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REVIEW

Role of cannabis and endocannabinoids in the genesis of schizophrenia

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Abstract
Rationale Cannabis abuse and endocannabinoids are associated to schizophrenia.
Objectives It is important to discern the association between schizophrenia and exogenous *Cannabis sativa*, on one hand, and the endogenous cannabinoid system, on the other hand.
Results On one hand, there is substantial evidence that cannabis abuse is a risk factor for psychosis in genetically predisposed people, may lead to a worse outcome of the disease, or it can affect normal brain development during adolescence, increasing the risk for schizophrenia in adulthood. Regarding genetic predisposition, alterations affecting the cannabinoid CNR1 gene could be related to schizophrenia. On the other hand, the endogenous cannabinoid system is altered in schizophrenia (i.e., increased density of cannabinoid CB1 receptor binding in corticolimbic regions, enhanced cerebrospinal fluid anandamide levels), and dysregulation of this system can interact with neurotransmitter systems in such a way that a "cannabinoid hypothesis" can be integrated in the neurobiological hypotheses of schizophrenia. Finally, there is also evidence that some genetic alterations of the CNR1 gene can act as a protectant factor against schizophrenia or can induce a better pharmacological response to atypical antipsychotics.
Conclusions Cannabis abuse is a risk factor for psychosis in predisposed people, it can affect neurodevelopment during adolescence leading to schizophrenia, and a dysregulation of the endocannabinoid system can participate in schizophrenia. It is also worth noting that some specific cannabinoid alterations can act as neuroprotectant for schizophrenia or can be a psychopharmacogenetic rather than a vulnerability factor.

Keywords Cannabis · Endocannabinoid · Psychosis · Schizophrenia · Neurobiology · Genetic · Epidemiology

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Introduction

Cannabis sativa contains several addictive cannabinoid substances such as (−)-Δ^9-tetrahydrocannabinol (Δ-9-THC) and (−)-Δ^8-tetrahydrocannabinol, and these exogenous cannabinoid substances influence the central nervous system through the endocannabinoid receptors. Cannabis, as a drug of abuse, induces changes in the nervous system which ultimately lead to dependence. Brain chemistry is modified after the action of repeated cannabis, and the drug could induce psychotic symptoms (among others), in a

similar fashion to other drugs such as psychostimulants. However, the link between cannabis and schizophrenic psychosis is a matter of controversy. Some authors defend that there is an independent nosological entity or "cannabis psychosis," as it is the case with "amphetamine psychosis" (Thacore and Sukhla 1976; Núñez and Gurpegui 2002). Other authors reject the existence of a nosological entity (Thornicroft 1990; Hall 1998), and they postulate that cannabis influences the development of schizophrenic psychosis, or it is a risk factor involved in the likelihood to suffer from schizophrenia. However, it is important to bear in mind that cannabis use was noted to be as high as 43% of patients who had schizophrenia (Bersani et al. 2002) and in 51% of patients with first-episode schizophrenia (Barnett et al. 2007). The greatest risk of onset of cannabis use is in the age range 15–20 years that coincides with the onset of schizophrenia (Grant et al. 2008).

Interestingly, acute intoxication with cannabis leads to a syndrome with similar characteristics to a psychotic state: confusion, depersonalization, paranoid delusions, hallucinations, blunted affect, anxiety, and agitation (D'Souza et al. 2004; Favrat et al. 2005). However, this acute episode is transient and wears off once the main psychoactive component of cannabis, Δ-9-THC, is eliminated from the blood. A similar syndrome takes place in schizophrenic patients where intravenous Δ-9-THC induces an increase of positive and negative schizophrenic symptoms (D'Souza et al. 2005). Chronic abuse seems not to be accompanied by such a bizarre state, and it has been suggested that frequent users of cannabis develop tolerance to these effects of cannabinoids (D'Souza et al. 2008a). It is hence important to differentiate chronic versus acute effects of cannabis/cannabinoids, and this review will deal with neurobiological, neurophysiological, and epidemiological data supporting a role for cannabis/cannabinoids in schizophrenia (the so-called cannabinoid hypothesis of schizophrenia), including a review of animal experimental studies on the topic. Neurobiological studies reveal that cannabis and endocannabinoids can dysregulate neurotransmitter systems involved in the pathophysiology of schizophrenia, such as the dopaminergic and glutamatergic systems, but also indicate that some endocannabinoids can act as "protective" compounds against the disorder. These are the two sides of cannabinoid effects on psychosis, at present known as the "ups and downs" theory of endocannabinoids in disease (Di Marzo 2008). This fact is linked to the pleiotropic nature of cannabinoids, and it is well known that the cannabinoid system is affected in more than just one way by a given pathological stimulus (Di Marzo 2008). In this context, the presence of a polymorphism (G allele) of the cannabinoid gene CNR1 has been associated with a better therapeutic effect of antipsychotics (Hamdani et al. 2008); and cannabis use in schizophrenics have been interpreted as "self-medication," at least at the beginning of the syndrome. However, epidemiological studies further support a link between cannabis abuse and schizophrenia, and they indicate that cannabis abuse is a risk factor in people with special vulnerability to schizophrenic psychosis, it influences the course of schizophrenia, or it can affect normal brain development during adolescence, increasing the risk for psychosis in adulthood (Verdoux and Tournier 2004; Stefanis et al. 2004). Experimental animal studies support that adolescence is a critical period, and drug contact during this period is a risk factor for suffering psychotic symptoms in the adulthood.

Cannabis and the endocannabinoid system

From a neurobiological point of view, it is important to note that the relationship between cannabis/cannabinoids and schizophrenia has two aspects (Müller-Vahl and Emrich 2008), which could be defined as endogenous and exogenous. The endogenous aspect is based on the endogenous cannabinoid system whose dysregulation could be a factor influencing the onset of schizophrenic psychosis per se or could indirectly modify other neurotransmitter systems either leading to schizophrenia or worsening it. The exogenous side refers to cannabis abuse as a risk factor that could alter the endocannabinoid system or other neurotransmitter systems, hence facilitating the onset of schizophrenia or aggravating its time course. It is crucial to understand how the endogenous cannabinoid system can be altered in schizophrenia or can affect those well-known disturbances of neural systems such as the dopamine and glutamate ones that have been associated to schizophrenia by many authors; in other words, it is necessary to integrate the "cannabinoid hypothesis" of schizophrenia in the "dopaminergic and glutamatergic hypotheses" of schizophrenia.

The endogenous cannabinoid system is a ubiquitous lipid signaling system which appeared early in evolution and which has important regulatory functions throughout the body in all vertebrates. The endogenous cannabinoid system was discovered thanks to the identification of the first receptor for the main psychoactive constituent of *Cannabis sativa* preparations, Δ-9-THC (Gaoni and Mechoulam 1964). This receptor termed cannabinoid CB_1 receptor (Devane et al. 1988; Herkenham et al. 1991) was rapidly cloned (Matsuda et al. 1990) and extensive structure–activity research led to the development of synthetic compounds with high potency and stereoselectivity (Howlett et al. 1990). The discovery of the cannabinoid receptor and the availability of very selective and potent cannabinomimetics led to the rapid identification of a family of lipid transmitters that serve as natural ligands for the cannabinoid CB_1 receptor: arachidonoylethanola-

mide, named anandamide from the Sanskrit "internal bliss" (Devane et al. 1992), and 2-arachidonoylglycerol (Mechoulam et al. 1995; Sugiura et al. 1995). The pharmacological properties of the endocannabinoids were found to be very similar to those of synthetic cannabinomimetics (Piomelli et al. 2000; Rodríguez de Fonseca et al. 2001).

Two major cannabinoid receptors have been cloned, both of which belong to the superfamily of G protein-coupled receptors. The first receptor described was named the CB_1 receptor and it is mainly located in the terminals of nerve cells (central and peripheral neurons and glial cells), the reproductive system (i.e., testicles), some glandular systems, and the microcirculation (Howlett et al. 1990). A remarkable characteristic of the CB_1 receptors is their very high expression in the brain. The CB_1 receptor is the most abundant G protein-coupled receptor with densities ten to 50 times above those of classical transmitters such as dopamine or opioid receptors (Howlett et al. 1990; Herkenham et al. 1991). The CB_2 cannabinoid receptor was found initially in multiple lymphoid organs with the highest expression detected in B lymphocytes, medium expression in monocytes and polymorphonuclear neutrophils, and the lowest expression in T lymphocytes, although subsequent studies also identified it in microglial cells (Galiègue et al. 1995; Munro et al. 1993; Piomelli 2003). Recent reports place the cannabinoid CB_2 receptor in neuronal nets of the brain stem and the cerebellum (Onaivi 2006; Suarez et al. 2008), although its role in neurotransmission remains obscure.

