Archival Report

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Rapid Changes in Cannabinoid 1 Receptor Availability in Cannabis-Dependent Male Subjects After Abstinence From Cannabis

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ABSTRACT

BACKGROUND: The widespread use of cannabis, the increasing legalization of "medical" cannabis, the increasing potency of cannabis, and the growing recreational use of synthetic cannabinoid 1 receptor (CB_1R) full agonists all underscore the importance of elucidating the effects of cannabinoids on the CB_1R system. Exposure to cannabinoids is known to result in CB_1R downregulation. However, the precise time course of changes in CB_1R availability in cannabis-dependent (CD) subjects after short-term and intermediate-term abstinence has not been determined.

METHODS: Using high-resolution research tomography and the reversible ligand [^{11}C]OMAR, CB_1R availability as indexed by the [^{11}C]OMAR volume of distribution was measured in male CD subjects ($n = 11$) and matched healthy control (HC) subjects ($n = 19$). The CD subjects were scanned at baseline (while they were neither intoxicated nor in withdrawal) and after 2 days and 28 days of monitored abstinence. The HC subjects were scanned at baseline, and a subset ($n = 4$) was scanned again 28 days later.

RESULTS: Compared with HC subjects, [^{11}C]OMAR volume of distribution was 15% lower in CD subjects (effect size Cohen's $d = -1.11$) at baseline in almost all brain regions. However, these group differences in CB_1R availability were no longer evident after just 2 days of monitored abstinence from cannabis. There was a robust negative correlation between CB_1R availability and withdrawal symptoms after 2 days of abstinence. There were no significant group differences in CB_1R availability in CD subjects after 28 days of abstinence.

CONCLUSIONS: Cannabis dependence is associated with CB_1R downregulation, which begins to reverse rapidly on termination of cannabis use and may continue to increase over time.

Keywords: Cannabinoids, Cannabis, CB_1R, Dependence, Downregulation, Recovery, Tolerance, Upregulation, Withdrawal

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Cannabis is the most commonly used illicit drug by adults in the United States (1). "Medical" marijuana is being legalized increasingly across the United States, and some states have legalized recreational cannabis use as well. The average Δ^9-tetrahydrocannabinol (THC) content of cannabis has increased (2), and highly potent, synthetic full cannabinoid 1 receptor (CB_1R) agonists (e.g., Spice and K-2) are being used recreationally (3). Collectively, these developments related to cannabis underscore the importance of elucidating the effects of cannabinoids (CBs) on the CB_1R system.

Synthetic CB_1R agonists and the CBs present in cannabis produce their psychoactive effects via activation of brain CB_1Rs (4). Repeated exposure to CBs is associated with the development of tolerance and dependence (5,6), which likely reflect adaptive changes in the CB_1R system. In animals, chronic CB exposure is associated with a reduction in the number and function of CB_1Rs (7–11). These changes have a distinct regional and temporal course and are related to the duration and magnitude of exposure, with greater downregulation in cortical versus subcortical regions (12,13). Discontinuation of chronic, heavy CB exposure and the administration of CB_1R antagonists to CB-dependent animals are associated with a withdrawal syndrome (14–16). Finally, prolonged abstinence in CB-dependent animals results in normalization of the number and function of CB_1Rs over 2 weeks, with faster recovery in subcortical versus cortical regions (10).

Hirvonen *et al.* (17), using positron emission tomography (PET) imaging and the CB_1R agonist ligand [^{18}F]FMPEP-d_2, demonstrated that individuals with chronic, heavy cannabis use had 20% lower CB_1R availability relative to control subjects. Consistent with animal studies, this reduction

occurred in cortical but not in subcortical regions. A subset of cannabis users (n = 14) who underwent scanning again after 13–32 days of monitored inpatient abstinence (17) showed an increase in CB_1R availability in the same regions that had shown decreased CB_1R availability at baseline. These findings were collectively interpreted as evidence of CB_1R downregulation with cannabis dependence that reversed with abstinence. This important first in vivo study also raised several questions. First, it is unclear how quickly reversal of downregulation occurs. Second, because the sample consisted of subjects with very heavy cannabis use (10 ± 6 joints/day) for 12 (± 7) years, it is unclear whether modest cannabis use is associated with a similar magnitude of downregulation. Third, given the known interplay between CB_1R and nicotinic receptor systems (18,19), the extent to which tobacco use influenced the results could not be conclusively determined because most (>80%) of the subjects were tobacco smokers. Fourth, because healthy control (HC) subjects were not scanned twice, there was no control for interscan variability. Finally, the variability in the duration between the first and second scans (13–32 days) did not afford precision in characterizing the temporal profile of CB_1R upregulation. A second study using [^{18}F]MK-9470, a different PET tracer, found reduced global CB_1R receptor availability (by 11.7%) in cannabis-dependent (CD) subjects (n = 10) relative to control subjects (20). However, the characteristics of [^{18}F]MK-9470, which shows primarily irreversible receptor binding, poses challenges. Furthermore, the validity of the simplified data analysis technique (modified standardized uptake value) used was challenged by several groups (21,22).

