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Therapeutic Potential of Cannabinoids in Schizophrenia

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Abstract: Increasing evidence suggests a close relationship between the endocannabinoid system and schizophrenia. The endocannabinoid system comprises of two G protein-coupled receptors (the cannabinoid receptors 1 and 2 [CB1 and CB2] for marijuana's psychoactive principle Δ^9-tetrahydrocannabinol), their endogenous small lipid ligands (namely anandamide [AEA] and 2-arachidonoylglycerol [2-AG], also known as endocannabinoids), and proteins for endocannabinoid biosynthesis and degradation. It has been suggested to be a pro-homeostatic and pleiotropic signalling system activated in a time- and tissue-specific manner during pathophysiological conditions. In the brain, activation of this system impacts the release of numerous neurotransmitters in various systems and cytokines from glial cells. Hence, the endocannabinoid system is strongly involved in neuropsychiatric disorders, such as schizophrenia. Therefore, adolescence use of *Cannabis* may alter the endocannabinoid signalling and pose a potential environmental risk to develop psychosis. Consistently, preclinical and clinical studies have found a dysregulation in the endocannabinoid system such as changed expression of CB1 and CB2 receptors or altered levels of AEA and 2-AG . Thus, due to the partial efficacy of actual antipsychotics, compounds which modulate this system may provide a novel therapeutic target for the treatment of schizophrenia. The present article reviews current available knowledge on herbal, synthetic and endogenous cannabinoids with respect to the modulation of schizophrenic symptomatology. Furthermore, this review will be highlighting the therapeutic potential of cannabinoid-related compounds and presenting some promising patents targeting potential treatment options for schizophrenia.

Keywords: Δ^9-tetrahydrocannabinol, animal models, antipsychotics, cannabidiol, cannabis, CB receptors, endocannabinoid system, schizophrenia.

1. INTRODUCTION

1.1. Current Pharmacological Approach for the Treatment of Schizophrenia

Schizophrenia (SCZ) is a chronic mental disorder affecting about 1 % of the population worldwide. It is characterized by three broad clusters of symptoms which result in enormous personal suffering, as well as social and economic burden. These symptom domains include positive symptoms such as delusions, hallucinations, disorganized speech and behaviour; negative symptoms including anhedonia and social withdrawal; and cognitive impairments in sensory information processing, attention, working memory and executive functions [1]. They occur in different combinations, differing degrees of severity and in a changing pattern over time in each patient. Thus, SCZ is regarded as a complex and highly heterogeneous disorder. Hyperfunction of dopaminergic (DAergic) system in the mesolimbic pathway was the original tenet of the theory underlying the basis of SCZ because antipsychotic drugs blocked dopamine D2 receptors (D2Rs) and amphetamine which indirectly increases the release of dopamine (DA) exacerbated positive symptoms and thus led to the *dopamine hypothesis of schizophrenia* [2]. The treatment of SCZ was revolutionized more than 50 years ago with the discovery - by serendipity rather than design - that chlorpromazine and haloperidol (called today typical neuroleptics or the first generation antipsychotics) alleviate the psychotic manifestations such as hallucinations and delusions by blocking the D2Rs. From the 1970's the second generation or atypical antipsychotics (including clozapine, olanzapine, risperidone and aripiprazole) were developed. These drugs still act mainly by DA antagonism in the central nervous system (CNS) but their effects are mediated by serotonin receptor subtypes (5-HT_{2A}/5-HT_{2c}), D3R and/or D4R in addition to D2Rs. This class is also known as Multi-acting Receptor Targeted Antipsychotics (MARTA) and has less tendency to produce unwanted extrapyramidal side effects and hyperprolactinemia [3]. Although current pharmacological armamentarium is generally effective treating positive symptoms, it is less effective in treating the negative and cognitive symptoms. In addition, it can induce several side effects resembling Parkinson's disease (known as extrapyramidal side effects) and metabolic syndrome. Furthermore, a significant proportion of patients are refractory to the available drugs. Thus, there is a need to develop new approaches for treating SCZ and appropriate animal models for preclinical testing [4, 5]. It is well accepted that the pathophysiological mechanisms underlying

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SCZ cannot be explained by simple changes in monoamine signalling such as DA and 5-HT but involves more complex alterations in brain circuits including glutamate, GABA and acetylcholine [6]. Thus, all these neurotransmitters could represent potential targets for pharmacological intervention [4]. In accordance, a driven focus on rational discovery of highly selective drugs with new mechanisms such as the glutamatergic, cholinergic neurotransmission or neuropeptidergic signalling affecting intracellular signal transduction pathways appeared in the past decade. Unfortunately, none of these drugs have reached the market yet [7]. Therefore, the partial efficacy of current pharmacological armamentarium, since approximately one third of psychotic patients are non-responders raises the central question to be addressed in this review: Should the pharmacological exploitation of the endocannabinoid system (ECS) be a promising therapeutic approach for treatment of the behavioural dimensions which are dysregulated in SCZ?