Endocannabinoids are released upon demand after cellular depolarization or receptor stimulation in a calcium-dependent manner. Once produced, they act in cannabinoid receptors located in cells surrounding the site of production. This property indicates that endocannabinoids are local mediators similar to the autacoids (i.e., prostaglandins). In the central nervous system, the highly organized distribution of endocannabinoid signaling elements in GABAergic and glutamatergic synapses and their preservation of this distribution throughout evolution suggest a pivotal role in synaptic transmission. Because of the inhibitory effects on adenylyl cyclase, the activation of K^+ currents and the inhibition of Ca^{2+} entry into cells, the net effect of cannabinoid CB_1 receptor stimulation is a local hyperpolarization that leads to the general inhibitory effects described. If endocannabinoids act postsynaptically, they will counteract excitatory inputs entering the postsynaptic cells. This mechanism has been proposed for postsynaptic interactions with dopaminergic transmission (Felder et al. 1998; Giuffrida et al. 2004; Rodríguez de Fonseca et al. 1998). Despite its importance, this effect is secondary to the important presynaptic actions whose existence is supported by two facts: (a) the concentration of cannabinoid CB_1 receptors in presynaptic terminals and (b) the well-documented inhibitory effects of cannabinoid CB_1 receptor agonists on the release of GABA, glutamate, acetylcholine, and noradrenaline (Piomelli 2003; Schlieker and Kathmann 2001). This inhibitory effect has also been demonstrated for neuropeptides such as corticotrophin-releasing factor and cholecystokinin (Beinfeld and Connolly 2001; Rodríguez de Fonseca et al. 1997). Presynaptic inhibition of neurotransmitter release is associated with the inhibitory action of endocannabinoids on Ca^{2+} presynaptic calcium channels through the activation of CB_1 receptors. Presynaptic inhibition of transmitter release by endocannabinoids may adopt two different forms of short-term synaptic plasticity, depending on the involvement of GABA or glutamate transmission, respectively: depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE) (Diana and Marty 2004; Wilson and Nicoll 2002). Both forms of synaptic plasticity involve the initial activation of a postsynaptic large projecting neuron (pyramidal or Purkinje cells) that sends a retrograde messenger to a presynaptic GABA terminal (DSI) or a presynaptic glutamate terminal (DSE), inducing a transient suppression of either the presynaptic inhibitory or the presynaptic excitatory input. The contribution of endocannabinoids to these forms of short-term synaptic plasticity has been described in the hippocampus and the cerebellum (Diana and Marty 2004; Wilson et al. 2001; Wilson and Nicoll 2001). The role of endocannabinoid-induced DSI or DSE seems to be the coordination of neural networks within the hippocampus and cerebellum that are involved in relevant physiological processes, such as memory or motor coordination.

Overall, endocannabinoids act as local messengers that adjust synaptic weight and contribute significantly to the elimination of information flow through specific synapses in a wide range of time frames. The fact that cannabinoid receptor stimulation has a major impact on second messengers involved not only in synaptic remodeling (Derkinderen et al. 1996; Piomelli 2003), but also in neuronal differentiation (Rueda et al. 2002) and neuronal survival (Marsicano et al. 2003), indicates that this signaling system is a major homeostatic mechanism that guarantees a fine adjustment of information processing in the brain and provides counter-regulatory mechanisms aimed at preserving the structure and function of major brain circuits. Both processes are relevant for homeostatic behavior, such as motivated behavior (motor learning, feeding, reproduction, relaxation, and sleep), and emotions, as well as for cognition, since learning and memory require dynamic functional and morphological changes in brain circuits. An experimental confirmation of this hypothetical role of the endogenous cannabinoid system was the demonstration of its role in the control of the extinction of aversive memories (Marsicano et al. 2002).

Disturbances of the endocannabinoid system in schizophrenia

Preclinical studies: alterations in endocannabinoid signaling in animal models of schizophrenia

It is evident that psychosis is difficult to study from an experimental point of view in laboratory animals, since cognitive deficits are crucial in human schizophrenia. However, certain "psychotic-like" alterations have an animal correlate, and their study is considered as acceptable. For instance, prepulse inhibition (PPI) is a phenomenon wherein the startle response is reduced when the startling stimulus is preceded by a low-intensity prepulse (Graham 1975; Hoffman and Ison 1980; Geyer et al. 2001). It represents a normal sensorimotor gating response that is typically impaired in schizophrenic patients (Geyer et al. 2001). In rats and mice, PPI is selectively disrupted (decreased PPI) by dopamine agonists such as apomorphine, serotonergic compounds acting at the 5-HT_{2A} serotonin receptor, as well as psychotomimetics (Mansbach et al. 1988; Ralph-Williams et al. 2001, 2002; Ouagazzal et al. 2001; Geyer et al. 2002). Disruption of PPI is attenuated by antipsychotic drugs; hence, it is considered as a valid predictor of "psychosis-like" drug properties in animal models (Geyer et al. 2001; Ouagazzal et al. 2001). Contradictory results have been reported regarding cannabinoid effects on PPI. Some authors have observed that CB_1 receptor agonists such as WIN55,212-2, AM404, or CP55,940 disrupt the PPI (Mansbach et al. 1996; Schneider and Koch 2002), but others have not seen changes (Stanley-Cary et al. 2002; Bortolato et al. 2006). The indirect agonist, AM404, that increases the availability of the endocannabinoids 2-AG and anandamide in the biophase also disrupts the PPI in Swiss mice (Fernández-Espejo and Galán-Rodríguez 2004), although this finding has not been corroborated by others (Bortolato et al. 2006). On the other hand, Ballmaier et al. (2007) report that the CB_1 antagonists SR141716A and AM251 act as antipsychotic compounds in rats reversing phencyclidine- and dizocilpine-induced disruption of PPI. It has been proposed that PPI changes in rodents may be masked by decreased startle response amplitudes (Martin et al. 2003) or that the use of ethanol as solvent can induce false results because ethanol has significant effects on PPI performance on its own (Stanley-Cary et al. 2002). Contradictory results on PPI seem to be more related to rearing condition or age of the animals, pointing to an individual susceptibility based on these factors. Thus, chronic Δ-9-THC does not affect adult rats reared in groups, but it disrupts PPI whether rats have been kept isolated to each other upon weaning (Malone and Taylor 2006). The cannabinoid WIN55,212-2 disrupts PPI in prepubertal rats but not in adult animals, and this disruption is selectively reversed with haloperidol (Schneider and Koch 2003).

Auditory-evoked potential can be recorded during sensory gating tests in laboratory animals. Sensory gating has been demonstrated to be impaired in schizophrenic humans as explained and, by using auditory-evoked electroencephalography responses, a positive wave occurring 50 ms (P50) following the auditory stimulus is the most widely used auditory-evoked response to assess gating in humans (Adler et al. 1982; Cadenhead et al. 2000). Studies using the auditory conditioning–testing paradigm in rats have shown gating of a negative auditory-evoked potential recorded from implanted skull electrodes and from the CA3 region of the hippocampus around 40 ms after an auditory stimulus (Adler et al. 1986). This wave, known as N40, is considered a homolog to the P50 wave recorded in humans (Adler et al. 1986). The cannabinoid agonist WIN55,212-2 disrupts auditory gating in rats, in the hippocampus (CA3, dentate gyrus) and the medial prefrontal cortex (mPFC), and this disruption is prevented by the CB_1 antagonist SR141716A (Dissanayake et al. 2008; Zachariou et al. 2008). The CB_1 agonist CP-55940 has been reported not only to impair PPI in rats but also auditory gating and neuronal synchrony in limbic areas such as the hippocampus and entorhinal cortex, as evaluated through theta field potential oscillations (Hajós et al. 2008). It seems clear that, at least in rats, cannabinoid agonists impair auditory gating function in the limbic circuitry, supporting a connection between cannabis abuse and schizophrenia as evaluated through this animal model.

