



## Review

## The endocannabinoid system and psychiatric disorders

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## ABSTRACT

The present review summarizes the latest information on the role and the pharmacological modulation of the endocannabinoid system in mood disorders and its potential implication in psychotic disorders such as schizophrenia.

Reduced functionality might be considered a predisposing factor for major depression, so boosting endocannabinoid tone might be a useful alternative therapeutic approach for depressive disorders. The picture regarding endocannabinoids and anxiety is more complicated since either too much or too little anandamide can lead to anxiety states. However, a small rise in its level in specific brain areas might be beneficial for the response to a stressful situation and therefore to tone down anxiety. This effect might be achieved with low doses of cannabinoid indirect agonists, such as blockers of the degradative pathway (i.e. FAAH) or re-uptake inhibitors.

Moreover several lines of experimental and clinical evidence point to a dysregulation of the endocannabinoid system in schizophrenia. The high anandamide levels found in schizophrenic patients, negatively correlated with psychotic symptoms, point to a protective role, whereas the role of 2-arachidonoyl glycerol is still unclear. There is a potential for pharmacological manipulation of the endocannabinoid system as a novel approach for treating schizophrenia, although experimental findings are still controversial, often with different effects depending on the drug, the dose, the species and the model used for simulating positive or negative symptoms. Besides all these limitations, SR141716A and cannabidiol show the most constant antipsychotic properties in dopamine- and glutamate-based models of schizophrenia, with profiles similar to an atypical antipsychotic drug.

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## Introduction

The endocannabinoid system is a recently discovered signaling system comprising the cannabinoid CB1 and CB2 receptors, their intrinsic lipid ligands, endocannabinoids (eCB) such as the N-arachidonoylethanolamide (anandamide, AEA) and the 2-arachidonoyl glycerol (2-AG), and associated proteins (transporters, biosynthetic and degradative enzymes).

The eCBs in the central nervous system are involved in numerous physiological functions and act on membrane receptors through paracrine and autocrine mechanisms. Dysregulation of the eCB system has been associated with various pathophysiological states, including psychiatric disorders. The high level of expression of CB1 receptors in brain areas involved in the regulation of cognition and mood functions (amygdala, cortex and hippocampus) implies that the eCB system is probably involved in emotional processing, mood and anxiety regulation and in the pathophysiology of depression. Recent data also suggest that changes in eCB signaling and the consequences on neuronal activity might be important in the etiology of schizophrenia and may help explain the impact of cannabis abuse in psychotic disorders.

The present review summarizes the latest breakthroughs on the eCB system's role and its pharmacological modulation in mood disorders and the potential implication in psychotic disorders such as schizophrenia.

## Mood disorders

### Depression

#### The eCB system in depression

*Cannabis sativa* has long been known by humans for its mood-elevating and stress-reducing properties. However, the first comprehensive scientific paper openly discussing the idea that the endocannabinoid system might play a role in the neurobiology of depression is fairly recent, dating back only to 2005 (Hill and Gorzalka, 2005a). Since then the literature on this topic has accumulated providing evidence of dysregulation in endocannabinoid signaling as a molecular underpinning for mood disorders.

A large amount of data comes from studies in CB1 knock out (ko) mice. These mice became anhedonic during chronic mild stress sooner than wild type (wt) mice, suggestive they are more vulnerable to the anhedonic effect of chronic stress (Martin et al., 2002). CB1 ko mice also showed an increase in passive coping behavior in the forced swim test (FST), illustrated by less struggling and more floating than wt mice (Steiner et al., 2008b). Similarly, mice lacking the CB1 receptor had a longer immobility time than wt littermates in the tail suspension test (TST) (Aso et al., 2008). CB1 ko mice also had higher corticosterone serum levels after exposure to stress, suggesting hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis (Uriguen et al., 2004), which is one of the most constant findings in major depressive disorder.

In line with these findings, we recently reported that long-lasting impairment of CB1 receptor function led to the development of a depressive phenotype characterized by anhedonic state, passive coping behavior in the FST and cognitive deficits (another major component of depression) (Rubino et al., 2008c, 2009). This behavioral picture was paralleled by well-known biochemical parameters of depression such as changes in CREB in specific brain areas, lower levels of markers of neuroplasticity and less active synapses with reduced ability to maintain normal synaptic efficiency in the prefrontal cortex (Pfc) (Rubino et al.,

2008c, 2009). All these data point to the idea that stable impairment of CB1 receptors leads to depression-like symptoms.

This conclusion appears to be questioned by some reports that blocking the cannabinoid receptor by cannabinoid antagonists induced an antidepressive-like response in the FST or the TST (Griebel et al., 2005; Shearman et al., 2003; Takahashi et al., 2008; Tzavara et al., 2003). However, the discrepancy is only apparent because of differences in the experimental conditions: on the one hand, a lasting deficit in the CB1 receptor (CB1 ko mice and Rubino's studies, see above), on the other hand, acutely blocked CB1 receptors (studies with acute antagonist treatment).

In line with this interpretation, Beyer recently reported that chronic treatment with rimonabant induced a depression-like phenotype in rats (Beyer et al., 2009), and chronic use of rimonabant as an antiobesity agent in humans was withdrawn on account of undesirable psychiatric side effects, particularly symptoms of depression (Nissen et al., 2008). Accordingly, a recent paper has suggested that genetic variation in CB1 receptor function can influence the risk of depression in humans in response to stressful life events (Juhász et al., 2009). Another human study described a role of CNR1 gene variation in depression, potentially mediated by subcortical hypo-responsiveness to social reward stimuli (Domschke et al., 2008).

Changes in CB1 receptors and other elements belonging to the eCB system have also been reported in animal models of depression (Tables 1 and 2). In the chronic mild stress paradigm, for example, there was a significant increase in CB1 receptor density or mRNA in the Pfc (Bortolato et al., 2007; Hill et al., 2008), together with a significant decrease in the hippocampus (Hill et al., 2005; Reich et al., 2009), hypothalamus, ventral striatum (Hill et al., 2008) and midbrain (Bortolato et al., 2007). Accordingly, a significant decrease in the CB1 receptor-mediated control of GABA transmission in the striatum was observed after a social defeat stress paradigm (Rossi et al., 2008). The increase in CB1 receptor density and function in the prefrontal cortex was seen in another animal model of depression too, bilateral olfactory bulbectomy in the rat (Rodríguez-Gaztelumendi et al., 2009). In rats exposed to chronic mild stress AEA content may decrease throughout the brain (Hill et al., 2008) or may show no changes (Bortolato et al., 2007), whereas 2-AG decreased in the hippocampus (Hill et al., 2005) but increased in the hypothalamus, midbrain (Hill et al., 2008) and thalamus (Bortolato et al., 2007).

