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Review

Cannabis use in young people: The risk for schizophrenia

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ABSTRACT

Cannabis is one of the most commonly used illicit drugs, and despite the widely held belief that it is a safe drug, its long-term use has potentially harmful consequences. To date, the research on the impact of its use has largely been epidemiological in nature and has consistently found that cannabis use is associated with schizophrenia outcomes later in life, even after controlling for several confounding factors. While the majority of users can continue their use without adverse effects, it is clear from studies of psychosis that some individuals are more vulnerable to its effects than others. In addiction, evidence from both epidemiological and animal studies indicates that cannabis use during adolescence carries particular risk. Further studies are warranted given the increase in the concentration of the main active ingredient (Δ^9-tetrahydrocannabinol) in street preparations of cannabis and a decreasing age of first-time exposure to cannabis.

Contents

1. Introduction

Cannabis is one of the most commonly used illicit drugs, in terms of both frequency of use and dosage. The World Drug Report 2009, published by the United Nations, estimates that the global number of people who used cannabis at least once in 2007 was between 143 and 190 million persons. The highest levels of use remain in the established markets of North America, Western Europe, West and Central Africa and Oceania (United Nation Office on Drugs and Crime, 2009).

The term cannabis refers to different types of preparation derived from the plant *Cannabis sativa*, which all contain chemical substances called cannabinoids. Until recently, the main types of cannabis available on the "street" were marijuana (grass) and resin (hash) but in recent years a more potent variant termed sinsemilla or skunk has become available in many countries. The psychoactive ingredient of cannabis is Δ^9-tetrahydrocannabinol (THC); marijuana and resin have traditionally contained about 4% THC but the concentration of THC in skunk in countries such as England and the

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Netherlands has increased to about 16 and 20% respectively (Potter et al., 2008; Hardwick, 2008), partly due to the use of intensive indoor cultivation methods (EMCDDA, 2004). Little is known about the risks associated with use of these stronger forms of cannabis.

The British Crime Survey, which assesses use based on self-reports, estimates that 8.2% of the total population of England and Wales have used cannabis and that use is predominantly among younger people (Murphy and Roe, 2007). Although overall rates of cannabis use appear to be on the decline, there is evidence for a disturbing reduction in the age of first use of cannabis, with estimates of an increase of a nearly 20 fold in first time use by those under the age of 18 (Hickman et al., 2007), with 40% of 15-year olds in the UK having experience of the drug (ESPAD: The European School Survey Project on Alcohol and Other Drugs, http://www.espad.org/). Although recent data suggests that use of cannabis is beginning to plateau among those aged 16–17 years in a number of countries (Kuntsche et al., 2009), there is still significant cause for concern given the trend to the use of more potent strains.

2. How does cannabis produce its effects?

The main active ingredient of cannabis, THC, was first identified in 1964 (Gaoni and Mechoulam, 1964) but it took several years for its endogenous target, the CB_1 receptor, to be discovered and cloned (Devane et al., 1988; Matsuda et al., 1990). We now know that the CB_1 receptor which is one of the most abundant G-protein-coupled receptors in the brain. Following its identification, the first endogenous ligand or endocannabinoid, N-arachidonoylethanolamine (anandamide), was discovered (Devane et al., 1992). Subsequently, other endocannabinoids have been identified (Mechoulam and Hanus, 2000) as well as a second cannabinoid receptor, CB_2 (Munro et al., 1993).

The endocannabinoid system is now well described (Piomelli, 2003), from synthesis of endocannabinoids like anandamide in neurones to the 'on demand' release of these endocannabinoids, and deactivation by transport into cells followed by intracellular hydrolysis by enzymes including fatty acid amide hydrolase (FAAH). The "normal" endogenous agonists of the CB_1 (and CB_2) receptors, anandamideand 2-arachidonoylglycerol (2-AG) (Di Marzo et al., 2004) are synthesized 'on demand' from membrane phospholipids and act as local mediators in an autocrine and paracrine manner (Di Marzo et al., 2004). In binding to CB_1, they further the closure of Ca^{2+} channels, the opening of k^+ channels, inhibition of adenylyl cyclase activity and stimulation of kinases (Piomelli, 2003).

Anandamide and 2-AG differ in their subcellular localization, and it is thought that anandamide may play a more important role postsynaptically and 2-AG presynaptically (Di Marzo et al., 2004). 2-AG is more abundant in the brain than anandamide and recent evidence suggests that 2-AG may be the more important ligand for the cannabinoid receptors in the brain (Chevaleyre et al., 2006). Altering 2-AG, but not anandamide levels, affects synaptic neurotransmission and the regional distribution of 2-AG overlaps with CB1 receptors (Katona and Freund, 2008). However, a role for anandamide in regulating the endocannabinoid system has not been ruled out. Endocannabinoids act presynaptically to inhibit the release of amino-acid neurotransmitters on the terminals of neighbouring GABAergic and glutamatergic neurons (see Fig. 1). They are synthesized by principal output neurons, such as Purkinje cells in cerebellum, pyramidal neurons in hippocampus and cortex, medium spiny neurons in striatum and dopaminergic neurons in midbrain (Freund et al., 2003). Thus, these neurons regulate their excitatory and inhibitory inputs by releasing endocannabinoids which intervene in both short-term and long-term forms of synaptic plasticity.

