finding in Alzheimer's disease, in which Aβ vascular deposits are featured in >80% of the cases. CAA can compromise cerebral blood flow causing cerebral hemorrage and cognitive impairment. Although the impact of these lesions is broadly recognized, very little is known about the mechanisms causing degeneration of cerebral vascular cells in CAA. Familial Aβ variants with substitutions at positions 21-23 are primarily associated with CAA, and they manifest clinically with cerebral hemorrhage or dementia. The recently reported Piedmont L34V Aβ mutant, located outside the hot-spot 21-23, shows a similar hemorrhagic phenotype, albeit less aggressive than the widely studied Dutch E22Q variant. **Methods:** In our studies we challenged human brain microvascular endothelial (EC) and smooth muscle cells (SMC) with both variants and wild-type Aβ40, and we studied the apoptotic pathways triggered by these peptides. **Results:** Structural analyses of the different Aβ variants showed that apoptosis preceded fibril formation in all cases, correlating with the presence of oligomers and/or protofibrils. Induction of analogous caspase-mediated mitochondrial pathways was elicited by all peptides, although within different time-frames and intensity. Furthermore, vessel-wall cell death was prevented either through pharmacological inhibition of mitochondrial cytochrome c release or by the action of pan- and pathway-specific caspase inhibitors, giving clear indication of the independent or synergistic engagement of both extrinsic and intrinsic apoptotic mechanisms. In particular, we found that the activation of caspase 8, usually triggered by death receptors, preceded that of caspase 9. We also confirmed the activation of BID, a downstream effector of caspase-8, known to contribute to the release of Cytochrome C from the mitochondria, causing in turn secondary engagement of caspase-9. Pathway specific PCR arrays demonstrated the involvement of TNF-receptor family members. **Conclusions:** Overall, our data suggests a primary involvement of death receptors in Aβ-induced vascular cell apoptosis. Our studies support the notion that rare genetic mutations constitute unique paradigms to understand the molecular pathogenesis of CAA, and could lead to the identification of new targets for therapeutic intervention.

P2-216 PROTEOMIC ANALYSIS OF TGCRND8 MICE BRAIN IN CONDITION OF ALTERED ONE-CARBON METABOLISM

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Background: Evidences suggest that alteration of one-carbon metabolism is associated with late-onset Alzheimer's disease (LOAD). We already demonstrated that B-vitamin deficiency induced hyperhomocysteinemia and imbalance of S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) in TgCRND8 AD mice. This effect was associated with PSEN1 and BACE1 up-regulation and increased amyloid plaque deposition. To further study the effects of B-vitamin deficiency, a proteomic approach was applied to detect differential protein expression in brain obtained from TgCRND8 mice grown in conditions of altered one-carbon metabolism. **Methods:** TgCRND8 and 129Sv wild type mice were fed for 90 days after weaning with either control or B-vitamin deficient diet, with or without SAM 400 μg/day. Proteins extracted from brain samples were analyzed by two-dimensional gel electrophoresis. Gel image analysis was performed using the Bio-Rad PDQuest 7.1 software; differentially expressed spots (±1.5 fold-change, t-test $p < 0.05$) were identified by MS. Protein-protein interaction was analyzed using the STRING software version 8.2. Protein expression profiles have also been evaluated by unsupervised cluster analysis using the Gene Spring software (Agilent Technologies). **Results:** Sixteen spots were detected with significantly altered levels in at least one experimental group. Eleven of these spots were unambiguously identified by MS as: complexin 1, prohibitin, dihydropyrimidinase-related protein 2 (2 isoforms), L-lactate dehydrogenase B chain, dynamin-like 120 kDa protein, nucleoside diphosphate kinase B, elongation factor 2 (3 isoforms) and transgelin-3. For most of the differentially expressed proteins, expression level was affected by B-deficiency and restored to control by SAM. On the identified proteins, we performed a search of the known molecular interactors. This approach highlighted energy metabolism, purine/pyrimidine metabolism and neuronal processes as the main biological processes affected by the experimental setting, and mitochondria and dendrites as the main cellular compartments involved. Moreover, unsupervised cluster analysis showed that protein profile in mice supplemented with SAM was more similar to the one observed in mice in control diet than in B-deficient diet. **Conclusions:** Identification of proteins whose brain expression is affected by B-vitamin deficiency and modulated by SAM may help to understand the molecular pathways that mediate the effects of one-carbon metabolism alterations in Alzheimer's disease processes.

P2-217 ALTERATIONS OF BRAIN AND CEREBELLUM PROTEOMES ASSOCIATED WITH MUTANT PS1M146V, APPSWE AND MAP TAUP301L EXPRESSION IN FEMALE 3XTG-AD MICE

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Background: The triple-transgenic Alzheimer (3xTg-AD) mouse expresses mutant PS1M146V, APPswe, and tauP301L transgenes and progressively develops plaques and neurofibrillary tangles with a temporal- and region-specific profile that resembles the neuropathological progression of Alzheimer's disease (AD). Thus, 3xTg-AD mice are a valuable tool for investigating the molecular mechanisms underlying the different stages of AD. **Methods:** In this study, we employed proteomic approaches, such as two-dimensional gel electrophoresis (2D-E) and mass spectrometry (MS) to investigate the alterations in protein expression occurring in the brain and cerebellum of 14-month old 3xTg-AD mice. Presenilin-1 knock-in (PS1KI) mice do not develop cognitive decline and were used as control. Finally, employing the Ingenuity Pathway Analysis (IPA) we evaluated novel networks and molecular pathways involved in this AD model. **Results:** We identified several differentially expressed spots, and analysis of 3xTg-AD brains showed a significant down-regulation of synaptic proteins that are involved in neurotransmitter synthesis, storage and release as well as a set of proteins that are associated with cytoskeleton assembly and energy metabolism. Interestingly, in the cerebellum, a structure not affected by AD, we found an up-regulation of proteins involved in carbohydrate metabolism and protein catabolism. **Conclusions:** Our proteomic study, in the brain and cerebellum of 3xTg-AD mice, shows an interesting divergence of effects between these two CNS regions. In the brain, we observe a significant down-regulation of synaptic, cytoskeletal, and mitochondrial proteins, suggesting that synaptic and mitochondrial dysfunction are playing a key role in the later stage of the AD-like pathology observed in this region. In contrast, in the cerebellum we find an up-regulation of proteins that are involved in energy metabolism, clearance of misfolded protein, and detoxification. These findings are particularly intriguing as they can shed new light on endogenous mechanisms set in motion by the cerebellum to counteract the pathogenic actions of A-beta and p-tau and ultimately offer novel targets for therapeutic intervention.

P2-218 GENETIC DISSECTION OF THE VARIATION EXPRESSION OF GSTO1 IN MOUSE HIPPOCAMPUS

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