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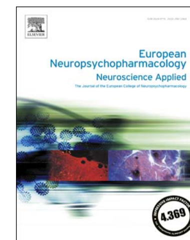

The acute effect of cannabis on plasma, liver and brain ammonia dynamics, a translational study

Osama A. Abulseoud[a,*], Maria Laura Zuccoli[a,b], Lifeng Zhang[c], Allan Barnes[a], Marilyn A. Huestis[a], Da-Ting Lin[c,**]

[a]*Chemistry and Drug Metabolism Section, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA*
[b]*Department of Internal Medicine, Pharmacology and Toxicology Unit, University of Genoa, Italy*
[c]*Neural Engineering Unit, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA*

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Abstract
Recent reports of ammonia released during cannabis smoking raise concerns about putative neurotoxic effects. Cannabis (54 mg) was administered in a double-blind, placebo-controlled design to healthy cannabis users (n=15) either orally, or through smoking (6.9%THC cigarette) or inhalation of vaporized cannabis (Volcano®). Serial assay of plasma ammonia concentrations at 0, 2, 4, 6, 8, 10, 15, 30, and 90 min from onset of cannabis administration showed significant time (P=0.016), and treatment (P=0.0004) effects with robust differences between placebo and edible at 30 (P=0.002), and 90 min (P=0.007) and between placebo and vaporized (P=0.02) and smoking routes (P=0.01) at 90 min. Furthermore, plasma ammonia positively correlated with blood THC concentrations (P=0.03). To test the hypothesis that this delayed increase in plasma ammonia originates from the brain we administered THC (3 and 10mg/kg) to mice and measured plasma, liver, and brain ammonia concentrations at 1, 3, 5 and 30 min post-injection. Administration of THC to mice did not cause significant change in plasma ammonia concentrations within the first 5 min, but significantly reduced striatal glutamine-synthetase (GS) activity (P=0.046) and increased striatal ammonia concentration (P=0.016). Furthermore, plasma THC correlated positively with striatal ammonia concentration ($P<0.001$) and negatively with striatal GS activity (P=0.030). At 30 min, we found marked increase in striatal ammonia ($P<0.0001$) associated with significant increase in plasma ammonia (P=0.042) concentration.

*Correspondence to: Chemistry and Drug Metabolism Research Section, National Institute on Drug Abuse, National Institutes of Health, Biomedical Research Center, Suite 200 Room 07A-514, 251 Bayview Boulevard, Baltimore, MD 21224, USA.
**Corresponding author.
E-mail addresses: osama.abulseoud@nih.gov (O.A. Abulseoud), da-ting.lin@nih.gov (D.-T. Lin).

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In conclusion, the results of these studies demonstrate that cannabis intake caused time and route-dependent increases in plasma ammonia concentrations in human cannabis users and reduced brain GS activity and increased brain and plasma ammonia concentrations in mice.
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1. Introduction