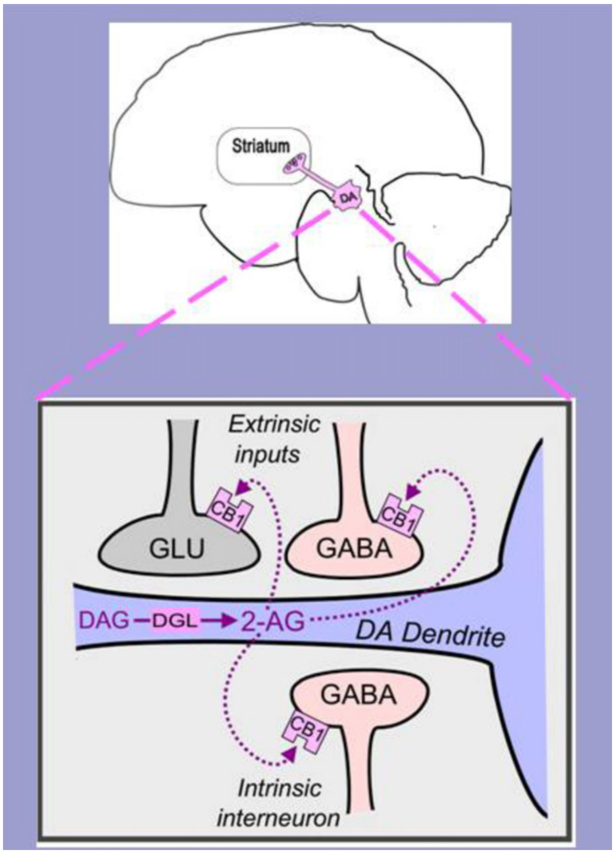

Fig. 1. The endocannabinoids "fine-tune" synaptic signalling. GABA and glutamate modulate the excitability of midbrain dopamine neurons and prefrontal cortical pyramidal cells. These are influenced by endocannabinoids via CB_1 receptors. THC is a CB_1 agonist and appears to switch off inhibitory inputs to dopamine neurons.

The endocannabinoids are involved in the regulation of cognitive functions in neuronal circuits of the cortex, memory in hippocampal neurons and emotions in neurons of the amygdala. The terminal fields of striatal projection neurons contain the highest densities of CB_1 receptors, implicating the endocannabinoid system in the modulation of motor activity. Cannabinoid agonists also influence the central processing of pain by interacting with CB_1 receptors in periaqueductal grey matter, the medulla and spinal trigeminal nucleus. Moreover they are involved in the reinforcing effects of substances of abuse in the mesolimbic system (Di Marzo et al., 2004; Piomelli, 2003).

THC is a cannabinoid agonist (Pertwee, 2008), and consequently repeated use of cannabis produces a prolonged and excessive stimulation of the CB_1 receptor and disrupts the system (Murray et al., 2007). The overstimulation of CB_1 receptor in the hippocampus, the cerebellum, the basal ganglia and neocortex is responsible for many of the cognitive and motor effects of THC, while its stimulation in peripheral nerve fibres, the dorsal root ganglion, the spinal dorsal horn and the peri-aquaductal grey matter accounts for its analgesic properties (Murray et al., 2007; Di Marzo et al., 2004). It is postulated that overstimulation of the CB_1 receptor on GABAergic and glutamatergic terminals modulating dopaminergic projection firing from the brain stem to the striatum may play an important role in the genesis of THC-induced psychosis (Morrison and Murray, 2009).

Although cannabis is widely considered to be a safe drug taken for its pleasurable effects of relaxation and euphoria, there are several, specific adverse effects of its use, including cognitive impairment (D'Souza et al., 2004; Sitskoorn et al., 2004), anxiety attacks and paranoia (Ames, 1958), and as we will now discuss, a risk of developing psychosis (Moore et al., 2007).

3. Is there a link between cannabis use and schizophrenia? Evidence from epidemiological studies

It has long been accepted that cannabis intoxication can lead to transient psychotic episodes (Mathers and Ghodse, 1992; Negrete et al., 1986; Thornicroft, 1990). However, from the 1990s onward, reports started to appear that patients suffering from schizophrenia are more likely to use cannabis than the general population (Thornicroft, 1990) and that continued cannabis use is associated with poor outcome in those with existing psychotic illness (Linszen et al., 1994; Grech et al., 2005). Furthermore, individuals who are predisposed to the development of psychosis seem at increased risk to the effects of cannabis (Verdoux et al., 2003). Of course such reports cannot answer the question of whether cannabis use caused the psychosis in the first place. Such a question can only be addressed by longitudinal studies in the general population. A number of studies of this type exist but it is important to observe that they use different diagnostic criteria: some refer to schizophrenia/psychosis using DSM-IV criteria, whereas others take DSM-IV schizophreniform disorder into consideration or treat the presence of psychotic symptoms in more general terms.

