

Therapeutic Potential of Cannabinoids in Psychosis

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ABSTRACT

Over recent years, the interest in the endocannabinoid system (ECS) as a new target for the treatment of schizophrenia has evolved. The ECS represents one of the most relevant neurotransmitter systems in the brain and mainly fulfills a homeostatic role in terms of neurotransmission but also with respect to inflammatory processes. Two main approaches to the modulation of endocannabinoid functioning have been chosen so far. First, the selective blockade or inverse agonism of the type 1 cannabinoid receptor has been tested for the improvement of acute psychotic symptoms, as well as for the improvement of cognitive functions in schizophrenia. This was not effective in either case. Second, the modulation of endocannabinoid levels by use of the phytocannabinoid cannabidiol and selective fatty acid amide hydrolase inhibitors has been proposed, and the antipsychotic properties of cannabidiol are currently being investigated in humans. Unfortunately, for most of these trials that have focused on psychopathological and cognitive effects of cannabidiol, no published data are available. However, there is first evidence that cannabidiol may ameliorate psychotic symptoms with a superior side-effect profile compared with established antipsychotics. In conclusion, several clinical trials targeting the ECS in acute schizophrenia have either been completed or are underway. Although publicly available results are currently limited, preliminary data indicate that selected compounds modulating the ECS may be effective in acute schizophrenia. Nevertheless, so far, sample sizes of patients investigated are not sufficient to come to a final judgment, and no maintenance studies are available to ensure long-term efficacy and safety.

Keywords: Antipsychotic, Cannabidiol, Cannabinoid receptors, Clinical trial, Endocannabinoids, Schizophrenia

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There is a long-standing history of the use of cannabis for both recreational and medicinal purposes. In the 19th century, Moreau de Tours (1) provided the first systematic work on the effects of acute cannabis intoxication: besides happiness and excitement, he described a plethora of symptoms resembling those of schizophrenia, including delusions, disorganized speech, and other psychotic symptoms. Far less recognized, his initial description (1) included the therapeutic use of cannabis in mental disorders. He treated seven patients suffering from depression as well as manic disorders with cannabis and, in some cases, observed temporary improvement, e.g., with regard to mood, sleep, and appetite. Unfortunately, the effects were quite mixed, likely due to the nonstandardized cannabinoid preparations available at that time. Noteworthy, in the 1930s, Beringer *et al.* (2) described in detail the effects of a standardized cannabis extract on altered perception, disorganized speech and thought, and emotion.

In the 1940s, the acutely hallucinogenic principal component of *Cannabis sativa*, tetrahydrocannabinol, was chemically identified and patented by Adams (3) and in parallel by Nobel laureate Todd (4). Allentuck and Bowman (5) were able to demonstrate the clinical activity of tetrahydrocannabinol in comparison with cannabis extract. In the 1960s, Gaoni and Mechoulam (6) made an important contribution to the field by

fully clarifying the exact position of the double bonds of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) using the then available nuclear magnetic resonance spectroscopy.

It took another 25 years to identify two G-protein-coupled receptors as type 1 cannabinoid receptor (CB₁R) (7,8) and type 2 cannabinoid receptor (CB₂R) (9) and to subsequently discover two major endogenous ligands to these receptors, *N*-arachidonylethanolamine (anandamide) (10) and 2-arachidonoyl-*sn*-glycerol (11,12). Most recently, Lutz *et al.* (13) provided a profound review of the endocannabinoid system (ECS). The enzymes involved in formation and hydrolysis of endocannabinoids are summarized in Table 1.

The other main component of cannabis, the nonhallucinogenic cannabidiol, was also characterized and later patented by Adams *et al.* (14). In contrast to Δ^9 -THC, cannabidiol does not relevantly bind to CB₁R and CB₂R but may have antipsychotic properties.