Differences in eCB levels might reflect differences in the stress paradigm and/or the time of tissue extraction (immediately or 2 h after the last stress), bearing in mind that these compounds are produced "on demand". Anyway, it seems likely that there is a general down-regulation of the eCB system function in most areas, although hyperfunction can also be apparent in the Pfc. In line with this last observation, a significant increase in CB1 receptor density and efficiency has been reported in the dorso-lateral Pfc of depressed suicide victims (Hungund et al., 2004).

Hypofunction in peripheral eCB activity has also been described, since the basal serum concentrations of AEA and 2-AG were significantly lower in women with major depression than in matched controls (Hill et al., 2009).

On the whole, the evidence points to a dysfunction in the eCB system as molecular underpinning for the development of depressive symptoms.

#### Pharmacological modulation of the eCB system in depression

Based on the assumption that a dysfunction in the eCB system is critically involved in the etiopathology of depression, manipulation of

**Table 1**  
Alterations in CB1 receptor density, and endocannabinoid levels in depression.

Species	Model	Brain region	CB1 receptor	Reference
Rat	Chronic mild stress	Prefrontal Cortex Midbrain	↑ ↓	Bortolato et al. (2007)
Rat	Chronic unpredictable stress	Prefrontal Cortex Hippocampus Hypothalamus Ventral striatum	↑ ↓ ↓ ↓	Hill et al. (2008)
Rat	Chronic mild stress	hippocampus	↓	Reich et al. (2009)
Rat	Bilateral olfactory bulbectomy	Prefrontal Cortex	↑	Rodriguez-Gaztelumendi et al. (2009)
Female rat	Adolescent exposure to THC	Nucleus accumbens Amygdala Ventral tegmental area	↓ ↓ ↓	Rubino et al. (2008a,b,c)
Human	Depressed suicide victims	Dorso-lateral Prefrontal Cortex	↑	Hungund et al. (2004)

the eCB tone might have a profound impact on the neuronal networks implicated in mood disorders. The general feeling is that enhancing in the eCB tone might be useful to overcome depression-like symptoms.

Acute intraperitoneal injection of different direct or indirect CB1 receptor agonists reversed behavioral despair in the FST (Bambico et al., 2007; Gobbi et al., 2005; Hill and Gorzalka, 2005b). This effect was also evident when cannabinoid agonists were injected in specific brain areas with key roles in emotion, such as the hippocampus (McLaughlin et al., 2007) and the PFC (Bambico et al., 2007). An antidepressant-like effect was still evident in the FST and/or TST after chronic cannabinoid agonist injection (Gobbi et al., 2005; Jiang et al., 2005; Morrish et al., 2009). Interestingly, chronic treatment with URB597, an inhibitor of fatty acid amide hydrolase (FAAH), the enzyme responsible for breakdown of AEA, exerted antidepressant-like effects in rats exposed to chronic mild stress, a highly specific, predictive animal model of depression. URB597 also overcame some of the depression-like symptoms seen in the complex depressive phenotype induced in adult animals by exposure to delta-9-tetrahydrocannabinol (THC) in adolescence (Rubino T., preliminary observations).

There is thus compelling evidence that facilitating eCB neurotransmission has antidepressant effects in rodent tests or models of depression. However, there are very few reports of an antidepressant effect induced by CB1 receptor antagonists (Griebel et al., 2005; Shearman et al., 2003; Steiner et al., 2008a; Takahashi et al., 2008; Tzavara et al., 2003). Except for the Takahashi et al. (2008), all the other studies used doses of 3 mg/kg or higher. A detailed behavioral analysis reported that the CB1 antagonist SR141716 induced significant behavioral activation already at the dose of 2.5 mg/kg (Rubino et al., 2000). Therefore, since those studies used tests of depressive-like symptoms where the motor component played a key role, the decrease in immobility observed with the CB1 antagonist might be due to behavioral activation and not to a proper antidepressant-like

effect. On the other hand, as already mentioned above, the clinical use of the antagonist in humans was stopped on account of psychiatric side effects, mainly depression.

#### Biochemical mechanisms underlying the antidepressant effect of cannabinoids

To explain the possible mechanisms by which cannabinoid compounds might induce an antidepressant effect, we should take into account the biochemical alterations thought to underline the depressive syndrome or at least the major neurobiological alterations induced by current antidepressant treatments. For example, all compounds that possess effective antidepressant properties act increasing the monoamine neurotransmitters, serotonin or norepinephrine (Berton and Nestler, 2006). Both CB1 receptor agonists and inhibitors of AEA hydrolysis increase the firing activity of neurons in the dorsal raphe, the major source of serotonin neurons, thus enhancing serotonin neurotransmission while exhibiting antidepressant activity (Bambico et al., 2007; Gobbi et al., 2005). Similarly, stimulation of CB1 activity has been shown to increase firing activity of noradrenergic neurons in the locus coeruleus as well as the release of norepinephrine in the prefrontal cortex (Gobbi et al., 2005; Oropeza et al., 2005). The involvement of the noradrenergic system in the antidepressant effect of a chronic CB1 agonist was further demonstrated by Morrish et al. (2009), who reported that co-treatment with both alpha- and beta-adrenoreceptor antagonists attenuated the reduction in immobility in the FST induced by the CB1 agonist HU210.

Moreover, changes in the hypothalamic–pituitary–adrenal (HPA) axis are characteristic of major depression and antidepressant agents normalize the hyperactivity of the HPA axis. Agents which act facilitating eCB neurotransmission (such as uptake inhibitors or metabolic enzyme inhibitors), facilitate adaptive stress coping

**Table 2**  
Alterations endocannabinoid levels in depression.

Species	Model	Brain region	Endocannabinoid		Reference
			AEA	2-AG	
Rat	Chronic mild stress	Midbrain	↔	↔	Bortolato et al. (2007)
		Thalamus	↔	↑	
		Striatum	↔	↔	
		Hippocampus	↔	↔	
		Prefrontal cortex	↔	↔	
Rat	Chronic unpredictable stress	Prefrontal cortex	↓	↔	Hill et al. (2008)
		Hippocampus	↓	↔	
		Hypothalamus	↓	↑	
		Amygdala	↓	↔	
		Midbrain	↓	↑	
		Ventral striatum	↓	↔	
Rat	Chronic unpredictable stress	Hippocampus	↓	↓	Hill et al. (2005)
Human	Women with major depression	Serum levels	↓	↓	Hill et al. (2009)

behaviors and attenuates the neuroendocrine response to psychological stressors (Patel et al., 2004; see for review Gorzalka et al., 2008).

It is well known that factors that predispose to depression such as stress suppress neurogenesis, whereas interventions that reduce depression stimulate neuron formation. These observations led to the hypothesis that modulation of hippocampal neurogenesis is crucial to both the onset and treatment of depression (Perera et al., 2008; Drew and Hen, 2007). In adult rats, administration of cannabinoid agonists as well as FAAH and re-uptake inhibitors has been shown to increase hippocampal neurogenesis (Marchalant et al., 2009; Goncalves et al., 2008; Hill et al., 2006; Jiang et al., 2005).

