both CB_1 receptor mRNA and protein were lower in subjects with schizophrenia than in well-matched controls. In a parallel study, mRNA levels in antipsychotic-exposed monkeys were analysed and it was found that they were unchanged compared to those in untreated animals. This finding limits the possibility that the reported post-mortem differences between schizophrenic patients and controls are due to antipsychotic treatment (Eggan et al. 2008).

2.3 Clinical Studies

Administration of intravenous Δ^9-THC to pharmacologically stabilised schizophrenic patients led to a transient worsening of psychotic symptoms and of cognitive function (D'Souza et al. 2005). Interestingly, another major non-psychotomimetic compound from *C. sativa*, cannabidiol, has been demonstrated to ameliorate psychotic symptoms and perceptual alterations induced by the synthetic Δ^9-THC analogue nabilone (Leweke et al. 2000), a finding in agreement with animal studies suggesting antipsychotic properties of cannabidiol (Zuardi et al. 1991).

In this context, pioneering clinical studies of the endocannabinoid system measured changes in the levels of anandamide, the most intensely investigated endogenous ligand of the CB_1 receptor, as well as its structural analogues palmitoylethanolamide and oleoylethanolamide in cerebrospinal fluid (CSF) of acutely psychotic schizophrenic patients and healthy controls (Leweke et al. 1999a). In this study, significantly elevated levels of both anandamide and palmitoylethanolamide were observed in the CSF of schizophrenic patients, suggesting up- or dysregulation of the endocannabinoid system in acute schizophrenia. This latter finding was replicated with a larger sample of schizophrenic patients revealing more detailed data on the role of the endocannabinoid system in the disorder (Giuffrida et al. 2004). Not only was a significant elevation of anandamide in the CSF of first-onset, antipsychotic-naïve schizophrenic patients observed, but it was also demonstrated – for the first time for any neurotransmitter investigated so far – that anandamide levels in CSF were significantly and inversely correlated to psychotic symptoms and to negative symptoms in particular (Fig. 1). In addition, neither anandamide nor palmitoylethanolamide or oleoylethanolamide levels were affected in serum, indicating the up-regulation of anandamide to be exclusive to the central nervous

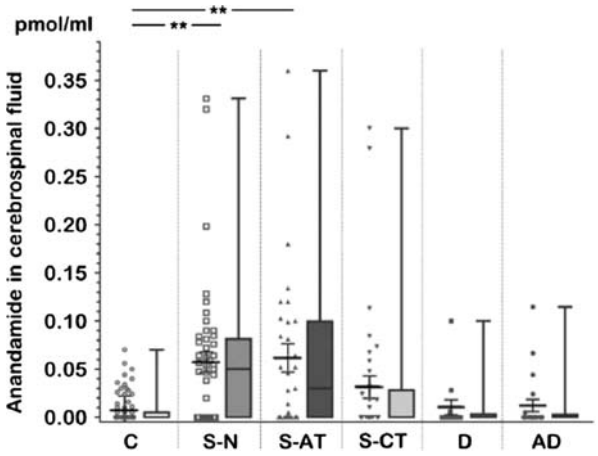

Fig. 1 Anandamide levels are elevated in the CSF of antipsychotic-free first-episode schizophrenic patients. CSF anandamide in healthy volunteers (C); antipsychotic-free schizophrenics with paranoid schizophrenia (S-N); acute schizophrenics (paranoid type) treated with 'atypical' (S-AT) or 'typical' (S-CT) antipsychotic drugs; and patients affected by dementia (D) or affective disorders (AD) without psychotic symptoms. Single values are given with mean ±SEM as well as corresponding boxplots illustrating median, range, and quartiles for each group. Statistically significant differences between groups are shown (*$P \leq 0.01$; **$P \leq 0.001$)

system and, since patients suffering affective disorders or dementia showed no such changes, to be specific to schizophrenia. Interestingly, patients treated with antipsychotic drugs predominantly blocking dopamine D_2 receptors showed much lower levels of anandamide in CSF that were not statistically different from those in healthy volunteers. This was not the case for combined serotonin $5HT_{2A}$ receptor and D_2 receptor blocking antipsychotics (so called second-generation antipsychotics), pointing to a D_2 receptor-mediated increase of anandamide in CSF that had been previously observed in relation to motor control in rodents (Giuffrida et al. 1999).

2.4 Cannabis Administration

At present we are only beginning to understand why cannabis abuse may have deleterious effects on the course of schizophrenia, both in its early stages and during the later course of the disease. Most recently, a study from our group investigated the influence of previous, more frequent, cannabis use in first-episode antipsychotic-naïve schizophrenia on anandamide levels in CSF and serum (Leweke et al. 2007a). This analysis revealed significantly elevated levels of anandamide in the CSF of acute schizophrenic patients with a frequency of lifetime cannabis use of less than five times. There was an even stronger significant inverse correlation between anandamide in CSF and psychotic negative symptoms compared to the entire sample of patients. Interestingly, those patients with a frequency of lifetime cannabis use

