Exploring the Impact of Alcohol on Cerebral Vasculature: Insights Into the ATX-LPA-LPP3 Axis

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Alcohol consumption leads to complications in brain blood vessels and biological function, but how alcohol damages such vessels is unclear. Lysophosphatidic acid (LPA) signaling, regulated by autotaxin (ATX) and lipid phosphate phosphatase 3 (LPP3), maintains vascular integrity in alcohol-exposed brains. Understanding blood-brain barrier (BBB) damaging factors and endothelial hyperpermeability following reperfusion are vital for aiding stroke treatment and managing vascular permeability. We hypothesize that high alcohol levels disrupt endothelial cell junctions by exacerbating oxidative stress, altering cellular permeability through LPA-mediated signaling. Mouse and human brain microvascular endothelial cells (MBMECs, HBMECs) were subjected to various ethanol concentrations. Molecular changes were analyzed via Western blot and qPCR. Endothelial permeability was monitored using an electrical cell-substrate impedance sensor, mitochondrial function via Seahorse assays, and ATX activity through AR-2 probe fluorescence. Ethanol at 50mM significantly increased ATX activity and LPA levels, while decreasing LPP3 and KLF2 expressions in HBMEC. ATX inhibitor PF8380 reduced ethanol-induced ICAM-1 elevation and permeability changes. LPA exacerbated MBMEC permeability and disrupted junctional protein continuity. The LPAR1 inhibitor AM095 and LPAR inhibitor Ki16425 mitigated these effects. LPA reduced mitochondrial function in MBMEC and hypoxic reperfusion raising ATX protein production, enhancing LPA production and increasing endothelial permeability. This study elucidates ATX-LPA-LPP3 pathway's role in vascular function, highlighting alcohol’s impact on permeability. Further exploring LPA pathway therapies will protect cerebrovascular health from the detrimental effects of alcohol.

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