The first longitudinal study was a cohort study of 45,570 Swedish conscripts who were followed up after 15 years (Andreasson et al., 1987). Those who had smoked cannabis by the age of conscription had double the risk of developing schizophrenia in the ensuing 15 years (adjusted OR = 2.3, 95% CI = 1.0–5.3). These findings were confirmed in a further follow-up of the cohort after 27 years. Moreover a dose–response relationship was observed: heavy cannabis users were six times more likely than non-users to subsequently receive a diagnosis of schizophrenia (Zammit et al., 2002).

Between 2002 and 2007, additional studies were published which substantiated the findings of the Swedish Army Study. For instance, a population-based prospective study in the Netherlands (Van Os et al., 2002) examined the effect of cannabis use on self-reported psychotic symptoms among 4045 psychosis-free people as well as 59 subjects with a baseline diagnosis of psychotic disorder who were assessed at baseline and then followed-up 1 year later, and again 3 years after the baseline assessment. Individuals using cannabis at baseline were nearly three times (adjusted OR = 2.8, 95% CI = 1.2–6.5) more likely to manifest psychotic symptoms at follow-up with a dose–response relationship between exposure load and psychosis outcome. A baseline lifetime history of cannabis use was a stronger predictor of psychosis outcome than was use over the follow-up period and use of other drugs. Moreover the difference in risk of psychosis at follow-up between those who did and did not use cannabis was much stronger for those with an established vulnerability to psychosis at baseline than for those without one. Data from these and other studies are shown in Table 1.

4. What are the other adverse effects of cannabis use?

Adolescent cannabis use is associated with other adverse effects including poor social and educational performance to anxiety and affective illness.

4.1. Education

The effects of cannabis on educational attainment have been studied extensively (Compton et al., 2011; Carr et al., 2009; Larsen et al., 2006). An important investigation (Van Ours and Williams, 2009) demonstrated that uptake of cannabis before the age of 18 for males, and the age of 20 for females, leads to a reduction in their expected years of completed education, and that this reduction is greater for those who initiate earlier. This may be due to the fact that earlier initiation into cannabis use has been shown to lead to higher levels and longer duration of use (Pudney, 2004; Van Ours and Williams, 2007); the magnitude of the effect was greater for females than males.

Compton and colleagues observed that those psychotic patients who had used cannabis prior to the age of 15 years had better early adolescent social functioning than those who had not used cannabis but those who had used cannabis before the age of 18 years had poorer late adolescent academic functioning.

4.2. Anxiety and affective disorders

Patton et al. (2002) showed that cannabis use in adolescence predisposes to higher rates of depression and anxiety in young adulthood. In particular, daily use in young women predicted a more than 5-fold increase in the odds of reporting depression and anxiety, whereas weekly use resulted in a 2-fold increase. In contrast, depression and anxiety in teenagers did not predict higher cannabis use.

Similar phenomena have also been observed in animal studies. For example Bambico et al. (2010) suggested that in rats, long-term exposure to cannabinoids during adolescence induces anxiety-like and depression-like behaviour in adulthood as a possible result of serotonergic hypoactivity and noradrenergic hyperactivity.

5. Who is vulnerable to the harmful effects of cannabis and what determines who develops psychosis?

While cannabis may have severe long-term effects in some users, it is clear from the epidemiological studies already discussed that only a minority of cannabis users develop psychosis. For example, in the Swedish Army study only 3% of heavy cannabis users went on to develop schizophrenia. The low incidence of development of psychosis in cannabis users can be attributed to several factors, particularly the degree of cannabis exposure, genetic pre-

Table 1
Longitudinal studies in the general population about the role of cannabis as risk factor for schizophrenia.

Country in which the study was conducted	Study design	Number of participants	Follow up	Odd ratio (95% CI) (adjusted risk)
United States (Tien and Anthony, 1990)	Population based	4494	NA	2.4 (1.2–7.1)
Sweden (Andreasson et al., 1987; Zammit et al., 2002)	Conscript cohort	50,053	15 years	2.3 (1.0–5.3)
			27 years	3.1 (1.7–5.5)
The Netherlands (NEMESIS) (Van Os et al., 2002)	Population based	4045	3 years	2.8 (1.2–6.5)
Israel (Weiser et al., 2002)	Population based	9724	4–15 years	2.0 (1.3–3.1)
New Zealand (Christchurch) (Fergusson et al., 2003)	Birth cohort	1265	3 years	1.8 (1.2–2.6)
New Zealand (Dunedin) (Arseneault et al., 2002)	Birth cohort	1034	15 years	3.1 (0.7–13.3)
The Netherlands (Ferdinand et al., 2005)	Population based	1580	14 years	2.8 (1.79–4.43)
Germany (EDSP) (Henquet et al., 2005a)	Population based	2437	4 years	1.7 (1.1–1.5)
United Kingdom (Wiles et al., 2006)	Population based	8580	18 months	1.5 (0.55–3.94)
Greece (Stefanis et al., 2004)	Birth cohort	3500	NA	4.3 (1.0–17.9)

disposition, other environmental risk factors and the age of first cannabis use.

