BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2010), 160, 511–522

0007-1188/10
www.brjpharmacol.org

THEMED ISSUE: CANNABINOIDS

REVIEW

Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models

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Cannabis is one of the most widely used illicit drugs among adolescents, and most users first experiment with it in adolescence. Adolescence is a critical phase for brain development, characterized by neuronal maturation and rearrangement processes, such as myelination, synaptic pruning and dendritic plasticity. The endocannabinoid system plays an important role in fundamental brain developmental processes such as neuronal cell proliferation, migration and differentiation. Therefore changes in endocannabinoid activity during this specific developmental phase, induced by the psychoactive component of marijuana, Δ^9-tetrahydrocannabinol, might lead to subtle but lasting neurobiological changes that can affect brain functions and behaviour. In this review, we outline recent research into the endocannabinoid system focusing on the relationships between adolescent exposure to cannabinoids and increased risk for certain neuropsychiatric diseases such as schizophrenia, as highlighted by both human and animal studies. Particular emphasis will be given to the possible mechanisms by which adolescent cannabis consumption could render a person more susceptible to developing psychoses such as schizophrenia.
British Journal of Pharmacology (2010) **160,** 511–522; doi:10.1111/j.1476-5381.2010.00721.x
This article is part of a themed issue on Cannabinoids. To view the editorial for this themed issue visit http://dx.doi.org/10.1111/j.1476-5381.2010.00831.x

Keywords: adolescence; cannabinoids; schizophrenia

Introduction

Cannabis is the most recreationally used illicit substance across the globe and has a long standing history in many cultures for its euphoric and psychotropic effects. The biochemical mechanism by which cannabis exerts its effects on physiology and behaviour remained a mystery until the components of cannabis were extracted and Δ^9-tetrahydrocannabinol (THC) was elucidated to represent the psychoactive constituent of cannabis (Mechoulam and Gaoni, 1965). The isolation of THC resulted in the characterization of a G protein-coupled receptor to which THC exerted specific and saturable binding (Devane *et al.*, 1988), indicating the presence of an endogenous receptor to which cannabinoids could exert their effects. In the early 1990s, this cannabinoid receptor was genetically determined, and its distribution was then mapped in the brain using *in situ* hybridization and radioligand binding analysis (Herkenham *et al.*, 1990; Matsuda *et al.*, 1990; Herkenham *et al.*, 1991). This receptor, termed the cannabinoid CB_1 receptor, was found to exist as a presynaptic receptor and its activation inhibits neurotransmitter release from the axon terminal, due to its ability to couple to inhibitory G_i and G_o proteins (reviewed in (Mackie, 2008) and (Freund *et al.*, 2003). Its distribution is widespread in the brain with high densities in several brain regions, such as the striatum, hippocampus and cerebellum, as well as moderate to low densities in the amygdala, midbrain and cerebral cortex (Herkenham *et al.*, 1991). Within these brain regions, immunohistochemical, pharmacological and electrophysiological studies revealed that the CB_1 receptors are situated on terminals that release gamma-aminobutyric acid (GABA), glutamate, serotonin, dopamine and acetylcholine (Freund *et al.*, 2003). CB_1 receptors are also expressed at low levels within microglial populations (Cabral *et al.*, 2008), and activation of CB_1 receptors has been shown to affect glial cell functions such as migration toward sites of

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Received 2 December 2009; revised 15 January 2010; accepted 21 January 2010

injury (Walter *et al*., 2003). CB_2 receptors were cloned a few years after CB_1 (Munro *et al*., 1993) and while they were thought to be predominately located in immune cells in tissues such as the spleen and liver, it is now thought that CB_2 receptors are expressed on peripheral and possibly central neurons (Ross *et al*., 2001; Van sickle *et al*., 2005; Wotherspoon *et al*., 2005; Beltramo *et al*., 2006; Gong *et al*., 2006; Brusco *et al*., 2008).

The presence of endogenous receptors for THC suggested the existence of an endogenous substance that naturally binds to these receptors. The discovery of endogenous ligands for the cannabinoid receptor (endocannabinoids) occurred soon after the characterization of the receptor. These ligands were found to be arachidonate-derived neuroactive lipids generated from phospholipids precursors in the membrane. *N*-arachidonylethanolamine, or anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the two primary ligands that have been most fully characterized as endocannabinoids. The molecular logic behind the presence of two endogenous ligands for one receptor has not been fully elucidated, but differences in pharmacokinetics and efficacy of these ligands have been demonstrated (Hillard, 2000), suggesting that they may exert distinct physiological roles. Furthermore, these ligands do not appreciably share biosynthetic or metabolic pathways, indicating distinct mechanisms of regulation. The synthesis of AEA can occur through multiple biochemical pathways (Ahn *et al*., 2008); however, the primary pathway for the generation of AEA within the CNS has not been explicitly determined to date. 2-AG, on the other hand, is primarily synthesized through activation of phospholipase C, and the subsequent generation of diacylglycerol, which is rapidly converted to 2-AG by diacylglycerol lipase (Bisogno, 2008). With respect to metabolism, AEA is hydrolysed by the enzyme fatty acid amide hydrolase, which results in the generation of arachidonic acid and ethanolamine, while 2-AG is primarily metabolized by monoacylglycerol lipase (MAG lipase), which results in the formation of arachidonic acid and glycerol (Freund *et al*., 2003).

