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Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans

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Abstract

Background—Acute and chronic exposure to cannabinoids has been associated with cognitive deficits, a higher risk for schizophrenia and other drug abuse. However, the precise mechanism underlying such effects is not known. Preclinical studies suggest that cannabinoids modulate brain-derived neurotrophic factor (BDNF). Accordingly, we hypothesized that Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the principal active component of cannabis, would alter BDNF levels in humans.

Materials and methods—Healthy control subjects ($n=14$) and light users of cannabis ($n=9$) received intravenous administration of (0.0286 mg/kg) Δ^9 -THC in a double-blind, fixed order, placebo-controlled, laboratory study. Serum sampled at baseline, after placebo administration, and after Δ^9 -THC administration was assayed for BDNF using ELISA.

Results— Δ^9 -THC increased serum BDNF levels in healthy controls but not light users of cannabis. Further, light users of cannabis had lower basal BDNF levels. Δ^9 -THC produced psychotomimetic effects, perceptual alterations, and “high” and spatial memory impairments.

Implications—The effects of socially relevant doses of cannabinoids on BDNF suggest a possible mechanism underlying the consequences of exposure to cannabis. This may be of particular importance for the developing brain and also in disorders believed to involve altered neurodevelopment such as schizophrenia. Larger studies to investigate the effects of cannabinoids on BDNF and other neurotrophins are warranted.

Keywords

Cannabinoids; BDNF; Abuse; Cognition; Cannabis; Marijuana; Neurotrophins; Δ^9 -Tetrahydrocannabinol; Psychosis

Introduction

Acute and chronic exposure to cannabinoids has been associated with short- and long-term effects. For example, acute exposure to cannabinoids produces transient cognitive impairments (Ranganathan and D'Souza 2006), and chronic exposure to cannabinoids may be associated with persistent cognitive deficits (Bolla et al. 2002; Pope and Yurgelun-Todd 1996; Solowij et al. 2002). Further, exposure to cannabinoids in adolescence and in the perinatal period (through maternal cannabis use) has been associated with a number of long-term negative outcomes, including cognitive impairments and a higher risk for schizophrenia and substance abuse disorders (reviewed in Sundram 2006). However, the precise mechanism underlying such effects is unknown.

In preclinical studies, Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the principal active component of cannabis, has been shown to alter brain-derived neurotrophic factor (BDNF) expression (Butovsky et al. 2005; Derkinderen et al. 2003; Maj et al. 2007; Rubino et al. 2006; Valjent et al. 2001). BDNF is a neurotrophin that is involved in the regulation of the genesis, differentiation, survival, and repair of neurons (Binder and Scharfman 2004; Chao et al. 2006). BDNF is known to modulate neuroplasticity and adaptive processes underlying learning and memory (Lu and Gottschalk 2000; Tyler et al. 2002; Yamada and Nabeshima 2003). BDNF binds to TrkB receptors, which are transactivated by endocannabinoids (Berghuis et al. 2005). Further, cannabinoids may alter BDNF expression via actions on the extracellular signal-regulated kinase (ERK) signaling pathway (Derkinderen et al. 2003; Rubino et al. 2006; Valjent et al. 2001). Accordingly, we hypothesized that acute and chronic exposure to cannabinoids would alter serum BDNF levels in humans.

Materials and methods

The study was conducted at the Neurobiological Studies Unit (VA Connecticut Healthcare System-VACHS), with the approval of the Institutional Review Boards of VACHS and Yale University School of Medicine, and in accordance with the Helsinki Declaration of 1975. Subjects were recruited by public advertisement and compensated for their participation.