5.1. Degree of cannabis exposure

The amount and duration of cannabis consumption can influence the onset of psychosis (Arseneault et al., 2002; Henquet et al., 2005a). The most clear-cut demonstration of this dose effect comes from Di Forti et al. (2009) who found that cannabis users in their first episode of psychosis were more likely to have taken cannabis for longer, and every day, than healthy controls from the general population. They also noted that the psychotic patients were much more likely to have used the high potency cannabis variety "skunk" (OR = 6.8 95% CI 2.6–25.4) which has three or four times more THC than traditional marijuana or resin (Potter et al., 2008; Hardwick, 2008).

5.2. Genetic susceptibility

There may be individual predisposing genetic factors that increase vulnerability, or resilience to schizophrenia (Harrison and Weinberger, 2005). To date, most research has focussed on COMT, the gene that encodes catechol-O-methyltransferase. COMT is the key enzyme involved in the prefrontal cortex metabolism of dopamine released into synapses, and contains a G to A missense mutation that generates a valine (Val) to methionine (Met) substitution at codon 158 (Val^{158}Met), producing less enzymatic activity and slower break down of dopamine. Caspi et al. (2005) found that adolescent cannabis use was associated with a significantly greater increase in the risk of subsequent schizophreniform disorder among Val/Val individuals, a lesser increase among Val/Met individuals, and no increase in Met/Met individuals.

Val158 carriers appear to be more sensitive to the psychotic experiences and cognitive impairments following administration of the main active component of cannabis, THC (Henquet et al., 2006, 2009). This interaction between cannabis and the COMT Val^{158}Met polymorphism gene was investigated experimentally by Henquet et al. (2006) who gave 300 μg of THC per kg of body weight or a placebo to patients with psychotic disorders, relatives of patients with a psychotic disorder and healthy controls. Those with the homozygous Val genotype were more likely to develop THC-induced psychotic symptoms, but this was dependent on prior evidence of psychometric psychosis liability. In a subsequent study, Henquet et al. (2009) used the experience sampling method (ESM), to collect data on cannabis use and the occurrence of psychotic symptoms in daily life. Use of cannabis significantly increased hallucinatory experiences only in those individuals who were carriers of the Val allele and had high levels of psychometric psychosis liability. Thus the COMT Val^{158}Met genotype moderated the association between cannabis and psychotic symptoms in the flow of daily life in psychosis prone people.

In contrast, a study in psychotic patients found no evidence for a differential effect of cannabis use on psychosis risk according to variation in COMT Val^{158}Met (Zammit et al., 2007). In the same study by Zammit et al. (2007), there was no evidence of association between schizophrenia and CNR1 (OR = 0.97, 95% CI 0.82–1.13), CHRNA7 (OR = 1.07, 95% CI 0.77–1.49), or of interactions between tobacco use and CHRNA7. In short there is intriguing evidence suggesting an interaction between cannabis use and the COMT genotype in provoking psychosis. However the hypothesis remains to be adequately confirmed or refuted, and of course, individual response to cannabis use is probably moderated by a number of genes rather a single polymorphism.

In very recent research into whether genetic variation moderates the association between recent cannabis use and psychosis, Van Winkel et al. (2011) examined the interactions between cannabis use and 152 single-nucleotide polymorphisms in 42 genes in 740 unaffected siblings of 801 patients with psychosis. The authors showed that genetic variation in AKT1 may mediate effects on psychosis expression associated with cannabis use. AKT1 is a serine/threonine kinase and is a focal point for many signal-transduction pathways. Cannabinoids are able to activate the AKT1 pathway by acting on CB1 And CB2 receptors. Polymorphisms in the AKT1 gene could be involved in cannabis induced psychosis possibly through a mechanism of cannabinoid-regulated AKY1/GSK-3 signalling downstream of the dopamine D_2 receptor.

A broader survey of the genome is clearly required to move beyond associating genes, towards the identification of actual casual mechanisms underlying individual susceptibility to the harmful effects of cannabis.

5.3. Other environmental factors

Other environmental risk factors can also be important. Harley et al. (2010) in studying the effects of childhood trauma, confirmed that cannabis use and childhood trauma were independently associated with the risk of psychotic symptoms (only cannabis use: OR = 1.9, 95% CI = 0.04–16.5, $p = 0.55$; only trauma: OR = 2.6, 95% CI = 0.25–14.6, $p = 0.23$; trauma and cannabis use: OR = 20.9, 95% CI = 2.3–173.5, $p = 0.00$), but that the joint presence of these two risk factors increased the likelihood of psychotic symptoms in adolescence to a much greater extent than would be expected if each risk factor were working independently.

