Multi-level biological network analysis of differentially expressed proteins in the corpus callosum of chronic alcohol users

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Introduction: The corpus callosum connects the left and right hemispheres of the brain, integrating sensory, motor, and cognitive information. Chronic alcohol intake is associated with demyelination and necrosis of the corpus callosum and adjacent subcortical white matter. Alcohol-induced damage in this brain area is seldom explored, even though it has been associated with impairment of visual and logical memories. Furthermore, metabolic or neuroinflammatory mechanisms may explain the effects of alcohol in the corpus callosum. In this multi-level biological network analysis, we aimed to characterize the expression pattern of proteins in the corpus callosum of chronic alcohol users.

Methods: We systematically reviewed the literature to identify reports of differentially expressed proteins (DEPs; log2 FC > 1: upregulated; log2 FC < ?1: downregulated) in the corpus callosum of alcohol users (post-mortem). After data extraction, we performed functional enrichment analysis in Metascape and constructed a protein-protein interaction (PPI) network using the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) platform. Lastly, we imported the PPI network into the software Cytoscape 3.10.2 and used MCODE and cytoHubba plugins to analyze protein clusters and hub/bottleneck genes of significance. Enrichment terms were considered significant when FDR *q*-value < 0.01, and clusters with a score > 5 in MCODE were selected.

Results: Our analysis revealed a total of 186 DEPs in the corpus callosum of alcohol users, being that the majority (69%) were upregulated. Functional enrichment analysis revealed that upregulated genes were mainly involved in metabolic processes of nucleobase-containing small molecules. Cytoscape PPI analysis identified two main clusters with 13 and 16 proteins each, and highlighted *ACTB* (actin beta) as the main hub (score: 50) and bottleneck (score: 2507) gene.

Conclusion: Chronic alcohol intake upregulated proteins involved with nucleotide metabolism in the corpus callosum with a prominent role of the actin beta gene, which correlates with its structural function. These results show the potential of proteomics-based multi-level biological network analyses for precise determination of the neurobiological hallmarks of chronic alcohol use and dependence.

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