Pathways to Psychosis in Cannabis Abuse

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Abstract

Cannabis has been implicated as a risk factor for the development of schizophrenia, but the exact biological mechanisms remain unclear. In this review, we attempt to understand the neurobiological pathways that link cannabis use to schizophrenia. This has been an area of great debate; despite similarities between cannabis users and schizophrenia patients, the evidence is not sufficient to establish cause-and-effect. There have been advances in the understanding of the mechanisms of cannabis dependence as well as the role of the cannabinoid system in the development of psychosis and schizophrenia. The neurobiological mechanisms associated with the development of psychosis and effects from cannabis use may be similar but remain elusive. In order to better understand these associations, this paper will show common neurobiological and neuroanatomical changes as well as common cognitive dysfunction in cannabis users and patients of schizophrenia. We conclude that epidemiologic evidence highlights potential causal links; however, neurobiological evidence for causality remains weak.

Key Words: Psychosis, Cannabis, Cannabinoid System, Schizophrenia, Transition to Psychosis

Introduction

Cannabis use is common amongst individuals who are Ultra High Risk (UHR) and those who have already developed psychosis. It has also been reported that 15% of cannabis users who do not fit into these two categories experience acute psychotic symptoms (1). Nevertheless, the question still remains whether or not cannabis use is a factor responsible for the development of psychosis in any persons, or if its abuse leads to psychosis in individuals already vulnerable to becoming psychotic. This paper will explore this issue and suggest possible directions of research on this subject.

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Submitted: January 30, 2012; Revised: August 8, 2012; Accepted: September 17, 2012

In the last few years, a plausible model has been proposed in which a number of factors are considered as causes for the development of schizophrenia (2, 3). This model emphasizes the interaction between genetic and environmental variables, and their influence on neurodevelopment (4). From an environmental perspective, there is growing evidence that suggests both early and heavy cannabis use increases the risk for the development of psychotic disorders such as schizophrenia (5, 6). The effect of cannabis is dose dependent and especially true for adolescents (7). Also observed is that individuals who have exhibited a first episode of psychosis (FEP) or are in the UHR population and those who are at an increased risk for developing psychosis are more susceptible to cannabis abuse and neuropsychological changes (8-10).

Many explanations describing the risk of cannabis stems from neurobiological and epigenetic research; however, studies in the field of neurochemistry, imaging, cognition and genetics offer possible alternative mechanisms (11, 12). In spite of these explanations, it is not clear how these chang-

es are interlinked to produce psychotic symptoms, and the small number of longitudinal follow-up studies available does not allow for a greater understanding of the long-term neurological changes. Nevertheless, one factor which appears to be involved in cannabis-related psychosis is the cannabinoid system, whose primary psychoactive ligand is delta-9-tetrahydrocannabinol (THC). The other is neuronal development as shown by ventricular dilation, suggesting that neuronal systems are affected. Studies investigating the acute effects of cannabis, cannabis users, and schizophrenics that do and do not abuse cannabis have provided exciting information (13-15). Also, both human and animal studies have contributed to this body of information, lending itself to a comprehensive overview of the development of psychosis.

Early onset of cannabis use has been found to be related to increased risk of development of schizophrenia later in life, and leads to impairments in cognitive processes reliant on the circuitry of the dorsolateral prefrontal cortex . . .

Method

We carried out a selective, unstructured review from the electronic database PubMed using key words of cannabis and psychosis, cannabis, imaging, cannabis THC, cannabis psychosis, and cannabis schizophrenia. We selected relevant publications explaining the relationship between cannabis and psychosis. This selection was based upon the contents of the abstracts. Content analysis was carried out on the selected papers and four main topics emerged: neurobiology, genetics, neuroanatomy, and cognitive dysfunction.