The molecular architecture of endocannabinoid signalling indicates that this system does not behave in the manner of most neurotransmitter systems. That is, endocannabinoids are believed to be released by post-synaptic cells, function as retrograde signals and traverse back across the synapse where they activate presynaptically located CB_1 receptors and limit synaptic transmitter release (Freund *et al*., 2003). As such, this system represents a critical player in the maintenance and determination of synaptic plasticity (Freund *et al*., 2003). Interestingly, a growing body of literature has demonstrated that this system may also play a highly specialized and functionally distinct role during development that extends beyond the regulation of transmitter release.

Endocannabinoid signalling and development: focus on adolescence

Endocannabinoid signalling has been found to be present during the gestational period (Berrendero *et al*., 1998; Biegon and Kerman, 2001; Mato *et al*., 2003; Wang *et al*., 2003), and a series of elegant studies have revealed the importance of this system for neural developmental processes (Berghuis *et al*., 2005; Berghuis *et al*., 2007; Mulder *et al*., 2008). During early phases of neuronal development, endocannabinoid signalling is integral for an array of processes including the proliferation and differentiation of progenitor cells, neuronal migration, axonal guidance, fasciculation, positioning of cortical interneurons, neurite outgrowth and morphogenesis (Harkany *et al*., 2007; Harkany *et al*., 2008a,b). The importance of this system during developmental periods is highlighted by the aberrations that occur following disruption of normal endocannabinoid signalling during ontogenetic phases. For example, pharmacological blockade of the CB_1 receptor in mid-to-late gestational periods impaired progenitor proliferation in the subventricular zone, disrupted axonal pathfinding and resulted in cortical delamination (Mulder *et al*., 2008). Alternately, *in utero* exposure to THC hampered appropriate interneuron positioning during corticogenesis and resulted in an increase in the density of CCK-positive interneurons in the hippocampus (Berghuis *et al*., 2005). Thus, the endocannabinoid system is a critical system for dictating multiple neurodevelopmental processes and alteration in endocannabinoid system through exogenous manipulations can have profound effects on the maturation and normative function of circuits in the developing brain.

Adolescence refers to the developmental time period between childhood and adulthood, and in humans is generally considered to encompass the ages of 12–17 years (Spear, 2000; Dahl, 2004). While infancy and childhood are periods of robust neurodevelopment, brain maturation continues well into adolescence. This development is largely seen in limbic structures, such as the hippocampus, but is particularly notable within the prefrontal cortex (PFC) that exhibits dynamic ontogenetic changes during development including synaptic pruning and development, receptor distribution, volumetric growth, myelination and programming of neurotrophic levels (Giedd *et al*., 1999; Spear, 2000; Bartzokis *et al*., 2001; Andersen and Teicher, 2008). While the exact role of endocannabinoid signalling during the adolescent period has not been experimentally mapped out (as it has during gestation and early life), it is reasonable to assume that the neurodevelopmental and morphogenic roles of endocannabinoids continue in adolescence. This hypothesis is reinforced by the dynamic changes that occur in the ontogenetic development of the endocannabinoid system during adolescence.

In humans, the expression patterns of the CB_1 receptor have been found to increase dramatically from infancy to young adulthood in regions such as the frontal cortex, striatum and hippocampus (Mato *et al*., 2003). While these studies did not directly address specific phases of adolescence, rodent studies have replicated these findings and demonstrated that CB_1 receptor expression increases in corticolimbic regions during adolescent periods into adulthood (Belue *et al*., 1995; Thanos *et al*., 2008). More temporally restricted studies have demonstrated that these changes in CB_1 receptor expression may be both regionally and temporally specific (Ellgren *et al*., 2008). Specifically, CB_1 receptor expression is found to increase progressively in the shell of the nucleus accumbens during adolescence, but correspondingly decrease in the core of the nucleus accumbens during this same period (Ellgren *et al*., 2008). Interestingly, in the PFC the expression of CB_1 receptors

dynamically changes such that there is a small reduction in CB_1 receptor levels in mid-adolescence, relative to early adolescence, but this change appears to normalize by late adolescence (Ellgren *et al*., 2008). Similarly, one study that looked at more temporally associated time points during adolescence demonstrated a transient increase in CB_1 receptor expression in early adolescence, which gave way to lower levels in adulthood (albeit, these levels were still higher than those seen in early life (Rodriguez de Fonseca *et al*., 1993). Thus, the general picture emerges that CB_1 receptor levels tend to increase throughout adolescent development, although there may be regional and time-specific changes that associate with this ontogeny. Clearly, more time-sensitive and region-specific studies are required to fully characterize the development of this system through the adolescent period.

Similar to the cannabinoid receptor, the endocannabinoid ligands themselves appear to exhibit developmental changes during adolescence, albeit far less research has examined the ontogeny of these changes. In the female hypothalamus, AEA levels are seen to peak at the onset of puberty and then decline into adulthood (Wenger *et al*., 2002). Similar to this phenomenon, it has also been reported that there is a spike in AEA content in the nucleus accumbens that occurs in mid-adolescence, while in the PFC AEA content is seen to progressively increase across adolescent development (Ellgren *et al*., 2008). Interestingly, levels of 2-AG are found to exhibit a mirrored pattern such that 2-AG levels dramatically decline in the nucleus accumbens and PFC across adolescence, although within the PFC this reduction is of greater magnitude during mid-adolescence and recovers to some degree in late adolescence (Ellgren *et al*., 2008).

