The Neurobiology of Suicide: Claudin-5 Is a Novel Biomarker of Suicide Pathogenesis

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Every forty seconds, suicide steals a life, yet no biomarkers exist for suicide. Suicide has largely been investigated from a psychological lens, and therefore the pathogenesis remains unclear. This study investigated blood-brain barrier (BBB) claudin-5 breakdown, the most enriched BBB tight junction, as a biomarker for suicide. Human de-identified postmortem brain tissue (n=20) was stratified based on suicide as a cause of death. ELISAs assessed cytokine and claudin-5 levels, St. Paul-Ramsey Scale (SPRS) evaluated stressful life events, and an immunolabeling solvent-cleared organs protocol determined claudin-5 anatomical localization. RNA-sequencing data from publicly available repositories was aligned to perform pathway enrichment and differential expression analyses. Molecular docking software PyRx determined whether current medications to treat suicide and anti-inflammatory compounds dock with claudin-5. IL-6 and IL-8 were higher in suicide cases ($p < 0.05$) indicating neuroinflammation and claudin-5 was increased in the brain of suicide cases ($p < 0.05$). Photomicrographs indicated mislocalization of claudin-5 in neurons and brain microvessels of suicides. Inflammatory and neurodegenerative pathways modulating claudin-5 degradation were found. BBB destabilizing matrix metalloproteinase-1 (MMP-1) was upregulated ($log2F2 = 4.10$, $p < 0.001$), and aquaporin-1 (AQP1) was downregulated ($log2F2 = -1.58$; $p < 0.001$) in suicide. Molecular docking indicated a weak affinity of antidepressant medications for claudin-5, but a strong affinity for medications targeting MMP-1 and AQP1. High claudin-5 levels and SPRS scores could serve as pre-markers for suicide. Future in vitro assessments should evaluate the novel therapeutics promoting claudin-5 for suicide risk prevention.

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