Cannabis and psychosis: an update on course and biological plausible mechanisms

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Purpose of review

Cannabis use is the most commonly abused illicit substance. Its relation with psychosis remains a topic of debate. Epidemiological studies suggest that cannabis is a component cause accounting for approximately 10% of cases. An increasing number of studies have been published on neurobiological effects of cannabis and vulnerability of psychosis.

Recent findings

Acute cannabis administration can induce memory impairments, sometimes persisting months following abstinence. There is no evidence that residual effects on cognition remain after years of abstinence. The scarce literature on neuro-imaging mainly done in nonpsychotic populations, show little evidence that cannabis has effects on brain anatomy. Acute effects of cannabis include increases of cerebral blood flow, whereas long-term effects of cannabis include attenuation of cerebral blood flow. In animals Δ9-tetrahydrocannabinol enhances dopaminergic neurotransmission in brain regions known to be implicated in psychosis. Studies in humans show that genetic vulnerability may add to increased risk of developing psychosis and cognitive impairments following cannabis consumption. Δ9-tetrahydrocannabinol induces psychotic like states and memory impairments in healthy volunteers.

Summary

Simultaneously with increasing understanding of neurobiological cannabis effects, there is a lack of studies in people with psychosis. There are plausible mechanisms that might explain the psychotogenic effects of cannabis.

Keywords

brain, cannabis, psychosis

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Abbreviations

CBF cerebral blood flow
THC Δ9-tetrahydrocannabinol

Introduction

Cannabis is one of the most commonly used illicit substances and although initially it was thought that cannabis would not lead to dependency it has become clear that cannabis use can lead to substance dependency, and abstinence to a withdrawal syndrome according to *Diagnostic and statistical manual for mental disorders* (DSM)-IV criteria [1•,2]. There has been a fierce debate in several countries over whether cannabis should be legalized or not. Although some people are campaigning for medicinal use of cannabis, such as pain relief in multiple sclerosis, others have emphasized the potential psychotogenic effects of cannabis and would like to see stricter regulations of cannabis consumption. The latter has led to a new debate: does cannabis induce psychosis or not, and if so is it reversible or not? During the past two decades several epidemiological studies have addressed this question and an increased risk of developing psychosis following cannabis consumption has been observed consistently. Two recent commentaries [3,4] discussed the above in a broader picture taking into account findings of several epidemiological studies that have been carried out to date. Both concluded that cannabis is neither a necessary nor a sufficient cause and thus a component cause, that is, it is co-dependent on some other factors in order to have causal influence on risk for psychosis. Cannabis abuse as a component individual risk factor for developing psychosis accounts for approximately 8–10% of the attrition rate. There has been less evidence of a reverse relationship, an increase in cannabis consumption following the development of psychosis, but this relationship has not been investigated to the same extent as such studies are difficult to realize.

Cannabis abuse has been associated with poor outcome of schizophrenia-like disorders over a 1–5-year period, at least in Europe [5–8]. Two short-term North American studies showed a different perspective. In Canada, a follow-up study of a regular treatment program over 1 year showed a beneficial effect on psychotic symptoms of the mainly alcohol and cannabis using and non co-morbid patients with schizophrenia-like disorders. Co-morbidity cases, however, showed higher depression and anxiety rates [9]. An interesting randomized clinical trial studying behavioral treatment over 6 months with patients with severe, chronic mental illness (40% DSM-IV schizophrenia and schizoaffective disorder) and drug abuse (cocaine, opiate, cannabis) showed a

positive effect on drug abuse as measured with repeated urine analysis and on community functioning variables [10•]. This trial underlines the poly-drug abuse patterns in co-morbid patients with schizophrenia in the United States, making it more difficult to examine cannabis abuse as an independent co-morbid risk factor for poor outcome. Moreover, the increasing availability and use of cocaine and amphetamines may affect European co-morbid substance abuse patterns in schizophrenia as well. The main question remains whether there is a biological plausible mechanism for cannabis to induce psychosis, or to cause brain damage. This has led to a recent increase in publications on cannabis and brain function, findings of which we will summarize in this review.

