disease and offers ground for the development of a therapeutic strategy. As a first step for designing an inhibitor of Aβ aggregation based on the mutated Aβ sequence, we synthesized a peptide homologous to residues 1-6 of Aβ with the A2 V substitution and tested its ability to bind to wild-type Aβ and inhibit amyloidogenesis. The study showed that the mutated hexapeptide retains the anti-amyloidogenic properties of the parent full-length Aβ. Molecular dynamics simulations suggest that this property may be related to the structural flexibility of the peptide that adopts dynamically ''closed'' and ''open'' configurations, at variance with the wild-type sequence which is characterized by a ''closed'' structure. **Conclusion:** The present data have important implications for genetic screening and the potential treatment of Alzheimer's disease based on A2 V-modified Aβ peptides or peptido-mimetic compounds.

O1-06-04 NEURONAL FUNCTION OF THE AMYLOID PRECURSOR PROTEIN OF ALZHEIMER'S DISEASE

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Background: The amyloid precursor protein (APP) is a type I transmembrane protein with several characterized biochemical domains. However, since APP -/- mice show a normal phenotype, the function of APP remains elusive. **Objective:** Neuronal function of APP was investigated by expression of human APP (hAPP) or inhibition of endogenous APP production in primary cultures of cortical neurons. **Methods:** Primary cultures of neurons were prepared from rat or mouse embryos. Mouse embryonic fibroblasts (MEFs) were maintained in culture as cell lines. hAPP or shRNA expression was performed using recombinant adeno- or lentiviruses. Calcium oscillations and calcium currents were measured using FURA2 and patch clamp, respectively. APP target genes, and HMGCoA reductase mRNA expressions were quantified by qRT-PCR, while the corresponding proteins were quantified by Western blotting. **Results:** Focal expression of hAPP in some neurons of a network interrupted spontaneous synchronous calcium oscillations in the entire network. hAPP expressing neurons showed increased activity of L-type voltage-dependent calcium channels. This in turn activated calcium-activated K+ channels, responsible for an increased medium afterhyperpolarisation (mAHP) phase following action potentials, preventing propagation of calcium oscillations (1). Neuronal expression of hAPP decreased HMGCoA reductase expression and cholesterol synthesis. This inhibition resulted from the impairment of SREBP processing in the Golgi compartment, where a direct interaction between SREPB and APP was demonstrated by co-immunoprecipitation. Expression of aquaporin 1 (AQP1) was strongly decreased in MEFs lacking APP. AQP1 expression was restored in these cells by expression of hAPP. The transcriptional activity of AQP1 gene promoter was identical in APP+/+ and APP-/- MEFs, as was the stability of AQP1 mRNA. Regulation of AQP1 expression by APP was sensitive to histone acetylation, and HDAC activity co-immunoprecipitated with APP. **Conclusion:** Efficient expression of hAPP in primary cultures of cortical neurons, as well as inhibition of endogenous APP expression allowed to identify important neuronal functions of APP, including control of neuronal excitability, cholesterol homeostasis, and epigenetic control of gene expression. (1) Ferrao Santos et al. (2009) J. Neurosci. 29, 4708-4718.

O1-06-05 BLOOD BORNE Aβ DIMER CORRELATES WITH CLINICAL MARKERS OF ALZHEIMER'S DISEASE

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Background: Unfortunately definitive diagnosis of Alzheimer's disease (AD) relies on post-mortem histological demonstration of amyloid-β (Aβ) plaques and tau neurofibrillary tangles. Aβ processing has been implicated in AD progression and many therapeutic strategies targeting various aspects of this biology under clinical investigation. However a lack of validated biomarkers has hampered the efficient design of appropriate trials. While Aβ deposition is the most prominent feature of AD, recent studies have implicated oligomeric forms of Aβ as the toxic species that induce the neuronal dysfunction associated with AD. These species include synaptotoxic Aβ dimers isolated from post mortem AD brain tissue. Currently there are no methods allowing routine monitoring of levels of such species in living populations. **Objective:** To determine whether oligomeric forms of Aβ can be identified in blood and if so do levels of the oligomers differ between healthy controls and diseased subjects. **Methods:** The blood of 43 AD, 23 mild cognitively impaired (MCI) and 52 healthy control (HC) subjects was analysed for the presence of APP/Aβ species by Surface Enhanced Laser Desorption Ionization Time of Flight (SELDI-TOF) mass spectrometry incorporating antibody capture. **Conclusion:** There are significant differences in the mass spectra profiles of the blood fractions from AD compared with HC subjects. These differences were consistent with there being two distinct processing pathways for APP with an amyloidogenic pathway favored in AD. This resulted in significantly higher levels of Aβ monomer and Aβ dimer in the blood of AD subjects with respectively 16% and 35% increases in the levels of these species over controls. Furthermore levels of these species correlated with clinical markers of AD including Mini-Mental State Examination scores, memory impairment and brain Aβ burden as determined by ^{11}C-PiB PET imaging. These results indicate that fundamental biochemical events relevant to AD such as Aβ generation and aggregation can be monitored in blood, and that the species detected may be useful clinical biomarkers for AD.

O1-06-06 DIAGNOSING AD BY DETECTING OLIGOMERIC FORMS OF BETA-AMYLOID IN BODILY FLUIDS

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Background: Alzheimer's Disease (AD), Parkinson's Diseases. Prion Diseases, Huntington's Diseases and many others are progressive neurodegenerative disorders with impairment in learning, memory, motor skills, and various cellular functions. It has been suggested that the detection of the aggregated or oligomeric forms of various biomarkers in bodily fluids would provide as robust targets for the diagnosis. **Objective:** In AD, the proteolytically generated amyloid beta (Aβ) peptide from the amyloid precursor protein (APP) could aggregate into insoluble fibril in senile plaques. Hence, the development of the sensitive detection methods for Aβ aggregates or oligomers in CSF or blood could be important for the therapeutic strategy and for the evaluation of the drugs, especially with upcoming releases if disease-modifying-drug candidates. **Methods:** Multimer Detection System (MDS) was initially developed for the detection of abnormal prion protein in blood, utilizing epitope-overlapping antibodies to create competition to discriminate oligomers from monomers. In scrapie, MDS differentiated preclinical scrapie infected sheep plasmas from normal controls. Here, MDS was used to detect spiked Aβ oligomers (SPPS) in plasma with upper nanogram/ml sensitivity. In addition, we were able to detect Aβ oligomers in bodily fluids from possible AD patients. **Conclusion:** MDS was able to differentiate Aβ oligomers from monomeric form in boldily fluids. The goal of MDS in AD is to develop promising HTS, diagnostic, prognostic assay systems for drug efficacy and therapies, and screening potential drug candidates against AD.