we treated neurons with various compounds to stimulate or inhibit neuronal activity. **Results:** We show that stimulation of neuronal activity by KCl or glutamate, or specific AMPA receptor activation, induces tau release from mature cortical neurons. Further analysis of secreted tau revealed that phosphorylation of extracellular tau appears reduced in comparison to intracellular tau. We also find that AMPA-induced release of tau is calcium-dependent, and is mimicked by treatment of neurons with the ionophore ionomycin. Blocking pre-synaptic vesicle release by tetanus toxin, and inhibiting neuronal activity with the neurotoxin tetrodotoxin, both significantly impair AMPA-stimulated tau release. Analysis of neuronal exosomes revealed barely detectable levels of tau, indicating that tau secretion is unlikely to occur via exosome release. **Conclusions:** Endogenous release of tau from neurons is a regulatable process, dysregulation of which could lead to the spread of tau pathology in disease.

O2-01-04 INFLAMMATORY PATHWAYS LINK AMYLOID AND TAU PATHOLOGY

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Background: Alzheimer's disease (AD) and non-AD tauopathies are a major cause of dementia, disability and death in the elderly. Neuropathological characteristics of AD include; intracellular aggregates of hyperphosphorylated microtubule associated protein tau (MAPT) in neurofibrillary tangles and extracellular deposits of the beta-amyloid peptide in senile plaques along with marked neuroinflammation, while non-AD tauopathies have both MAPT aggregates and neuroinflammation. While these pathological alterations are invariably observed within the diseased brain the exact relationship between neuroinflammatory processes, beta-amyloid, and MAPT pathologies remains unclear. Increasing evidence suggests that inflammatory processes may contribute to the pathopysiology of AD as well as non-AD tauopathies. First, there are increased numbers of activated astrocytes and microglia as well as increased expression of numerous pro-inflammatory molecules within the brain. Second, retrospective epidemiological studies demonstrated that long-term use of non-steroidal anti-inflammatory drugs substantially reduces AD risk. Third, recent studies utilizing genetically modified mouse models have implicated several different inflammatory pathways in AD-like pathologies. **Methods:** Neuronal-microglial communication through the chemokine fractalkine (CX3CL1) and its cognate receptor, CX3CR1, plays a critical role in neuroinflammation and neuroprotection. Notably, CX3CL1 is highly expressed by neurons while CX3CR1 is only expressed by microglia within the CNS. In the current studies, we provide evidence that membrane-tethered neuronal CX3CL1 signals to microglial CX3CR1 and in the process regulates both beta-amyloid and MAPT pathologies in opposing directions. Briefly, animals that were deficient for CX3CR1, CX3CL1 or the membrane anchored form of CX3CL1 were mated to the APPPS1 mouse model of beta-amyloid deposition and the htau mouse model of MAPT pathology and aged to determine the effects of the development of these two hallmark AD pathologies. **Results:** Our results demonstrate that loss of either total or membrane anchored CX3CL1 as well as CX3CR1 leads to reduced beta-amyloid pathology, but enhanced MAPT pathology. Current studies are focused on identifying alterations in microglia that could explain the potential disease mechanisms linking CX3CL1-CX3CR1 signaling to both beta-amyloid and MAPT pathologies. **Conclusions:** In summary, our results suggest that a specific inflammatory pathway between neurons and microglia links beta-amyloid and MAPT pathologies that could serve as a potential therapeutic target in future translational studies.

O2-01-05 THE RELATIONSHIP AMONG MTOR, BETA-AMYLOID AND TAU: THERAPEUTIC IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Background: Accumulation of beta-amyloid and tau is an invariant feature of Alzheimer's disease (AD). The upstream role of beta-amyloid accumulation in disease pathogenesis is widely accepted, and there is strong evidence showing that beta-amyloid accumulation causes cognitive impairments. However, the molecular mechanisms linking beta-amyloid to cognitive decline remain to be elucidated. Several lines of evidence indicate that deregulation in the balance between protein synthesis and degradation, which is crucial for maintaining neuronal function, may play a role in the disease pathogenesis. The mammalian target of rapamycin (mTOR) plays a key role in maintaining protein homeostasis as it regulates both protein degradation (via autophagy) and protein synthesis. **Methods:** Using several mouse models of AD and related disorders, we employ multidisciplinary approaches to dissect the molecular mechanisms linking beta-amyloid, tau and mTOR signaling. **Results:** We will show that the buildup of beta-amyloid increases the mammalian target of rapamycin (mTOR) signaling, while decreasing mTOR signaling reduces beta-amyloid levels, thereby highlighting an interrelation between mTOR signaling and beta-amyloid. Also, we will show that genetically increasing mTOR activity, significantly increase tau levels and phosphorylation. Further, using complementary animal models of AD, we will show that pharmacologically restoring mTOR signalling with rapamycin rescues cognitive deficits and ameliorates beta-amyloid and tau pathology by increasing autophagy. **Conclusions:** The results presented here provide a molecular basis for the beta-amyloid-induced cognitive deficits and show that mTOR dysregulation may be a valid terapeutic target for AD and related disorders. Indeed, we show that rapamycin, an FDA approved drug, improves learning and memory and reduces beta-amyloid and tau pathology.

O2-01-06 THE NUCLEOTIDE BINDING DOMAIN OF HEAT SHOCK COGNATE PROTEIN 70 (HSC70) REGULATES TAU CLEARANCE AND STABILITY

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Background: Alzheimer's disease (AD) is characterized by deposition of pathological protein inclusions of beta-amyloid (amyloid plaques) and tau (neurofibrillary tangles). The accumulation of the intrinsically disordered tau into conformations that lead intracellular tangles is linked to neuronal loss and cognitive dysfunction, which are hallmarks of AD. These structural changes in tau are mediated by Hsp70 and Hsp90 families chaperone proteins. We have previously demonstrated that Hsp70 proteins can interact with both normal and pathological tau and can clear tau via proteasome-mediated and autophagic mechanisms. In addition to degradation, Hsp70s can alter the stability and phosphorylation state of tau. To that end, we recently discovered that drugs targeting the nuclear binding domain (NBD) of the constitutively expressed heat shock cognate protein 70 (Hsc70) inhibited Hsc70 ATPase activity and potently reduced tau levels in a proteasome-dependent manner. To understand the mechanism of this drug, we introduced point mutations in this region to gain insight into how the nucleotide-bound status of Hsc70 impacted tau stability and clearance. **Methods:** Purified recombinant Hsc70 with or without point mutations in the NBD were subjected to ATPase and luciferase refolding assays. Hsc70-mediated effects on tau stability and clearance were analyzed in neuronal cells overexpressing wt or mutant Hsc70. **Results:** Point mutants of Hsc70 had distinct stimulatory or inhibitory effects on ATPase activity and luciferase refolding activity. In particular, one mutant inhibited both activities (E175S). Overexpression of the E175S mutant in neuronal cells resulted in a reduction in tau levels, decreased tau co-localization with tubulin and decreased microtubule stability. In contrast, the Hsc70 mutant F68L, which stimulated both ATPase activity and refolding activity, did not impact tau levels. E175S expression increased levels of polyubiquitnated tau, and inhibition of the proteasome restored tau levels in E175S-expressing cells to that of wt Hsc70, thereby suggesting E175S stimulates tau clearance via the proteasome. **Conclusions:** These data indicate regulation of the conformation of the NBD of Hsc70 may be a potential for therapeutic intervention for the treatment of AD.