Blood-Brain Barrier Dysfunction in Alzheimer’s Disease: An Environmental Health Perspective

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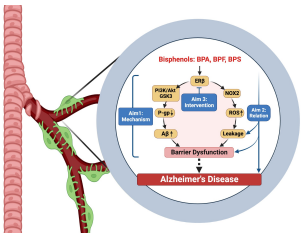

Blood-brain barrier dysfunction contributes to cognitive decline in Alzheimer’s disease. Two key elements of barrier dysfunction include loss of P-glycoprotein, a transporter that clears Ab from the brain, and development of barrier leakage. We focus on environmental factors that trigger loss of P-glycoprotein and barrier leakage, and thus, pose a risk factor for cognitive impairment in Alzheimer’s disease. Our study funded by a UK-CARES grant and a NIHR01, showed that the xenoestrogen bisphenol A (BPA) triggers barrier dysfunction and causes cognitive impairment in vivo in mice. We also found barrier dysfunction, high oxidative stress levels, and high BPA levels in human brain samples from CAA patients compared to cognitively normal individuals, suggesting a potential role for BPA in AD. Data from our ongoing study indicate that the FDA-approved estrogen receptor blocker Fulvestrant reduces BPA-induced loss of P-gp, barrier leakage, Aβ capillary levels, and memory deficits in vivo. Based on our existing data, we are currently in the process of developing therapeutic strategies to repair barrier dysfunction to lower Aβ brain burden with the ultimate goal of improving memory loss and delaying onset and slowing progression of Alzheimer’s disease.