Time-dependent Analysis of Oxylipins and Lipidomic Profiling of Brown Adipose Tissue: Implications for Amyotrophic Lateral Sclerosis

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INTRODUCTIONAmyotrophic lateral sclerosis (ALS) results in complex metabolic consequences, including hypermetabolism, muscle atrophy, weight loss, and dysregulation of lipid metabolism. The systemic inflammatory response and the role of oxylipins, oxidized lipid mediators, are key aspects. Understanding these metabolic changes is crucial for developing effective therapeutic approaches in managing ALS.OBJECTIVESOur study aims to map lipid and oxylipin alterations potentially linked to dysregulated energy metabolism in ALS.MATERIALS AND METHODSBlood plasma was collected every two weeks from the rats\' 50th day of life until the manifestation of symptoms in the severe form, clinical score 5 (time points: 50, 64, 78, 92, 106, 120, 134, 148 days); and brown adipose tissue (BAT) was collected from male WT and SOD1-G93A (ALS) rats at asymptomatic (70 days) and symptomatic (128 days) stages. Symptomatic animals were divided into fast progressors (fpALS, clinical score = 5) and slow progressors (spALS, clinical score = 2). Blood plasma and BAT homogenate oxylipins were enriched by SPE and then analyzed by UHPLC coupled to ESI-TOF-MS.DISCUSSION AND RESULTSLipidomic analyses highlighted significant changes in the lipid composition of BAT, including triglycerides (-20%, ALS70 vs WT70), diglycerides (+50%, ALS70 vs spALS), cholesterol (+25%, ALS70 vs spALS), plasmalogens (+45%, ALS70 vs spALS), and ubiquinones (+75%, ALS70 vs spALS), other significant changes were noted in specific lipid classes influenced by age. Oxylipin analysis in blood plasma showed significant alterations in linoleic acid diols (9,10- and 12,13-DiHOMEs) as well as in eicosanoids derived from arachidonic acid in the early life. Notably in BAT in asymptomatic stages exhibited an increase in inflammatory mediators such as Prostaglandin D2 (PGD2).CONCLUSIONOur data show a reduction of octadecanoids at the onset of ALS, and a lipid remodeling in BAT, which was followed by a marked increase in plasmalogens, cholesterol and ubiquinones. These data open new frontiers for the molecular investigation of dysregulated lipid pathways in ALS. Further studies are being conducted to investigate lipid remodeling and oxylipin alterations and their functional role in ALS disease progression.

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