Another "psychotic-like" test is based on the induction of disorganized behavior in rodents (oral stereotypies) by psychotomimetic drugs and its attenuation with antipsychotics. These responses are considered as to be a consequence of the hyperdopaminergic activity induced by the drug. These types of stereotypies are also observed in psychotic humans, and they are exacerbated with dopaminergic agonists and attenuated by antipsychotics, being considered as a "psychotic-like" sign in animal models of psychosis (Giuliani and Ferrari 1997). In this respect, Δ-9-THC has been reported to potentiate the stereotyped behavior in rats after amphetamine (Gorriti et al. 1999). Figure 1 depicts two examples on the role of the endogenous cannabinoid system as a potential modulator of disorganized behavior. Moreno et al. (2005) reported that chronic treatment with HU-210, a potent THC-like cannabinoid agonist, resulted in an exacerbation to dopamine D_2-mediated disorganized behaviors. This was observed after the induction of CB_1 receptor desensitization with HU-210 and was evident after a washout period of the drug, when a substantial CB_1 downregulation is present. These results support the idea that cannabinoid CB_1 receptors serves as a brake for disorganized behavior mediated by dopaminergic

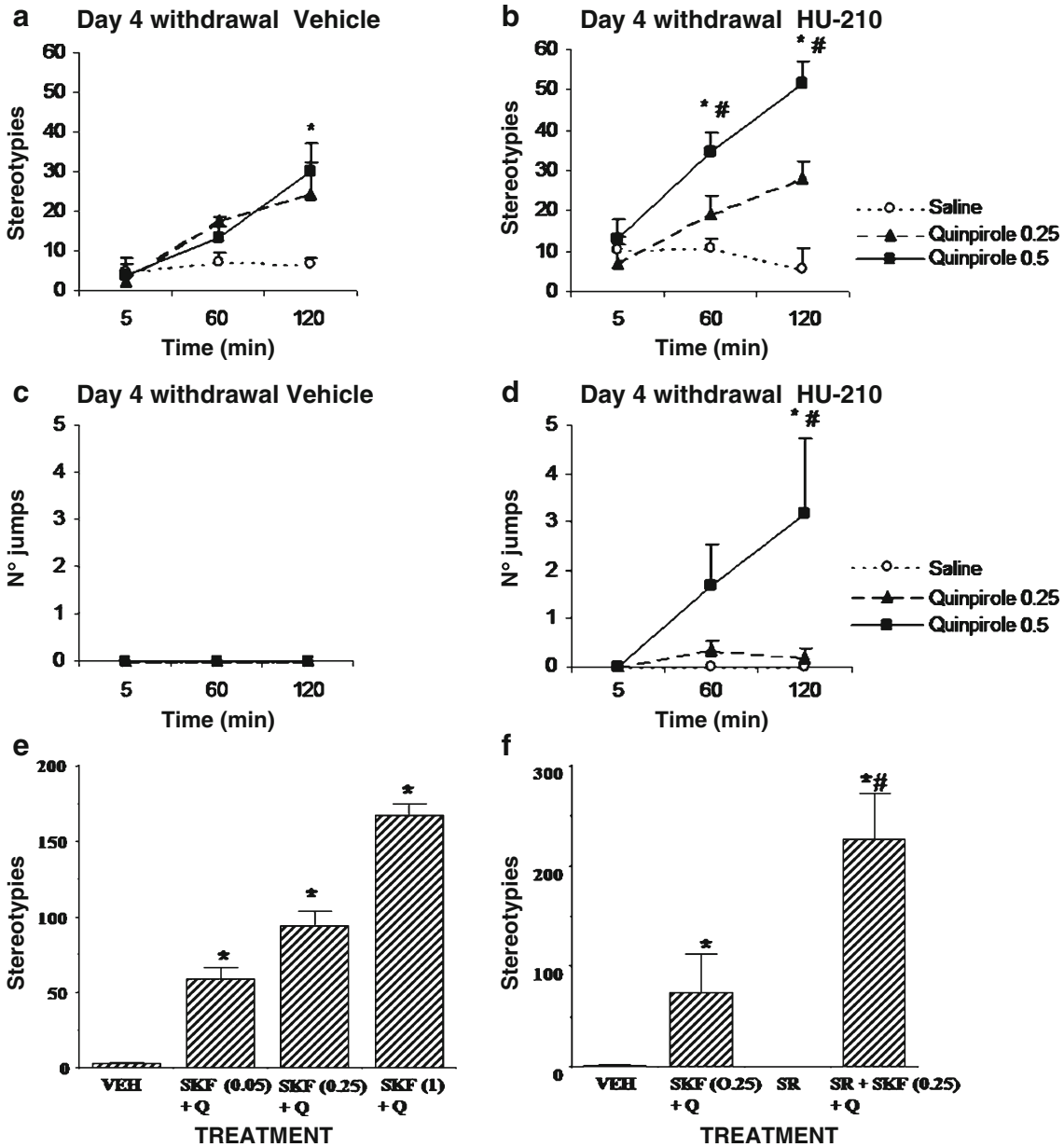

Fig. 1 Desensitization (**a**–**d**) or blockade (**e**, **f**) of cannabinoid receptors increases dopamine-mediated disorganized behaviors and panic-like escape reactions. Stereotyped activity (**a**, **b**) and jumping escape behavior (**c**, **d**) (during 5-min scoring periods over a 125-min session) exhibited in an observation box after administration of dopamine D_2 agonist quinpirole (saline, 0.25, 0.5 mg/kg) at day 4 of withdrawal from chronic HU-210 (20 μg/kg, 14 days, i.p.) or vehicle treatment. Treatment effect, *$p<0.05$ versus acute saline administration in same chronic treatment; interaction chronic treatment × acute administration × time effect, #$p<0.05$ versus control group. Simultaneous administration of a fixed dose of the dopamine D_2 receptor agonist quinpirole (*Q*, 0.25 mg/kg) with increasing doses of the dopamine D_1 agonist SKF 38393 (*SKF*, 0.05, 0.25, and 1 mg/kg) produced disorganized behavior, as reflected in the increasing stereotyped activity (**e**). Blockade of cannabinoid CB_1 receptors with SR141716A (*SR*, 1 mg/kg) markedly enhanced the response to quinpirole (0.25 mg/kg) plus SKF (0.25 mg/kg), increasing the stereotyped behavior (**f**). *$p<0.01$, different doses versus vehicle-treated animals; #$p<0.01$, SR + SKF + Q versus SKF + Q. All data are presented as the means ± standard error of the mean of eight to ten determinations per group, Newman–Keul's test (modified from Moreno et al. 2005 and Ferrer et al. 2007)

transmission overactivity. Removal of this brake by desensitizing cannabinoid CB_1 receptor sensitizes to dopamine-mediated behavioral disorganization. This was further confirmed by Ferrer et al. (2007) in a simple experiment: acute blockade of central CB_1 receptors with a selective cannabinoid CB_1 receptor antagonist led to potentiation of dopamine D_1 and D_2 receptor-mediated induction of stereotypies. Additionally, Beltramo et al.

(2000) have observed that dopamine D_2 receptor-mediated head stereotypies are reversed by AM404 (10 mg/kg), an indirect cannabinoid agonist. This AM404-induced effect is inhibited by pretreatment with the selective CB_1 receptor antagonist SR141716A, confirming the participation of cannabinoid receptors in these effects. Overall, these results show two important sides: while the endogenous cannabinoid system is protective against behavioral disorganization, its dowregulation may result in a sensitization to psychosis-like states.