1.2. Cannabis and Schizophrenia: Clinical Evidence

Cannabis (or marijuana) is the most frequently abused illicit "recreational" substance in the Western society. Its popularity is due to its capacity to alter sensory perception, to induce euphoria and to increase sociability. Although the association between *Cannabis sativa* and psychopathologic conditions had been known for thousands of years, only in the last 50 years the identification of the chemical structure of marijuana components, cloning of specific cannabinoid receptors and discovery of the ECS in the brain has triggered an exponential growth of studies to explore its real effects on mental health [8, 9]. The *Cannabis* plant contains over 100 terpenophenolic pharmacologically active compounds, known as cannabinoids. Of these, Δ^9-tetrahydrocannabinol (THC), characterized in 1964 [10], was identified as the main psychoactive component of *Cannabis* and later shown to act as a direct agonist on cannabinoid CB1 and CB2 receptors. Other cannabinoids include cannabidiol (CBD), cannabichromene and cannabigerol which do not induce any THC-like psychoactivity. They act via several mechanisms, including modulation of endocannabinoid system tone [11-13], interaction with transient receptor potential vanilloid 1 (TRPV1) channels [11] and serotonin 5-HT_{1A} receptors [14], and enhancement of adenosine signalling [15, 16]. As recently reviewed, the above mentioned mechanisms could underlie the positive effects induced by CBD treatment in preclinical and clinical studies of several disorders [17, 18].

In addition, accumulating evidence suggests that the recreational use of *Cannabis* during adolescence increases the relative risk for psychotic disorders. However, it is still unknown whether *Cannabis* use is an independent risk factor for SCZ or simply that the high prevalence of *Cannabis* use in SCZ patients as an attempt of self-medication due to *Cannabis's* euphoric effects and increased sociability to relieve negative symptoms [19, 20]. Furthermore its use may instead contribute as an environmental risk factor in vulnerable individuals with genetic mutation of COMT (Catechol-O-methyltransferase) enzymes [21] given that the majority of *Cannabis* users do not develop SCZ. Multiple lines of evidence have shown that frequent *Cannabis* consumption could down regulate anandamide (AEA) signalling in schizophrenic but not in healthy individuals. Also, it is associated to brain abnormalities in regions which are known to be rich in CB1 receptors such as the *anterior* and *posterior cingulated cortex*, as suggested by magnetic resonance imaging studies [22-25]. Although the exact relationship between *Cannabis* and SCZ is not fully elucidated, alterations of ECS elements as receptors and their endogenous activators seem to be involved in pathophysiology of SCZ. More specifically, previous studies have reported an increase in CB1 receptor binding in prefrontal area of brains from schizophrenic patients [26-31]. However, other studies failed to demonstrate any alteration [32] or reduction of CB1 density on the neuronal surface [33] and CB1 mRNA expression [34]. This contradiction might result from other neuroplastic alterations which further complicate the situation as another study detected lower CB1 receptor density but no differences on the level of CB1 mRNA expression [35]. Although several confounding factors such as *Cannabis* consumption, treatment with antipsychotics or different biochemical techniques used for the determination of CB1 receptors density and proteosynthesis might explain the apparent opposite results; in general, the presence of a dysfunction in CB1 receptors in selected brain regions of patients is supported. Furthermore, polymorphisms in the CB1 receptor gene CNR1, which could be correlated with an increased probability to develop psychosis, have also been described. Yet, the data are still controversial [23, 36-39].

Recently, the potential involvement of CB2 receptors in the pathogenesis of SCZ has been also supported by clinical findings. Patients with first-episode psychosis have a decreased expression of peripheral CB2 receptors in comparison to healthy controls [40, 41], which is in accordance with preclinical studies [42]. Thus, the altered expression of both receptors in SCZ patients confirms that they possess a certain homeostatic role.

Besides CB receptor dysfunctions, alteration in endocannabinoid levels seems to be implicated in the pathophysiology of SCZ as well. AEA levels have been found elevated in cerebrospinal fluid which were negatively correlated with psychotic symptoms and normalized by treatments with typical antipsychotics [43, 44]. In contrast, Muguruza *et al.* showed in cerebellum, hippocampus and prefrontal cortex of schizophrenic subjects lower AEA and higher 2-arachidonylglycerol (2-AG) levels [45]. Considering the glutamate hypothesis of SCZ and the role of 2-AG in the modulation of glutamatergic neurotransmission, this could represent an adaptive response to reduce glutamatergic hyperactivity in schizophrenics. Yet, it must be taken in to account that these alterations in opposite directions may be due to the different regulation of 2-AG and AEA levels under both physiological and pathological conditions [46]. Moreover, the difference of endocannabinoid levels in cerebrospinal fluid may be related to alterations in peripheral amounts of endocannabinoids, so the neuronal origin of the AEA and 2-AG in the cerebrospinal fluid remain conjectural [45]. Evidence of potential endocannabinoid signalling dysregulation in SCZ is also supported by the decreased expression of endocannabinoid synthesizing enzymes NAPE (N-acyl-phosphatidylethanolamine phospholipase) and DAGL (diacylglycerol lipase) in the peripheral blood mononuclear cells of patients with first episode of psychosis [40].

Based on the evidence presented above, functional abnormalities in the endocannabinoid system could be involved in the pathophysiology of SCZ; thus there is increasing interest to explore potential antipsychotic properties of compounds modulating the endocannabinoid signalling.

2. THE ENDOCANNABINOID SYSTEM (ECS)

The endogenous cannabinoid system (ECS) is a neuromodulatory system which is involved in a variety of physiological processes both in the brain and in the periphery. Within the CNS, it acts at the level of inhibitory and excitatory synapses in brain regions involved in emotional or non-emotional processes, and mediates the effects of THC, the main psychoactive constituent of *Cannabis* [47]. Increasing evidence suggest that altered EC signalling could play a role in the pathophysiology of several diseases such as pain and inflammation [48]; immunological disorders [49, 50]; neurodegenerative [9] and stress-related conditions [51]; obesity, metabolic [52, 53] and cardiovascular [54] diseases; cancer [55], gastrointestinal [53, 56] and hepatic [57] disorders. However, the exact pathophysiological mechanisms through which the ECS plays are not clearly understood at present.