Participants

Current light users of cannabis and healthy controls were studied. Current light users of cannabis, heretofore referred to as light users, are described elsewhere (D'Souza et al. 2008a, b) and were characterized as having (1) a positive urine toxicological test for cannabis, (2) 10 exposures to cannabis in the past month, (3) 100 lifetime cannabis exposures, and (4) current DSM-IV cannabis abuse disorder. Since most cannabis use in the general population is intermittent, sporadic, and low in amount, we chose to study light users. Healthy controls were characterized as having (1) a negative urine toxicological test, (2) no lifetime cannabis use disorder, and (3) no exposure to cannabis in the past week.

After obtaining written informed consent, subjects (18-55 years) underwent a structured psychiatric interview for DSM-IV (First et al. 2002) and were screened for any DSM Axis I or II lifetime psychiatric disorder and any family history of a major Axis I disorder. Subjects had to estimate their lifetime cannabis exposure (# times), heaviest exposure, and last exposure to cannabis. Subjects were excluded for recent abuse (3 months) or dependence (1

year) to alcohol or any substances other than nicotine dependence in both groups and cannabis abuse in the light user group. Cannabis dependent individuals were excluded as well as cannabis-naïve individuals. Information provided by subjects was confirmed with an individual (spouse or family member) identified by the subject prior to screening. A general physical and neurological examination, EKG and laboratory tests, were conducted. Subjects were instructed to refrain from alcohol, illicit drugs, any medications, or dietary supplements for 2 weeks prior to testing. Light users were permitted to use cannabis until 24 h prior to testing to minimize cannabis withdrawal.

Experimental design

Under double-blind conditions, subjects received in fixed order, placebo (vehicle), followed 125 min later by active Δ^9 -THC (0.0286 mg/kg) administered intravenously (IV) over 20 min (Fig. 1).

Drugs

The dosing paradigm was chosen to model recreational cannabis use and is equivalent to about one (± 0.5) standard National Institute of Drug Abuse (NIDA) cannabis cigarette. The preparation, formulation, and storage of Δ^9 -THC solution and vehicle and the choice of administration route are detailed elsewhere (D'Souza et al. 2008a, b).

Outcome measures

Venous blood sampled from the IV line of the arm opposite to the one used for administering study drug was collected in anticoagulant-free tubes. Immediately after collection, blood samples were placed on ice and centrifuged at 2,000 rpm, and the extracted serum was aliquoted into vials for storage at -80°C .

Samples were assayed in one batch under blinded conditions. Thawed samples were diluted with assay buffer containing a protease inhibitor cocktail ("COMPLETE" Protease Inhibitor—Roche Diagnostics, Germany) to minimize protein degradation. BDNF concentrations were determined using ELISA assays (DuoSet ELISA Development Kit, R&D Systems Minneapolis, MN, USA). Serum samples were diluted 20-fold by combining 12 μl of serum with 228 μl of sample diluent (1% BSA in PBS, pH 7.2-7.4) and thoroughly mixed. ELISA assays were performed according to the manufacturer's directions in 96-well ELISA plates (Corning Costar 3590), and absorbance was determined with a DTX880 Multimode plate reader (Becton-Dickinson) at 450 nm. Standard curves were determined using human BDNF as a reference (R&D Systems) diluted in sample diluent at concentrations from 23.4 to 1,500 pg/ml and were run in duplicate on each plate. Sample BDNF concentrations were then determined by non-linear regression from the standard curves. The detection limit for BDNF was 4 pg/ml. A total of 258 assays were performed on 129 samples, and three samples (2.3%) were dropped from further analysis because of absorbance values outside of the range of the assay. Measurements were performed in duplicate and averaged and are expressed as picograms per milliliter. Crossreactivity of this kit to other neurotrophins (NT-3; NT-4) is reportedly less than 3%.

Psychotomimetic effects were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1989) and Clinician Administered Dissociative Symptoms Scale (CADSS) (Bremner et al. 1998). "High" associated with cannabis intoxication was measured using a visual analog scale described elsewhere (D'Souza et al. 2008a, b). Spatial working memory (SWM) was tested using the Cambridge Neuroscience Test Battery (CANTAB; <http://www.camcog.com>; Sahakian and Owen 1992).