Cannabis and cognition

The effects of cannabis on cognitive function in the healthy population have been studied extensively. Findings include deficits in memory formation, but results have been difficult to interpret because of methodological issues like multiple drug abuse, small sample sizes, sample selection and sensitivity of psychological tests for subtle differences. Overall, Δ9-tetrahydrocannabinol (THC) has been shown to induce memory impairments that mimic memory deficits seen in schizophrenia including working memory, encoding episodic memory, impaired retrieval as well as attentional deficits [11,12]. From the current literature it seems evident that acute administration of cannabis leads to cognitive impairments and that these impairments are reversible, and occur in a dose and delay-dependent manner [13••]. Findings on chronic cannabis use have been inconsistent. Long-term use of cannabis has been related to a generalized memory deficit with impaired learning, retention and retrieval on neuropsychological tests [14]. Heavy cannabis use is associated with reduced function of the attentional/executive system, as exhibited by decreased mental flexibility, increased perseverance, reduced learning to shift and sustain attention also with worse performance on overall IQ, processing speed, immediate and delayed memory. There is support for effects continuing beyond the intoxication period, but there is little evidence that cognitive deficits persist after abstinence for a longer period [15,16]. Non-using monozygotic co-twins differed only on one cognitive subtest (block design) compared with their prior cannabis-using co-twin. The authors conclude an absence of marked long-term residual effects on cognitive abilities [17]. There have been fewer studies on the effects of cannabis on cognitive function in people with psychosis. Interestingly, recent studies have demonstrated that people with first episode psychosis who had used cannabis before illness had a relative sparing of cognitive functions and did not perform worse than those who had not used cannabis before illness [18]. These findings were supported by McCleery *et al.*, who demonstrated that first episode psychosis patients with no substance abuse had the poorest cognitive functioning and performance in patients with both mild use and misuse was better at baseline and at 2-year follow-up [19•]. In summary, acute effects of cannabis include memory and attention impairments, heavy users display several cognitive impairments which can disappear after long-term abstinence. Cannabis use did not adversely affect cognitive functioning in patients with psychosis as suggested by some recent findings.

Cannabis and brain imaging

There have been relatively few neuroimaging studies that study effects of cannabis exposure on brain structure and function. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) have been employed to measure effects of cannabis on cerebral blood flow (CBF). Chronic cannabis users demonstrated decreased CBF in frontal, parietal, temporal, and occipital lobes compared to controls. Acute administration or intoxication with cannabis led to increases in CBF including in frontal cortex and basal ganglia [20–22]. Herning *et al.* [23•] found that chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated, in part, in blood vessels or in the brain parenchyma. They suggest that this might provide a partial explanation for the cognitive deficits observed in chronic marijuana users. Similarly, there have been few studies investigating the effects of cannabis on brain anatomy. Block *et al.* [24] did not find any differences in (regional) grey and white matter structures in cannabis users compared to nonusers, however a (small) recent study did find several localized grey and white matter differences [25]. Tzilos *et al.* [26] suggested that cannabis use is not associated with structural changes within the brain as a whole or the hippocampus in particular, or with age of onset of use or total lifetime episodes of use. In a recent, small diffusion tensor imaging (DTI) study frequent cannabis use was found unlikely to be neurotoxic to the normal developing adolescent brain [27]. The only study to date studying cannabis and brain morphology in recent-onset schizophrenia did not find any differences in grey and white matter structures between users and nonusers [28]. With regard to functional MRI more studies have been published recently. Jager *et al.* [29] did not find evidence for long-term deficits in working memory and selective attention in frequent cannabis users after 1 week of abstinence although altered neurophysiological dynamics in the left superior parietal cortex during working memory processing was observed. In another study, active and abstinent marijuana users showed decreased activation in right prefrontal, medial and dorsal parietal, and medial cerebellar regions, but greater activation in various frontal, parietal and occipital brain regions during

the visual-attention tasks despite similar task and cognitive test performance compared with control subjects [30•]. Using resting state MRI daily cannabis users demonstrated significantly increased blood volumes in right frontal and left temporal area, and cerebellum relative to comparison subjects. Within cannabis users, urinary THC concentrations or lifetime episodes of smoking did not correlate to cerebral blood volume [31]. Others found that recent cannabis users displayed greater and more widespread brain activation than normal subjects when attempting to perform a spatial working memory task. The authors suggested that recent cannabis users may experience subtle neurophysiological deficits, and that they compensate for these deficits by 'working harder', calling upon additional brain regions to meet the demands of the task [32]. Gruber *et al.* [33] demonstrated differences in patterns of signal intensity change within anterior cingulate and dorsolateral prefrontal cortex evidence during a STROOP interference test in chronic users compared to controls. In conclusion, to date there is no evidence that chronic cannabis use leads to structural brain abnormalities, also not in recent/onset schizophrenia. With regards to functional anatomy, changes in brain activity globally have been demonstrated in subjects that use cannabis on a regular basis: abstinence results in decreases, and administration results in increases in brain activation. Chronic cannabis use leads to attenuated brain activity in task-activated regions or activation of compensatory regions. The literature is still very scarce and mainly on healthy people, with use of different methodology, tests and definitions of cannabis consumption, issues that need to be addressed in future studies [34].