Animal research also indicates that neuregulin 1 (Nrg1), a gene from chromosome 8p, seems to be a susceptibility gene for schizophrenia (Stefansson et al. 2002; Karl et al. 2007). Mutant mice heterozygous for the transmembrane domain of Nrg1 (Nrg1 HET mice) exhibit a schizophrenia-related behavioral phenotype (Stefansson et al. 2002; Karl et al. 2007). Boucher et al. (2007a, b) have studied the relationship between neuregulin, schizophrenia, and cannabinoids in mice. Nrg1 HET mice are more sensitive to the acute effects of Δ-9-THC in an array of different behaviors including those that model symptoms of schizophrenia. It appears that variation in the schizophrenia-related neuregulin 1 gene alters the sensitivity to the behavioral effects of cannabinoids. It is worth noting that neurodevelopmental alterations take place in neuregulin 1 mutant mice. Nrg1 is a ligand for ErbB receptor tyrosine kinases which, when stimulated, may affect schizophrenia-related neurodevelopmental processes such as myelination, axon guidance, neuronal migration, and glial differentiation (Falls 2003). Neurodevelopmental alterations linked to cannabis abuse have been associated with schizophrenia in humans (see the "Clinical studies" section).

There is indeed preclinical evidence indicating that chronic administration of cannabinoid agonists during the periadolescent period causes diverse persistent behavioral alterations in adulthood. For instance, chronic administration of the cannabinoid receptor agonist CP 55,940 (CP) from PND 35 to PND 45 in rats resulted in marked sex-dependent alterations in motor and exploratory activity (Biscaia et al. 2003) and a 21-day treatment with the same drug in 30-day-old rats resulted in long-term increased anxiety and a lasting impairment of working memory (O'Shea et al. 2004). Interestingly, these later behavioral changes were observed in adolescent but not adult drug-treated rats. In another study, chronic pubertal treatment with another cannabinoid agonist, WIN 55,212-2 (WIN), resulted in impaired memory in adulthood as well as in a disrupted PPI of the acoustic startle response and lower breakpoints in a progressive ratio operant behavior task (Schneider and Koch 2003). Since PPI deficits, object recognition memory impairments, and anhedonia/avolition are among the endophenotypes of schizophrenia, the authors of this study proposed chronic cannabinoid administration during pubertal development as a neurodevelopmental animal model for some aspects of the etiology of schizophrenia. In line with the study by O'Shea et al. (2004), these authors also showed that chronic treatment with WIN during adulthood did not lead to changes in any of the behaviors tested (Schneider and Koch 2003). Thus, the early adolescent period appears to have a unique vulnerability to at least some of the adverse effects of cannabis. On the other hand, in a recent study by O'Shea et al. (2006), it was found that chronic exposure to the cannabinoid agonist CP during perinatal, adolescent, or early adulthood induced similar long-term memory impairments and increased anxiety in male rats. To explain the different results with respect to their previous study performed in female rats (O'Shea et al. 2004, see above), they claimed that adult males might be more vulnerable than adult females to some of the detrimental effects of cannabinoids, such as cognitive disturbances. It would be very interesting to directly address possible sexual dimorphisms regarding increased risk to show schizophrenic-like symptoms in adolescent animals exposed to cannabinoids. Moreover, the effect of sex should be more carefully considered in epidemiological studies.

The three-hit model of schizophrenia proposes the following sequence: Genetic and early environmental factors disrupt central nervous system development and together act as a vulnerability factor that produces a long-term susceptibility to an additional adverse event (usually around puberty) that then precipitates the onset of schizophrenic symptoms (Maynard et al. 2001; Ellenbroek 2003). Based on this concept, Schneider and Koch (2005, 2007) have analyzed the effects of neonatal excitotoxic lesions of the mPFC and a chronic pubertal treatment with WIN on various forms of social and nonsocial behaviors. Their results indicated that behavioral deviations induced by neonatal mPFC lesions can be exacerbated by pubertal chronic cannabinoid treatment, leading to long-lasting impairments of mnemonic short-term information processing and reduced interest for social interaction. Inadequate social behavior and cognitive impairments are among the symptoms of schizophrenia (Robertson et al. 2006). In particular, object recognition memory is impaired in schizophrenic patients (Heckers et al. 2000; Doniger et al. 2002). Thus, animal models such as the one proposed by Schneider and Koch (2005, 2006) may be useful in elucidating the mechanisms by which adolescent cannabis exposure triggers psychotic symptoms in vulnerable individuals. With respect to possible neurochemical correlates of long-term effects of adolescent cannabis exposure, the PPI deficit induced by chronic peripubertal WIN treatment observed in the study by Schneider and Koch (2003, see above) was reversed by acute administration of the dopamine antagonist haloperidol 85 days after the chronic

treatment, which suggests persistent alterations in the dopaminergic system (Schneider and Koch 2003). A more recent study has examined the effects of repeated cannabinoid administration on mesoaccumbens dopaminergic neuronal functions and responses to drugs of abuse. Animals were pretreated during adolescence or adulthood, for 3 days, with WIN or vehicle and allowed a 2-week interval. In WIN-administered rats, dopaminergic neurons were significantly less responsive to the stimulating action of the cannabinoid, regardless of the age of pretreatment. However, in the adolescent group, but not in the adult group, long-lasting cross-tolerance developed to morphine, cocaine, and amphetamine (Pistis et al. 2004). Thus, cannabis exposure at a young age may induce long-term neuronal adaptations in the mesolimbic dopaminergic system and hence affect the responses to both natural rewards and drugs of abuse.

Clinical studies

Genetic studies

Several genetic alterations have been linked to a higher predisposition to suffer from schizophrenia after cannabis abuse. Thus, the gene codifying the enzyme catechol-*O*-methyl-transferase (COMT), which is involved in dopamine degradation, shows a functional polymorphism (Val158Met) with two variants (G and A) that induce a single amino acid change in the protein (valine or methionine, respectively). Those individuals with the G variant (Val/Val genotype) or Val/Met heterozygotes have a greater likelihood to suffer from psychotic disorder after cannabis abuse (Caspi et al. 2005). These two COMT isoforms degrade dopamine at a higher rate than the Met/Met homozygotes, and dopamine dysregulation is related to schizophrenia.

Genetic alterations affecting the CNR1 gene which codes for the cannabinoid CB_1 receptor could also be related to schizophrenia. Ujike et al. (2002) reported that hebephrenic schizophrenia could be linked to a nine-time repetition of the triplet AAT in the 3′ region of the codifying exon of the gene. Recently, Chavarría-Siles et al. (2008) have confirmed that hebephrenic schizophrenia is associated with the CNR1 gene and present a type of symptomatology that resembles cannabinoid-induced psychosis. It, therefore, seems that the CNR1 gene and its molecular expression could be linked to a special predisposition to suffer from this type of schizophrenia. However, alterations in the CNR1 gene leading to an increase risk for schizophrenia is substantiated in a small number of human studies, and alternative possibilities have not been ruled out (i.e., other consequences of the mutated gene).

On the other hand, polymorphisms in the CNR1 gene can also be associated to protection for psychosis or to better therapeutic outcome. Ujike et al. (2002) also report that 17-time repetition of the AAT triplet confers protection against the disorder, although this hypothesis cannot be validated using epidemiological evidence because of the possible changes in other brain systems that might result from such a mutation. The CNR1 gene has also been associated to the therapeutic effects of antipsychotics. A 1359G/A polymorphism of the CNR1 gene (G allele) is associated to a better pharmacological response to atypical antipsychotics with a clear dose effect of the G allele in a population of French schizophrenic patients (Hamdani et al. 2008). The G allele of the CNR1 gene polymorphisms could be a psychopharmacogenetic rather than a vulnerability factor regarding schizophrenia and its treatment. In conclusion, genetic studies confirm the two sides of the coin: some polymorphisms are associated to higher risk for schizophrenia, and others are associated to protection against the disorder or better response to antipsychotic therapy.

Endogenous ligand studies

An involvement of the endogenous cannabinoid system in schizophrenia is also supported by findings in the cerebrospinal fluid (CSF) in patients with schizophrenia. Leweke et al. (1999) reported that the endocannabinoids anandamide (AEA) and palmitoylethanolamide (PEA) are elevated in the CSF of untreated schizophrenic patients, and they proposed a relationship between the onset of schizophrenia and altered AEA and PEA levels. Levels of 2-arachidonylglycerol (2-AG) were not observed to be affected because they were below detection. Di Marzo's group reported that anandamide levels are also enhanced in the blood of patients with schizophrenia (De Marchi et al. 2003).