6. Age of starting to use cannabis

Epidemiological studies have found that the age of first exposure to cannabis may be a key factor for vulnerability to the harmful effects of cannabis (Fergusson et al., 2003; Arseneault et al., 2004; Stefanis et al., 2004; McGrath et al., 2010). Two birth cohort studies from New Zealand reported an association between age of exposure to cannabis and psychosis. The Christchurch study (Fergusson et al., 2003) which has examined the development of its participants for more than two decades, showed that individuals with cannabis dependence disorder at age 18 years had a 2-fold (adjusted OR = 1.8, 95% CI = 1.2–2.6) increased risk of psychotic symptoms compared with those without cannabis dependence. Statistical control for previous psychotic symptoms clarified the temporal sequence, ruling out the alternative explanation that psychotic symptoms cause cannabis use. The Dunedin study (Arseneault et al., 2002) showed that individuals using cannabis at the age of 15 years reported significantly more schizophreniform disorder at 26 years of age compared with non-users (OR = 4.50, 95% CI = 1.11–18.21); those who started by age 18 years showed a non-significant increase in risk. This was the only study to demonstrate a specific temporal link even after taking into account childhood psychotic symptoms antedating cannabis use (self-reported psychotic symptoms at age 11 years). Cannabis use was associated with an increased risk of schizophreniform disorder even after controlling for psychotic symptoms preceding the onset of cannabis use (OR = 3.12 95% CI 0.73–13.29) though the adjusted OR just failed to reach significance, probably due to lack of statistical power.

Recently another prospective study has been published based on the Mater-University Study of Pregnancy conducted on 7223 women in Brisbane, Australia (McGrath et al., 2010). 3801 of their children were assessed at 21 years of age for cannabis use (retrospectively) and psychosis-related outcomes. Among these there were 228 sibling pairs. Longer duration since first cannabis use was associated with multiple psychosis-related outcomes in young adults. Furthermore this association persisted when examined in sibling pairs, thus reducing the likelihood that the association was due to unmeasured shared genetic and/or environmental influences. Compared with those who had never used cannabis, young adults who had 6 or more years since first use of cannabis (i.e. who commenced use when around 15 years or younger) were twice as likely to develop a non-affective psychosis.

Schubart et al. (2010) studied 18.000 Dutch adolescents by administering an online version of the Community Assessment of Psychic Experiences (CAPE). They investigated the association between the initial age of cannabis use and the occurrence of psychiatric experiences in positive, negative and depressive dimensions. Cannabis use at age 12 years was strongly associated with a score in the top 10% on psychotic experiences – OR 3.1, 95% CI 2.1–4.3. Schubart et al. (2011) particularly underlined that early (under 12 years of age) and heavy cannabis use (>25 euro/week) were each strongly and independently associated with an increased likelihood of psychiatric hospitalizations.

Depressive symptoms were not found to be associated with a young initial age of cannabis use (Schubart et al., 2010; Stefanis et al., 2004).

Henquet et al. (2005a) carried out a prospective study of 2437 young Germans (aged 14–24 years) with a 4-year follow-up. Cannabis use moderately increased the risk of psychotic symptoms in young people (OR = 1.7, 95% CI = 1.1–1.5) and again there was a dose–response relationship with increasing frequency of cannabis use. Cannabis use had a much stronger effect in those with psychosis vulnerability at baseline but predisposition for psychosis at baseline did not significantly predict cannabis use at follow-up, thus refuting the self-medication hypothesis. Meta-analyses of prospective studies considering relationship between cannabis and psychosis were carried out by Henquet et al. (2005b) who found a pooled adjusted OR = 2.1 (95% CI = 1.7–2.5) and by Moore et al. (2007) who reported a pooled OR = 1.41 (95% CI = 1.20–1.65). Subsequent studies by Stefanis et al. (2004) and Konings et al. (2008) also reported an association between first time cannabis use in adolescence and lifetime psychotic symptoms in Western and non-Western populations respectively.

Possible explanations for the greater risk in those who start cannabis use early include:

- This association reflects an increased propensity of young people with psychotic experiences to commence cannabis use (reverse causality);
- Higher cumulative exposure to cannabis of early users;
- Increased vulnerability to THC during critical phases of brain maturation, such as in early puberty, is reflected in a specific association between psychotic experiences and young initial age of THC exposure.

Much research has focussed on this last possibility: i.e. that adolescence may be a vulnerable period for an individual exposed to cannabis. The brain is more vulnerable to the harmful effects of psychoactive drugs in the young, given that neuronal networks are still under development (Compas et al., 1995; Romeo, 2003). Throughout adolescence, a considerable degree of neuronal rearrangement occurs, including synaptic remodelling and enhanced connectivity (Giedd et al., 1999). Regions of the brain have unique developmental courses, with key regions such as the cortex and hippocampus developing later than other areas, accompanied by changes in many neurotransmitter systems (Andersen, 2003). The endogenous target for cannabis, the endocannabinoid system, and other systems associated with an increased vulnerability to behavioural and psychiatric disorders undergo considerable development during adolescence (Fernandez-Ruiz et al., 2000; Schneider, 2008; Spear, 2009).

