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Psychiatry Research: Neuroimaging Section 107 (2001) 173–177

PSYCHIATRY RESEARCH NEUROIMAGING

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Case report

Cannabis induced dopamine release: an in-vivo SPECT study

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Received 29 January 2001; received in revised form 6 June 2001; accepted 25 June 2001

Abstract

In a research study aimed at examining the alterations in dopaminergic function in schizophrenia, the authors identified a surreptitious case scenario which provided new insights into the subjective and neurochemical effects of cannabis. A 38-year-old drug-free schizophrenic patient took part in a single photon emission computerized tomographic (SPECT) study of the brain, and smoked cannabis secretively during a pause in the course of an imaging session. Cannabis had an immediate calming effect, followed by a worsening of psychotic symptoms a few hours later. A comparison of the two sets of images, obtained before and immediately after smoking cannabis, indicated a 20% decrease in the striatal dopamine D_2 receptor binding ratio, suggestive of increased synaptic dopaminergic activity. This observation offers a plausible biological explanation for the psychotogenic effects of cannabis in vulnerable individuals, and also raises speculations about an interaction between cannabinoid and dopaminergic systems in the brain reward pathways.

Keywords: Psychosis; Cannabinoids; Schizophrenia; Neuroimaging

1. Introduction

Clinical observations suggest that cannabis could induce or exacerbate psychosis, and epidemiological surveys confirm a five-fold increase of cannabis use associated with schizophrenia (Linszen et al., 1994; Negrete and Gill, 1999). However, the nature of the association between cannabis and psychosis has not been adequately studied, and 'cannabis psychosis' remains an elusive entity. Research in this field has been limited by ethical considerations, although cannabis remains the most widely used drug after nicotine and alcohol (Watson et al., 2000). A comprehen-

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0925-4927/01/$ - see front matter
PII: S0925-4927(01)00104-4

sive investigation into various aspects of cannabis psychosis is urgently indicated for two reasons. First, there is the lack of an adequate scientific knowledge base relative to the magnitude of the problem; secondly, cannabis could be viewed as a pharmacological probe, and the study of cannabis psychosis may provide clues into the pathophysiology of schizophrenia. Preliminary results from ongoing studies show that the intravenous administration of tetrahydro-cannabinol results in the induction or worsening of psychotic symptoms among healthy volunteers and schizophrenic subjects (D'Souza et al., 2000). Further work is indicated to delineate the underlying neurobiological mechanisms, especially the dynamic events at the chemical, receptor and molecular levels. In the following case study, we present results of an in-vivo single photon emission computed tomographic (SPECT) brain study of an individual with a recurrent psychotic disorder that were suggestive of increased striatal dopaminergic transmission immediately after smoking cannabis.

2. Case study

The patient was a 38-year-old right-handed, single, white male factory worker who was originally referred for a psychiatric assessment at age 33 because he had experienced hallucinations and persecutory delusions during the previous four years. There was no history suggestive of negative symptoms, disorganization, cognitive deficits, or other comorbid psychiatric conditions. His premobid intelligence and personality profile were unremarkable; and his father and a brother were treated for unidentified psychiatric disorders. The patient had been smoking cannabis for recreational purposes since the age of 16, though the frequency and pattern of use did not meet DSM-IV criteria for substance abuse. Subjective responses to the drug usually consisted of relief of tension and 'feeling calm', but at times included panic symptoms and 'breakdowns'. The latter were suggestive of positive psychotic symptoms, which persisted during prolonged periods of abstinence (from cannabis). Differential diagnosis included schizophrenia and substance-induced psychotic disorder. Counseling and anti-psychotic treatment (risperidone, 2–4 mg) brought about symptomatic relief and a sustained improvement in social and occupational functioning. Clinical monitoring over the 5-year period indicated a pattern of remissions and relapses, the latter attributable to a combination of non-compliance with anti-psychotic medication and smoking cannabis. There was no evidence of deterioration in cognitive and psychosocial functioning during the follow-up, though the cannabis use decreased significantly due to fear of recurring psychotic symptoms.