Finally, according to the neurotrophic hypothesis of depression, decreased BDNF expression in the hippocampus seems to be associated with depression, whereas increased BDNF expression with antidepressant action (Duman and Monteggia, 2006). THC treatment significantly increased the level of BDNF in the hippocampus (Rubino et al., 2006; Derkinderen et al., 2003).

Collectively these data indicate that increasing cannabinoid signaling exerts antidepressant properties through mechanisms that resemble the ones triggered by conventional antidepressant drugs. This suggests that enhancers of the cannabinoid signaling might represent a novel class of antidepressant agents whose therapeutic exploitation is strongly advisable.

## Anxiety

### *The eCB system in anxiety*

The idea that the eCB system is involved in the control of anxiety-like behavior is rooted in the fact that *C. sativa* is used recreationally mainly for its euphoric effects, often accompanied by a reduction in anxiety and a boost in sociability. However, this picture is confounded by the fact that cannabis abusers sometimes experience dysphoric reactions, with feelings of anxiety and panic.

This biphasic effect has been demonstrated in animal models of anxiety too (Hill and Gorzalka, 2009; Lafenetre et al., 2007). In general, an anxiolytic-like effect tends to appear after low doses of cannabinoid agonists, while higher doses produce an anxiogenic response. The reason for these dose-dependent patterns is still not clear. We can put forward two different hypotheses that might even both be true! First, different receptors sensitive to the cannabinoid's action might be involved, with different activities on anxiety responses. Along this line, Rubino et al. (2008b) reported that in the PFC, tonic activation of CB1 by AEA and, at higher concentrations, of transient receptor potential vanilloid (TRPV1) receptors, affected anxiety in opposite ways. The opposing roles of these receptors in the control of anxiety-like behavior has been well documented in different rodent species as well as in various animal models of anxiety (Aguiar et al., 2009; Micale et al., 2009; Terzian et al., 2009). According to this hypothesis, if the tissue levels of AEA become either too low or too high, leading either lack of CB1 activation or to TRPV1 stimulation, anxiogenic responses are observed. Physiological increases of AEA, on the other hand, promote an anxiolytic response through activation of CB1 receptors. Thus, Scherma et al. (2008) reported that a low dose of AEA and URB597 had anxiolytic effects when given singly, but anxiogenic effects when combined. Similarly, a higher dose of AEA had anxiogenic effects when given alone but the effects were stronger after URB597 treatment (Scherma et al., 2008).

Since facilitation of the eCB signaling plays a functional role in some neurobehavioral responses to stress, such as tone-down anxiety behavior (Finn, 2009), blocking CB1 receptors through pharmacological or genetic strategies should lead to an anxiogenic response as a result of exposure to aversive situations. This was demonstrated in mice with the genetic deletion of the CB1 receptor. These mice gave anxiety-like responses in different tests of anxiety such as the elevated plus-maze, the light-dark box, the open-field and the social interaction test (Haller et al., 2002, 2004b; Maccarrone et al., 2002; Martin et al., 2002; Uriguen et al., 2004); only few studies found no changes in their anxiety profile

(Houchi et al., 2005; Ledent et al., 1999; Marsicano et al., 2002). This might well be because the anxiogenic-like effect is restricted to the more stressful unfamiliar environment (Haller et al., 2004a). In fact, since eCBs are produced "on demand" and stress and/or aversive situations can trigger their production to induce the physiological coping mechanisms involved in the stress response, mice with genetically disrupted cannabinoid signaling can be expected to show increased anxiety only in relatively aversive conditions.

This same observation can also be raised for experiments with cannabinoid antagonists. Most papers found an anxiogenic-like response after peripheral administration of CB1 receptor antagonists although a few reported no effects on anxiety or even an anxiolytic effect (reviewed in Lafenetre et al., 2007). It is likely that in these latter studies, the experimental conditions were not aversive enough to raise the eCB tone whose action should have been blocked by the antagonist. Finally, in the same line, Haller and colleagues recently reported (Haller et al., 2009) that conflicting findings with URB597 – generally considered a putative anxiolytic drug but sometimes ineffective – can be explained by differences in test conditions, considering that FAAH inhibition does not affect anxiety under mildly stressful circumstances but protects against the anxiogenic effects of aversive stimuli.

Our second hypothesis to explain the dose-dependent cannabinoid effect on anxiety relies on the fact that activation of CB1 receptors in different brain areas appears to promote different behaviors. For instance, in intra-cerebral microinjection studies activation of CB1 receptors in the PFC, ventral hippocampus (vHip) and periaqueductal gray induced an anxiolytic response (Moreira et al., 2009; Rubino et al., 2008a), whereas their activation in the amygdala and dorsal hippocampus (dHip) gave rise to an anxiogenic one (Roohbakhsh et al., 2007; Rubino et al., 2008a). Therefore the overall effect might depend on the amount of receptors saturated in each brain region, as already proposed by Hill and Gorzalka (Hill and Gorzalka, 2009).

Finally, among anxiety disorders, post-traumatic stress disorder (PTSD) calls for specific discussion on account of its different components, mainly the inappropriate perseveration of emotionally aversive memories. The involvement of the eCB system and its possible exploitation has been reviewed extensively elsewhere (Fraser, 2009; Lutz, 2007). However, it is worth recalling that current data suggest that cannabinoids or agents that facilitate eCB signaling may offer therapeutic benefit for PTSD too.

## Psychosis: focus on schizophrenia

### *The eCB system in schizophrenia*

#### *CB1 receptor*

Schizophrenia may be associated with anomalies in the functions of the cannabinoid receptors and their attendant system of endogenous activators. These receptors are the pharmacological target of cannabis derived drugs that contain THC and convergent findings from epidemiological studies indicate that cannabis consumption constitutes a substantial environmental risk factor for schizophrenia, especially when exposure occurs during adolescence (Henquet et al., 2005; Moore et al., 2007). These findings, although still unclear at the molecular level, are consistent with the neuroanatomical distribution of cannabinoid CB1 receptors, which present a high density in brain regions implicated in schizophrenia such as PFC, basal ganglia, hippocampus and anterior cingulate cortex (Glass et al., 1997). Finally, long term users of cannabis show deficits in cognitive functions, such as working memory (Solowij et al., 2002), that are also impaired in schizophrenia (Elvevag and Goldberg, 2000).

