Investigating proteomic and metabolomic signatures in mesial temporal lobe epilepsy: insights into novel therapeutic strategies

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Introduction: Mesial temporal lobe epilepsy (MTLE) is the most prevalent form of focal epilepsy in adults, characterized by a significant proportion of patients who do not respond to conventional antiseizure medications. Synaptic transmission is a key element in normal brain function and may also play an important role in epilepsy. Thus, we may gain additional insights into the mechanisms driving MTLE by studying synaptic transmission. Synaptosomes, which preserve the critical machinery for neurotransmitter release, reuptake, and storage, offer a valuable opportunity to study synaptic function in normal brain and disease tissue. This study examines synaptosome proteomic and metabolomic profiles from patients with MTLE displaying typical signs of hippocampal sclerosis. Materials and Methods: Synaptosomes were isolated from hippocampal and anterior temporal lobe tissues collected during epilepsy surgery from pharmacoresistant MTLE patients (N=20) and post-mortem controls (N=5). We used an Orbitrap EclipseTM TribridTM mass spectrometer for proteomic analysis and an LCMS-9030 quadrupole time-of-flight (Q-TOF) Shimadzu instrument for metabolomic signatures acquisition. Our results were analyzed and integrated using bioinformatics tools implemented in the ProteomeDiscoverer and R software, supported by SynGO, STRING PPI, and ClueGO tools to explore biological abnormalities found. Results:The analysis revealed significant variations in synaptosome protein and metabolite compositions from different brain regions. Proteins identified in patient synaptosomes were predominantly associated with the presynaptic compartment, followed by postsynaptic and synaptic membrane components. Our integrative analysis indicated heightened hippocampal responses in serotonin and dopamine release cycles and notable changes in NMDA receptor expression and insulin receptor dynamics. Additionally, increased sensitivity to toxic substances suggested potential implications for drug metabolism within the hippocampus. Discussion: This study identifies distinct proteomic and metabolomic profiles in synaptosomes from various brain regions in patients with pharmacoresistant MTLE. The predominance of presynaptic proteins and observed changes in neurotransmitter release cycles and receptor dynamics emphasize the complex molecular basis of MTLE. These findings offer valuable insights into potential therapeutic targets and provide a foundation for future research to improve treatment strategies for pharmacoresistant MTLE. Conclusion:The comprehensive multiomics analysis conducted in this study sheds light on the intricate molecular mechanisms underlying pharmacoresistant MTLE. By unraveling the proteomic and metabolomic signatures associated with synaptic dysfunction, neurotransmitter dynamics, and drug metabolism, our findings pave the way for future studies on targeted therapeutic interventions and personalized management strategies that may be directed to patients who do not respond to conventional treatments.

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