This study aimed first to compare CB_1R availability between CD subjects and HC subjects and then to characterize the temporal course of changes in CB_1R availability in CD subjects after short-term (2 days) and intermediate-term (28 days) abstinence. To increase generalizability and to address gaps in the literature, another aim was to measure CB_1R availability in subjects with modest cannabis exposure. To address the potential confound in previous studies, this study aimed to measure CB_1R availability in subjects who did not use tobacco. Finally, to rule out interscan variability as an explanation for any changes in CB_1R availability in CD subjects, a small subset of HC subjects were scanned 4 weeks apart. The CB_1R availability was measured using the reversible ligand [^{11}C]OMAR (23) based on absolute quantification using arterial sampling with metabolite analysis and tracer kinetic modeling (22), a method that does not have the limitations associated with the modified standardized uptake value outcome measure. The CB_1R availability was hypothesized to 1) be lower in CD subjects at baseline, 2) increase after 2 days of abstinence as a result of compensatory upregulation, and 3) recover to normal levels after 28 days of abstinence.

METHODS AND MATERIALS

Subjects

The CD subjects studied were men 18–35 years old. Cannabis dependence was operationalized as 1) use of ≥30 joints or equivalents in the past 30 days, ≥21 days of cannabis use in the past 30 days, and ≥120 days of cannabis use in the past 6 months as estimated by a Timeline Followback approach; 2) regular cannabis use for ≥2 years; 3) positive urine screen for cannabinoids but not any other drugs on at least two separate screening visits; 4) DSM-IV cannabis dependence; and 5) no self-reported problematic illicit substance use during the past 3 months as assessed by 6-month Timeline Followback. The comparison group comprised age-matched (± 3 years) HC subjects without any DSM-IV Axis I or II disorders. Exclusion criteria common to both groups were 1) major DSM-IV diagnosis of Axis I disorder, 2) nicotine-dependent tobacco users, 3) weekly alcohol consumption exceeding National Institute on Alcohol Abuse and Alcoholism guidelines (≥4 drinks on any single day and ≥14 drinks per week), and 4) significant medical or neurologic disease. Regulatory approvals, screening process, contingency management, and study procedures are detailed in Supplement 1. Subjects also were screened for current and lifetime substance abuse and psychiatric problems using the Structured Clinical Interview for DSM-IV conducted by a research assistant and psychiatric evaluations by psychiatrists.

Magnetic resonance imaging scans (3T) were collected during screening. Eligible CD subjects were instructed not to use cannabis after 6 PM on day −1 and were admitted to a closed inpatient research unit to ensure abstinence from cannabis. Both CD subjects and HC subjects underwent a PET scan on day 0, the first full day of abstinence. The CD subjects remained hospitalized and were scanned again after 2 days of abstinence. They were then discharged and required to attend the outpatient research clinic twice per week for 1) motivational enhancement, 2) escalating contingency management (Supplement 1), 3) assessment of cannabis withdrawal, and 4) confirmation of abstinence. Abstinence was confirmed at every visit by immediate spot urine drug testing and later offsite quantification of THC carboxylic acid (COOH) by gas chromatography-mass spectrometry (threshold of detection 5 ng/mL) (24,25). To account for deliberate dilution of urine, urine collection was observed on a random basis, and urinary THC-COOH/creatinine ratio was calculated. Subjects were determined to be abstinent if their urinary THC-COOH/creatinine ratio decreased over time and did not increase by >50% relative to the prior test (26–28). The CD subjects who demonstrated maintained abstinence (based on progressive decrease in urinary THC-COOH/creatinine ratio and self-reported abstinence) throughout the outpatient phase underwent a third PET scan on day 28 of abstinence.

Imaging

The CD subjects were scanned with PET and [^{11}C]OMAR 1) no less than 8 hours but no more than 24 hours following last use (i.e., while still dependent but neither intoxicated nor in withdrawal); 2) after 2 days of confirmed acute inpatient abstinence, to coincide with the time when cannabis withdrawal was expected to peak; and 3) after 28 days of confirmed outpatient abstinence, when the CB_1R system is expected to recover completely (Supplement 1; Table S2 in Supplement 1). The HC subjects were scanned once, and a subsample (n = 4) was scanned again within 28 days to confirm long-term test-retest reliability.