Statistical analysis

Each outcome was tested for normality using Kolmogorov-Smirnov test statistics and normal probability plots. After log transformation, BDNF levels were approximately normal. Linear mixed models were used to analyze BDNF levels (log) with group (light users versus healthy controls) included as a between-subjects factor and time (-90, -10, 20, 65, 145, and 190) included as a within-subjects explanatory factor. The interaction between group and time was fitted. PANSS, CADSS, and VAS high were analyzed using the nonparametric approach for repeated measures data (Brunner 2002) using the same factors above. Spatial working memory data was approximately normal and analyzed using linear mixed models. As above, these models included group as a between-subjects factor; however, since SWM was done only once after placebo and active Δ^9 -THC administration, the time factor was replaced by Δ^9 -THC (placebo and active) as a within-subject factor. Significant interactions were explained by appropriate post hoc tests and graphical displays. Psychotomimetic outcomes were adjusted for multiple comparisons using the Bonferroni correction. All results were considered statistically significant at $p < 0.05$, and data were analyzed using SAS, version 9.1 (SAS Institute, Cary, NC, USA).

Results

The sample consisted of nine light users of cannabis and 14 healthy control subjects. All subjects had been exposed to cannabis primarily by smoking. The groups were matched for most variables except that relative to healthy control subjects; light users had (1) less education and (2) significantly heavier current cannabis use and greater lifetime exposure to cannabis (Tables 1 and 2).

Serum BDNF levels

In both groups, BDNF levels changed over time (time: $F_{5,95}=5$, $p=0.0004$; Fig. 2). Post hoc pair wise comparisons of time points revealed that BDNF levels at the -90 time point (first baseline) were higher than at -10, +20, +65, and +190 time points (all $p < 0.01$). Further, there were group effects with light users of cannabis having lower BDNF levels than healthy controls (group: $F_{1,21}=7.93$, $p < 0.01$); relative to healthy controls, light users had significantly lower serum BDNF levels at all time points except at the -90 and +65 time points. Finally, there was a trend toward a group by time interaction ($F_{5,95}=2.18$, $p=0.06$), with light users of cannabis showing lower BDNF levels relative to healthy controls at the -10 (second baseline), +20, +145, and +190 time points.

Additional pairwise comparisons were conducted between time points. There were no changes in serum BDNF levels following placebo Δ^9 -THC administration, i.e., between the -10 and +20 time points. However, there was an increase in serum BDNF levels between the +65 and +145 min time points trending towards significance ($F_{1,95}=1.77$, $p=0.08$). These data suggest that acute administration Δ^9 -THC increased BDNF levels; this was driven by the control group. Thus, at +145 min, i.e., at the end of the 20-min intravenous infusion of Δ^9 -THC, there were group differences in serum BDNF levels ($F_{1,95}=4.83$, $p=0.03$), with light users failing to show an increase in BDNF levels (Fig. 2).

There were insufficient women in the sample to determine gender effects. Nevertheless, reanalysis of the data excluding the three women in the healthy control group did not change the results. Similarly, reanalysis of the data excluding the two subjects in the healthy control group who had 100 lifetime exposures to cannabis did not change the results.

Behavioral, subjective, and cognitive effects

Consistent with the other reports of intravenous Δ^9 -THC (D'Souza et al. 2008a, b), as illustrated in Fig. 3, Δ^9 -THC produced statistically significant increases (all $p < 0.0001$) in positive symptoms of psychosis (PANSS), perceptual alterations (CADSS), and subjective high (VAS). Spatial working memory deficits (CANTAB) were also observed (group by Δ^9 -THC interaction: $F_{1,20} = 6.6$, $p < 0.05$), predominantly in healthy controls. Further, as reported elsewhere (D'Souza et al. 2008a, b), light users showed blunted responses to most Δ^9 -THC effects (Fig. 3).