Cannabinoids have been shown to be both beneficial and detrimental to neuronal and glial activity and brain plasticity dependent on the dose, route, cannabinoid in question and experimental conditions (Campbell, 2001; Chan et al., 1998; Harper et al., 1977; Heath et al., 1980; Landfield et al., 1988; Rocchetti et al., 2013; Scallet et al., 1987). However, the underlying mechanisms of potential cannabis-induced neurotoxicity remain poorly understood (Scallet, 1991). Recent reports demonstrate that cannabis smoke and heated cannabis plant contain high concentrations of ammonia (Bloor et al., 2008; Moir et al., 2008) and chronic parenteral administration of cannabis resin to dogs was associated with significant increase in blood ammonia concentration (de Pasquale et al., 1978) while exposing rabbits to hashish smoke every other day for a period of one month resulted in a marked increase in blood ammonia concentration (Ghoneim et al., 1980). Inhaled ammonia (released during smoking) is absorbed quickly through the large surface area of the lungs into the systemic circulation where it diffuses passively through the blood brain barrier (BBB) (Keiding et al., 2006). The brain, with limited capacity to detoxify ammonia through the urea cycle (Ratner et al., 1960), sequesters ammonia into glutamine by astrocytic glutamine synthetase (GS) enzymes (Cooper and Jeitner, 2016). Astrocytic glutamine serves as an energy metabolite or gets shuttled to glutamatergic neurons where it is converted into glutamate by glutaminase or shuttled to GABAergic neurons where it produces GABA by glutamic acid decarboxylase (Albrecht et al., 2007). In addition, part of the astrocytic glutamine leaves the brain to the blood in exchange for large neutral amino acids tryptophan, phenylalanine, and tyrosine (James et al., 1978; Jessy et al., 1990; Mans et al., 1982). Under normal physiological conditions brain GS operates at near maximum capacity (Butterworth et al., 1988; Cooper and Plum, 1987; James et al., 1978). An increase in systemic blood ammonia could cause a corresponding increase in brain glutamine and brain ammonia concentrations. Increased brain glutamine may increase brain tyrosine and tryptophan concentrations, which could accelerate brain dopamine and serotonin synthesis (Wurtman and Fernstrom, 1975). On the contrary, high brain ammonia is neurotoxic through the disruption of mitochondrial energy metabolism (Lai and Cooper, 1991), alteration in neuronal firing patterns (Dynnik et al., 2015), activation of glutamatergic signaling (Albrecht et al., 2007; Hermenegildo et al., 1998), and astrocytic swelling (Gorg et al., 2013). In these studies, we aimed to measure plasma ammonia concentrations during and after controlled cannabis administration to cannabis users via different routes. Additionally, we used a translational approach to examine the acute effect of delta-9-tetrahydrocannabinol (THC) on plasma, liver and brain ammonia concentrations and on the activities of GS and GA at different time points.

2. Experimental procedures

2.1. Human study

The study protocol was approved by the National Institute on Drug Abuse Institutional Review Board and all participants provided written informed consent. An investigational new drug (IND) exemption was obtained from the Food and Drug Administration and the Drug Enforcement Agency approved cannabis administration. Study procedures took place at the NIDA Intramural Research Program during the interval form September 2014 through September 2015 (ClinicalTrials.gov Identifier NCT02177513).

2.1.1. Study design

The study design was double blind, placebo-controlled, randomized, and crossover study with four sessions. In each session, healthy occasional (smoking frequency $\geq$ 2x/month but $<$ 3x/week) and frequent cannabis smokers (smoking frequency $\geq$ 5x/week) were asked to consume a placebo or active oral (baked in a brownie) cannabis dose (contains $\approx$ 54 mg THC) followed by either placebo (contains $<$ 0.001 mg THC) or active smoked or vaporized cannabis. Only one active and one placebo dose was administered in each dosing session. [either active brownie, and placebo vaporized, or active brownie and placebo cigarette, or placebo brownie and active vaporized, or placebo brownie and active cigarette] or two placebo doses [placebo brownie and placebo vaporized, or placebo brownie and placebo cigarette] were administered in each dosing session. Oral cannabis doses were prepared per Duncan Hines® Double Fudge cake-like brownie instructions. The contents of an active or placebo cigarette were ground, baked for 30 min at 121 °C in aluminum foil, and mixed into equal portions of batter in a muffin tin. Following baking, individual doses were stored frozen, but allowed to thaw refrigerated overnight before dosing. Participants consumed the oral and smoked or vaporized dose *ad libitum* over 10 min. Randomization was accomplished with the aid of a random number generator. The order for all four sessions was randomly assigned. Additionally, whether the smoked or vaporized placebo is paired with the active oral dose was also randomly rotated between participants. Randomization was generated by computer algorithm operated by NIDA pharmacy.

Study inclusion criteria were: males and females 18-50 years of age, consuming cannabis in the past 3 months. A positive urine cannabinoid screen was required for frequent cannabis smokers. Exclusion criteria were: use of cannabis for medical purposes to avoid the confounding of two active cannabis doses (i.e. medical cannabis dose and study controlled cannabis dose), history of significant adverse events associated with cannabis intoxication, current physical dependence (DSM-IV) on any drug other than cannabis, caffeine, or nicotine, history or presence of any clinically significant illness. Pregnant or nursing females were also excluded

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