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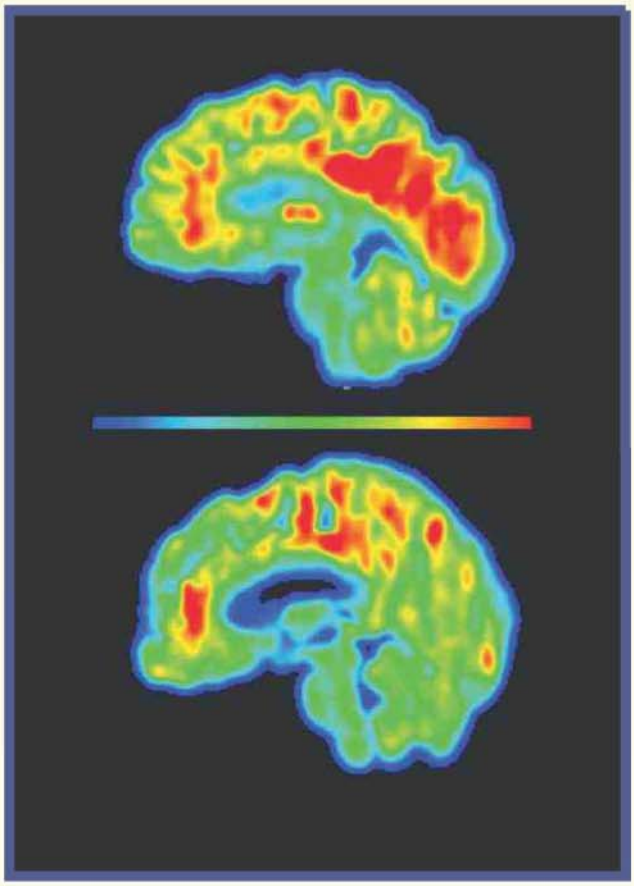
Abstracts



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elevated levels of soluble Abeta40 and Abeta42 in the brain, we hypothesized that IDE deficiency enhances local Abeta clearance mechanisms triggered by the age-dependent accumulation of Abeta fibrils and/or oligomeric intermediates in the brain. **Methods:** To determine whether the astrocytic or microglial inflammatory response contributes to enhanced Abeta clearance in IDE KO/J9 mice, GFAP and CD45 immunohistochemical staining was performed in aged mice (13 and/or 16 months old). MCID Elite Imaging software was used for densitometric quantitation of load in the hippocampus. **Results:** Densitometric quantitation of GFAP in IDE KO/J9 and J9 hippocampi revealed a trend towards increased astrocytic activation in the J9/IDE KO mice (% hippocampal area 1.73 and 1.25 at 13 months; 1.30 and 1.16 at 16 months; respectively). In contrast, our preliminary data on CD45 microglia show a decreased microglial response in 16 month-old IDE KO/J9 mice. Abeta immunohistochemical staining of 16 month-old IDE KO/J9 and J9 brains confirmed our previous findings that hippocampal Abeta load in IDE KO/J9 mice is lower than in J9 controls (57%, $p<0.05$, $n=6$ and 7). No differences in the levels of the following Abeta degrading enzymes: neprilysin, cathepsin B and cathepsin D, were observed in 13 month-old IDE KO/J9 and J9 brain extracts. **Conclusions:** Our results indicate that IDE deficiency slows Abeta deposition in J9 APP transgenic mice and that this may be due to enhanced Abeta clearance by activated astrocytes. The possibility that IDE deficient astrocytes contribute directly to enhanced Abeta clearance is currently being studied.

P1-022 CELLULAR MECHANISMS UNDERLYING ABERRANT EEG ACTIVITY AND COGNITIVE DEFICITS IN MOUSE MODELS OF ALZHEIMER'S DISEASE

Peter Reinhart, Steven Leiser, Huai-Ping Ling, Jon Brown, Tom Comery, Menelas Pangalos, Andy Randall, Andrew Wood, Mark Bowlby, Jeannie Chin, *Wyeth Research, Princeton, NJ, USA. Contact e-mail: reinhap@wyeth.com*

Background: The amyloid precursor protein (APP) and amyloid β peptides (Aβ) cleaved from it contribute to cognitive impairments in Alzheimer's disease (AD). The mechanisms that link APP/Aβ to cognitive deficits are unknown. Recent reports have demonstrated that APP/Aβ perturb neuronal activity and might underlie the clinical observations that AD is associated with increased seizure incidence. Although it was previously unclear whether seizures are secondary to the disease or contribute to cognitive impairments, new results from transgenic mouse models of AD suggest that seizure activity and resulting compensatory responses of the brain play an important role in AD-related cognitive decline. **Methods:** Recent reports suggested that alterations in voltage-gated sodium channels (VGSCs) might underlie epileptiform activity in AD and related mouse models. VGSCs are also substrates for BACE1 and γ-secretase, the two proteases responsible for production of neurotoxic Aβ. Since alterations in VGSCs lead to aberrant neuronal activity and seizures, the increased levels/activities of BACE1 in AD patients and mice may impact overall neuronal activity by altering VGSC levels. We used biochemical, immunohistochemical, and electrophysiological methods to determine whether AD mouse models exhibit alterations in VGSCs that correspond to aberrant brain activity and cognitive deficits. **Results:** We found that both Tg2576 and PS1/APP mouse models of AD exhibit altered levels of VGSCs. Moreover, such biochemical alterations were associated with functional changes in VGSCs demonstrated by patch-clamp recordings. These types of changes in VGSCs have been reported to contribute to some forms of epilepsy, which when uncontrolled is associated also with cognitive decline. Accordingly, we found that our mouse models of AD also exhibit aberrant, epileptiform activity measured by in vivo EEG recordings. Such aberrant brain activity was similar in some respects to the epileptiform activity previously reported in other AD models. Importantly, the aberrant activity was apparent at ages at which VGSC alterations and memory impairments are observed, indicating that such aberrant brain activity is a general feature of AD mouse models that may underlie cognitive impairments. **Conclusions:** Together, these results indicate that restoring neuronal activity by both regulating APP processing and normalizing VGSCs may provide therapeutic benefit for AD-related memory impairments.