Thus, while more in depth characterization of the ontogenetic development of the endocannabinoid system across adolescence is required, the current body of data clearly demonstrates that this system undergoes functional development and change throughout adolescence. Given the important role of the endocannabinoid system in modulating multiple neurodevelopmental processes, the possibility exists that endocannabinoid signalling is an important determinant of maturation of the adult brain. Similar to what was seen during early life development (Berghuis *et al*., 2005; Mulder *et al*., 2008), it seems quite likely that disruption of normative endocannabinoid signalling during adolescence may have long-standing consequences on adult brain function.

Schizophrenia is increasingly viewed as a subtle neurodevelopmental disorder characterized by disrupted brain connectivity and altered circuitries (Lewis and Sweet, 2009). The periods of brain development that are important for synapse and circuit development are not only the pre- and perinatal ones, but also the adolescent one. And, in fact, neurodevelopmental views of schizophrenia have posited that the illness may result from either an early (pre- or perinatal), static brain lesion with a long latency or a late (adolescence) brain disturbance of limited duration and short latency (Lewis and Levitt, 2002). Therefore, the alleged role played by the endocannabinoid system in late developmental phases such as the adolescent one, prompted to the speculation that alteration in the endocannabinoid tone induced by cannabis consumption during the adolescent developmental window might represent a risk factor for developing schizophrenia.

Epidemiological evidence and human studies of cannabis use, schizophrenia and psychotic symptoms

In terms of the number of people that use recreational cannabis, uncertainties exist due to a lack of timely, good-quality data in most countries (Hall and Degenhardt, 2009). Generally speaking, the USA, Australia and New Zealand have the highest incidence of cannabis use, followed by Canada and countries in the European Union, while African, Asian and South American countries tend to have the lowest use (Rey *et al*., 2004). Many surveys have been conducted indicating a high rate of use of cannabis among young people, but methodological and population differences make it difficult to compare these studies over time. Lifetime prevalence of use in grade 12 students in the USA was 49% in 2007 (Eaton *et al*., 2008), while in 2008 over 15% of 12th graders reported using cannabis daily for at least a month at some point in their lives (Johnston *et al*., 2009). Thus, it is crucial to critically evaluate whether there is a greater risk for adverse outcomes such as psychosis in those that consume cannabis during adolescence.

The belief that cannabis can induce psychotic-like symptoms has been reported for over 50 years. A study was published in 1958 describing psychotic-like symptoms (e.g. thought disorder, delusions and disturbances of visual perception) in healthy volunteers following a single ingestion of cannabis (Ames, 1958). Furthermore, a cannabis-induced psychosis was described in the Bahamas (Spencer, 1970) and India (Chopra and Smith, 1974) nearly 40 years ago, and it has been reported that 15% of cannabis users experience acute psychotic symptoms (Thomas, 1996). However, whether cannabis use causes schizophrenia has been a matter for debate for decades. It is thought that in terms of the onset of cannabis use and the onset of the first symptoms of schizophrenia, a number of groups can be differentiated: (i) either patients abuse cannabis for a number of years before developing schizophrenic symptoms; (ii) patients develop symptoms immediately after the first use of cannabis; or (iii) cannabis consumption occurs after schizophrenic symptoms are already established (Hambrecht and Hafner, 2000). What does appear to be consistent is that in individuals with a predisposition for schizophrenia, ingesting 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 suggest that cannabis is a risk factor for the onset of schizophrenia. One of the most comprehensive studies investigating the epidemiological link between cannabis use and psychosis was published over 20 years ago (Andreasson *et al*., 1987). In this 15 year follow-up study on over 45 000 Swedish conscripts, the relative risk for schizophrenia among high consumers of cannabis (defined as having used cannabis on more than 50 occasions) was 6.0 compared with non-users. This figure was determined even after allowance for other psychiatric illnesses and social background, thus indicating that cannabis is an independent risk factor for schizophrenia (Andreasson *et al*., 1987). Similar results were obtained by the same group whereby analysis of over 50 000 Swedish subjects determined an adjusted odds ratio of 6.7 in heavy cannabis users (Zammit *et al*., 2002). A

Dutch study using a population-based sample of over 4000 subjects found that the baseline use of cannabis conferred a threefold increase in psychotic symptoms when followed up 3 years later (van Os *et al*., 2002). This study also found that those with an established vulnerability to psychotic disorders are especially sensitive to the effects of cannabis. In addition, the risk of developing schizophrenia has been reported to increase in a dose-dependent manner with increasing frequency of cannabis use (Zammit *et al*., 2002; Fergusson *et al*., 2005; Henquet *et al*., 2005). Reviews of these and other longitudinal and case–control studies confer that lifetime cannabis use increases the risk of developing psychosis (Arseneault *et al*., 2004; Rey *et al*., 2004; Moore *et al*., 2007; Zammit *et al*., 2008).

