Background: Trans-synaptic spread of tau pathology is AD is generally accepted but the process is poorly understood. We have recently reported that most synaptic tau is c-terminal truncated, and have also demonstrated depolarization-induced release of total tau from AD but not aged control synapses. Release of tau from synapses is a presumed major source of CSF tau, which is a core CSF biomarker for AD and other neurodegenerative diseases, including traumatic brain injury. The importance of extracellular tau is highlighted by a recent literature documenting success with tau immunotherapy; however a lack of clarity about the precise species of tau peptide that is released presents a significant barrier with respect to tau immunotherapeutic approaches. **Methods:** We examined the supernatants from depolarized synaptosomes to categorize the peptide species of tau and investigate release of exosomes in a series of normal and AD cases. Release experiments used cryopreserved synaptosomes prepared from samples with a post-mortem interval less than 12h; synaptosomes were depolarized in a 5 min incubation in Kreb's Ringer buffer containing 50mM KCl. **Results:** In the present experiments, tau release supernatants were probed with an antibody directed against the intact C-terminus of tau, and demonstrated a 6-fold increase in release of intact C-terminal tau by depolarization in AD samples (79.25 vs. 494 RFU, $p<0.002$); no significant depolarization-induced release was observed in aged control synaptosomes. An antibody directed against caspase-cleaved tau (TauC3 antibody; D421) did not reveal differential release. Release of exosomes into tau release supernatants was probed with the exosome-associated protein Alix (PDCD61P), an auxillary ESCRT protein that supportes viral budding. Alix is detected as a ~75 kDa protein in tau release supernatants, but shows only a trend for depolarization-induced release in the control samples. **Conclusions:** These results demonstrate robust depolarization-induced release of tau from cryopreserved postmortem AD synaptic terminals, and indicate release of multiple tau peptide species along with synaptic release of exosomal markers. Because C-terminal truncated tau is associated with increased aggregation, release of tau with an intact C terminal may follow from retention of fragmented tau in intraterminal aggregates.

O2-06-04 TAU DELETION TRIGGERS AGE-DEPENDENT SCIATIC NERVE MORPHOFUNCTIONAL DEFICITS AND MOTOR IMPAIRMENT

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Background: Dementia is the cardinal feature of Alzheimer's disease (AD) but the clinical symptoms of this disorder also include a marked loss of motor function. While Tau hyperphosphorylation and malfunction are well-established key events in AD neuropathology, the impact of the loss of normal Tau function in neuronal degeneration and subsequent behavioral deficits is still debated. Indeed, animals lacking Tau protein (Tau-KO) exhibit motor impairment but the underlying mechanism(s) are still largely unknown. **Methods:** In this study, we provide a detailed characterization of motor deficits in old (17-22-months old) Tau-KO animals followed by ultrastructural, molecular and functional impairments of efferent fibers that convey motor-related information. **Results:** Using a battery of motor-related tests, we demonstrated the establishment of motor deficiency in Tau-KO by aging while the sciatic nerve of old Tau-KO mice displays increased degenerating myelinated fibers and diminished conduction properties, as compared to age-matched wild-type (WT) littermates and younger (4-6 months old) Tau-KO and WT mice. In addition, the sciatic nerves of Tau-KO mice exhibit a progressive hypomyelination (assessed by g-ratio) specifically affecting large-diameter, motor-related axons in old animals. **Conclusions:** These findings suggest that loss of Tau protein may progressively impact on peripheral motor system adding to our understanding of peripheral neurological deficits in AD and other tauopathies.

O2-06-05 TOWARD UNDERSTANDING PATHOGENESIS OF UBQLN2-MEDIATED FTD/ALS

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Background: Mutations in Ubiquilin2 (UBQLN2) were recently identified as a cause of Frontotemporal Dementia/ Amyotrophic Lateral Sclerosis (FTD/ALS) associated with TDP43 deposition. The involvement of UBQLN2 in ALS/FTD – and of the broader family of Ubiquilin proteins in a wide variety of neurodegenerative diseases – may reflect the fact that this family of ubiquitin receptor proteins normally helps maintain neuronal protein homeostasis. The function of Ubiquilins in health and disease, however, remains poorly understood. **Methods:** To explore disease pathogenesis of UBQLN2-mediated FTD/ALS, we employed a combination of protein biochemistry, cell-based expression studies and transgenic mouse models of disease. **Results:** In vitro studies of full length, recombinant UBQLN2 protein support the view that the protein can form dimers and is intrinsically prone to form aggregates. Data from transgenic mice expressing wild type or mutant UBQLN2 further support the view that UBQLN2 is an intrinsically aggregate-prone protein and that pathogenic mutations accelerate the aggregation process. In transgenic mice expressing a pathogenic form of UBQLN2, the protein becomes sequestered in large aggregates found throughout the central nervous system. UBQLN2 aggregate pathology is particularly robust in the hippocampus, where the aggregates localize with ubiquitin and p62. A fraction of aggregates also stain positively for proteasome markers. In contrast, wild type UBQLN2 largely remains diffusely distributed in neurons, though some neurons display spherical puncta enriched for UBQLN2. Additional results describing UBQLN2 interactors and their potential contribution to FTD/ALS will be presented. **Conclusions:** Our results support a dominant toxic effect of mutant UBQLN2 driving disease, associated with aggregation of the disease protein.

O2-06-06 TAU TUBULIN KINASES PROMOTE PROTEINOPATHY IN BOTH FTLD-TAU AND FTLD-TDP-43

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Background: Pathological aggregates of phosphorylated TDP-43 characterize many neurodegenerative diseases including frontotemporal lobar degeneration, amyotrophic lateral sclerosis and Alzheimer's disease. The regulation of phosphorylated TDP-43 accumulation is poorly understood. Kinase hyperactivity may be a consistent feature of FTLD, as phosphorylated TDP-43 is not