Key elements of the endocannabinoid system are present early in development, with functional CB1 receptors detected from gestational day 11–14 in rodents (Berrendero et al., 1998). The distribution and number of CB1 receptors in rodents also differs in the developing brain compared with the adult brain (Romero et al., 1997; Berrendero et al., 1999). During adolescence, levels of endocannabinoids and cannabinoid receptors increase, peaking at puberty (Schneider, 2008). The levels of endocannabinoids 2-AG and anandamide change through development, 2-AG levels peak early in postnatal development and are much higher than anandamide but anandamide levels increase following birth, peaking during adolescence (Berrendero et al., 1999). In addition to its own development, the endocannabinoid system is thought to play a functional role in the maturation of other neurotransmitter systems in both human and rodent brains (Fernandez-Ruiz et al., 2000). Developmental processes such as cell proliferation, migration and differentiation in the brain are influenced by the endocannabinoid system (Malone et al., 2010). Exposure to cannabinoids early in life influences the development of many neurotransmitter systems in animal models including the glutamate (Suárez et al., 2004), catecholamine (García-Gil et al., 1997) and serotonergic (Molina-Holgado et al., 1996) systems. Given the presence of the endocannabinoid system early in development and that this system exhibits continued dynamic changes through to adolescence, exposure to cannabis during critical developmental periods could therefore impact on the maturation of this system and other key neurotransmitter systems.

Studies in humans and other mammalian species indicate that core elements of the dopaminergic system such as synthesis and breakdown enzymes, levels of dopamine and its target receptors increase over the adolescent period (Seeman et al., 1987; Pitts et al., 1990). Significant changes in the level and timing of release of hormones in the hypothalamic–pituitary–adrenal (HPA) axis also occur during adolescence, particularly during puberty, in response to stress (Dahl and Gunnar, 2009; Spear, 2009). Both these systems are known to interact with the endocannabinoid system (French et al., 1997; Freund et al., 2003; Rodriguez de Fonseca et al., 1997).

However, there has been little human research on the effects of cannabis exposure during childhood or adolescence when key areas of the brain are still developing. The majority of work into the effects of cannabis during development has focused on prenatal and perinatal exposure periods (Viveros et al., 2005). Two longitudinal cohort studies reported an association between heavy cannabis use during pregnancy and subsequent behavioural problems and impaired executive function in the prenatally exposed children (Fried et al., 1998; Leech et al., 1999). Rodent studies have shown that prenatal (Navarro et al., 1995) and perinatal (Campolongo et al., 2007) exposure to THC or synthetic cannabinoid compounds caused long-lasting changes in a wide range of behaviours including social and sexual behaviours, emotional reactivity and cognition (for review, see Trezza et al., 2008).

7. Evidence from studies of immature animals

As we have noted, epidemiological studies suggest that cannabis use during adolescence confers an increased risk of developing schizophrenia and related disorders. However, epidemiological studies can only establish an association between the two, and this does not necessarily indicate a causal relationship although a recent study has provided evidence against the self-medication hypothesis (Fergusson et al., 2005). While human studies are valuable in the identification of psychiatric associations with cannabis, it is more difficult to determine whether exposure to cannabis during adolescence confers an increased vulnerability to its harmful effects and assess the underlying pathophysiological aspects of this interaction. Animal models and experimental studies on the active constituents of cannabis attempt to bridge this gap in our understanding.

Animal studies on the effects of adolescent exposure to cannabis are sparse but there are a few key studies that support the human research, providing direct evidence for a causal link between cannabis, developmental and behavioural problems (Trezza et al., 2008). Early experiments on the effects of exposure to a cannabis extract suggested that immature rats were more sensitive to its cognitive effects than mature rats (Stiglick and Kalant, 1982, 1985). In a subsequent key experiment, Schneider and Koch (2003) demonstrated that chronic administration of the synthetic cannabinoid agonist WIN 55,212-2 during adolescence, but not adulthood, resulted in recognition memory impairments, sensory motor gating deficits and anhedonia. Some of these findings were confirmed in separate studies using another synthetic cannabinoid agonist CP 55,940 (O'Shea et al., 2004) and THC (Quinn et al., 2008), which found memory and social interaction deficits following adolescent but not adult exposure. However, a study that exposed juveniles to CP 55,940 found reduced anxiety in the rats when tested as adults (Biscaia et al., 2003).

There may be specificity in the cognitive deficits seen following cannabinoid exposure as spatial learning was not affected in adolescent rats chronically exposed to THC (Cha et al., 2006). Studies by Schneider and colleagues (Schneider and Koch, 2003; Schneider et al., 2005; Schneider and Koch, 2005, 2007) attempted to define the developmental period that is most sensitive to the effects of cannabinoids on memory and found that exposure to WIN 55,212-2 during puberty (late adolescence) was more impairing than exposure during prepuberty (early adolescence).

Furthermore, it appears that the detrimental effects of acute cannabinoids on behaviour are greater during puberty compared to adulthood (Schneider et al., 2008). Interestingly, development of the endocannabinoid system appears to peak during the pubertal period (Rodriguez de Fonseca et al., 1993; Wenger et al., 2002). Puberty thus appears to be a critical period for cannabis exposure.

