“Metabolic Profiling”: a new strategy for the study of metabolic diseases.

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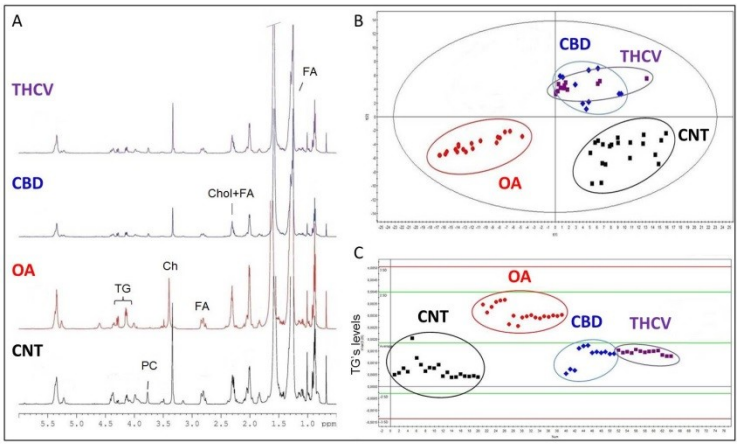
Metabolomics describes the chemical profile of an organism in terms of metabolites, which are the end products of all chemical reactions of metabolism. The metabolic profile can be defined as a 'fingerprint’ as it characterizes the biochemical phenotype of a biological system as a whole, by taking a snapshot of the overall metabolic levels. The study of the alterations induced by a disease, for instance, may help to highlight any dysfunction of the related metabolic pathways, thus revealing metabolites that can be considered as putative biomarkers useful for diagnostic purposes. Indeed, in agreement with the School of Medicine at Harvard University, Metabolomics is currently considered as one of the most effective methods of analysis to ascertain the state of health of a person (see: http://harvardmagazine.com/2011/05/fathoming-metabolism).

The research group of the Institute of Biomolecular Chemistry in Pozzuoli (ICB), working in this field since long time, is currently involved in metabolomics and lipidomics through Nuclear Magnetic Resonance (NMR) spectroscopy and Mass Spectrometry coupled to Liquid Chromatography (LC MS) analysis of biofluids, cells and tissues, for the characterization of a wide range of pathologies ranging from respiratory airway diseases to metabolic disorders. One of the latest applications is dealing with the study of hepatosteatosis, by investigating the effects of non-psychoactive cannabinoids on lipid levels in hepatocytes[1].

Multivariate statistical data analysis applied to NMR metabolic profiles (see fig. A) highlighted significant variations of some metabolite levels in human hepatocytes (HHL-5) after cannabidiol (CBD) and Δ9-tetrahydrocannabivarin (THCV) administration in samples treated with oleic acid. The applied projection method, named Projection to Latent Structure Discriminant Analysis (PLS-DA), generates a statistical model which allows a clear visualization and classification of samples according to their common alterations found in spectral profiles (see fig. B). In particular, cells treated with CBD and THCV showed increasing levels of polar compounds glutathione (GSH), adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD), which are essential metabolites involved in the antioxidant activity and the energetic process. More interestingly, an intense decrease of triglycerides down to control levels (see fig. C) was observed together with a simultaneous increase of free fatty acids. This may suggest the effect of the two cannabinoids to consist in the ‘speeding-up' of lipid metabolism and the increase of mitochondrial activity in hepatocytes. Moreover, one can suppose the breakdown of triglycerides in favor of the release of ‘free’ lipids as possible mechanism of action. Those findings have been further confirmed by in *vivo* data obtained from zebrafish and obese mice.



A) NMR spectra of lipophilic extracts obtained from HHL-5 control (CNT) and treated cells with oleic acid (OA), CBD or THCV. B) PLS-DA scores plot showing spectral projections and samples separation. C) Signal variations of triglycerides levels measured in all sample classes.

Our results suggest that THCV and CBD might be used as new therapeutic agents for the pharmacological treatment of obesity and the metabolic syndrome, by pointing out the ‘omic’ approach as an increasingly feasible strategy, whose future direction is currently defined as ‘personalized medicine’.

[1]C Silvestri, D Paris, A Martella, D Melck, I Guadagnino, M Cawthorne, A Motta, V Di Marzo. *Two non-psychoactive cannabinoids reduce intra-cellular lipid levels and inhibit hepatosteatosis.* Journal of Hepatology, *IN PRESS*.