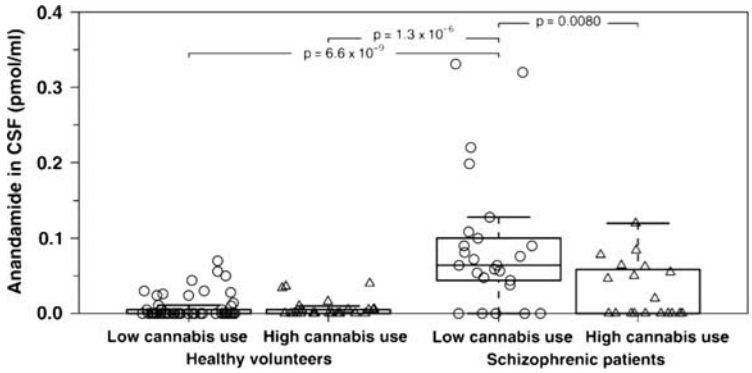

Fig. 2 Box-whiskers-plots (box shows 25th, 50th and 75th percentile of the empirical distribution; whiskers extend to smallest and largest value excluding outliers) of anandamide levels in cerebrospinal fluid (CSF) of schizophrenic patients and healthy volunteers. Left panel, anandamide levels in CSF of healthy volunteers with lowfrequency cannabis use ($\leq$ 5 times in life; column with circles, left panel; n = 55) or with high-frequency cannabis use ($<$ 20 and $>$50 times in life; column with triangles, left panel; n = 26). Right panel, anandamide levels in CSF of acute antipsychoticnaïve patients suffering from paranoid schizophrenia or schizophreniform psychosis with $\leq$ 5 times of cannabis use in life (column with circles, right panel; n = 25) or $>$20 times of cannabis use in life (column with triangles, right panel; n = 19).

of more than 20 times showed significantly lower levels of anandamide in CSF than schizophrenic patients who had used cannabis less than five times in total (Fig. 2). In addition, CSF anandamide levels from schizophrenic patients who frequently used cannabis did not significantly differ from matched controls.

3 Conclusions and Model

Accordingly, a model of dopamine/endocannabinoid interaction in acute schizophrenia was proposed in which over-activation of dopamine D_2 receptors is associated with an increased release of anandamide, counterbalancing dopamine-mediated psychotic symptoms by strengthening the endogenous adaptive feedback loop (Fig. 3). This model suggests an adaptation of endocannabinoid function over a longer period of time in response to a slowly, potentially stepwise, increasing level of dopaminergic neurotransmission. While the endocannabinoid system in this hypothetical model may fail to fully counterbalance dopaminergic over-excitation during the initial course of the illness, those patients able to raise levels of anandamide higher than others suffer fewer symptoms (Leweke et al. 2007a). This view is further supported by recent data from patients at risk of psychosis (initial prodromal states of psychosis) showing significantly elevated levels of anandamide in CSF already at this stage of their illness. In addition, those patients with higher levels of anandamide in CSF are less likely to develop frank psychosis during an observational period of at least 42 months (Leweke et al. 2007b).

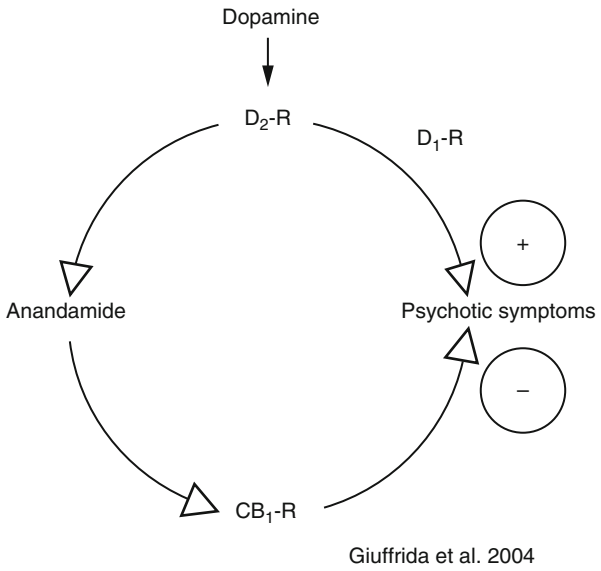

Fig. 3 Model of dopamine/endocannabinoid ineraction in acute schizophrenia. Increased anandamide release, associated with over-activation of dopamine D2 receptors, counterbalances dopamine-mediated psychotic symptoms.

Giuffrida et al. (1999, 2004) suggested a model based upon a dopamine/endocannabinoid interaction in which the activation of CB_1 receptors by anandamide serves as a feedback loop for D_2 receptor-mediated motor control in rodents (Giuffrida et al. 1999) as well as psychotic symptoms in humans (Giuffrida et al. 2004) (Fig. 2). Based on this model, chronic and more frequent administration of Δ^9-THC in schizophrenic patients may disrupt anandamide release and may, thereby, weaken the proposed inhibitory feedback loop on dopamine-mediated processes (Fig. 2). This model is further supported by the fact that schizophrenic patients treated primarily with dopamine D_2-antagonist antipsychotics show markedly lower anandamide levels in CSF than antipsychotic-naïve or those patients treated with $5HT_{2A}$-/weaker D_2-antagonistic antipsychotics (Giuffrida et al. 2004). For the first time, a potential neurobiological mechanism for the negative influence of more frequent use of Δ^9-THC-containing cannabis preparations on schizophrenia symptoms and outcome is provided.

Over recent years, our understanding of the pathophysiolgical role of the endocannabinoid system in schizophrenia has been expanded far beyond expectations. The pre-clinical and clinical data support the contention that this highly expressed regulatory neurotransmitter system is deeply involved in the underlying neurobiological processes in schizophrenia. However, many open questions and controversial results still remain and further research is required to clarify and extend the findings in this area. Successful outcomes will not only contribute to our understanding of this complex disease but will also open new avenues for the treatment of affected patients.

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