Neurobiology

THC, the main metabolite of cannabis, is associated with transient exacerbation of core psychotic and cognitive deficits in patients already diagnosed with schizophrenia (16). THC might differentially affect schizophrenia patients relative to control subjects; however, it is not yet confirmed if enhanced sensitivity to the cognitive effects of THC affects neuronal cannabinoid receptors (8). THC easily reaches the brain where it stimulates cannabinoid receptor type 1 (CB1) receptors and their ubiquity underlies a wide variety of effects. Neurocognitive studies suggest that THC inhaled from smoking cannabis is linearly associated with a slower response time in all tasks (simple reaction time, visuospatial selective attention, sustained attention, divided attention and short-term memory tasks) and motor control impairment in motor control tasks (17). Similarly, the number of errors associated with short-term memory and sustained attention tasks increases significantly with dose. Interestingly, some subjects show no impairment in motor control even at higher levels of THC serum concentration (18). The endocannabinoid system modulates neurotransmission at inhibitory and excitatory synapses in brain regions relevant to the regulation of pain, emotion, motivation, and cognition (19). As such, this system represents a critical player in the maintenance and modulation of synaptic plasticity (20). During frequent cannabis use, a series of poorly understood neuroplastic changes occur which can lead to the development of dependence. Early onset of cannabis use has been found to be related to increased risk of development of schizophrenia later in life, and leads to impairments in cognitive processes reliant on the circuitry of the dorsolateral prefrontal cortex (DLPFC) (21, 22). Animal model studies show that prenatal cannabinoid exposure has long-term consequences on behavior and mental health (23). Prenatal as well as developmental exposure to cannabinoids induces subtle neurofunctional alterations in the offspring (7, 24).

Recent evidence suggests that the mesocorticolimbic neuronal circuits remain vulnerable to dysfunction later in life and, thus, could be sensitive to developmental events and environmental stressors that can influence the onset and course of neuropsychiatric disorders (25). THC and cannabinoid agonists enhance striatal and mesocorticolimbic dopamine levels, and affect the maturation of the dopamine system, which directly regulates motor function, cognition, motivation, and emotional processes (26, 27).

Genetics

There is suggestion of cannabis dependence being a heritable one, which has been partly explained by twin studies and epigenetic involving gene-gene and gene-environment interactions.

Recent studies indicate the involvement of regions on chromosomes 1, 3, 4, 9, 14, 17 and 18, which harbor candidates of predicted biological relevance (28, 29). Twin studies have also reported evidence for both genetic and environmental influences on vulnerability, but due to considerable variation in the results it is difficult to draw clear conclusions regarding the relative magnitude of these influences. Studies of systematic literature search show that vulnerability to "cannabis use initiation" as well as "problematic use" was influenced significantly by both shared and unshared environments (30-32). The Val158Met polymorphism of the catechol-O-methyltransferase (COMT) gene, which is involved in dopamine regulation and related to negative symptoms,

has been previously thought to interact with cannabis use in the modulation of risk of psychosis (33). The cannabis-COMT interaction has a significant effect on both duration of untreated psychosis and age of onset. The effects of THC on cognition and psychosis have been shown to be moderated by COMT genotype; the Val158Met polymorphism moderated sensitivity to the effect of THC on psychotic symptoms (12). Genetic variants of the CB1 have also been linked to differential risk for substance abuse in patients of schizophrenia (11). One implication of these findings could be a common genetic pathway through the cannabinoid system for schizophrenia and substance abuse.

There are several endophenotypes of cannabis use: for example, cannabis craving and cannabis withdrawal types, which have different mechanisms underlying expression of genetic material. Some of the chromosomes involved in these endophenotypes have been identified.

Suppression of "delay effect" in gene-environment interactions leads to increased chances of vulnerability for individuals for cannabis abuse. The changes at early age may be responsible for early-onset psychosis.