At present, only a few studies are available on the therapeutic use of cannabinoids in psychosis and schizophrenia. In particular, it has been controversial for a while as to whether the ECS plays a protective or harmful role in the pathogenesis of schizophrenia (15). Thus, two main approaches targeting the ECS have been systematically studied so far: first, trials using CB₁R antagonists to treat both psychotic and cognitive

Table 1. Summary of the Enzymes Involved in Formation and Hydrolysis of the Endocannabinoids Anandamide and 2-Arachidonoyl-*sn*-Glycerol

	Anandamide	2-Arachidonoyl- <i>sn</i> -Glycerol (2-AG)
Synthesizing Enzymes	<i>N</i> -acyltransferase (NAT) ^a	Phospholipase C-β (PLC-β) ^a
	<i>N</i> -acyl phosphatidylethanol-selective phosphor-lipase D (NAPE-PLD) ^a	Diacylglycerol lipase-α (DGL-α) ^a
	α/β-hydrolase 4 (ABDH 4)	Phospholipase A ₁ (PLA ₁)
	Phosphodiesterase	Lyso-phospholipase C (lyso-PLC)
	Phospholipase A ₂ (PLA ₂)	
	Lyso-phospholipase D (lyso-PLD)	
Degrading Enzymes	Fatty acid amide hydrolase (FAAH 1; FAAH 2) ^a	Monoacylglycerol lipase (MAGL) ^a
	<i>N</i> -acylethanolamine-hydrolyzing acid amidase (NAAA)	α/β-hydrolase 6 and 12 (ABDH 6; ABDH 12)
	Cyclooxygenase 2 (COX2)	Cyclooxygenase 2 (COX2)
	Lipoxygenase 12 and 15	Lipoxygenase 12 and 15
	Cytochrome p450	Cytochrome p450

Modified with permission from Rohleder and Leweke (99).

^aEnzyme of the most important biosynthesis and inactivation pathways.

symptoms of schizophrenia, and second, trials modulating metabolizing enzymes of endocannabinoids. In addition, there is a single clinical case series on dronabinol (Δ^9 -THC) in treatment-refractory severe chronic schizophrenia (16).

METHODS

We searched PubMed until March 31, 2015, for randomized clinical trials (RCT) investigating cannabinoid receptor antagonists in schizophrenia or psychotic disorders (any diagnostic criteria). The search terms were schizophreni* AND (endocannab* OR cannab* OR anandamide* OR 2-AG OR FAAH inhibitio* OR MAGL inhibitio*) with article types as clinical trials or randomized controlled trials. There were no restrictions for drugs and doses used or language. In addition, the clinical trial registers clinicaltrials.gov and clinicaltrialsregister.eu were searched for completed or ongoing studies investigating cannabinoid-receptor antagonists or endocannabinoid modulators, such as cannabidiol, and the selective fatty acid amide hydrolase (FAAH)-inhibitors URB-597 (KDS-4103), OL-135, PF-3845, PF-04457845, ST-4070, JNJ-1661010, arachidonoyl serotonin (additionally a transient receptor potential vanilloid type 1 [TRPV1] antagonist), AM-3506, JP-104, and Cay-10570, as well as monoacylglycerol lipase (MAGL) inhibitors in schizophrenia or psychotic disorders.

RESULTS

Clinical trials were identified first for CB₁R antagonists in the treatment of psychotic or cognitive symptoms of schizophrenia (17) and second for modulation of the activity of one of the ECS ligands. Third, a single case series on Δ^9 -THC in chronic treatment-resistant schizophrenia was found. Published clinical trials and selected case series are provided in Table 2.

Cannabinoid-Receptor Antagonists

The very first neurobiological evidence for a potential role of the ECS in schizophrenia was published in 1999, when Leweke *et al.* (18) reported on elevated levels of anandamide in cerebrospinal fluid (CSF) in acute schizophrenia. At that

time, it was controversial if anandamide acted similar to the CB₁R agonist Δ^9 -THC and thereby an activated ECS could relate to psychotic symptoms in acute disease states (15). Alternatively, an adaptive or even protective role of anandamide was discussed and demonstrated in 2004 (19). However, the first hypothesis made it appealing to block CB₁R for therapeutic purposes in schizophrenia.

