CSF/ISF highways for tau brain clearance

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Research Abstract
? DESCRIPTION (provided by applicant): Monomeric tau, an intracellular microtubule-associated protein, undergoes a progressive transition to insoluble aggregates of the tau filaments (neurofibrillary tangles (NFTs), a feature of tauopathies, such as Alzheimer’s disease (AD). Recently it was shown that wild type monomeric tau is released into the interstitial fluid (ISF) from healthy normal young brains which, under favorable conditions, could enhance the

formation of extracellular tau aggregates. However, the mechanism of monomeric tau clearance from the ISF is unknown. In AD, aggregated tau is present in the perivascular space, and tau oligomers are associated with arterioles. In corticobasal degeneration, tau is deposited around blood vessels and associated with astrocytic plaques and tuft-shaped astrocytes. In AD, levels of cerebrospinal fluid (CSF) tau are increased. These observations may suggest possible clearance routes from brain. Since monomeric tau is the precursor of the misfolded and aggregated tau, its removal from the CSF/ISF is critical in reducing tau accumulation. Recently, the glymphatic system was shown to play a major role in clearance of by-products of neural activity. This system consists of three main pathways: (1) influx of sub-arachnoid CSF via the para-arterial space, (2) astrocytic aquaporin 4 (AQP4)-dependent convective flow of brain ISF, and (3) efflux via para-venous clearance. In addition, CSF can be cleared from brain via the cervical lymph. Our preliminary data show that monomeric tau was cleared from the CSF and from brain parenchyma via the glymphatic and cervical lymphatic systems, and that this was reduced with aging and in Aqp4 ko mice. However, short fibrils were retained longer in brain. We hypothesize that the glymphatic/lymphatic systems are critical for brain-wide clearance of tau and that age-related failure in these systems contributes to its accumulation. There are two aims, 1) Characterization of the tau clearance mechanisms from CSF and brain ISF in mice, and 2) Evaluating the effects of aging and AQP4 on the clearance of tau protein species from brain. The kinetics of 125I-tau distribution and elimination will be determined by using our non-invasive technique and recording brain radioactivity with an external counter after intracisternal injection. We will use in vivo real-time 2-photon and confocal microscopy to delineate the influx of tau, CSF/ISF exchange and clearance pathways. Cervical lymph clearance kinetics will be analyzed using real-time in vivo imaging of the cervical lymphatic vessels and nodes. We expect that the data will show that tau (monomer >fibril) is cleared via CSF/ISF exchange and convective ISF flow, and by the cervical lymph. Clearance via both pathways will be reduced with aging and in Aqp4-/- mice. Tau fibrils will be retained longer in brain due to cellular bindin. These studies may lead to entirely novel targets for tau clearance to slow or even prevent AD related neurocognitive decline by improving glymphatic/lymphatic clearance of tau, and other toxic molecules.

Further information available at:

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