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Neuroanatomy

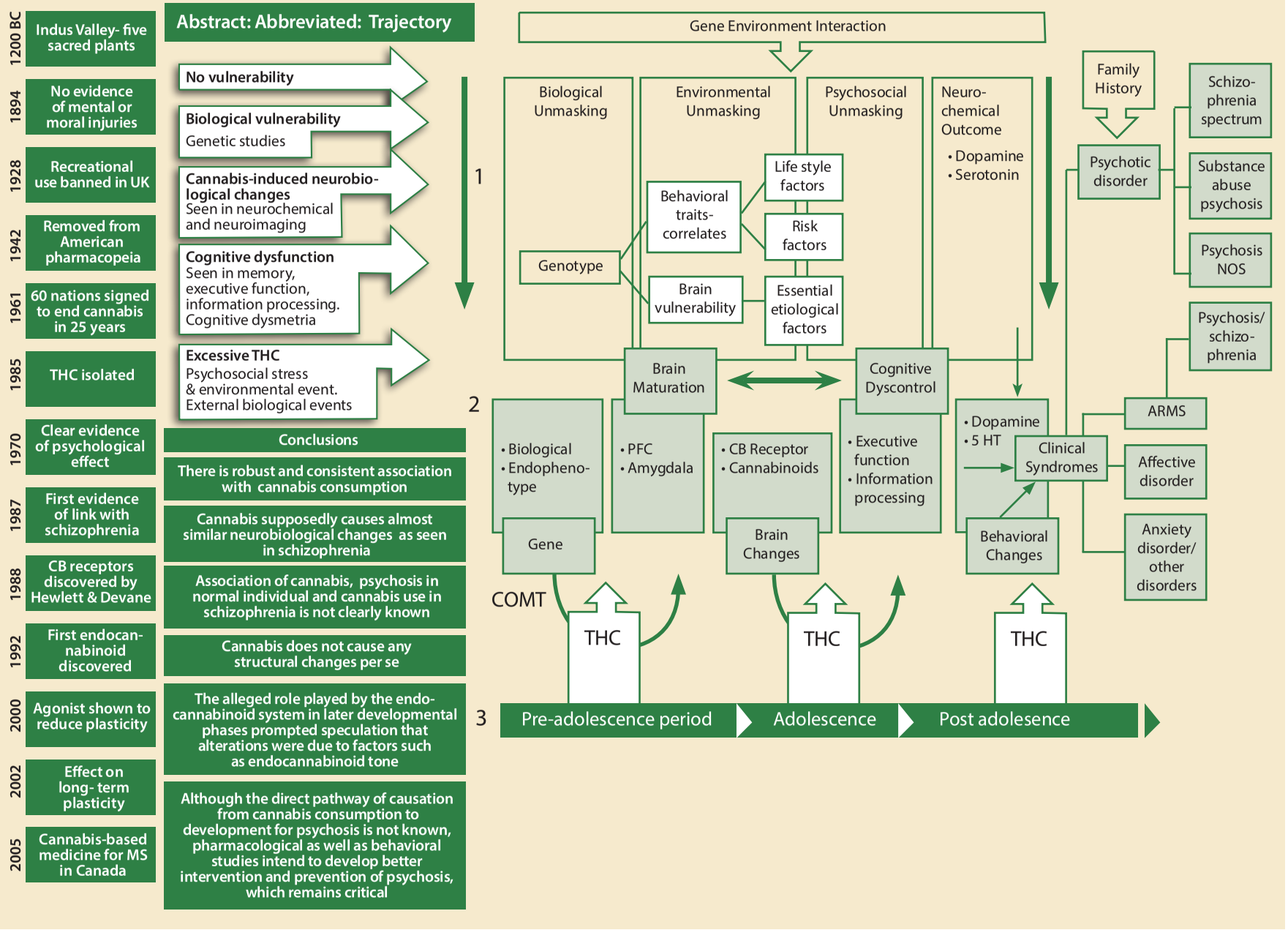
A number of studies has been carried out on patients consuming cannabis with and without psychosis in order to find possible anatomical or structural changes, as well as changes occurring in physiological activity. These studies have also helped in confirming neurochemical changes occurring at receptor sites and neurotransmissions. Long-term users who started regular use in early adolescence have exhibited cerebral atrophy as well as a reduction in gray matter volume (34). Functional neuroimaging studies have reported increases in neural activity in regions that may be related to cannabis intoxication or mood altering effects such as the orbital and medial frontal lobes, insula cortex, and anterior cingulate cortex (35). There have also been observed decreases in activity of regions related with cognitive functions during acute intoxication resulting in impairments (36). These functional studies suggest that resting global and prefrontal blood flow is lower in cannabis users than in controls, which is consistent with the observed impairments. Modulation of global and prefrontal metabolism is reduced both during the resting state and after the administration of THC or marijuana, but only minimal evidence of major effects of cannabis on brain structure has been reported (37). Studies of acute administration of THC or marijuana report increased resting activity and activation of the frontal and anterior cingulate cortex during cognitive tasks (38). The anterior cingulate and amygdala play key roles in the inhibition of impulsive behavior and affective regulation, and studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have demonstrated changes within these regions in marijuana smokers (39).

A family history of schizophrenia may render the brain particularly sensitive to the risk-modifying effects of these substances. Furthermore, light users of cannabis have lower basal brain-derived neurotropin factor (BDNF) levels (40), which have been implicated in the development of psychosis in general. THC produced psychotomimetic effects, perceptual alterations, and spatial memory impairments; however, the results of several reviews regarding connection between cannabis and cognition remain inconclusive in subjects who go on to develop psychosis (41, 42). It is likely that THC changes the neuroprotection of neuron, thereby increasing the vulnerability for psychosis, much in the same way as postulated for schizophrenia.

