Modeling the Alzheimer's disease network

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Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting over 10% of the population over the age of 65 years. Clinically, AD is described by the symptom set of short term memory loss and cognitive decline, changes in mentation and behavior, and eventually long-term memory deficit as the disease progresses. On imaging studies, significant atrophy with subsequent increase in ventricular volume have been observed. Pathology on post-mortem brain specimens demonstrates the classic findings of increased beta amyloid (Aβ) deposition and the presence of neurofibrillary tangles (NFTs) within affected neurons. Neuroinflammation, dysregulation of blood-brain barrier (BBB) transport and clearance, deposition of Aβ in cerebral blood vessels, vascular risk factors such as atherosclerosis and diabetes, and the presence of the apolipoprotein E4 (apoE4) allele have all been identified as playing possible roles in AD pathogenesis. Given the variety of hypotheses that have been proposed for AD pathogenesis, an interconnected, multilayer network model offers a unique opportunity to combine these ideas into a single unifying model.

The model developed in this paper uses a combination of network theory and chemical rate equations from transport analysis to describe the interactions between the above pathogenesis hypotheses. We further introduce the idea of the role of the brain interstitial fluid (ISF) to transport Aβ towards the paravascular space surrounding cerebral blood vessels to be cleared by either the glymphatic pathway or by receptors (the low density lipoprotein receptor-related protein, LRP1) at the BBB, recent pathways that have been observed *in vivo* with imaging experiments. Briefly, the brain is divided into 3 main compartments: the brain parenchyma, the paravascular space (including the glymphatic clearance route, BBB and brain endothelial cells of the vessel), and the blood in the cerebral blood vessel. Within each compartment, a network is used to describe the interactions between Aβ generation from the amyloid precursor protein (APP), inflammatory markers, expression of key transport markers at the BBB, and the survival of neurons. The interactions between these molecules can be turned on or off dependent on whether conditions exist to change what molecules are currently being expressed. Transport of Aβ through the brain parenchyma is modeled via transport by brain ISF where ISF flow rate is a function of heart rate and vessel stiffness of the nearest artery or arteriole.

Results of this model demonstrate that there are several key interactions that have not previously been studied or discussed much, including the role that changes in cerebral vasculature during aging can have on clearance of Aβ from the brain and the role that vessel inflammation may have on local function of the BBB. Possible future areas of experimental and mathematical work will also be discussed.

References

[1] Salminen, A et al, "Inflammation in Alzheimer's disease: amyloid-beta oligomers trigger innate immunity defence via pattern recognition receptors" Prog Neurobiol 87(3) pp. 181-94, 2009.

[2] Potter, H, T Wisniewski, "Apolipoprotein E: essential catalyst of the Alzhimer amyloid cascade" Int J Alz Dis doi:10.1155/2012/489428, 2012.

[3] Zlokovic, BV, "The blood-brain barrier in health and chronic neurodegenerative disorders" Neuron 57(2) pp. 178-201, 2008.

[4] Iliff, J.J., M. Wang, Y. Liao, B.A. Plogg, W. Peng, G.A. Gundersen, H. Benveniste, G.E. Vates, R. Deane, S. A. Goldman, E. A. Nagelhus, M. Nedergaard, "A Paravascular Pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β" Sci Transl Med 4(147) pp. 147, 2012.