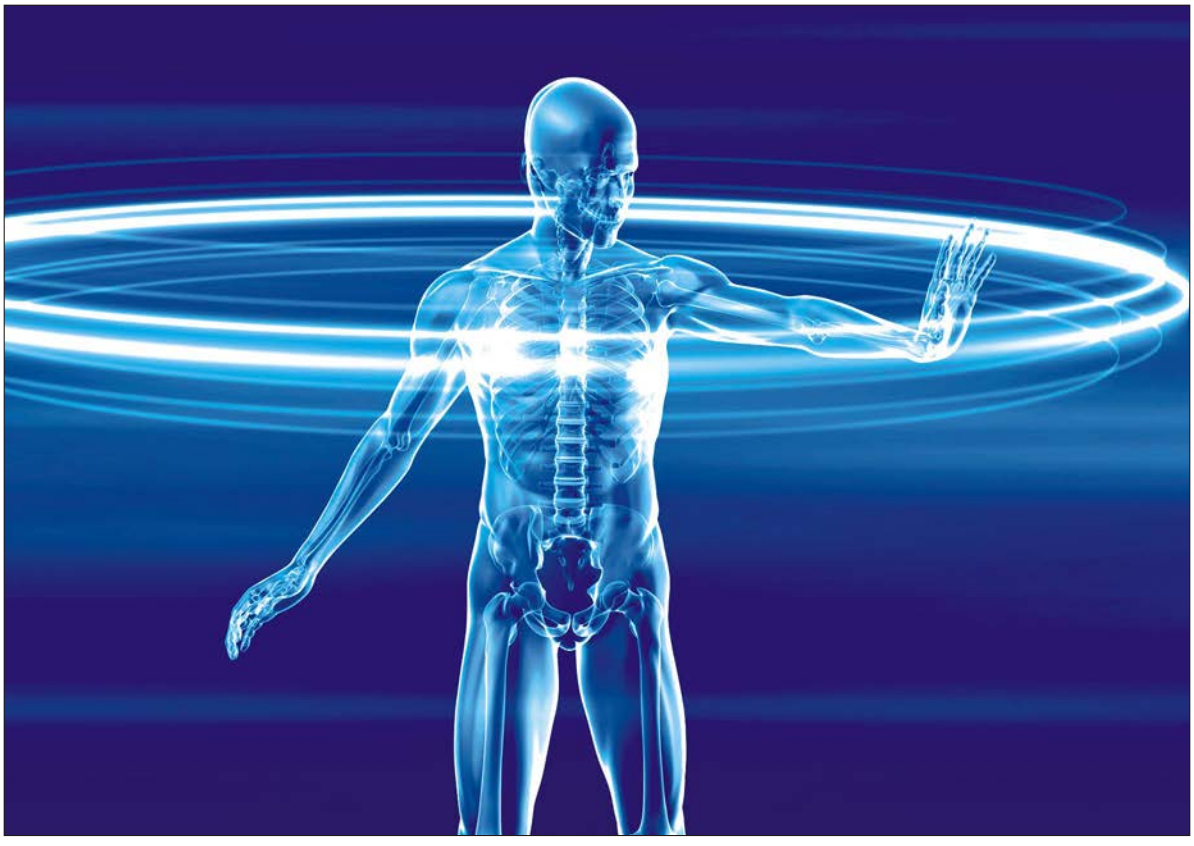

Research Journal of Immunology

ISSN 1994-7909

science alert

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Neuropathology and the Neuroinflammation Idea

Robert E. Mrak (*Communicated by Xiongwei Zhu*)

Abstract: A role for innate immunity in neurodegenerative diseases is now widely accepted, although debate continues over the relative contributions of these processes to disease progression and/or to disease amelioration. The idea that microglia and cytokines are important in neurodegeneration arose from neuropathological observations, especially in Alzheimer's disease. Microglia are invariant components of the Aß plaques of Alzheimer's disease, where they show a waxing and waning of numbers, activation state, and cytokine expression during plaque progression. This is in contrast to diffuse Aß deposits sometimes found in abundance in the brain of non-demented elderly individuals, which do not contain activated microglia. In Alzheimer's disease, plaque-associated astrocytes, which also produce paracrine mediators, show a pattern similar to that of microglia; and the associated plaque progression is accompanied by progressive damage to and loss of adjacent neurons. Further, activated microglia and astrocytes show a progressive pattern of association with neurofibrillary tangles. These observations, together with known functions of the involved cytokines, originally suggested a central role for immunological phenomena in driving disease progression in Alzheimer's disease. Further observations have extended these ideas to a-synuclein-based diseases (Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy) as well as other neurodegenerative diseases and conditions.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 473-481

Insulin is a Two-Edged Knife on the Brain

Susana Cardoso, Sónia Correia, Renato X. Santos, Cristina Carvalho, Maria S. Santos, Catarina R. Oliveira, George Perry, Mark A. Smith, Xiongwei Zhu, Paula I. Moreira *(Handling Associate Editor: Jose Viña; Handling Editor: Jesus Avila)*

Abstract: Insulin, long known as an important regulator of blood glucose levels, plays important and multifaceted roles in the brain. It has been reported that insulin is an important neuromodulator, contributing to several neurobiological processes in particular energy homeostasis and cognition. Dysregulation of insulin signaling has been linked to aging and metabolic and neurodegenerative disorders. The first part of this review is devoted to discussion of the critical role of insulin signaling in normal brain function. Then the involvement of impaired insulin signaling in the pathophysiology of diabetes, Alzheimer's, Parkinson's and Huntington's diseases and amyotrophic lateral sclerosis will be discussed. Finally, the potential therapeutic effect of insulin and insulin sensitizers will be examined.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 483-507

Effects of Memantine on Cerebrospinal Fluid Biomarkers of Neurofibrillary Pathology

Lidia Glodzik, Susan De Santi, Kenneth E. Rich, Miroslaw Brys, Elizabeth Pirraglia, Rachel Mistur, Remigiusz Switalski, Lisa Mosconi, Martin Sadowski, Henrik Zetterberg, Kaj Blennow, Mony J. de Leon

Abstract: Previous studies showed that memantine inhibits tau hyperphosphorylation *in vitro*. In this study, phosphorylated tau (P-tau) and total tau (T-tau) were measured before and after 6 month treatment with memantine in 12 subjects ranging from normal cognition with subjective memory complaints, through mild cognitive impairment to mild Alzheimer's disease. Thirteen non-treated individuals served as controls. Treatment was associated with a reduction of P-tau in subjects with normal cognition. No treatment effects were seen among impaired individuals, suggesting that longer treatment time may be necessary to achieve biomarker effect in this group.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 509-513

Increased Inflammatory Response Both in Brain and in Periphery in *Presenilins* Conditional Double Knock-Out Mice

Xu Jiang, Dongli Zhang, Jianting Shi, Yiqun Chen, Ping Zhang, Bing Mei

Abstract: It has been reported that conditional double knockout of *presenilin-1* and *presenilin-2 in forebrain of mice (dKO* mice) induce symptoms most analogous to that of neurodegenerative diseases, especially Alzheimer's disease, however, there is no deposition of extra amyloid-ß (Aß)40 or Aß42 in dKO brain. In the present study, we thoroughly measured the inflammatory response in dKO mice, which is another global symptom in neurodegenerative diseases. We demonstrated that glial cells were dramatically activated from early age (3 months) in dKO brain when compared with control mice. In addition, complement C1qa and C4, the key components in the classical complement pathway, were also stimulated in dKO mice brain. Antibody array and ELISA analysis indicated that cytokine and chemokine levels were also significantly increased in dKO brain. Moreover, we found that leukocytes were elevated beginning at 6 months of age, and multiple inflammatory mediators changed in dKO mice serum at 9 months, showing that the inflammatory responses gradually expanded to systemic tissue. These findings confirm that *presenilins* double knockout results in robust inflammatory response both in brain and in periphery and suggest that dKO mice may be useful to further understand the effects of inflammation on the pathological processes of neurodegenerative diseases.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 515-523

Neurological Soft Signs in Nursing Home Residents with Alzheimer's Disease

Ulrich Seidl, Philipp A. Thomann, Johannes Schröder

Abstract: Neurological soft signs (NSS), i.e., minor motor and sensory changes, are a common feature in psychiatric disorders related to brain changes. Nevertheless, they have rarely been investigated in patients with Alzheimer's disease (AD). NSS were examined in 104 nursing home residents with AD with respect to dementia severity, neuropsychiatric symptoms, and Parkinsonian signs as well as potential medication effects. 16 cognitively unimpaired residents served as a control group. NSS scores were significantly higher in residents with AD and were associated with both severity of cognitive deficits and non-cognitive symptoms, in particular apathy, but neither with Parkinsonian signs nor with antipsychotic medication. Our results demonstrate that NSS increase with progression of AD and one may hypothesize that they are linked to degenerative cerebellar changes. NSS in AD are clinically significant and thus, besides other neurological symptoms, are to be considered in diagnostics and therapy.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 525-532

Impact of APOE e4 on the Cognitive Performance of a Sample of Non-Demented Puerto Rican Nonagenarians

José R. Carrión-Baralt, Josefina Meléndez-Cabrero, Heide Rodríguez-Ubiñas, James Schmeidler, Michal Schnaider Beeri, Gary Angelo, Mary Sano, Jeremy M. Silverman

Abstract: APOE e4 is a major risk factor for Alzheimer's disease. It has also been associated with cognitive impairment and cognitive decline in young-olds, but the impact of the e4 allele on cognitive function in very late life is still unclear. The object of this study was to evaluate the association of the e4 allele of APOE with the cognitive performance of a sample of non-demented oldest-olds. Eighty-seven Spanish-speaking Puerto Rican non-demented nonagenarians were administered a complete neuropsychological assessment and provided a blood sample used for APOE genotyping. A factor analysis generated two factors: 1) verbal memory; and 2) visuo-spatial, naming and attention tasks, accounting for 43.6% of the overall variance in the 13 original neuropsychological variables. The multivariate analysis reflected, after controlling for gender, education, and age, the APOE e4 carriers performed better in overall cognition (both factors analyzed together) than non-carriers ($T2$ = 0.082, F(2,80) = 3.289, p = 0.042). Neither gender nor the gender by APOE e4 status interaction was associated with differences in cognition. In conclusion, the results of this study suggest that, among these Puerto Rican non-demented nonagenarians, being an APOE e4 allele carrier is associated with better cognition.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 533-540

Differential Patterns of Implicit Emotional Processing in Alzheimer's Disease and Healthy Aging

Beatriz García-Rodríguez, Anna Fusari, Beatriz Rodríguez, José Martín Zurdo Hernández, Heiner Ellgring

Abstract: Implicit memory for emotional facial expressions (EFEs) was investigated in young adults, healthy old adults, and mild Alzheimer's disease (AD) patients. Implicit memory is revealed by the effect of experience on performance by studying previously encoded versus novel stimuli, a phenomenon referred to as perceptual priming. The aim was to assess the changes in the patterns of priming as a function of aging and dementia. Participants identified EFEs taken from the Facial Action Coding System and the stimuli used represented the emotions of happiness, sadness, surprise, fear, anger, and disgust. In the study phase, participants rated the pleasantness of 36 faces using a Likert-type scale. Subsequently, the response to the 36 previously studied and 36 novel EFEs was tested when they were randomly presented in a cued naming task. The results showed that implicit memory for EFEs is preserved in AD and aging, and no specific age-related effects on implicit memory for EFEs were observed. However, different priming patterns were evident in AD patients that may reflect pathological brain damage and the effect of stimulus complexity. These findings provide evidence of how progressive neuropathological changes in the temporal and frontal areas may affect emotional processing in more advanced stages of the disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 541-551

Impact of APOE on the Healthy Aging Brain: A Voxel-Based MRI and DTI Study

Robyn A. Honea, Eric Vidoni, Amith Harsha and Jeffrey M. Burns

Abstract: Neuroimaging studies of apolipoprotein E (ApoE4) have implicated its association with brain atrophy in Alzheimer's disease. To date, few studies have used automated morphological analysis techniques to assess ApoE4-related brain structure change in both gray and white matter in nondemented older adults. Nondemented (CDR=0, n=53) subjects over 60 had MRI, diffusion tensor imaging, and neurocognitive assessments. We assessed differences in cognition and brain structure associated with ApoE4 genetic variation using voxel-based morphometry techniques, tract-based spatial statistics of fractional anisotropy change. In nondemented older adults with the ?4 allele, cognitive performance was reduced, and atrophy was present in the hippocampus and amygdala compared to ApoE4 negative participants. We also report that E4 carriers have decreased fractional anisotropy in the left parahippocampal gyrus white matter. In conclusion, the presence of an ApoE4 allele in nondemented older adults is associated with decreases in cognition and gray and white matter changes in the medial temporal cortex. Overall we provide further evidence of the effects of

genetic variance related to imaging and cognitive measures of risk for Alzheimer's disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 553-564

The Effects of Enhanced Zinc on Spatial Memory and Plaque Formation in Transgenic Mice

David H. Linkous, Paul A. Adlard, Patricia B. Wanschura, Kathryn M. Conko, Jane M. Flinn

Abstract: There is considerable evidence suggesting that metals play a central role in the pathogenesis of Alzheimer's disease. Reports suggest that elevated dietary metals may both precipitate and potentiate an Alzheimer's disease phenotype. Despite this, there remain few studies that have examined the behavioral consequences of elevated dietary metals in wild type and Alzheimer's disease animals. To further investigate this in the current study, two separate transgenic models of AD (Tg2576 and TgCRND8), together with wild type littermates were administered 10 ppm (0.153 mM) Zn.Tg2576 animals were maintained on a zinc-enriched diet both pre- and postnatally until 11 months of age, while TgCRND8 animals were treated for five months following weaning. Behavioral testing, consisting of "Atlantis" and "moving" platform versions of the Morris water maze, were conducted at the end of the study, and tissues were collected for immunohistochemical analysis of amyloid-ß burden. Our data demonstrate that the provision of a zinc-enriched diet potentiated Alzheimer-like spatial memory impairments in the transgenic animals and was associated with reduced hippocampal amyloid-ß plaque deposits. Zinc-related behavioral deficits were also demonstrated in wild type mice, which were sometimes as great as those present in the transgenic animals. However, zinc-related cognitive impairments in transgenic mice were greater than the summation of zinc effects in the wild type mice and the transgene effects.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 565-579

Gene Expression Profiles in the Olfactory Bulb from a Rat Model of Alzheimer's Disease

Ying-Ying Zhu, Dao-Feng Ni, Cai-Min Xu

Abstract: Abnormalities and impaired functions of the olfactory system have been reported in Alzheimer's disease (AD), and these changes may appear much earlier than other clinical symptoms of AD. However, little is known about these abnormalities at the level of gene expression. In this study, we investigated alterations of expression of 22,012 genes in the olfactory bulbs of a rat model of AD by using a microarray approach. The rat model was produced by intracerebroventricular injection of amyloid-ß25-35, which demonstrated pathological changes in olfactory bulbs and memory impairment in the Morris

water maze test. We found that expression of 811 genes among the 22,012 genes was altered by more than 1.5-fold in the amyloid-ß-injected rats as compared with control injected rats. We analyzed the distribution of the 811 altered genes according to the Affymetrix criteria and found that the majority of these genes were related to cellular processes, binding, and enzyme activities. The alterations of three of these genes, i.e. calcineurin, olfactory receptor, and protein kinase C, were also confirmed by RT-PCR and Western blots. These studies provide new insight into the abnormalities of the olfactory system in AD and might help to further the understanding of the molecular mechanisms of AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 581-593

Effects of Insulin and Octreotide on Memory and Growth Hormone in Alzheimer's Disease

G. Stennis Watson, Laura D. Baker, Brenna A. Cholerton, Kristoffer W. Rhoads, George R. Merriam, Gerard D. Schellenberg, Sanjay Asthana, Monique Cherrier, Suzanne Craft

Abstract: Both insulin alone and the somatostatin analogue octreotide alone facilitate memory in patients with Alzheimer's disease (AD). Since octreotide inhibits endogenous insulin secretion, the cognitive effects of insulin and octreotide may not be independent. This study tested the individual and interactive effects of insulin and octreotide on memory and plasma growth hormone (GH) levels in older adults. Participants were 16 memory-impaired (AD=7, amnestic mild cognitive impairment=9; apolipoprotein E [*APOE*] e4- [no e4 alleles]=9, e4+ [1-2 e4 alleles]=7), and 19 cognitively-intact older adults (*APOE* e4-=17, e4+=1). On separate days, fasting participants received counterbalanced infusions of: 1) insulin (1 mU·kg-1·min-1) and dextrose to maintain euglycemia; 2) octreotide (150 µg/h); 3) insulin, dextrose, andoctreotide; or 4) saline. Story recall was the principal endpoint. Insulin alone facilitated delayed recall for e4- patients, relative to e4+ patients (P=0.0012). Furthermore, e4- patients with higher Mattis Dementia Rating Scale (DRS) scores had greater octreotide-induced memory facilitation (P=0.0298). For healthy adults, octreotide facilitated memory (P=0.0122). Unexpectedly, hyperinsulinemia with euglycemia increased GH levels in healthy controls (P=0.0299). Thus, insulin and octreotide appear to regulate memory in older adults. *APOE* e4 genotype modulates responses to insulin and octreotide. Finally, insulin may regulate GH levels during euglycemia.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 595-602

Rs5848 Variant Influences *GRN* mRNA Levels in Brain and Peripheral Mononuclear Cells in Patients with Alzheimer's Disease

Chiara Fenoglio, Daniela Galimberti, Francesca Cortini, John S.K. Kauwe, Carlos Cruchaga, Eliana Venturelli, Chiara Villa, Maria Serpente, Diego Scalabrini, Kevin Mayo, Laura M. Piccio, Francesca Clerici, Diego Albani, Claudio Mariani, Gianluigi Forloni, Nereo Bresolin, Alison M. Goate, Elio Scarpini *(Communicated by Amalia Bruni)*

Abstract: Mutations in the progranulin gene (*GRN*), causative for Frontotemporal Lobar Degeneration with ubiquitin-immunoreactive neuronal inclusions (FTLD-U), could also be associated with Alzheimer's disease (AD). The influence of *GRN* genetic variability on susceptibility to AD and on expression levels in a series of neuropathologically-confirmed AD patients as well as in peripheral mononuclear cells (PBMC) and in cells isolated from cerebrospinal fluid (CSF) was investigated. An association study of rs9897526 and rs5848 was carried out in an Italian population and in a replication population of European American patients and controls. None of the variants tested act as unequivocal susceptibility factor in both populations although rs9897526 anticipated the onset of the disease in the Italian population. *GRN* expression in the parietal lobe of AD cases showed a 0.76-fold decrease compared with controls (1.31±0.07 versus 1.73±0.12, P=0.0025). Patients carrying the rs5848 *TT* genotype had the lowest *GRN* expression levels (0.96±0.12, P=0.014). Despite no significant differences were found in the relative PBMC and CSF *GRN* expression in patients compared to controls, stratifying patients according to the presence of rs5848 *T* allele, a 0.57-fold decrease in *GRN* mRNA levels over *C* carriers was found in PBMC (1.22±0.23 versus 0.70±0.12, P=0.04). Similarly to data obtained in brain samples, patients carrying the *TT* genotype showed the lowest *GRN* mRNA levels (*TT*= 0.46±0.14, *CC*=1.22±0.23; P=0.013). These data argue against a direct role of *GRN* as a susceptibility factor for sporadic AD but support a role of *GRN* as a disease-modifying gene, possibly contributing to the failure of neuronal survival.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 603-612

Measurement of ERK 1/2 in CSF from Patients with Neuropsychiatric Disorders and Evidence for the Presence of the Activated Form

Hans-Wolfgang Klafki, Piotr Lewczuk, Heike Kamrowski-Kruck, Juan Manuel Maler, Katharina Müller, Oliver Peters, Isabella Heuser, Frank Jessen, Julius Popp, Lutz Frölich, Stefanie Wolf, Berit Prinz, Christian Luckhaus, Johannes Schröder, Johannes Pantel, Hermann-Josef Gertz, Heike Kölsch, Bernhard W. Müller, Hermann Esselmann, Mirko Bibl, Johannes Kornhuber, Jens Wiltfang

Abstract: The clinical diagnosis of neurodegenerative disorders can be supported by soluble biomarkers in cerebrospinal fluid (CSF), such as tau protein, phospho-tau, and amyloid-ß peptides. In particular, increased CSF levels of phospho-tau in Alzheimer's disease appear to reflect disease specific pathological processes. We report here evidence for the presence of soluble MAP-kinase ERK1/2 in a small set of human CSF samples from patients with Alzheimer's disease,

frontotemporal degeneration, and mild cognitive impairment. The level of total ERK1/2 in CSF as measured by electrochemiluminescent assay was correlated with that of total tau and phospho-tau. A small fraction of ERK1/2 in a pooled CSF sample was found to be in the doubly phosphorylated (activated) state. Our findings suggest that i) MAP kinase ERK1/2 is apparently released under neurodegenerative conditions in parallel with tau and phospho-tau and ii) in the future, it might be possible to find in CSF samples evidence for disease related alterations in brain kinase signaling pathways by use of highly sensitive and activation-state specific anti-kinase antibodies.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 613-622

The Spectrum Series: Grappling with the Overlap between Alzheimer's and Parkinson'sDiseases 9th International Conference on Alzheimer's and Parkinson's Diseases, 11-15 March 2009, Prague, Czech Republic

Mini-Forum on Clinical-Pathologic Correlations in Population- and Community-Based Studies of Brain Aging (Guest Editors: Thomas Montine and Joshua Sonnen)

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 625-640

Foreword: Population-based Neuropathology: The Best of Times

Eric B. Larson

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 643-644

Neuropathological Correlates of Dementia in Over-80-Year-Old Brain Donors from the Population-Based Cambridge City over-75s Cohort (CC75C) Study

Carol Brayne*, Kathryn Richardson*, Fiona E. Matthews, Jane Fleming, Sally Hunter, John H. Xuereb, Eugene Paykel, Elizabeta B. Mukaetova-Ladinska, Felicia A. Huppert, Angela O'Sullivan, Tom Dening, and the Cambridge City over-75s Cohort (CC75C) study neuropathology collaboration; *Joint first authors

Abstract: Key neuropathological changes associated with late-onset dementia are not fully understood. Population-based longitudinal studies offer an opportunity to step back and examine which pathological indices best link to clinical state. CC75C is a longitudinal study of the population aged 75 and over at baseline in Cambridge, UK. We report on the first 213 participants coming to autopsy with sufficient information for an end of life dementia diagnosis. Clinical diagnosis

was ascertained by examining retrospective informant interviews, survey responses, and death certificates according to DSM-IV criteria. The neuropathological protocol was based on the Consortium to Establish a Registry of Alzheimer's Disease (CERAD). Clinical dementia was present in 113 participants (53%): 67% with Alzheimer's disease, 4% vascular dementia, 22% mixed dementia, and 1% dementia with Lewy bodies. As Alzheimer-type pathology was common, the mutually blinded clinical and neuropathological diagnoses were not strongly related. Multivariable analysis identified associations between dementia during life and entorhinal cortex neuritic plaques, hippocampal diffuse plaques, neocortical neurofibrillary tangles, white matter pallor, Lewy bodies, and hippocampal atrophy. These results were consistent in those with clinical Alzheimer's disease. Vascular pathologies, especially microinfarcts, were more common in those with clinical diagnoses including vascular dementia. Alzheimer-type and cerebrovascular pathology are both common in the very old. A greater burden of these pathologies, Lewy bodies, and hippocampal atrophy, are associated with a higher risk of, but do not define, clinical dementia in old age.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 645-658

Cohort profile: Epidemiological Clinicopathological Studies in Europe (EClipSE)

EClipSE Collaborative Members (Carol Brayne, Paul G. Ince, Hannah A.D. Keage, Ian G. McKeith, Fiona E. Matthews, Tuomo Polvikoski, Raimo Sulkava)

Abstract: Epidemiological Clinicopathological Studies in Europe (EClipSE) is the harmonization of neuropathological and longitudinal clinical data from three population-based prospective longitudinal studies of aging. The EClipSE database (Version 1.0) comprises data from the first 970 people who donated their brain at death and this number will increase. EClipSE enables sociodemographic, health, cognitive, and genetic measures collected during life to be related to neuropathology at death, testing hypotheses which require more power than has been previously possible. EClipSE aims to help throw light on relationships between biological, health and psychological factors underlying ageing and the manifestation of clinical dementia.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 659-663

Neuropathologic Studies of the Baltimore Longitudinal Study of Aging (BLSA)

Richard J. O'Brien, Susan M. Resnick, Alan B. Zonderman, Luigi Ferrucci, Barbara J. Crain, Olga Pletnikova, Gay Rudow, Diego Iacono, Miguel A. Riudavets, Ira Driscoll, Donald L. Price, Lee J. Martin, Juan C. Troncoso

Abstract: The Baltimore Longitudinal Study of Aging (BLSA) was established in 1958 and is one the oldest prospective studies of aging in the USA and the world. The BLSA is supported by the National Institute of Aging (NIA) and its mission is to learn what happens to people as they get old and how to sort out changes due to aging and from those due to disease or other causes. In 1986, an autopsy program combined with comprehensive neurologic and cognitive evaluations was established in collaboration with the Johns Hopkins University Alzheimer's Disease Research Center (ADRC). Since then, 211 subjects have undergone autopsy. Here we review the key clinical neuropathological correlations from this autopsy series. The focus is on the morphological and biochemical changes that occur in normal aging, and the early neuropathological changes of neurodegenerative diseases, especially Alzheimer's disease (AD). We highlight the combined clinical, pathologic, morphometric, and biochemical evidence of asymptomatic AD, a state characterized by normal clinical evaluations in subjects with abundant AD pathology. We conclude that in some individuals, successful cognitive aging results from compensatory mechanisms that occur at the neuronal level (i.e., neuronal hypertrophy and synaptic plasticity) whereas a failure of compensation may culminate in disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 665-675

Neuropathologic findings of Dementia with Lewy bodies (DLB) in a population-based Vantaa 85+ study

Minna Oinas, Tuomo Polvikoski, Raimo Sulkava, Liisa Myllykangas, Kati Juva, Irma-Leena Notkola, Sari Rastas, Leena Niinistö, Hannu Kalimo, Anders Paetau

Abstract: The consortium on dementia with Lewy bodies has established consensus guidelines for the neuropathologic diagnosis of dementia with Lewy bodies (DLB) including the likelihood that the neuropathologic findings associate with the clinical syndrome. Nevertheless, clinico-pathological correlations remain controversial. We applied the consensus guidelines for determining Lewy-related pathology (LRP) and evaluated the clinical presentation in the prospective, population-based Vantaa 85+ study consisting of individuals at least 85 years of age. LRP was seen in 36% of 304 subjects and categorized as follows: 3% brainstem-predominant, 14% limbic, 15% diffuse neocortical type (4% could not be categorized). The likelihood that the neuropathology predicts the DLB clinical syndrome was low in 6%, intermediate in 13%, and high in 13% of all 304 subjects. In the latter two groups, 77% were demented, 35% had at least one extrapyramidal symptom, and 15% had visual hallucinations. Surprisingly, DLB clinical features associated better with high neurofibrillary stage than with diffuse neocortical LRP. Moreover, the neurofibrillary stage, substantia nigra neuron loss, and grade of Lewy neurites in hippocampal CA2-3 region, each showed a significant association with the extent of LRP. In conclusion, the neuropathological DLB in this very elderly population was common, but the clinical symptoms tended to associate better with severe neurofibrillary pathology than with extensive LRP.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 677-689