Two CB₁R antagonists/inverse agonists have been clinically investigated in schizophrenia so far: rimonabant (SR-141716A) and AVE1625. Rimonabant has been tested for both improvement of psychotic symptoms in acute schizophrenia and enhancement of cognitive functioning. Molecular biology and animal studies (20) initially suggested antipsychotic properties of rimonabant. In a rodent behavioral model, the compound suppressed the locomotor hyperactivity induced in gerbils by propsychotic drugs (cocaine, *d*-amphetamine, morphine, and WIN 55212-2 intraperitoneally) (21). In addition, it was demonstrated by dopamine microdialysis experiments in awake rats that rimonabant stimulates *c-fos* expression in limbic and cortical regions with a regional pattern of distribution similar to that observed for newer antipsychotics (22).

However, in a large-scale, explorative randomized placebo and active controlled RCT investigating four novel candidate compounds in 481 acute schizophrenia patients, there was no significant effect, beneficial or deleterious, on psychopathology in the 72 patients treated with rimonabant (20 mg/day) versus placebo (23).

CB₁R binding studies laid the groundwork for the investigation of cognitive effects of CB₁R antagonists in schizophrenia (17). Postmortem tissue studies using receptor autoradiography or radioimmunocytochemistry and more recently in vivo positron emission tomography studies with selective radioligands strongly indicated a role of CB₁R in schizophrenia. The majority of postmortem autoradiography studies observed an increased CB₁R binding in schizophrenia in the anterior and posterior cingulate cortex and in the dorsolateral prefrontal cortex in particular (24–27). Unaltered (28) or decreased CB₁R binding (29) or lower levels of CB₁R immunoreactivity (30,31) have also been described. Lower CB₁R messenger RNA (mRNA) levels were reported using

Table 2. Published Trials and Case Series on Cannabinoid-Based Treatments of Schizophrenia

Investigated Drug	Design, Condition, Duration, and Comparator	N ^a (Active)	Primary Efficacy End Point	Outcome	References
Type 1 Cannabinoid Receptor Antagonists					
Rimonabant (20 mg/day)	Double-blind five-arm placebo-controlled RCT, acute schizophrenia, 6 weeks	72	Psychotic symptoms (PANSS)	No significant effect	(23)
Rimonabant (20 mg/day)	Double-blind, placebo-controlled RCT, schizophrenia, 16 weeks	17	Cognitive impairment (RBANS)	Significant improvement with placebo but not rimonabant	(41)
AVE1625	Double-blind, placebo-controlled, dose-ranging, add-on RCT, schizophrenia, 24 weeks	655	Cognitive impairment (MATRICS)	Terminated - interim analysis revealed insufficient level of efficacy	(42)
Type 1 Cannabinoid Receptor Agonists					
Dronabinol (up to 20 mg/day)	Open-label, case series, treatment-resistant schizophrenia	6	Clinical impression (CGI), Psychotic symptoms (BPRS)	Improvement in four patients, reduction of core psychotic symptoms in three of the four responders	(16)
Cannabinoid Modulators					
Cannabidiol (600 to 800 mg/day)	Double-blind, active-controlled RCT, acute schizophrenia, 4 weeks	21	Psychotic symptoms (PANSS/ BPRS)	Significant improvement vs. baseline on days 14 and 28 for CBD and amisulpride, superior side-effect profile for CBD vs. amisulpride	(55)
Cannabidiol (1500 mg/day)	Single case report, open-label, treatment-resistant schizophrenia	1	Psychotic symptoms	Improvement in a treatment-resistant patient	(63)
Cannabidiol (up to 1280 mg/day)	Open-label, case series, treatment-resistant schizophrenia	3	Psychotic symptoms (BPRS)	One patient showed mild improvement	(64)

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCT, randomized clinical trial.

^aNumber of patients treated with cannabinoid compound.

in situ hybridization (30), while others observed an unchanged CB₁R mRNA expression in brains of antipsychotic-naïve and antipsychotic-treated schizophrenic individuals (29). Potential explanations for this are, first, different cohort structures (e.g., antipsychotic medication, stage of the disease, comorbid factors); second, observed differences of CB₁R protein levels reflecting the dynamic modulation of CB₁R expression due to postmortem tissue changes; and third, an agonist-induced internalization of CB₁R in hippocampal neurons indicating an intracellular reserve in CB₁R protein (32). This might explain divergent results when comparing CB₁R protein of the cell surface with total CB₁R protein. Fourth, some CB₁R antibodies may not quantitatively or qualitatively stain receptors in all cell types or subcellular compartments and may therefore fail to detect receptors detectable using radioligand binding (27). Fifth, the conformational change in CB₁R by binding of an allosteric modulation site increases the affinity of ligands such as CB₁R agonists for the orthosteric binding site on CB₁R (33); thereby, higher CB₁R binding may only reflect a higher receptor affinity and not an obligatory higher CB₁R density. Interestingly, Volk *et al.* (34) found a negative correlation between lower CB₁R mRNA and protein immunoreactivity in postmortem tissue of schizophrenic patients. They concluded that the total amount of CB₁R may be reduced, while higher levels of membrane-bound CB₁R may be available for ligand binding.

