Background: Cerebral Amyloid Angiopathy (CAA) is present in most cases of Alzheimer's disease (AD), and it is characterized by the deposition of beta-amyloid (Aβ) in cerebral cortical and meningeal blood vessels (Kawai M. et al., 1993), inducing degeneration of vascular cells. Semicarbazide-sensitive amine oxidase (SSAO) [E.C. 1.4.3.6] is present in vascular cells and in plasma. It metabolizes primary amines (Lyles GA., 1996) generating hydrogen peroxide (H_2O_2), ammonia (NH_3) and the corresponding aldehyde, that contribute to the oxidative stress, advanced glycation end-product generation (Gubisne-Haberle D. et al., 2004), and beta amyloid aggregation (Chen K. et al., 2006). Furthermore in endothelial cells, SSAO is induced under inflammatory conditions (Smith D.J. et. al., 1998). We have reported that SSAO is overexpressed in cerebrovascular tissue of patients with CAA-AD, and that it colocalizes with beta-amyloid deposits (Ferrer I. et al., 2002). This over-expression correlates with high SSAO activity in plasma of severe AD patients (del Mar Hernandez M. et al., 2005). We have also described that plasma SSAO is able to induce apoptosis in vascular cells (Hernandez M. et.al., 2006). The aim of this work is to demonstrate whether Aβ is able to induce SSAO overexpression in HUVEC cells as vascular cell type. **Methods:** Because of the SSAO/VAP-1 expression fenotype is lost in cultured cells, HUVEC (human umbilical vein endothelial cells) cells, were stably transfected with vector pcDNA 3.1 containing hVAP-1/SSAO. Cells were treated with Aβ 1-40 Dutch type (mutation E22Q) and/or Methylamine as SSAO substrate. Cell viability, SSAO activity and its expression were determined using specific antibodies against SSAO. **Results:** Herein we report that Aβ 1-40 E22Q induces the SSAO activity and expression in HUVEC cells. This increasing activity promotes oxidative stress that enhances the toxicity generated by Aβ alone. This toxicity is reverted by specific SSAO inhibitors, confirming SSAO as the responsible of such effect. **Conclusions:** These results allow us to postulate that deposits of Aβ in cerebrovascular tissue, induce SSAO expression that may contribute to the vascular damage associated to CAA-AD.

P4-299 NEURON-BINDING AUTOANTIBODIES IN HUMAN SERA ENHANCE ABETA42 ACCUMULATION IN ADULT MOUSE BRAIN NEURONS

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Background: Alzheimer's disease (AD) brains are marked by deposition of amyloid peptides, especially amyloid $beta_{1-42}$ (Aβ42), within neurons and amyloid plaques. Causal mechanisms for Aβ42 deposition remain unknown. Several studies have reported that neurons in post-mortem AD brains are immunopositive for immunoglobulins (Igs), suggesting that serum Igs gain access to neurons in AD brains by penetrating the blood-brain barrier. In the present study, we tested the possibility that binding of Igs to neurons contributes to neuronal internalization and accumulation of Aβ42 during AD pathogenesis. **Methods:** Sera from AD and healthy, non-demented individuals were screened for neuron-binding autoantibodies by using it as primary antibody on histological sections of human AD and age-matched control brains and in western blots of proteins isolated from brain membranes. The effects of human neuron-binding antibodies on Aβ42 deposition were tested in adult mouse brain neurons *in vitro* (using organotypic brain slice cultures) and *in vivo* (using direct stereotaxic intracranial injection). **Results:** Neuron-binding autoantibodies were detected in nearly all sera from AD individuals and control subjects**.** These antibodies immunolabeled comparable neurons in histological sections of both human and adult mouse brain. Taking advantage of this species cross-reactivity, we demonstrate that binding of human autoantibodies to neurons dramatically enhances the rate and extent of Aβ42 accumulation in neurons in brain slice cultures as well as in mice receiving stereotaxic intracranial injections of human antibodies and Aβ42. Furthermore, individual sera that most intensely immunolabeled neurons in sections of human brain tissue and brain membrane proteins in western blots were also found to be the most effective at inducing internalization of soluble exogenous Aβ42 in mouse neurons. **Conclusions:** The high prevalence of neuron-binding autoantibodies in human serum leads us to propose that these autoantibodies may be a risk factor for AD as well as other neurodegenerative diseases that involve BBB compromise. Moreover**,** influx of blood-borne, neuron-binding autoantibodies and soluble Aβ42 into the brain may contribute to AD by exacerbating the intraneuronal accumulation of Aβ42 and amyloid deposition in the brain tissue.

P4-300 GENE EXPRESSION PROFILING TO IDENTIFY MICROVASCULAR CHANGES IN ALZHEIMER'S DISEASE MOUSE MODELS

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Background: Dense-core amyloid-β (Aβ) plaques and congophilic amyloid angiopathy are pathological hallmarks of Alzheimer's disease (AD). However, it is not yet clear how these deposits initially aggregate, i.e. whether aggregation is spontaneous or is mediated by specific interactions of Aβ with other brain proteins. We recently showed that dense-core plaques in Tg2576 and PSAPP mouse models and in Flemish APP A692G AD patients are centered on vessel walls and this is also supported by similar recent observations on AD and Down's syndrome patients. Even more importantly, considerable microvascular damage and blood-brain barrier abnormalities were also identified in both amyloid-associated and non-amyloidogenic vessels in the AD mouse models and in AD patients. Objectives: To identify seeding factors responsible for the vascular entrapment of Aβ and to elucidate changes occurring in blood vessels even prior to amyloid deposition by a mixed transcriptomic and proteomic approach. **Methods:** Tg2576, TgN, BRI-Aβ42, and BRI-Aβ40 AD mouse models and littermate controls of different ages are utilized to isolate vascular early dense-core plaques and non-amyloidotic vessels by laser microdissection (PALM MicroBeam, Zeiss) for transcriptional profiling by Agilent microarrays. Frontal neocortical and entire hippocampal tissue of Tg2576 mice and littermate controls are also laser-microdissected as these are the first regions where Aβ is being deposited in these mice. In addition, 2D-DIGE and MALDI-TOF MS/MS analyses will also be performed on this tissue. **Results:** For optimal transcript preservation, a short twenty-minutes staining protocol has been optimized to visualize early Aβ deposits and/or vessels in brains of transgenic mice and littermate controls. Frozen brain sections were fixed with ice-cold 70% ethanol and fluorescently stained with Thioflavin-S and collagen IV. High-quality total RNA suitable for microarray studies as measured with Experion HighSens chip was extracted from the laser-microdissected tissue. Currently, microarray analyses are being done to elucidate changes in the gene expression profile. **Conclusions:** Our data suggest that extraction of high-quality RNA from small amounts of laser-microdissected tissue is possible. The strategy discussed here will be important to elucidate the molecular mechanisms of plaque formation and the vascular changes that occur in blood vessels prior to Aβ deposition in Alzheimer Disease.

P4-301 INSULIN AND THE BRAIN: IS ALZHEIMER'S DISEASE TYPE 3 DIABETES?

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Background: Diabetes mellitus (DM), both insulin-dependent and non-insulin dependent has a proven negative influence on the level of cognitive functions. Apart from hypertension, ischaemic heart disease, dyslipidaemia, DM is considered one of the primary risk factors for vascular demen-