The Neuropathology of Older Persons With and Without Dementia from Community versus Clinic Cohorts

Julie A. Schneider, Neelum T. Aggarwal, Lisa Barnes, Patricia Boyle, David A. Bennett

Abstract: Community-based cohorts of older persons may differ neuropathologically from clinic-based cohorts. This study investigated age-related pathologies in persons with and without dementia and included autopsied participants from two community-based cohorts, the Rush Religious Orders Study (n= 386) and the Memory and Aging Project (n=195), and one clinic-based cohort, the Clinical Core of the Rush Alzheimer's Disease Center (n=392). Final clinical diagnoses included no cognitive impairment (n= 202), mild cognitive impairment (MCI) (n= 150), probable Alzheimer's disease (AD) (n=474), possible AD (n=88), and other dementias (n=59). Postmortem diagnoses included pathologic AD, cerebral infarcts, and Lewy body disease. Community-based persons with clinical AD had less severe AD pathology ($p<0.001$) and had more cerebral infarcts ($p<0.001$) compared to clinic-based persons. Additionally, community-based persons with MCI had more infarcts compared to clinic-based persons. Overall, there was a higher proportion of Lewy bodies and atypical pathologies in the clinic-based compared to the community-based cohorts ($p<0.001$). Community-based persons with probable AD show less severe AD pathology and more often have infarcts and mixed pathologies; those with MCI more often have infarcts and mixed pathologies. Overall, clinic-based persons have more Lewy bodies and atypical pathologies. The spectrum of pathologies underlying cognitive impairment in clinic-based cohorts differs from community-based cohorts.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 691-701

Neuropathology in the Adult Changes in Thought Study: A Review

Joshua A. Sonnen, Eric B. Larson, Sebastien Haneuse, Randy Woltjer, Ge Li, Paul K. Crane, Suzanne Craft, Thomas J. Montine

Abstract: The neuropathology underlying dementia syndromes in older populations is complex. The contributions of Alzheimer's and Lewy body pathology are well appreciated. Recent studies with brain autopsies have highlighted the high prevalence of vascular disease as an independent, but often co-morbid contributor to dementia. The Adult Changes in Thought Study is a community-based, longitudinal study of brain aging and cognitive decline which has recently confirmed cerebral microinfarcts as a strong correlate of cognitive impairment and dementia. This study examines correlations between clinical characteristics including extensive, longitudinal medication histories, and longitudinal cognitive testing against structural and biochemical features of disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 703-711

Brain Lesions at Autopsy in Older Japanese-American Men as Related to Cognitive Impairment and Dementia in the Final Years of Life: A Summary Report from the Honolulu-Asia Aging Study

Lon White

Abstract: This report summarizes findings from 443 autopsies on Japanese-American men followed as active participants in the Honolulu-Asia Aging Study from 1991 through 2003. Five distinct neuropathological lesion types were found to have strong, partially, or completely independent associations with cognitive impairment and/or dementia in the final years of life. They were: Alzheimer lesions (neocortical neurofibrillary tangles and neuritic plaques), microvascular infarcts (microinfarcts and lacunar infarcts), neocortical Lewy bodies, hippocampal sclerosis, and generalized brain atrophy. Atrophy was strongly associated with both Alzheimer lesions and microvascular infarcts, but was also observed in decedents with negligible levels of these and the other lesions. About half of the hippocampal sclerosis cases appeared to be linked to Alzheimer lesions. A weak association of hippocampal sclerosis with microvascular infarcts was also noted. Comparable 3-level indices were defined for each of the five lesion types to facilitate comparisons of associations with cognitive impairment and dementia. All possible combinations of the five lesion types were observed. The development of dementia in the final years of life was more closely correlated with their combined numbers and severities than with specific lesion types. In this autopsy panel, microvascular infarcts were identified as the sole or dominant lesion in 33.8% of the demented or definitely impaired decedents, compared with Alzheimer lesions in 18.6% and co-dominant lesions (most often Alzheimer and microvascular) in 14.2%. These or one or more of the other lesion types were observed in 87.9% of the demented or definitely impaired decedents.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 3, November 2009, Pages 713-725

Modeling Sporadic Alzheimer's Disease: The Insulin Resistant Brain State Generates Multiple Long-Term Morphobiological Abnormalities Inclusive Hyperphosphorylated Tau Protein and Amyloid-ß. A Synthesis

Melita Salkovic-Petrisic, Jelena Osmanovic, Edna Grünblatt, Peter Riederer, Siegfried Hoyer

Abstract: Nosologically, Alzheimer's disease (AD) is not a single disorder. Missense gene mutations involved in increased formation of the amyloid-ß protein precursor derivatives amyloid-ß (Aß)1-40 and Aß1-42/43 lead to autosomal dominant familial AD, found in the minority of AD cases. However, millions of subjects suffer from sporadic AD (sAD) of late onset, for which no convincing evidence suggests Aß as the primary disease-generating compound.

Environmental factors operating during pregnancy and postnatally may affect susceptibility genes and stress factors (e.g., cortisol), consequently affecting brain development both structurally and functionally, causing disorders becoming manifest late in life. With aging, a desynchronization of biological systems may result, increasing further brain entropy/declining criticality. In sAD, this desynchronization may involve stress components, cortisol and noradrenaline, reactive oxygen species, and membrane damage as major candidates causing an insulin resistant brain state with decreased glucose/energy metabolism. This further leads to a derangement of ATP-dependent cellular and molecular work, of the cell function in general, as well as derangements in the endoplasmic reticulum/Golgi apparatus, axon, synapses, and membranes, in particular. A self-propagating process is thus generated, including the increased formation of hyperphosphorylated tau-protein and Aß as abnormal terminal events in sAD rather than causing the disorder, as elaborated in the review.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 729-750

GOLPH2 Gene Markers are Not Associated with Alzheimer's Disease in a Sample of the Spanish Population

Carmen Antúnez, Mercé Boada, Jesús López-Arrieta, Reposo Ramirez-Lorca, Isabel Hernández, Juan Marín, Pablo Martínez-Lage, Antonio González-Pérez, José Jorge Galan, Javier Gayán, Luis M. Real, Agustín Ruiz

Abstract: GOLPH2 gene SNP variants Rs10868366 and Rs7019412 were reported to decrease the risk of Alzheimer's disease in a recent Whole Genome Association Study. We have investigated these genetic variants in 2470 individuals from Spain to conduct an independent replication study of the proposed SNP markers. We found no evidence of association between *GOLPH2* markers and susceptibility to Alzheimer's disease in our series. We concluded that *GOLPH2* gene does not contribute to risk of disease in this study sample.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 751-754

Extracellular Amyloid-ß and Cytotoxic Glial Activation Induce Significant Entorhinal Neuron Loss in Young PS1M146L/ APP751SL Mice

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Abstract: Here we demonstrated that extracellular, not intracellular, amyloid-ß (Aß) and the associated cytotoxic glial neuroinflammatory response are major contributors to early neuronal loss in a PS1xAPP model. A significant loss of

principal (27%) and SOM/NPY (56-46%) neurons was found in the entorhinal cortex at 6 months of age. Loss of principal cells occurred selectively in deep layers (primarily layer V) whereas SOM/NPY cell loss was evenly distributed along the cortical column. Neither layer V pyramidal neurons nor SOM/NPY interneurons displayed intracellular Aß immunoreactivity, even after formic acid retrieval; thus, extracellular factors should be preferentially implicated in this selective neurodegeneration. Amyloid deposits were mainly concentrated in deep layers at 4-6 months, and of relevance was the existence of a potentially cytotoxic inflammatory response (TNFa, TRAIL, and iNOS mRNAs were upregulated). Moreover, non-plaque associated activated microglial cells and reactive astrocytes expressed TNFa and iNOS, respectively. At this age, in the hippocampus of some animals, extracellular Aß induced a non-cytotoxic glial activation. The opposite glial activation, at the same chronological age, in entorhinal cortex and hippocampus strongly support different mechanisms of disease progression in these two regions highly affected by Aß pathology.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 755-776

Bone Density and Brain Atrophy in Early Alzheimer's Disease

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Abstract: Studies suggest a link between bone loss and Alzheimer's disease. To examine bone mineral density (BMD) in early Alzheimer's disease (AD) and its relationship to brain structure and cognition, we evaluated 71 patients with early stage AD (Clinical Dementia Rating (CDR) 0.5 and 1) and 69 non-demented elderly control participants (CDR 0). Measures included whole body BMD by dual energy x-ray absorptiometry (DXA) and normalized whole brain volumes computed from structural MRI scans. Cognition was assessed with a standard neuropsychological test battery. Mean BMD was lower in the early AD group (1.11 ± 0.13) compared to the non-demented control group (1.16 ± 0.12, p=0.02), independent of age, sex, habitual physical activity, smoking, depression, estrogen replacement, and apolipoprotein E4 carrier status. In the early AD group, BMD was related to whole brain volume (b=0.18, p=0.03). BMD was also associated with cognitive performance, primarily in tests of memory (logical memory [b=0.15, p=0.04], delayed logical memory [b=0.16, p=0.02], and the selective reminding task, free recall [b=0.18, p=0.009]). BMDy is reduced in the earliest clinical stages of AD and associated with brain atrophy and memory decline, suggesting that central mechanisms may contribute to bone loss in early AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 777-785

Stimulation of Neurogenesis and Synaptogenesis by Bilobalide and Quercetin via Common Final Pathway in Hippocampal Neurons

Flaubert Tchantchou, Pascale N. Lacor, Zhiming Cao, Lixing Lao, Yan Hou, Changhai Cui, William L. Klein, Yuan Luo *(Communicated by Thomas Shea)*

Abstract: Loss of synapses has been correlated with dementia in Alzheimer's disease (AD) as an early event during the disease progression. Hence, synaptogenesis and neurogenesis in adulthood could serve as a therapeutic target for the prevention and treatment of AD. Recently, we have demonstrated enhanced hippocampal neurogenesis by oral administration of *Ginkgo biloba* extract (EGb 761) to a mouse model of AD. This study aims to identify the constituents that contribute to EGb 761-induced neurogenesis. Among the constituents tested, bilobalide and quercetin significantly increased cell proliferation in the hippocampal neurons in a dose-dependent manner. Bilobalide and quercetin also enhanced phosphorylation of cyclic-AMP Response Element Binding Protein (CREB) in these cells, and elevated the levels of pCREB and , brain-derived neurotrophic factor in mice brain. Immunofluorescence staining of synaptic markers shows remarkable dendritic processes in hippocampal neurons treated with either quercetin or bilobalide. Furthermore, both constituents restored amyloid-ß oligomers (also known as ADDL)-induced synaptic loss and phosphorylation of CREB. The present findings suggest that enhanced neurogenesis and synaptogenesis by bilobalide and quercetin may share a common final signaling pathway mediated by phosphorylation of CREB. Despite a recent report showing that EGb 761 was insufficient in prevent dementia, its constituents still warrant future investigation.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 787-798

Coordinating to Three Histidine Residues: Cu(II) Promotes Oligomeric and Fibrillar Amyloid-ß Peptide to Precipitate in a Non-ß Aggregation Way

Xiao-Hui Yang, Han-Chang Huang, Lin-Chen, Wei-Xu, Zhao-Feng Jiang *(Communicated by Ralph Martins)*

Abstract: Cu(II) has been shown *in vitro* to profoundly promote the aggregation of amyloid-ß peptide (Aß), a key pathological event in Alzheimer's disease. We investigated both the effect of Cu(II) on the secondary structure transformation of Aß and the probable residues involved in the chelation to Cu(II). The effect of Cu(II) on Aß was analyzed by the circular dichroism spectra, Th-T fluorescence, and sedimentation assay and the results indicated that Cu(II) could disrupt the already formed ß-sheet structure, convert ß-sheeted aggregates into non-ß-sheeted aggregates and promote oligomeric Aß to precipitate in a non-ß-sheeted aggregation way. Additionally, we confirmed that the function of Cu(II) discussed above was achieved through its interaction with His6, His13, and His14 by investigating with an Aß mutant, ^{23,6,13,14}Aß1-40.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 799-810

Copper Abolishes the ß-Sheet Secondary Structure of Preformed Amyloid Fibrils of Amyloid-ß42

Emily House, Matthew Mold, Joanna Collingwood, Alex Baldwin, Steven Goodwin, Christopher Exley

Abstract: The observation of the co-deposition of metals and amyloid-ß42 (Aß42) in brain tissue in Alzheimer's disease prompted a myriad of investigations into the role played by metals in the precipitation of this peptide. Copper is bound by monomeric Aß42 and upon precipitation of the copper-peptide complex thereby prevents Aß42 from adopting a ß-sheet secondary structure. Copper is also bound by ß-sheet conformers of Aß42, and herein we have investigated how this interaction affects the conformation of the precipitated peptide. Copper significantly reduced the thioflavin T fluorescence of aged, fibrillar Aß42 with, for example, a 20-fold excess of the metal resulting in a *ca* 90% reduction in thioflavin T fluorescence. Transmission electron microscopy showed that copper significantly reduced the quantities of amyloid fibrils while Congo red staining and polarized light demonstrated a copper-induced abolition of apple-green birefringence. Microscopy under cross-polarized light also revealed the first observation of spherulites of Aß42. The size and appearance of these amyloid structures were found to be very similar to spherulites identified in Alzheimer's disease tissue. The combined results of these complementary methods strongly suggested that copper abolished the ß-sheet secondary structure of pre-formed, aged amyloid fibrils of Aß42. Copper may protect against the presence of ß-sheets of Aß42 *in vivo*, and its binding by fibrillar Aß42 could have implications for Alzheimer's disease therapy.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 811-817

Homocysteine Metabolism and Cerebrospinal Fluid Markers for Alzheimer's Disease

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Abstract: Disturbed homocysteine metabolism is a risk factor for Alzheimer's disease (AD) and may contribute to the disease pathophysiology by increasing both amyloid-ß (Aß) production and phosphorylated tau (P-tau) accumulation. Here, we evaluated the relationship between the cerebrospinal fluid (CSF) concentrations of homocysteine (Hcys), S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), and 5-methyltetrahydrofolate (5-MTHF), and the markers for AD pathology, amyloid-ß (Aß)1-42 and P-tau181, in 98 cognitively healthy subjects aged 16-81 years and 54 AD patients. In multivariate regression tests including age, gender, creatinine, and presence of the apolipoprotein E e4 allele, P-tau181 was associated with SAH (ß=0.490; p<0.001), 5-MTHF (ß=-0.273; p=0.010) levels, and SAM/SAH ratio (ß=-0.319; p=0.013) in controls, and with SAH (ß=0.529; p=0.001) in AD patients. The levels of Aß1-42 were not

associated with the CSF concentrations of Hcys, SAM, SAH, or 5-MTHF neither in the AD nor in the control group. The results suggest that alteration of the homocysteine metabolism is related to increased accumulation of phosphorylated tau and may contribute to the neurofibrillary pathology in normal aging and in AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 819-828

Altered Cholesterol Ester Cycle in Skin Fibroblasts from Patients with Alzheimer's Disease

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Abstract: Intracellular cholesterol metabolism was reported to modulate amyloid-ß (Aß) generation in Alzheimer's disease (AD). Results presented herein demonstrated that, like brain cells, cultured skin fibroblasts from AD patients contained more cholesterol esters than fibroblasts from healthy subjects. Particularly, Oil Red-O, Nile Red, and filipin staining highlighted higher levels of neutral lipids which responded to inhibitors of acyl-coenzyme A:cholesterol acyl-transferase (ACAT-1), associated with an increase in free cholesterol. ACAT-1 mRNA levels increased significantly in AD fibroblasts, whereas those of sterol regulatory element binding protein-2, neutral cholesterol ester hydrolase, and ATP-binding cassette transporter member 1 were markedly down-regulated. Instead, mRNA levels of low-density lipoprotein receptor, hydroxy-methyl-glutaryl-coenzyme A reductase, caveolin-1, and amyloid-ß protein precursor (AßPP) were virtually unchanged. Notably, mRNA levels of both ß-site AßPP-cleaving enzyme 1 (BACE1) and neprilysin were significantly down-regulated. An increase in Aß40 and Aß42 immunostaining and a decrease in BACE1 active form were also found in AD versus control fibroblasts. Altogether, these findings support the hypothesis that the derangement of cholesterol homeostasis is a systemic alteration involving central but also peripheral cells of AD patients, and point to cholesterol esters levels in AD fibroblasts as an additional metabolic hallmark useful in the laboratory and clinical practice.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 829-841

Memantine Inhibits Calpain-Mediated Truncation of GSK-3 Induced by NMDA: Implications in Alzheimer's Disease

Paloma Goñi-Oliver, Jesús Avila and Félix Hernández

Abstract: Deregulation of glycogen synthase kinase-3 (GSK-3) activity is believed to play a key role in the pathogenesis of Alzheimer's disease (AD). GSK-3 activity is regulated by phosphorylation and through interaction with

GSK-3-binding proteins. Previously, we demonstrated that calpain activation produces a truncation of GSK-3. In this study, we show that calpain-mediated GSK-3 truncation, induced by N-methyl-D-aspartic acid (NMDA), depends on extracellular calcium. Primary cultures of cortical neurons treated with NMDA reduce GSK-3 levels up to 75%, although the truncated form of GSK-3 does not accumulate, suggesting that a short-lived product is formed. The data obtained with human AD samples suggest that, although a great variability exists at least in postmortem samples, truncated GSK-3 does not accumulate. However, memantine, a non-competitive NMDA receptor which has been approved for the treatment of moderate to severe AD, is able to inhibit GSK-3 truncation induced by NMDA in primary cultures of cortical neurons in a dose-dependent manner. Thus, memantine modulates GSK-3 signaling, which might explain its protective role in AD. Overall, our data reinforces the important relationship between NMDA receptors and GSK-3 and their involvement as one of the first steps in neurodegenerative diseases such as AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 843-848

A Diet Enriched in Polyphenols and Polyunsaturated Fatty Acids, LMN Diet, Induces Neurogenesis in the Subventricular Zone and Hippocampus of Adult Mouse Brain

Tony Valente, Juan Hidalgo, Irene Bolea, Bartolomé Ramirez, Neus Anglés, Jordi Reguant, José Ramón Morelló, Cristina Gutiérrez, Mercè Boada, Mercedes Unzeta

Abstract: At present it is widely accepted that there are at least two neurogenic sites in the adult mammalian brain: the subventricular zone (SVZ) of lateral ventricles and the subgranular zone (SGZ) of the hippocampus dentate gyrus. The adult proliferation rate declines with aging and is altered in several neurodegenerative pathologies including Alzheimer's disease. The aim of this work was to study whether a natural diet rich in polyphenols and polyunsaturated fatty acids (LMN diet) can modulate neurogenesis in adult mice and give insight into putative mechanisms. Results with BrdU and PCNA demonstrated that the LMN fed mice had more newly generated cells in the SVZ and SGZ, and those with DCX (undifferentiated neurons) and tyrosine hydroxylase, calretinin, and calbindin (differentiated neurons) immunostainings and western blots demonstrated a significant effect on neuronal populations, strongly supporting a positive role of the LMN diet on adult neurogenesis. In primary rat neuron cultures, the LMN cream dramatically protected against damage caused by both hydrogen peroxide and Aß1-42, demonstrating a potent antioxidant effect that could play a major role in the normal adult neurogenesis and, moreover, the LMN diet could have a significant effect combating the cognitive function decline during both aging and neurodegenerative diseases such as Alzheimer's disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 849-865

BDNF Genetic Variations Increase the Risk of Alzheimer's Disease-Related Depression

Barbara Borroni, Mario Grassi, Silvana Archetti, Chiara Costanzi, Marta Bianchi, Luigi Caimi, Carlo Caltagirone, Monica Di Luca, Alessandro Padovani (*Communicated by Valeria Drago)*

Abstract: The gene encoding the brain-derived neurotrophic factor (*BDNF*) has been demonstrated as a candidate for Alzheimer's disease-related depression (AD-D) susceptibility. Additionally, an association between AD-D and the functional valine to methionine (Val66Met) polymorphism has been reported. The aim of this study was to assess the genetic contribution of other *BDNF* variants to AD-D. Two-hundred forty-five AD patients were divided into two subgroups according to the presence (AD-D) or the absence (AD-nD) of depressive symptoms. Four single-nucleotide polymorphisms within *BDNF* gene were considered, i.e., C270T, rs2049045 C/G, G196A (Val66Met), and G11757C. In our sample, 35.5% of patients (n=87) reported AD-related depressive symptoms. The individual SNP analysis showed an association between G196A and G11757C genotypes and AD-D. Accordingly, considering the allele frequencies, *BDNF* 196*A allele was significantly overrepresented in AD-D compared to AD-nD (OR=1.80, 95% CI=1.19-2.72), as well as BDNF 11757*C allele (OR=1.90, 95% CI=1.25-2.90). Haplotype analyses revealed that the alleles at four loci (C270T, rs2049045 C/G, G196A, G11757C) interacted to further increase the risk of AD-D. Compared to the most common *not-at-risk* C-C-G-G haplotype, C-G-A-C (OR=3.55, 95% CI=1.44-8.76, *P*=0.006) and C-C-A-C haplotypes (OR=1.72, 95% CI=1.03-2.87, *P*=0.037) were overrepresented in AD-D. This study suggests that *BDNF* genetic variations play a role in the susceptibility to AD-related depression.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 867-875

Protein Kinase C Involvement in the Acetylcholine Release Reduction Induced by Amyloid-ß25-35 Aggregates on Neuromuscular Synapses

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*These authors contributed equally to this work

Abstract: Using intracellular recording of the diaphragm muscle of adult rats, we have investigated the short-term functional effects of amyloid-ß (Aß)25-35 peptide aggregates in the modulation of acetylcholine (ACh) release and the involvement of protein kinase C (PKC). The non-aggregated form of this peptide does not change the evoked and spontaneous transmitter release parameters on the neuromuscular synapse. However, the aggregated form of Aß25-35 acutely interferes with evoked quantal ACh release (~40% reduction) when synaptic activity in the *ex vivo* neuromuscular preparation is maintained by low frequency (1 Hz) electrical stimulation. This effect is partially dependent on the activity of

PKC that may have a permissive action. The end result of Aß25-35 is in opposition to the PKC-dependent maintenance effect on ACh release manifested in active synapses.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 877-884

Galanin Fiber Hyperinnervation Preserves Neuroprotective Gene Expression in Cholinergic Basal Forebrain Neurons in Alzheimer's Disease

Scott E. Counts, Bin He, Shaoli Che, Stephen D. Ginsberg, Elliott J. Mufson

Abstract: Fibers containing galanin (GAL) hyperinnervate cholinergic basal forebrain nucleus basalis neurons in late stage Alzheimer's disease (AD), yet the molecular consequences of this phenomenon are unknown. To determine whether GAL alters the expression of genes critical to cholinergic basal forebrain cell survival in AD, single cell microarray analysis was used to determine mRNA levels within nucleus basalis neurons lacking GAL innervation from subjects who died with a clinical diagnosis of no cognitive impairment (NCI) compared to nucleus basalis neurons from AD cases either lacking GAL hyperinnervation (AD/GAL-) or those displaying prominent GAL hyperinnervation (AD/GAL+). Levels of mRNAs encoding putatively neuroprotective proteins such as the GluR2 Ca2+-impermeable glutamate receptor subunit, superoxide dismutase 2, and the GLUT2 glucose transporter were significantly decreased in AD/GAL- nucleus basalis neurons compared to NCI and AD/GAL+ neurons. By contrast, mRNAs encoding calpain catalytic and regulatory subunits, which may contribute to cell death in AD, were increased in AD/GAL- compared to NCI and AD/GAL+ neurons. Hence, GAL fiber hyperinnervation appears to preserve the expression of genes subserving multiple neuroprotective pathways suggesting that GAL overexpression regulates cholinergic basal forebrain neuron survival in AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 885-896

Human Truncated Tau is Using a Different Mechanism from Amyloid-ß to Damage the Blood-Brain Barrier

Andrej Kovac, Monika Zilkova, Maria A. Deli, Norbert Zilka and Michal Novak

Abstract: Recent findings showed that vascular dysfunction is considered to be an integral part of Alzheimer's disease pathology. Increased microvascular permeability is mainly associated with cerebrovascular amyloid-ß deposits. In contrast, little is known about the relationship between functional impairment of the blood-brain barrier and misfolded tau. In the present study, we examined whether human truncated tau is able to impair blood-brain barrier in an *in vitro* model. We have found that truncated tau induced a very strong polarity-

dependent effect in the rat blood-brain barrier model. When the tau was added to the upper compartment of the model containing endothelial cells (apical treatment), no effect was observed. However, the application of tau to the lower compartment (basolateral treatment), consisting of astroglia-microglia culture, triggered significant decrease of transendothelial electrical resistance and increase of endothelial permeability for mannitol. Further, we found that truncated tau showed cytotoxic effects on astroglia-microglia culture manifested by increased extracellular adenylate kinase levels. Molecular analysis of underlying mechanisms of tau induced blood-brain barrier damage revealed the contribution of pro-inflammatory cytokine tumor necrosis factor-a and chemokine MCP-1 released from activated microglial cells. This study for the first time uncovers novel toxic gain of function of misfolded tau that could contribute to the cerebral microvascular damage in human tauopathies.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 897-906

Increased Total Tau But Not Amyloid-ß42 in Cerebrospinal Fluid Correlates with Short-Term Memory Impairment in Alzheimer's Disease

Yuh-Te Lin, Jiin-Tsuey Cheng, Yun-Chin Yao, Liang-I Juo, Yuk-Keung Lo, Ching-Hwung Lin, Luo-Ping Ger, Pei-Jung Lu

Abstract: Given the need for tools for early and accurate diagnosis, prediction of disease progression, and monitoring efficacy of therapeutic agents for AD, the study of cerebrospinal fluid (CSF) biomarkers has become a rapidly growing field of research. Several studies have reported conflicting data regarding the relationships between CSF biomarkers and dementia severity. In this study, we have focused on the identification of CSF biomarkers and their correlations with the impairment of different cognitive domains measured using the Cognitive Abilities Screening Instrument (CASI). Patients with AD (n=28), non-AD dementia (n=16), other neurological disorders (OND, n=14), and healthy controls (HC, n=21) were enrolled. Our results revealed significantly higher CSF total tau (t-tau) and lower amyloid-ß42 levels in AD patients compared with those in HC and OND groups. Moreover, our data show that CSF t-tau levels, but not Aß42 levels, have an inverse correlation with the score of short-term memory in CASI for patients with AD (Spearman: r=-0.444; p=0.018). This data might indicate that the higher CSF t-tau level is associated with more NFT pathology and more severe impairment of short-term memory in AD patients.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 907-918

Pathological-Like Assembly of tau Induced by a Paired Helical Filament Core Expressed at the Plasma Membrane

Victoria Campos-Peña, José Tapia-Ramírez, Carmen Sánchez-Torres, Marco Antonio Meraz-Rios

