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## The acute effect of *cannabis* on plasma, liver and brain ammonia dynamics

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Cannabis is a psychoactive substance widely used for both medicinal and recreational purposes. Cannabis-induced acute cognitive and motoric side effects are common and remain without effective treatment. A better understanding of the neurobiological mechanisms underlying cannabis-related effects is urgently needed to facilitate the discovery of novel therapeutics. We recently observed elevation in ammonia plasma concentrations during and after oral, smoke or vapor cannabis controlled administration (54mg) to 15 healthy cannabis users. Cannabis produced significant time ($p<0.05$) and treatment ($p<0.001$) effects, with differences in plasma ammonia between placebo and edible cannabis administration at 30 ($p<0.05$) and 90min ($p<0.05$), between placebo and vaporized ($p<0.05$) and smoking routes ($p<0.05$) at 90min. Plasma ammonia concentration positively correlated with blood -9-tetrahydrocannabinol (THC) concentrations ($p<0.05$). Using a translational approach, we then examined the acute effect of THC on plasma, liver and brain ammonia concentrations and enzyme activity in different brain regions of mice at 1, 3, 5 and 30min after a single THC injection. We found significant reduction in striatal glutamine synthetase (GS) activity ($p<0.05$) and increase in striatal ammonia concentration ($p<0.05$) 5min post-injection. THC plasma concentration correlated positively with striatal ammonia ($p<0.001$) and negatively with striatal GS activity ($p<0.05$). At 30min, we found marked increase in striatal ammonia ($p<0.001$), associated with significant increase in plasma ammonia ($p<0.05$). For the first time, we demonstrate that plasma ammonia concentration increases after controlled cannabis administration and we provide evidence that this increase could be generated in the brain through suppression of striatal GS activity.

### Recent Publications

1. Rangroo Thrane V, Thrane A S, Wang F, Cotrina M L, Smith N A, et al. (2013) Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering. Nat Med. 19(12):1643–8.
2. Eid T and Lee T S (2013) Reassessing the role of astrocytes in ammonia neurotoxicity.Nat Med. 19(12):1572–4.
3. Bloor R N, Wang T S, Spanel P, Smith D (2008) Ammonia release from heated 'street' cannabis leaf and its potential toxic effects on cannabis users. Addiction 103:1671–1677.
4. Landfield P W, Cadwallader L B and Vinsant S (1988) Quantitative changes in hippocampal structure following long-term exposure to delta9-tetrahydrocannabinol:possiblemediationbygluco-corticoid systems. BrainRes. 443:47–62.

### Biography

Maria Laura Zuccoli obtained my medical degree from the University of Genoa, Italy, and I completed the residency in Clinical Toxicology at the University of Florence, in Italy. I am currently a PhD candidate in Experimental Medicine at the University of Genoa and a Visiting Fellow at the National Institute on Drug Abuse, in Baltimore, USA. My main research topics focus on the understanding of neurobiological mechanisms involved in the effects of widely abused substances such as cannabinoids, opioids and alcohol, using *in vivo* two-photon endomicroscopy, optogenetic and chemogenetic behavioral assays and molecular biology techniques.

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