Modulation of tau pathogenesis by high dietary fat, gender and ApoE isoform

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Research Abstract
? DESCRIPTION (provided by applicant): Genes, environment and gender influence Alzheimer (AD) risk, but the development of models to investigate common risk factors like age, ApoE4, high fat and gender on tauopathy and their interaction is surprisingly limited. Tau, the main tangle protein, can be downstream of ?-amyloid (A?), the main constituent of the neuritic

plaque, but tau can accumulate independent of A? in response to other factors including neuroinflammation. High saturated fat Western diet is an AD risk factor that increases neuroinflammation and tau expression, independent of A? deposition. High saturated fat diet increases human ApoE4 risk and src/fyn kinase activation in lipid rafts upstream of JNK activation that is opposed by dietary n-3 fatty acids. In our preliminary data high fat increased src/fyn site pY307 PP2A inactivation, pJNK and ptau. Integrated genomic analysis of human ApoE4 data reveals increased FYN kinase at the center of an E4 network hub. Although E4 can modulate A? deposition, female E4 carriers have much higher risk, now confirmed in recent AD Neuroimaging Initiative (ADNI) data, that also finds that female E4 carriers have more CSF tau - irrespective of A?. This argues that E4/gender/tau interactions contribute to E4 gender risk. However, there are no tauopathy models currently available to test gender risk mechanisms or treatments and interactions involving E4 and tau. Introducing an ApoEKO background into a mutant tauopathy model increased the number of ptau positive neurites, suggesting loss of function of ApoE accelerates tauopathy. In Aim 1 we will cross the hutauTg mouse onto the ApoE KO background (EKO-TAU) to determine the impact on tau pathogenesis, influence of gender and gonadectomy to emulate loss of gonadal steroids with aging. In Aim 2 we cross human TR ApoE3 or ApoE4 into this EKO-TAU line, to generate the E3TAU and E4TAU model, creating resources for the exploration of understanding tau-ApoE isoform associations, independent of (or dependent on) A?. This aim will determine ApoE modulatory and interactive effects of gender and high fat on tau pathogenesis. Since our preliminary data support a role for saturated fat/src/fyn/PP2A/JNK and AKT/GSK3 pathway and gender effects, Aim 3 uses a pure tauopathy model to determine the effects of Western diet (17% fat) and gender and their interaction on tau pathogenesis, neuroinflammation, src/fyn, RACK1 and PP2Aand AKT/GSK3 regulation during aging and independent of A?. We will evaluate synaptic and cognitive deficits, changes in activity of tau kinases including fyn, neuroinflammation and our focus, the dysregulation of PP2A. Completion of these aims will have broad implications, including development of a novel model for ApoE-tau interactions, demonstrating isoform-differences in tau accumulation, kinase regulation and neuroinflammation and ApoE x gender- specificity for high fat induced tauopathy. The new models will permit testing novel therapeutics targeting ApoE dependent effects on tau. This is high impact because of compelling data that both AD and ApoE4 modulate PP2A activity-now linked to tauopathy and disease progression.

Further information available at:

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