If cannabis use was actually causing schizophrenia (as opposed to merely precipitating it in already 'schizophrenically vulnerable' individuals), then it would be expected that the incidence of schizophrenia would increase at the same rate as any increase in cannabis consumption over a defined period. Whether this occurs is debatable and difficult to determine. According to a study on frequency of use and long-term trends in a large national sample of high-school students in the USA, exposure to cannabis increased in the 1970s, peaking in 1979 but then decreased in the 1980s (Johnston *et al*., 2009). The 1990s saw an increase in cannabis use among adolescents, followed by a decline through the 2000s (Johnston *et al*., 2009). Degenhardt *et al*. (2003) found that despite a rapid increase in cannabis use in Australia during 1980–2000 (as well as a corresponding decrease in the age of initiation of cannabis use), there was no clear evidence of an increase in psychosis in the general Australian population during this time (Degenhardt *et al*., 2003). A similar study found substantial increases in cannabis use in the UK population over the last 30 years but concluded it was too early to know whether this has led to an increased incidence of schizophrenia (Hickman *et al*., 2007). Another British study reported an increase in the incidence of cannabis use in the year prior to presentation of schizophrenia over a similar time period, suggesting that cannabis use might have an aetiological role in the development of schizophrenia (Boydell *et al*., 2006). In addition, a number of studies have concluded that the effect of cannabis in terms of producing psychotic symptoms is much stronger in subjects that had evidence of a predisposition to psychosis (van Os *et al*., 2002; Verdoux *et al*., 2003; Henquet *et al*., 2005).

A number of studies have investigated the acute effects of cannabis or the major psychoactive constituent THC in human subjects. D'Souza *et al*., (2004) found in a double-blind study that intravenous THC administration produced positive and negative symptoms (as measured by the Positive and Negative Symptom Scale questionnaire) that peaked in the first 80 min after administration but then decreased to baseline within 4 h (D'Souza *et al*., 2004). Studies have used a binocular depth inversion illusion (BDII) test (a measure of impaired visual processing that occurs in various psychotic states) to measure the prodromal states of psychoses and found that cannabis resin (Emrich *et al*., 1991), nabilone (a synthetic analogue structurally related to THC) (Leweke *et al*., 2000) and dronabinol (a synthetic form of THC) (Koethe *et al*., 2006) induce BDII similar to that observed in patients suffering from acute paranoid schizophrenic or schizophreniform psychosis (Koethe *et al*., 2006). Also, BDII has been shown to be increased in regular cannabis users (Semple *et al*., 2003).

It is possible that some subjects that are prone to psychosis may seek out cannabis as a means of self-medication. However, using structural equation modelling, it was shown by Fergusson *et al*. (2005) that increasing psychotic symptoms were not positively associated with increased rates of cannabis use, suggesting that such a population among those who ingest cannabis and have psychotic symptoms was small (Fergusson *et al*., 2005). More recent evidence suggests that four out of six patients that had a self-reported history of cannabis improving their schizophrenic symptoms showed improvement following administration of a synthetic form of THC called dronabinol (Schwarcz *et al*., 2009). Thus it is possible that for a small subset of schizophrenic patients, cannabis ingestion may offer some relief of symptoms. In addition, it is thought that low doses of cannabis may acutely increase blood flow to cortices concerned with cognition, mood and perception, thus improve frontal lobe functioning (Cohen *et al*., 2008). However, there is overwhelming support in the literature for the lack of evidence for the 'self-medication' hypothesis of cannabis (Zammit *et al*., 2002; Hall *et al*., 2004; Stefanis *et al*., 2004; Verdoux *et al*., 2005; Leweke and Koethe, 2008; Fernandez-Espejo *et al*., 2009; Hides *et al*., 2009; Pujazon-Zazik and Park, 2009; Sugranyes *et al*., 2009).

Adolescent cannabis use and schizophrenia

A number of studies have investigated whether exposure to cannabis during adolescence is a risk factor for psychoses such as schizophrenia. Arseneault *et al*. (2002) investigated this in subjects from Dunedin, New Zealand. In this longitudinal study, cannabis users by age 15 and 18 years had more schizophrenic symptoms than controls (never used cannabis or had used cannabis 'once or twice') at age 26 years (Arseneault *et al*., 2002). This result took into account psychotic symptoms preceding the onset of cannabis use, indicating that cannabis use is not secondary to a pre-existing psychosis. In addition, earlier use at age 15 years conferred a greater risk of schizophrenia outcomes than later use (Arseneault *et al*., 2002). Contrary to these studies, a systematic review of longitudinal studies published in 2004 found no causal relation between cannabis use by young people and psychosocial harm, but could not exclude the possibility that such a relation exists (Macleod *et al*., 2004). As mentioned by Fergusson (2004), different conclusions can be reached based on the same evidence if a review focuses on uncontrolled or residual confounding [as was done in the Macleod *et al*. (2004) review] rather than taking the evidence on face value in terms of controlling for confounding.

More recently, a study conducted in Zurich, Switzerland, showed that there was an increase in first admission rates of patients with schizophrenia and other psychotic disorders in boys aged between 15 and 19 years in the second half of the 1990s (Ajdacic-Gross *et al*., 2007). During this same period there was an increase in the use of cannabis among 15–16-year-old Swiss boys from 15% in 1990 to 41% in 1998, leading

the authors to suggest that this may be the reason for the higher admission rates (Ajdacic-Gross *et al*., 2007). Stefanis *et al*. (2004) performed perhaps the most comprehensive study on adolescent cannabis and psychotic symptoms on 3500 representative 19-year-olds in Greece (Stefanis *et al*., 2004). They found that adolescent use of cannabis was positively associated with both the positive and negative symptoms of schizophrenia, thus suggesting cannabis is a risk factor for the development of schizophrenia when used in adolescence (Stefanis *et al*., 2004). In a large Finnish study on 15–16-year-old adolescents, those who had tried cannabis were more likely to present three or more symptoms of psychosis (Miettunen *et al*., 2008). Two studies have found increased schizotypy among American undergraduate college students (mean age 21.7 years) (Schiffman *et al*., 2005) and English University students (mean age 22 years) who used cannabis (Barkus and Lewis, 2008).