The ECS consists of: (1) the cannabinoid receptors CB1 and CB2 [58-60], (2) the endogenous cannabinoid CB receptor agonists, AEA and 2-AG [61, 62], (3) a specific and not yet identified cellular uptake mechanism and [63, 64], (4) the enzymes for endocannabinoid biosynthesis: *N*-acyl-phosphatidylethanolamine-selective phosphodiesterase or glycerophosphodiesterase E1 and diacylglycerol lipase α or β [65, 66]; or degradation: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [67, 68], respectively for AEA and 2-AG. Despite it is well accepted that AEA is an endogenous agonist for cannabinoid CB1 receptors in the brain, some of the typical cannabimimetic effects of AEA are still present in transgenic mice lacking CB1 receptors. These effects may be due to AEA capability to act as a full agonist for the TRPV1 channels [69] resulting in mechanisms distinct from CB1 and CB2 receptors activation. However, additional "players" which target TRPV1 and/or CB1 receptors, including putative CB1 antagonist peptides like hemopressins, peroxisome proliferator-activated receptor-α (PPAR-α) and γ (PPAR-γ) ligands, such as oleoylethanolamide (OEA) or palmitoylethanolamide (PEA), and N-arachidonoyl-dopamine (NADA) are described as potential members of this signalling system. Although the existence of a third cannabinoid receptor subtype has been also suggested [70], to date only CB1 and CB2 receptors are recognized as G protein coupled receptors for endocannabinoids [71].

The cannabinoid CB1 and CB2 receptors which are encoded by two different genes on human chromosomes: 6q14-q15 (CNR1) and 1p36.11 (CNR2), are 7 transmembrane Gi/o coupled receptors that share 44 % protein identity but they display different pharmacological profiles and patterns of expression, a dichotomy that provides a unique opportunity to develop pharmaceutical approaches. The cannabinoid CB1 receptors are highly expressed in the *basal ganglia*, *frontal cortex*, *hippocampus* and *cerebellum*. They are expressed with a moderate/low density in the *amygdala*, *nucleus accumbens*, *medulla*, *periaqueductal gray* and *thalamus* [72]; as well as they are also described in non-neuronal cells of the brain such as microglia, oligodendrocytes and astrocytes [73]. Within these cortical areas, they are expressed at the GABAergic interneurons and glutamatergic neurons, which are the two major neuronal subpopulations expressing the CB1 receptors [74]. These neurotransmitter systems represent the two major opposing players regulating the excitation state of the brain; GABAergic interneurons being inhibitory and glutamatergic neurons being excitatory. Recent studies have demonstrated that CB1 receptors are also located in neurons of the *dorsal raphe nucleus* and in the *nucleus coeruleus* which are the major source of serotonin and noradrenalin in the brain [75, 76]. Thus, the direct or indirect modulation by monoamine activity on GABA and glutamate neurons could underlie the psychotropic and non-psychotropic effects of CB1 activation, respectively.

The cannabinoid CB2 receptors, also activated by AEA and 2-AG, are mostly peripherally located on immunological tissues. CB2 receptors are also detected in glia cells and in neurons of several brain regions such as *cerebral cortex*, *amygdala*, *hippocampus*, *hypothalamus* and *cerebellum* but in a much lesser extent [77, 78]. They play an important part in regulation of pain and inflammation even though recent data also suggest their involvement in emotional and non-emotional processes [79]. The observation that the elements of such neuromodulator system are prevalent throughout the neuroanatomical structures and circuits implicated in emotionality provides a rationale for the preclinical development of agents targeting the ECS to treat multiple psychiatric disorders including SCZ.

3. EFFECTS OF PHARMACOLOGICAL MANIPULATION OF THE ENDOCANNABINOID SIGNALLING IN PRECLINICAL AND CLINICAL STUDIES OF SCHIZOPHRENIA

Schizophrenia is a unique human disorder characterized by specific clinical manifestations such as delusions, thought disorders and hallucinations, which was described in 1896 by Kraepelin as *dementia praecox*. Due to the nature of the disease it is impossible to develop an animal model which would fully mimic its symptoms [1]. Thus, a greater understanding of the disorder might arise from modelling specific signs and symptoms, rather than mimicking the entire syndrome. In accordance with this strategy, the most reliable behavioural indices of positive symptoms in experimental models are hyperlocomotor activity and behavioural stereotypes which mimic the psychomotor agitation and presence of stereotyped behaviours in acutely psychotic patients since positive symptoms such as hallucinations and delusions cannot be measured in animals [80]. These are based on the rationale that the hyperfunctioning of the mesolimbic DAergic system, which seems to underlie the enhanced locomotor activity and stereotyped behaviour, is consistent with the human conditions where an enhanced subcortical DAergic activity plays a pivotal role to precipitate positive symptoms [81]. However, some behavioural aspects of SCZ seem to be modelled and objectively assessed in rodents. More specifically, hallmarks of negative symptoms, deficits in social behaviour and anhedonia, can be assessed both in humans and rodents with the pre-pulse inhibition (PPI) as an index of disrupted sensory gating abilities both in schizophrenic pa-

tients and in experimental animal models [82]. Interestingly, the various cognitive deficits in SCZ, as identified by the NIH (National Institute of Health) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, could be experimentally assessed by the use of specific rodent behavioural tasks [83]. As recently estimated, more than 20 different rodent models of SCZ have been developed, which fit into four different categories depending on the type of manipulation, namely 1) pharmacological, 2) genetic, 3) lesion based and 4) neurodevelopmental models. First experimental models were developed on the basis of the theory that SCZ is a disorder related to an excessive DAergic activity; accordingly, the DAergic agents such as amphetamine and apomorphine attempt to mimic this feature. However, due to the increased understanding of the genetic basis and potential involvement of glutamate and adverse environmental insults, different experimental manipulations for animal models of SCZ have also been developed [84].