However, Giuffrida et al. (2004), while confirming these findings, observed that typical antipsychotic treatment reversed CSF AEA excess, in contrast to treatment with atypical antipsychotics. In accordance, they suggest that anandamide hyperactivity is not involved in the onset of psychosis, but it seems to be a homeostatic mechanisms tending to reduce hyperdopaminergia. Typical antipsychotics antagonize D_2, dopamine receptors, while atypical compounds possess a wider receptorial spectrum, acting upon other receptors such as serotonergic 5-HT2A and 5-HT2C receptors. It is known that D_2 stimulation increases AEA release that otherwise reduces dopamine release through a feedback mechanism, hence inhibition of AEA augmentation after typical antipsychotics relieving schizophrenia would indicate that hyperanandamidergia is a compensatory homeostatic mechanisms tending to reduce excessive dopaminergic stimulation. In fact, there is a clear negative correlation between psychotic symptoms and CSF AEA levels (Giuffrida et al. 2004).

In another study, Leweke et al. (2007) examined whether cannabis use alters serum and CSF anandamide levels in first-episode antipsychotic-naïve schizophrenic humans. In patients with low-frequency cannabis use, CSF AEA levels were more than tenfold higher than in high-frequency users. They propose that frequent cannabis exposure may down-regulate anandamide signaling in the CNS of patients with schizophrenia, and this fact could increase the risk for new psychotic episodes.

CB_1 receptor studies in postmortem

Three independent research groups have performed post-mortem evaluations of CB_1 receptors densities in the brain of schizophrenic patients. Dean et al. (2001) reported upregulation of CB_1 receptors in the dorsolateral prefrontal cortex by using autoradiography and in situ binding with the radioligand [^{3}H]CP-55940, a nonselective cannabinoid agonist. The prefrontal cortex belongs to the dopaminergic mesocorticolimbic system, and it is involved in attentional and cognitive processes. Zavitsanou et al. (2004), by using the more selective radioligand [^{3}H]SR141716A, found that there is an upregulation of around 64% in density of CB_1 receptors in the anterior cingulate cortex, a cortical area intimately connected with the prefrontal cortex. Finally, Mewell et al. (2006) detected an increase in the density of receptors in the posterior cingulate cortex, another region of the cingulate cortex involved in cognition. In this context, the cingulate cortex is a site of integration of information sources that include cognitive, emotional, and interoceptive signals, and it is considered as divided into four regions with different roles in the processing of emotional information (the four-region model; Vogt 2005), these regions being activated in important cognitive processes such as fear, sadness, self-awareness, normal social cognition, and decision-making (Gallagher et al. 2003; Wicker et al. 2003; Vogt 2005). The prefrontal cortex is also known to participate in negative aspects of schizophrenia such as anhedonia, poor thinking, apathy, blunted social interaction, and amotivation; hence, all data point to a possible role of CB_1 receptor changes in these areas in the symptomatology of schizophrenia. These studies have been criticized due to the low number of studied patients and the possible interference of the antipsychotic medication, but they point to an intrinsic disturbance of the endocannabinoid system in frontal and cingulate areas in schizophrenia.

Cannabis abuse, schizophrenia, and brain morphology

As already mentioned, the greatest risk of onset of cannabis use is in the age range 15–20 years that coincides with the onset of schizophrenia (Grant et al. 2008). It is possible that cannabis may affect neurodevelopmental processes, such as synaptic plasticity, thought to be impaired in schizophrenia (Feinberg 1982; Keshavan et al. 1994): Exogenous cannabinoids could alter endogenous cannabinoid-mediated synaptic plasticity, affecting brain maturation in adolescence (Robbe et al. 2003). Magnetic resonance imaging studies in cannabis users without schizophrenia have revealed reductions of gray matter density (Matochik et al. 2005). However, this reduction was not found by Block et al. (2000), but they did find that cannabis users have lower ventricular CSF volume compared with nonusers. A recent study by Bangalore et al. (2008) indicates that cannabis-using patients with first-episode schizophrenia have more prominent gray matter density and volume reduction in the right posterior cingulate cortex compared to patients not using cannabis or healthy subjects. Rais et al. (2008) confirmed that first-episode schizophrenia patients who use cannabis show a more pronounced brain volume reduction over a 5-year follow-up than patients with schizophrenia who do not use cannabis. However, brain volume reduction has not been found by other authors (Cahn et al. 2004) by using magnetic resonance acquisition and processing procedures. It is also important to note that antipsychotic use has been shown to affect brain structure in patients with first-episode psychosis (Lieberman et al. 2005) and causes volume changes in the caudate nucleus (Scheepers et al. 2001), and this factor is a confounding variable in many studies. To sum up, contradictory results have been reported regarding the association between cannabis-induced neuroplastic changes and first episode of schizophrenia.

Cannabis abuse, schizophrenia, and neurodevelopment during adolescence

According to the Feinberg hypothesis (Feinberg 1982, 1987), a substantial reorganization of cortical connections, involving a programmed synaptic pruning, takes place during adolescence in humans. An excessive pruning of the prefrontal corticocortical and corticosubcortical synapses, perhaps involving the excitatory glutamatergic inputs to pyramidal neurons, may underlie schizophrenia. A reciprocal failure of pruning in certain subcortical structures, such as the lenticular nuclei, may also occur. Several developmental trajectories, related to early brain insults as well as genetic factors affecting postnatal neurodevelopment, could lead to the illness (Spear 2000; Adriani and Laviola 2004; Marek and Merchant 2005). The high rates of cannabis use among adolescents and young adults (Hall and Degenhardt 2007; United Nations Office on Drugs and Crime, http://www.unodc.org/unodc/index.html; The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), http://www.emcdda.europa.eu/) makes it pertinent to investigate the short-term and long-term conse-

quences of cannabis use during this critical period of development. Indeed, the research of the last decade has provided substantial evidence indicating that cannabis use in adolescence increases the likelihood of experiencing symptoms of schizophrenia in adulthood (Andreasson et al. 1987; Arseneault et al. 2002; Stefanis et al. 2004). This association has very important consequences in terms of risk-reduction strategies, which would contribute to prevention and early implementation of therapeutic programs (De Irala et al. 2005; Verdoux et al. 2005; Miettunen et al. 2008). The evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes has been recently reviewed by Moore et al. (2007). The authors found that there was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1.41, 95% confidence interval [95%CI]=1.20–1.65). Findings were consistent with a dose–response effect with greater risk in people who used cannabis most frequently (odds ratio=2.09, 95% CI=1.54–2.84) and suggested that cannabis increases the risk of psychotic outcomes, independently of confounding and transient intoxication effects.

It is as yet unclear what the causal relationship between cannabis use during adolescence and the development of schizophrenia in adulthood is. It is also important to note that the conclusion that early chronic cannabinoid use is detrimental to those at risk for schizophrenia as adults is based largely on animal data. The ultimate proof of a causal relationship between cannabis use and psychotic illness later in life would come from studies in which healthy young people were exposed to Δ-9-THC and followed up until adulthood. Obviously, for practical and ethical reasons, such an approach is impossible. In fact, among many other important health risks, it is well known that cannabis induces harmful effects on cognitive function (Nordentoft and Hjorthøj 2007; Solowij and Michie 2007; Solowij et al. 2002). On the other hand, such studies can be performed in animals under well-controlled conditions. Hence, such animal models can shed light on the underlying neurobiological mechanisms and the relationship between cannabis use and schizophrenia, as detailed in a previous section of this review. As discussed in previous sections of this review, a dysregulation of the endocannabinoid system may be implicated in the pathogenesis of schizophrenia. The peripubertal period appears to be critical for the development of cannabinoid CB_1 receptors and endocannabinoid levels (Rodriguez de Fonseca et al. 1993; Wenger et al. 2002). Therefore, it is conceivable that chronic interference by cannabis with the developing endocannabinoid system during this critical time interval leads to severe and persistent functional impairments (Schneider and Koch 2007) that might reflect, at least in part, psychosis-related symptoms.

The association between neuregulin 1 and neurodevelopment alterations is also of interest. Human and animal research indicates that neuregulin 1 (Nrg1), a gene from chromosome 8p, seems to be a susceptibility gene for schizophrenia (Stefansson et al. 2002; Karl et al. 2007, Walss-Bass et al. 2006a, b). Walss-Bass et al. have identified a missense mutation (Val to Leu) in exon 11, which codes for the transmembrane region of the neuregulin 1 protein, and this mutation is associated with psychosis (p=0.0049) and schizophrenia (p=0.0191). As explained, Nrg1 is a ligand for ErbB tyrosine kinase receptor which may affect schizophrenia-related neurodevelopmental processes such as myelination, axon guidance, neuronal migration, and glial differentiation after stimulation (Falls 2003). The variation in the schizophrenia-related neuregulin 1 gene alters the sensitivity to the behavioral effects of cannabinoids.