Several papers suggest that changes in CB1 receptors may be involved in schizophrenia. Dean et al. (2001) reported that binding of [<sup>3</sup>H]CP55940 to cannabinoid CB1 receptors in the dorso-lateral PFC of schizophrenic patients was higher than in controls, independently of recent ingestion of cannabis. However, there was also a significant

increase in the caudate putamen from subjects who had ingested cannabis within five days of death, and this was independent of diagnosis. In contrast a recent paper from [Eggan et al. \(2008\)](#) found significantly lower levels (14%) of CB1 receptor mRNA and protein (about 12%) in the dorso-lateral PFC of subjects with schizophrenia. The differences in CB1 mRNA levels were significantly correlated with those in glutamic acid decarboxylase and cholecystokinin (CCK) mRNA. This combination suggests that the low CB1 receptor mRNA and protein levels in schizophrenia might reflect a compensatory mechanism to increase GABA transmission from perisomatic-targeting CCK interneurons with impaired GABA synthesis. A lower density of CB1 receptors, by reducing the eCB mediated suppression of GABA release from the perisomatic terminals of CB1R and CCK containing interneurons, could contribute to a partial normalization of gamma band power and working memory function strongly impaired in schizophrenics.

[Zavitsanou et al. \(2004\)](#) showed that the binding of [<sup>3</sup>H]SR141716A, an antagonist that specifically targets CB1 receptors, was significantly elevated (64%) in the anterior cingulate cortex (ACC) of schizophrenic patients compared to control. The ACC plays an important role in normal cognition, particularly in relation to attention and motivation. Impairments of cognitive functioning in this area have been seen in long term cannabis users ([Solowij, et al., 2002](#)) and the same conditions resemble the core negative/cognitive symptoms of schizophrenia. Therefore changes in CB1 receptors in the ACC might well be involved in schizophrenia, particularly in relation to negative/cognitive symptoms. In contrast, [Koethe et al., 2007](#)), analyzing the expression of CB1 receptors in the ACC using immunohistochemistry, did not find any difference between the density of immunoreactive cells in schizophrenics and healthy controls. They themselves note that the study shows some features that might explain the different results: there were only a small number of cases, there was no information on life-long cannabis consumption and usage patterns and a different methodological approach was used.

Finally [Newell et al. \(2006\)](#) found a significant increase in CB1 receptor binding in another area relevant for schizophrenia, the posterior cingulate cortex (PCC) where the CB1 receptor density was increased of 25% in schizophrenic subjects compared to controls, none of whom had recently used cannabis.

As a general comment, human studies support the presence of a dysfunction in CB1 receptors in selected brain areas of schizophrenic patients, specifically localized in cortical regions (ACC, the dorso-lateral PFC, and PCC) involved in cognition and memory, two functions highly compromised in schizophrenia. Either increase or decrease in CB1 receptors has been reported in these areas but several confounding factors might explain the apparent opposite results: first of all cannabis consumption and treatment with antipsychotic drugs are events that *per se* can affect the CB1 receptor expression; secondly different biochemical techniques were used for the determination of CB1 receptors (binding vs immunoreactivity).

Studies in animals would provide more reliable data but the difficulty here is selecting an experimental model really resembling schizophrenia. The models currently available suffer several limitations and often represent only certain aspects of the pathology, making it difficult to translate the findings to the human condition. Moreover, only very few studies have examined the CB1 receptor system in experimental models of schizophrenia. N-methyl-D-aspartate (NMDA) antagonists (including phencyclidine, PCP) induce psychotic symptoms in humans, and are used to model schizophrenia in various experimental conditions. PCP increases locomotion and stereotyped behaviors, reduces social interactions and induces cognitive impairment in experimental animals. These changes are consistent with a schizophrenia-like effect ([Bubeníková-Valesová et al., 2008](#)).

[Vigano et al. \(2009\)](#) using a model based on repeated PCP injection in rats, found that the [<sup>3</sup>H]CP55940 receptor binding was significantly enhanced in the amygdala (15%) and in the ventral tegmental area (48%), among all the brain areas expressing CB1 receptors. Results

with CP55940-stimulated GTPgammaS binding are also interesting. Prolonged exposure to PCP significantly reduced the percentage of CB1 net stimulation in the PFC (41%), hippocampus (40%), substantia nigra (29%) and cerebellum (39%) and raised it in the globus pallidus (77%) compared to controls. Thus the changes in the CB1 receptor efficiency were widely distributed through the brain, but mainly localized in brain areas specifically involved in schizophrenia.

Recently, [Seillier et al. \(2009\)](#) using a subchronic PCP model of schizophrenia in rats, saw no changes in CB1 receptor expression. In PCP-treated rats, increases in the receptor stimulated GTPgammaS binding were observed in the ACC and nucleus accumbens (NAc), while a reduction in the CA2/3 fields of the hippocampus was reported. These findings disagree with those of [Vigano et al. \(2009\)](#) although both are obtained with PCP injections in rats. Differences in drug regimen (intermittent or repeated PCP; 72 h withdrawal for Vigano and 5–10 days for Seillier) and the age of the animals (juveniles in Vigano but adult rats in Seillier) might explain the differences.

Finally [Malone et al. \(2008\)](#), using the model of post weaning social isolation in rats, which produces behavioral and neurochemical alterations similar to those in psychoses such as schizophrenia, noted CB1 receptor down-regulation in the caudate putamen and amygdala. Summarizing, the experimental data too point to a dysregulation of CB1 receptor in experimental models of schizophrenia but the entity of alteration (increase or decrease) and the brain region involved can differ depending on the adopted model, as each of them reproduces only few and limited aspects of the pathology, which are mediated by different brain areas, differently modulated by the eCB system.

Another important approach for determining the CB1 receptor's role in schizophrenia is the use of ko mice. In wt mice, 5 mg/kg PCP increased locomotion and stereotyped behaviors, and reduced social interactions. These changes are consistent with a schizophrenia-like effect ([Haller et al., 2005](#)). In CB1-ko mice, PCP reduced locomotion and enhanced ataxia and stereotypy more than in wt animals, but did not affect social interactions. Locomotion showed a significant negative correlation with both ataxia and stereotypy, suggesting that in CB1 ko mice, PCP's locomotor-suppressive effect was secondary to changes in these variables ([Haller et al., 2005](#)). These findings indicate that CB1 gene disruption dramatically alters the behavioral effects of the NMDA antagonist PCP, suggesting that the CB1 receptor is involved in schizophrenia. As social disruption and stereotypy are believed to model respectively negative and positive symptoms of schizophrenia, it can be tentatively suggested that cannabinoids play different parts in these two symptom categories, possibly inhibiting positive but facilitating negative ones.

Finally, polymorphisms in the CB1 receptor gene CNR1, correlated with an increased probability of developing psychosis or some types of schizophrenia, have also been described ([Chavarría-Siles et al., 2008](#); [Martínez-Gras et al., 2006](#)), although their importance is still debated ([Seifert et al., 2007](#); [Hamdani et al., 2008](#)).