While making the first step towards elucidating the impact of cannabis exposure, the majority of studies to date have only used synthetic cannabinoids that are full agonists at the cannabinoid receptor (CB_1) – THC is a low efficacy ligand that acts as a partial agonist, at least in glutamate axon terminals in the hippocampus (Pertwee, 2008; Laarisa et al., 2010) – or used low/moderate doses of THC, or focused on one developmental period in adolescence. Furthermore, an important element missing from the majority of these studies is the pharmacokinetic analysis of cannabinoid levels in animals following repeated administration. Several studies used an incremental or irregular dosing regimen (Schneider and Koch, 2003) and so metabolic differences between the exposure periods cannot be excluded. Only one study measured THC levels following exposure but the measurements were limited to confirming that animals were drug-free and following a single acute injection (Quinn et al., 2008). Pharmacokinetic studies will not only address whether metabolic factors play a role in determining individual sensitivity to cannabis but will also provide valuable information on whether higher concentrations of THC increase the risk potential which will be particularly relevant in the light of increasing levels of THC in street preparations of cannabis.

In animal models an interesting interaction between cannabis exposure and genotype has been observed. Boucher et al. (2007a) investigated whether dysfunction in the Nrg1 gene modulates the behavioural effects of THC. Male heterozygous neuregulin 1 transmembrane domain (Nrg1 HET) mice were more sensitive to the acute effects of THC in an array of different behaviours including those that model symptoms of schizophrenia, particularly under stressful conditions (Boucher et al., 2007b). A subsequent study (Long et al., 2010) on female Nrg1 HET mice did not confirm the results: female Nrg1 HET mice showed similar or reduced sensitivity to the acute effects of THC compared with wild type controls. These data suggest an interaction of the cannabinoid system and neuregulin 1 signalling and indicates that it is possible that manipulation of schizophrenia risk genes has sex-specific effects on how cannabis impacts on schizophrenia-related behavioural domains.

Long-lasting effects of THC on exploration, spatial working memory and anxiety were seen in COMT knockout mice exposed to THC during adolescence, suggesting a specific role of COMT in conferring vulnerability to cannabis during development (O'Tuathaigh et al., 2010). However, to date, there are no studies on the chronic effects of cannabis or THC on Cnr1 mutant mice.

8. The effects of cannabis on neuropsychology and brain structure

Although there have only been a few studies on the effects of adolescent cannabis use on neurocognitive function, there is evidence for learning and memory deficits and reduced attention (Millsaps et al., 1994; Tapert et al., 2002; Fried et al., 2005) that persist even after several weeks of abstinence (Schwartz et al., 1989). A reduced ability to process and regulate emotions also has been reported in cannabis dependent adolescents and young adults (Dorard et al., 2008a,b; Troisi et al., 1998). The study by Dorard et al. (2008b) found that cannabis dependence in young users was related to a range of emotional problems including severe psychological distress, anxiety and anhedonia. Alexithymia, or a reduced ability to understand or describe emotions, was measured in 88 young cannabis abusers by Troisi et al. (1998). The prevalence of alexithymia was increased in the young cannabis users to about twice the level reported in a sample of general adolescents (Säkkinen et al., 2007). Another recent study also reported elevated alexithymia rates in young cannabis abusers (Dorard et al., 2008a).

A surprise has come from studies conducted with magnetic resonance imaging (Arnone et al., 2008; Rais et al., 2008; Yucel et al., 2008) which have suggested that heavy cannabis use may modify brain structure. Yucel et al. (2008) studied users who had taken more than 5 joints daily for more than 10 years, and compared them with non-users. The heavy cannabis users had bilaterally reduced hippocampal and amygdala volumes with greater effect in the former. Left hemisphere hippocampal volume was inversely associated with cumulative exposure to cannabis and with sub-threshold positive psychotic symptoms. Hippocampal abnormalities in schizophrenia are more prominent in the left hemisphere (Petty, 1999). Rais et al. (2008) followed up first-episode patients with schizophrenia. Those who continued to use cannabis showed a more pronounced grey matter loss together with lateral and third ventricle enlargement over the 5-year follow-up period than both healthy subjects and non-using patients with schizophrenia.

In another imaging study, long-term use of cannabis during adolescence was associated with gyrification abnormalities in the cortex, suggesting that early cannabis use affected normal neurodevelopment (Mata et al., 2010). Arnone et al. (2008) also examined the effects of prolonged heavy cannabis use in 11 subjects and a similar number of non-users, using diffusion tensor imaging (DTI) which can examine white matter tracts. They observed a significant increase in diffusivity in cannabis users relative to controls in the region of the corpus callosum where white matter passes between the prefrontal lobes. This implies that cannabis exerts an effect on white matter structural integrity. However, a study of schizophrenic patients using DTI did not see a relationship between white matter abnormalities in schizophrenic patients and adolescent-onset cannabis use (Dekker et al., 2010).

