Hippocampal Gray Matter of Cannabis Users is correlated with Cannabidiol Obtained from Hair Analysis

T. Demirakca[1], G. Ende[1], A. Sartorius[2], N. Meyer[1], H. Welzel[1], A. Meyer-Lindenberg[2], G. Skopp[3], K. Mann[4], and D. Hermann[4]

[1]Neuroimaging, Central Institute of Mental Health, Mannheim, Germany, [2]Psychiatry, Central Institute of Mental Health, Mannheim, Germany, [3]Institute of Forensic and Traffic Medicine, Heidelberg, Germany, [4]Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health

Introduction

In search of an explanation of cannabis associated memory alterations, several studies investigated the hippocampal volume of chronic cannabis users. Three volumetric studies analyzing the hippocampus failed to show differences between cannabis users and control subjects, even in cannabis users with very heavy and long-term cannabis use (4,5,6). A recent, study of hippocampal and amygdala volume using manual delineation showed decreased bilateral volumes negatively correlated with the self-reported amount of cannabis consumption (2). Concerning the tissue composition one study showed lower gray matter density in the right parahippocampal gyrus (7). None of these studies has accounted for the proportion of delta-9-tetrahydrocannabinol (THC) and the non-psychogenic cannabidiol (CBD) included in the consumed cannabis products. Preclinical research gave evidence that THC acts as a partial agonist of cannabinoid (CB) receptors and CBD as an antagonist of CB-receptor agonists (1). This controversial action of THC and CBD is confirmed by the clinical observation that THC is associated with psychotic symptoms (2), whereas CBD prevents psychotic symptoms (3).

We present the first voxel-based-morphometry (VBM) analysis of the hippocampus correlating the results of hair analyses of THC and CBD with the results of VBM to further differentiate what effect the main ingredients of cannabis have on hippocampal structure.

Methods and Materials

Ten healthy, male, non-treatment seeking recreational cannabis users and 13 age- and IQ- matched male control subjects, all students, were included. Cannabis was used for 5.4 years in an average daily dose of 0.27 g. The concentration of THC and CDB in hair samples was determined by gas chromatography-/mass spectrometry and was 0.31±0.2 ng THC/mg hair and 0.13±0.14 ng CBD/mg.

Isotropic T1-weighted MR images of 1 mm thickness were obtained on a 1.5 T Siemens Vision System and analysed with SPM5 and the VBM5 toolbox (Gaser, C. http://dbm.neuro.uni-jena.de/vbm/). Images were segmented and normalized to the MNI–template. After smoothing with a 12 mm^3 isotropic Gaussian kernel, modulated and unmodulated gray matter (GM) images were used for group comparison and regression analysis.

Results

The results of the ANCOVA of VBM data with nuisance variables alcohol and nicotine consumption revealed no significant differences in hippocampal GM and WM concentration or GM and WM volume between cannabis users and controls. A multiple regression analysis of CBD and THC with GM concentration in cannabis users showed a significant positive correlation of CBD with hippocampal GM concentration (unmodulated data, Figure 1 (red)). Small clusters of the right hippocampus GM tissue were also correlated with THC but the significance did not reach the defined threshold for multiple comparisons.

Discussion

Although hippocampal volume and tissue composition showed no significant differences between groups, a significant correlation of unmodulated hippocampal gray matter and CBD was observed bilaterally, indicating a positive influence of CBD on hippocampal neurons. High variation in the proportion of THC and CBD may therefore contribute to divergent results of other studies. Furthermore the observed positive correlation might indicate neuroprotective properties of CBD. As a possible mechanism of morphologic alterations the influence of cannabinoids on hippocampal neurogenesis has to be discussed.

The correlation of CBD with GM argues for a causal effect of cannabis use, but this is no proof. Molecular and cell biology research suggests a cannabinoid mechanism being able to alter brain volume by influencing hippocampal neurogenesis. Other studies reported that the number of neurons and synapses was decreased after THC administration and hippocampal neurons were smaller (8,9). Altogether these preclinical studies support the view of THC inhibiting neurogenesis, which may be observed as volume reduction in vivo. Corresponding studies of CBD are missing and may be of interest for several neuropsychiatric diseases/deficits with impairment of the hippocampus, e.g. memory deficits or depression.

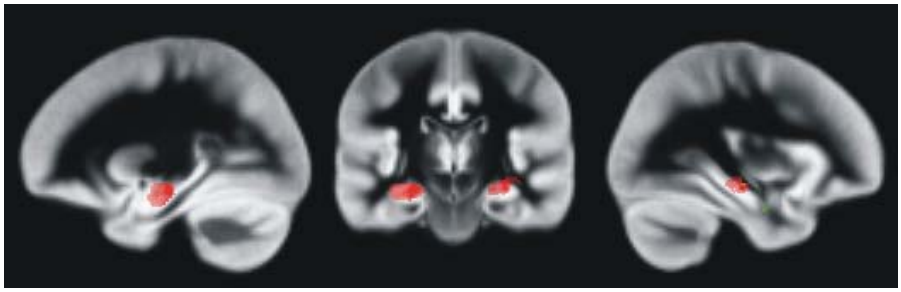

Figure 1: Regression of CBD and THC with gray matter concentration in cannabis users, ROI analysis of positive correlation CBD-GM (red) and THC-GM (green), p 0.005 uncorrected.

1. Pertwee RG. (2008) Br J Pharmacol. 153:199-215
2. Yücel M. et al. (2008) Arch Gen Psychiatry. 65:694-701
3. Leweke M. et al. (2007) European Psychiatry 22: S21
4. Block RI. et al. (2000) Neuroreport. 11:491-6.
5. Jager G. et al. (2007) Eur Neuropsychopharmacol. 17:289-97.
6. Tzilos GK: et al. (2005) Am J Addict. 14:64-72.
7. Matochik JA. et al. (2005) Drug Alcohol Depend. 77:23-30
8. Landfield PW.et al. (1988) Brain Res. 443:47-62
9. Scallet AC. et al. (1987) Brain Res. 436:193-8.