Discussion

This is the first study that we are aware of characterizing the acute, acute on chronic, and chronic effects of cannabinoids in humans. Thus, any baseline group differences might reflect the effects of chronic exposure to cannabinoids, whereas the immediate effects of Δ^9 -THC represent the acute effects of cannabinoids. Finally, any group differences in the immediate effects of Δ^9 -THC might reflect acute on chronic differences.

The relatively rapid increase in serum BDNF levels in healthy controls but not light users following Δ^9 -THC administration, i.e., difference in BDNF levels between the +65 and +145 time points, suggests a direct effect of Δ^9 -THC. Further, light users had lower basal serum BDNF levels, and in the absence of any other obvious baseline group differences, the most likely explanation for this finding is the group difference in cannabis exposure. Light users in this study used cannabis intermittently and modestly in contrast to other samples (Haney et al. 1999; Hart et al. 2001; Heishman et al. 1997), and therefore it will be important to estimate the effect of heavier cannabis use on serum BDNF levels.

In preclinical studies, Δ^9 -THC (1-1.5 mg/kg i.p.) induced a 10-30% increase in BDNF messenger RNA (mRNA) in certain brain regions (Butovsky et al. 2005; Derkinderen et al. 2003). However, the effects of longer cannabinoid exposure are mixed. While not equivalent to the chronic intermittent exposure to cannabis in our sample, subacute daily Δ^9 -THC exposure (1.5 mg/kg i.p. daily $\times$ 7 days) up-regulated BDNF in a region-specific manner in rats (Butovsky et al. 2005). In contrast, Maj showed that adult rats exposed to CB1 agonist in their prenatal period (through maternal exposure) show significantly lower BDNF levels in the hippocampus and frontal cortex (Maj et al. 2007).

The lack of Δ^9 -THC-induced effects on serum BDNF levels in light users is consistent with other recent reports showing that light users of cannabis show blunted responses to many of the other acute behavioral, cognitive, physiologic, and endocrine effects of Δ^9 -THC (D'Souza et al. 2008a, b). As reported elsewhere, these group differences cannot be explained by pharmacokinetic differences (D'Souza et al. 2008a, b). Similarly, the lower basal serum BDNF levels in light users of cannabis is consistent with other reports of basal endocrine differences in light users of cannabis (Ranganathan et al., in review).

Δ^9 -THC may alter BDNF levels by a mechanism involving the activation of ERK. Acute injection of Δ^9 -THC has been shown to induce BDNF mRNA transcription by stimulating CB1 receptors and activating the ERK signaling pathway (Derkinderen et al. 2003; Rubino et al. 2006; Valjent et al. 2001). Moreover, the time frame of this response is consistent with the Δ^9 -THC-induced increase in serum BDNF levels observed in our study.

Chronic exposure to cannabinoids is associated with downregulation and desensitization of CB1 receptors (Gonzalez et al. 2005; Lichtman and Martin 2005). The blunted Δ^9 -THC-induced BDNF release observed in light users of cannabis may reflect a downregulation of CB-1R associated with chronic cannabis exposure. Of note, Δ^9 -THC-induced activation of

ERK may be a critical event in triggering the alteration in CB1 receptor function underlying tolerance (Rubino et al. 2004, 2005, 2006). Perhaps, the effects of cannabinoids on ERK signaling are central both to their effects on BDNF and the development of tolerance. The lower basal BDNF levels in light users of cannabis suggest that chronic exposure to cannabinoids can lead to a suppression of BDNF release.

Implications

The effects of cannabinoids on BDNF provide a mechanism by which exposure to cannabinoids may interfere with normal brain development and contribute to the development of some neuropsychiatric disorders.