#### ECBs

Clinical and laboratory findings suggest that, besides alteration in the CB1 receptor, variations in eCB level are implicated in schizophrenia. [De Marchi et al. \(2003\)](#) measuring AEA levels from blood of volunteers or patients with schizophrenia, found significantly more AEA in schizophrenic patients, and clinical remission was accompanied by a significant drop in the levels of AEA and the mRNA transcript for CB2 receptors and FAAH. Thus eCB signaling might be altered during the acute phase of schizophrenia not only in the central nervous system but also in the blood. These researchers suggested that the changes might be related to the immunological alterations described in schizophrenia.

[Giuffrida et al. \(2004\)](#) found that the cerebrospinal fluid (CSF) levels of AEA were markedly elevated in neuroleptic-naïve schizophrenic patients. Differently from De Marchi, they found no changes in serum, thus strengthening the idea that these changes in AEA level were

presumably of central origin. Other lipid molecules such as oleoylethanolamide and palmitoylethanolamide were not increased in schizophrenics, thus excluding any generalized alteration in lipid signaling. The AEA alteration was apparently restricted to schizophrenia since it was not found in patients with dementia or affective disorders.

The negative correlation of CSF AEA levels with psychopathological symptoms in acute, non-medicated schizophrenic patients suggests that AEA might play an adaptive role, counteracting the neurotransmitter abnormalities in acute schizophrenia, and confirms the existence of an “anandamid-ergic” dysregulation in schizophrenia. The adaptive function of AEA in acute schizophrenic patients is in apparent contrast with the association between cannabis use and precipitation of psychotic symptoms which has been shown in numerous clinical studies (Arseneault et al., 2002; Henquet et al., 2005; Zammit et al. 2002). At this regard, Leweke et al. (2007b) examined whether cannabis use might alter the adaptive role played by AEA in schizophrenia. Frequent cannabis use by schizophrenic patients down-regulated CSF AEA levels but it had no such effect in healthy volunteers. Therefore the possible mechanism is that cannabis consumption, when exceeds a certain level, may provoke a down-regulation of AEA signaling in the CNS through a decrease in AEA biosynthesis or an increase in its degradation (see for review Piomelli, 2003). Accordingly, changes in AEA signaling secondary to cannabis exposure might be an important component of the mechanism through which cannabis might precipitate psychotic symptoms.

Finally another important aspect is the impact of the treatment with antipsychotics of different classes on AEA levels. Giuffrida et al. (2004) found that patients treated with a “typical” antipsychotic had CSF AEA levels similar to healthy subjects, whereas patients treated with an “atypical” drug had increased levels similar to naive schizophrenic. This is consistent with the theory that “typical” antipsychotics normalize AEA levels by blocking D2-like receptors that initiate AEA synthesis in limbic and motor areas, while “atypical” preferentially interact with serotonin 5-HT<sub>2A</sub> receptors.

To date, disturbances in eCB levels have been reported only in two animal models of schizophrenia (Seillier et al., 2009; Vigano et al., 2009) using a PCP model. Vigano et al. (2009) ran behavioral tests (novel object recognition test) 72 h after the last PCP injection and measured the eCB levels immediately after the task. In these conditions there was no change in AEA level in either the PFC or the hippocampus, whereas 2-AG rose significantly in the hippocampus. In contrast, Seillier et al. (2009) measuring AEA and 2-AG in a separate group of rats that did not undergo behavioral testing, found increases in AEA level in the NAc and ventral tegmental area (VTA) and a trend, although not statistically significant, in the PFC. 2-AG levels were increased only in the VTA.

As discussed above, both studies used a schizophrenia model based on PCP injections but with substantial differences in the experimental design. Moreover, a relevant aspect is the time of eCBs measure: immediately after the behavioral test (as in Vigano's study) or in animals that had not been tested (as in Seillier's one). Thus, in the former case the level of eCBs reflects their production in response to neuronal activity, but in the latter it reflects the basal level.

#### *Pharmacological modulation of CB1 receptors in schizophrenia*

In the last few years an impressive amount of experimental work has been done to clarify the effect of CB1 receptor modulation in psychotic symptoms. Schizophrenic patients have symptoms that are considered positive (hallucination, delusions, disordered thinking and paranoia) and negative (deficit in social interaction, emotional expression and motivation).

The two most widely used animal approaches for reproducing schizophrenia-like symptoms are based on the dopamine or glutamatergic hypothesis of schizophrenia and on the observation that dopaminergic agents (amphetamine, quinpirole, cocaine), and non-competitive blockers of NMDA glutamate receptors (MK801 and PCP) induce hyperlocomotion and stereotyped behaviors resembling the

positive symptoms, and reduced the acoustic startle reflex, modeling the impairment of sensorimotor gating present in schizophrenic patients. Moreover the NMDA non-competitive blockers also reproduce negative symptoms such as the deficit in social interaction, avolition, and cognitive impairment.

The next section briefly looks at the importance of pharmacological manipulation of CB1 receptor with agonists, indirect agonists or antagonists on the different symptoms of schizophrenia.

#### *Positive symptoms*

Several studies investigated the effects of acute or chronic stimulation with cannabinoid receptor agonists or antagonists on the hyperlocomotion and/or stereotypies induced mainly by dopaminergic agents (Table 3).

In 1999, Gorriti et al. (1999) reported that acute THC antagonized the amphetamine-induced dose-dependent increases in locomotion and exploration, and decrease in inactivity. Chronic exposure induced tolerance to this antagonistic effect on locomotion and inactivity but not on exploration, and potentiated the amphetamine-induced stereotypies. Later Gorriti et al. (2005) described a contrasting result, in that acute exposure to THC facilitated quinpirole-induced hyperlocomotion. Biochemical analysis showed THC-induced cannabinoid receptor desensitization in the striatum, which can enhance the dopamine D2 receptor's sensitivity to dopamine, explaining the enhanced psychotic behavior. Przegalinski et al. (2005) examined the effect of WIN 55,212-2 and its enantiomer WIN 55,212-3, on cocaine-induced locomotor hyperactivity in rats. WIN 55,212-2, but not the enantiomer, in doses that did not affect the basal locomotor activity, dose-dependently antagonized the hyperactivation evoked by cocaine. The inhibitory effect of WIN 55,212-2 was not reversed by the CB1 receptor antagonist SR141716, indicating that this effect is stereoselective and not mediated by cannabinoid receptors.

The CB1 receptor agonist CP55940 at a dose that did not change basal locomotion, blocked quinpirole-induced increases in locomotor activity (Marcellino et al., 2008). In addition, not only the CB1 receptor antagonist rimonabant but also the specific A2A receptor antagonist MSX-3 blocked the inhibitory effect on D2-like receptor agonist-induced hyperlocomotion. This suggests that the CB1 negative modulation of D2 signaling is dependent on tonic A2A activation on the brain.

Finally cannabidiol (CBD), a non psychoactive component of *C. sativa*, as well as haloperidol, reduced apomorphine-induced stereotyped behavior in rats without inducing catalepsy, even at the high dose of 480 mg/kg (Zuardi et al., 1991). In agreement, CBD caused dose-dependent inhibition of the hyperlocomotion induced in mice by ketamine (Moreira and Guimarães, 2005) without inducing catalepsy.

