AAV-Induced Upregulation of Aquaporin-4 Expression as a Means of Bolstering Beta-Amyloid Oligomer Eflux

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Alzheimer's Disease is a terminal illness which accounts for 60-80% of all cases of dementia; despite this, there are no effective treatments/cures, only "disease-modifying drugs" which temporarily delay the largely invariable prognosis. In 2012, the work of Iliff et al. discovered a (pseudo-lymphatic microglia-dependent) nonspecific metabolite waste clearance system hence termed the "glymphatic system". Further research into this system's involvement in neurodegenerative pathologies implicated this system as a principal actor in proper brain metabolite flux, and its sleep-dependent, aquaporin-4 (AQP4)-facilitated "washing" was found to be paramount in maintaining proper synaptic function. Loss of glymphatic functionality, due to AQP4 dysfunction or otherwise, led to the exacerbation of aggregate-related neurodegenerative disorders such as Alzheimer's Disease or amyotrophic lateral sclerosis (ALS) and effecting in systemic neural failure, cognitive decline, and more rapid neurodegeneration than in functional glymphatic system controls. Although the pathological consequences of glymphatic failure have been extensively characterized, there is yet no research investigating whether glymphatic supplementing procedures may yield a neurologically protective effect. Therefore, reinforcing the glymphatic system's functional longevity, such as through upregulation of AQP4 expression/polarization, is a logical step in the evaluation of potential therapeutic avenues against neurodegenerative diseases, especially in the context of under-studied biological pathways. We thereby intend to utilize murine models of Alzheimer's Disease and an adeno associated virus (AAV) vector hybridized with a copy of the AQP4 gene in order to evaluate the risk-benefit balance between the clinical efficacy of this procedure and its potential complications.