Modulation of endocannabinoid signaling by antipsychotics

Haloperidol medication is known to worsen the cognitive effects of Δ-9-THC in schizophrenics, indicating that there is a cross-talk between the cannabinoid and dopaminergic systems in schizophrenic patients (D'Souza et al. 2008b). On the other hand, cannabis-induced psychosis is responsive to treatment with antipsychotic drugs (Berk et al. 1999), further suggesting that the endocannabinoid system is involved in psychosis or the therapeutic effects of antipsychotics. The atypical antipsychotic drug clozapine decreases the use of cannabis in patients with schizophrenia (Drake et al. 2000). In this context, Sundram et al. (2005) have reported that, by using in situ radioligand binding and quantitative autoradiography with the selective cannabinoid CB_1 receptor agonist (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol (side chain-2,3,4(N)-3H) ([^{3}H] CP 55940) to measure the density of the CB_1 receptor in the frontal cortex, hippocampus, nucleus accumbens, and striatum, the antipsychotic clozapine significantly decreased [^{3}H] CP 55940 binding in the nucleus accumbens compared with vehicle. This effect is not observed with haloperidol, chlorpromazine, or olanzapine; hence, this effect of clozapine is a mechanism that makes it uniquely effective in schizophrenia and comorbid cannabis use. Antipsychotics also influence the density of the CB_1 receptor and the actions of Δ-9-THC. Thus, Wiley et al. (2008) report that subchronic treatment with haloperidol and clozapine decreases CB_1 receptor-mediated G protein activity in specific forebrain regions in adult female rats without affecting CB_1 receptor densities. In vivo, subchronic treatment with clozapine, but not haloperidol, attenuates Δ-9-THC-induced suppression of activity in adult females. In contrast, antipsychotic treatment did not change CB_1 receptor-mediated G protein activation in

any brain region in adult male rats and in adolescents of either sex. In vivo, haloperidol, but not clozapine, enhanced Δ-9-THC-mediated suppression of activity and hypothermia in adult male rats whereas neither antipsychotic affected Δ-9-THC-induced in vivo effects in adolescent rats. These findings suggest that modulation of the endocannabinoid system might contribute in a sex- and age-selective manner to differences in motor side effects of clozapine versus haloperidol.

Finally, it is worth mentioning that typical antipsychotic treatment reverses CSF excess of the endocannabinoid anandamide in schizophrenics, in contrast to treatment with atypical antipsychotics (Giuffrida et al. 2004). Since haloperidol medication worsens the cognitive effects of Δ-9-THC in schizophrenics, this later fact is in contrast with the proposed homeostatic protective role of anandamide excess in schizophrenics (Giuffrida et al. 2004).

Neurobiological integration of cannabinoid dysregulation with current theories of schizophrenia

Schizophrenic symptoms are attributed, among other mechanisms, to a hyperdopaminergic state in the mesolimbic system (the ventral striatum as the main region) together with a hypodopaminergic tone in the mesocortical system, the prefrontal cortex being the main region (Grace 1991; Moore et al. 1999). Schizophrenia has consistently been related to increased dopamine function in the striatum (Seeman and Lee 1975; Angrist and Van Kammen 1984), possibly caused by a disinhibition of striatal dopamine transmission (Laruelle et al. 1996). Biochemical information confirms that neural dopaminergic systems are altered in schizophrenia because striatal D_2 receptors are upregulated in schizophrenic brains (Hirvonen et al. 2005) and the dopamine transporter DAT is downregulated in the prefrontal cortex, a homeostatic response suggestive of reduced dopamine release in the biophase (Sekine et al. 2003). The dopaminergic hypothesis of schizophrenia is strongly supported by the fact that the most effective antipsychotics are antidopaminergic compounds, mostly acting upon D_2 receptors.

Exogenous or endogenous cannabinoids could participate in the dysregulation of the mesocorticolimbic dopaminergic activity in schizophrenia (Gardner and Vorel 1998) because the endocannabinoid system is a feedback mechanism negatively regulating dopamine release (Rodríguez de Fonseca et al. 1998). Exogenous administration of cannabinoid agonists enhances activity of dopamine neurons located in the ventral tegmental area (VTA; French et al. 1997), leading to augmentation of dopamine release in the ventral striatum or nucleus accumbens (Gardner et al. 1988). Although stimulation of CB_1 autoreceptors is known to reduce dopamine release (Beltramo et al. 2000; Wilson and Nicoll 2002), systemic administration of CB_1 agonists enhances dopamine release. This is due to the inhibitory effects of CB_1 agonists on GABAergic interneurons in the VTA, which leads to a disinhibition of VTA neurons (see Fig. 2). Recently, Bossong et al. (2009) have demonstrated that Δ-9-THC induces dopamine release in the human striatum. Using the dopamine D_2/D_3 tracer [^{11}C]raclopride and positron emission tomography, they demonstrate that Δ-9-THC inhalation reduces [^{11}C]raclopride binding in the ventral striatum and the precommissural dorsal putamen, which is consistent with an increase in dopamine levels in these regions.

It can be speculated that dysregulation of the endocannabinoid system in the VTA or excessive stimulation of CB_1 receptors (for instance, after prolonged abuse of Δ-9-THC) could be linked to schizophrenia through a facilitation of dopamine release in the mesolimbic system, a dysregulation of dopaminergic activity or a desensitization of limbic CB_1 receptors (Pertwee 2005). At a molecular level, both dopamine D_2 and cannabinoid CB_1 receptor stimulation induces a decrease in cAMP content in limbic regions such as the nucleus accumbens. When dopamine activity is enhanced (as it is the case in schizophrenia), heterologous sensitization develops: D_2 receptor stimulation enhances cAMP levels instead. CB_1 stimulation opposes D_2-mediated cAMP augmentation (Jarrahian et al. 2004), a fact that could help explain why anandamide is enhanced in schizophrenics' CSF. However, prolonged endocannabinoid action (or Δ-9-THC abuse) would desensitize CB_1 receptors which would no longer oppose D_2-mediated effects, facilitating hyperdopaminergic effects and surely aggravating the course of schizophrenic psychosis. In this context, as already mentioned, cannabis abuse is also known to reduce CSF hyperanandamidergia, indicating that cannabis abuse would antagonize the "protective" role attributed to anandamide (Leweke et al. 2007). The neurophysiological integration of the endocannabinoid system with the dopaminergic hypothesis of schizophrenia is also favored by the fact that there is augmentation of CB_1 receptor density in the prefrontal cortex of schizophrenics (Dean et al. 2001). Logically, upregulation of cannabinoid receptors and a higher endocannabinoid tone would reduce dopamine release at a presynaptic level, which could help explain hypodopaminergic activity in the prefrontal cortex.