Abstract: The hallmark of Alzheimer's disease is the pathological aggregation of tau proteins into paired helical filaments and neurofibrillary tangles. This paper evaluates the abnormal expression and localization of chimeric tau molecules at the plasma membrane of COS-7 cells and its relationship with tau polymerization. Overexpression of these proteins, in combination with either tau441 or tau391, induces tau to assemble into ß-pleated sheets that are recognized by Thiazin red. Immunoelectromicroscopy analysis revealed the presence of filaments close to the plasma membrane resembling those found in Alzheimer's disease. The capacity of plasma membrane-associated chimeric tau proteins to capture full length tau was increased in the presence of H2O2 or okadaic acid treatments. This suggests that hyperphosphorylation or an oxidative environment could both influence the biochemical properties of the cell that lead to assembly of paired helical filaments. The altered localization of tau protein at the plasma membrane could play a key role in the assembly of pathological tau.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 919-933

Early Biochemical and Morphological Modifications in the Brain of a Transgenic Mouse Model of Alzheimer's Disease: A Role for Peroxisomes

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*These authors contributed to the present work equally

Abstract: The central role of peroxisomes in reactive oxygen species and lipid metabolism and their importance in brain functioning are well established. The aim of this work has been to study the peroxisomal population in the Tg2576 mouse model of Alzheimer's disease (AD), at the age of three months when no apparent signs of behavioral, neuroanatomical, cytological, or biochemical alterations have been so far described. The expression and localization of peroxisomal (PMP70, CAT, AOX, and THL) and peroxisome-related proteins (PEX5p, GPX1, SOD1, and SOD2) were studied in the neocortex and hippocampus of transgenic and wild-type animals. Oxidative stress markers (TBARS, acrolein, and 8-OHG) were also evaluated. Our results demonstrate that significant alterations are already detectable at this early stage of the disease and also involve peroxisomes. Their number and protein composition change concomitantly with early oxidative stress. Interestingly, the neocortex shows a compensatory response, consisting in an increase of reactive oxygen species scavenging enzymes, while the hippocampus appears more prone to the oxidative insult. This different behavior could be related to metabolic differences in the two brain areas, also involving peroxisome abundance and/or enzymatic content.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 935-952

Genetic Variation in the *G72/G30* Gene Locus (*DAOA*) Influences the Occurrence of Psychotic Symptoms in Patients with Alzheimer's Disease

Emilio Di Maria, Cristian Bonvicini, Cristina Bonomini, Antonella Alberici, Orazio Zanetti, Massimo Gennarelli *(Communicated by Alessandro Serretti)*

Abstract: The occurrence of neuropsychiatric symptoms in patients with Alzheimer's disease hampers the clinical management and exacerbates the burden for caregivers. To what extent psychotic symptoms are genetically determined and which are the genes involved has to be established. We tested the hypothesis that the occurrence of delusions and hallucinations in AD is associated with variations in the *G72/DAOA* gene, which is supposed to play a key role in the glutamate pathway regulated through the NMDA receptors. A panel of single nucleotide polymorphisms were genotyped in a cohort of 185 Alzheimer's disease patients. The analysis demonstrated a nominally significant association ($p<0.05$) with one single nucleotide polymorphisms (rs2153674). In addition, multivariate regression showed that the rs2153674 genotype accounts for up to 15% of the variance in delusions severity, as assessed by using the Neuropsychiatric Inventory. If the results from the present study will be replicated, the glutamate hypothesis could be invoked to explain the occurrence of psychosis in neurodegenerative disorders.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 953-960

Diminished Amyloid-ß Burden in Tg2576 Mice Following a Prophylactic Oral Immunization with a Salmonella-Based Amyloid-ß Derivative Vaccine

Allal Boutajangout, Fernando Goni, Elin Knudsen, Fernanda Schreiber, Ayodeji Asuni, David Quartermain, Blas Frangione, Alejandro Chabalgoity, Thomas Wisniewski, Einar M. Sigurdsson *Contributed equally to the project

Abstract: Immunotherapy holds great promise for Alzheimer's disease (AD) and other conformational disorders but certain adverse reactions need to be overcome. Prior to the side effects in the first Elan/Wyeth AD vaccine trial, we proposed using amyloid-ß (Aß) derivatives as a safer approach. The route of administration may also affect vaccine safety. To assess the feasibility of oral immunization that promotes mucosal immunity, Tg2576 AD model mice were treated prophylactically three times over 6 weeks starting at 3-5 months of age with a Salmonella vaccine expressing K6Aß1-30. At 22-24 months of age, cortical Aß plaque burden and total Aß40/42 levels were reduced by 48-75% in the immunized mice compared to controls, which received unmodified Salmonella. Plaque clearance was not associated with increased microglial activation which may be explained by the long treatment period. Furthermore, cerebral microhemorrhages were not increased in the treated mice in contrast to

several passive Aß antibody studies. These results further support our findings with this immunogen delivered subcutaneously and demonstrate its efficacy when given orally which may provide added benefits for human use.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 4, December 2009, Pages 961-972

The Microtubule-Associated Protein Tau is Also Phosphorylated on Tyrosine

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Abstract: Tau protein is the principal component of the neurofibrillary tangles found in Alzheimer's disease (AD), where it is hyperphosphorylated on serine and threonine residues. It is hypothesized that this hyperphosphorylation contributes to neurodegeneration through the destabilization of microtubules. There is now evidence that phosphorylation of tau can also occur on tyrosine residues. Human tau has five tyrosines numbered 18, 29, 197, 310, and 394, according to the sequence of the longest CNS isoform. Tyrosines 18, 197, and 394 have been shown to be phosphorylated in the brain of patients with AD whereas tyrosine 394 is the only residue that has been described to date that is phosphorylated in physiological conditions. Src family kinases and spleen tyrosine kinase (Syk) have been shown to phosphorylate tyrosine 18 while c-Abl is capable of phosphorylating tyrosine 394. Recently, a dual specificity kinase termed TTBK1 has been characterized in human brain and shown to be able to phosphorylate residue 197 of tau. Data about the role of tau tyrosine phosphorylation in neuronal physiology are still scarce and preliminary. In contrast, there is mounting evidence suggesting that tau tyrosine phosphorylation is an early event in the pathophysiology of AD and that Fyn and c-Abl are critical in the neurodegenerative process which occurs in tauopathies.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 1, September 2009, Pages 1-9

A Systematic Review of Neuropsychiatric Symptoms in Mild Cognitive Impairment

Roberto Monastero, Francesca Mangialasche, Cecilia Camarda, Sara Ercolani, Rosolino Camarda *(Communicated by Patrizia Mecocci)*

Abstract: Mild cognitive impairment (MCI) is a clinical concept proposed as an intermediate state between normal aging and dementia. This condition has multiple heterogeneous sources, including clinical presentation, etiology, and prognosis. Recently, the prevalence and associated features of neuropsychiatric symptoms (NPS) in MCI have been described. We systematically searched the PudMed database (last accessed on August 31, 2008) for articles on NPS in MCI. Included articles used strict selection criteria, and outcome variables were

extracted in duplicate; of the 27 articles included, 14 (52%) used prospective cohorts. The global prevalence of NPS in MCI ranged from 35% to 85%. The most common behavioral symptoms were depression, anxiety, and irritability. Hospital-based samples reported a higher global prevalence of NPS than population-based studies; this discrepancy probably reflected differences in demographics, study setting, MCI diagnostic criteria, and behavioral instruments used. Prospective studies showed that NPS, particularly depression, may represent risk factors for MCI or predictors for the conversion of MCI to Alzheimer's disease (AD). NPS are very prevalent in subjects with MCI, displaying a similar pattern of symptoms compared to dementia and AD. Large cohort studies using standardized MCI criteria and behavioral instruments are required to evaluate the prognostic role of NPS in MCI.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 1, September 2009, Pages 11-30

Alzheimer's Amyloid-ß Rescues Yeast from Hydroxide Toxicity

Ashok K. Dubey, Prashant R. Bharadwaj, Joseph N. Varghese, Ian G. Macreadie

Abstract: Amyloid-ß (Aß42), which is known to be toxic to neuronal cells, protects yeast cells from severe sodium hydroxide toxicity. More than 85% cell death was caused by treatment with 1 mM NaOH and approximately 95% was observed at a 2 mM concentration. However, greater than 55% cells survived the treatment in the presence of Aß42. A strong protective effect of the peptide was also evident from the differential staining of the treated culture with propidium iodide.

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Mapping Cofilin-Actin Rods in Stressed Hippocampal Slices and the Role of cdc42 in Amyloid-ß-Induced Rods

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Abstract: Dissociated hippocampal neurons exposed to a variety of degenerative stimuli form neuritic cofilin-actin rods. Here we report on stimulus driven regional rod formation in organotypic hippocampal slices. Ultrastructural analysis of rods formed in slices demonstrates mitochondria and vesicles become entrapped within some rods. We developed a template for combining and mapping data from multiple slices, enabling statistical analysis for the identification of vulnerable sub-regions. Amyloid-ß (Aß) induces rods predominantly in the dentate gyrus region, and Aß-induced rods are reversible following washout. Rods that persist 24 h following transient (30 min) ATP-depletion are broadly distributed, whereas rods formed in response to excitotoxic glutamate localize within and nearby the pyramidal neurons. Time-lapse imaging of cofilin-GFP-expressing neurons within slices shows neuronal rod formation

begins rapidly and peaks by 10 min of anoxia. In ~50% of responding neurons, Aß-induced rod formation acts via cdc42, an upstream regulator of cofilin. These new observations support a role for cofilin-actin rods in stress-induced disruption of cargo transport and synaptic function within hippocampal neurons and suggest both cdc42-depedent and independent pathways modulate cofilin activity downstream from Aß.

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A Study of the SORL1 Gene in Alzheimer's Disease and Cognitive Function

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Abstract: Several studies have investigated the role of the neuronal sortilin-related receptor (SORL1) gene in Alzheimer's disease (AD), but findings have been inconsistent. We conducted a study of 7 single nucleotide polymorphisms (SNPs), rs668387, rs689021, rs641120, rs1699102, rs3824968, rs2282649, and rs1010159, in the SORL1 gene that were associated to AD in previous studies. We tested for association with AD and cognitive function in 6741 participants of the Rotterdam Study and in 2883 individuals from the Erasmus Rucphen Family study. We performed meta-analyses on AD using our data together with those of previous studies published prior to September 2008 in Caucasians. Further, we studied up to 76 SNPs in a 400 kb region within and flanking the gene to evaluate the evidence that other genetic variants are associated with AD or cognitive function. There was no significant evidence for association between SORL1 SNPs and incident AD patients in the Rotterdam Study. In a meta-analysis of our data with those of others, six out of seven SNPs attained borderline significance. However, removal of the first study reporting association from the meta-analysis resulted in non-significant odds ratios for all SNPs. SNPs rs668387, rs689021, and rs641120 were associated with cognitive function in non-demented individuals at borderline statistical significance in two independent Dutch cohorts, but in the opposite direction. Testing for association using dense SNPs in the SORL1 gene did not reveal significant association with AD, or with cognitive function when adjusting for multiple testing. In conclusion, our data do not support the hypothesis that genetic variants in SORL1 are related to the risk of AD.

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The Role of Neuropsychology in Distinguishing the Posterior Cortical Atrophy Syndrome and Alzheimer's Disease

Anna Aresi and Anna Rita Giovagnoli

Abstract: This study investigated the neuropsychological hallmarks of posterior cortical atrophy (PCA). Seventeen patients with PCA, 17 patients with probable Alzheimer's disease (PAD), and 17 healthy age-matched subjects underwent neuropsychological testing for abstract reasoning, visuospatial abilities, memory, language, executive functions, praxes, and attention. The PCA patients were significantly more impaired in visual perception, spatial memory, visual attention, and visuospatial reasoning compared to the PAD patients who were relatively more impaired in episodic memory. In the PCA group, no test score correlated with disease duration or age of clinical onset, whereas, in the PAD group, several scores correlated with disease duration. Compared to the healthy subjects, both patient groups showed multiple cognitive deficits. Thus, PCA is characterized by distinctive visuospatial deficits that reflect the distribution of brain damage and contrast with the memory impairment of PAD patients. Specific neuropsychological tests may contribute to early identification of cortical dementia for diagnostic and research purposes.

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Systemic Tocopherols and F2-Isoprostanes and the Risk of Alzheimer's Disease and Dementia: A Prospective Population-Based Study

Johan Sundelöf, Lena Kilander, Johanna Helmersson, Anders Larsson, Elina Rönnemaa, Malin Degerman-Gunnarsson, Per Sjögren, Hans Basun, Lars Lannfelt, Samar Basu

Abstract: Oxidative stress in the brain is suggested to be involved in the pathophysiology of Alzheimer's disease (AD). In this study, serum a- and ?-tocopherol, the two major systemic antioxidants, were analyzed at two examinations of the ULSAM-study, a longitudinal, community-based study of elderly men (age 70, n=616 and age 77, n=761). In addition, urinary F2-isoprostane levels, as markers of systemic oxidative stress, were analyzed at the age of 77 in this cohort (n=679). Cox regression analyses were used to examine associations between serum a-, ?-tocopherol and urinary F2-isoprostane levels and AD, any type of dementia (all-cause dementia) and non-AD dementia. On follow-up (median, 12.3 years), 40 subjects developed AD and 86 subjects developed all-cause dementia. Serum a- and ?-tocopherol or urinary F2-isoprostane levels were not associated with the future risk of AD or dementia. In conclusion, systemic serum a- and ?-tocopherol and urinary F2-isoprostane levels are not associated with the future risk of AD or dementia and do not seem to be useful predictors of clinical AD or dementia.

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Systemic Inflammation and the Risk of Alzheimer's Disease and Dementia: A Prospective Population-Based Study

Johan Sundelöf, Lena Kilander, Johanna Helmersson, Anders Larsson, Elina Rönnemaa, Malin Degerman-Gunnarsson, Hans Basun, Lars Lannfelt, Samar Basu

Abstract: Inflammation is suggested to be involved in the pathogenesis of Alzheimer's disease (AD). Serum interleukin-6 (IL-6) and high sensitivity serum reactive protein C (hsCRP) as markers of systemic inflammation were analyzed at two examinations of the ULSAM-study, a longitudinal, community-based study of elderly men (age 70, n=1062 and age 77, n=749). In addition, serum amyloid protein A (SAA) and urinary prostaglandin F2a (PGF2a) metabolite levels were analyzed at age 77 in this cohort. Two serial samples (at ages 70 and 77) were available from 704 individuals. Using Cox regression analyses, associations between serum IL-6, hsCRP, SAA and PGF2a metabolite levels and risk of AD, any type of dementia (all-cause dementia) and non-AD dementia were analyzed. On follow-up (median, 11.3 years) in the age 70 cohort, 81 subjects developed AD and 165 subjects developed all-cause dementia. Serum IL-6, hsCRP, SAA, or PGF2a levels were not associated with risk of AD. At age 70, high IL-6 levels were associated with an increased risk of non-AD dementia (Hazard ratio 2.21 for above vs. below/at median, 95% confidence interval 1.23-3.95, p-value=.008). A longitudinal change in CRP or IL-6 levels was not associated with AD or dementia. In conclusion, Serum IL-6, hsCRP, SAA, and PGF2a levels are not associated with the risk of AD. High serum IL-6 levels may be associated with increased risk of non-AD dementia.

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Validity of Cerebrospinal Fluid Biomarkers as Endpoints in Early-Phase Clinical Trials for Alzheimer's Disease

Bin Zhou, Satoshi Teramukai, Kenichi Yoshimura, Masanori Fukushima

Abstract: A systematic literature review was performed to assess the suitability of cerebrospinal fluid (CSF) levels of protein amyloid-ß42 (Aß42) and tau as markers to detect the disease-modifying effects of drugs in clinical trials of AD treatments. All databases were searched for observational studies, single-arm clinical trials, and randomized controlled trials involving patients with AD in which CSF Aß42 and tau were measured. A meta-analytic random-effects model was used to evaluate the mean absolute change in protein concentration over time. Spearman correlation was used to assess the association between change in CSF protein concentration and change in cognitive function. The mean changes per month in observational studies were -0.4 pg/ml/month (95% CI: -1.9 to 1.1) for 8 CSF Aß42 and 1.5 pg/ml/month (95% CI: 0.1 to 3.0) for 12 CSF tau studies. The correlation coefficients for the relationship between CSF protein concentration and cognition were 0.43 (p=0.068) for all 18 Aß42 studies and -

0.05 (p=0.857) for all 18 tau studies. A trend in which CSF Aß42 decreases and tau protein increases over time was identified in AD patients. CSF Aß42 and tau concentrations should be used with caution as surrogate endpoints in early-phase clinical trials for AD.

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Failure of Biomarkers in Clinical Trials of Alzheimer's Disease: Blaming the Messenger?

Joseph Quinn, Christoper M. Clark

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Gelsolin is Proteolytically Cleaved in the Brains of Individuals with Alzheimer's Disease

Lina Ji, Abha Chauhan, Jerzy Wegiel, Musthfa M. Essa, Ved Chauhan

Abstract: Gelsolin, a multifunctional actin-binding protein, forms a complex with amyloid-ß protein and reduces the amyloid load in the transgenic mouse model of Alzheimer's disease (AD). Gelsolin consists of six homologous domains, which have specific affinities for phosphatidylinositol 4, 5-bisphosphate, calcium, and actin. During apoptosis, gelsolin is cleaved by the caspase-3 resulting in a 48 kDa carboxyl-terminal fragment (gelsolin-CTF). We report here that gelsolin is significantly cleaved in the frontal cortex of individuals with AD as compared to age-matched controls. A positive correlation was observed between the appearance of gelsolin-CTF in frontal cortex and severity of AD. Gelsolin-CTF was also observed in apoptotic SH-SY5Y cells induced by H2O2 or calcium ionophore A23187. In addition, lipid peroxidation was increased in the frontal cortex of AD suggesting that oxidative stress occurs in AD brain. Taken together, these results suggest that there may be a link among oxidative stress, neuronal apoptosis, and gelsolin cleavage in AD.

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Bioavailability of Gallic Acid and Catechins from Grape Seed Polyphenol Extract is Improved by Repeated Dosing in Rats: Implications for Treatment in Alzheimer's Disease

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Abstract: The present study explored the bioavailability and brain deposition of a grape seed polyphenolic extract (GSPE) previously found to attenuate cognitive

deterioration in a mouse model of Alzheimer's disease (AD). Plasma pharmacokinetic response of major GSPE phenolic components was measured following intragastric gavage of 50, 100, and 150 mg GSPE per kg body weight. Liquid chromatography-mass spectrometry (LC-MS) analysis identified gallic acid (GA), catechin (C), and epicatechin (EC) in plasma of rats gavaged acutely with GSPE. Additionally, 4-methylgallic acid (4-OMeGA), 3'-methytlcatechin (3'-OMeC), and 3'-methylepicatechin (3'-OMeEC) were identified as circulating metabolites of GSPE phenolic constituents. Cmax for individual GSPE constituents and their metabolites increased in a dose-dependent fashion (with increasing GSPE oral dose). Repeated daily exposure to GSPE was found to significantly increase bioavailability (defined as plasma AUC0-8h) of GA, C, and EC by 198, 253, and 282% relative to animals receiving only a single acute GSPE dose. EC and C were not detectable in brain tissues of rats receiving a single GSPE dose but reached levels of 290.7 ± 45.9 and 576.7 ± 227.7 pg/g in brain tissues from rats administered GSPE for 10 days. This study suggests that brain deposition of GA, C, and EC is affected by repeated dosing of GSPE.

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The Serotonin Transporter Promoter Polymorphic Region is not a Risk Factor for Alzheimer's Disease Related Behavioral Disturbances

Diego Albani, Francesca Prato, Mauro Tettamanti, Carlo Lovati, Daniela Galimberti, Ilaria Restelli, Claudio Mariani, Pier Luigi Quadri, Elio Scarpini, Ugo Lucca, Gianluigi Forloni *(Communicated by Alessandro Serretti)*

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory loss and often accompanied during its progression by behavioral and psychological symptoms of dementia (BPSD). We decided to evaluate the association between AD-related behavioral disturbances and the short/long (S/L) polymorphism of the promoter region of the 5-hydroxytryptamine (5-HT) transporter gene (*SLC6A4*). This functional polymorphism modulates *SLC6A4* transcription rate, with the S-allele having a 2-fold reduced efficiency, leading to a diminished availability of 5-HT that might in turn trigger behavioral and cognitive alterations. The *SLC6A4* promoter functional single nucleotide polymorphism *rs25531* (AàG) was genotyped as well. We collected 235 sporadic AD subjects that were classified as AD with (n=122) or without (n=113) behavioral alterations, assessed with the Spontaneous Behavior Interview scale, section Behavioral Problems (SBI-BP). Comparing the genotypic and allelic frequencies of AD without and with BPSD, we did not find a difference for the *5-HTTLPR* or the *rs25531*, even after stratification according to single SBI-BP item. We conclude that *5-HTTLPR* and *rs25531* are not major genetic modulators of BPSD development in AD.

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Dysregulation of Histone Acetylation in the APP/PS1 Mouse Model of Alzheimer's Disease

Yitshak I Francis*, Mauro Fà*, Haider Ashraf, Hong Zhang, Agnieszka Staniszewski, David S. Latchman, Ottavio Arancio *(Communicated by Luciano D'Adamio)* *These authors have contributed equally to the studies presented in this manuscript

Abstract: Epigenetic mechanisms such as post-translational histone modifications are increasingly recognized for their contribution to gene activation and silencing in the brain. Histone acetylation in particular has been shown to be important both in hippocampal long-term potentiation (LTP) and memory formation in mice. The involvement of the epigenetic modulation of memory formation has also been proposed in neuropathological models, although up to now no clear-cut connection has been demonstrated between histone modifications and the etiology of Alzheimer's disease (AD). Thus, we have undertaken preclinical studies in the APP/PS1 mouse model of AD to determine whether there are differences in histone acetylation levels during associative memory formation. After fear conditioning training, levels of hippocampal acetylated histone 4 (H4) in APP/PS1 mice were about 50% lower than in wild-type littermates. Interestingly, acute treatment with a histone deacetylase inhibitor, Trichostatin A (TSA), prior to training rescued both acetylated H4 levels and contextual freezing performance to wild-type values. Moreover, TSA rescued CA3-CA1 LTP in slices from APP/PS1 mice. Based on this evidence, we propose the hypothesis that epigenetic mechanisms are involved in the altered synaptic function and memory associated with AD. In this respect, histone deacetylase inhibitors represent a new therapeutic target to effectively counteract disease progression.

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Tau Aggregation Followed by Atomic Force Microscopy and Surface Plasmon Resonance, and Single Molecule Tau-Tau Interaction Probed by Atomic Force Spectroscopy

Alejandro Barrantes, Javier Sotres, Mercedes Hernando-Pérez, Maria J. Benítez, Pedro J. de Pablo, Arturo M. Baró, Jesus Ávila, Juan S. Jiménez

Abstract: Intracellular neurofibrillary tangles, composed mainly of tau protein, and extracellular plaques, containing mostly amyloid-ß, are the two types of protein aggregates found upon autopsy within the brain of Alzheimer's disease patients. Polymers of tau protein can also be found in other neurodegenerative disorders known as tauopathies. Tau is a highly soluble protein, intrinsically devoid of secondary or tertiary structure, as many others proteins particularly prone to form fibrillar aggregations. The mechanism by which this unfolded molecule evolves to the well ordered helical filaments has been amply studied. In fact, it is a very slow process when followed in the absence of aggregation

inducers. Herein we describe the use of surface plasmon resonance, atomic force microscopy, and atomic force spectroscopy to detect tau-tau interactions and to follow the process of aggregation in the absence of aggregation inducers. Tau-tau interactions are clearly detected, although a very long period of time is needed to observe filaments formation. Tau oligomers showing a granular appearance, however, are observed immediately as a consequence of this interaction. These granular tau oligomers slowly evolve to larger structures and eventually to filaments having a size smaller than those reported for paired helical filaments purified from Alzheimer's disease.

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A Natural Squamosamide Derivative FLZ Reduces Amyloid-ß Production by Increasing Non-Amyloidogenic AßPP Processing

Yan Hou, Young-Beob Yu, Gengtao Liu, Yuan Luo

Abstract: Substantial evidence supports a central role of Aß in the pathogenesis of Alzheimer's disease (AD). We have demonstrated that FLZ, a synthetic cyclic analogue of natural squamosamide, exhibits neuroprotective actions in cells and mouse models, suggesting future investigation of FLZ as a candidate compound for the treatment of AD. In this study, we found that production of amyloid-ß (Aß) was reduced by FLZ in Aß-expressing neuroblastoma cells, which correlates with an increase in the soluble a-secretase derived fragment of the amyloid-ß protein precursor (sAßPPa) in the medium. Moreover, the active form of ADAM10 and AßPP were elevated at the cell surface of FLZ-treated cells, consistent with an enhanced co-localization of ADAM10 and AßPP on the membrane. Pretreatment with brefeldin, a protein trafficking inhibitor, blocked FLZ-induced translocation of ADAM10 to the cell surface and release of sAßPPa to the culture medium. Furthermore, oral administration of FLZ to APPswe/PS1 transgenic mice significantly reduced the levels of Aß, parallel with activation of ADAM10, in the hippocampus. *In silico* prediction indicates that the structure of FLZ agree with the drug-like rules for absorption and permeability. These findings suggest that reducing Aß production by FLZ may be mediated by its promotion of AßPP non-amyloidogenic a-secretase processing, and FLZ has therapeutic potential for the treatment of AD.

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The GxxxG Motif in the Transmembrane Domain of AßPP Plays an Essential Role in the Interaction of CTFß with the ?-secretase Complex and the Formation of Amyloid-ß

Guozhang Mao, Jianxin Tan, Mei-Zhen Cui, Dehua Chui, Xuemin Xu

Abstract: g-secretase-mediated processing of the amyloid-ß protein precursor (AßPP) is a crucial step in the formation of the amyloid-ß peptide (Aß), but little

is known about how the substrate AßPP interacts with the g-secretase complex. To understand the molecular events involved in g-secretase-mediated AßPP processing and Aß formation, in the present study we determined the role of a well conserved GxxxG motif in the transmembrane domain of AßPP. Our data clearly demonstrate that substitution of aspartic acid for the key glycine residues in the GxxxG motif almost completely abolished the formation of Aß. Furthermore, our data revealed that substitution of aspartic acid for the glycine in this GxxxG motif disrupts the interaction of AßPP with the g-secretase complex. Thus, the present study revealed an essential role for the GxxxG motif in the interaction of AßPP with the g-secretase complex and the formation of Aß.