Since the identification of cannabinoid CB1 and CB2 receptors and their endogenous ligands (AEA and 2-AG), a key aspect to assess the function and therapeutic potential of the ECS for SCZ treatment has been the availability of selective pharmacological tools. They vary from directly acting compounds, such as agonists and inverse agonists, to agents that enhance indirectly endocannabinoid signalling by affecting the cellular reuptake of endocannabinoids (experimental agents: AM404 or VDM11) or by inhibiting the hydrolytic enzymes FAAH and MAGL (experimental agents: URB597, AA-5-HT or JZL184). However, several additional elements which can be described as potential members of the ECS such as ligands (i.e. noladin, virodhamide), receptors (GPR55, PPARγ, TRPV1) and synthetic or degradative pathways, could participate in the mechanism of action of the compounds described above [85].

3.1. Studies on Positive- and Negative-like Symptoms

Different substances modulating the endocannabinoid signalling have been evaluated in several animal (mostly pharmacological) models for affecting positive- and/or negative-like symptoms of SCZ, as summarized in Table **1**. In a recent study, Spano *et al.* have shown that chronic exposure to the CB1 agonist WIN55,212-2 reduces phencyclidine (PCP)-induced hyperlocomotion [86], in agreement with previous studies, showing a reduction of cocaine- or quinpirole- induced hyperactive behaviour by direct CB1 activation [87, 88]. Interestingly, stereotyped and hyperlocomotor behaviours, an index of positive-like symptoms, were also reduced by the non-psychoactive component of *Cannabis sativa* cannabidiol (CBD) [89-92]. Although in a recent study CBD failed to reverse the amphetamine-induced hyperactivity, it elicited certain neuroprotective effects [93]. In additional, CBD prevented human experimental psychosis. More specifically, it was effective in open case reports and clinical trials in psychotics with a remarkable safety profile, [94-97] as well as it and others phytocannabinoids such as cannabidiolic acid, tetrahydrocannabivarin, tetrahydrocannabivarin acid, cannabichromene, cannabichromenic acid, cannabigerol, and cannabigerolic acid were patented for their use in combination with one or more anti-psychotic medicaments to prevent or treat psychosis and psychotic disorders [98]. Yet, it is still unknown the exact mechanism(s) of action underlying its antipsychotic effects, but it is clear that CBD does not only act through ECS (as weak partial antagonist at CB1/CB2 receptors or inhibitor of AEA hydrolysis and reuptake), but also activates serotonin 5-HT_{1A} or adenosine receptors or targets nuclear receptors of the PPAR family as well as modulates ion channels including TRPV1 [18]. Regardless the exact mechanism of action, attention has been focused on the potential therapeutic use of CBD in further mental diseases such as mood (i.e. anxiety and depression) and neurodegenerative (Alzheimer's or Parkinson's disease) disorders [17].

In the last years, selective antagonist/inverse agonists of CB1 receptors were some of the most promising molecules in pharmacological research for the treatment of obesity and addictive disorders. The first such compound was rimonabant (SR141716) [99] introduced into clinical practice as antiobesity agent in several countries. However, due to the higher incidence of psychiatric side effects such as anxiety, depression and suicidal tendencies, rimonabant was very soon withdrawn from the market [100]. In contrast to CBD, the ability of CB1 antagonists on positive-like symptoms is still under debate due to the contradictory results. In 1999, Poncelet *et al.* reported that rimonabant as well as clozapine or haloperidol antagonized the hyperlocomotor activity induced by d-amphetamine, cocaine and morphine in gerbils [101]. Potential therapeutic effects on positive symptoms were then also confirmed by Tzavara and colleagues in the PCP animal model [102]. However, in other studies, it failed to ameliorate the hyperlocomotor activity [103-105] or instead increased stereotype behaviour [106]. Although the discrepancies among these studies could be due to interspecies differences, or physiochemical differences between drugs or experimental models, the preclinical data described above suggest that the CB1 blockade might have a limited potential to treat positive symptoms. In line with this concept, AVE1625 (drinabant, so far reported as the CB1 antagonist) has partially reversed the positive-like symptoms in experimental models with an improved side effects profile [107].

