The Role of Autotaxin-LPA-LPP3 Axis in Ischemic Stroke

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Ischemic stroke is one of the leading causes of death and permanent disability. Blood- brain barrier (BBB) disruption greatly contributes to ischemic brain damage. Lysophosphatidic acid (LPA) is an important signaling lipid. It is produced by autotaxin and inactivated by lipid phosphate phosphatase-3 (LPP3). The goal was to investigate the role of autotaxin-LPA- LPP3 axis in BBB disruption following ischemic stroke. In in vivo studies, adult male C57BL/6J mice were subjected to ischemia or sham ischemia for 90 minutes. Protein and mRNA expression of autotaxin and LPP3 in the brain tissue were examined using Western Blot analysis and Real-Time PCR, respectively. LPA concentration in plasma was measured by liquid chromatography-mass spectrometry. In in vitro studies, C57BL/6J mouse brain microvascular endothelial cells (MBMVECs) were treated with LPA. Barrier integrity of MBMVECs was evaluated by immunofluorescence staining and transendothelial electrical resistance (TER) measurement. Autotaxin was found to be significantly upregulated and LPP3 was dramatically downregulated in the ischemic brain. Consistently, plasma LPA increased significantly from 0.51 +/- 0.01 μM to 1.82 +/- 0.03 μM after ischemic stroke. In in vitro studies, 1 μM LPA treatment induced a discontinuous junctional protein alignment and significantly reduced TER, suggesting an increase in endothelial barrier permeability. Furthermore, LPP3 siRNA transfection downregulated LPP3 protein expression and exacerbated LPA-induced TER reduction. However, LPA-induced TER reduction could be completely abolished by the inhibition of LPA receptors in LPP3 siRNA-transfected MBMVECs. Thus, the autotaxin-LPA- LPP3 axis may play a crucial role in ischemic brain damage by compromising BBB integrity.

Awards Won:

Fourth Award of $500

American Physiological Society: Third Award of $500