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Astrocyte Function is Modified by Alzheimer's Disease-like Pathology in Aged Mice

Oliver Peters, Carola G. Schipke, Andreas Philipps, Brigitte Haas, Ulrike Pannasch, Li Ping Wang, Bruno Benedetti, Ann E. Kingston, Helmut Kettenmann

Abstract: Alzheimer's disease (AD) may affect all cell types in the central nervous system. Astrocytes have rarely been investigated in the aged brain and the role of astrocytes in AD is poorly understood. In this study, we used acute brain slices from an amyloid-ß overexpressing double transgenic mouse line where astrocytes express the enhanced green fluorescent protein under the control of the glial fibrillary acidic protein promoter. Using the patch-clamp technique, we analyzed cell coupling and glutamate reactivity, two main features of astrocytes, in the living tissue of aged mice in an AD mouse model. We found large astrocytic networks in the aged (20 to 27 months) transgenic animals in the neocortex, but not in the hippocampus. In contrast, coupling was low in all brain regions of aged control mice. We furthermore noticed significant changes in the responses of astrocytes to glutamate. The expression of functional glutamate transporters and AMPA/kainate-type glutamate receptors increases in the amyloid-ß protein precursor overexpressing mice. Thus, exposure to amyloid-ß leads to altered astrocyte properties and this change might be beneficial to maintain synaptic function.

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The Multidimensional Prognostic Index (MPI) Based on a Comprehensive Geriatric Assessment Predicts Short- and Long-Term Mortality in Hospitalized Older Patients with Dementia

Alberto Pilotto, Daniele Sancarlo, Francesco Panza, Francesco Paris, Grazia D'Onofrio, Leandro Cascavilla, Filomena Addante, Davide Seripa, Vincenzo Solfrizzi, Bruno Dallapiccola, Marilisa Franceschi, Luigi Ferrucci

Abstract: Aim of this study was to evaluate the usefulness of a Multidimensional Prognostic Index (MPI) based on a Comprehensive Geriatric Assessment (CGA) for predicting mortality risk in older patients with dementia. The present was a retrospective study with a year of follow-up that included 262 patients aged 65 years and older with a diagnosis of dementia. A standardized CGA that included information on clinical, cognitive, functional, and nutritional aspects, as well as comorbidity, medications, and social support network, was used to calculate MPI. The predictive value of the MPI for all-cause mortality over 1 month, 6 months, and 12 months of follow-up was evaluated. Higher MPI values were significantly associated with higher mortality at 1 month (MPI-1, low risk=0%, MPI-2, moderate risk=5.2%, MPI-3, severe risk=13.7%; $p<0.002$), 6-months (MPI-1=2.7%, MPI-2=11.2%, MPI-3=28.8%; $p<0.001$), and 12-months (MPI-1=2.7%, MPI-2=18.2%, MPI-3=35.6%; $p<0.001$) of follow-up. The discrimination of the MPI was also good, with areas under the ROC curves of 0.77 (sensitivity=82.9%, specificity=66.0%, with a cut off value > 0.16) at 12-months of follow up. In conclusion, the MPI, calculated from information collected in a standardized CGA, accurately stratified hospitalized elderly patients with dementia into groups at varying risk of short- and long-term mortality.
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Iron Regulatory Protein 2 is Involved in Brain Copper Homeostasis

Claudius Mueller, Shino Magaki, Matthew Schrag, Manik C. Ghosh, Wolff M. Kirsch *(Communicated by Othman Ghribi)*

Abstract: Trace metal homeostasis is tightly controlled in the brain, as even a slight dysregulation may severely impact normal brain function. This is especially apparent in Alzheimer's disease, where brain homeostasis of trace metals such as copper and iron is dysregulated. As it is known that iron and copper metabolism are linked, we wanted to investigate if a common mechanism could explain the increase in iron and decrease in copper seen in Alzheimer's disease brain. Amyloid-ß protein precursor (AßPP) has been implicated in copper efflux from the brain. Furthermore, it was shown that iron regulatory proteins (IRP), which regulate iron homeostasis, can block AßPP mRNA translation. In a correlative study we have therefore compared brain regional copper levels and AßPP expression in mice with a targeted deletion of IRP2-/-. Compared with controls, six week old IRP2-/- mice had significantly less brain copper in the parietal cortex, hippocampus, ventral striatum, thalamus, hypothalamus, and whole brain, while AßPP was significantly upregulated in the hippocampus ($p<0.05$) and showed a trend toward upregulation in the thalamus ($p<0.1$). This is the first study to demonstrate that iron regulatory proteins affect brain copper levels, which has significant implications for neurodegenerative diseases.

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Lifespan Profiles of Alzheimer's Disease-Associated Genes and Their Products in Monkeys and Mice

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Abstract: Alzheimer's disease (AD) is characterized by plaques of amyloid–ß (Aß) peptide, cleaved from amyloid-ß protein precursor (AßPP). Our hypothesis is that lifespan profiles of AD-associated mRNA and protein levels in monkeys would differ from mice and that differential lifespan expression profiles would be useful to understand human AD pathogenesis. We compared profiles of AßPP mRNA, AßPP protein, and Aß levels in rodents and primates. We also tracked a transcriptional regulator of the AßPP gene, specificity protein 1 (SP1), and the ß amyloid precursor cleaving enzyme (BACE1). In mice, AßPP and SP1 mRNA and their protein products were elevated late in life; Aß levels declined in old age. In monkeys, SP1, AßPP, and BACE1 mRNA declined in old age, while protein products and Aß levels rose. Proteolytic processing in both species did not match production of Aß. In primates, AßPP and SP1 mRNA levels coordinate, but an inverse relationship exists with corresponding protein products as well as Aß levels. Comparison of human DNA and mRNA sequences to monkey and mouse counterparts revealed structural features that may explain differences in transcriptional and translational processing. These findings are important for selecting appropriate models for AD and other age-related diseases.

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Human Amyloid Imaging, Seattle, Washington, 24 April 2009

Meeting Report from the Alzheimer Research Forum

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Alzheimer's disease selective vulnerability and modelling in transgenic mice

Jürgen Götz, Nicole Schonrock, Bryce Vissel, Lars M. Ittner

Abstract: Neurodegenerative diseases are characterized by 'hot spots' of degeneration. The regions of primary vulnerability vary between different neurodegenerative diseases. Within these regions, some neurons are lost whereas others that are morphologically indiscriminate survive. The enigma of this selective vulnerability is tightly linked to two fundamental problems in the neurosciences. First, it is not understood how many neuronal cell types make up the mammalian brain; estimates are in the order of more than a thousand. Second,

the mechanisms by which some nerve cells undergo functional impairment followed by degeneration while others do not, remain elusive. Understanding the basis for this selective vulnerability has significant implications for understanding the pathogenesis of disease and for developing treatments. Here, we review what is known about selective vulnerability in Alzheimer's disease, frontotemporal dementia, and Parkinson's disease. We suggest, since transgenic animal models of disease reproduce aspects of selective vulnerability, that these models offer a valuable system for future investigations into the physiological basis of selective vulnerability.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 243-251

Regulation of the Physiological Function and Metabolism of AßPP by AßPP Binding Proteins

Hidenori Taru, Toshiharu Suzuki

Abstract: Amyloid-ß protein precursor (AßPP) is a receptor-like, type-I membrane protein that plays a central role in the pathogenesis of Alzheimer's disease. The cytoplasmic domain of AßPP is important for the metabolism and physiological functions of AßPP and contains a GYENPTY motif that interacts with proteins that contain a phosphotyrosine binding (PTB) domain such as X11/Mint, FE65, and the JIP family of proteins. X11 and X11-like proteins are neuronal adaptor proteins involved in presynaptic function and the intracellular trafficking of proteins. Recent studies in X11s knockout mice confirmed findings from *in vitro* studies that X11 proteins affect AßPP metabolism and the generation of amyloid-ß peptide. FE65 proteins are involved in transactivation in coordination with the intracellular domain fragment of AßPP, and/or in cellular responses to DNA damage. Neurodevelopmental defects observed in FE65s double knockout mice suggest that FE65 proteins cooperate with AßPP to play a role in neuronal cytoskeletal regulation. c-Jun N-terminal kinase (JNK) interacting protein-1, a scaffolding protein for the JNK kinase cascade, has been suggested to mediate the intracellular trafficking of AßPP by molecular motor kinesin-1. This article reviews some of the recent findings regarding the regulation of physiological function and metabolism of AßPP by AßPP binding proteins.

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Amyloid-ß42 Plasma Levels are Elevated in Amnestic Mild Cognitive Impairment

Sergio Cammarata, Roberta Borghi, Luca Giliberto, Matteo Pardini, Valeria Pollero, Cristina Novello, Michele Fornaro, Antonella Vitali, Laura Bracco, Carlo Caltagirone, Paola Bossù, Patrizio Odetti, Massimo Tabaton

Abstract: Amnestic mild cognitive impairment (aMCI) is considered a prodromal stage of Alzheimer's disease (AD). We measured plasma levels of amyloid-ß40

(Aß40) and Aß42 in 191 subjects with aMCI. Seventy-nine of them were clinically followed for two years. In the total cohort of aMCI cases, the average level of Aß42, as well as the Aß42/Aß40 ratio, was significantly higher than those of the 102 cognitively normal age-matched subjects. The aMCI cases that converted to probable AD within 2 years had higher levels of Aß42 and, to a lesser extent, Aß40 than the stable cases. However the large variability of measured values indicates that plasmatic Aß is not a suitable marker of incipient AD.

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Complexes of Amyloid-ß and Cystatin C in the Human Central Nervous System

Weiqian Mi, Sonia S. Jung, Haung Yu, Stephen D. Schmidt, Ralph A. Nixon, Paul M. Mathews, Fabrizio Tagliavini, Efrat Levy *(Communicated by Luciano D'Adamio)*

Abstract: A role for cystatin C (CysC) in the pathogenesis of Alzheimer's disease (AD) has been suggested by the genetic linkage of a CysC gene (*CST3*) polymorphism with late-onset AD, the co-localization of CysC with amyloid-ß (Aß) in AD brains, and binding of CysC to soluble Aß *in vitro* and in mouse models of AD. This study investigates the binding between Aß and CysC in the human central nervous system. While CysC binding to soluble Aß was observed in AD patients and controls, an SDS-resistant CysC/Aß complex was detected exclusively in brains of neuropathologically normal controls, but not in AD cases. The association of CysC with Aß in brain from control individuals and in cerebrospinal fluid reveals an interaction of these two polypeptides in their soluble form. The association between Aß and CysC prevented Aß accumulation and fibrillogenesis in experimental systems, arguing that CysC plays a protective role in the pathogenesis of AD in humans and explain why decreases in CysC concentration caused by the *CST3* polymorphism or by specific presenilin 2 mutations can lead to the development of the disease. Thus, enhancing CysC expression or modulating CysC binding to Aß have important disease modifying effects, suggesting a novel therapeutic intervention for AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 273-280

Deficits in Aversive but not in Safe Taste Memory in the APPswe/PS1dE9 Mouse Model of Alzheimer's Disease

Leticia Ramírez-Lugo, Morten S. Jensen, Andreas Søderman and Mark J. West

Abstract: Age-related changes in taste memory were evaluated in APPswe/PS1dE9 transgenic (Tg) mice and age matched wild type littermate controls (Wt). These Tg mice produce increasing amounts of amyloid-ß in the brain with age, develop significant amounts of plaques by 9 months of age, and

provide an opportunity to study the effects of Alzheimer's disease-like amyloidosis on different aspects of taste memory. In groups of mice ranging from 15-16 months of age, the neophobic response and its attenuation were similar in Tg and Wt mice. However, conditioned taste aversion (CTA), which resulted from the association between a new taste and an artificially induced gastric malaise, was significantly reduced in the 15-16 month old Tg mice compared to the Wt mice, but not in the 3-4 or 7-8 month old mice. The extinction of CTA was normal in 3-4 month old Tg mice, but occurred more rapidly in the 7-8 and 15-16 months old Tg mice than in the age-matched controls. These results provide evidence of differences in the neuronal systems involved in the attenuation of neophobia and CTA and suggest that the progressive amyloidosis that takes place in APPswe/PS1dE9 mice selectively affects the aversion component of taste memory.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 281-293

Novel T719P AßPP Mutation Unbalances the Relative Proportion of Amyloid-ß Peptides

Roberta Ghidoni, Valentina Albertini, Rosanna Squitti, Anna Paterlini, Anna Bruno, Silvia Bernardini, Emanuele Cassetta, Paolo Maria Rossini, Ferdinando Squitieri, Luisa Benussi, Giuliano Binetti

Abstract: A novel missense mutation (T719P) in the amyloid-ß protein precursor (AßPP) gene was discovered in a 46-year old patient affected by early onset familial Alzheimer's disease. Using surface enhanced laser desorption/ionization mass spectrometry (SELDI-TOF MS), we determined mass profiles of amyloid-ß peptides (Aß) in cerebrospinal fluid (CSF) of the AßPP mutated patient, healthy control subjects (n=10), and of two subjects carrying mutations in presenilins genes (PS) (i.e., PS1 P117L and PS2 T122R): seven different C-terminally and three N-terminally truncated Aß peptides were found in CSF. The investigated AßPP as well as PS mutations were associated with an overall reduction of Aß species, except for Aß10-40. Interestingly, the AßPP T719P mutation unbalanced the relative proportion of Aß peptides with a reduction of Aß1-40 and Aß1-42 paralleled by an increase of Aß1-38 and Aß10-40. Despite the specific neuropeptidomic phenotype associated with the AßPP T719P mutation, the enrichment in Aß10–40 paralleled by depletion of Aß1–42 seems to be a common theme in familial AD. The AßPP T719P mutation is of particular interest because it is the only mutation located in close proximity to the AßPP e-cleavage site.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 295-303

Complex Splicing and Neural Expression of Duplicated Tau Genes in Zebrafish Embryos

Mengqi Chen, Ralph N. Martins, Michael Lardelli

Abstract: Microtubule-associated protein tau (MAPT) is the major component of the neurofibrillary tangles found in the brains of those suffering from Alzheimer's disease. Various forms of tau lesions are found in other neurodegenerative diseases (tauopathies). We report identification of two *MAPT* paralogous genes in zebrafish, *mapta* and *maptb*, and analysis of their expression patterns during embryonic development. The two paralogues appear to have arisen by duplication of an ancestral teleost *MAPT* orthologue. Analysis of the splicing of transcripts from both genes during embryogenesis showed that *mapta* can be spliced into isoforms with between four and six tubulin-binding repeats (4R - 6R), while *maptb* is mainly spliced into 3R isoforms. Expression of both genes is observed predominantly in the developing central nervous system. A particularly large isoform of *maptb* is specifically expressed in the trigeminal ganglion and in dorsal sensory neurons of the spinal cord. Changes in the subcellular ratio of 3R and 4R isoforms can have pathological consequences in mammals. The predominant production of 4R-6R isoforms from *mapta* and of 3R isoforms from *maptb* suggests that zebrafish embryos will be a useful tool with which to study the discrete functions and interactions of the 3R and 4R MAPT isoforms.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 305-317

Absence of ApoE Upregulates Murine Brain ApoD and ABCA1 Levels, But Does Not Affect Brain Sterol Levels, While Human ApoE3 and Human ApoE4 Upregulate Brain Cholesterol Precursor Levels

Paula J. Jansen, Dieter Lütjohann, Karin M. Thelen, Klaus von Bergmann, Fred van Leuven, Frans C.S. Ramaekers, Monique Mulder

Abstract: Apolipoprotein E (apoE) is a regulator of peripheral cholesterol homeostasis, and the apoE-isoform E4 is a major risk factor for the development of Alzheimer's disease (AD). Accumulating evidence suggests a key role for aberrant cholesterol metabolism in AD. We hypothesized that apoE-deficiency in mice not only affects cholesterol homeostasis in the periphery, but also in the brain, and that this can be restored by astrocyte-specific expression of human apoE3, but not apoE4. Using gas-chromatography mass-spectrometry, we found that absence of apoE in mice does not affect brain cholesterol homeostasis although serum sterol levels increase dramatically, especially when the apoE-knockout mice are fed a high fat diet. We provide evidence suggesting that apoD and the ATP-binding Cassette Transporter A1 (ABCA1) play a compensatory role in the apoE-deficient brain. Surprisingly, astrocyte-specific expression of human apoE3 or apoE4 in brains of apoE-knockout mice significantly increases brain levels of cholesterol and its precursors compared to control mice, indicative of an increased cholesterol synthesis rate in the brain. This increase is independent of the apoE-isoform, suggesting that the detrimental effect of apoE4 on the pathogenesis of AD is unlikely to be due to an apoE-isoform effect on brain cholesterol homeostasis.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 319-329

Glial Cell-Line Derived Neurotrophic Factor (GDNF) Concentrations in Cerebrospinal Fluid and Serum of Patients with Early Alzheimer's Disease and Normal Controls

Guido Straten, Gerhard W. Eschweiler, Walter Maetzler, Christoph Laske, Thomas Leyhe

Abstract: As neurotrophic factors play an important role in development and maintenance of global central nervous system (CNS) function, we supposed that glial cell-line derived neurotrophic factor (GDNF), which has been extensively studied for its survival promoting effects especially concerning catecholaminergic neurons, also plays a significant role in neurodegenerative disease characterized mainly by damage of cholinergic CNS neurons like AD. Here we compared GDNF concentrations in serum and cerebrospinal fluid (CSF) of patients with probable Alzheimer´s disease (AD) and normal controls (NC). While GDNF concentrations in CSF were significantly increased in patients with AD (291.7 ± 85.8 pg/ml) compared with NC subjects (218.7 ± 93.3 pg/ml, $p = 0.012$), GDNF concentration of AD patients (486.5 ± 72.3 pg/ml) in serum were significantly decreased compared with the NC group (711.5 ± 186.5 pg/ml, $p < 0.001$). Increased GDNF in CSF of AD might be due to an upregulated expression in CNS as an adaptive process of the impaired brain to enhance neurotrophic support at least in early stages of disease and/or impairment of CSF turnover. Decreased serum concentration of GDNF might be related to altered function of the blood brain barrier thus disturbing clearance or facilitating passover of potentially harmful metabolites.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 331-337

Ginseng for Cognitive Function in Alzheimer's Disease: A Systematic Review

Myeong Soo Lee, Eun-Jin Yang, Jong-In Kim, Edzard Ernst

Abstract: The objective of this review is to assess the clinical evidence for or against ginseng as a treatment for Alzheimer's disease (AD). We searched 20 databases from their inception to January 2009 and included all randomized clinical trials (RCTs) of any type of *Panax ginseng* to treat human patients suffering from AD. Methodological quality was assessed using the Jadad score. Two RCTs met all inclusion criteria. They assessed the effectiveness of ginseng as an adjunct to drug therapy on cognitive function compared with conventional drug therapy. Their results suggested significant effect in favor of ginseng on the Mini-Mental Status Examination (n=174, weight mean difference (WMD), 1.85; 95% confidence intervals, CIs 0.88 to 2.82, P=0.0002) and on the Alzheimer's

Disease Assessment Scale (ADAS)-cognitive (n=174, WMD, 3.09; 95% CIs 1.08 to 5.09, P=0.003). Both of these studies are burdened with serious methodological limitations. In conclusion, the evidence for ginseng as a treatment of AD is scarce and inconclusive. Further rigorous trials seem warranted.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 339-344

Heteroplasmy of Mitochondrial D310 Mononucleotide Repeat Region in the Blood of Patients with Alzheimer's Disease

Pei-Ning Wang, Hsin-Chen Lee, Chun-Hui Wang, Yueh-Hsin Ping, Tsung-Yun Liu, Chin-Wen Chi, Ker-Nen Lin, Hsu-Chih Liu

Abstract: There is increasing evidence of oxidative stress in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Because mitochondrial DNA (mtDNA) is susceptible to oxidative damage, somatic mtDNA mutations may be induced by oxidative stress. Most of the studies examining mitochondrial mutations have been performed on postmortem brain tissues of AD patients. This study examined peripheral blood samples of AD and MCI patients to determine if peripheral mtDNA mutations are associated with these two conditions. A total of 236 subjects, including 71 AD patients, 84 amnestic MCI patients, 41 cognitively normal aging controls, and 40 young controls, were recruited. There was heteroplasmy of the mtDNA D310 polycytosine repeat region in 37 of 71 (52.1%) AD patients and this was significantly more frequent than in MCI patients (31.0%), normal aging (31.7%), and young controls (27.5%). However, subjects with amnestic MCI did not have a significantly higher rate of heteroplasmy in D310 than cognitively normal elderly subjects. The heteroplasmic alterations of D310 were more frequently in subjects with a larger number of polycytosine repetitions. Insertion of cytosine was the most common mutation type. The results suggest that mutations of mtDNA 310 region are frequently present in the peripheral blood of AD patients. Further prospective investigations to determine if MCI subjects with D310 mutations develop AD is warranted.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 345-353

7th Annual Mild Cognitive Impairment (MCI) Symposium: Focus on Early Alzheimer's Disease and Non-Alzheimer's Prodromal Dementia, Miami, Florida, 27-28 March, 2009

Meeting Report from the Alzheimer Research Forum

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 355-363

Mini-Forum on Roles of Amyloid-ß and Tau Phosphorylation in Neuronal Repair and Protection (Guest Editor: Garth Bissette)

Ischemia and Loss of Vascular Autoregulation in Ocular and Cerebral Diseases: A New Perspective by Maurice E. Langham, Springer-Verlag New York, LLC, 2009, 192 pp. Reviewed by Joseph LaManna.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 365-366

Preface: Mini-Forum: Roles of Amyloid-ß and Tau Phosphorylation in Neuronal Repair and Protection

Garth Bissette

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 369-370

Does Alzheimer's Disease Result from Attempts at Repair or Protection After Transient

Garth Bissette

Abstract: This review explores the data indicating that the initial production of amyloid-ß precursor protein and phosphorylated tau are associated with physiological mechanisms for repair or protection of neurons exposed to significant disturbances in homeostasis. Stimuli as diverse as head injury, inhaled anesthetic agents, stimulant drugs, and both physiological (restraint) and psychological stress (social isolation) have been shown to increase brain expression of amyloid-ß and hyperphosphorylated tau without accompanying neurodegeneration. This review aims to encompass these responses as indicators of normal physiological processes that, in the case of Alzheimer's disease, are either unable to successfully repair or protect vulnerable neuronal populations from eventual neurodegeneration, but that are necessary components of an integrated nervous system that would be more susceptible to pathology if such processes were blocked in an attempt to minimize or prevent future damage.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 371-380

Amyloid-ß, Tau Protein, and Oxidative Changes as a Physiological Compensatory Mechanism to Maintain CNS Plasticity under Alzheimer's Disease and Other Neurodegenerative Conditions

Alexei Koudinov, Elena Kezlya, Natalia Koudinova, Temirbolat Berezov

Abstract: In this review, we propose that the neurodegenerative changes in the neurochemistry of amyloid-ß (Aß) aggregation, tau phosphorylation, cytoskeleton rearrangement, oxidative stress, and lipid peroxidation in Alzheimer's disease (AD), and a number of other neurodegenerative diseases, are secondary pathological features. In fact, we believe that these phenomena represent natural compensatory mechanisms for impaired primary neurodegeneration, membrane dynamic deterioration, and/or associated failures of neurotransmission, synaptic function, and neuroplasticity. Physiologically, Aß, lipid peroxidation, and tau protein may function to sense changes in activity-dependent membrane properties and therefore biochemically modulate membrane lipid homeostasis for more efficient synaptic action. As such, the previously proposed therapeutic tackling of amyloid, tau, oxidative stress, and other brain disease markers may have no ability to cure AD or other devastating central nervous system pathologies and peripheral nervous system diseases. This unfortunate realization provides a wake-up call to the neuroscience community, demanding open-minded approach.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 381-400

Functional Roles of Amyloid-ß Protein Precursor and Amyloid-ß Peptides: Evidence from Experimental Studies

Mikko Hiltunen, Thomas van Groen, Jukka Jolkkonen

Abstract: Amyloid-ß (Aß) has remained a central feature in research into Alzheimer's disease (AD). Yet the function of the amyloid-ß protein precursor (AßPP) and its processing products in the central nervous system is controversial. This review examines experimental literature from cell cultures to transgenic AD and brain injury models with a special emphasis on the functional role of AßPP and AßPP-derived peptides. AßPP knock-out mice exhibit severe metabolic abnormalities and behavioral deficits, indicating an important physiological function of AßPP. Also, an increasing body of evidence suggests that while Aß is undoubtedly linked to neurodegeneration, the soluble amino-terminal fragment of AßPP (sAßPPa) has neuroprotective, neurotrophic, and cell adhesive functions. Moderate overexpression of human AßPP in rodents does not produce apparent Aß pathology and has no significant effect on cognitive or sensorimotor behavior and, surprisingly, may even provide histological neuroprotection against focal cerebral ischemia. In contrast, phenotypes with more severe Aß pathology show impaired cognitive performance, increased vulnerability to brain ischemia and trauma, and less favorable functional outcome even before Aß deposition. A delicate balance in AßPP processing seems to determine its functional consequences. Thus, it is tempting to speculate that promotion of a-secretase-mediated cleavage of AßPP, which leads to increased sAßPPa production, provides a novel therapeutic strategy in the treatment of AD and brain injury.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 401-412

Cerebrospinal Fluid Biomarkers for Alzheimer's Disease

Kaj Blennow and Henrik Zetterberg

Abstract: Research progress has given detailed knowledge on the molecular pathogenesis of Alzheimer's disease (AD), which has been translated into an ongoing development of disease-modifying treatments. These new drug candidates are targeted on inhibiting amyloid-ß (Aß) production and aggregation or tau aggregation. If these drugs prove to be efficient, diagnostic tools enabling early diagnosis of AD will be of great value. Also in drug development, it is important to co-develop biomarkers to serve as tools to identify and monitor the biochemical effect of the drug directly in patients. Molecular aberrations in the AD brain are reflected in the cerebrospinal fluid (CSF). The core candidate CSF biomarkers Aß42, total tau (T-tau), and phosphorylated tau (P-tau) have been shown to have a high diagnostic performance to identify AD also in the early phase of the disease. This paper reviews recent research advances on these CSF biomarkers for use in clinical diagnosis and in clinical trials in AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 413-417

Brain Imaging and Neuropathologic Mechanisms in Alzheimer's Disease: Vascular Versus Neurodegenerative and Amyloid-ß Versus Tau

Parekkat M. Menon, Jean Paul Vonsattel, Paul R. Jolles

Abstract: Over the past several decades, there has been extensive research devoted toward determining the cause of Alzheimer's disease. Numerous biochemical, histological, and imaging investigations have elegantly characterized the neuropathologic and functional changes associated with AD. Proponents of one theory or another can find supporting data among the myriad of studies in the literature. This paper attempts to summarize some of the major conclusions and controversies in imaging literature (especially, magnetic resonance imaging and nuclear medicine) in relation to pathogenesis theories of Alzheimer's disease. In spite of considerable progress, the primary cause of Alzheimer's disease remains elusive.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 419-427

Lesion-Induced Hippocampal Plasticity in Transgenic Alzheimer's Disease Mouse Models: Influences of Age, Genotype, and Estrogen

Inga Kadish, Thomas van Groen

Abstract: We have studied entorhinal cortex lesion-induced sprouting in the hippocampus in young, adult, and aged control and transgenic Alzheimer's disease model mice. The entorhinal cortex was unilaterally, partially lesioned, and four weeks later the subsequent axonal sprouting in dentate gyrus was analyzed. Our data demonstrate that young and adult, control and amyloid-ß protein precursor (AßPP)/presenilin 1 (PS1) mice display a significantly increased density of staining for synaptophysin in dentate gyrus, indicative of axonal sprouting. However, whereas young and adult mice demonstrate sprouting, aged mice (control and AßPP/PS1) do not show a significant upregulation of synaptophysin staining following the lesions. In contrast, aged mice overexpressing PS1 show an increased regenerative response compared to age-matched control mice and mice overexpressing AßPP which do not show sprouting. Further, the data demonstrate that a significant Aß load in the dentate gyrus does not prevent axonal sprouting. Lastly, only aged mice show significant shrinkage of the molecular layer of dentate gyrus following entorhinal cortex lesions. Further, adult ovariectomized females (control and AßPP/PS1) are significantly reduced in their plasticity following lesions. Taken together, the data indicate that amyloid-ß deposits do not negatively impact plasticity in the brain and that overexpression of AßPP is not beneficial, but that normal estrogen levels are beneficial for plasticity.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 429-445

Reexamining Alzheimer's Disease: Evidence for a Protective Role for Amyloid-ß Protein Precursor and Amyloid-ß

Rudy J. Castellani, Hyoung-gon Lee, Sandra L. Siedlak, Akihiko Nunomura, Takaaki Hayashi, Masao Nakamura, Xiongwei Zhu, George Perry, Mark A. Smith *(Handling Editor: Jesus Avila)*

Abstract: Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized clinically by cognitive decline and pathologically by the accumulation of amyloid-ß-containing senile plaques and neurofibrillary tangles. Attention, not surprisingly, focused on amyloid-ß as the major pathogenic mechanism, with the ultimate goal of selective amyloid-ß targeting as an avenue of treatment. Unfortunately, nearly a quarter century later, no tangible progress has been offered, whereas spectacular failure tends to be the most compelling. We have long contended, as has substantial literature, that proteinaceous accumulations are simply downstream and, often, endstage manifestations of disease. Their overall poor correlation with the level of dementia, and their presence in the cognitively intact is evidence that is often ignored as an inconvenient truth. Current research examining amyloid oligomers, therefore, will add copious details to what is, in essence, a reductionist distraction from upstream pleiotrophic processes such as oxidative stress, cell cycle dysfunction, and inflammation. It is now long overdue that the neuroscientists avoid the pitfall

of perseverating on "proteinopathies" and recognize that the continued targeting of end stage lesions in the face of repeated failure, or worse, is a losing proposition.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 447-452

Stress-Induced Tau Phosphorylation: Functional Neuroplasticity or Neuronal Vulnerability?

