Systemic cannabidiol administration in healthy mice induces changes in energy metabolism and reduces protein translation in ventral CA1 neurons

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Introduction: Cannabidiol (CBD) is one of the main cannabinoids present in *Cannabis sativa*. CBD interacts indirectly with the endocannabinoid receptors and also modulates multiple non-endocannabinoid signaling systems. Thus, CBD has already been explored as a therapeutic strategy showing anticonvulsant, neuroprotective, and antiepileptic effects under various conditions, both in humans and animal models. To explore the CBD effect on the transcriptome we used RNAseq to quantify gene expression of the ventral CA1 hippocampal region after intraperitoneal administration of CBD for 1 or 7 days, and compare to their controls. After this, we analyze how much and which genes were differentially expressed and how they may affect biological processes when compared to control animals.

Methods: Adult C57BL/6JUnib mice (Animal Use Ethics Committee protocol 5367-1/2019) were separated in 4 experimental groups: CR1 - 1 day administration of NaCl 0,15 M, i.p., CBD1 - 1 day treatment with CBD (100 mg/kg, i.p.), CR7 - 7 days administration of NaCl 0,15 M, i.p. and CBD7 - 7 days treatment with CBD (100 mg/kg, i.p.). Animals were euthanized 24h after the last administration, and their brains processed for laser microdissection using Zeiss PALM LCM. The ventral CA1 pyramidal layer was collected from each sample, total RNA was extracted, and libraries were prepared for RNA-seq in the Illumina Hiseq platform. Sequences were aligned, quantified and compared with the STAR Aligner/DESeq2 pipeline. Gene Ontologies (GO) were analyzed with the clusterProfiler R-package.

Results: We ran two pairwise comparisons in DESeq2 for CBD treatments and obtained the following differentially expressed genes results (adjusted $p<0,05$): 299 (CBD1xCR1) and 1936 (CBD7xCR7). PCA displays an evident clustering of CBD7xCR7 samples, while CBD1xCR1 samples overlap. GO analysis revealed a distribution of just one significant (p.adjust < 0.05) GO term for CBD1xCR1 considering all differentially expressed genes. On the other hand, CBD7xCR7's GO analysis evidenced 76 terms significantly enriched (p.adjust <0.05). Downregulated genes list provided top enriched terms like: '*mitochondrion organization*', '*cytoplasmic translation*', '*oxidative phosphorylation*' and '*ribosome biogenesis*'. Furthermore, GO analysis for upregulated genes in CBD7xCR7 displays the following top enriched biological terms: '*covalent chromatin modification*', '*regulation of cell morphogenesis involved in differentiation*', and '*synapse organization*'.

Conclusion: Here we present many biological processes found enriched in CBD treatments and present an extensive list of molecular components for each of these processes. Furthermore, the dataset indicates that 7 days of systemic CBD treatment in healthy mice induces an extensive change in energy metabolism and marked reduction of protein translation in ventral CA1 neurons.