Several studies have indicated that CB₁R activation reduces gamma-aminobutyric acid (GABA) release from axon terminals of cholecystikinin-containing GABA basket neurons and suppresses type A GABA receptor-mediated inhibitory postsynaptic currents in pyramidal neurons (35–37). Thus,

lower levels of CB₁R may represent a compensatory response to the decrease in prefrontal GABAergic tone (30,38). Accordingly, CB₁R antagonists could decrease GABAergic interneuron inhibition, increase GABAergic-mediated inhibition of prefrontal pyramidal neurons, and consequently enhance cognition in schizophrenia. In contrast, the two in vivo positron emission tomography studies in the field using selective CB₁R radioligands both show significantly altered availabilities of CB₁R in frontal cortical and other brain areas (39,40).

The hypothesis of a compensatory downregulation of CB₁R in the frontal cortex in schizophrenia to improve cognition was tested in two large-scale RCTs. In a 16-week, double-blind, placebo-controlled RCT in 17 patients, a neurocognitive battery (the Repeatable Battery for the Assessment of Neuropsychological Status) was administered before and after treatment. Rimonabant (20 mg/day) showed only very limited effects on cognitive functioning (41), while the placebo group showed a significant improvement of Repeatable Battery for the Assessment of Neuropsychological Status total scores. Thus, this small sample size investigation did not indicate a positive effect of CB₁R antagonists on cognition in schizophrenia.

Sanofi (42) initiated another RCT investigation of the procognitive effects of another selective CB₁R antagonist, AVE-1625. This 24-week, multicenter, double-blind, parallel-group, dose-ranging RCT on the efficacy and safety of three oral doses and placebo as add-on to antipsychotic medication tested the effects of AVE-1625 in 873 stable schizophrenia patients using the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (43). According to clinicaltrials.gov, this study has

been terminated, “following a pre-specified interim analysis and Data Monitoring Committee recommendation due to insufficient level of efficacy” (42).

Rimonabant was tested independently in a 16-week double-blind RCT for weight reduction in overweight schizophrenia patients. Sixty participants were planned, but the study was terminated when rimonabant was withdrawn from worldwide marketing due to psychiatric side effects. Thus, only 15 patients were randomized. A mild but significant improvement was found in the Brief Psychiatric Rating Scale total score, anxiety/depression, and hostility factors (44), as well as an observed trend toward lower caloric consumption for rimonabant (45).

In summary, the two CB₁R antagonists/inverse agonists tested in schizophrenia had no significant effects on psychopathology and cognition.

Dronabinol

Δ^9 -THC, also known as dronabinol in its medicinal purified form, is the major propsychotic compound of cannabis (3,5). It has been approved by the US Food and Drug Administration for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome, as well as nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Epidemiologic data indicate a strong relationship between cannabis use and psychosis and schizophrenia beyond transient intoxication, with an increased risk of any psychotic outcome in individuals who have ever used cannabis (46). The effect seems dose dependent, with higher risk with more frequent cannabis use. Recently, the importance of the cannabinoid composition of cannabis was investigated. Morgan and Curran (47) analyzed hair samples of 140 volunteers. Δ^9 -THC-only subjects showed higher levels of positive schizophrenia-like symptoms compared with no-cannabinoid and Δ^9 -THC + cannabidiol subjects and higher levels of delusions compared with those in the no-cannabinoid group. In a case-control study, 280 first-episode psychosis patients and 174 healthy control subjects were investigated, with no significant difference in whether they had ever taken cannabis or age at first use found (48). Yet high- Δ^9 -THC (skunk-like) cannabis carries the highest risk for psychotic disorders, indicating that Δ^9 -THC may be the driving force behind an increased risk of psychosis (48). Additional studies raise evidence that Δ^9 -THC may also have a negative impact on the course of schizophrenia (49) and eventually the function of the ECS (50,51). It is noteworthy that although Δ^9 -THC acts as an agonist on CB₁R, its action in complex neuronal networks may result in a functional disruption of the ECS rather than mimicking the effects of endocannabinoids (52). This may be linked to a more wide and tonic activation of CB₁R by Δ^9 -THC when compared with endocannabinoids (52). Although recent studies have demonstrated a correlation between (high-potency) cannabis use and psychotic disorders, a causal relationship is still discussed as controversial.

