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

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**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 (Ab) in cerebral cortical and meningeal blood vessels (Kawm et al., 1993), inducing degeneration of vascular cells. Semicarbazide-sensitive amine oxidase (SSAO) [EC 1.4.3.6] is present in vascular and in plasma. It metabolizes primary amines (Lyes GA., 1996) generating hydrogen peroxide (H2O2), ammonia (NH3) and the corresponding aldehyde, that contribute to the oxidative stress, advanced glycation end-product generation (Gubinse-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 Ab is able to induce SSAO overexpression in HUVEC cells as vascular cell type. **Methods:** Because of the SSAO/VAP-1 expression phenotype 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 Ab I-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 Ab I-40 E22Q induces the SSAO activity and expression in HUVEC cells. This increasing activity promotes oxidative stress that enhances the toxicity generated by Ab 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 Ab in cerebrovascular tissue, induce SSAO expression that may contribute to the vascular damage associated to CAA-AD.

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**GENE EXPRESSION PROFILING TO IDENTIFY MICROVASCULAR CHANGES IN ALZHEIMER’S DISEASE MOUSE MODELS**

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**Background:** Dense-core amyloid-β (Ab) 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 Ab 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 Ab and to elucidate changes occurring in blood vessels even prior to amyloid deposition by a mixed transcriptomic and proteomic approach. **Methods:** Tg2576, TgN, BRI-Ab42, and BRI-Ab40 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 Ab 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 Ab 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 sample for microarray studies were 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 Ab deposition in Alzheimer Disease.

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**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-