A recent study found that cannabis use was significantly associated with a decrease in age of onset of schizophrenia (Sugranyes *et al*., 2009). This is concerning as the early onset of schizophrenia has been proven to be a negative outcome factor (Malla and Payne, 2005; Rabinowitz *et al*., 2006). A study in Spain found that patients presenting with first episode psychosis (average age 15.5 years) had a higher rate of positive symptoms and less negative symptoms if they were cannabis users compared with non-cannabis users (Baeza *et al*., 2009). In addition, the increases in cannabis use in the UK population over the last 30 years as reported by Hickman *et al*. (2007) were concluded by the authors to be mainly due to more prolonged use initiated at younger ages (Hickman *et al*., 2007). Thus, despite some variables factors such as the measurement of psychotic symptoms and control for confounding factors, it appears that there is a causal link between adolescent cannabis use and the development of psychoses such as schizophrenia. With a greater amount of adolescents consuming cannabis, it has become imperative to critically evaluate whether this age group is particularly vulnerable to developing psychoses such as schizophrenia compared with adolescents that do not consume cannabis, and to elucidate mechanisms responsible for this vulnerability.

Effects of cannabinoid exposure during adolescence on psychosis-related behaviours in adult rodents

Animal models are critical for the study of psychiatric disorders as they enable the use of invasive methods that cannot be used for ethical reasons in humans, to examine the mechanisms underlying pathophysiology of disease states. However, a significant hindrance to the development of any animal model is the ability to evaluate the inherently human psychopathology. For example, schizophrenia has been characterized by symptoms traditionally divided into three main clusters: positive, negative and cognitive. Positive symptoms consist of items indicative of overall hyperactivity such as agitation, paranoia and hallucinations. In contrast, negative symptoms refer to social withdrawal, lack of motivation and abnormalities in social interaction. Cognitive symptoms include deficits in attention and working memory that lead to an inability to organize one's life and to work effectively. Obviously it is impossible to model schizophrenia in its entirety including all the aspects of the positive, negative and cognitive symptoms in an animal. However, a number of behavioural paradigms have been considered to be valid translational models to assess the three different symptoms, such as prepulse inhibition of startle (PPI – a measure of sensorimotor gating, or the ability of an organism to attain information and process it correctly), social interaction, latent inhibition (a measure of a reduction in learning of sensory input to which prior exposure has occurred without any consequence), working memory tasks and drug-induced hyperactivity (Powell and Miyakawa, 2006; Lodge and Grace, 2009). In addition, there are a number of means to induce psychotic-like symptoms in rodents that can then be used to assess the effects of cannabinoids on a 'vulnerable to psychosis' phenotype. Treatment with drugs that induce psychotic symptoms in humans such as phencyclidine (PCP) can create such a phenotype, as can rearing rats in isolation from weaning until adulthood, or depriving rat pups from their mother (typically at post-natal day 9) for 24 h. These models produce abnormalities also observed in schizophrenia such as disruptions in PPI (Domeney and Feldon, 1998; Ellenbroek, 1998; Geyer *et al*., 2001; Rasmussen *et al*., 2007).

Despite the increasing use of cannabis among adolescents, experimental studies dealing with long-lasting effects of adolescent cannabinoid exposure on psychosis-related behaviours in adult rodents are very scarce. The most remarkable and consistent part of data regards the cognitive deficit. Adolescent exposure to synthetic or natural cannabinoid agonists has been reported to induce impairments in object recognition memory at adulthood in both male and female rats (Schneider and Koch, 2003; O'Shea *et al*., 2004; 2006; Quinn *et al*., 2008), suggestive of working memory dysfunction (Ennaceur and Delacour, 1988). Similarly, spatial working memory deficits (tested by the 8-arm radial maze) have been observed after adolescent THC exposure in adult male and female rats (Rubino *et al*., 2009a,b). When other forms of memory were considered, no lasting effects were observed in aversive memory (Rubino *et al*., 2009a,b) or spatial learning (Cha *et al*., 2007), so the effect appears to be specifically restricted to the working memory component. Disruption in PPI was observed after chronic pubertal treatment with the cannabinoid agonist WIN 55,212-2 (Schneider and Koch, 2003; Wegener and Koch, 2009), suggestive of deficits in sensorimotor gating. Chronic CP-55,940 treatment during adolescence induced a significant decrease in social behaviour measured in the social interaction test (O'Shea *et al*., 2004; 2006). Similar findings were reported also after adolescent treatment with THC (Quinn *et al*., 2008). Finally, adult rats exposed to WIN 55,212-2 during adolescence showed a significant increase in locomotor activity when tested in the open field (Wegener and Koch, 2009).