Recently, attention has been drawn to the expression of CB2 receptor in the CNS [77, 78]. Further supporting that cannabinoid CB2 receptors may play a role in psychiatric disorder, it has been seen that pharmacological or genetic CB2 receptor blockade increased susceptibility to develop positive-like symptoms [41]. As a result, the CB2 agonist beta-caryophyllene has been recently patented for potential efficacy for SCZ treatment [108]. The ECS seems to play a role in the social behaviour of rodents and the resistance of negative symptoms to pharmacological interventions; therefore, the effects of pharmacological modulation of endocannabinoid signalling on the social deficits of experimental models of schizophrenia have been recently examined. Direct activation of CB1 receptors through the use of CB1 agonists WIN55,212-2 or CP55,940 reversed the PCP-induced social deficits [86, 109]. Interestingly, the pharmacological enhancement of endocannabinoid levels via systemic treatment with the FAAH inhibitor URB597 also reversed the social deficits in the PCP model, but at the same time elicited, as well as the cannabinoid CB1 blockade, harmful effects in the social behaviour of control animals, maybe by

Table 1. Effects of pharmacological modulation of the endocannabinoid system on schizophrenia-like symptoms.

a) Positive-like symptoms

Mechanism	Drug: Effective Dose (Range tested)	Animals	Models	Behavioral Response	Positive Control	Ref.
CB1/CB2 receptor agonists:	WIN: 6 (3-6) mg/kg, i.p.	Wistar rats	cocaine (10 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[88]
	CP: (0.0025-0.01 mg/kg, s.c.)	*Cebus* monkeys	d-amphetamine (0.25 mg/kg, s.c.)	no effect on arousal and stereotypy	not determined	[103]
	CP: 0.1/0.25 (0.01-0.25) mg/kg, i.p.	Wistar rats	quinpirole (0.5 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[87]
	WIN: 0.3 mg/kg/day, i.v. for 14 days	Lister Hooded rats	PCP (2.5 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[86]
CB1 antagonists:	RIM: 1/3 (0.3-3) mg/kg, i.p.	Gerbils	cocaine (5-15 mg/kg, i.p.) d-amphetamine (2.5 mg/kg, i.p.) morphine (4 mg/kg, i.p.) WIN-55,212-2 (1 mg/kg, i.p.)	↓ hyperlocomotion in habituated gerbils	clozapine (3 mg/kg, i.p.) haloperidol (0.1 mg/kg, i.p.)	[101]
	RIM: 3-10 mg/kg, i.p.	Bl6 mice	PCP (4 mg/kg, i.p.) d-amphetamine (2.5 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[102]
	RIM: (0.0005-5) mg/kg, i.p.	Wistar rats	d-amphetamine (3 mg/kg, i.p.)	no effect on hyperlocomotion and stereotypy	haloperidol (0.25 mg/kg, i.p.)	[104]
	RIM: 0.1-0.5 (0.1-0.75) mg/kg, s.c.	*Cebus* monkeys	d-amphetamine (0.25 mg/kg, s.c.)	↓ arousal no effect on stereotypy	not determined	[103]
	RIM: 1 (0.1-1) mg/kg, i.p.	Wistar rats	SKF38393 (0.05-1 mg/kg, s.c.) quinpirole (0.25 mg/kg, s.c.)	↑ stereotypy	not determined	[106]
	RIM: 1 mg/kg, i.p.	Sprague-Dawley rats	amphetamine (1 mg/kg, i.p.)	no effect on hyperlocomotion	not determined	[105]
	AVE: 1- 3-10 mg/kg, i.p.	Wistar rats	MK-801 (0.05 mg/kg, i.p.)	↓ disrupted LI	risperidone (0.01-1 mg/kg, i.p.)	[107]
CB2 antagonist:	AM630: 3-30 mg/kg, i.p.	Bl6/JJ mice	MK-801 (0.5 mg/kg, i.p.) methamphetamine (2 mg/kg, i.p.)	↑ hyperlocomotion	not determined	[41]
AEA reuptake inhibitor:	AM404: 10 µg/rat, i.c.v.	Wistar rats	quinpirole (0.25 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[156]
Non-psychotropic cannabinoid:	CBD: 30/60 (15-60) mg/kg, i.p.	Swiss mice	d-amphetamine (5 mg/kg, i.p.) ketamine (60 mg/kg, i.p.)	↓ hyperlocomotion	haloperidol (0.15-0.6 mg/kg, i.p.) clozapine (1.25-5 mg/kg, s.c.)	[91]
	CBD: 20 (5-20) mg/kg, i.p.	Sprague-Dawley rats	THC (1 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[90]
	CBD: 50 (1-50) mg/kg/day, i.p. for 3 weeks	Bl6/Jarc mice	d-amphetamine (5 mg/kg, i.p.)	↓ hyperlocomotion	not determined	[89]
	CBD: (15-60) mg/kg, i.p. for 7 days	Wistar rats	d-amphetamine (2 mg/kg, i.p.)	no effect on hyperlocomotion	not determined	[93]

(Table 1) contd…..

