Dopamine challenge reveals neuroadaptive changes in marijuana abusers

Bertha K. Madras[1]

Division on Alcohol and Drug Abuse, Harvard University Medical School, McLean Hospital, Belmont, MA 02478

The current watershed in legal status and rising use of marijuana can be traced to a California ballot initiative (Prop. 215, its legal successor SB420), that enabled widespread access to smokeable or edible forms of marijuana for self-reported medical conditions. Circumventing the Food and Drug Administration (FDA) drug approval process, the movement in California was replicated by ballot or legislative initiatives in 23 states and the District of Columbia, and culminated in the legalization of marijuana in 2012 by Washington state and Colorado. The shifting status of marijuana reflects a change in public perception and belief that marijuana is harmless. Marijuana use in the population over age 12 is escalating; 60% of 12th graders do not perceive marijuana as harmful, and daily or nearly daily use has risen dramatically in this cohort (1, 2). Paradoxically, public perception of marijuana as a safe drug is rising simultaneously with accumulating evidence that frequent marijuana use is associated with adverse consequences, especially among youth (3). In PNAS, Volkow et al. register compelling new observations that marijuana abusers manifest adaptive behavioral, physiological, and biological responses, which conceivably contribute to marijuana addiction and compromised function (4). In response to a dopamine challenge (methylphenidate) and compared with non-using controls, marijuana abusers self-reported blunted reward (less "high") and heightened negative responses (anxiety and restlessness), which were associated with attenuated dopamine responses in brain and cardiovascular responses.

Dopamine, Reward, the Adapted Brain

The role of the neurotransmitter dopamine in drug reward and addiction is the key to understanding the rationale for interrogating dopamine function in long-term marijuana abusers. The dopamine hypothesis of addiction was formulated by preclinical observations showing that opiates, cocaine, amphetamine, nicotine, alcohol, and (delta-9)-tetrahydrocannabinol (THC, the psychoactive constituent of marijuana), raise extracellular dopamine levels in the dopamine-rich nucleus accumbens, a brain region associated with reward (5, 6). Repeated drug-induced dopamine surges were subsequently shown to engender neuroadaptive changes in brain regions implicated in drug salience, drug reward, motivation, memory, and executive function (7–9). In humans dependent on alcohol, cocaine, methamphetamine, nicotine, or heroin, adaptation of dopamine signaling is manifest by reduced D2 dopamine receptor availability and blunted dopamine release in cocaine, heroin, and alcohol abusers challenged with a psychostimulant (10–14). Interrogation of whether marijuana abusers manifest parallel adaptive changes in dopamine signaling has yielded inconsistent results (15).

By integrating behavioral and brain-imaging measures following a dopamine challenge (methylphenidate) in marijuana abusers, Volkow et al. (4) add a new dimension to clarifying the impact of long-term marijuana use on brain dopamine response. Methylphenidate, a surrogate for dopamine, elevates extracellular levels of dopamine (and norepinephrine) by blocking the dopamine transporter (DAT) in dopamine-expressing neurons. As the DAT sequesters dopamine in dopamine-releasing neurons, the blockade raises extracellular dopamine levels in dopamine-rich brain regions. The rapid rise in dopamine triggers self-reports of a "high." Marijuana abusers self-reported blunted measures of "high," drug effects, increased anxiety, and restlessness. The magnitude and peak behavioral effects of methylphenidate were more robust in controls than marijuana abusers. Cardiovascular responses (diastolic blood pressure, pulse rate) were also attenuated in the abusers. Significantly, the younger marijuana use was initiated, the higher the scores for negative emotionality. These findings reinforce the accumulating evidence that earlier age of initiation of marijuana abuse is associated with worse outcomes (3, 16). Collectively this phase of the study suggests that brain dopaminergic, possibly noradrenergic systems, are significantly modified in long-term, heavy marijuana abusers. These changes conceivably contribute to reduced rewarding effects, emotionality and motivation, increased propensity for addiction, with early initiators being more vulnerable.