While Δ^9 -THC has mainly been recognized as having a negative impact on psychosis and schizophrenia, a positive effect of up to 20 mg/day of dronabinol in four out of six

treatment-resistant chronic schizophrenia patients on antipsychotic polypharmacy was reported in an open-label case series (16). This is in contrast to the induction of acute psychotic symptoms by Δ^9 -THC in stable schizophrenia (53).

Modulators of Endocannabinoid Activity

Besides the blockade of cannabinoid receptors, there are herbal/natural cannabinoids, as well as synthetic compounds, that are suggested to modulate, for example, the enzymatic apparatus that metabolizes endogenous cannabinoids. While the latter compounds currently focus on inhibition of the FAAH and/or the MAGL enzymes, of the phytocannabinoids, cannabidiol has come into focus.

Cannabidiol

In contrast to Δ^9 -THC, cannabidiol represents a nonhallucinogenic component of *Cannabis sativa*. Several binding studies showed no significant affinity of cannabidiol to CB₁R and CB₂R (7,54–57), and most efficacy studies found no clear receptor response (8,57–59). However, it was reported that cannabidiol partly antagonizes CB₁R agonists like WIN-55212 and CP-55940 (58,60,61). More importantly, cannabidiol may inhibit the hydrolysis of anandamide and its related fatty acids palmitoylethanolamide and oleoylethanolamide by blocking FAAH (54,62).

In 1995, Zuardi *et al.* (63) reported on a case of treatment-resistant schizophrenia, where cannabidiol monotherapy (up to 1500 mg/day) was able to improve symptoms. In a subsequent case series of three additional treatment-resistant cases on mixed antipsychotic polypharmacy, they reported a slight improvement in one case only (cannabidiol dosages: 150–1280 mg/day) with no relevant side effects (64).

Meanwhile, five RCTs and one open-label study investigating the acute antipsychotic and potential procognitive effects of cannabidiol have been initiated; only two have published data.

The first double-blind, parallel-group RCT comparing cannabidiol with the highly effective, selective dopamine D_{2/3}-receptor antagonist amisulpride (65) was published in 2012 (54). Forty-two schizophrenic patients were randomized, receiving either cannabidiol (600–800 mg/day) or amisulpride (600–800 mg/day) for 4 weeks. Both conditions showed significant clinical improvement assessed by the Positive and Negative Syndrome Scale (PANSS) (66) and the Brief Psychiatric Rating Scale. Albeit the number of cases of this explorative phase IIa RCT was not sufficient to test for superiority or noninferiority, the antipsychotic effects of both drugs were comparable. Cannabidiol, however, possessed a significantly superior side-effect profile (no prolactin increase, weight gain, or extrapyramidal symptoms). Remarkably, the reduction of psychotic symptoms was significantly associated with a significant increase of anandamide levels in serum for cannabidiol but not for amisulpride. These results support the hypothesis that cannabidiol exerts its antipsychotic properties by a moderate FAAH inhibition (54).

A second RCT by this group (67) compared cannabidiol with placebo in a double-blind cross-over design. Twenty-nine patients were enrolled and treated with either cannabidiol (600 mg/day) or placebo for 2 weeks. Treatment was subsequently crossed over and patients were treated for 2 more weeks. Results are pending publication.