Another interesting phenomenon observed in schizophrenics who do not consume cannabis is the reduction in striatal DAT expression, as measured through [^{3}H]mazindol binding, while these levels are normal in patients who are also cannabis abusers (Dean et al. 2003). This effect would point to a modulation of DAT levels after repeated Δ-9-THC which could counteract limbic hyperdopaminergia,

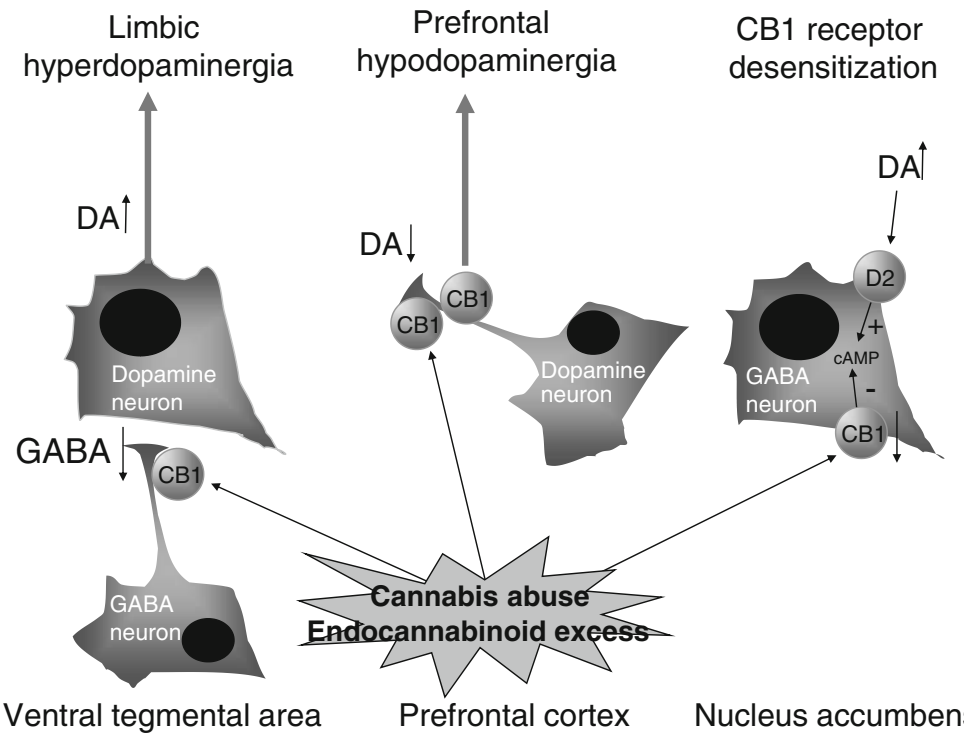

Fig. 2 Cannabis abuse/endocannabinoid excess, and the dopaminergic system in schizophrenia. Cannabis abuse, mostly its active component Δ-9-THC (or endogenous cannabinoid excess), acts upon CB_1 receptors inducing *a* limbic dopaminergic hyperactivity (through inhibition of GABA neurons of the VTA), *b* prefrontal dopaminergic hypoactivity (CB_1 receptors density is enhanced in the prefrontal cortex of schizophrenics, and stimulation of CB_1 receptors reduces tonic dopamine release), and *c* desensitizes CB_1 receptors (i.e., in the nucleus accumbens) thereby blocking antagonistic properties between CB_1 and D_2 dopamine receptors (leading to upregulation of cAMP, as detected in schizophrenics). *DA* dopamine, *GABA* gamma-aminobutyric acid, *CB_1* cannabinoid receptor type 1, *D_2* dopamine receptor type 2

suggesting a potentially "self-medication" role for Δ-9-THC. However, it is also evident that with repeated Δ-9-THC consumption and the subsequent desensitization of the CB_1 receptors, the "self-medication" effect would likely wear off.

The *N*-methyl-D-aspartate (NMDA) receptor hypothesis of schizophrenia states that there is an impairment of the glutamatergic neurotransmission in limbic and cortical regions and reduced activity of NDMA receptors is a central factor. This hypothesis helps explain why NMDA receptor antagonist such as phencyclidine and ketamine induce psychotic symptoms (Javitt and Zukin 1991), acting as hallucinogenic drugs. With regard to the endocannabinoid system, 2-AG, unlike anandamide, is especially involved in glutamatergic neurotransmission, and this endocannabinoid negatively modulates glutamate release acting through presynaptic CB_1 receptors (Katona et al. 2006). It is worth noting that data supporting an interaction between endocannabinoids and glutamate underlying schizophrenia are only preclinical, and there is so far no clinical evidence. The endocannabinoid 2-AG is known to reduce glutamate release in several neuronal areas related to schizophrenia such as the hippocampus (Fujiwara and Egashira 2004), prefrontal cortex (Auclair et al. 2000), nucleus accumbens (Robbe et al. 2001), and amygdala (Azad et al. 2003). Glutamate and NMDA receptor hypoactivity in the prefrontal cortex is also important for understanding some changes in dopamine neurotransmission because reduced glutamate release in the prefrontal cortex is accompanied by reduced dopamine release as well (see Fig. 3). Taken all together, these data are in accordance with the proposed hypodopaminergic state in the prefrontal cortex in schizophrenia.

Experimentally, it is known that glutamate release in the striatum or accumbens induces the postsynaptic production and release of 2-AG through the activation of mGluR5 receptors. The endocannabinoid 2-AG acts through CB_1 autoreceptors by blocking glutamate release (Katona et al. 2006). It is of interest that the antipsychotic effects of the cannabinoid antagonist rimonabant in animal models are due to changes in glutamatergic transmission in the nucleus accumbens, without dopaminergic participation (Soria et al. 2005), suggesting an important role for the interaction of endocannabinoids and glutamate in this nucleus in psychotic effects. Recently, it has been reported that there is a functional interaction between 2-AG and AEA in striatal areas because AEA downregulates the other endocannabinoids (Maccarrone et al. 2008), even though effects can

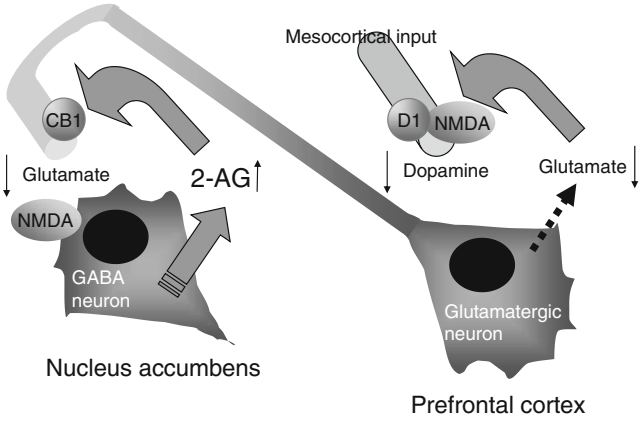

Fig. 3 Endocannabinoids, the NDMA glutamatergic system, and schizophrenia. In schizophrenic brains, medium spiny GABA neurons located in the nucleus accumbens would have an enhanced endocannabinoid tone (mostly affecting 2-AG release and its biophase levels). Enhanced 2-AG diminishes corticostriatal glutamatergic release through presynaptic CB_1 receptors. In parallel, a reduced glutamate release in the prefrontal cortex would in turn reduce dopamine release from mesocortical terminals (prefrontal dopaminergic hypoactivity). *GABA* gamma-aminobutyric acid, CB_1 cannabinoid receptor type 1, D_1 dopamine receptor type 1, *NMDA* *N*-methyl-D-aspartate receptor

also be synergic, and the picture is far from being fully understood (Di Marzo and Maccarrone 2008). It is interesting to note that neuregulin 1 mutant mice display a hypofunctional glutamatergic system with a deficit in NMDA receptor expression (Stefansson et al. 2002; Karl et al. 2007). In addition, stimulation of tyrosine kinase ErbB receptor affects glutamate transmission, which is in line with the NMDA hypothesis of schizophrenia.

At a clinical level, it is possible that there are local changes of 2-AG in striatal areas. However, Leweke et al. (2007) reported that, in patients with high-frequency cannabis use, CSF AEA levels were more than tenfold lower than in patients with low-frequency use. Taken together, these facts allow us to propose a hypothesis based on an opposing role for 2-AG and AEA in schizophrenia, a hypothesis that needs to be tested with clinical studies. Thus, a possible dysregulation of both endocannabinoids could affect glutamate release in limbic and cortical areas, and the 2-AG/AEA ratio in these areas could be important for predicting whether or not there is a special risk for psychosis. To sum up, chronic exposure to cannabinoids or dysregulation of the endocannabinoid system could alter dopamine and glutamate systems in such a way that a "cannabinoid hypothesis" can be integrated in the neurobiological hypotheses of schizophrenia. However, it is important to note that cannabinoid function affects multiple systems in the brain and other neurotransmitter systems could be involved or neurobiological compensatory processes could also occur.