There is growing interest in the association between cannabinoids and schizophrenia, but little is known about the mechanisms underlying this association. One view of schizophrenia is that it is a neurodevelopmental disorder (Rapoport et al. 2005; Weinberger 1996), and neurotrophic factors have been implicated in its pathophysiology (Buckley et al. 2007; Pillai 2008; Shoval and Weizman 2005). Thus, acute and repeated exposure to cannabis in adolescence and young adulthood may further compound an already abnormally developing brain by altering BDNF levels in a nonphysiologic manner. While admittedly speculative, this may provide a mechanism underlying the observation that cannabis precipitates schizophrenia or alters the course of the disorder.

Similarly, if decreased neurogenesis in the hippocampus is a mechanism underlying mood changes, such as depression (Duman 2002; Duman et al. 2000), then cannabis exposure may promote the development of mood disorders by altering BDNF and consequently neurogenesis.

Cognition

BDNF is known to modulate synaptic plasticity and adaptive processes underlying learning and memory, leading to long-term functional and structural modification of synaptic connections (Lu and Gottschalk 2000; Malcangio and Lessmann 2003; Tyler et al. 2002; Yamada and Nabeshima 2003, 2004). Healthy controls showed a Δ^9 -THC-induced increase in serum BDNF levels and Δ^9 -THC-induced worsening in spatial working deficits. The disruption in spatial working memory (Ranganathan and D'Souza 2006; Riedel and Davies 2005) and the increase in BDNF levels (Derkinderen et al. 2003; Rubino et al. 2006; Valjent et al. 2001) following acute administration of Δ^9 -THC are consistent with the literature. However, since learning is associated with increased BDNF levels in the hippocampus (Lu et al. 2008), tying the findings of an increase in serum BDNF levels together with spatial working memory deficits in healthy controls is challenging. Several provisional interpretations are offered. The changes in serum BDNF levels associated with Δ^9 -THC administration being nonphysiological may contribute to a disruption, rather than a facilitation of learning. Further, perhaps peripheral BDNF levels may not accurately reflect the changes in BDNF levels associated with learning in relevant brain areas, e.g., hippocampus.

Chronic exposure to cannabis may be associated with persistent cognitive deficits (Bolla et al. 2002; Pope and Yurgelun-Todd 1996; Solowij et al. 2002). Light users of cannabis did not show increases in serum BDNF levels or spatial working memory deficits induced by Δ^9 -THC-induced. This blunted response is consistent with blunted responses to the cognitive, behavioral, and endocrine effects of cannabinoids in frequent users of cannabis (D'Souza et al. 2008a, b).

Strengths and limitations

The use of placebo, the double-blind design, the weight-adjusted dose, the standardized delivery of Δ^9 -THC, the temporal relationship between Δ^9 -THC administration and changes in serum BDNF levels, and the use of well-validated measures are some of the strengths of this study. Further, the study of light users of cannabis increases the generalizability of the findings given that cannabis use in the general population is generally light.

While limited, the sample size of this preliminary study is comparable to that of some published reports on the effects of interventions (e.g., exercise, electroconvulsive therapy) on serum BDNF (Ferris et al. 2007; Gronli et al. 2007; Rojas Vega et al. 2006; Tang et al. 2008). Nevertheless, for a follow-up study with a larger sample groups more distinct for their cannabis exposure, the inclusion of women and characterization of the influence of polymorphisms of the BDNF gene are warranted.

In this preliminary study, central BDNF levels were not assayed. Hence, the source of the increase in serum BDNF levels, i.e., central vs. peripheral source, cannot be determined conclusively. While BDNF has been described as not being able to cross the blood-brain barrier by some (Pardridge et al. 1994), experimental studies demonstrate that peripherally administered BDNF passes through the blood-brain barrier (Pan et al. 1998; Poduslo and Curran 1996) and can have central effects (Berger et al. 2004; Muller et al. 2008; Schabitz et al. 2000; Schabitz et al. 2007). Further, it has been shown that disruption of the blood-brain barrier enhances the passage of BDNF across the blood-brain barrier. Therefore, it is possible that BDNF released in the CNS could cross the blood-brain barrier and spillover into serum. It is also possible that Δ^9 -THC induces changes in serum BDNF levels via direct effects on peripheral cells known to release BDNF. Future studies will need to be conducted to localize the source of Δ^9 -THC-induced increases in serum BDNF levels.