The behavioural picture arising from these results supports the hypothesis that adolescence exposure to cannabinoids might represent a risk factor for developing psychotic-like symptoms at adulthood. This statement appears to acquire more consistence when the two-hit hypothesis of schizophrenia is taking into account. According to this model, a genetic

defect or prenatal or post-natal developmental aberration leads to a deficient neuronal network (first hit) followed by an additional adverse environmental hazard (second hit), such as a viral infection or drug exposure that modulates the mutant candidate gene activity leading to an ongoing psychotic illness (Bayer *et al*., 1999). A combination of neonatal prefrontocortical lesion with chronic pubertal cannabinoid administration has been shown to lead to greater impairments in various forms of social behaviour (Schneider *et al*., 2005), as well as object recognition memory (Schneider and Koch, 2007), thus suggesting that pubertal cannabinoid administration in vulnerable individuals might act as a risk factor for inducing enhanced behavioural disturbances. Furthermore, it has been shown that THC worsens disruptions of PPI induced by isolation rearing, but has no effect on PPI in rats that are not socially isolated (Malone and Taylor, 2006). Another recent study in line with the two-hit hypothesis demonstrated that adolescent exposure to THC worsened the cognitive impairment in the object recognition test induced by intermittent chronic administration of phencyclidine, an animal model of schizophrenia-like cognitive deficit (Vigano *et al*., 2009).

In addition to behavioural studies, the molecular and cellular mechanisms by which adolescent exposure to cannabinoids promote or increase the probability to develop schizophrenia-like symptoms are still unclear. Very few studies have dealt with biochemical correlates of behavioural findings; however, some intriguing data appear to arise. First, when an animal model used to induce schizophrenia-like symptoms was administered during the periadolescent period, mainly a decrease in CB_1 receptor expression and/or G protein coupling has been observed in cerebral areas relevant to schizophrenia (Malone *et al*., 2008; Vigano *et al*., 2009). Whether or not this is triggered by a general increase in endocannabinoid levels is still unclear; however, this conclusion might be supported by the reciprocal increase in fatty acid amide hydrolase and decrease CB_1 receptor expression observed in the caudate putamen of socially isolated rats (Malone *et al*., 2008), as well as by the specific increase in 2-AG levels observed in the PFC of rats chronically treated with PCP, which was associated with reduced functionality of the CB_1 receptor in this brain area (Vigano *et al*., 2009). Accordingly, THC administration to PCP-treated animals worsened PCP-induced cognitive impairments (Vigano *et al*., 2009), whereas co-treatment with the CB_1 receptor antagonist AM251 recovers it (Guidal *et al*., 2010). In line with this, studies using the maternal deprivation model have shown that a decrease in CB_1 receptor expression (Suarez *et al*., 2009) and an increase in 2-AG levels (Llorente *et al*., 2008) have been observed in the hippocampus of maternally deprived rats.

In a similar manner to the animal models used to induce schizophrenia-like symptoms, adolescent cannabinoid exposure has been reported to produce a long-lasting decrease in CB_1 receptor expression and/or G protein coupling in specific brain areas (Rubino *et al*., 2008). Moreover, adolescent cannabinoid exposure triggers a plethora of cellular and molecular events in the brain that could be involved in the development of the different symptoms of schizophrenia. For example there is general agreement that schizophrenic patients display hippocampal as well as PFC abnormalities (Boyer *et al*., 2007; Ranganath *et al*., 2008). Adolescent THC exposure in male rats induced lasting changes in the hippocampal protein expression profiles related to degenerative and oxidative changes (Quinn *et al*., 2008) as well as an impairment in concerted structural and functional plasticity of both neurons and glia in this brain region, paralleled by a reduction in dendrite length and complexity and number of dendritic spines in the dentate gyrus (Rubino *et al*., 2009b). When female rats were used, adolescent THC exposure induced a molecular picture in the PFC characterized by less synaptic density and/or efficiency (Rubino *et al*., 2009a).

As mentioned previously, CB_2 receptors are also expressed in the brain. Interestingly, it has recently been reported that maternal deprivation significantly increased CB_2 receptor expression in hippocampal regions (Suarez *et al*., 2009). The authors suggested from this that CB_2 receptors may be involved in the psychotic-like behavioural alterations observed. Moreover, Ishiguro *et al*. described a polymorphism in the gene encoding for CB_2 receptors associated with schizophrenia in a Japanese population, and how administration of a CB_2 receptor antagonist worsened disruption of PPI induced by the NMDA receptor antagonist MK-801 in rats (Ishiguro *et al*., 2009). Thus, the recent proposal that CB_2 receptors could be involved in schizophrenia provides another possible mechanism by which cannabis use could affect psychoses such as schizophrenia.

Adolescent cannabis and schizophrenia: possible mechanisms

A number of hypotheses have been put forward to attempt to explain the mechanism by which adolescent cannabis consumption could render a person more susceptible to developing psychoses such as schizophrenia. As described above, it is now well known that the endocannabinoid system undergoes substantial changes during adolescence (Rodriguez de Fonseca *et al*., 1993; Belue *et al*., 1995; Wenger *et al*., 2002; Ellgren *et al*., 2008; Thanos *et al*., 2008). In addition, a number of studies have found that endocannabinoid signalling is implicated in schizophrenia (Leweke *et al*., 1999; Giuffrida *et al*., 2004; Leweke *et al*., 2007), and post-mortem CB_1 receptor changes have been observed in brains of schizophrenic patients in some studies (Dean *et al*., 2001; Zavitsanou *et al*., 2004; Newell *et al*., 2006; Eggan *et al*., 2008) but not in one other study (Koethe *et al*., 2007). These and other studies have lead to the postulation of an 'endocannabinoid hypothesis of schizophrenia' (Emrich *et al*., 1997; Muller-Vahl and Emrich, 2008). Thus, consuming exogenous cannabinoids in the form of cannabis ingestion during adolescence may alter the normal endocannabinoid changes occurring in adolescence.