Robert A. Rissman

Abstract: Abnormally phosphorylated tau protein is a key component of the pathology seen in neurodegenerative tauopathies, such as Alzheimer's disease (AD). Despite its association with disease, tau phosphorylation (tau-P) also plays an important role in neuroplasticity, such as dendritic/synaptic remodeling seen in the hippocampus in response to environmental challenges, such as stress. To define the boundaries between neuroplasticity and neuropathology, studies have attempted to characterize the paradigms, stimuli, and signaling intermediates involved in stress-induced tau-P. Supporting an involvement of stress in AD are data demonstrating alterations in stress pathways and peptides in the AD brain and epidemiological data implicating stress exposure as a risk factor for AD. In this review, the question of whether stress-induced tau-P can be used as a model for examining the relationship between functional neuroplasticity and neuronal vulnerability will be discussed.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 453-457

Effects of Stress and Stress Hormones on Amyloid-ß Protein and Plaque Deposition

Hongxin Dong and John G. Csernansky

Abstract: Growing evidence indicates that physical and psychosocial stressors, in part acting through the hypothalamic-pituitary-adrenal (HPA) axis, may accelerate the process of Alzheimer's disease (AD). In this review, we summarize recent research related to the effects of stress and stress hormones on the various disease process elements associated with AD. Specifically, we focus on the relationships among chronic stressors, HPA axis activity, amyloid-ß protein, and amyloid-ß plaque deposition in mouse models of AD. The potential mechanisms by which stress and stress-related components, especially corticotrophin-releasing factor and its receptors, influence the pathogenesis of AD are discussed.

JOURNAL OF ALZHEIMER'S DISEASE Volume 18, Number 2, October 2009, Pages 459-469

Robert Katzman, MD: In Memoriam

Claudia H. Kawas

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 1-3

Alcohol Drinking, Cognitive Functions in Older Age, Predementia, and Dementia Syndromes

Francesco Panza, Cristiano Capurso, Alessia D'Introno, Anna M Colacicco, Vincenza Frisardi, Maria Lorusso, Andrea Santamato, Davide Seripa, Alberto Pilotto, Emanuele Scafato, Gianluigi Vendemiale, Antonio Capurso, Vincenzo Solfrizzi

Abstract: Among lifestyle-related factors, low to moderate alcohol drinking has been proposed as a protective factor against the development of age-related changes in cognitive function, predementia syndromes, and cognitive decline of degenerative (Alzheimer's disease, AD) or vascular origin (vascular dementia, VaD) in several longitudinal studies, but contrasting findings also exist. Furthermore, many of these studies were limited by cross-sectional design, restriction by age or sex, or incomplete ascertainment. Different outcomes, beverages, drinking patterns, or follow-up periods, or possible interactions with other lifestyle-related (i.e., smoking) or genetic factors [i.e., apolipoprotein E (APOE) genotyping] may be sources of great variability. Light to moderate alcohol use may be associated with a reduced risk of unspecified incident dementia and AD, while for VaD, cognitive decline, and predementia syndromes, the current evidence is only suggestive of a protective effect. In conclusion, as intervention studies are not feasible in this area, the best evidence comes from an overview of epidemiological studies, suggesting that the protective effects are more likely with wine consumption and the absence of an APOE e4 allele. At present, there is no indication that light to moderate alcohol drinking would be harmful to cognition and dementia, but it is not possible to define a specific beneficial level of alcohol intake.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 7-31

The Quest for Small Molecules as Amyloid Inhibiting Therapies for Alzheimer's Disease

Hozefa Amijee and David I. C. Scopes

Abstract: Amyloid-ß (Aß) peptide is one of the most promising targets for the development of new therapies for Alzheimer's disease (AD). A growing body of evidence suggests a key pathogenic role for soluble oligomers of Aß, and therapeutics which block the generation of toxic Aß assemblies may provide

successful new treatments for AD. This is therapeutically attractive because the aggregation process is believed to be an exclusively pathological event and therefore compounds targeting this mechanism are more likely to have an acceptable safety profile. A number of studies have shown that AD severity correlates more closely with soluble oligomeric forms of Aß than with fibrillar forms of the peptide. Thus, blocking the initial stages of Aß aggregation with small molecules could hold considerable promise as an entry to new therapies for AD. The rapid development in our understanding of toxic amyloid assemblies now provides fresh impetus for this interesting approach, and this review assesses the status of drug development in this area. Recent progress with clinical studies and highlights of new structural series that are showing promise in the discovery/pre-clinical phase are discussed.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 33-47

The Question of Cell Cycle Reentry by Mature Neurons in Response to Amyloid-ß and Tau Pathology

Zixu Mao

Commentary on Lopes et al., J Alzheimers Dis 16(3), 541-549, 2009

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 49-51

CSF Studies Facilitate DNA Diagnosis in Familial Alzheimer's Disease Due to a Presenilin-1 Mutation

Susanne T. de Bot, H.P.H. Kremer, Dennis Dooijes, Marcel M. Verbeek
(Communicated by Sanna-Kaisa Herukka)

Abstract: In sporadic Alzheimer's disease (AD), cerebrospinal fluid (CSF) analysis is becoming increasingly relevant to establish an early diagnosis. We present a case of familial AD due to a presenilin-1 mutation in which CSF studies suggested appropriate DNA diagnostics. A 38 year old Dutch man presented with dementia, spastic paraparesis, and frontal executive function impairments, mimicking familial Creutzfeldt Jakob disease and frontotemporal dementia. CSF studies, revealing increased total tau and phosphorylated-tau levels with decreased amyloid ß42, distinguished familial AD from Creutzfeldt Jakob disease and frontotemporal dementia. A causative p.L424R *PSEN1* mutation was subsequently identified.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 53-57

Aß-Dependent Inhibition of LTP in Different Intra-Cortical Circuits of the Visual Cortex: The Role of RAGE

Nicola Origlia, Simona Capsoni, Antonino Cattaneo, Fang Fang, Ottavio Arancio, Shi Du Yan, Luciano Domenici

Abstract: Oligomeric amyloid-ß (Aß) interferes with long term potentiation (LTP) and cognitive processes, suggesting that Aß peptides may play a role in the neuronal dysfunction which characterizes the early stages of Alzheimer's disease (AD). Multiple lines of evidence have highlighted RAGE (receptor for advanced glycation end-products) as a receptor involved in Aß-induced neuronal and synaptic dysfunction. In the present study, we investigated the effect of oligomeric soluble Aß1-42 on LTP elicited by the stimulation of different intracortical pathways in the mouse visual cortex. A variety of nanomolar concentrations (20-200 nM) of Aß1-42 were able to inhibit LTP in cortical layer II-III induced by either white matter (WM-Layer II/III) or the layer II/III (horizontal pathway) stimulation, whereas the inhibition of LTP was more susceptible to Ab1-42, which occurred at 20 nM of Aß, when stimulating layer II-III horizontal pathway. Remarkably, cortical slices were resistant to nanomolar Aß1-42 in the absence of RAGE (genetic deletion of RAGE) or blocking RAGE by RAGE antibody. These results indicate that nanomolar Aß inhibits LTP expression in different neocortical circuits. Crucially, it is demonstrated that Aß-induced reduction of LTP in different cortical pathways is mediated by RAGE.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 59-68

The Relationship Between Memory Complaints, Perceived Quality of Life and Mental Health in Apolipoprotein Ee4 Carriers and Non-Carriers?

Hamid R. Sohrabi, Kristyn A. Bates, Mark Rodrigues, Kevin Taddei, Georgia Martins, Simon M. Laws, Nicola T. Lautenschlager, Satvinder S. Dhaliwal, Jonathan K. Foster, Ralph N. Martins

Abstract: Apolipoprotein E e4 (*APOE-e4*) is a major genetic risk factor for Alzheimer's disease. In this study, we addressed the question of whether possession of the *APOE-e4* allele results in adverse effects on perceived health-related quality of life (HRQL) and on symptoms of depression and anxiety in people with subjective memory complaints (SMC). 138 healthy, community-dwelling elderly volunteers, aged 52 to 85, were assessed for HRQL, depression, and anxiety. The participants were classified as i) *APOE-e4* carriers or ii) non-carriers with a) SMC or b) without memory complaints. The possible interactions of *APOE* genotype, gender, and SMC on HRQL, depression, and anxiety were investigated statistically. SMC was significantly associated with poorer outcomes on measures of depression, trait anxiety, and mental health. *APOE-e4* carriers did not significantly differ from non-carriers on HRQL, depression, and anxiety.

However, significant interaction was found between *APOE-e4* genotype and SMC on depression. These findings are important from a health perspective and suggest that memory complaints are associated with markers of mental health and quality of life that are independent of possession of the *APOE-e4* allele, despite the importance of this polymorphism in the risk of AD and other health problems.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 69-79

Interaction between Alzheimer's Amyloid-ß and Amyloid-ß-Metal Complexes with Cell Membranes

Mario Suwalsky, Silvia Bolognin, Paolo Zatta

Abstract: A number of observations indicate that the primary target of amyloid-ß (Aß) peptide is the cellular membrane of neurons. In the context of these observations we investigated, using X-ray diffraction techniques, whether Aß-metal complexes were able to affect lipid bilayers as a model of cell membranes. The binding of Al to Aß gave particular conformational properties to the peptide that led to a marked alteration of the lipid bilayer representing phospholipids located in the outer monolayer of cell membranes. This effect was peculiar, since in our experimental conditions Aß alone did not affect the lipid architecture, whereas the Al salt did, but only at concentrations several orders of magnitude higher than those of the Aß-Al complex, which produced similar alterations to the lipid. In accordance with the effects observed with lipid bilayers, studies with human neuroblastoma cells demonstrated an impairment of cell functioning only in the presence of Aß-Al complex. Our findings imply that Al, compared to the other Aß-metal complexes tested, could have a specifically relevant effect in enhancing Aß toxicity.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 81-90

Dramatic Shifts in Circulating CD4 but not CD8 T Cell Subsets in Mild Alzheimer's Disease

Anis Larbi, Graham Pawelec, Jacek M. Witkowski, Hyman M. Schipper, Evelyna Derhovanessian, David Goldeck, Tamas Fulop *(Communicated by Marcella Reale)*

Abstract: The distribution of peripheral T cell subsets in young and healthy old people is markedly different, characterized by decreased numbers of naïve cells and increased numbers and clonal expansions of memory cells, predominantly in the CD8+ MHC class I-restricted subset. Here, however, we document dramatic alterations in naïve and memory subsets of CD4+ cells in patients with mild Alzheimer's disease (AD), with greatly decreased percentages of naïve cells, elevated memory cells, and increased proportions of CD4+ but not CD8+ cells

lacking the important costimulatory receptor CD28. CD4+CD25 high potentially T regulatory cells with a naïve phenotype are also reduced in AD patients. Together these data provide stronger evidence than hitherto presented for more highly differentiated CD4+ as well as CD8+ T cells in AD patients, consistent with an adaptive immune system undergoing persistent antigenic challenge and possibly manifesting dysregulation as a result.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 91-103

Does cognitive impairment influence burden in caregivers of patients with Alzheimer's disease?

Sophie Germain, Stéphane Adam, Catherine Olivier, Helen Cash, Pierre Jean Ousset, Sandrine Andrieu, Bruno Vellas, Thierry Meulemans, Emma Reynish, Eric Salmon, the ICTUS-EADC Network

Abstract: Alzheimer's disease (AD) is characterized by a progressive deterioration of various cognitive and behavioral abilities, and it also has a health impact on the patients' caregiver. Our aim was to determine the patient (and to a lesser extent the caregiver) characteristics that contribute most to the caregiver burden. We used the baseline data from the ICTUS study, a European longitudinal cohort of patients with mild to moderate AD. Data from 1091 patients and their caregivers was used for analysis. Three principal components analyses were performed on variables from the domains of cognition, neuropsychiatric symptoms, and daily function using the MMSE plus the ADAS-Cog, NPI, and IADL subscores, respectively. These were followed by a stepwise logistic regression to identify patient characteristics which best predict caregiver burden. The regression model ($R2 = 0.35$, $p < 0.001$) shows that the best explanatory variables are: 1) neuropsychiatric symptoms (NPI); 2) difficulties in the IADL; 3) time taken by caregiving; 4) demographic variables such as caregiver's age and patient sex; and 5) severity of cognitive impairment. In conclusion, our results demonstrate that although the strongest determinant of the caregiver burden is behavioral disturbance, the impact of the degree of cognitive impairment on burden is also significant.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 105-144

Decreased Plasma Levels of Granulocyte-Colony Stimulating Factor (G-CSF) in Patients with Early Alzheimer's Disease

Christoph Laske, Konstantinos Stellos, Elke Stransky, Thomas Leyhe, Meinrad Gawaz *(Communicated by Milan Fiala)*

Abstract: Alzheimer's disease (AD) is characterized by massive neuronal cell loss in the brain. Granulocyte-colony stimulating factor (G-CSF) is a hematopoietic growth factor that promotes neuroprotective effects and supports

neurogenesis in the brain. In the present study, we found significantly lower G-CSF plasma levels in 50 early AD patients in comparison with 50 age-matched healthy controls. In AD patients, G-CSF levels showed a significant inverse correlation with amyloid-ß (Aß1-42) levels in cerebrospinal fluid, but not with levels of tau protein in cerebrospinal fluid or Mini-Mental Status Examination scores. In addition, G-CSF plasma levels were significantly inversely correlated with age in AD patients and healthy controls. In conclusion, decreased G-CSF plasma levels in early AD patients may contribute to a deficient hematopoietic brain support with putative pathogenic relevance. Further studies are needed to examine whether a modulation of hematopoietic growth factors such as G-CSF could be a promising new therapeutic strategy for AD.

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MCP-1 A-2518G Polymorphism: Effect on Susceptibility for Frontotemporal Lobar Degeneration and on Cerebrospinal Fluid MCP-1 Levels

Daniela Galimberti, Eliana Venturelli, Chiara Villa, Chiara Fenoglio, Francesca Clerici, Alessandra Marcone, Luisa Benussi, Francesca Cortini, Diego Scalabrini, Luca Perini, Ilaria Restelli, Giuliano Binetti, Stefano Cappa, Claudio Mariani, Nereo Bresolin, Elio Scarpini

Abstract: The distribution of the *MCP-1 A-2518G* single nucleotide polymorphisms (SNP) was analyzed in a population of 212 patients with frontotemporal lobar degeneration (FTLD) compared with 203 age-matched controls. A significantly decreased allelic frequency of the *G* allele in patients compared with controls was observed (21.1 versus 29.3%, *P*=0.011, OR: 0.59, CI: 0.40-0.87). Stratifying according to gender, the association was maintained in male patients versus male controls (17.8 versus 29.4%, *P*=0.016, OR=0.46, 95% CI: 0.25-0.84), but not in female patients compared with female controls (23.5 versus 29.2%, *P*>0.05). The frequency of apolipoprotein E e4 carriers was increased in patients (26.4 versus 13.8%, *P*=0.0015, OR: 2.24, 95% CI: 1.37-3.67). Apolipoprotein E status did not influence the distribution of the *A-2518G* SNP. Monocyte chemotactic protein (MCP)-1 levels were determined in cerebrospinal fluid (CSF) collected from 23 patients and 17 controls. MCP-1 CSF levels were increased in patients compared with controls (449.01±27.57 versus 364.19±23.75 pg/ml, *P*=0.011). Stratifying patients according to the presence of the polymorphic allele, significantly increased CSF MCP-1 levels were observed in carriers of the *G* allele compared with non-carriers (502.21±44.57 versus 395.87±21.92 pg/ml, *P*=0.045). The *MCP-1 A-2518G* SNP acts as protective factor for sporadic FTLD, possibly by influencing MCP-1production.

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Olfactory Dysfunction is Associated with Subjective Memory Complaints in Community-Dwelling Elderly Individuals

Hamid R. Sohrabi, Kristyn A. Bates, Mark Rodrigues, Kevin Taddei, Simon M. Laws, Nicola T. Lautenschlager, Satvinder S. Dhaliwal, Amy N.B. Johnston, Alan Mackay-Sim, Samuel Gandy, Jonathan K. Foster, Ralph N. Martins

Abstract: Olfactory dysfunction has been reported in clinical and preclinical phases of Alzheimer's disease. Subjective memory complaints have been proposed as a potential early indicator for increased risk of Alzheimer's disease, but have also been associated with depression, personality characteristics, and health problems. In this study, we aimed to determine which of these putative markers can predict memory complaints in community-dwelling elderly individuals, focusing on olfactory symptoms. A cohort of 144 elderly volunteers (42 males and 102 females), aged 50 to 86, was recruited from an ongoing longitudinal study. Participants were assessed for olfactory capacities (threshold, discrimination, and identification), subjective memory complaints, depression, and cognitive functions. Subjective memory complaints were significantly associated with olfactory discrimination and identification but not with threshold. Olfactory functions and depressive symptoms were both significantly associated with subjective memory complaints. In addition, memory complainers were significantly worse than non-complainers with respect to olfactory discrimination, identification, and overall olfactory functioning. The findings suggest that olfactory capacity may be a potentially significant biomarker for identifying community-dwelling elderly with memory complaints who are at increased risk for age-related cognitive decline and Alzheimer's disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 135-142

Vitamin E Paradox in Alzheimer's Disease: It Does Not Prevent Loss of Cognition and ay Even Be Detrimental

Ana Lloret, Mari-Carmen Badía, Nancy J. Mora, Federico V. Pallardó, Maria-Dolores Alonso, Jose Viña

Abstract: There is controversy as to whether vitamin E is beneficial in Alzheimer's disease (AD). In this study, we tested if vitamin E prevents oxidative stress and loss of cognition in AD. Fifty-seven AD patients were recruited and divided in two groups: placebo or treated with 800 IU of vitamin E per day for six months. Of these 57 patients, only 33 finished the study. We measured blood oxidized glutathione (GSSG) and used the following cognitive tests: Mini-Mental State Examination, Blessed-Dementia Scale, and Clock Drawing Test. Of those patients treated with vitaimin E, we found two groups. In the first group, "respondents" to vitamin E, GSSG levels were lower after the treatment and scores on the cognitive tests were maintained. The second group, "non-respondents", consisted of patients in which vitamin E was not effective in

preventing oxidative stress. In these patients, cognition decreased sharply, to levels even lower than those of patients taking placebo. Based on our findings, it appears that vitamin E lowers oxidative stress in some AD patients and maintains cognitive status, however, in those in which vitamin E does not prevent oxidative stress, it is detrimental in terms of cognition. Therefore, supplementation of AD patients with vitamin E cannot be recommended without determination of its antioxidant effect in each patient.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 143-149

Does Vitamin D Reduce the Risk of Dementia?

William B. Grant

Abstract: The understanding of the role of vitamin D in maintaining optimal health has advanced sharply in the past two decades. There is mounting evidence for beneficial roles for vitamin D in reducing the risk of bone diseases and fractures, many types of cancer, bacterial and viral infections, autoimmune diseases, and cardiovascular diseases. Recently, several reports have also been published regarding the role of vitamin D in neuroprotection. This article develops the hypothesis that vitamin D can reduce the risk of developing dementia, presenting the evidence from observational and laboratory studies. The observational evidence includes that low serum 25-hydroxyvitamin D [25(OH)D] has been associated with increased risk for cardiovascular diseases, diabetes mellitus, depression, dental caries, osteoporosis, and periodontal disease, all of which are either considered risk factors for dementia or have preceded incidence of dementia. The laboratory evidence includes several findings on the role of vitamin D in neuroprotection and reducing inflammation. Although this evidence is supportive, there do not appear to be observational studies of incidence of dementia with respect to prediagnostic serum 25(OH)D or vitamin D supplementation. Such studies now appear to be warranted.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 1, May 2009, Pages 151-159

Cognitive Performances of Cholinergically Depleted Rats Following Chronic Donepezil Administration

Debora Cutuli, Francesca Foti, Laura Mandolesi, Paola De Bartolo, Francesca Gelfo, Francesca Federico, Laura Petrosini *(Communicated by Sigfrido Scarpa)*

Abstract: Since acute and chronic administration of the acetylcholinesterase inhibitors, namely donepezil, improves cognitive functions in patients afflicted by mild to moderate dementia and reverses memory deficits in experimental models of learning and memory, it seemed interesting to assess the effects of

chronic donepezil treatment on cognitive functions in adult rats with forebrain cholinergic depletion. Lesions were performed by means of intracerebroventricular injections of the immunotoxin 192 IgG-saporin. The cognitive functions of lesioned animals treated or not treated with donepezil were compared with those of intact animals. Cholinergic depletion affected working memory functions, weakened procedural competencies, affected the acquisition of localizing knowledge, and evoked remarkable compulsive and perseverative behaviors. In lesioned animals, chronic donepezil treatment ameliorated localizatory capabilities, performances linked to cognitive flexibility and procedural abilities. Furthermore, it attenuated compulsive deficits. The present data indicate positive effects of chronic donepezil treatment on specific cognitive performances, suggesting that an aimed use of acetylcholinesterase inhibitors, targeting some symptoms more than others, may be beneficial in the case of cholinergic hypofunction. The animal model used in the present research may provide an efficient method for analyzing cognition-enhancing drugs before clinical trials.

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Effects of Chronic Donepezil Treatment and Cholinergic Deafferentation on Parietal Pyramidal Neuron Morphology

Paola De Bartolo, Francesca Gelfo, Laura Mandolesi, Francesca Foti, Debora Cutuli, Laura Petrosini *(Communicated by Sigfrido Scarpa)*

Abstract: Although clinical and experimental research has demonstrated that acetylcholinesterase inhibitors, such as donepezil, are able to enhance cognitive functioning in intact subjects as well as in patients affected by different degrees of dementia, no morphological study has ever analyzed whether donepezil treatment is able to modify neocortical neuronal morphology in the intact brain and in response to cholinergic depletion. Spines (number, density, distribution) and branching (length, intersections, nodes) of apical and basal dendrites of III-layer parietal pyramidal neurons were evaluated following chronic donepezil treatment in intact animals and in animals in which the cholinergic lesion was produced by intracerebroventricular injections of immunotoxin 192 IgG-saporin. In intact animals, the drug treatment provoked a proximal shift of spines towards the cell soma in basal dendrites. In lesioned animals, donepezil treatment reduced the upregulation of the spines induced by the cholinergic lesion in both apical and basal dendrites. Thus, while in the intact brain chronic donepezil treatment induced plastic changes in the dendritic morphology of pyramidal neurons of parietal cortex, in the presence of cholinergic depletion, it prevented the compensatory response of parietal pyramidal neurons to the loss of cholinergic inputs from basal forebrain.

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Hippocampal Alterations in Rats Submitted to Streptozotocin-Induced Dementia Model are Prevented by Aminoguanidine

Letícia Rodrigues, Regina Biasibetti, Alessandra Swarowsky, Marina C Leite, André Quincozes-Santos, Jorge A Quilfeldt, Matilde Achaval, Carlos-Alberto Gonçalves

Abstract: Although the exact cause of Alzheimer's disease remains elusive, many possible risk factors and pathological alterations have been used in the elaboration of *in vitro* and *in vivo* models of this disease in rodents, including intracerebral infusion of streptozotocin (STZ). Using this model, we evaluated spatial cognitive deficit and neurochemical hippocampal alterations, particularly astroglial protein markers such as glial fibrillary acidic protein (GFAP) and S100B, glutathione content, nitric oxide production, and cerebrospinal fluid (CSF) S100B. In addition, prevention of these alterations by aminoguanidine administration was evaluated. Results confirm a spatial cognitive deficit and nitrative stress in this dementia model as well as specific astroglial alterations, particularly S100B accumulation in the hippocampus and decreased CSF S100B. The hippocampal astroglial activation occurred independently of the significant alteration in GFAP content. Moreover, all these alterations were completely prevented by aminoguanidine administration, confirming the neuroprotective potential of this compound, but suggesting that nitrative stress and/or glycation may be underlying these alterations. These findings contribute to the understanding of diseases accompanied by cognitive deficits and the STZ-model of dementia.

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Delusion Symptoms and Response to Antipsychotic Treatment are Associated with the 5-HT2A (102T/C) Receptor Polymorphism in Alzheimer's Disease: A 3-Year Follow-up Longitudinal Study

Francesco Angelucci, Sergio Bernardini, Paolo Gravina, Lorenza Bellincampi, Alberto Trequattrini, Fulvia Di Iulio, Diego Vanni, Giorgio Federici, Carlo Caltagirone, Paola Bossù, Gianfranco Spalletta *(Communicated by Christian Jacob)*

Abstract: Although the etiology of psychotic symptoms (hallucinations and delusions) in Alzheimer's disease is still not known, alterations in serotonergic neurotransmission have been proposed. In a 3-year follow-up study, we evaluated the association of serotonin (5-HT) receptor 5-HT2a 102T/C polymorphism (allelic variants CC, CT and TT) with psychotic symptom severity and response to treatment with atypical antipsychotics (risperidone, olanzapine and quietapine) in 80 patients with a diagnosis of probable Alzheimer's disease. The Neuropsychiatric Inventory (NPI) was administered to determine the frequency

and severity (FxS) of psychotic and other behavioral symptoms. There was a significant difference in the NPI FxS delusion score among the three variants of the 5-HT2a 102T/C polymorphism, with patients carrying the TT genotype the most delusional during the follow-up period. In particular, NPI FxS delusion score was higher in TT than in CC genotype at year 2. Moreover, patients with delusion symptoms carrying the CT and TT genotypes were resistant to the treatment with antipsychotic drugs. Thus our study, although at preliminary level, suggests that the presence of T allele of the 102T/C polymorphism in patients with Alzheimer's disease is associated with both increased presence of delusion symptoms and treatment-resistance to second generation antipsychotic drugs.