Cannabis and biological plausibility

THC, the principal psychoactive constituent of exogenous cannabis, has been increasingly employed to study its psychotropic properties. These are mostly mediated by (partial) agonistic effects at the CB1 G protein-coupled receptors, which are widely distributed throughout the central nervous system, particularly in the hippocampus, cerebellum, basal ganglia and frontal cortex. CB1 receptors are primarily expressed on neurons, where most of the receptors are found on axons and synaptic terminals, emphasizing the important role of this receptor in modulating neurotransmission at specific synapses. Animal studies have shown that THC increases the length of the dendrites as well as the number of dendritic branches in nucleus accumbens and medial prefrontal cortex [35•]. Also, THC impairs prepulse inhibition, a neurophysiological marker of information processing that is impaired in schizophrenia, and this effect can be reversed by antipsychotic treatment [36]. Administration of THC increased dopaminergic activity in the mesolimbic dopaminergic system, and (indirectly) acetylcholine release in hippocampus and prefrontal cortex [37], whereas THC (twice daily for 7 or 14 days) caused a persistent and selective reduction in medial prefrontal cortical dopamine turnover [38]. Also, THC increases dopamine synthesis, (possibly by increasing activity and expression of tyrosine hydroxylase), and inhibits dopamine uptake [39]. These THC effects on dopaminergic neurotransmission suggest increased availability of dopamine in the synaptic cleft and could explain psychotogenic properties of THC and partially resemble those that have been described in schizophrenia. Studies in humans have demonstrated that orally and intravenously administered THC induces psychotic symptoms in healthy volunteers [39,40•,41], induces altered states of consciousness that resemble prodromal states [40•], and exacerbates psychotic symptoms, cognitive impairment and medication side effects in patients with schizophrenia [42]. Subjects who carry the Val (high activity) allele of the catechol-O-methyltransferase (COMT) gene were most sensitive to THC-induced psychotic experiences and to THC-induced memory and attention impairments, but this was conditional on psychosis susceptibility [43•]. In another study, carriers of the Val allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis use had no such adverse influence on individuals who were homozygous for the Met allele [44]. Thus both studies suggest that carriers of the Val allele of the COMT gene (who are hypothesized to have relatively less dopamine available in the prefrontal cortex compared to Met homozygotes) may have increased susceptibility for schizophrenia when exposed to cannabis. Other support for biological plausibility for the cannabinoid hypothesis of schizophrenia includes an increase of anandamide, an endogenous cannabinoid, in cerebrospinal fluid in patients with schizophrenia [45,46]; an association of the CNR1 gene, which encodes CB1 receptors, with schizophrenia, especially the hebephrenic type; a significant 25% increase in CB1 receptor binding in the superficial layers (layer I, II) of the posterior cingulated cortex in schizophrenia subjects compared to controls, none of whom had recently used cannabis [47]; decreased EEG power and signal-to-noise ratio reflecting early-stage sensory processing deficits in cannabis users along with increased rates of schizotypy [48]. In summary there is evidence both from animal and human studies that the central cannabinoid system is involved in the pathogenesis of schizophrenia at least partially by modulation of dopaminergic neurotransmission.

Conclusion

There seems to be no doubt that cannabis can induce psychosis in a subgroup of people who already are susceptible for developing psychotic symptoms. The majority of people who use cannabis, however, do not develop psychosis and the majority of cases of schizophrenia are not caused by cannabis. Cannabis abuse

remains to be associated with poor outcome of schizophrenia-like disorders despite some results of recent short-term interventions. Two recent studies, however, did not find adverse effects of cannabis on cognition in people with psychosis.

This review demonstrates that increasingly plausible biological mechanisms are surfacing that may explain possible psychotogenic properties of cannabis.

From the still scarce literature it appears that there may be a dissociation between acute effects and chronic effects of cannabis on brain structure and function. With regards to cognitive function, acute and chronic cannabis consumption are leading to impairments particularly memory and attention. The studies that use 'pure' THC do demonstrate acute psychotogenic effects of THC, but they are performed in controlled situations. Difficulties in interpreting most studies are polydrug abuse, the lack of clear definitions of cannabis use, different concentrations of THC in 'coffee-shop' cannabis preparations, and often unreliable self-reports on cannabis consumption. Also nowadays proper baseline 'cannabis-naïve' measures are difficult to obtain. Most studies have focused on nonpsychotic cannabis-users. A proportion of these people may still go on to develop psychosis. Also, there is as yet no clear picture of the effects of cannabis on neurobiology in the already psychotic population. There are biological plausible mechanisms, particularly those interfering with dopaminergic neurotransmission, but the exact nature of these effects in different brain regions is still unclear. Future larger and longitudinal studies will need to address this to extend our knowledge and understanding. Until then the debate on cannabis and psychosis will probably continue.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 180–181).

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