b) Negative-like Symptoms

Mechanism	Drug: Effective Dose (Range tested)	Animals	Models	Behavioral Response	Positive Control	Ref.
CB1/CB2 agonists:	WIN: 0.3 mg/kg/day, i.v. for 14 days	Lister Hooded rats	intermittent PCP (2.5 mg/kg/day, i.p.)	↓ social deficit in PCP ↑ social deficit in control	not determined	[145]
	CP: 0.01 mg/kg, i.p.	Wistar rats	PCP (5 mg/kg/day, i.p.) twice a day for 7 days	↓ social deficit in PCP	not determined	[109]
	THC: 2.5 mg/kg/day, i.p. (PND37-39); 5 mg/kg/day, i.p. (PND40-43); 10 mg/kg/day, i.p. (PND44-47)	Sprague-Dawley rats	maternal deprivation	↓ aggressive behavior of female in the SI no effect in the FST	not determined	[157]
CB1 antagonists/invesre agonists:	AM251: 0.5 mg/kg/day, i.p. for 3 weeks	Lister Hooded rats	PCP (2.58 mg/kg/day, i.p.) for 4 weeks	↓ immobility time in the FST	clozapine (5 mg/kg/day, i.p.) for 3 weeks	[115]
	AM251: 0.5 mg/kg/day, i.p. for 3 weeks	Lister Hooded rats	social isolation	↓ aggressive behavior in the SI	not determined	[129]
	AM251: 3 (0.3-3) mg/kg, i.p. RIM: 0.3/1 (0.1-1) mg/kg, i.p.	Wistar rats	PCP (5 mg/kg/day, i.p.) twice a day for 7 days	↑ social withdrawal in control rats	not determined	[109]
TRPV1 antagonist:	capsazepine: 1 (1-10) mg/kg, i.p.	Wistar rats	PCP (5 mg/kg/day, i.p.) twice a day for 7 days	↓ social withdrawal in control rats	not determined	[109]
FAAH inhibitor:	URB597: 0.1/0.3/1 mg/kg, i.p.	Wistar rats	PCP (5 mg/kg/day, i.p.) twice a day for 7 days	↓ social withdrawal in PCP rats ↑ social withdrawal in control rats	not determined	[109]

Table 1. The table summarizes the effects of direct pharmacological manipulation of the endocannabinoid signalling on positive and negative-like symptoms in rodent models of schizophrenia. Acronyms: THC: Δ^9-tetrahydrocannabinol, AEA: anandamide, CBD: cannabidiol, CP: CP55940, FAAH: fatty acid amide hydrolase, FST: forced swim test, i.c.v.: intracerebroventricular, i.p.: intraperitoneal, i.v.: intravenous, LI: latent inhibition, PCP: phencyclidine, PND: postnatal day, RIM: rimonabant (SR141716), s.c.: subcutaneous, SI: social interaction, TRPV1: transient receptor potential vanilloid 1 channels, WIN: WIN55,212-2.

disturbing the ECS tone through the activation of TRPV1 channels [109, 110]. In accordance, it has been seen that chronic Cannabis consumption improves negative symptoms in schizophrenic subjects [111, 112], as well as it also induces an amotivational syndrome, which mimics negative symptoms in non schizophrenics [113]. This suggests different effects of cannabinoids on healthy or schizophrenic subjects. Chronic treatment with the CB1 receptor antagonist AM251 counteracted the aggressive behaviour and reversed the PCP-induced immobility in the forced swim test which was accompanied by the rescue of CB1 receptor functionality in a neurodevelopmental animal model based on a social isolation procedure [114, 115]. Although the genetic CB1 disruption in mice was also able to counteract the PCP-induced social deficit [116] further supporting the potential antipsychotic properties of the CB1 blockade, human experimental studies have so far shown controversial results. More specifically, Meltzer *et al*. have not seen a clinical improvement in schizophrenic patients after rimonabant treatment. In contrast, Kelly *et al*. found a significant reduction of psychotic symptomatology in obese patients with SCZ [117, 118]. Thus, further clinical studies are necessary to elucidate the therapeutic potential of CB1 antagonists. To date, several compounds of this pharmacodynamic profile have been patented for potential efficacy for treating SCZ symptoms [119-123].

3.2. Studies on Cognitive/Attention Deficits

It has become clear that SCZ cannot be reduced to its psychotic symptoms and the cognitive deficits of these patients are the most debilitating and remain resistant to treatment. Thus, the development of new drugs has been hampered by the lack of existing drugs for treating the cognitive impairment in schizophrenic patients, since there is not gold standard positive control drug that can be used in cognitive assays. Thus, in light of the high density of cannabinoid CB1 receptors in cortical regions involved in cognition and memory processes, the cognitive effects of the modulation of the endocannabinoid signalling could be one of the potential pharmacological targets for the SCZ treatment. The existing evidence of involvement of ESC in the cognitive/attention processes in animal models of SCZ is presented in the Table **2**.

Table 2. Effects of pharmacological modulation of the endocannabinoid system on cognitive/attention deficits of a schizophrenia-like phenotype.