Other studies focused on whether the CB1 receptor antagonist SR141716 reduced positive symptoms (Table 3). In one study, d-amphetamine-induced hyperlocomotion in habituated rats was attenuated by administration of SR141716A while increasing the level of serotonin, dopamine and noradrenaline in the PFC, suggesting a potential for treatment of psychosis (Tzavara et al. 2003).

In a study in gerbils, Poncelet et al. (1999) showed that SR141716 as well as clozapine dose-dependently suppressed the stimulation of locomotor activity produced by d-amphetamine, cocaine and morphine but only in habituated gerbils. However, haloperidol antagonized the hyperlocomotion in both habituated and non-habituated gerbils. These authors therefore suggested that the eCB system may preferentially modulate brain circuits underlying cognitive or motivational processes rather than those involved in motor control (e.g., nigrostriatal pathways). Madsen (Madsen et al., 2006) in a monkey study with the hydrochloride salt SR141716A showed that the drug had no observable effect on d-amphetamine-induced unrest or stereotypy, whereas it significantly reduced d-amphetamine-induced arousal. In agreement, SR141716A did not reverse the d-amphetamine-induced hyperactivity or stereotypy in rats (Martin et al., 2003). Furthermore Ferrer et al. (2007) found that SR141716A

**Table 3**  
Effect of cannabinoid agonists/antagonists and cannabidiol on schizophrenia-like positive symptoms.

Drug	Species	Model	Effect	Reference
THC	Rat	d-amphetamine-induced hyperlocomotion	Reduction	Gorriti et al. (1999)
THC	Rat	Quinpirole-induced hyperlocomotion	Increase	Gorriti et al. (2005)
WIN55,212-2	Rat	Cocaine-induced hyperlocomotion	Reduction	Przegalinski et al. (2005)
CP55940	Rat	Quinpirole-induced hyperlocomotion	Reduction	Marcellino et al. (2008)
SR141716	Rat ( <i>habituated</i> )	d-amphetamine-induced hyperlocomotion	Reduction	Tzavara et al., 2003
SR141716A	Gerbil ( <i>habituated</i> )	Cocaine-, d-amphetamine-, morphine-induced hyperlocomotion	Reduction	Poncelet et al. (1999)
SR141716A	Monkey	d-amphetamine-induced unrest and stereotypy; d-amphetamine-induced arousal	No effect reduction	Madsen et al. (2006)
SR141716A	Rat	d-amphetamine-induced hyperactivity and stereotypy	No effect	Martin et al. (2003)
SR1716A	Rat	SKF38393- and Quinpirole-induced stereotypy	Increased	Ferrer et al. (2007)
Cannabidiol	Rat	d-amphetamine-induced hyperlocomotion	Reduction	Moreira and Guimarães (2005)
Cannabidiol	Rat	Apomorphine-induced stereotypy	Reduction	Zuardi et al. (1991)

enhanced stereotypy induced in rats by either the dopamine D1 receptor agonist SKF38393 or the dopamine D2 receptor agonist quinpirole. A potential explanation for this phenomenon is the removal of the eCB brake to dopaminergic overactivation. These findings suggest that the eCB system plays a relevant role in the pathogenesis of psychosis.

As a whole, we can conclude that CB1 receptor agonists can either reduce, enhance or have no effect on positive symptoms induced by dopaminergic agents. The agonist's protective effect agrees with Giuffrida's hypothesis of the adaptive/protective role of AEA in schizophrenia (Giuffrida et al., 2004). In line with this, the blockade of CB1 receptors through SR141716, removing the eCB brake, enhances the dopaminergic positive symptoms. Similarly, an excessive CB1 stimulation, inducing CB1 receptor desensitization/internalization, reduces the inhibitory control of the eCB system on dopaminergic pathways, thus worsening the symptoms.

Concerning the protective effect of SR141716, its ability to reverse dopaminergic symptoms appears more questionable inasmuch as it was reported only in habituated animals.

#### Sensorimotor gating

Studies of sensorimotor gating of startle responses to strong exteroceptive stimuli provide an excellent method for exploring information processing and attentional deficits in schizophrenia. Prepulse inhibition (PPI) is defined as the decrease in the acoustic startle response when a non-startling prepulse is presented before the startling pulse. Numerous studies have shown that chronic schizophrenic and non-medicated first-episode schizophrenic patients have a marked deficit in PPI. Similar deficits are produced in rats by pharmacological or developmental manipulations. In rodents and healthy human volunteers, disruptions in PPI of startle are produced by: stimulation of D2 dopamine receptors by amphetamine or apomorphine; activation of serotonergic systems by direct 5-HT<sub>2A</sub> receptor agonists such as LSD or psilocybin; and blockade of NMDA receptors produced by drugs such as ketamine and PCP. In this respect, several studies show that the CB1 agonists too can alter PPI, and their concordant results indicate that either CP55940 as well as WIN 55,212-2 reduced sensorimotor gating in rats (Martin et al., 2003; Schneider and Koch, 2002) although Bortolato et al. (2005) observed no changes in PPI after WIN 55,212-2 treatment, at whatever dosage and schedule. More recently Nagai et al. (2006) demonstrated in mice that THC impaired PPI, while also reducing the startle response. Antipsychotics such as haloperidol and risperidone, which are potent dopamine D2 receptor antagonists, and the CB1 cannabinoid receptor antagonist SR141716 reversed the THC-induced PPI deficit. THC (10 mg/kg) raised dopamine release in the NAc but not in the medial PFC in the 50–100 min (time of PPI test) after treatment, and SR141716 (10 mg/kg) reversed this increase. Therefore it appears that dopaminergic hyperfunction in the NAc may be involved in THC-induced PPI deficit. Wegener investigated the acute effect of WIN 55,212-2 on PPI of the acoustic startle response (ASR),

after local intra-cerebral microinfusion in rat different brain areas (Wegener et al., 2008). WIN55,212-2 infused into the NAc (core or shell), dorsal Hippocampus or VTA did not affect PPI, whereas the inhibition was significantly reduced after intra-medial PFC and intra-ventral hippocampus infusion of the drug. These data support the notion that CB1 receptor stimulation impairs sensorimotor gating most likely by affecting neurotransmitter release in the medial PFC and vHip likely leading to NAc DA over-activity. Specifically, WIN-induced disruption of PPI might be due to an intrahippocampal inhibition of GABA release (Hajos et al., 2000), so that subsequent disinhibition of hippocampal Glu release on spiny NAc neurons, a site of convergence with DA afferents from the VTA (Sesack and Pickel, 1990), might finally have led to NAc DA over-activity. Similarly, intra-medial PFC WIN may have impaired PPI by decreasing cortical glutamatergic output to the NAc, thereby reducing the activity of GABAergic NAc medium spiny neurons projecting to DA neurons in the VTA, followed by a disinhibition of DA neurons (Sesack and Carr, 2002; Lupica et al. 2004).

