Review

Biological Psychiatry

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 (CB_1R) (7,8) and type 2 cannabinoid receptor (CB_2R) (9) and to subsequently discover two major endogenous ligands to these receptors, *N*-arachidonoylethanolamine (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 CB_1R and CB_2R 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 CB_1R antagonists to treat both psychotic and cognitive

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

	Anandamide	2-Arachindonoyl-*sn*-Glycerol (2-AG)
Synthesizing Enzymes	*N*-acyltransferase (NAT)[a]	Phospholipase C-β (PLC-β)[a]
	N-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]
	N-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).
[a]Enzyme 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 CB_1R 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 CB_1R 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 CB_1R for therapeutic purposes in schizophrenia.

Two CB_1R 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).

CB_1R binding studies laid the groundwork for the investigation of cognitive effects of CB_1R 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 CB_1Rs in schizophrenia. The majority of postmortem autoradiography studies observed an increased CB_1R binding in schizophrenia in the anterior and posterior cingulate cortex and in the dorsolateral prefrontal cortex in particular (24–27). Unaltered (28) or decreased CB_1R binding (29) or lower levels of CB_1R immunoreactivity (30,31) have also been described. Lower CB_1R messenger RNA (mRNA) levels were reported using