Mechanism	Drug: Effective Dose (Range tested)	Animals	Models	Behavioral Response	Positive Control	Ref.
CB1/CB2 receptor agonists:	THC: 0.5 mg/kg/day, i.p. for 3 weeks	Lister Hooded rats	PCP (2.58 mg/kg/day, i.p.) for 4 weeks	↑ cognitive deficit	clozapine (5 mg/kg/day, i.p.) for 3 weeks	[126]
	THC: 0.3/1/3 mg/kg, i.v.	Sprague-Dawley rats	social isolation	↑ disruption of PPI	not determined	[144]
	WIN: 3 mg/kg, i.p.	Bl6/J	psychosocial stress	↓ disruption of PPI	not determined	[143]
	THC: 2.5 mg/kg/day, i.p. (PND35-37); 5 mg/kg/day, i.p. (PND38-41); 10 mg/kg/day, i.p. (PND42-45)	Sprague-Dawley rats	maternal deprivation	↑ cognitive deficit in control female	not determined	[157]
	WIN: 0.3 mg/kg/day, i.v. for 14 days	Lister Hooded rats	chronic PCP (2.5 mg/kg/day, i.p.)	↓ disruption of PPI ↓ cognitive deficit	not determined	[145]
CB1 antagonists/inverse agonists:	RIM: (0.3-5) mg/kg, i.p.	Sprague-Dawley rats	apomorphine (0.5 mg/kg, s.c.) MK-801 (0.1 mg/kg, s.c.) d-amphetamine (5 mg/kg, s.c.)	no effect on PPI	clozapine (10 mg/kg, i.p.); olanzapine (10 mg/kg, i.p.); haloperidol (0.3 mg/kg,1 i.p.)	[104]
	RIM: 3 (0.3-3) mg/kg, i.p.	Swiss mice	apomorphine (3 mg/kg, i.p.)	↓ disruption of PPI	not determined	[150]
	AM251: 0.5 mg/kg/day, i.p. for 3 weeks	Lister Hooded rats	PCP (2.58 mg/kg/day, i.p.) for 4 weeks	↓ cognitive deficit	clozapine (5 mg/kg/day, i.p.) for 3 weeks	[130]
	AM251: 0.5 mg/kg/day, i.p. for 3 weeks	Lister Hooded rats	social isolation	↓ cognitive deficit	not determined	[129]
	AM251: 0.5 mg/kg/day, i.p. for 3 weeks	Lister Hooded rats	social isolation	↓ disruption of PPI	not determined	[114]
	AM251: 1 mg/kg, i.p.	Wistar rats	PCP (5 mg/kg/day, i.p.) twice a day for 7 days	↓ cognitive deficit in PCP ↑ cognitive deficit in control	not determined	[110]
	RIM: 0.75/1/3 mg/kg, s.c. AM251: 1.4/1.8 mg/kg, s.c.	Sprague-Dawley rats	PCP (1.25 mg/kg, s.c.)	↓ disruption of PPI	clozapine (7.5 mg/kg, i.p.)	[149]
CB2 antagonist:	AM630: 30 (3-30) mg/kg, i.p.	Bl6/6JJmsSlc mice	MK-801 (0.5 mg/kg, i.p.) methamphetamine (2 mg/kg, i.p.)	↑ disruption of PPI in MK-801 mice no effect on PPI in methamphetamine pretreated mice	not determined	[41]
FAAH Inhibitor:	URB597: 0.3 mg/kg, i.p.	Wistar rats	PCP (5 mg/kg/day, i.p.) twice a day for 7 days	↓ cognitive deficit	not determined	[110]
Non-psychotropic cannabinoid:	CBD: 0.5 mg/kg, i.m.	Rhesus monkeys	THC (0.2-0.5 mg/kg, i.m.)	↓ cognitive deficit	not determined	[138]
	CBD: 5 (1-15) mg/kg, i.p	Swiss mice	MK-801 (1 mg/kg, i.p.)	↓ disruption of PPI	clozapine (4 mg/kg, i.p.)	[154]

Table 2. The table summarizes the effects of direct pharmacological manipulation of the endocannabinoid signalling on cognitive/attention deficits in rodent models of schizophrenia. Acronyms: THC: Δ^9-tetrahydrocannabinol, CBD: cannabidiol, FAAH: fatty acid amide hydrolase, FST: forced swim test, i.c.v.: intracerebroventricular, i.m.: intramuscular, i.p.: intraperitoneal, i.v.: intravenous, LI: latent inhibition, PCP: phencyclidine, PND: postnatal day, PPI: prepulse inhibition, RIM: rimonabant (SR141716), s.c.: subcutaneous, SI: social interaction, WIN: WIN55,212-2.

Acute administration of the main pharmacologically active principle of the *Cannabis sativa*, THC, as well as the CB1 agonists such as WIN55,212-2, CP55,940 or AEA induce in animals and healthy humans memory deficits similar to those seen in SCZ, which could be mediated through a disruption of prefrontal and hippocampal functions [124, 125]. However, in the PCP-induced animal model controversial data have been obtained following CB1 activation. While Vigano and colleagues found that chronic THC treatment in juvenile rats worsened cognitive impairment [126], by contrast the CB1 agonist WIN55, 212-2 attenuated the PCP cognitive deficits in adult rats [86]. Although the authors used the same experimental model, the discrepancies between these studies could be due to either physiochemical differences between CB1 agonists or the different age of pharmacological treatment (juvenile vs. adult). Furthermore, Seillier and colleagues found that indirect activation of CB1 receptors through the use of FAAH inhibitor URB597 caused working memory deficits in saline treated rats comparable to those after PCP treatment, which may arise due to perturbing the endocannabinoid tone [110]. In contrast, other evidence from animal studies suggests that pharmacological CB1 receptor blockade could exert promnesic effects. In this context, it has been seen that the memory disruptive effects induced by CB1 agonists such as THC, AEA or WIN55,212-2 were counteracted by rimonabant treatment [124, 127, 128]. Furthermore, the CB1 receptor antagonist/inverse agonist AM251 reversed memory impairment in pharmacological and neurodevelopmental models of SCZ [110, 114, 129, 130]. Despite potential pro-cognitive effects of CB1 antagonists described above, in the few clinical studies assessing its role on cognitive functioning in human, rimonabant worsened ketamine induced deficits [131] or did not improve global cognitive functioning. In this later study just a specific learning deficit in schizophrenic patients based on response to positive feedback was recorded [132]. In a recent clinical trial assessing the potent and selective CB1 antagonist AVE1625 for improving cognitive deficits in schizophrenic, there was an insufficient efficacy of the treatment (Clinical Trials.gov identifier: NTC00439634). The withdrawal of rimonabant, due to the psychiatric side effects in the metabolic syndrome treatment, interrupted the entire industrial development of CB1 antagonists/inverse agonists. However, several CB1 receptor inverse agonist compounds have been patented for the treatment of cognitive impairment associated with SCZ [133, 134]. Thus, a possible solution for the safe use of this class of compounds could be to determinate which patients are at high risk of psychiatric side effects through detailed phenotypic assessment and genetic testing [135] or change to the use of neutral CB1 antagonist [136, 137].