D2/D3 dopamine receptors are critical mediators of the initial responses to drugs of abuse. PET imaging of brain revealed a more complex pattern of change in dopamine signaling than previously reported for other specific drugs of abuse. D2/D3 dopamine receptor availability, measured with the D2/D3 receptor antagonist [11C]raclopride, was not reduced in marijuana abusers, in contrast to reduced dopamine receptor availability observed in subjects with other specific substance use disorders (11–14). This conclusion remains tentative, as the age of the marijuana-abusing cohort was considerably younger than drug-abusing subjects previously interrogated for D2 dopamine receptor availability.

[11C]Raclopride can also serve as an indirect measure of dopamine production, release, and extracellular levels (17). Reduced [11C]raclopride binding-site availability is detectable following administration of a psychostimulant (e.g., methylphenidate or amphetamine), which elevates the extracellular dopamine by blocking transport or promoting its release from neurons. The dopamine surge competes with [11C]raclopride for binding to the D2/D3 receptor, with [11C]raclopride displacement proportional to extracellular dopamine. In marijuana abusers, diminished dopamine responses were observed in the ventral striatum compared with controls, and were inversely correlated with addiction severity and craving. The attenuated responses to methylphenidate are consistent with decreased brain reactivity to dopamine stimulation in marijuana abusers, which conceivably contributes to the increase in stress responses, irritability,

Author contributions: B.K.M. wrote the paper.

The author declares no conflict of interest.

See companion article on page E3149 in issue 30 of volume 111.

[1]Email: bertha_madras@hms.harvard.edu.

and addictive behaviors. Thus, marijuana joins the roster of other abusable drugs in promoting blunted dopaminergic responses in a brain region implicated in drug reward, but deviates from other drugs in that it apparently does not promote a decline in D2/D3 receptor availability.

The study yielded several unanticipated discoveries. Marijuana abusers displayed enhanced dopamine release in the substantia nigra/subthalamic nucleus, which correlated with marijuana and tobacco craving, as well as addiction severity. Because this brain region has relatively high densities of the D3 receptor, this preliminary finding reinforces the need to expand PET imaging to multiple, discrete brain regions, with higher-resolution cameras, and to enlist other probes capable of selective monitoring of each of five dopamine receptor subtypes. Another surprising observation was the decrease in distribution volume in the cerebellum by methylphenidate in controls, but not in marijuana abusers, another manifestation of a blunted response. This brain region characteristically is used as a reference region to normalize for nonspecific binding ("baseline") of PET imaging probes if comparing group differences, possibly resulting in overestimates of the methylphenidate response in other brain regions of marijuana abusers. This finding, which may reflect vascular changes engendered by marijuana, highlights the necessity of heightened scrutiny of the cerebellum as a "neutral" baseline region for dopamine receptor monitoring in group comparisons.

Collectively, abnormal behavioral responses to a methylphenidate challenge implicate dopamine signaling adaptation in marijuana abusers. Even though a decrease in striatal D2 receptor density does not account for the responses, other components of the synapse (e.g., DAT, dopamine synthetic capacity, the dopamine signaling cascade, events downstream of dopamine receptors) conceivably contribute to manifestations of blunted subjective responses.

Future Multidisciplinary Research

The current research (4), providing strong evidence that marijuana abuse is associated with blunted dopamine responses and reward, is a major contribution to a growing body of evidence that heavy marijuana use is associated with brain changes that could be detrimental to normal brain function. Numerous other brain-imaging studies have been conducted in heavy adult marijuana users (e.g., ref. 18), with reported changes in brain morphology and density, deformation of specific structures, altered connectome (e.g., hippocampus), and function. The current research, which integrates behavioral and physiological changes within the context of a specific neurochemical substrate, dopamine, provides important leads for integrating with other changes gleaned from MRI technologies. Intriguingly, evidence that dopamine receptor signaling can affect expression of genes encoding axonal guidance molecules that are critical for brain development and neuroadaptation (19) may provide a link between drug-induced receptor activity and gross and discrete altered morphology and circuitry characteristic of the drug-adapted brain.

There remains a compelling need for prospective, integrated longitudinal research in this field, especially in adolescent marijuana users, as the impact of marijuana on the developing brain is more robust with early age of initiation (3, 16). Imaging studies are predominantly snapshots in time, relying on self-reports of marijuana use, dose, and frequency, with subjects of varying ages, group sizes, differing imaging techniques, and other variables that confound meta-analyses or integration of data from different sites to expand study power. A critical longitudinal study showing a significant IQ decline in early marijuana users is a prime example of the direction in which the field should be going, but with coordinated brain-imaging approaches (20).