On the most recent occasion, the patient stopped anti-psychotic therapy for 8 months, and presented with a recurrence of psychotic symptoms of approximately 6 months' duration. He was asked to participate in a neuroimaging study aimed at examining the relationship between anti-psychotic drug effects and striatal D_2 receptor status in unmedicated (drug-free) schizophrenic patients (Voruganti et al., in press). The protocol was approved by the institutional review board. The subject was deemed competent and eligible to participate in the study, and an informed consent was obtained. A comprehensive mental status examination was performed, and the severity of psychotic symptoms was recorded with the Positive and Negative Syndromes Scale (PANSS). A urine screen was done to rule out the use of cannabis and other commonly used street drugs, and the result was negative. Prior to scanning, fiducial markers were placed on the head to ensure consistent head positioning and motion detection. Iodobenzamide [^{123}I-IBZM] (135 MBq), a D_2 radiotracer, was given as a bolus injection, and 240 MBq as a continuous infusion over 6 h (Abi-Dargham et al., 1998). Scanning began after 3.5 h of infusion, using a Siemens MULTISPECT II camera fitted with fan beam collimators. As per the protocol, the subject was scheduled to have eight image acquisitions of 12 min each, but the procedure was interrupted after six acquisitions since he experienced anxiety and requested to have a break. During the interval, he used the bathroom and returned after 15 min feeling better, wishing to continue the procedure. Since the

intravenous infusion was maintained in the meantime, the head was re-positioned with the help of fiducial markers, and scanning resumed after 45 min to acquire six more acquisitions (additional images were obtained to compensate for any potential movement artifacts). Observation at the time of repeat scan indicated a relaxed and jovial subject who was able to complete the procedure without further discomfort.

A scheduled mental status examination on the following morning, however, suggested an acute exacerbation of psychotic symptoms (total PANSS score increased from 48 to 60, and the score on the positive symptom subscale increased from 13 to 19). Further questioning revealed that he smoked cannabis during the pause in the scanning session on the previous evening, to relieve the tension and unease experienced during the imaging procedure. A repeat urinanalysis was positive for cannabinoids, confirming the consumption of the drug. The subject was withdrawn from the protocol, re-started on anti-psychotic medication and counseled against further substance abuse.

In the analysis, SPECT images were co-registered with MRI (Siemens-Varian 4 Tesla) scans to facilitate precise anatomical delineation of the regions of interest, and dopamine D_2 receptor binding ratios were calculated. We used an automated image-registration technique to ensure that the two scans were spatially coregistered to each other. Rigid-body parameters (three translations and three rotations) were adjusted on the second scan to match the first scan. To eliminate any bias in image quantification due to the tri-linear interpolation of the data, we also coregistered the SPECT images to the MRI scans for visual verification of the anatomical shape of the basal ganglia. After registration, the regions of interest were drawn for left and right basal ganglia on the slice containing the image. The maximum count was then found in the whole three-dimensional region of the left and right basal ganglia, which included up to four contiguous transverse slices and, therefore, would not be affected by any misorientation in the coronal plane. The maximum value was chosen instead of the average counts for the basal ganglia region because of partial volume effects, which resulted in poor definition of the anatomical boundaries of the basal ganglia on the SPECT scan and the possibility of variation in the image orientation. The maximum count is less affected by these imaging limitations, and such a definition is less operator-dependent. This quantification was repeated on the scans registered in the reverse order (second scan to the first scan), and the mean of both binding ratios was used in further calculations.

Raw data on the total counts measured before and after cannabis use were as following: right striatum — 582 and 560; left striatum — 618 and 545. A comparison of the two sets of images (obtained before and after the pause) indicated a 20% decrease in the striatal D_2 receptor binding ratio following cannabis use (see Figs. 1 and 2).

3. Discussion

The case study lacks experimental rigor since the type of cannabis preparation used and the dose of cannabinoids smoked were not precisely identified. Hence, the results warrant systematic replication and a cautious interpretation.

However, the report illustrates several important issues. The results suggest that among vulnerable individuals: (i) cannabis use could be associated with a sustained psychotic state that is clinically indistinguishable from schizophrenia; (ii) cannabis use results in increased synaptic dopamine activity; and (iii) cannabis-induced dopaminergic overactivity seems to reveal itself as an initial euphoric–anxiolytic effect, followed by later psychotic manifestations. Though these inferences are made from an isolated case study, they are consistent with previous research in the substance abuse literature, and also add a new dimension to the growing body of knowledge on the effects of cannabis.