Cognitive Dysfunction

Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia. The theoretical and clinical significance of further research in this field is enhancing our understanding of underlying pathophysiology and is improving the provision of treatments for substance use and mental illness. Heavy cannabis use during adolescence has been shown to interfere with normal brain development and to result in diffusion tensor imaging results similar to individuals with schizophrenia (43). An interesting issue is that adolescent cannabis use, childhood trauma and general predictors of later psychosis are intricately related. In fact, a recent study has shown that there is a greater incidence of childhood sexual abuse in the schizophrenic population (44). Of particular interest is that the risk for schizophrenia increases with urban birth and/or upbringing, especially among males (45). The mechanism of association is unclear but may be related to biological, social/environmental factors or both, and may have considerable impact before psychotic symptoms manifest. Several psychosocial and environmental factors have synergetic effects on genetic vulnerability in light of gene-environment interactions; some of these factors are: urbanicity in developing countries, cultural variables and geographical location. These factors together suggest a relationship between urban city and neural maldevelopment (46).

Figure 1 **Model of the Pathways Linking Cannabis Use and Psychosis**



ARMS=at risk mental state, THC=tetrahydrocannabidol, PFC=prefrontal cortex, COMT=catechol-O-methyltransferase, 1, 2 and 3 different levels biological events

Summary

It appears that cannabis does not cause any structural changes per se, but deficits in areas of the brain responsible for memory and emotion do show some changes. Despite these findings, it is still not known if these changes are transitory or permanent, and whether or not they contribute to the pathophysiology of schizophrenia. The mystery of the neural effects in cannabis abusers developing schizophrenia remains in spite of these advancements. Many studies now show a robust and consistent association between cannabis consumption and the development of psychosis, but this may not be the case for schizophrenia specifically. Our better understanding of the biological correlates of cannabis use allows for the proposal of a plausible hypothetical model, based notably on possible interactions between cannabis and dopaminergic neurotransmission (47).

Many studies now show a robust and consistent association between cannabis consumption and the development of psychosis, but this may not be the case for schizophrenia specifically.

Schizophrenia is increasingly viewed as a subtle neurodevelopmental disorder characterized by disrupted brain connectivity and altered circuitries (48). It is clear now that periods of brain development are particularly important in adolescence. It has been suggested that the illness may result from either an early (pre- or perinatal) static brain lesion with a long latency or a late brain disturbance of limited duration and short latency during adolescence (49). Therefore, the alleged role played by the endocannabinoid system in later developmental phase—such as the adolescent one—prompted speculation that alterations in the endocannabinoid tone, induced by cannabis consumption during the adolescent developmental window, might represent a risk factor for developing schizophrenia (50). The data so far do not provide a reason to explain why schizophrenia patients use or misuse cannabis. Furthermore, THC might differentially affect schizophrenia patients relative to control subjects. Finally, the enhanced sensitivity to the cognitive effects of THC warrants further investigation into whether neural cannabinoid receptor dysfunction contributes to the pathophysiology of the cognitive deficits associated with schizophrenia (51).

Recent studies suggest that cannabinoids such as CB1 have a pharmacological profile similar to that of atypical antipsychotic drugs (52). The mechanisms by which cannabinoids produce transient psychotic symptoms, while unclear, may involve dopamine, GABA, and glutamate neurotransmission; however, only a very small proportion of the general population exposed to cannabinoids develop a psychotic illness. It is likely that cannabis exposure is one variable that interacts with other factors to "cause" schizophrenia or other psychotic disorders, but is neither necessary nor sufficient for the development of psychosis. Nevertheless, in the absence of known causes of schizophrenia, the role of component causes such as cannabis use is important and warrants further study. Dose, duration of exposure and age of first exposure to cannabinoids may be important factors. The genetic factors that interact with cannabinoid exposure to amplify the risk of a psychotic disorder are beginning to be understood. In this connection, novel hypotheses—including the role of cannabinoids on neurodevelopmental processes relevant to psychotic disorders—are being studied (53). Figure 1 provides a model of the many pathways and risk factors linking cannabis and psychosis as discussed throughout this review.

In conclusion, there have been significant advances in the understanding of cannabis with respect to transition to psychosis in vulnerable individuals that is similar to what has been reported in schizophrenia. Although the direct pathway of causation from cannabis consumption to development for psychosis is not known, pharmacological as well as behavioral studies intend to develop better intervention and prevention of psychosis, all of which remain critical.

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