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MRI-Derived Atrophy of the Olfactory Bulb and Tract in Mild Cognitive Impairment and Alzheimer's Disease

Philipp A. Thomann, Vasco Dos Santos, Ulrich Seidl, Pablo Toro, Marco Essig, Johannes Schröder *(Communicated by Cynthia Carlsson)*

Abstract: There is increasing histopathological evidence that the olfactory bulb and tract (OBT) is a primary focus of neurodegenerative changes in Alzheimer's disease (AD). Correspondingly, high-resolution magnetic resonance imaging revealed significant atrophy of the OBT in manifest AD. Whether these alterations are already present in mild cognitive impairment, the assumed preclinical stage of AD, has not been investigated yet. OBT volumes were assessed by manual tracing in 29 patients with mild cognitive impairment, 27 patients with probable AD, and 30 healthy controls. In a second step, voxel based morphometry was used to investigate the potential association between OBT atrophy and morphological changes in other brain regions. Patients had significantly lower OBT volumes when compared to controls, with atrophy being most prominent in the AD group. In addition, OBT atrophy was associated with a decreased medial temporal lobe (MTL) gray matter density bilaterally. Our findings indicate that neurodegeneration in OBT and MTL regions is linked and suggest that OBT volume might be a surrogate marker in AD.

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Late-Life Body Mass Index and Waist Circumference in Amnestic Mild Cognitive Impairment and Alzheimer's Disease

Leung-Wing Chu, Sidney Tam, Peter WH Lee, Ping-Yiu Yik, Youqiang Song, Bernard MY Cheung, Karen SL Lam

Abstract: We investigated the progressive associations of late-life body mass index (BMI) and waist circumference (WC) with amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) in Chinese older adults in a case-control study. Late-life BMI and WC were measured. AD was diagnosed by

the NINCDS-ADRDA criteria for probable AD and aMCI by the Petersen's criteria. 426 Chinese older adults [125 AD, 125 aMCI and 176 controls with normal cognition (NC)], aged 55 to 93 years old, were recruited. Both BMI and WC decreased significantly across the normal, aMCI, and AD groups (dementia diagnostic group: p for trend <0.001 and 0.016 respectively, 1-way ANOVA). After adjustment for significant confounders, multivariate general linear model analyses showed that the dementia diagnostic group (AD/aMCI/NC) was asignificant independent predictor of both the late-life BMI and late-life WC (p=0.002 and 0.018 respectively). In conclusion, late-life BMI and WC progressively decrease in older adults with normal cognition, aMCI, and AD. Low late-life BMI and WC represent potentially useful pre-clinical markers of aMCI and AD.

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Alzheimer Research Forum Live Discussion: Meet New Players, Histone Deacetylase and Sirtuin—Will They Help the Cell Cycle, DNA Repair, and Gene Expression Break Into Alzheimerology's Major League?

Transcript of Live Discussion held at the Alzheimer Research Forum

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Anti-Amyloid-ß Immunotherapy in Alzheimer's Disease: ACC-001 Clinical Trials are Ongoing

J. Michael Ryan, Michael Grundman

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Oxidative Stress in Vascular Dementia and Alzheimer's Disease: A Common Pathology

Stuart Bennett, Melissa M Grant, Sarah Aldred

Abstract: Alzheimer's disease and vascular dementia are the two most common types of dementia with the former being the most predominant. It is evident that oxidative stress, an environment where pro-oxidant species overwhelm antioxidant species, is involved in the pathogenesis of both forms of dementia. An increased level of reactive oxygen species in the vasculature, reduced nitric oxide bioavailability, and endothelial dysfunction leading to vascular disease is associated with vascular dementia. In Alzheimer's disease, an increased amount of amyloid-ß peptide induces elevated reactive oxygen species production thereby causing neuronal cell death and damage. The recent observation that

increased atherosclerotic plaque formation is present in the main artery to the brain in Alzheimer's disease, coupled with the association of vascular risk factors with this disease, suggests a link between these two dementias. This review will argue that Alzheimer's disease and vascular dementia are two extremes of one disease, thus assuming a hypothesis where the clinical conditions referred to as dementia are part of a continuum. We propose that the majority of cases share a vascular pathology and that oxidative stress is central to this common pathology.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 245-257

Genotype-Phenotype Relationships of Presenilin-1 Mutations in Alzheimer's Disease: An Update

Andrew J. Larner, Mark Doran

Abstract: It is now more than ten years since pathogenic mutations were first described in the gene encoding presenilin 1 (PSEN1) on chromosome 14. Although PSEN1 mutations are "deterministic" for Alzheimer's disease, they are associated with marked heterogeneity in the clinical expression of neurological features. We review recent publications on the clinical neurological phenotype of PSEN1 mutations, many of which now appear only in abstracts or brief communications, perhaps because PSEN1 mutations are no longer regarded as "novel". However, the clinical heterogeneity associated with these mutations prompts important questions about possible genetic and epigenetic factors which may modify disease phenotype. This area, which may also be relevant to neurodegenerative disorders resulting from other genetic mutations, such as those in the tau gene, currently remains ill-understood.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 259-265

Unraveling the Molecular Mechanisms Behind the Metabolic Basis of Sporadic Alzheimer's Disease

Adnan Erol

Abstract: Peripheral insulin resistance is associated with hyperinsulinemia, which may be associated with brain insulin deficiency that is characteristic of sporadic Alzheimer's disease (sAD). Oxidative insult, which is the result of insulin associated disordered brain energy metabolism, is a significant early event in the pathological cascade of sAD. Aggregation of disease-specific proteins such as amyloid-ß and tau may act as a compensatory response against the oxidative insult at the early periods. In the later stages, oxidative stress stimulates c-Jun N-terminal kinase (JNK) activation. The deficient insulin signaling is ultimately linked to protein kinase B (Akt) pathway and subsequently glycogen synthase kinase-3 (GSK3) and forkhead transcription factors (FOXO). Peripheral insulin resistance related intense interactions between JNK, GSK3, FOXO factors, and p53, which may lead to apoptotic neuronal death, are outlined in a postulate. In

light of this postulate, the importance of detailed knowledge of these common physiological processes for the opportunities of treatment that could prevent or reduce the onset of sAD is discussed as well.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 267-276

Bovine Spongiform Encephalopathy and Aquaculture

Robert P. Friedland, Robert B. Petersen, Richard Rubenstein

Abstract: Dietary consumption of fish is widely recommended because of the beneficial effects of omega-3 polyunsaturated fatty acids on the risks of cardiovascular and Alzheimer's diseases. The American Heart Association currently recommends eating at least two servings of fish per week. We are concerned that consumption of farmed fish may provide a means of transmission of infectious prions from cows with bovine spongiform encephalopathy to humans, causing variant Creutzfeldt Jakob disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 277-279

A New Function of Human HtrA2 as an Amyloid-ß Oligomerization Inhibitor

Joel Kooistra, Julijana Milojevic, Giuseppe Melacini, Joaquin Ortega *(Communicated by Jesus Avila)*

Abstract: Human HtrA2 is part of the HtrA family of ATP-independent serine proteases that are conserved in both prokaryotes and eukaryotes and localizes to the intermembrane space of the mitochondria. Several recent reports have suggested that HtrA2 is important for maintaining proper mitochondrial homeostasis and may play a role in Alzheimer's disease (AD), which is characterized by the presence of aggregates of the amyloid-ß peptide 1-42 (Aß1-42). In this study, we analyzed the ability of HtrA2 to delay the aggregation of the model substrate citrate synthase (CS) and of the toxic Aß1-42 peptide. We found that HtrA2 had a moderate ability to delay the aggregation of CS *in vitro*, and this activity was significantly enhanced when the PDZ domain was removed suggesting an inhibitory role for this domain on the activity. Additionally, using electron microscopy and nuclear magnetic resonance analyses, we observed that HtrA2 significantly delayed the aggregation of the Aß1-42 peptide. Interestingly, the protease activity of HtrA2 and its PDZ domain were not essential for the delay of Aß1-42 peptide aggregation. These results indicate that besides its protease activity, HtrA2 also performs a chaperone function and suggest a role for HtrA2 in the metabolism of intracellular Aß and in AD.

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(-)-Epigallocatechin-3-Gallate Protects SH-SY5Y Cells Against 6-OHDA-Induced Cell Death through STAT3 Activation

Lili Wang, Shengli Xu, Xianhao Xu, Piu Chan *(Communicated by Xiongwei Zhu)*

Abstract: As a natural product, (-)-Epigallocatechin-3-gallate (EGCG), has demonstrated remarkable neuronal protection by depressing oxidative stress in Parkinson's disease (PD). However, the molecular mechanisms underlying EGCG neuronal protection have not been clarified. Using 6-hydroxydopamine (6-OHDA)-treated human neuroblastoma SH-SY5Y cells as a PD cell model, we found that 6-OHDA can cause neuronal death by regulating the activity of STAT3. Pretreatment of SH-SY5Y cells with EGCG (0.1-10 μM) significantly attenuated the cell death induced by 6-OHDA. In addition, the STAT3 activity decline induced by 6-OHDA in SH-SY5Y cells can be completely prevented by the presence of 1 μM of EGCG, and neuronal cell proliferation can be stimulated by EGCG treatment. These results clearly demonstrate that the disruption of STAT3 signaling by 6-OHDA makes significant contribution to the neuronal death in PD, and the protection of EGCG on neurons against oxidative stress-induced cell death may result from the re-stimulation of STAT3 signaling pathway. Our study not only clarified the role of STAT3 signaling pathway in oxidative stress-induced neuronal cell death, but also identified its involvement in the protection mechanism of EGCG on neurons in PD. The data resulting from our study also suggest that STAT3 may serve as a potential therapeutic target for the drug development in PD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 295-304

Association of Cardiovascular Factors and Alzheimer's Disease Plasma Amyloid-ß Protein in Subjective Memory Complainers

Kristyn A. Bates, Hamid R. Sohrabi, Mark Rodrigues, John Beilby, Satvinder S. Dhaliwal, Kevin Taddei, Arthur Criddle, Megan Wraith, Matthew Howard, Georgia Martins, Athena Paton, Pankaj Mehta, Jonathan K. Foster, Ian J. Martins, Nicola T. Lautenschlager, Frank L. Mastaglia, Simon M. Laws, Samuel E. Gandy, Ralph N. Martins

Abstract: A strong link is indicated between cardiovascular disease (CVD) and risk for developing Alzheimer's disease (AD), which may be exacerbated by the major AD genetic risk factor apolipoprotein Ee4 (APOEe4). Since subjective memory complaint (SMC) may potentially be an early indicator for cognitive decline, we examined CVD risk factors in a cohort of SMC. As amyloid-ß (Aß) is considered to play a central role in AD, we hypothesized that the CVD risk profile (increased LDL, reduced HDL, and increased body fat) would be associated with plasma Aß levels. We explored this in 198 individuals with and without SMC (average age=63 years). Correlations between Aß40 and HDL were observed, which were stronger in non-APOEe4 carriers (rho=-0.315, $p<0.001$) and in SMC (rho=-0.322, $p=0.01$). There was no relationship between percentage

body fat and Aß40 in this cohort. Age and HDL remained predictive for plasma Aß40 using multivariate regression analysis. We report a novel negative association between HDL and Aß, which if demonstrated to be causal has implications for the development of lifestyle interventions and/or novel therapeutics. The relationship between HDL and Aß and the potential significance of such an association needs to be validated in a larger longitudinal study.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 305-318

Binding of Hsp90 to Tau Promotes a Conformational Change and Aggregation of Tau Protein

Elena Tortosa, Ismael Santa-Maria, Francisco Moreno, Filip Lim, Mar Perez, Jesús Avila

Abstract: Tau pathology, associated with Alzheimer's disease, is characterized by the presence of phosphorylated and aggregated tau. Phosphorylation of tau takes place mainly in the vicinity of the tubulin-binding region of the molecule and its self aggregation is also mediated via this tubulin-binding region. Tau phosphorylation and aggregation have been related with conformational changes of the protein. These changes could be regulated by chaperones such as heat shock proteins, since one of these, heat shock protein 90 (Hsp90), has already been described as a putative tau-binding protein. In this work, we have confirmed the interaction of Hsp90 with tau protein and report that binding of Hsp90 to tau facilitates a conformational change that could result in its phosphorylation by glycogen synthase kinase 3 and its aggregation into filamentous structures.

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Pretreatment with Lovastatin Prevents N-Methyl-D-Aspartate-Induced Neurodegeneration in the Magnocellular Nucleus Basalis and Behavioral Dysfunction

Amalia M. Dolga, Ivica Granic, Ingrid M. Nijholt, Csaba Nyakas, Eddy A. van der Zee, Paul G.M. Luiten, Ulrich L.M. Eisel *(Communicated by Angelika Bierhaus)*

Abstract: Besides a beneficial cardiovascular effect, it was recently suggested that statins can also exert neuroprotective actions. In a previous study, we provided *in vitro* evidence that lovastatin treatment abates excitotoxic cell death in primary cortical neurons. Here, we investigated the neuroprotective effect of lovastatin in an *in vivo* mouse model We found that administration of lovastatin (20 mg/kg) significantly protects cholinergic neurons and their cortical projections against N-methyl-D-aspartate (60 nmol)-induced cell death in the magnocellular nucleus basalis, a neuronal cell group that is characteristically

affected in Alzheimer's disease. Furthermore, lovastatin-mediated neuroprotection was shown to be dependent on protein kinase B (PKB)/Akt signaling since treatment with the PKB/Akt inhibitor LY294002 blocked the lovastatin-induced neuroprotective effect. The loss of cholinergic neurons after the lesion in the magnocellular nucleus basalis resulted in memory impairment as tested in a passive avoidance paradigm. This was reverted by pre-lesion lovastatin treatment. From these studies we conclude that treatment with lovastatin may provide protection against neuronal injury in excitotoxic conditions associated with neurodegenerative diseases including Alzheimer's disease.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 327-336

Brain-Derived Neurotrophic Factor Levels in Alzheimer's Disease

Sid E. O'Bryant, Valerie Hobson, James R. Hall, Stephen C. Waring, Wenyan Chan, Paul Massman, Laura Lacritz, C. Munro Cullum, Ramon Diaz-Arrastia; for the Texas Alzheimer's Research Consortium *(Communciated by Marwan Sabbagh)*

Abstract: The current search for biomarkers that are diagnostic and/or prognostic of Alzheimer's disease (AD) is of vital importance given the rapidly aging population. It was recently reported that brain-derived neurotrophic factor (BDNF) fluctuated according to AD severity, suggesting that BDNF might have utility for diagnostics and monitoring of therapeutic efficacy. The current study sought to examine whether BDNF levels varied according to AD severity, as previously reported. There were 196 participants (Probable AD, n = 98; Controls, n = 98) in the Texas Alzheimer's Research Consortium (TARC) Longitudinal Research Cohort available for analysis. BDNF levels were assayed via multiplex immunoassay. Regression analyses were utilized to examine the relation between BDNF levels, Mini-Mental Status Examination, and Clinical Dementia Rating scores adjusting for age and gender. In adjusted models, BDNF levels did not distinguish between AD patients and normal controls and did not significantly predict AD severity or global cognitive functioning. In conclusion, these findings do not support the notion that BDNF serves as a diagnostic marker for AD or disease severity. It is likely that the most accurate approach to identifying biomarkers of AD will be through an algorithmic approach that combines multiple markers reflective of various pathways.

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Plasma Level of Amyloid ß1-42 Is Independent of Neuronal Function in Alzheimer's Disease

Fereshteh Sedaghat, Eleni Dedousi, Vasiliki Costa, Athanasios S. Dimitriadis, Stavros J. Baloyannis *(Communicated by Kurt Jellinger)*

Abstract: The aggregation of amyloid-ß42 (Aß42) constitutes one of the major pathogenic events in Alzheimer's disease (AD), and the study of regional cerebral blood flow (rCBF), using single photon emission computed tomography (SPECT), aids the diagnosis of AD. In this study, we evaluated whether there was a correlation between rCBF in brain regions and plasma levels of Aß1-42 in AD. 29 patients (mean age 71 ± 9) with a diagnosis of AD who fulfilled NINCDS-ADRDA criteria with a mean Mini-Mental Status Examination score of 15 ± 9 and 16 normal controls (mean age 64 ± 8) underwent SPECT brain imaging with hexamethylpropylene amine oxime, and semiquantitative analysis of rCBF was performed. Plasma samples were collected the same day of the SPECT and plasma Aß1-42 measured by ELISA. A significant reduction of rCBF was observed in most regions in AD compared to controls, whereas mean plasma Aß42 did not differ between the two groups. There was no correlation between rCBF in any region and plasma Aß42 nor any correlations between gender, age, and severity with plasma levels of Aß42. Since rCBF is coupled to neuronal activity, we conclude that plasma Aß1-42 concentration is independent of neuronal function in every single region of the brain.

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Increase of Theta/Gamma and Alpha3/Alpha2 Ratio is Associated with Amygdalo-Hippocampal Complex Atrophy

Vito Davide Moretti, Michela Pievani, Claudia Fracassi, Giuliano Binetti, Sandra Rosini, Cristina Geroldi, Orazio Zanetti, Paolo M. Rossini, Giovanni B. Frisoni

Abstract: We evaluated the association between amygdalo-hippocampal complex (AHC) atrophy and two electroencephalography (EEG) markers of cognitive decline: increase of theta/gamma and increase of alpha3/alpha2 relative power ratio. Seventy-nine subjects with mild cognitive impairment (MCI) underwent EEG recording and magnetic resonance imaging scan. Based on the tertiles values of decreasing AHC volume, three groups of AHC growing atrophy were obtained. The groups were characterized by the performance to cognitive tests and theta/gamma and alpha3/alpha2 relative power ratio. AHC atrophy is associated with memory deficits as well as with increase of theta/gamma and alpha3/alpha2 ratio. Moreover, when the amygdalar and hippocampal volume are separately considered within AHC, the increase of theta/gamma ratio is best associated with amygdalar atrophy whereas alpha3/alpha2 ratio is best associated with hippocampal atrophy. AHC atrophy is associated with memory deficits and EEG markers of cognitive decline. So far, these EEG markers could have a prospective value in differential diagnosis between patients with MCI who develop dementia and those who do not as well as between MCI patients who will develop Alzheimer's disease and those who develop non-Alzheimer's disease dementias. The alterations of the functional connections, inducing global network pathological changes, in the whole AHC could better explain MCI state.

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Earlier Onset of Alzheimer's Disease: Risk Polymorphisms Within *PRNP*, *PRND*, *CYP46*, and *APOE* Genes

Ewa Golanska, Krystyna Hulas-Bigoszewska, Monika Sieruta, Izabela Zawlik, Monika Witusik, Sylwia M. Gresner, Tomasz Sobow, Maria Styczynska, Beata Peplonska, Maria Barcikowska, Pawel P. Liberski, Elizabeth H. Corder *(Communicated by Eliecer Coto)*

Abstract: We studied eight polymorphisms within *APOE*, *PRNP*, *PRND*,and *CYP46* genes in 213 Polish late-onset patients with Alzheimer's disease (AD) and 171 non-demented elderly controls. A latent classification approach, grade-of-membership analysis, was taken to identify three extreme pure type risk sets defined by the probabilities of being affected with AD and for genotypes found at the examined genes. Sets I and II represented high intrinsic risk, having a higher density of various genotypes compared to set III, at low intrinsic risk. A gradient of onset age depending on membership in the risk sets was also observed. Logistic regression analysis showed that the highest risk for AD was found for individuals who co-inherited *APOE* e4 allele, *PRNP* codon 129 homozygosity, *PRND* codon 174 Thr allele, and *CYP46* rs754203 g allele. AD can be influenced by genetic profiles leading to appearance of the disease, composed of genes which separately evoke a little or unnoticeable effect. Moreover, there may be multiple sufficient risk sets for AD. Looking at multiple genes together rather than analyzing them individually, may improve identification of risk alleles.

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Acute but not Chronic Donepezil Administration Increases Muscarinic Receptor-Mediated Brain Signaling Involving Arachidonic Acid in Unanesthetized Rats

Mireille Basselin, Henry N. Nguyen, Lisa Chang, Jane M. Bell, Stanley I. Rapoport *(Communicated by Marwan Sabbagh)*

Abstract: Donepezil, an acetylcholinesterase (AChE) inhibitor used for treating Alzheimer's disease patients, is thought to act by increasing brain extracellular acetylcholine (ACh), and ACh binding to cholinergic receptors. Muscarinic receptors are coupled to cytosolic phospholipase A2 (cPLA2) activation and arachidonic acid (AA) release from synaptic membrane phospholipid. This activation can be imaged in rodents as an AA incorporation coefficient k*, using quantitative autoradiography. Acute and chronic effects of donepezil on the AA signal, k* for AA, were measured in 81 brain regions of unanesthetized rats. Twenty min after a single oral dose (3.0 mg/kg) of donepezil, k* was increased significantly in 37 brain regions, whereas k* did not differ from control 7 h afterwards or following chronic (21 days) of donepezil. Pretreatment with

atropine prevented the 20-min increments in k* following donepezil. Donepezil also increased the brain ACh concentration and reduced brain AChE activity, but did not change cPLA2 activity, regardless of administration regimen. These results show that donepezil acutely increases the brain AA signal that is mediated by ACh acting at muscarinic receptors, but that this signal is rapidly desensitized despite continued elevated brain ACh concentration. In contrast, the AA signal in response to arecoline was not altered following donepezil.

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AßPP A713T Mutation in Late Onset Alzheimer's Disease with Cerebrovascular Lesions

Livia Bernardi, Silvana Geracitano, Rosanna Colao, Gianfranco Puccio, Maura Gallo, Maria Anfossi, Francesca Frangipane, Sabrina A.M. Curcio, Maria Mirabelli, Carmine Tomaino, Franca Vasso, Nicoletta Smirne, Raffaele Maletta, Amalia C. Bruni *(Communicated by Patrizia Mecocci)*

Abstract: Mutations in the amyloid-ß protein precursor (AßPP) gene can cause autosomal dominant early-onset Alzheimer's disease, Alzheimer's disease (AD) associated with cerebral amyloid angiopathy (CAA), cerebral hemorrhage, or both defining AD-AßPP related as a complex disease. We have previously reported that the AßPP A713T mutation is associated with AD and subcortical ischemic lesions at magnetic resonance imaging in a large family in which neuropathology evidenced CAA, stroke, and AD lesions. The objective of this clinical and molecular study was to investigate AßPP gene mutations in 59 patients affected by AD with cerebrovascular lesions (CVLs) and a family history of dementia. We identified three affected subjects with the AßPP A713T mutation. Since the prevalence of this mutation worldwide is very low, this suggests that a common founder could exist in southern Italy. The pathogenicity of this mutation was confirmed and the clinical AD phenotype with CVLs seems to be a distinctive feature at least in the southern Italian population. The identification of these patients suggests that genetic epidemiology in large cohorts of familial late onset AD with CVLs would increase the probability of identifying AßPP mutations still underestimated.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 393-389

Near-Infrared Spectroscopy of Blood Plasma for Diagnosis of Sporadic Alzheimer's Disease

David H. Burns, Scott Rosendahl, Dirk Bandilla, Olivier C. Maes, Howard M. Chertkow, Hyman M. Schipper *(Communicated by Othman Ghribi)*

Abstract: There are currently no accepted blood-based biomarkers of sporadic Alzheimer's disease (AD). Augmented oxidative stress has been implicated in both neural and peripheral AD tissues. In this study, we determined whether

short-wavelength near-infrared (NIR) spectrophotometry of blood plasma differentiates mild sporadic AD from normal aging. NIR analysis was conducted on 75 μl plasma samples from 19 AD, 27 amnestic MCI, and 17 normal elderly control (NEC) persons using an optical fiber-coupled, holographic grating-based NIR spectrograph. Five spectral bands associated with heme, R-CH, R-OH, H2O, and R-NH functional groups, were sensitive to oxidative modification in pre-clinical studies and were pre-selected to develop a logistic regression model for sample classification. This model differentiated AD from NEC samples with a sensitivity of 80% and specificity of 77%. Fifteen and twelve MCI patients were classified with the NEC and AD groups, respectively. The spectra were not influenced by age, gender, exposure to cholinesterase inhibitors or vitamin E, or sample storage time. The NIR data further implicate oxidative stress in the systemic pathophysiology of sporadic AD and differentiate mild (and possibly pre-clinical) AD from NEC individuals with moderate-high accuracy. The procedure is minimally-invasive, rapid, relatively-inexpensive, and may provide a useful biological marker of sporadic AD.

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Clinical Epidemiology and In-Patient Hospital Use in the Last Year of Life (1990-2005) of 29,884 Western Australians with Dementia

Renate R. Zilkens, Katrina Spilsbury, David G. Bruce, James B. Semmens

Abstract: Dementia-related healthcare planning requires accurate information on dementia patient characteristics and hospitalization trends at a population level. This population-based retrospective cohort study was designed to evaluate factors associated with total hospital length-of-stay (tLOS) in the last year of life (1990-2005) in Western Australians with dementia. Using linked hospital and death records, 29,884 dementia cases were identified. The average tLOS in the last year of life for all cases was 31.8 days. tLOS was longer for vascular dementia than Alzheimer's disease (41 versus 28 days; Rate Ratio (RR) 1.4; 95% CI 1.3-1.6). After multivariate adjustment, tLOS was longer for males than females (RR 1.4; 95% CI 1.3-1.4); longer for remote (RR 1.7; 95% CI 1.4-2.0) and very remote (RR3.0; 95% CI 2.4-3.9) compared to metropolitan areas; and shorter with increasing age. 62% of admissions were emergency admissions. "Problems accessing alternative medical facilities" and "problems related to care provider dependency" accounted for a total of 16.4% of all bed days. In conclusion, people with dementia spend a considerable period of time in the hospital during their last year of life. Consideration of geographic isolation and accessibility to non-hospital facilities in dementia-related healthcare planning may liberate in-patient beds for more elective and acute care admissions.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 2, June 2009, Pages 399-407

Altered Subcellular Distribution of c-Abl in Alzheimer's Disease

Zheng Jing, John Caltagarone, Robert Bowser

Abstract: c-Abl is a non-receptor tyrosine kinase that participates in multiple signaling pathways linking the cell surface, cytoskeleton, and the nucleus. Recent *in vitro* studies have also linked c-Abl to amyloid-ß-induced toxicity and tau phosphorylation. To further characterize a potential role of c-Abl in Alzheimer's disease (AD), we examined the expression and distribution of total and phosphorylated forms of c-Abl in the hippocampus of AD and control subjects. Laser scanning confocal microscopy was used to examine the colocalization of c-Abl with AD pathology. Our results demonstrate alterations in the presence and distribution of c-Abl and phosphorylated isoforms of c-Abl within the hippocampus during AD. Total unphosphorylated c-Abl was highest in non-demented control hippocampus. Activated isoforms of c-Abl were most abundant in AD hippocampus and co-localized with AD pathology, including granulovacuolar degeneration bodies. c-Abl interacts with phosphorylated tau in AD brain and may contribute to the formation of tau pathology. These studies demonstrate altered activation and distribution of c-Abl during AD, suggesting a role for c-Abl in Ab signal transduction and generation of tau pathology in AD.