P1-023 THE PROTEOMIC STUDY OF SAMP8 BRAIN CULTURES REVEALS AGE-RELATED ALTERATIONS IN NEURONS AND ASTROCYTES

Coral Sanfeliu[1], Cristina Díez-Vives[1], Marina Gay[2], Joaquín Abián[2], Francesc Comellas[3], Rosa Cristòfol[1], *[1]Dept. Brain Ischemia & Neurodegeneration, IIBB, CSIC-IDIBAPS, Barcelona, Spain; [2]CSIC-UAB Proteomics Laboratory, Barcelona, Spain; [3]Dept. Applied Mathematics IV, UPC, Barcelona, Spain. Contact e-mail: coral.sanfeliu@iibb.csic.es*

Background: The senescence-accelerated prone mouse strain 8 (SAMP8) is an established animal model for studying age-related cognitive decline, including the contribution of amyloid beta neuropathology. In a search for the astrocyte role in the brain neurodegeneration, we recently demonstrated that SAMP8 cultured astrocytes exhibited age-related disturbances and reduced neuroprotective capacity, as compared to astrocytes from the senescence-resistant strain 1 (SAMR1). In the present work we applied proteomics techniques to study neuron and astrocyte specific early markers of brain aging-related degeneration in SAMP8. **Methods:** We established neuron and astrocyte neocortical cultures from E18 embryos and newborns SAMP8, respectively. Control cultures were obtained from SAMR1. The 2-D protein expression patterns of the SAMP8 neuron and astrocyte cultures were compared to those obtained from SAMR1 cultures. Differentially expressed spots were identified by MALDI-TOF MS. A network analysis was performed with the identified proteins and their links within the whole protein-protein interactome. **Results:** Thirty-one and eighteen differentially expressed spots were obtained in neurons and astrocytes, respectively. Identified proteins belonged to cell pathways of energy metabolism, biosynthesis, cell transduction and signaling, stress response and the maintenance of cytoskeletal functions. Most of the proteomic changes were cell type specific. However, there was a general increase in cell transduction, signaling and stress-related proteins and a decrease in cytoskeletal proteins. In addition, neurons showed an increased expression of several proteins that are involved in biosynthetic pathways. In general, alterations in their proteoma indicated that both cell types are involved in the brain degenerative changes of SAMP8 mice. However, network analysis suggests that neuronal changes are more complex and have a greater influence. **Conclusions:** The proteins that were abnormally expressed in cultures of SAMP8 neurons and astrocytes were associated with pathways similar to those reported as altered in the brain tissue of SAMP8, aged brain or AD brain. The study demonstrated that both cells types, neurons and astrocytes, are implicated in the brain protein pathway alterations of this mouse model of age-related neurodegeneration. (This work was supported by grants SAF2006-13092-C02-02 from MEC, and RD06/0913/1004 from ISCIII, Spain).

P1-024 ALZHEIMER-LIKE CHANGES ARE FOUND IN MALE, BUT NOT FEMALE HYPOGONADAL MICE AND APPEAR EXACERBATED AFTER INJURY

Eleanor Drummond, Ralph N. Martins, Alan R. Harvey, *University of Western Australia, Perth, Australia. Contact e-mail: edrummond@anhb.uwa.edu.au*

Background: Depletion of sex hormones with age may be a risk factor for Alzheimer's disease (AD). This study examined the relationship between sex hormones and proteins related to AD using hypogonadal (hpg) mice, a novel animal model in the AD field. Hpg mice have a naturally occurring genetic mutation in the gene encoding gonadotrophin releasing hormone, resulting in sustained low levels of gonadotrophins and circulating sex hormones. **Methods:** Levels of amyloid precursor protein (APP), the C-terminal fragment of APP (APP-CTF), presenilin 1 (PS1), apolipoprotein E (apoE) choline actelyltransferase (ChAT) and interleukin 1 beta (IL-1β) were measured in the brains of aged (12-18 months) hpg and wild-type mice using western blots, immunohistochemistry and luminex. To examine the effect of injury on the expression of these proteins, a proportion of the male hpg and wild-type mice sustained a stab injury through the hippocampus. **Results:** Male uninjured hpg mice had significantly lower APP and higher APP-CTF and PS1 in the hippocampus than wild-types, suggesting an increase in amyloidogenic processing. This effect was brain region