Early onset cannabis use is associated with dependence among many users, with youths aged 12–17 years constituting the majority of admissions to treatment facilities for cannabis abuse (Chen *et al*., 2004; Hartman *et al*., 2008). Early onset cannabis use has also been associated with cognitive deficits that may be linked to neurotoxic effects of cannabis on the developing brain (Pope *et al*., 2003). Studies of white matter brain morphology from cannabis users compared with non-using control subjects have shown equivocal results

(Bava *et al*., 2009). An MRI and PET study showed that subjects starting the use of cannabis before age 17 years had smaller whole brain and percent cortical grey matter and larger white matter volumes (Wilson *et al*., 2000). Matochik *et al*. (2005) found that heavy cannabis users had higher white matter density in some hippocampal areas and lower white matter density in the parietal lobe (Matochik *et al*., 2005). Other studies have found no such white matter changes (Block *et al*., 2000; Gruber and Yurgelun-Todd, 2005), although cortical processes used when undergoing a test that challenges the ability to inhibit inappropriate responses and resist interference were different in heavy cannabis users compared with non-cannabis-using control subjects (Gruber and Yurgelun-Todd, 2005). Other studies have reported long-term white matter changes in adolescent cannabis-using adults in prefrontal fibre bundles of the corpus callosum (Arnone *et al*., 2008), changes in fronto-parietal circuitry (Bava *et al*., 2009) and increased directional coherence in the bilateral uncinate fasciculus, anterior internal capsule and frontal white matter (Peters *et al*., 2009). Conversely, an MRI scan study investigating 18–27-year-old subjects that used cannabis frequently during adolescence revealed no changes in white matter integrity compared with age-matched cannabis näive subjects (Delisi *et al*., 2006). Similarly, another study found no major hippocampal alterations in adolescent cannabis users compared with cannabis näive subjects (Medina *et al*., 2007). However, in both studies the sample size was relatively small and subjects were asked to report on their former adolescent cannabis use rather than following the subjects through a longitudinal-type study. Slight gender-specific changes in PFC volumes have been observed in adolescent cannabis users compared with controls (Medina *et al*., 2009).

Because of the number of studies reporting white matter changes, and as CB_1 receptors are present on cells such as astrocytes, microglia and oligodendrocytes, it was postulated by Bava *et al*. (2009) that these processes may be adversely impacted upon by early cannabis use, thus result in an alteration in the trajectory of white matter development (Bava *et al*., 2009). With regard to studies on grey matter, heavy cannabis users have been found to have lower grey matter density in some hippocampal areas and greater grey matter density in other regions such as the thalamus (Matochik *et al*., 2005). In addition, a more prominent grey matter density and volume reduction in the right posterior cingulate cortex in young adults with first episode schizophrenia and history of adolescent marijuana was shown compared with non-using counterparts (Bangalore *et al*., 2008). A morphological study found evidence for bilateral hippocampus and amygdala volume reductions in adults with history of long-term cannabis use, where left hippocampal volume was inversely related to length of exposure to cannabis (Yucel *et al*., 2008).

As mentioned above, PFC neurons undergo a distinct developmental refinement during adolescence (Giedd *et al*., 1999; Spear, 2000; Bartzokis *et al*., 2001; Andersen and Teicher, 2008). It is well known that GABAergic neurons in the PFC have CB_1 receptors, which when activated result in a decrease in extracellular GABA release [for review see Egerton *et al*., (2006)]. Thus, it has been suggested that exogenous activation of CB_1 receptors during adolescence may alter the balance of GABAergic inhibitory inputs to pyramidal neurons in the PFC that could result in impaired cognitive function (Eggan *et al*., 2009). More specifically, Eggan *et al*. (2009) hypothesize that an increased risk of schizophrenia following adolescent cannabis exposure may be due to an adolescent change in normal refinements of CB_1 receptor containing GABAergic axon innervation patterns (Eggan *et al*., 2009).

It is well known that cannabis, like most drugs of abuse, causes an increase in extracellular dopamine [for review see Gardner, (2005)]. This most probably arises from activation of CB_1 receptors on GABAergic interneurons that synapse with dopaminergic neurons (Pistis *et al*., 2002). Psychosis is thought to result from aberrant reward prediction and abnormal attribution of salience caused by disordered dopamine transmission (Kapur, 2004). Dopamine sensitization has been postulated to underlie the development of dopaminergic abnormalities associated with schizophrenia and is thought to begin in adolescence (Laruelle, 2000). The endocannabinoid system is an activity-dependent modulator of dopaminergic transmission (Rodriguez De Fonseca *et al*., 2001). Furthermore, it has been suggested that the endocannabinoid system may act as a protective mechanism whereby endocannabinoids are released in response to a hyperdopaminergic state in an attempt to decrease dopaminergic transmission (Rodriguez De Fonseca *et al*., 2001; Koethe *et al*., 2009). Thus, it is possible that repeated use of cannabis in adolescence leads to sensitization of the endogenous mesolimbic dopaminergic system and this is why cannabis use during adolescence results in a worse outcome with respect to development of schizophrenia compared with ingesting cannabis during adulthood (Stefanis *et al*., 2004).