A recent review provides further interesting data about the effects of cannabis on brain function (Martin-Santos et al., 2010). Functional neuroimaging studies suggest that resting global, prefrontal and anterior cingulated cortex blood flow are lower in cannabis users than in controls. Evidence of effects of THC on activity in these areas is consistent with the relatively high concentration of CB_1 receptors in the prefrontal and cingulate cortex. Moreover functional imaging studies that examined brain activity after the acute experimental administration of THC or marijuana cigarettes showed an increased prefrontal, insular and anterior cingulated activity both during the resting state and during cognitive tasks. Studies on abstinent adolescent cannabis users have found evidence for altered fMRI activity related to a spatial working memory task after both short (8 days) and long (28 days) periods of abstinence (Tapert et al., 2007; Schweinsburg et al., 2005, 2008). This would suggest that cannabis use during adolescence leads to long-lasting effects on neurodevelopment and cognitive performance.

In one fMRI study, Bhattacharyya et al. (2009) investigated the effect of THC on brain function as the subjects performed various verbal learning tasks. THC modulated mediotemporal and anterocingulate as well as medioprefrontal cortex function in the context of learning, and appeared to induce psychotic symptoms by modulating ventrostriatal activity. The effect on hippocampal activation is consistent with the evidence that the CB_1 receptor is highly expressed there and with the well known detrimental effect of cannabis on memory function. Evidence that THC influences activation in the striatum (Bhattacharyya et al., 2009) is consistent with a study by Bossong et al. (2009) who used a dopamine D_2/D_3 receptor tracer (raclopride) and positron emission tomography, to examine striatal synaptic dopamine release. The tracer binding was significantly reduced in the ventral striatum and the precommisural dorsal putamen after inhalation of THC compared to placebo, implying an increased release of endogenous dopamine in these regions. The ability of THC to induce dopamine release in the striatum suggests that THC shares addictive properties with other drugs of abuse, as dopamine has a central role in their rewarding effects, but the increase was modest compare to that obtained with other drugs like cocaine, nicotine or alcohol. This modest effect on dopamine release in the striatum might be explained by the indirect effects of THC through cannabinoid CB_1 receptors on glutamate and GABA neurons in the nucleus accumbens and the ventral tegmental area.

The finding of THC-induced release of dopamine in the striatum suggests that human striatal dopamine release is partly under the control of the endogenous cannabinoid system, and could explain how cannabis use contributes to the development and pathophysiology of schizophrenia (Bossong et al., 2009). However, another PET study by Stokes et al. (2009) failed to replicate excess dopamine in the striatum following oral THC. The dose was not large in the latter study so whether or not THC provokes a modest alteration in the striatal dopamine system remains unclear.

Bossong and Niesink (2010) reviewing the available literature regarding the relationship between adolescent brain maturation and cannabis use, found strong evidence that exposure to cannabis during adolescence results in disturbance of the experience-driven refinement of certain local neural circuits within the prefrontal cortex. In particular, this disturbance occurs as an interaction between THC and the CB1 receptor involved in the control of GABA and glutamate release, which results in an alteration in the glutamatergic pathway possibly leading to an anomaly of synaptic connections.

9. Conclusions

There is now a large body of epidemiological evidence that cannabis use does indeed play a causal role in the aetiology of some psychotic illnesses (see Table 1). However, cannabis use is clearly not an essential or sufficient risk factor as not all schizophrenic patients have used cannabis and the majority of cannabis users do not develop schizophrenia. While cannabis does not have long-term adverse effects for the majority of users, it is clear from studies of psychosis that some individuals are more vulnerable to its effects that others, and that the degree of cannabis exposure and age of first use amplify the harmful effects of cannabis. The evidence for the impact of cannabis potency on the magnitude of risk for psychosis has been found in all the studies which have collected data on degree of exposure to cannabis (Andreasson et al., 1987; Henquet et al., 2005a; Van Os et al., 2002; Zammit et al., 2002), most clearly demonstrated in the study of Di Forti et al. (2009).

Regarding age of first use of cannabis, a number of studies in both Western and non-Western populations have found that first time cannabis use during adolescence is associated with an increased risk for the psychotic symptoms in adulthood (Fergusson et al., 2003; Arseneault et al., 2004; Stefanis et al., 2004; Konings et al., 2008). Prospective studies suggest that adolescent-onset cannabis use may carry a higher risk because the brain is still developing (Pope et al., 2003), and that subjects with an established vulnerability to psychosis (Van Os et al., 2002; Verdoux et al., 2003) are more at risk. A developmental link between cannabis and increased vulnerability to behavioural and cognitive impairments is supported by animal research (Trezza et al., 2008). There is also some tentative evidence for individual predisposing genetic factors that increase vulnerability, or resilience, to the effects of cannabis (Henquet et al., 2006).

Research into the underlying mechanism(s) that may be mediating the link between adolescent cannabis use and psychotic illness is still at an early stage. However, key processes such as neurotransmitter system maturation are influenced by the endocannabinoid system which itself is still undergoing maturation during adolescence (Fernandez-Ruiz et al., 2000). Brain imaging studies hint at long-lasting neurodevelopmental effects of cannabis as use during adolescence led to altered white matter structural integrity (Arnone et al., 2008) and altered fMRI activity related to spatial working memory processes (Schweinsburg et al., 2005, 2008).

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