A third double-blind RCT by Ranganathan *et al.* (68) compared cannabidiol (600 mg/day) versus placebo as an add-on to a stable risperidone treatment focusing on the improvement of cognitive symptoms. Thirty-six schizophrenia patients were treated for 6 weeks and assessed by use of the Measurement and Treatment Research to Improve Cognition in Schizophrenia. Results have not been published.

Recently, a fourth double-blind, parallel-group RCT investigating 88 randomized patients suffering schizophrenia or related disorders (e.g., schizoaffective or schizophrenia-like disorder) for 6 weeks was completed (69). In contrast to the aforementioned clinical trials, either cannabidiol (1000 mg/day) or placebo was administered in an oily solution (GW42003) as add-on to an antipsychotic medication that had to have been stable for at least 4 weeks. Patients were required to have a PANSS total score of no less than 60 points (whereas ≥ 75 points is standard in respective acute RCTs). However, while not formally published in a peer review process yet, the sponsor of this trial recently announced that cannabidiol was consistently superior to placebo with regard to psychopathology and showed no relevant side-effect profile (70).

Two more clinical trials are currently recruiting patients suffering acute early-stage schizophrenia. In a multicenter double-blind, active- and placebo-controlled, parallel-group RCT (71), the efficacy and safety of a 4-week cannabidiol treatment (800 mg/day) is compared with placebo and olanzapine. One hundred fifty acute (PANSS ≥ 75), early-stage schizophrenic patients (within 3 years after initial diagnosis) will be randomized. The second ongoing study is an open-label, add-on trial investigating the efficacy of cannabidiol (200 to 800 mg/day, 6 weeks) in 20 first-episode psychotic patients who did not recover despite preceding treatment with at least one standard antipsychotic (72).

In summary, currently available data on the acute antipsychotic effects of cannabidiol in schizophrenia are still limited with promising initial results. Yet there is a consistent signal pointing to a preferable side-effect profile of cannabidiol. Unfortunately, current trials are limited to 6 weeks of treatment at maximum. No information on long-term efficacy and tolerability is available yet. To prove the safety and efficacy of cannabidiol in schizophrenia, large-scale clinical trials both in the acute treatment, as well as in the maintenance phase, for 6 months or even longer are needed.

FAAH and/or MAGL Inhibitors

With regard to modulators of the enzymatic apparatus that metabolizes endogenous cannabinoids, solely one of anandamide's metabolizing enzymes, FAAH, has been targeted [e.g., (73,74)], while selective MAGL inhibitors for 2-arachidonylethanolamide or compounds blocking both enzymes have not been investigated so far in humans. Despite the findings on effects and potential mechanism of action of cannabidiol in acute schizophrenia, no trials have been performed using a FAAH inhibitor. Several of these compounds have been reported as safe drugs in phase I clinical trials and have already been tested in other conditions (73).

DISCUSSION

The ECS represents a major homeostatic system and may play a role in several disorders, including a number of psychiatric conditions.

In 1997, a "cannabinoid hypothesis of schizophrenia" was suggested (15). By then, it was not clear whether endocannabinoids had a protective or deleterious role in schizophrenia. Today, an increasing body of evidence suggests that an upregulation of anandamide (75) and an increase in CB₁R availability (40) in certain brain areas serve a counter-balancing if not protective role toward psychotic symptoms in schizophrenia and at-risk mental states.

Since data from rodents suggested an antipsychotic profile of SR141716 (rimonabant) (21) and based on first neurobiological data, the investigation of CB₁R antagonistic/inverse agonistic compounds such as rimonabant seemed promising. However, the reported inverse correlation between psychotic symptoms and increased anandamide in CSF (19), as well as regionally increased availability of CB₁R in acute, unmedicated early schizophrenia (40), may contribute to our understanding of why this treatment approach may have failed.

The case series on dronabinol (Δ^9 -THC) in treatment-resistant schizophrenia (16) most likely does not lead to a general treatment option. Yet it underlines the complexity of the function of the ECS and its interplay with other neurotransmitters in schizophrenia. In this context, the use of certain antipsychotics may be associated with a reduced release of anandamide (19). It may be speculated that the resulting lack of anandamide tone in certain brain areas may, in turn, be partially compensated by Δ^9 -THC under these particular circumstances (52).