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Clioquinol Decreases Amyloid-ß Burden and Reduces Working Memory Impairment in a Transgenic Mouse Model of Alzheimer's Disease

Cristina Grossi, Simona Francese, Angela Casini, Maria Cristina Rosi, Ilaria Luccarini, Anna Fiorentini, Chiara Gabbiani, Luigi Messori, Gloriano Moneti, Fiorella Casamenti *(Communicated by Juha Rinne)*

Abstract: Clioquinol (CQ) is a "metal protein attenuating compound" that crosses the blood-brain barrier and binds, with high affinity, copper(II) and zinc(II), two metal ions critically involved in amyloid-ß aggregation and toxicity. CQ was recently proposed for the treatment of Alzheimer's disease, but controversial data have been reported so far concerning its real therapeutic advantages. We describe here results of chronic CQ treatment in the TgCRND8 mouse model of Alzheimer's disease. Remarkably, based on classical behavioral tests, CQ treatment was found to revert, to a large extent, the working memory impairments that are characteristic of this mouse model. Pairwise, a significant reduction of amyloid-ß plaque burden, both in the cortex and in the hippocampus, was detected as well as an attenuation of astrogliosis. MALDI Mass Spectrometry Imaging technique revealed a specific localization of CQ in the above mentioned brain areas. Modest but significant effects on the absolute and relative brain concentrations of the three most important biometals (i.e., copper, zinc, and iron) were highlighted following CQ treatment. The pharmacological and mechanistic implications of the above findings are thoroughly discussed.

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Dopamine D3 Receptor Gene Polymorphism Influences on Behavioral and Psychological Symptoms of Dementia (BPSD) in Mild Dementia of Alzheimer's Type

Noriko Sato, Akinori Ueki, Hideo Ueno, Hidetaka Shinjo, Yoshio Morita

Abstract: Dopamine D3 receptor (DRD3) is present in the limbic system, which is thought to regulate affect, cognition, and activity. Thus a functional change in the DRD3 gene could in turn affect the cognitive and psychiatric symptoms of dementia of Alzheimer's type (DAT). We investigated a possible association of DRD3 genotype with DAT and the behavioral and psychological symptoms of dementia (BPSD) in mild DAT. The genotyping for DRD3 and apolipoprotein E (ApoE) was determined using restriction fragment length polymorphism in 210 patients with mild DAT and 224 age- and sex-matched non-demented controls. The occurrence of BPSD during the course of mild dementia was demonstrated using the Behavioral Pathology in Alzheimer's Disease rating scale (BEHAVE-AD). No significant differences in DRD3 genotype were identified between DAT and controls, regardless of ApoE e4. Among the DAT with BPSD, however, a significant association was observed between the presence of the DRD3 glycine allele and paranoid and delusional ideation, regardless of ApoE e4. In conclusion, DRD3 gene polymorphism is unlikely to play a substantial role in conferring susceptibility to DAT, but it may be involved in the development of paranoid and delusional ideation during the course of mild DAT.

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Alzheimer Research Forum Live Discussion: Can We (Should We?) Develop "Smart Drugs" to Stave Off Age-Related Memory Loss?

Transcript of Live Discussion held at the Alzheimer Research Forum

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Challenges Associated with Metal Chelation Therapy in Alzheimer's Disease

Muralidhar L. Hegde, Bharathi, Anitha Suram, Chitra Venugopal, Ramya Jagannathan, Pankaj Poddar, Pullabhatla Srinivas, Kumar Sambamurti, Kosagisharaf Jagannatha Rao, Janez Scancar, Luigi Messori, Luigi Zecca, Paolo Zatta

Abstract: A close association between brain metal dishomeostasis and the onset and/or progression of Alzheimer's disease (AD) has been clearly established in a number of studies, although the underlying biochemical mechanisms remain

obscure. This observation renders chelation therapy an attractive pharmacological option for the treatment of this disease. However, a number of requirements must be fulfilled in order to adapt chelation therapy to AD so that the term "metal targeted strategies" seems now more appropriate. Indeed, brain metal redistribution rather than brain metal scavenging and removal is the major goal of this type of intervention. The most recent developments in metal targeted strategies for AD will be discussed using, as useful examples, clioquinol, curcumin, and epigallocatechin, and the future perspectives will also be outlined.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 457-467

Pathological Synergism Between Amyloid-ß and Apolipoprotein E4—The Most Prevalent Yet Understudied Genetic Risk Factor for Alzheimer's Disease

Haim Belinson and Daniel M. Michaelson

Abstract: This review focuses on apolipoprotein E4 (apoE4), the most prevalent genetic risk factor of Alzheimer's disease, and on *in vivo* and *in vitro* model studies of the mechanisms underlying its pathological phenotype. The review will first center on *in vivo* studies with transgenic mice that express human apoE4 and other human apoE alleles, and on the extent to which this model mimics and reproduces the human apoE4 phenotypes. The second part of this review will address apoE4-related *in vitro* studies, with particular emphasis on the effects of the state of lipidation of apoE4 on its biochemical properties and on the extent to which the *in vitro* results can be generalized and applied to the *in vivo* situation. The third part of this review will focus on a novel pharmacological *in vivo* system that was recently developed in our laboratory, which is based on activation of the amyloid cascade in apoE transgenic mice by prolonged inhibition of the Aß-degrading enzyme neprilysin and on what this system and its high spatio-temporal resolution has taught us about the mechanisms underlying the pathological effects of apoE4 *in vivo*.

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Dietary Deficiency in Folate and Vitamin E Under Conditions of Oxidative Stress Increases Phospho-Tau Levels: Potentiation by ApoE4 and Alleviation by S-Adenosylmethionine

Amy Chan, Eugene Rogers and Thomas B. Shea

Abstract: Prior studies link dietary deficiency and genetic risk factors for Alzheimer's disease (AD). In the present report, mice expressing human apolipoprotein E4 (associated with increased risk of AD) and apolipoprotein E3 were subjected to a diet lacking folate and vitamin E, and containing iron as a pro-oxidant. Consistent with prior studies, E4 mice displayed more phospho-tau

than E3 mice prior to dietary challenge. The deficient diet increased phospho-tau in E4 but not E3 mice, which was prevented by S-adenosyl methionine supplementation. Since neurofibrillary tangles are comprised of phospho-tau, investigation of the impact of dietary deficiency and S-adenosyl methionine supplementation on neurofibrillary tangle formation are warranted.

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Effects of 4-Hydroxy-Nonenal and Amyloid-ß on Expression and Activity of Endothelin Converting Enzyme and Insulin Degrading Enzyme in SH-SY5Y Cells

Rui Wang*, Suqing Wang*, James S. Malter and Deng-Shun Wang (*Equal Contributor)

Abstract: The cerebral accumulation of amyloid-ß (Ab) is a consistent feature of and likely contributor to the development of Alzheimer's disease (AD). In addition to dysregulated production, increasing experimental evidence suggests reduced catabolism plays an important role in Aß accumulation. Although endothelin converting enzyme (ECE) and insulin degrading enzyme (IDE) degrade and thus contribute to regulating the steady-state levels of Aß, how these enzymes are regulated remain poorly understood. In this study, we investigated the effects of 4-hydroxy-nonenal (HNE) and Aß on the expression and activity of ECE-1 and IDE in human neuroblastoma SH-SY5Y cells. Treatment with HNE or Aß upregulated ECE-1 mRNA and protein, while IDE was unchanged. Although both ECE-1 and IDE were oxidized within 24 h of HNE or Aß treatment, ECE-1 catalytic activity was elevated while IDE specific activity was unchanged. The results demonstrated for the first time that both ECE-1 and IDE are substrates of HNE modification induced by Aß. In addition, the results suggest complex mechanisms underlying the regulation of their enzymatic activity.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 489-501

Neuroprotective Effects of Statins in an *In Vitro* Model of Alzheimer's Disease

Ana Catarina R.G. Fonseca, Teresa Proença, Rosa Resende, Catarina R. Oliveira, Cláudia M.F. Pereira

Abstract: Statins, used as cholesterol-lowering drugs, were reported to reduce the progression of Alzheimer's disease (AD). However, the molecular mechanisms underlying these findings remain to be clarified and it is not well understood whether this beneficial effect is due to simply lowering cholesterol levels. This study was aimed to investigate the neuroprotective effect of simvastatin and lovastatin, lipophilic statins that can transverse the blood brain barrier, against

the toxicity triggered by the AD-associated amyloid-ß (Aß) peptides and to analyze if such protection is cholesterol-independent. Using primary cultures of cortical neurons treated with Aß1-40 peptide, we have demonstrated that pre-incubation with statins prevents the rise in cytosolic Ca2+ concentration and the accumulation of reactive oxygen species induced by Aß through mechanisms independent of cholesterol reduction. The neuroprotective actions of statins were rather attributable to their ability to reduce isoprenyl intermediates levels in the cholesterol biosynthetic pathway since their effect was reversed by geranyl pyrophosphate while cholesterol addition was ineffective. Consequently, statins were shown to rescue cortical neurons from Aß1-40-induced caspase-3-dependent apoptosis. Moreover, our results revealed that simvastatin, at neuroprotective concentrations against Aß-induced toxicity, is not able to activate Akt or ERK2, two signaling kinases with neuroprotective roles against apoptosis.

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Epidemilogical Trends Strongly Suggest Exposures as Etiologic Agents in the Pathogenesis of Sporadic Alzheimer's Disease, Diabetes Mellitus, and Non-Alcoholic Steatohepatitis

Suzanne M. de la Monte, Alexander Neusner, Jennifer Chu and Margot Lawton
(Communicated by Paula Moreira)

Abstract: Nitrosamines mediate their mutagenic effects by causing DNA damage, oxidative stress, lipid peroxidation, and pro-inflammatory cytokine activation, which lead to increased cellular degeneration and death. However, the very same pathophysiological processes comprise the "unbuilding" blocks of aging and insulin-resistance diseases including, neurodegeneration, diabetes mellitus (DM), and non-alcoholic steatohepatitis (NASH). Previous studies demonstrated that experimental exposure to streptozotocin, a nitrosamine-related compound, causes NASH, and diabetes mellitus Types 1, 2 and 3 (Alzheimer (AD)-type neurodegeneration). Herein, we review evidence that the upwardly spiraling trends in mortality rates due to DM, AD, and Parkinson's disease typify exposure rather than genetic-based disease models, and parallel the progressive increases in human exposure to nitrates, nitrites, and nitrosamines via processed/preserved foods. We propose that such chronic exposures have critical roles in the pathogenesis of our insulin resistance disease pandemic. Potential solutions include: 1) eliminating the use of nitrites in food; 2) reducing nitrate levels in fertilizer and water used to irrigate crops; and 3) employing safe and effective measures to detoxify food and water prior to human consumption. Future research efforts should focus on refining our ability to detect and monitor human exposures to nitrosamines and assess early evidence of nitrosamine-mediated tissue injury and insulin resistance.

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Dysregulation of Tau Phosphorylation in Mouse Brain during Excitotoxic Damage

Zhihou Liang, Fei Liu, Khalid Iqbal, Inge Grundke-Iqbal, Cheng-Xin Gong
(Communicated by Xiongwei Zhu)

Abstract: Glutamate receptor–mediated excitotoxicity is thought to contribute to the development of Alzheimer's disease (AD), but the underlying mechanism is unknown. In this study, we investigated the dynamic changes of tau phosphorylation and tau-related protein kinases and protein phosphatase 2A (PP2A) in the mouse brain during excitotoxicity induced by intraperitoneal injection of 20 mg/kg kainic acid (KA). We found that KA-induced excitotoxicity led to transient dephosphorylation of tau (within 6 hr post-injection), followed by sustained hyperphosphorylation of tau at multiple sites that are hyperphosphorylated in AD brain. The initial dephosphorylation of tau may result from activation of PP2A, and the sustained hyperphosphorylation may be due mainly to activation of cdk5 and down-regulation of PP2A during the later phase. Because abnormal hyperphosphorylation of tau plays a crucial role in neurodegeneration and in the formation of neurofibrillary tangles, our results suggest that glutamate receptor–mediated excitotoxicity might contribute to AD partially via promoting abnormal hyperphosphorylation of tau in AD brain.

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Glial Fibrillary Acidic Protein and Protein S-100B: Different Concentration Pattern of Glial Proteins in Cerebrospinal Fluid of Patients with Alzheimer's Disease and Creutzfeldt-Jakob Disease

Sarah Jesse, Petra Steinacker, Lukas Cepek, Christine V. Arnim, Hayrettin Tumani, Stefan Lehnert, Hans A. Kretzschmar, Michael Baier, Markus Otto
(Communicated by Khalid Iqbal)

Abstract: Glial fibrillary acidic protein (GFAP) and protein S-100B are established indicators of astrogliosis in neuropathology. As GFAP and S-100B are expressed in different cell populations, variable cerebrospinal fluid (CSF) concentrations of these proteins might reflect disease-specific pathological profiles. Therefore we investigated CSF of patients with Alzheimer's disease (AD), patients with Creutzfeldt-Jakob disease (CJD), and non-demented control patients (CON). Measurement of GFAP and S-100B in CSF was performed by commercially available ELISA. Our results show that, in AD, there are significantly higher levels of GFAP concentrations, compared to CON ($p = 0.001$) and CJD patients ($p = 0.009$), whereas S-100B is much higher in CJD, compared to AD ($p = 0.001$) and CON ($p = 0.001$). In conclusion, GFAP and S-100B represent astroglial markers and the different levels of these proteins in CSF of AD and CJD patients might point to a distinct pathophysiological

involvement in these diseases. Apart from pathophysiological aspects, GFAP in particular might serve as an additional diagnostic tool for AD, due to the fact that this protein does not correlate to established markers like tau and amyloid-ß such that analysis of GFAP may be useful for further differential diagnostic approaches in neurodegenerative diseases.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 541-551

Testing the Neurovascular Hypothesis of Alzheimer's Disease: LRP-1 Antisense Reduces Blood-brain Barrier Clearance and Increases Brain Levels of Amyloid-ß Protein and Impairs Cognition

Laura B. Jaeger, Shinya Dohgu, Mark C. Hwang, Susan A. Farr, M. Paul Murphy, Melissa A. Fleegal-DeMotta, Jessica L. Lynch, Sandra M. Robinson, Michael L. Niehoff, Steven N. Johnson, Vijaya B. Kumar, William A. Banks

Abstract: Decreased clearance is the main reason amyloid-ß protein (Aß) is increased in the brains of patients with Alzheimer's disease (AD). The neurovascular hypothesis states that this decreased clearance is caused by impairment of low density lipoprotein receptor related protein-1 (LRP-1), the major brain-to-blood transporter of Aß at the blood-brain barrier (BBB). As deletion of the LRP-1 gene is a lethal mutation, we tested the neurovascular hypothesis by developing a cocktail of phosphorothioate antisenses directed against LRP-1 mRNA. We found these antisenses in comparison to random antisense selectively decreased LRP-1 expression, reduced BBB clearance of Aß42, increased brain levels of Aß42, and impaired learning ability and recognition memory in mice. These results support dysfunction of LRP-1 at the BBB as a mechanism by which brain levels of Aß could increase and AD would be promoted.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 553-570

White Matter Microstructure in Relation to Education in Aging and Alzheimer's Disease

Stefan J. Teipel, Thomas Meindl, Maximilian Wagner, Thomas Kohl, Katharina Bürger, Maximilian F. Reiser, Sabine Herpertz, Hans-Jürgen Möller, Harald Hampel *(Communicated by Diana Woodruff-Pak)*

Abstract: The reduced risk of dementia in high-educated individuals has been suggested to reflect brain reserve capacity. In the present study, we determined the association between integrity of white matter microstructure and education separately in twenty-one patients with clinically probable Alzheimer's disease (AD) and 18 healthy elderly subjects. We used fractional anisotropy derived from high-resolution diffusion-tensor weighted imaging at 3 Tesla as an *in vivo* marker

of white matter microstructure. Based on multivariate network analysis, more years of education were associated with reduced white matter integrity of medial temporal lobe areas and association fiber tracts when age, gender, and dementia severity had been controlled for ($p < 0.001$). In controls, higher education was associated with greater white matter integrity in medial temporal lobe areas and association fiber tracts ($p < 0.001$). In multiple regression models, education was the main factor accounting for fiber tract integrity even when occupation was taken into account. Reduced fiber tract integrity with higher education at the same level of cognitive impairment in AD patients and higher fiber tract integrity with higher education in similar white matter areas in cognitively healthy controls agrees with the hypothesis that white matter microstructure may contribute to brain reserve capacity in humans.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 571-583

Cinnamon Extract Inhibits Tau Aggregation Associated with Alzheimer's Disease *In Vitro*

Dylan W. Peterson, Roshni C. George, Francesca Scaramozzino, Nichole E. LaPointe, Richard A. Anderson, Donald J. Graves, John Lew *(Communicated by James Joseph)*

Abstract: An aqueous extract of Ceylon cinnamon (*C. zeylanicum*) is found to inhibit tau aggregation and filament formation, hallmarks of Alzheimer's disease (AD). The extract can also promote complete disassembly of recombinant tau filaments and cause substantial alteration of the morphology of paired-helical filaments isolated from AD brain. Cinnamon extract was not deleterious to the normal cellular function of tau, namely the assembly of free tubulin into microtubules. An A-linked proanthocyanidin trimer molecule was purified from the extract and shown to contain a significant proportion of the inhibitory activity. Treatment with polyvinylpyrolidone effectively depleted all proanthocyanidins from the extract solution and removed the majority, but not all, of the inhibitory activity. The remainder inhibitory activity could be attributed to cinnamaldehyde. This work shows that compounds endogenous to cinnamon may be beneficial to AD themselves or may guide the discovery of other potential therapeutics if their mechanisms of action can be discerned.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 585-597

Serial Susceptibility Weighted MRI Measures Brain Iron and Microbleeds in Dementia

Wolff Kirsch, Grant McAuley, Barbara Holshouser, Floyd Petersen, Muhammad Ayaz, Harry V. Vinters, Cindy Dickson, E. Mark Haacke, William Britt III, James Larsen, Ivan Kim, Claudius Mueller, Matthew Schrag, Daniel Kido *(Communicated by Othman Ghribi)*

Abstract: A new iron sensitive MR sequence (susceptibility weighted imaging – SWI) enabling the simultaneous quantitation of regional brain iron levels and brain microbleeds (BMB) has been acquired serially to study dementia. Cohorts of mildly cognitively impaired (MCI) elderly (n=73) and cognitively normal participants (n=33) have been serially evaluated for up to 50 months. SWI phase values (putative iron levels) in 14 brain regions were measured and the number of BMB were counted for each SWI study. SWI phase values showed a left putaminal mean increase of iron (decrease of phase values) over the study duration in 27 participants who progressed to dementia compared to Normals (p=0.035) and stable MCI (p=0.01). BMB were detected in 9 out of 26 (38%) MCI participants who progressed to dementia and are a significant risk factor for cognitive failure in MCI participants [risk ratio = 2.06 (95% confidence interval 1.37-3.12)]. SWI is useful to measure regional iron changes and presence of BMB, both of which may be important MR-based biomarkers for neurodegenerative diseases.

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PAN-811 Inhibits Oxidative Stress-Induced Cell Death of Human Alzheimer's Disease-Derived and Age-Matched Olfactory Neuroepithelial Cells Via Suppression of Intracellular Reactive Oxygen Species

Valery M. Nelson, Chanteé M. Dancik, Weiying Pan, Zhi-Gang Jiang, Michael S. Lebowitz, Hossein A. Ghanbari

Abstract: Oxidative stress plays a significant role in neurotoxicity associated with a variety of neurodegenerative diseases including Alzheimer's disease (AD). Increased oxidative stress has been shown to be a prominent and early feature of vulnerable neurons in AD. Olfactory neuroepithelial cells are affected at an early stage. Exposure to oxidative stress induces the accumulation of intracellular reactive oxygen species (ROS), which in turn causes cell damage in the form of protein, lipid, and DNA oxidations. Elevated ROS levels are also associated with increased deposition of amyloid-ß and formation of senile plaques, a hallmark of the AD brain. If enhanced ROS exceeds the basal level of cellular protective mechanisms, oxidative damage and cell death will result. Therefore, substances that can reduce oxidative stress are sought as potential drug candidates for treatment or preventative therapy of neurodegenerative diseases such as AD. PAN-811, also known as 3-aminopyridine-2-carboxaldehyde thiosemicarbazone or Triapine, is a small lipophilic compound that is currently being investigated in several Phase II clinical trials for cancer therapy due to its inhibition of ribonucleotide reductase activity. Here we show PAN-811 to be effective in preventing or reducing ROS accumulation and the resulting oxidative damages in both AD-derived and age-matched olfactory neuroepithelial cells.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 611-619

Altered Cerebral Hemodynamics in Early Alzheimer Disease: A Pilot Study Using Transcranial Doppler

Jurgen A.H.R. Claassen, Ramon Diaz-Arrastia, Kristin Martin-Cook, Benjamin D. Levine, Rong Zhang

Abstract: Cerebrovascular disease may contribute to the development and progression of Alzheimer's disease (AD). This study investigated whether impairments in cerebral hemodynamics can be detected in early-stage AD. Nine patients with mild AD and eight cognitively normal controls matched for age underwent brain magnetic resonance imaging and neuropsychological evaluation, followed by assessment of steady-state cerebral blood flow velocity (CBFV, transcranial Doppler), blood pressure (BP, Finapres), and cerebrovascular resistance index (BP/CBFV). Cerebral hemodynamics were quantified using spectral and transfer function analysis of BP and CBFV in rest, during standing up after squat, and during repeated squat-stand maneuvers. Compared to controls, AD patients had lower CBFV and higher cerebrovascular resistance index, unexplained by brain atrophy. Low-frequency variability of BP was enhanced, suggesting impaired arterial baroreflex function. However, CBFV variability was reduced despite enhanced BP variability, and dynamic cerebral autoregulation was not impaired. In conclusion, despite a distinct pattern of altered cerebral hemodynamics, AD patients may have normal autoregulation. However, the challenges for autoregulation in AD are higher, as our data show enhanced BP fluctuations. Increased cerebral vasoconstriction or reduced vasomotion also may attenuate CBFV variability.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 621-629

Biphasic Effects of Forskolin on Tau Phosphorylation and Spatial Memory in Rats

Qing Tian, Jun-Xia Zhang, Yao Zhang, Feng Wu, Qian Tang, Cheng Wang, Zhi-Yong Shi, Jing-Hui Zhang, Sang Liu, Yue Wang, Qi Zhang, Jian-Zhi Wang *(Communicated by Xiongwei Zhu)*

Abstract: To explore the role of protein kinase A (PKA) in regulating tau phosphorylation and spatial memory, we injected forskolin, an activator of PKA, at different concentrations into the rat brains. We found that forskolin at concentrations up to 80 μM enhanced tau phosphorylation and was associated with prominent spatial memory impairment. Higher concentrations of forskolin, up to 200 μM, were associated with reduced phosphorylation levels of tau and no memory deficits. Forskolin elevated cAMP and activated PKA in a dose-dependent manner. When infused at 200 μM, forskolin also resulted in the activation and overexpression of protein phosphatase-2A (PP-2A) and attenuated the okadaic acid-induced PP-2A inhibition. These data suggest that the upregulation of PKA by forskolin to a certain level may activate PP-2A but that

the latter can ameliorate the PKA-induced tau phosphorylation and memory impairment in the rats.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 631-642

Morphological Hippocampal Markers for Automated Detection of Alzheimer's Disease and Mild Cognitive Impairment Converters in Magnetic Resonance Images

Luca Ferrarini, Giovanni B. Frisoni, Michela Pievani, Johan H.C. Reiber, Rossana Ganzola, Julien Milles

Abstract: In this study, we investigated the use of hippocampal shape-based markers for automatic detection of Alzheimer's disease (AD) and converted mild cognitive impairment (MCI-c). Three-dimensional T1-weighted magnetic resonance images of 50 AD subjects, 50 age-matched controls, 15 MCI-c, and 15 MCI-non-converters (MCI-nc) were taken. Manual delineations of both hippocampi were obtained from normalized images. Fully automatic shape modeling was used to generate comparable meshes for both structures. Repeated permutation tests, run over a randomly sub-sampled training set (25 controls and 25 ADs), highlighted shape-based markers, mostly located in the CA1 sector, which consistently discriminated ADs and controls. Support vector machines (SVMs) were trained, using markers from either one or both hippocampi, to automatically classify control and AD subjects. Leave-1-out cross-validations over the remaining 25 ADs and 25 controls resulted in an optimal accuracy of 90% (sensitivity 92%), for markers in the left hippocampus. The same morphological markers were used to train SVMs for MCI-c versus MCI-nc classification: markers in the right hippocampus reached an accuracy (and sensitivity) of 80%. Due to the pattern recognition framework, our results statistically represent the expected performances of clinical set-ups, and compare favorably to analyses based on hippocampal volumes.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 643-659

Caffeine Reverses Cognitive Impairment and Decreases Brain Amyloid-ß Levels in Aged Alzheimer's Disease Mice

Gary W. Arendash, Takashi Mori, Chuanhai Cao, Malgorzata Mamcarz, Melissa Runfeldt, Alexander Dickson, Kavon Rezai-Zadeh, Jun Tan, Bruce A. Citron, Xiaoyang Lin, Valentina Echeverria, Huntington Potter

Abstract: We have recently shown that Alzheimer's disease (AD) transgenic mice given a moderate level of caffeine intake (the human equivalent of 5 cups of coffee per day) are protected from development of otherwise certain cognitive impairment and have decreased hippocampal amyloid-ß (Aß) levels due to suppression of both ß-secretase (BACE1) and presenilin 1 (PS1)/g-secretase expression. To determine if caffeine intake can have beneficial effects in "aged"

APPsw mice already demonstrating cognitive impairment, we administered caffeine in the drinking water of 18-19 month old APPsw mice that were impaired in working memory. At 4-5 weeks into caffeine treatment, those impaired transgenic mice given caffeine (Tg/Caff) exhibited vastly superior working memory compared to the continuing impairment of control transgenic mice. In addition, Tg/Caff mice had substantially reduced Aß deposition in hippocampus (down 40%) and entorhinal cortex (down 46%), as well as correlated decreases in brain soluble Aß levels. Mechanistically, evidence is provided that caffeine suppression of BACE1 involves the cRaf-1/NF?B pathway. We also determined that caffeine concentrations within human physiological range effectively reduce active and total glycogen synthase kinase 3 levels in SweAPP N2a cells. Even with pre-existing and substantial Aß burden, aged APPsw mice exhibited memory restoration and reversal of AD pathology, suggesting a treatment potential of caffeine in cases of established AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 661-680

Caffeine Suppresses Amyloid-ß Levels in Plasma and Brain of Alzheimer's Disease Transgenic Mice

Chuanhai Cao, John R. Cirrito, Xiaoyang Lin, Lilly Wang, Deborah K Verges, Alexander Dickson, Malgorzata Mamcarz, Chi Zhang, Takashi Mori, Gary W. Arendash, David M. Holtzman, Huntington Potter

Abstract: Recent epidemiologic studies suggest that caffeine may be protective against Alzheimer's disease (AD). Supportive of this premise, our previous studies have shown that moderate caffeine administration protects/restores cognitive function and suppresses brain amyloid-ß (Aß) production in AD transgenic mice. In the present study, we report that acute caffeine administration to both young adult and aged AD transgenic mice rapidly reduces Aß levels in both brain interstitial fluid and plasma without affecting Aß elimination. Long-term oral caffeine treatment to aged AD mice provided not only sustained reductions in plasma Aß, but also decreases in both soluble and deposited Aß in hippocampus and cortex. Irrespective of caffeine treatment, plasma Aß levels did not correlate with brain Aß levels or with cognitive performance in individual aged AD mice. Although higher plasma caffeine levels were strongly associated with lower plasma Aß1-40 levels in aged AD mice, plasma caffeine levels were also not linked to cognitive performance. Plasma caffeine and theophylline levels were tightly correlated, both being associated with reduced inflammatory cytokine levels in hippocampus. Our conclusion is two-fold: first, that both plasma and brain Aß levels are reduced by acute or chronic caffeine administration in several AD transgenic lines and ages, indicating a therapeutic value of caffeine against AD; and second, that plasma Aß levels are not an accurate index of brain Aß levels/deposition or cognitive performance in aged AD mice.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 681-697

Coffee "Breaks" Alzheimer's Disease

Massimo Tabaton

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 699-700

Response to Commentary

Gary Arendash

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 701-702

1a,25-dihydroxyvitamin D3 Interacts with Curcuminoids to Stimulate Amyloid-ß Clearance by Macrophages of Alzheimer's Disease Patients

Ava Masoumi, Ben Goldenson, Senait Ghirmai, Hripsime Avagyan, Justin Zaghi, Ken Abel, Xueying Zheng, Araceli Espinosa-Jeffrey, Michelle Mahanian, Phillip T. Liu, Martin Hewison, Matthew Mizwicki, John Cashman, Milan Fiala

Abstract: Patients with Alzheimer's disease (AD) suffer from brain amyloidosis related to defective clearance of amyloid-ß (Aß) by the innate immune system. To improve the innate immune system of AD patients, we studied immune stimulation of macrophages by 1a,25(OH)2-vitamin D3 (1,25D3) in combination with curcuminoids. AD patients' macrophages segregate into Type I (positively stimulated by curcuminoids regarding *MGAT-III* transcription) and Type II (not stimulated). In both Type I and Type II macrophages, 1,25D3 strongly stimulated Aß phagocytosis and clearance while protecting against apoptosis. Certain synthetic curcuminoids in combination with 1,25D3 had additive effects on phagocytosis in Type I but not Type II macrophages. In addition, we investigated the mechanisms of 1,25D3 and curcuminoids in macrophages. The 1,25D3 genomic antagonist analog MK inhibited 1,25D3 but not curcuminoid effects, suggesting that 1,25D3 acts through the genomic pathway. *In silico*, 1,25D3 showed preferential binding to the genomic pocket of the vitamin D receptor, whereas bisdemethoxycurcumin showed preference for the non-genomic pocket. 1,25D3 is a promising hormone for AD immunoprophylaxis because in Type I macrophages combined treatment with 1,25D3 and curcuminoids has additive effects, and in Type II macrophages 1,25D3 treatment is effective alone. Human macrophages are a new paradigm for testing immune therapies for AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 703-717

Prague: What Say You, Alois—Should It Be "Alzheimer-Fischer" Disease?

