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Imaging dopamine transmission parameters in cannabis dependence

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ABSTRACT

Low striatal dopamine D2/3 receptor (D2/3) availability and low ventrostriatal dopamine release have been observed in alcoholism, cocaine and heroin dependence. Multiple studies to date have examined D2 availability in cannabis dependence and have consistently failed to demonstrate alterations. In addition, the response of the dopamine system to an amphetamine challenge and to a stress challenge has also been examined, and did not show alterations. We review these studies here and conclude that cannabis dependence is an exception among commonly abused drugs in that it is not associated with blunting of the dopamine system.

1. Introduction

It has been repeatedly shown that chronic drug dependent subjects display low D2 receptors and blunted dopamine release compared to demographically matched controls, when imaged in vivo using Positron Emission Tomography and D2 radiotracer scans before and after a stimulant challenge (Martinez et al., 2005, 2007; Volkow et al., 1997), see also review in Martinez and Narendran (2010). Fewer studies have examined these dopaminergic indices in cannabis abuse and dependence. This review will summarize first the literature regarding the acute effects of cannabis use on dopamine release, followed by a review of the longer term effects of its chronic misuse. As cannabis use is starting to receive approvals for medical use in certain countries, questions are raised regarding its similarity to other drugs of abuse. This review is an objective assessment of the available data regarding the effects on the dopaminergic system.

Cannabis is the most frequently used drug in North America (SAMHSA, 2010), starting in adolescence and following a predictable path leading to dependence (Budney et al., 2003), anxiety and depression (Degenhardt et al., 2001; Troisi et al., 1998), but also see Moore et al. (2007). Associations with the onset of psychosis and schizophrenia have also been described (Henquet et al., 2008). It is suggested that cannabis may have long-lasting effects on the brain by interacting with normal maturational processes (Pistis et al., 2004). Abnormal brain structure, with smaller hippocampal and amygdala volumes (Yucel et al., 2008) and cognitive disturbances including deficits in verbal learning and working memory, particularly in adolescents have been reported (Schweinsburg et al., 2008). Altogether, these reports suggest changes in brain function especially with adolescent use, which may lead to long lasting effects on brain and behavior. Here we will review the imaging studies that have examined the effects of cannabis use on the dopaminergic system.

2. Effect of acute cannabinoid administration on the dopamine system

The direct psychopharmacological effects of delta-9-tetrahydrocannabinol (THC) are mediated by endocannabinoid (CB1) receptors, which are predominantly localized in the basal ganglia, and at lower density in the ventral midbrain, among other regions (Freund et al., 2003). CB1 receptors are located on glutamate and gamma-aminobutyric acid (GABA) terminals where they inhibit release. They are also co-localized with dopamine-2/3 (D2/3) receptors in the midbrain, prefrontal cortex and basal ganglia and may have synergistic effects with D2/3 activation through augmentation of cAMP (Glass and Felder, 1997). Thus, cannabinoid stimulation of the CB1 receptor affects multiple neurotransmitter systems, including dopamine.

Cannabinoids, including THC (Gaoni and R.M., 1964), stimulate neuronal firing of mesolimbic dopamine neurons (French, 1997; Gessa

Abbreviations: CB1, cannabinoid 1; cAMP, cyclic adenosine monophosphate; PET, Positron Emission Tomography; THC, tetrahydrocannabinol; DA, dopamine; [11C]PHNO, Carbon-11 labelled (+)-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1, 4]oxazin-9-ol; HC, Healthy controls; CD, Cannabis dependents; CAN, Cannabis; CU, Cannabis Users; MP, Methylphenidate; VT, Total volume of distribution; [^{18}F]FMPEP-d_2, (3*R*,5*R*)-5-(3-[^{18}F] Fluoromethoxy-d_2)phenyl)-3-((*R*)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one; AST, associative striatum.

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et al., 1998) leading to increase in striatal dopamine levels, as measured with microdialysis (Chen et al., 1990; Fadda et al., 2006; Ng Cheong Ton et al., 1988).

Imaging studies have examined the effect of acute THC administration on dopamine release in vivo and have shown overall small but detectable dopamine release measured indirectly via displacement of Positron Emission Tomography (PET) D2 radiotracers. These studies started with an initial anecdotal case report by Voruganti et al. (Voruganti et al., 2001), followed by a study in 7 healthy participants which reported that THC inhalation reduced [^{11}C]raclopride binding in the ventral striatum (VST) and the precommissural dorsal putamen (preDPU), compared to placebo, consistent with an increase in dopamine levels in these regions (Bossong et al., 2009). A third study using the synthetic cannabinoid, dronabinol compared to placebo (Stokes et al., 2009) confirmed these findings and showed displacement of 0.6 to 3% in some striatal subregions not reaching significance but, consistent in magnitude with the other reports. A fourth study showed no effects in that, the doses of IV THC which are sufficient to provoke psychotic symptoms, revealed no significant difference from placebo in stimulating DA release in the striatum (Barkus et al., 2011). There were no relation between positive psychotic symptoms and DA release. **However, this discrepant result could be explainable by a suboptimal experimental design in that, the authors used pseudo-equilibrium methods to derive the binding potential. Pseudo-equilibrium designs are not considered fully quantitative methods, as they may lead to outcome measures that are affected by peripheral clearance and metabolism, or blood flow differences, rather than central receptor related parameters**.