Finally Dissanayake et al. (2008) and Hajos et al. (2008) showed that a single injection of WIN55,212-2 or CP55940 in rats disrupted auditory gating in the CA3 region, the dentate gyrus and medial PFC, similar to the effects in schizophrenia. These effects were reversed by CB1 receptor antagonists such as SR141716 or AM 251 (Dissanayake et al., 2008; Hajos et al., 2008).

The CB1 receptor antagonist's ability to relieve the PPI disruption provoked by cannabinoids or other psychotomimetic drugs has been extensively examined (Table 4). Martin et al. (2003) found that the PPI disruption induced by the CB1 agonist CP55940 in rats was significantly reversed by the CB1 antagonist SR141716, in agreement with the results reported by Mansbach et al. (1996). In the same study, SR141716 did not reverse the PPI disruption produced by the D2 receptor agonist apomorphine or d-amphetamine, or the NMDA antagonist MK-801, which were blocked by haloperidol, clozapine and olanzapine. SR141716 also failed to reverse hyperactivity and stereotypy induced by these psychotomimetic agents, suggesting that blockade of the CB1 receptor on its own is not sufficient for antipsychotic therapy. In contrast, a more recent study in rats (Ballmaier et al., 2007) demonstrated that SR141716 significantly counteracted the PPI disruption produced by the NMDA antagonists PCP and dizocilpine, and by apomorphine. Since clozapine revealed similar results, the authors suggested an atypical antipsychotic profile of the cannabinoid antagonist. Similarly, Malone et al. (2004) demonstrated that SR141716 antagonized the disruptive PPI effects of apomorphine also in mice. The different findings of these studies might be explained by the dose range used, the SR141716 preparation and the route of administration.

Apparently the ability of the CB1 antagonist to reverse PPI deficit is in contrast with previous literature highlighting an antipsychotic action of AEA (Giuffrida et al., 2004). AEA may be implicated in the negative regulation of dopamine release by acting retrogradely on CB1 receptors in dopaminergic presynaptic terminals lowering dopamine release. In contrast AEA seems to have no effect on glutamate release. In this view

the ability of rimonabant to reverse PPI inhibition induced by glutamatergic agent could be justified by its ability to prevalent block the action of 2AG, the most probable retrograde mediator at glutamatergic synapses. Under this perspective, it is possible to speculate that AEA and 2-AG might play different roles in the pathophysiology of schizophrenia.

Subsequently, Malone and Taylor tested the efficacy of SR141716 using a non-pharmacological model of psychosis based on behavioral and neurochemical changes resulting from social isolation (Malone and Taylor, 2006). The protocol induces behavioral and neurochemical alterations similar to those in schizophrenic patients (increased spontaneous locomotor activity, disrupted PPI, increased anxiety, deficits in learning and memory, and neurochemical changes such as increased presynaptic dopaminergic activity in NAc and PFC, decreased prefrontal serotonergic function, and an imbalance between dopamine and serotonin in the frontal cortex). Social isolation, as expected, disrupted PPI in rats, more so after weaning (Malone and Taylor, 2006). Administration of THC as well caused reduced PPI in socially isolated rats more than social isolation alone, but had no influence on PPI in rats reared in groups. SR141716 reversed the further decrease in PPI induced by THC, indicating that this effect depended on activation of CB1 receptors. In contrast SR141716 did not reverse the isolation-induced reductions in PPI. The authors clearly suggest that antagonism of CB1 receptors is probably not enough to normalize the PPI disruption induced by developmental manipulations. These findings indirectly support the theory that THC significantly worsens the sensorimotor gating in rats with already dysfunctional sensorimotor gating processes but not in normal rats. We can therefore presume that cannabis consumption in humans is more likely to exacerbate psychosis such as schizophrenia in people who already have abnormal neurochemistry than to induce psychosis in “normal” individuals.

As a whole, SR141716 certainly reverses the PPI disruption induced by cannabinoid drugs, probably affecting the neurotransmitter release in the medial PFC and VTA, whereas its effect on PPI induced by other pharmacological agents and/or developmental models are uncertain and needs further investigations.

In contrast, Spano et al. (2009), have recently reported very intriguing results since the cannabinoid agonist WIN 55,212-2 self-administration in rats attenuated PCP-induced deficits in PPI of the acoustic startle reflex, suggesting that cannabis consumption may in fact reduce the severity of some psychotic symptoms, and that the eCB system is likely to play a more multifaceted role in schizophrenia than had previously been thought.

Finally interesting findings have been reported also with the non psychoactive CBD. Long et al. (2006) showed that in mice CBD significantly reversed PPI deficits induced by MK-801 whereas did not affect PPI on its own. Because clozapine (4 mg/kg) gave the same results, it was concluded that CBD may have atypical antipsychotic potential.

#### Other negative symptoms and cognitive deficit

Animal and human studies suggest that CB1 receptor agonists such as THC, WIN 55,212-2, CP55940 and AEA, cause memory deficits

similar to those seen in schizophrenic patients, but few studies have examined the effect of cannabinoid receptor pharmacological modulation in reversing cognitive or social deficits in different experimental schizophrenia models.

Vigano and coworkers showed that in juvenile rats chronic THC co-treatment worsened PCP-induced cognitive impairment tested in the novel object recognition test, but had no effect *per se* (Vigano et al., 2009). In parallel, THC markedly reduced the levels of AEA, compared to either vehicle (73%) or PCP (64%), pointing to the eCB system's involvement in this pharmacological model of cognitive dysfunction, suggesting that prolonged cannabis use might aggravate cognitive performances induced by chronic PCP by throwing the eCB system off-balance.

In contrast, Spano et al. (2010) showed that WIN 55,212-2 self-administration in adult rats attenuates PCP-induced deficits in cognitive skills and sociability, strengthening the idea of a protective role for the CB1 receptor agonist. Spano and Vigano reported divergent results even though they used the same PCP protocol (THC worsened PCP's effect in Vigano's study, while WIN 55,212-2 improved PCP's effect in the study by Spano's group). There may be three main reasons: differences in CB1 receptor affinity between THC and WIN 55,212-2, the different age of PCP-treated animals (juveniles in Vigano's and adult in Spano's studies) and, finally, the different ages at cannabinoid treatment. Younger animals are known to show different vulnerability to aversive situations, drug treatment included.

Finally, Seillier and coworkers showed that URB597, a FAAH inhibitor, reversed PCP-induced social withdrawal but caused social withdrawal and working-memory deficits in saline-treated rats comparable to those after PCP treatment (Seillier et al., 2009). AM251 ameliorated the working-memory deficit in PCP-treated rats, but impaired working memory in saline-injected controls. These findings suggest that FAAH inhibition might improve negative symptoms in PCP-treated rats but could have harmful effects in untreated animals, possibly by disturbing the eCB tone. In agreement, our recent work (Guidali et al., 2010) in rats supports the protective effect of chronic AM251 treatment on cognitive deficit and on the decrease in social interaction provoked by chronic PCP, but in our hand AM251 did not affect behavior *per se*.