It has been suggested that in a vulnerable minority, early and heavy use of cannabis has negative effects on youth psychosocial functioning and psychopathology (Rey *et al*., 2004). If a vulnerable minority had a predisposition for developing schizophrenia, a gene polymorphism in this cohort could be responsible. Catechol-o-methyltransferase (COMT) is an enzyme involved in the metabolism of synaptic dopamine, and disturbances in dopaminergic function are implicated in the pathogenesis of schizophrenia (Moore *et al*., 1999; Kapur, 2004). A functional polymorphism of the COMT gene whereby a variant at codon 158 (G to A missense mutation resulting in valine instead of methionine) is associated with a substantial decrease in enzyme activity (Lotta *et al*., 1995; Lachman *et al*., 1996). While this polymorphism has been found to predict performance on dopamine-mediated prefrontal tasks, there is inconclusive evidence of a strong link between this polymorphism and schizophrenia (Lewandowski, 2007). However, 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 this COMT valine polymorphism following adolescent cannabis exposure (Caspi *et al*., 2005; Henquet *et al*., 2006; Hides *et al*., 2009). First, a longitudinal study of over 800 participants in New Zealand with this COMT gene polymorphism found that those who ingested cannabis during adolescence had an increased risk of adult psychotic symptoms (Caspi *et al*., 2005). These authors suggested that the observed gene–environment interaction may be limited to a sensitive period of brain development in adolescence. However, this was not replicated in a cohort of approximately 500 UK patients with schizophrenia (Zammit *et al*., 2007).

As Africans have a higher rate of the valine COMT gene polymorphism than Caucasians (Palmatier *et al*., 1999), another study investigated the association between this gene polymorphism and adolescent cannabis use in African-American and Caucasian subjects (Kantrowitz *et al*., 2009). No significant difference was found in either group compared with subjects without the valine COMT polymorphism. One caveat that these authors mention is that this study did not compare against non-ill controls as with the Caspi *et al*. (2005) study, which perhaps may explain the lack of results particularly if those with the valine gene polymorphism are more likely to develop schizophrenia. However, this has not been conclusively determined. In addition, a double-blind placebo controlled study on subjects in the Netherlands found that carriers of the same polymorphism on the COMT gene were more sensitive to memory and attention impairments of THC (the major psychoactive constituent of cannabis), again suggesting a gene–environment interaction (Henquet *et al*., 2006). Thus, conflicting results regarding the possibility that a COMT polymorphism × adolescent cannabis exposure interaction exist and further longitudinal studies are required to investigate this. However, it does fit nicely with the 'two-hit' hypothesis of schizophrenia which, as mentioned above, states that an early first hit (e.g. prenatal or early post-natal developmental insult) acts as a vulnerability factor and produces a long-term susceptibility to an additional adverse event (second hit), which then precipitates psychotic symptoms.

There are certain factors that make it difficult to state one way or another whether adolescent cannabis causes schizophrenia. Frequency and amount of cannabis consumed in addition to the different forms of preparation are factors that are difficult to take into account (Moore *et al*., 2007; Sugranyes *et al*., 2009). Also, cannabis varieties vary greatly in the amount of the major psychoactive constituent THC. While an average 1 g cannabis cigarette or 'joint' was thought to contain approximately 2% THC, in recent times more potent forms of cannabis have become available in which the THC content has been estimated to be up to 20% (Hunault *et al*., 2009). A recent human study found that smoking higher potency cannabis (sinsemilla or 'skunk') leads to an increase in the risk of developing psychosis (Di forti *et al*., 2009). This is consistent with the hypothesis that THC exposure increases the risk of psychosis. In addition, the concentration of other cannabinoids in cannabis preparations may be important in terms of whether a person develops schizophrenia following cannabis use. For example, a number of animal studies (Guimaraes *et al*., 2004; Long *et al*., 2006) as well as clinical studies (Leweke *et al*., 2000; Zuardi *et al*., 2006; Morgan and Curran, 2008) suggest that the non-psychoactive constituent cannabidiol has antipsychotic activity. In addition, it has been suggested that cannabidiol may protect against some pro-psychotic effects of THC (Bhattacharyya *et al*., 2010; Malone *et al*., 2009).

Conclusion

Epidemiological evidence suggests that cannabis use is a risk factor for schizophrenia, while cannabis use in individuals with a predisposition for schizophrenia results in an exacerbation of symptoms and worsening of the schizophrenic prognosis. The neurodevelopmental characteristic of adolescence probably creates a more vulnerable circumstance for cannabis to produce psychotic-like symptoms and possibly cause schizophrenia.

In the past few years there has been an increase in evidence of the important role of the endocannabinoid system in moderating adolescent neurodevelopmental processes such as synaptic pruning. We can speculate that adolescent exposure to cannabinoids might tamper with the normal developmental neuronal processes occurring in the still developing adolescent brain, thus leading to a predisposition to develop schizophrenia, possibly involving GABAergic and dopaminergic dysfunction. As with adults, there are definitely some adolescents that are more susceptible to the pro-psychotic effects of cannabis, possibly because of a genetic vulnerability such as a polymorphism in the COMT gene.

Longitudinal studies that evaluate adolescents prior to initiation of regular cannabis use and compare brain function indicators as well as the development of schizophrenia are required. Also, preclinical studies to further investigate the role of the endocannabinoid system in neurodevelopment, as well as molecular and neurochemical effects of adolescent cannabinoid exposure would greatly enhance the knowledge on the propensity for adolescent use of cannabis to induce schizophrenia.

Conflict of interest

The authors have no conflict of interest to declare.

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