3. Effect of chronic cannabis use on the dopamine system

A first report in 6 patients and 6 controls using [^{11}C]raclopride in chronic users of cannabis showed no group differences in D2/3 receptor availability and no correlations between striatal D2/D3 receptor availability and normalized glucose metabolism in any region of the frontal cortex or striatum (Sevy et al., 2008). This was followed by other negative reports including one in a larger cohort (Stokes et al., 2012), and our own study examining the long-term effects of chronic use of cannabis on both D2/3 receptor availability and striatal dopamine release capacity in chronic non nicotine smokers cannabis dependent participants ($n = 16$), compared to matched controls ($n = 16$). Our study used similar methodology to the above-cited studies in other addictions. Participants were imaged within a similar time frame of abstinence, within a few weeks of last use, as confirmed by urine toxicology (Urban et al., 2012). The most recent study included ten chronic cannabis using subjects and eight demographically matched controls showing also no group differences (Albrecht et al., 2013).

Striatal and extrastriatal dopamine transporter (DAT) were measured using the PET tracer [11C]PE2I (Leroy et al., 2012) in 11 healthy non-smoker subjects, 14 tobacco-dependent smokers and 13 cannabis and tobacco smokers. DAT availability was significantly reduced in the drug users groups, compared to controls. However, since all drug users used nicotine, it is not possible to know if cannabis on its own would have been associated with changes in DAT. A recent study also examined the response of the dopaminergic system to a stress paradigm, using the D3 preferring mixed D3/2 radiotracer [11C]PHNO in cannabis users, and found that chronic cannabis use is not associated with alterations in stress-induced dopamine release (Mizrahi et al., 2013).

A recent study (Bloomfield et al., 2013) compared dopamine synthesis in 19 regular cannabis users who experienced psychotic-like symptoms when they used cannabis with 19 non-users. Positron Emission Tomography (PET) and 3,4-Dihydroxy-6-[^{18}F]-Fluoro/-Phenylalanine ([^{18}F]-DOPA) measured dopamine synthesis capacity. The results indicated that long-term cannabis use was correlated with a dose-dependent decrease in dopamine synthesis capacity in the striatum especially in subjects meeting criteria for cannabis abuse or dependence (effect size: .85; $t36 = 2.54$, $p = .016$). Furthermore, dopamine synthesis capacity was negatively associated with magnitude of cannabis use ($r = -.77$, $p < .001$) and positively associated with age of onset of cannabis use ($r = .51$, $p < .027$) but not with cannabis-induced psychotic-like symptoms ($r = .32$, $p = .19$). The authors conclude that the psychosis induced by cannabis use may not be mediated by dopamine transmission. However, interactions between CB1 and D2 receptors as they colocalize in the striatum in the D2 bearing medium spiny neurons may result in a state of altered D2 signaling regardless of the magnitude of dopamine release, and may contribute to the emergence of psychotic symptoms. Because these interactions are complex, it is difficult to derive conclusive mechanistic insights from imaging studies. In terms of the overall decrease in dopamine synthesis rate seen in this study, as opposed to the remaining literature showing no change, one possible explanation for the discrepancy is that cannabis users in this study had comorbid nicotine and other substance use.

In summary, unlike other addictions, such as alcohol, heroin, cocaine, and methamphetamine (Martinez and Narendran, 2010), **the majority of the studies cited above show that** chronic cannabis abuse or dependence is not associated with alterations in dopaminergic parameters, both pre and postsynaptic (Table 1). This suggests that striatal dopamine transmission, although involved in the acute effects of cannabis, does not play a major role in the neurochemical adaptations thought to be involved in chronic drug addiction. The imaging phenotype measured consistently with alcohol, cocaine and heroin dependence may be a consequence of use of these drugs or a predisposing factor, more studies are needed to clarify this. But, regardless of its nature, it **does not seem to be** associated with cannabis dependence.

Another possible explanation is that the lack of alteration in dopamine may be related to the low severity of dependence in **some of** the studies mentioned above. For example, in our own study, subjects used an average of 517 puffs per month, equivalent to 1–2 puffs a day 5 times per week. Twenty one percent of the initially enrolled participants were disqualified from the study due to their inability to abstain from cannabis use at all. These cases presented with more severe use (2628 estimated puffs per month on average, between 4 and 10 blunts per day and generally daily use) and dependence, which prevented them from going through detoxification without relapsing. Severe cannabis dependence has a similarly high relapse rate and significant withdrawal symptoms comparable to other drugs of abuse (Budney et al., 2003; Kadden et al., 2007). It is possible that more severe use could be associated with alterations in the dopamine system similar to what is seen in other addictions. Stimulant dependent participants with more blunted dopamine transmission are more likely to relapse into drug use than those with more preserved dopamine activity (Martinez et al., 2011; Wang et al., 2012), and our study design may have prevented heavier users from participation, possibly accounting for the absence of a group difference. A study of heavier users is warranted to confirm absence of dopaminergic alterations in the more severe stages of cannabis dependence. However, this potential explanation for our negative results may not necessarily be applicable to the other published reports, as comparable information regarding frequency and severity of use is needed to clarify this issue. One complicating factor in assessing severity across studies is the strength of cannabis used by individual participants in different studies. It is well known that cannabis preparations may vary in potency depending on plant strains, -parts, and preparation (NIDA, 2011 rev.).

Timing of the scan relative to last use is an additional consideration. Normalization of the CB1 receptor in cannabis users within a few weeks of abstinence was recently reported with the CB1 receptor-selective radioligand [^{18}F]FMPEP-d_2. Chronic heavy users showed reduction of CB1 receptor binding in most brain regions that began to reverse after 4 weeks of abstinence (Hirvonen et al., 2012). Also cognitive impairment found in users immediately after