As reviewed in Leweke (75), there is evidence that anandamide has a protective role in schizophrenia. This hypothesis is supported by the fact that at-risk mental states patients with higher anandamide in CSF seem to have a lower risk to transition into frank psychosis (76). Therefore, it has been suggested that anandamide is able to counteract neurotransmitter abnormalities such as dopaminergic abnormalities in both conditions (Figure 1A). Supporting this model, the treatment with modern antipsychotics blocking serotonin 2A receptors seems to rarely influence anandamide, whereas those antipsychotics that antagonize dopamine at D₂ and D_{2/3} receptors were accompanied by CSF anandamide levels close to control subjects (19). Thus, increasing anandamide by FAAH inhibition seems to be a viable new treatment approach in schizophrenia (Figure 1B).

Unfortunately, none of the available FAAH inhibitors have been investigated in a RCT in schizophrenia so far, except for cannabidiol, which has a mode of action that is yet controversial (54–56,61). However, it seems to exhibit its main antipsychotic effect by blocking FAAH and thereby raising anandamide (54). In mouse brain microsomes (77), cannabidiol decreased FAAH activity by up to 66% (160 μ mol/L). In N18TG2 cell membrane preparations, cannabidiol inhibited FAAH with a half maximal inhibitory concentration (IC₅₀) < 100 μ mol/L (54) or 28 ± 3 μ mol/L (78), respectively. The lowest IC₅₀ was found in homogenates of rat brain membranes. A cannabidiol concentration of already 10 μ mol/L to 15.2 μ mol/L was sufficient to reduce FAAH activity by about 50% (79,80). In addition, it was demonstrated that cannabidiol also may block an anandamide transporter, since it inhibited anandamide uptake by RBL-2H3 cells (78,80,81), as well as by N18TG2 cells (54), with an IC₅₀ of about 22 to 25.3 μ mol/L. A FAAH-like anandamide transporter, which seems to be a

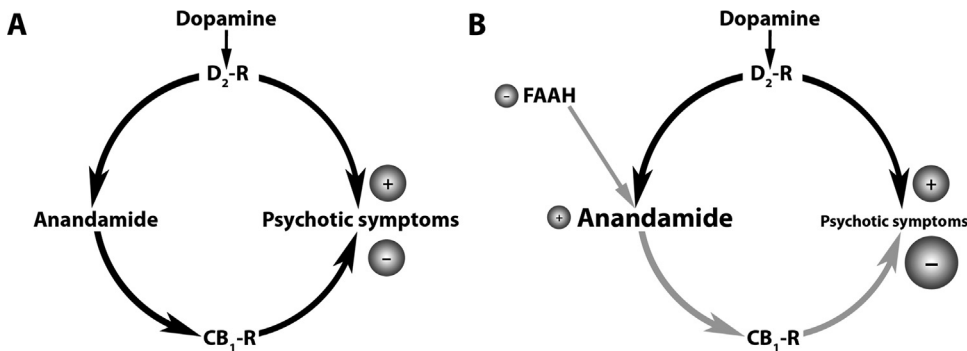


Figure 1. (A) Schematic model of the systemic interaction of anandamide activation of type 1 cannabinoid receptors (CB₁-R) and psychotic symptoms induced by dopamine D₂-receptor (D₂-R) activation. (B) Proposed action of fatty acid amide hydrolase (FAAH) inhibitors on the interaction depicted in (A). [Modified with permission from Leweke and Koethe (100)].

splicing variant of the *Faah 1* gene, has been described (82). Although controversially discussed, it may be speculated that cannabidiol eventually may bind to similar binding sites of the FAAH and FAAH-like anandamide transporter proteins and thereby block both anandamide degradation and uptake. In addition, the increase of peripheral anandamide after systemic administration of cannabidiol is strongly related to its anti-psychotic effects (Figure 1B) (54). Other suggested molecular targets may also contribute to cannabidiol's antipsychotic effects, but further studies are needed to prove their pharmacologic relevance. For example, it was shown that cannabidiol binds to the peroxisome proliferator-activated receptor- γ , which contributes to metabolic regulation and energy homeostasis with an IC₅₀ of 5 $\mu\text{mol/L}$ (83). Therefore, cannabidiol may also enhance cerebral glucose metabolism via peroxisome proliferator-activated receptor- γ activation and thereby ameliorate the observed disturbances of glucose metabolism in schizophrenia (84).