Epidemiological studies

The emergence of psychotic symptoms have been reported following chronic cannabis use (Castle and Ames 1996; Hall and Solowij 1997), the age of first use being important, which confirms the importance of adolescence as a critical period (Zammit et al. 2002; Henquet et al. 2005). The initial study by Andreasson et al. (1987) postulated a relation between cannabis use and the development of schizophrenic syndrome. They studied the association between level of cannabis consumption and development of schizophrenia during a 15-year follow-up in a cohort of 45,570 Swedish conscripts. They concluded that the relative risk for schizophrenia among high consumers of cannabis (use on more than 50 occasions) was 6.0 (95%CI=4.0–8.9) compared with nonusers. Other authors have carried out similar studies leading to similar conclusions (Zammit et al. 2002; Arseneault et al. 2002; van Os et al. 2002), as summarized in Table 1. Ferdinand et al. (2005) carried out a 14-year follow-up study of 1,580 initially 4- to 16-year-old Dutch individuals and they concluded that the link between cannabis use and psychotic symptoms is specific, not depending on the earlier presence of other types of psychopathology. Recently, Fergusson et al. (2005) have studied 1,055 members of New Zealand birth cohort during 4 years and they found that the relative risk for schizophrenic psychosis in cannabis abusers is 2.23 and rates of psychotic symptoms were between 1.6 and 1.8 times higher ($p<0.001$) than nonusers of cannabis. Moreover, cannabis is associated with an increased risk of developing schizophrenia in a dose-dependent fashion (Zammit et al. 2002; Henquet et al. 2005). This association between cannabis and schizophrenia is not explained by use of other psychoactive drugs. In the studies by Zammit et al. (2002), Arseneault et al. (2002), van Os et al. (2002), and Fergusson et al. (2005), the effects of the use of other drugs (cocaine, amphetamine, alcohol, and nicotine) have also been evaluated, and the odds ratios remain being significant after controlling for this confounding factor (Smit et al. 2004). Semple et al. (2005) reviewed all previous epidemiological studies and conclude that cannabis is a risk factor for psychosis and psychotic symptoms, independently of the presence of other factors (i.e., genetic factors). More recent studies have been carried out in different countries: Stefanis et al. (2004) in Greece shows that cannabis use is also an important risk factor for the negative dimensions of schizophrenia; Rössler et al. (2007) in Switzerland found significant relationships between cannabis use in adolescence and the nuclear syndrome of schizophrenia. The latest one is carried out in Trinidad and Tobago by Konings et al. (2008) with similar results concerning the importance of age of beginning. In a recent meta-analysis, Moore et al. (2007) concluded that cannabis use increases the risk for

Table 1 Summary of prospective studies of cannabis use and psychotic symptoms

Study	Sample	Assessment	Outcome measure	Cannabis use criteria	Association between cannabis and psychosis (95%CI)
Andreasson et al. (1987)	45,570 male Swedish military conscripts aged 18 to 21	At 15 year follow-up	Clinical diagnosis of schizophrenia	Structural interview	Relative risk 6 (4.0 to 8.9)
Tien and Anthony (1990)	4,994 adult household residents		Diagnostic interview	Self-report (daily use)	Odds ratio 2.62
Arseneault et al. (2002)	759 members of New Zealand birth cohort	At age 26	DMS-IV criteria for schizophreniform disorder	Cannabis use (three times or more)	Cannabis users by age 15; odds ratio 1.95 (0.76 to 5.01)
van Os et al. (2002)	4,104 participants in Dutch general population study	Assessed three times over 4 years	BPRS (>1 positive rating on psychotic symptom items)	Cannabis use derived from Composite International Diagnostic Interview (CIDI)	Odds ratio 6.81 (1.79 to 25.92)
Zammit et al. (2002)	50,087 Swedish subjects	>97% population aged 18 to 20	Admissions to hospital for ICD-8/9 schizophrenia and other psychoses	Structure interview	Odds ratio 1.3 (1.1 to 1.5) in cannabis only users; odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7)
Caspi et al. (2005)	803 members of New Zealand birth cohort	At age 26	DMS-IV criteria for schizophreniform disorder	Self-report	Participants with Val/Val variant of COMT gene; odds ratio 10.9 (2.2 to 54.1)
Henquet et al. (2005)	2,437 German participants aged 14 to 24	At baseline and 4 year follow-up	One or two psychotic outcomes	L-section of M-CIDI	Odds ratio 2.23 (1.30 to 3.84)
Ferdinand et al. (2005)	1,580 Dutch individuals	At 14-year follow-up (initially 4- to 16-year-old subjects)	Psychotic symptoms were assessed with the CIDI	CIDI	Odds ratio 2.81 (1.79 to 4.43)
Fergusson et al. (2005)	1,055 members of New Zealand birth cohort	At age 25	No. of psychotic symptoms in past month	Cannabis dependence	Daily cannabis users; incident rate ratio 1.77 (1.28 to 2.44)

Despite considerable variation in how cannabis exposure and psychosis were elicited or defined, there is a notable consistency in unadjusted odds ratio across the population groups studied. This table suggests that cannabis abuse is a risk factor, increasing the chance for developing schizophrenia or a schizophrenic-like psychotic illness by approximately threefold

psychosis, independently of the presence of several confounding factors, and the presence of an alteration in COMT is just representative for a small group of persons.

On the other hand, some epidemiological studies are in disagreement with the hypothesis of a causal relationship between cannabis abuse and schizophrenic psychosis. Macleod et al. (2004) think that the relationship is confounded by many uncontrolled factors. A major disagreement is that the prevalence of schizophrenia remains stable, despite of the increased amount of cannabis abuse worldwide. However, at a local level, Boydell et al. (2006) and Ajdacic-Gross et al. (2007) have found an increase in the prevalence of schizophrenia, related with the increase of cannabis abuse in South London and Switzerland, respectively.

Some authors consider cannabis-induced psychosis as a first step towards schizophrenia (Hart 1978). A recent study by Arendt et al. (2005) has shown that, in a sample of subjects with a diagnosis of cannabis-induced psychosis, close to 50% of them developed a schizophrenia spectrum disorder in a 3-year follow-up study; and male gender and early beginning of cannabis use appeared to be additional risk factors. Personality traits also seem to influence the onset of schizophrenia. Núñez and Gurpegui (2002) report that the risk of schizophrenia is higher in subjects with antisocial personality traits and prolonged cannabis abuse with respect to subjects with different personality traits. Schneier and Siris (1987) propose that there is a clear association between the emergence of psychotic symptoms and personality alterations in cannabis abusers. Mendhiratta et al. (1988) reported that neuroticism as evaluated through the Minnesota Multiphasic Personality Inventory test is more intense in subjects with toxic psychosis, and Negrete (1983) reported similar results.

Few studies have tried to discern the role of genetic factors in the relative risk for schizophrenia. McGuire et

al. (1993) found a high percentage of relative risk among those cannabis abusers suffering from psychosis. Varma and Sharma (1993) found that 30% among siblings of schizophrenic patients use cannabis. A recent genetic study found that the link between cannabis and psychosis is stronger in those who have the Val/Val variant of the COMT gene (Caspi et al. 2005) with odds ratio being high (10.9, from 2.2 to 54.1). This enzyme is quite important in the regulation of dopamine levels since it mediates dopamine degradation, and dopamine is known to be involved in schizophrenia. This fact indicates that a genetic enzymatic alteration is able to enhance the risk for developing schizophrenia in susceptible cannabis users.

Conclusions

Available epidemiological and neurobiological data suggest that cannabis abuse is a risk factor for psychosis in genetically predisposed people, may lead to a worse outcome of the disease, or it can affect normal brain development during adolescence, increasing the risk for schizophrenia in adulthood. Regarding genetic predisposition, alterations affecting the CNR1 gene which codes for the cannabinoid CB_1 receptor could be related to schizophrenia, although this is substantiated in a small number of human studies, and a missense mutation in the gene which codes for the transmembrane region of the neuregulin 1 protein is also associated with schizophrenia and alters the sensitivity to the behavioral effects of cannabinoids. The endogenous cannabinoid system is altered in schizophrenia (i.e., increased density of cannabinoid CB_1 receptor binding in corticolimbic regions, enhanced anandamide levels in the CSF), and dysregulation of this system (that could be induced by exogenous cannabis) can interact with neurotransmitter systems in such a way that a "cannabinoid hypothesis" can be integrated in the neurobiological hypotheses of schizophrenia (dopamine and glutamate ones). Finally, there is also evidence that some genetic alterations of the CNR1 gene can act as protectant against schizophrenia rather than as a risk factor or they can be a psychopharmacogenetic rather than a vulnerability factor.

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