The in-vivo demonstration of the effect of cannabis on increased dopaminergic activity in a human subject is a novel finding, though the interaction was noted earlier in animal experiments (French et al., 1997). Increased synaptic dopamine transmission, of a similar magnitude,

Fig. 1

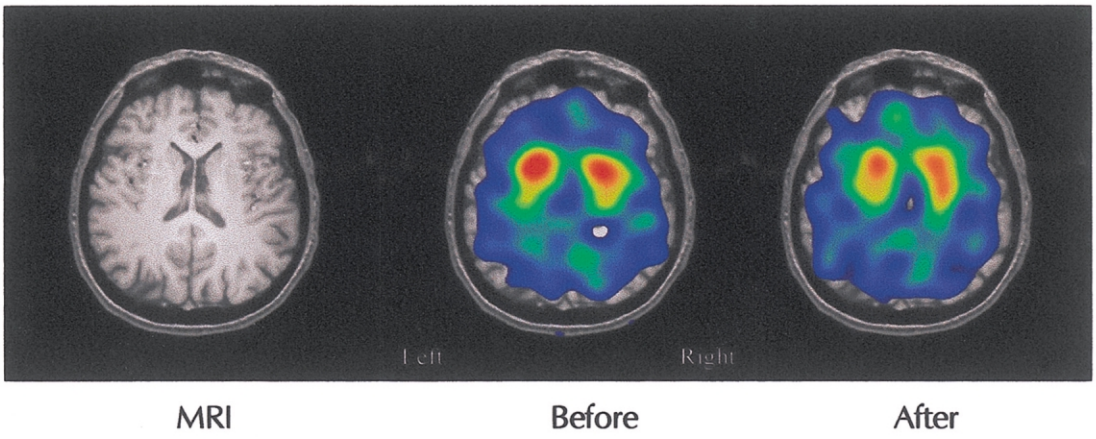

Fig. 2

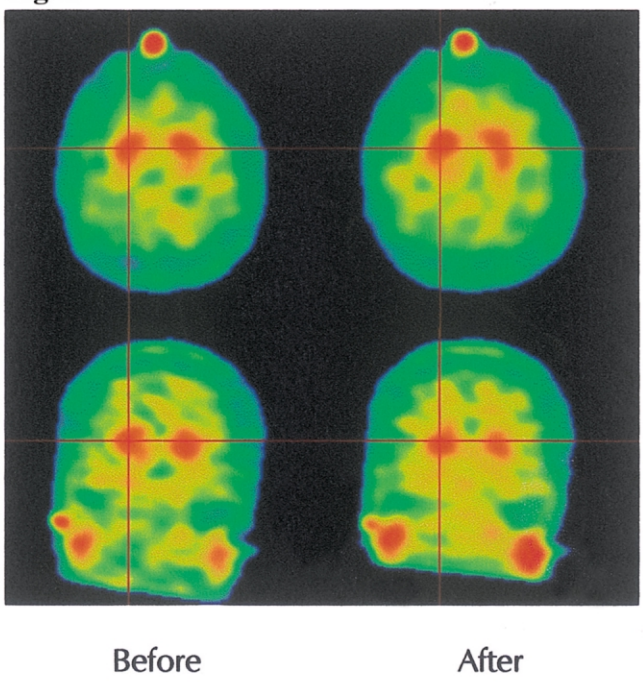

Fig. 1. Coregistered MRI-SPECT images with ^{123}IBZM showing changes in striatal D_2 receptor status after cannabis consumption.
Fig. 2. SPECT images (transverse and coronal sections) showing changes in striatal D_2 receptor status after cannabis consumption.

has been observed during amphetamine and cocaine administration studies in humans (Volkow et al., 1997; Abi-Dargham et al., 1998). However, in the case of cannabis, it is unclear if the observed increase in dopaminergic activity resulted from a pre-synaptic release of dopamine, or an inhibition of its reuptake mediated through presynaptic cannabinoid [CB_1] receptors (D'Souza, 2001). The latter suggestion intensifies speculations about potential interactions between cannabinoid and

other neurotransmitter systems in brain regions that have been implicated in the mediation of pleasurable responses to positive reinforcers (Tanda et al., 1997).

Drugs with abuse potential seem to exert their effects through increased dopaminergic activity, which could be a final common pathway responsible for the experience of a subjective 'high', as well as a worsening of positive psychotic symptoms (Wise, 1996). This dual mode of action could explain why many schizophrenic patients continue to use cannabis, despite an increased risk of psychosis. It has been postulated that anti-psychotic drugs with a predominant dopaminergic blocking action induce dysphoric responses, and schizophrenic patients learn to overcome the unpleasant feelings through the use of illicit drugs, as a self-medication strategy (Voruganti et al., 1997).

Exploring these themes has implications for understanding the pathophysiology of cannabis abuse as well as that of schizophrenia.

Acknowledgements

This work was conducted at the London Health Sciences Center affiliated with the University of Western Ontario, and was supported by a grant from the internal research fund [IRF #0159] awarded by the London Health Sciences Center Research Institute, London, Ontario, Canada.

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