Furthermore, the activation of TRPV1 receptors (TRPV1Rs) was suggested as an alternative mechanism. In HEK-HsTRPV1 cells, a maximal effect of about 44.7% to 64.1% with a half maximal effective concentration of 1.0 to 3.5 $\mu\text{mol/L}$ was observed (78,80). One study using the glutamatergic MK-801 animal model found that pretreatment with the TRPV1R antagonist capsazepine prevented reversal of the MK-801-induced prepulse inhibition decrease (85). However, capsazepine blocks nicotinic cholinergic receptors (86), as well as calcium channels (87), and these mechanisms might have contributed to the effect. It is noteworthy that TRPV1Rs mediate the perception of spiciness. Upon stimulation, this subjective perception may be expected if this mechanism is relevant at the dosage used in humans—a side effect so far not reported [e.g., (54,88)]. Thus, evidence for a role of TRPV1R activation in schizophrenia is lacking. However, the influence of TRPV1Rs on dopaminergic (89) and glutamatergic neurotransmission (90) may be relevant in schizophrenia.

Cannabidiol may also regulate serotonin levels by facilitation of serotonin 1A (5HT_{1A}) receptor-mediated neurotransmission, as cannabidiol displaced the 5HT_{1A} receptor agonist [3H]8-OH-DPAT by about 73% at 16 $\mu\text{mol/L}$ in Chinese hamster ovary cells transfected with the human receptor (91). In the same study, cannabidiol increased [35S]GTP γ S binding by about 67% at 16 $\mu\text{mol/L}$. In rat brainstem membrane preparations, cannabidiol neither displaced [3H]8-OH-DPAT binding nor

stimulated [35S]GTP γ S binding at up to 10 $\mu\text{mol/L}$, but it increased the maximal efficacy of 8-OH-DPAT at 100 nmol/L. Interestingly, cannabidiol had no effect on maximal efficacy of 8-OH-DPAT at 1, 10, or 31.6 nmol/L or at 1 $\mu\text{mol/L}$ (92). Further studies are needed to elucidate more precisely the binding affinity and efficacy of 5HT_{1A} receptor activation by cannabidiol.

Additional suggested molecular targets of cannabidiol are, among others, the GPR55 receptor, α 3 glycine receptors, enzymes of the arachidonic acid cascade, voltage-gated calcium channels or mitochondrial sodium ion/calcium ion exchange, nitric oxide signaling, and inflammatory cytokines (93). However, these mechanisms have not been directly linked to the antipsychotic properties of cannabidiol but may become relevant in other neuropsychiatric conditions (94).

The question arises of how to reconcile the hypothesized protective role of elevated endocannabinoid levels with the triggering and worsening of psychotic symptoms following acute or chronic cannabis consumption. It was demonstrated that elevations in anandamide by blocking FAAH resulted in multiple CB₁- and/or CB₂-dependent behavioral effects in rodents, including reduction in pain sensation, inflammation, anxiety, and depression (95). Other well-known behavioral effects of direct CB₁R agonists, such as hypothermia and movement disorders, were not observed in the FAAH-disrupted animals, suggesting a ligand-dependent and perhaps even a dose-dependent activation pattern of the CB₁R. This is in line with the observation of Δ^9 -THC-like effects after dual inhibition of both FAAH and MAGL (96). Δ^9 -THC seems to mimic activity of both endocannabinoids due to overall CB₁R activation, whereas anandamide and 2-arachidonylglycerol, respectively, display distinct activation patterns and regional distribution (97).

In summary, the substantial evidence from preclinical studies for a relevant role of the ECS in schizophrenia and the potential to therapeutically target this system has led to several clinical trials focusing on CB₁R antagonists and cannabidiol. While the latter showed promising antipsychotic effects (if reported), there is substantially more clinical work needed to prove the efficacy and safety of cannabidiol in acute and maintenance schizophrenia treatment. Furthermore, the current evidence that the antipsychotic action of cannabidiol may be mediated by FAAH inhibition might bring selective FAAH inhibitors into clinical trials in this area of urgent need for mechanistically new drugs (98).

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