#### Human studies

The relationship between cannabis consumption and schizophrenia is beyond the scope of this review as several recent reviews have covered the topic in detail (Luzi et al., 2008; Sewell et al., 2009; D'Souza et al., 2009). However, we want to briefly mention that in individuals with a predisposition for schizophrenia, the ingestion of cannabis exacerbates symptoms and worsens the schizophrenic prognosis (for review see Hall et al., 2004). In addition to cannabis producing acute psychotic like symptoms, epidemiological data suggests that cannabis is a risk factor for the onset of schizophrenia. The risk of developing schizophrenia has been reported to increase in a dose-dependent manner with increasing frequency of cannabis use (Fergusson et al., 2005; Henquet et al., 2005; Zammit et al., 2002), and when cannabis is used in adolescence (Stefanis et al., 2004).

**Table 4**  
Effect of cannabinoid antagonists and cannabidiol on sensorimotor gating disruption induced by different agents.

Drug	Species	Effect	Reference
SR141716	Mouse	Reversed THC-induced PPI deficit	Nagai et al. (2006)
SR141716A	Rat	Reversed CP55940-induced PPI deficit	Martin et al. (2003)
SR141716	Rat	Reversed WIN55,212-2 induced disruption of auditory gating	Dissanayake et al. (2008)
SR141716A	Rat	Reversed CP55940-induced PPI deficit	Mansbach et al. (1996)
AM251	Rat	Reversed WIN55,212-2 induced disruption of auditory gating	Hajos et al. (2008)
SR141716A	Rat	No effect on MK801- induced PPI deficit	Martin et al. (2003)
Rimonabant and AM251	Rat	Reversed PCP-, dizocilpine-, apomorphine-induced PPI deficit	Ballmaier et al. (2007)
SR141716	Mouse	Reversed apomorphine-induced PPI deficit	Malone et al. (2004)
SR141716	Rat	No effect on isolation- induced PPI deficit;reversed THC increase in isolation- induced PPI deficit	Malone and Taylor, 2006
Cannabidiol	Mouse	Reversed MK801- induced PPI deficit	Long et al. (2006)



Moreover, in the last 5 years evidence from a number of studies has emerged that an increased risk of developing adult psychosis exists in patients with COMT Valine polymorphism following adolescent cannabis exposure (Caspi et al., 2005; Henquet et al., 2006; Hides et al., 2009).

Nevertheless the aim of this section is to examine what data are available suggesting that action on the cannabinoid system can be regarded as a promising new tool for the treatment of schizophrenia.

After earlier studies in healthy subjects, Meltzer et al. (2004) compared the antipsychotic effects of SR141716A and haloperidol in 72 patients with schizophrenic or schizoaffective disorders. Only 15 completed the study according to protocol. SR141716A was used at a daily dose of 20 mg but no clinical improvement was seen, as indicated by the Positive and Negative Syndrome Scale (PANS) and by the global clinical impression, compared to placebo. The authors speculated that the dose was not high enough, which might explain the negative outcome.

In contrast, results with CBD seem more promising. The pioneering study of Zuardi et al. (1995) reported significant improvement of the symptomatology, assessed through the Brief Psychiatric rating scale (BPRS) in a single case, a 19-year-old female schizophrenic patient given increasing doses of oral CBD up to 1500 mg/day for four weeks. However in 2006 the same group (Zuardi et al., 2006) reported negative results in three 22- to 23-year-old males with treatment-resistant schizophrenia, given CBD monotherapy for four weeks. The authors suggest that this may have been due to the short treatment mainly with the highest dose and by fact that the patients were also insensitive to clozapine. It is perhaps worth recalling that, despite the high doses, CBD was very well tolerated and no side effects were reported.

In 2007 Leweke et al. (2007a) found that CBD significantly reduced psychotic symptoms in acute schizophrenia with potency similar to amisulpiride but with fewer side effects such as EPS, increase in prolactin, and weight gain.

## Conclusions

### Mood disorders

Alterations in the eCB system appear to play a key role in mood disorders. Reduced functionality might be considered a predisposing factor for major depression, so boosting the eCB tone might be a useful alternative therapeutic approach for depressive disorder.

The picture regarding eCBs and anxiety is more complicated since either too much or too little AEA can lead to anxiety states. However, a small raise in its level in specific brain areas might be beneficial for the response to a stressful situation and therefore to tone down anxiety. Based on this last assumption, a slight increase in eCB tone only in the brain areas where it is needed could help control anxiety. This effect might be achieved with low doses of CB1 indirect agonists, such as blockers of the degradative pathway (i.e. FAAH) or re-uptake inhibitors.

### Schizophrenia

As outlined here, several lines of experimental and clinical evidence point to a dysregulation of the cannabinoid system in schizophrenia. Hyper- or hypo-activity of CB1 receptor function in specific brain areas can markedly affect several neuronal pathways, contributing to or counteracting the pathology. The high AEA level found in schizophrenic patients negatively correlated with psychotic symptoms, pointing to a protective role, whereas the role of 2-AG is still not clear. As a whole, the eCB system presents several abnormalities in receptor function as in eCBs which, depending on the cerebral areas affected, might contribute differently to the pathology. Knowledge of the precise localization of the affected

areas and their influence on other neurotransmitter systems might extend our understanding of eCB system's role.

Concerning the potentiality of the pharmacological manipulation of the eCB system as a novel approach for treating schizophrenia, the experimental findings are still controversial, often with different effects depending on the drug, the dose, the species and the model used for simulating positive or negative symptoms. Considering all these limitations, SR141716 and CBD show the most constant antipsychotic properties in dopamine- and glutamate- based models of schizophrenia with profile similar to an atypical antipsychotic drug. The findings with SR141716 are often variable, mainly considering its ability to reverse NMDA-antagonist induced disruption of PPI, considered a characteristic of atypical antipsychotic. Unfortunately there is only one clinical trial where SR141716 was ineffective. CBD however is effective in humans and experimental animals with a low toxicity profile.

The mechanisms of action of both drugs need further investigations, but particularly for CBD. It is conceivable that SR141716 abolishes many of the physiological and psychological effects of CB1 activation, whereas different theories can be put forward for CBD, from inhibition of AEA uptake, to CB1 receptor antagonism and non-cannabinoid-mediated mechanisms. Interestingly for both drugs only a few studies have investigated their ability to improve the psychosis-related cognitive impairment that is one of the main debilitating symptoms.

Further investigation of the eCB system should not only elucidate its role in the schizophrenia but should also provide a valuable target for psychopharmacological intervention opening up new prospects for treatment.

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