Clinical and preclinical data suggest that CBD which is the most extensively investigated phytocannabinoid for potential use in psychiatric disorders, is also able to ameliorate cognitive deficits. More specifically, it was able to reverse the THC-induced deficits in rhesus monkeys [138], as well as THC induced cognitive impairment in human [139]. Moreover, CBD effects on cognitive function in schizophrenic patients are currently under investigation in a phase II clinical trial (Clinical Trials.gov identifier: NCT00588731). Patients with SCZ exhibit deficits in an operational measure of sensorimotor gating: pre-pulse inhibition (PPI) of startle reaction. Similar deficits in PPI are produced in animals by pharmacological or developmental manipulations. These experimentally induced PPI deficits in rats clearly do not represent animal models of schizophrenia per se, but provide us an investigative tool with high face, predictive, and construct validity for sensorimotor gating deficits in SCZ patients [140]. To confirm that younger animals have different vulnerability to cannabinoid treatment in development of SCZ-like symptoms, rats treated at adulthood with CB1 receptor agonist WIN55,212-2 have not shown disruption of PPI [141]; in comparison, the prepubertal CB1 agonist treatment induced PPI deficits in adult age [142]. However, at adulthood, WIN55,212-2 and THC improved and impaired the PPI of the startle response in psychosocially stressed rodents, respectively [143, 144]. Discrepancies between these studies could be due to interspecies (rat vs. mice) dissimilarities in response to treatments (e.g. pharmacokinetic issues), to physiochemical characteristics of the specific compounds (THC vs. WIN) and to the different experimental procedures. Nevertheless, in an experimental model of SCZ, CB1 agonist WIN 55,212-2 was able to attenuate the PCP-induced deficit in PPI [145]. Controversial data were obtained following enhancement of AEA level through the use of AM404, an AEA reuptake inhibitor. While in mice AM404 disrupts sensorimotor gating [146]; in contrast it was ineffective in the PPI test in rats [147], suggesting an interspecies (rats vs. mice) difference in the response to the pharmacological modulation of AEA levels.

The potential antipsychotic properties of CB1 antagonists have also been explored in the impaired sensorimotor gating, as a model of perceptual distortion [148]. It has been seen that the antagonists/inverse agonists rimonabant and AM251 reversed the disrupted PPI in several experimental models of SCZ, similarly as the conventional neuroleptics [114, 149, 150]. On the other hand, the genetic blockade of CB1 signalling resulted in unaltered PPI response, as shown by the phenotype of mice with a complete deletion of CB1 receptors; however, they have shown a decreased parvalbumin immunoreactivity in the cortex and striatum, which is typical in schizophrenic human subjects [151, 152]. Again it is still unknown the exact mechanisms underling these discrepancies, but compensatory mechanisms in knock out mice could be involved. Given recent attention has been drawn to the role of CB2 receptors in psychiatric disorders, preclinical and clinical data indicate that a reduced CB2 signalling elicited a sensorimotor gating and an increased risk of SCZ in human, respectively [41, 42]. The potential antipsychotic-like property of CBD have also been supported by its ability to reverse the sensorimotor gating deficits in different experimental models, similarly to that induced by clozapine [153, 154].

4. CURRENT & FUTURE DEVELOPMENTS

As outlined above, preclinical and clinical evidence strongly suggest a dysregulation of the ECS in schizophrenia, such as abnormalities in cannabinoid (CB1 and/or CB2) receptor function and endocannabinoid (AEA and/or 2-AG) levels in different cerebral areas. However, so far, the full picture on the role of the endocannabinoid system in this

pathology has yet to emerge. To date, the pharmacotherapy of negative symptoms and cognitive deficits of SCZ has been disappointing; as antipsychotics have not met the expectations and the development of more effective therapies have been inadequate [155]. Thus, the ability of cannabinoids to modulate schizophrenia-like symptoms is extremely attractive for the development of novel antipsychotics agents. Although use of CB1 antagonists/inverse agonists is hampered by unwanted psychiatric side effects and that the possibly safer direct modulation of CB2 receptors still lacks sufficient experimental evidence to justify its use, the use of CBD has produced very promising results in animal models with a pharmacological profile resembling that of atypical antipsychotics. Clinical evidence also suggests that CBD, being devoid of psychotropic activity, could represent a reliable compound for psychosis in schizophrenia especially in view of its lack of extrapyramidal side effects [96]. Further clinical studies will determine if CBD treatment would be the novel pharmacotherapy for the disturbances in the social and cognitive functions in schizophrenic patients.

AUTHOR CONTRIBUTIONS

Jana Kucerova has collected the literature sources, was involved in the discussion of the manuscript structure and wrote a substantial part of the text.

Katarina Tabiova was responsible for cross-checking the literature, preparation of the tables and reference collection.

Filippo Drago was involved in the discussion of the structure and revised both the draft and final version of the manuscript.

Vincenzo Micale has organized the structure of the whole text and wrote a substantial part of the manuscript.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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