Preclinical studies can circumvent the limitations of some clinical metrics, and establish causality for specific changes that are not feasible to measure in humans. Yet the divergence of the human brain anatomically and functionally limits unfettered extrapolation from animals to humans. Large-scale, multicenter prospective longitudinal human research starting before initiation of drug use and extending for three decades of life is needed to further pursue causal relationships of marijuana and adverse consequences reported in numerous shorter-term studies. Research design could include: (*i*) brain imaging to document occurrence of, resolution, or persistence of structural, circuitry, vascular, and associated and neuropsychological decrements; (*ii*) neurocognitive function; (*iii*) behavioral, emotional assessment; (*iv*) neural, cognitive, epigenetic, proteomic, and affective markers; and (*v*) preclinical, relevant parallel studies.

In view of the growing public health concerns of escalating high-dose, high-frequency marijuana use, early age of initiation and daily use, high prevalence of marijuana addiction, rising treatment needs, the void of effective treatment, high rates of relapse, association with psychosis and IQ reduction, a rising tide of emergency room episodes, and vehicular deaths, constitute compelling reasons to expand marijuana research and to clarify its underlying biology and treatment targets/strategies. Longitudinal studies that begin before initiation of use, and that integrate brain imaging with behavioral, cognitive, and other parameters, will facilitate shaping of public perception and public policy with more informed scientific evidence.

1 Center for Behavioral Health Statistics and Quality (2013) *National Survey on Drug Use and Health* (Substance Abuse & Mental Health Services Administration, Rockville, MD).

2 Johnston LD, et al. (2013) *Monitoring the Future: National Survey Results on Drug Use, 1975–2013 — Overview, Key Findings on Adolescent Drug Use*. (Institute for Social Research, University of Michigan, Ann Arbor) Avaliable at http://monitoringthefuture.org//pubs/monographs/mtf-vol1_2013.pdf. Accessed July 13, 2014.

3 Volkow ND, Baler RD, Compton WM, Weiss SR (2014) Adverse health effects of marijuana use. *N Engl J Med* 370(23):2219–2227.

4 Volkow ND, et al. (2014) Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proc Natl Acad Sci USA* 111(30): E3149–E3156.

5 Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* 85(14):5274–5278.

6 Chen JP, et al. (1990) Delta 9-tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. *Psychopharmacology (Berl)* 102(2):156–162.

7 Hyman SE, Malenka RC, Nestler E (2006) Neural mechanisms of addiction: The role of reward-related learning and memory. *Annu Rev Neurosci* 29:565–598.

8 Koob GF, Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacology* 35(1):217–238.

9 Volkow ND, Wang GJ, Fowler JS, Tomasi D (2012) Addiction circuitry in the human brain. *Annu Rev Pharmacol Toxicol* 52:321–336.

10 Volkow ND, et al. (1997) Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature* 386(6627):830–833.

11 Martinez D, et al. (2005) Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry* 58(10):779–786.

12 Martinez D, et al. (2012) Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: Commonalities and differences with other types of addiction. *Biol Psychiatry* 71(3): 192–198.

13 Wang GJ, et al. (2012) Decreased dopamine activity predicts relapse in methamphetamine abusers. *Mol Psychiatry* 17(9):918–925.

14 Fehr C, et al. (2008) Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *Am J Psychiatry* 165(4):507–514.

15 Ghazzaoui R, Abi-Dargham A (2014) Imaging dopamine transmission parameters in cannabis dependence. *Prog Neuropsychopharmacol Biol Psychiatry* 52:28–32.

16 Lynskey MT, et al. (2003) Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA* 289(4): 427–433.

17 Seeman P, Guan HC, Niznik HB (1989) Endogenous dopamine lowers the dopamine D2 receptor density as measured by [3H]raclopride: Implications for positron emission tomography of the human brain. *Synapse* 3(1):96–97.

18 Batalla A, et al. (2013) Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLoS ONE* 8(2):e55821.

19 Jassen AK, Yang H, Miller GM, Calder E, Madras BK (2006) Receptor regulation of gene expression of axon guidance molecules: Implications for adaptation. *Mol Pharmacol* 70(1):71–77.

20 Meier MH, et al. (2012) Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA* 109(40):E2657–E2664.