Alternatively, increases in serum BDNF may be related to the effects of Δ^9 -THC on platelets (Fujimura et al. 2002; Radka et al. 1996), lymphocytes (Kerschensteiner et al. 1999; Noga et al. 2003), and endothelial cells (Nakahashi et al. 2000). Of note, lymphocytes carry cannabinoid receptors (Pettit et al. 1996; Schatz et al. 1997), and platelets derive most of their BDNF from neuronal and glial cells.

Given that the only known mechanism by which Δ^9 -THC and other cannabinoids induces BDNF release is via stimulation of CB1 receptors (Derkinderen et al. 2003; Rubino et al. 2006; Valjent et al. 2001) and that CB1 are distributed principally in the brain, it may be reasonable to expect that the alterations in serum BDNF levels that were observed in this study may be accompanied by similar changes in brain BDNF levels.

Platelets release BDNF into the serum in response to coagulation stimuli (Yamamoto and Gurney 1990). Since the amount of BDNF released from platelets (serum/whole-blood BDNF) was not measured in this study, it is not clear whether the reduction in serum BDNF in light users of cannabis is due to reduced release from platelets rather than to reduced production.

BDNF levels are modulated by various other factors, including but not limited to age, gender, stress, endocrine function, exercise, and mood. The two groups were matched on most variables to the extent possible, and the most obvious difference between the two groups was their exposure to cannabis. However, there remains the possibility that factors other than cannabis exposure might account for the group differences in basal and Δ^9 -THC-induced BDNF levels.

In conclusion, preliminary evidence suggests that acute and chronic intermittent exposure to socially relevant doses of Δ^9 -THC alter serum BDNF levels in humans. These findings suggest a mechanism by which cannabinoids can influence neuroplasticity in humans. Clearly, further studies are warranted to investigate the effects of cannabinoids on neurotrophins.

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Abbreviations

Δ-9-THC	delta-9-tetrahydrocannabinol
CB	Cannabinoid
BDNF	brain derived neurotrophic factor

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Fig. 1.
Schedule of procedures

Fig. 2.
Serum BDNF levels (*T bars* indicate SEMs)

Fig. 3.

a Positive symptoms of psychosis measured by the positive symptoms subscale of the PANSS. **b** Perceptual alterations measured by the subject rated subscale of the CADSS. **c** High measured by the VAS. **d** SWT: Spatial Working Memory measured by the CANTAB (*T* bars indicate SEMs)

Table 1

Demographics [mean (SD)]

	All	Healthy subjects	Light users
Total (<i>n</i> =23)	23	14 (3 females)	9
Age years	24.6 (±6.56)	25.85 (±7.98)	22.66 (±2.82)
Current tobacco smokers (≤ 5 cigarettes/day)	1	0	1
Years of education ^a	15.7 (2.07)	16.2 (±2.4)	14.77 (±.97)
Weight	160.9 (±30.23)	159.8 (±33)	162.5 (±27.3)

^a *t* test; *p*=0.08

Table 2**Cannabis use histories**

	Healthy subjects	Light users
Estimated self-reported lifetime cannabis exposure		
Less than 5 times	2	0
5-10 times	2	0
11-20 times	2	0
21-50 times	3	0
51-100 times	3	1
>100 times	2	8
Group difference (Wilcoxon Signed Rank Test) $p<0.0001$		
Last exposure to cannabis		
Past week	0	9
1 week-1 month	5	0
1-6 months	3	0
6 months-1 year	2	0
1-5 years	4	0
5-10 years	1	0
Group difference (Wilcoxon Signed Rank Test) $p<0.0001$		