Differentially Expressed Proteins in the Prefrontal Cortex of Individuals with Alcohol Use Disorder: a Multi-level Biological Network Analysis

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Introduction: Alcohol use disorder (AUD) is a chronic medical condition characterized by a dysfunctional pattern of alcohol consumption that persists despite adverse consequences. To date, few studies have explored differentially expressed proteins (DEPs) and potential targets implicated in the neurobiology of AUD. A better understanding of these mechanisms, supported by precision medicine, is of utmost importance to develop innovative treatments for reducing alcohol addiction symptoms. In this study, we propose a multi-level biological network analysis using proteomic data to identify the most prevalent changes in protein expression in the prefrontal cortex (PFC) of individuals with AUD. **Methods:** We conducted a systematic review to identify databases with DEPs in the PFC of post-mortem individuals with AUD. Afterward, we identified hub and bottleneck genes via protein-protein interactions network analysis using Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) and Cytoscape tools. Finally, we used the Metascape web-based tool for the analysis and visualization of functional enrichment and biological networks. **Results:** We identified 331 DEPs in a network of 4450 edges. Most DEPs identified in the PFC of individuals with AUD were downregulated (68%) and correlated to metabolic processes such as aerobic respiration, vesicle-mediated transport, and cellular responses to stress. We identified four clusters, each one with 46, 33, 26, and 16 proteins that were involved in metabolic pathways. The determination of hub and bottleneck genes in the network and the survival analysis showed notable importance of GAPDH (Glyceraldehyde 3-phosphate dehydrogenase) and ACTB (Actin Beta) expression with a degree of 159 and 139, respectively. **Conclusion:** Globally, our results showed that AUD is associated with a notable decrease in metabolic processes in the PFC, suggesting a potential impact of alcohol addiction on executive functions and decision-making behaviors. Therefore, the application of multi-level biological network analyses is useful in precision medicine, providing insights into altered brain metabolism and its implications.

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