News Report from the Alzheimer Research Forum

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 3, July 2009, Pages 721-723

Amyloid-ß, Tau, and Dementia

Akihiko Takashima

Abstract: Alzheimer's disease (AD) is clinically characterized as a progressive dementia starting with memory dysfunction and characterized pathologically as neurodegeneration accompanied by deposition of amyloid-ß, neurofibrillary tangles, and neuronal loss. AD research has endeavored to explain the clinical symptoms of AD through pathological changes and to develop various therapies for AD. Fulfillment of these goals, however, remains on the horizon. In this article, I review the relationship between neuropathological changes that occur in the brain and clinical progression of AD, and propose a hypothesis that brain aging, characterized by neurofibrillary tangles in entorhinal cortex, is pre-requisite for development of AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 729-736

The Neurodegenerative Mitochondriopathies

Russell H. Swerdlow *(Communicated by Xiongwei Zhu)*

Abstract: Mitochondria are physically or functionally altered in many neurodegenerative diseases. This is the case for very rare neurodegenerative disorders as well as extremely common age-related ones such as Alzheimer's disease and Parkinson's disease. In some disorders very specific patterns of altered mitochondrial function or systemic mitochondrial dysfunction are demonstrable. Some disorders arise from mitochondrial DNA mutation, some from nuclear gene mutation, and for some the etiology is not definitively known. This review classifies neurodegenerative diseases using mitochondrial dysfunction as a unifying feature, and in doing so defines a group of disorders called the neurodegenerative mitochondriopathies. It discusses what mitochondrial abnormalities have been identified in various neurodegenerative diseases, what is currently known about the mitochondria-neurodegeneration nexus, and speculates on the significance of mitochondrial function in some disorders not classically thought of as mitochondriopathies.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Page 737-751

Immunoglobulin GM Genes as Functional Risk and Protective Factors for the Development of Alzheimer's Disease

Janardan P. Pandey

Abstract: There is growing body of evidence for the involvement of herpes simplex virus type 1 (HSV1) in the etiology of Alzheimer's disease (AD). HSV1 has evolved strategies for decreasing the efficacy of the host immune response and interfering with viral clearance. Based on their putative role as the modulators of these immune avoidance strategies, I hypothesize that immunoglobulin (Ig) GM genes—genetic markers of IgG heavy chains located on chromosome 14—are functional risk and protective factors for AD. Results from genome-wide association and linkage studies in support of this hypothesis, testable predictions, and possible therapeutic implications are discussed.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 753-756

Why Did Tarenflurbil Fail in Alzheimer's Disease?

Bruno P. Imbimbo

Abstract: There has been a lot of disappointment surrounding the recent failure of the largest ever study in patients with Alzheimer's disease (AD) with tarenflurbil, a compound believed to modulate the activity of ?-secretase, the pivotal enzyme that generates the amyloid-ß (Aß) peptide from the amyloid-ß protein precursor. What are the reasons for this setback after the previous apparently encouraging results in a Phase II study? A straightforward explanation of this failure is that the ?-secretase is not the right target for therapy or that, in general, blocking Aß does not produce clinical benefits in AD. If one still accepts a physiopathological role of Aß in AD, tarenflurbil could not be the right compound because of its weak pharmacological activity as an Aß1-42 lowering agent and its poor brain penetration. In addition, based on previous negative results with several anti-inflammatory drugs in AD, it is hypothesized that the residual anti-inflammatory activity of tarenflurbil may have a detrimental effect on disease progression.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Page 757-760

SPECT Predictors of Cognitive Decline and Alzheimer's Disease in Mild Cognitive Impairment

(Communicated by Patrizia Mecocci)

Abstract: Baseline brain single photon emission computed tomography (SPECT) was evaluated in eighty subjects with mild cognitive impairment (MCI) who were followed for a mean of about two years, when twelve patients developed Alzheimer's disease (AD), nineteen showed memory decline (D), and forty-three had normal cognition assessment (stable: S) (six drop-out). Volumetric Regions of Interest (VROI) analysis was performed in six associative cortical areas in each hemisphere. ANOVA for repeated measures showed significant effects for both the group (S, D, and AD; $p<0.004$) and VROI ($p<0.0001$) factors, with significant group*region interaction ($p<0.01$). At post-hoc comparison,

hippocampal VROIs values were lower in AD than in D and S, while parietal VROIs values were lower in D and AD than in S. These four VROI significantly correlated with verbal delayed recall score at follow-up visit.Receiver operating characteristic (ROC) curves for the mean hippocampal VROI value showed 0.81 sensitivity with 0.86 specificity in separation of S+D from AD ($p<0.0001$), and 0.69 sensitivity with 0.75 specificity in separation of S from D+AD ($p<0.0002$). ROC curves for the mean parietal VROI value showed 0.62 sensitivity with 0.70 specificity in separation of S from D+AD ($p<0.0002$). Baseline SPECT can support outcome prediction in subjects with MCI.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 761-772

Early Changes in Hippocampal Eph Receptors Precede the Onset of Memory Decline in Mouse Models of Alzheimer's Disease

Ana María Simón, Rakel López de Maturana, Ana Ricobaraza, Luis Escribano, Lucio Schiapparelli, Mar Cuadrado-Tejedor, Alberto Pérez-Mediavilla, Jesús Avila, Joaquín Del Río and Diana Frechilla

Abstract: Synapse loss occurs early in Alzheimer's disease (AD) and is considered the best pathological correlate of cognitive decline. Ephrins and Eph receptors are involved in regulation of excitatory neurotransmission and play a role in cytoskeleton remodeling. We asked whether alterations in Eph receptors could underlie cognitive impairment in an AD mouse model overexpressing human amyloid-ß protein precursor (hAßPP) with familial mutations (hAßPPswe-ind mice). We found that EphA4 and EphB2 receptors were reduced in the hippocampus before the development of impaired object recognition and spatial memory. Similar results were obtained in another line of transgenic AßPP mice, Tg2576. A reduction in Eph receptor levels was also found in postmortem hippocampal tissue from patients with incipient AD. At the time of onset of memory decline in hAßPPswe-ind mice, no change in surface expression of AMPA or NMDA receptor subunits was apparent, but we found changes in Eph-receptor downstream signaling, in particular a decrease in membrane-associated phosho-cofilin levels that may cause cytoskeletal changes and disrupted synaptic activity. Consistent with this finding, Eph receptor activation in cell culture increased phosho-cofilin levels. The results suggest that alterations in Eph receptors may play a role in synaptic dysfunction in the hippocampus leading to cognitive impairment in a model of AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 773-786

On the Diagnosis of CADASIL

Israel Ampuero, Javier Alegre-Abarrategui, Izaskun Rodal, Antonio España, Raquel Ros, José Luis Lopez Sendón, Eva García Galloway, Ángeles Cervelló, Ana Belén Caminero, Antxon Zabala, Elena Erro, Fernando Jarauta, Lorenzo

Morlán, Eva López-Valdés, Yolanda Aladro, Manuel Seijo, Guillermo García Rivas, David G. Muñoz and Justo García de Yébenes

Abstract: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic arteriopathy related to Notch3 mutations, is difficult to diagnosis. The goal of this study was to determine the value of clinical, immunohistochemical, and molecular techniques for the diagnosis of CADASIL. Clinical features and the immunohistochemical and molecular findings in 200 subjects with suspected CADASIL in whom 93 biopsies and 190 molecular studies are reported. Eighteen pathogenic mutations of the Notch3 gene, six of them previously unreported, were detected in 67 patients. The clinical features did not permit differentiation between CADASIL and CADASIL-like syndromes. The sensitivity and specificity of the skin biopsies was 97.7% and 56.5%, respectively, but increased to 100% and 81.5%, respectively, in cases with proven family history. In conclusion, a clinical diagnosis of CADASIL is difficult to determine and confirmatory techniques should be used judiciously.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 787-794

Albumin-Blunted Deleterious Effect of Amyloid-ß by Preventing the Internalization of the Peptide into Neurons

Lourdes Vega, Ángel A. Arroyo, Arantxa Tabernero and José M. Medina

Abstract: Amyloid-ß (Aß) is the main component of senile plaques, one of the hallmarks of Alzheimer's disease. Our results showed that Aß25-35 decreased neuronal viability while it increased generation of reactive oxygen species (ROS). Under these circumstances, albumin (BSA) prevented ROS production and neuronal death in a dose- and time-dependent manner. In addition, BSA partially prevented the decrease in the expression of GAP-43, MAP-2, and tubulin, and the phosphorylation of tau protein caused by Aß, suggesting that BSA protects against the loss of plasticity caused by the peptide. Our findings suggest that BSA exerts its protective effect by binding to Aß in an equimolecular way, which prevents heterodimer (Aß-BSA) entry into neurons. In fact, BSA prevented Aß internalization, as shown by confocal immunocytochemistry, suggesting that BSA causes its protective effect by sequestrating Aß, which cannot reach its intracellular targets. This is consistent with the idea that Aß must enter neurons to exert its deleterious effects.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 795-805

The Accuracy of Medicare Claims as an Epidemiological Tool: The Case of Dementia Revisited

Donald H. Taylor, Jr., Truls Østbye, Kenneth M. Langa, David Weir, Brenda L. Plassman

Abstract: Our study estimates the sensitivity and specificity of Medicare claims to identify clinically-diagnosed dementia, and documents how errors in dementia assessment affect dementia cost estimates. We compared Medicare claims from 1993-2005 to clinical dementia assessments carried out in 2001–2003 for the Aging Demographics and Memory Study (ADAMS) cohort (n= 758) of the Health and Retirement Study. The sensitivity and specificity of Medicare claims was 0.85 and 0.89 for dementia (0.64 and 0.95 for AD). Persons with dementia cost the Medicare program (in 2003) $7,135 more than controls (P<0.001) when using claims to identify dementia, compared to $5,684 more when using ADAMS (P<0.001). Using Medicare claims to identify dementia results in a 110% increase in costs for those with dementia as compared to a 70% increase when using ADAMS to identify disease, net of other variables. Persons with false positive Medicare claims notations of dementia were the most expensive group of subjects ($11,294 versus $4,065, for true negatives P<0.001). Medicare claims undercount the true prevalence of dementia, but there are both false positive and negative assessments of disease. The use of Medicare claims to identify dementia results in an overstatement of the increase in Medicare costs that are due to dementia.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 807-815

Mechanisms of Nitrosamine-Mediated Neurodegeneration: Potential Relevance to Sporadic Alzheimer's Disease

Suzanne M. de la Monte and Ming Tong *(Communicated by Paula Moreira)*

Abstract: Streptozotocin (STZ) is a nitrosamine-related compound that causes Alzheimer's disease (AD)-type neurodegeneration with cognitive impairment, brain insulin resistance, and brain insulin deficiency. Nitrosamines and STZ mediate their adverse effects by causing DNA damage, oxidative stress, lipid peroxidation, pro-inflammatory cytokine activation, and cell death, all of which occur in AD. We tested the hypothesis that exposure to N-nitrosodiethylamine (NDEA), which is widely present in processed/preserved foods, causes AD-type molecular and biochemical abnormalities in central nervous system (CNS) neurons. NDEA treatment of cultured post-mitotic rat CNS neurons (48 h) produced dose-dependent impairments in ATP production and mitochondrial function, and increased levels of 8-hydroxy-2'-deoxyguanosine, 4-hydroxy-2-nonenal, phospho-tau, amyloid-ß protein precursor-amyloid-ß (AßPP-Aß), and ubiquitin immunoreactivity. These effects were associated with decreased expression of insulin, insulin-like growth factor (IGF)-I, and IGF-II receptors, and choline acetyltransferase. Nitrosamine exposure causes neurodegeneration with a number of molecular and biochemical features of AD including impairments in energy metabolism, insulin/IGF signaling mechanisms, and acetylcholine homeostasis, together with increased levels of oxidative stress, DNA damage, and AßPP-Ab immunoreactivity. These results suggest that environmental exposures and food contaminants may play critical roles in the pathogenesis of sporadic AD.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 817-825

Nitrosamine Exposure Causes Insulin Resistance Diseases: Relevance to Type 2 Diabetes Mellitus, Non-Alcoholic Steatohepatitis, and Alzheimer's Disease

Ming Tong, Alexander Neusner, Lisa Longato, Margot Lawton, Jack R. Wands and Suzanne M. de la Monte *(Communicated by Paula Moreira)*

Abstract: The current epidemics of type 2 diabetes mellitus (T2DM), non-alcoholic steatohepatitis (NASH), and Alzheimer's disease (AD) all represent insulin-resistance diseases. Previous studies showed that streptozotocin, a nitrosamine-related compound, causes insulin resistance diseases including, T2DM, NASH, and AD-type neurodegeneration. We hypothesize that chronic human exposure to nitrosamine compounds, which are widely present in processed foods, contributes to the pathogenesis of T2DM, NASH, and AD. Long Evans rat pups were treated with N-nitrosodiethylamine (NDEA) by i.p. (x3) or i.c. (x1) injection, and 2-4 weeks later, they were evaluated for cognitive-motor dysfunction, insulin resistance, and neurodegeneration using behavioral, biochemical, and molecular approaches. NDEA treatment caused T2DM, NASH, deficits in motor function and spatial learning, and neurodegeneration characterized by insulin resistance and deficiency, lipid peroxidation, cell loss, increased levels of amyloid-ß protein precursor-amyloid-ß, phospho-tau, and ubiquitin immunoreactivities, and upregulated expression of pro-inflammatory cytokine and pro-ceramide genes, which together promote insulin resistance. In conclusion, environmental and food contaminant exposures to nitrosamines play critical roles in the pathogenesis of major insulin resistance diseases including T2DM, NASH, and AD. Improved detection and prevention of human exposures to nitrosamines will lead to earlier treatments and eventual quelling of these costly and devastating epidemics.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 827-844

Vascular Endothelial Barrier Dysfunction Mediated by Amyloid-ß Proteins

Enika Nagababu*, Peter V. Usatyuk*, Divya Enika, Viswanathan Natarajan, Joseph M. Rifkind *Equal contribution *(Communicated by Jack de la Torre)*

Abstract: Neuronal inflammation is very common in Alzheimer's disease (AD). This inflammation can be caused by infiltration of neutrophils across the blood brain barrier. Endothelial permeability changes are required for the infiltration of high molecular weight components to the brain. Deposition of toxic amyloid-ß (Aß) fibrils in the cerebral vasculature, as well as in brain neurons, has been implicated in the development of AD. This study investigates the effect of Aß fibrils on the permeability of the endothelium and the mechanism for the observed permeability changes. Aß1-40 and Aß1-42 fibrils, but not monomers, were found to increase permeability of bovine pulmonary arterial endothelial

cells in a dose- and time-dependent manner as detected by transendothelial electrical resistance. This increase in permeability is only partially (25%) inhibited by catalase and is not associated with an increase in cytosolic Ca+2 or tyrosine phosphorylation. These results indicate that hydrogen peroxide is not the primary mediator for the permeability changes. Treatment of cells with both amyloid fibrils resulted in stress fiber formation, disruption and aggregation of actin filaments, and cellular gap formation. The results of this study reveal that Aß increases the permeability of endothelium by inducing change in the cytoskeleton network.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 845-854

Education Attenuates the Effect of Medial Temporal Lobe Atrophy on Cognitive Function in Alzheimer's Disease: The MIRAGE Study

Robert Perneczky, Stefan Wagenpfeil, Kathryn L. Lunetta, L. Adrienne Cupples, Robert C. Green, Charles DeCarli, Lindsay A. Farrer, Alexander Kurz, for the MIRAGE Study Group *(Communicated by Kurt Jellinger)*

Abstract: Functional imaging and neuropathological studies suggest that individuals with higher education have better cognitive performance at the same level of brain pathology than less educated subjects. No *in vivo* studies are available that directly test how education modifies the effect of structural pathology on cognition in Alzheimer's disease (AD). The present study therefore aimed to measure this effect using data from a large multi-center study. 270 patients with AD underwent cognitive testing using the Mini Mental State Examination (MMSE), apolipoprotein E (APOE) genotyping, and cerebral magnetic resonance imaging. A linear regression analysis was used to examine the relation of medial temporal lobe atrophy (MTA), as a proxy of AD pathology, to MMSE score, adjusting for age, gender, APOE, cerebrovascular disease, ethnicity, education, and disease duration. An interaction term for MTA and education was introduced to test the hypothesis that education modifies the effect of MTA on cognition. There was a significant inverse association between MTA and cognition. Most interestingly, the interaction term between education and MTA was significant suggesting that education modifies the relation of MTA to cognition. At any level of pathology, cognition remained higher for better educated individuals.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 855-862

Total Prion Protein Levels in the Cerebrospinal Fluid are Reduced in Patients with Various Neurological Disorders

Felix Meyne, Sara Friederike Gloeckner, Barbara Ciesielczyk, Uta Heinemann, Anna Krasnianski, Bettina Meissner, Inga Zerr

Abstract: We performed a study on levels of the total prion protein (PrP) in humans affected by different neurological diseases and assessed the influence of several factors such as age, gender, and disease severity on the cerebrospinal fluid PrP levels. PrP-ELISA technique was used to analyze cerebrospinal fluid (CSF) samples. 293 CSF samples of patients with Creutzfeldt-Jakob-disease (CJD), Alzheimer's disease, dementia with Lewy-bodies, Parkinson's disease, multiple sclerosis, cerebral ischemia, generalized epileptic seizures, and meningitis and encephalitis in comparison to controls were analyzed. We found a significant reduction of CSF PrP levels in patients suffering from all neurodegenerative disorders analyzed. This group exhibited mean PrP values of 164 ng/ml while non-neurodegenerative disorder patients and healthy controls showed PrP levels of 208 ng/ml and 226 ng/ml, respectively. CSF levels correlated with disease severity in CJD, Alzheimer's disease, and dementia with Lewy-bodies. The finding of decreased PrP levels in the CSF of patients not only with CJD but also in other neurodegenerative disorders is intriguing. Age-, gender-, and genetic-specific factors might be involved in the PrPc regulation.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 863-873

Neuropathology-Based Risk Scoring for Dementia Diagnosis in the Elderly

Sebastien Haneuse, Eric Larson, Rod Walker, Thomas Montine, Joshua Sonnen
(Communicated by Sara Debanne)

Abstract: Current neuropathologic consensus criteria for diagnosis of dementia yield a classification of processes that likely contributed to dementia in that individual. While dementia diagnosis currently relies on clinical criteria, practicing neuropathologists and researchers might benefit from a simple, accurate risk scoring protocol for the neuropathologic diagnosis of dementia. Using 232 consecutive autopsies from the population-based Adult Changes in Thought study, we developed two logistic regression-based risk scoring systems; one solely using neuropathologic measures and a second additionally including demographic information. Inverse-probability weighting was used to adjust for inherent selection bias in autopsy-based studies of dementing illnesses. Both systems displayed high levels of predictive accuracy; bias-adjusted area-under-the-curve statistics were 0.78 (95% CI 0.71, 0.85) and 0.87 (95% CI 0.83, 0.92), indicating improved performance with the inclusion of demographic characteristics, specifically age and birth cohort information. Application of the combined neuropathlogy/demographic model yielded bias-adjusted sensitivity and specificity of 81% each. In contrast, application of NIA-Reagan criteria yielded sensitivity and specificity of 53% and 84%. Our proposed scoring systems provide neuropathologists with tools to make a diagnosis, and interpret their diagnosis in the light of known sensitivity and specificity estimates. Evaluation in independent samples will be important to verify our findings.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 875-885

BDNF Variants, Premorbid Educational Attainment, and Disease Characteristics in Alzheimer's Disease: An Exploratory Study

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Abstract: Brain-derived neurotrophic factor (BDNF) is a neurotrophin that promotes neuronal survival, growth, and differentiation. The role of BDNF in learning and memory suggests that it may also modulate the clinical course of Alzheimer's disease (AD). This study aimed to determine whether *BDNF* genetic variants are related to premorbid educational attainment, progression of cognitive and functional decline, and associated neuropsychiatric symptoms in AD patients. A sample of AD subjects (N=341) was genotyped for the *BDNF* polymorphisms: Val66Met, C270T, and G-712A. Subjects received tests of cognition and daily function at baseline and at multiple subsequent time points. They were also characterized for the frequency and severity of neuropsychiatric symptoms. There was a significant effect of Val66Met genotype on educational attainment (F=7.49, df=2, 329, P=.00066), with Met/Met homozygotes having significantly lower education than both the Val/Met and Val/Val groups. No association was observed between any *BDNF* polymorphism and measures of cognitive or functional decline. The T-allele of the C270T polymorphism was associated with a higher prevalence of neuropsychiatric symptoms and specifically with the presence of hallucinations. The effect of the Val66Met polymorphism on premorbid educational attainment is intriguing and should be verified in a larger sample.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 887-898

Temporal Relationship between Depressive Symptoms and Cognitive Impairment: The Italian Longitudinal Study on Aging

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Abstract: The temporal relationship between depression and cognitive decline has not been extensively investigated in prospective population-based studies, and most of these have only looked in one direction. We estimated the bidirectional temporal relationship between depressive symptoms and cognitive function in older subjects, excluding subjects with a clinical diagnosis of

dementia or mild cognitive impairment (MCI). In a total of 2,963 individuals from the Italian Longitudinal Study on Aging, depressive symptoms, global cognitive function, and episodic memory were measured. Dementia, Alzheimer's disease, vascular dementia, and MCI were classified using current clinical criteria. Depressive symptoms at baseline were associated with an accelerated global cognitive function decline and an accelerated rate of episodic memory delayed recall decline in a 3.5-year follow-up. Finally, an accelerated increase with time of depressive symptoms during the same follow-up period was not associated with global cognitive function and episodic memory (immediate and delayed recall). In older subjects non-cognitively impaired, depressive symptoms at baseline predicted change over time of global cognitive decline and episodic memory delayed recall. Global cognitive function and episodic memory at baseline were not associated with the course of depressive symptoms during the follow-up.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 899-911

Expression of a Truncated Human Tau Protein Induces Aqueous-Phase Free Radicals in a Rat Model of Tauopathy: Implications for Targeted Antioxidative Therapy

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Abstract: Oxidative stress has been implicated in the pathogenesis of many neurodegenerative diseases including Alzheimer's disease (AD). We investigated the effect of a truncated form of the human tau protein in the neurons of transgenic rats. Using electron paramagnetic resonance we observed significantly increased accumulation of ascorbyl free radicals in brains of transgenic animals (up to 1.5-fold increase; $P<0.01$). Examination of an *in vitro* model of cultured rat corticohippocampal neurons revealed that even relatively low level expression of human truncated tau protein (equal to 50% of endogenous tau) induced oxidative stress that resulted in increased depolarization of mitochondria (~1.2-fold above control, $P<0.01$) and increases in reactive oxygen species (~1.3-fold above control, $P<0.001$). We show that mitochondrial damage-associated oxidative stress is an early event in neurodegeneration. Furthermore, using two common antioxidants (vitamin C and E), we were able significantly eliminate tau-induced elevation of reactive oxygen species. Interestingly, vitamin C was found to be selective in the scavenging activity, suggesting that expression of truncated tau protein preferentially leads to increases in aqueous phase oxidants and free radicals such as hydrogen peroxide and hydroxyl and superoxide radicals. Our results suggest that antioxidant strategies designed to treat AD should focus on elimination of aqueous phase oxidants and free radicals.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 913-920

High Fruit and Vegetable Intake is Positively Correlated with Antioxidant Status and Cognitive Performance in Healthy Subjects

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Abstract: A higher daily intake of fruits and vegetables in healthy elderly is associated with an improved antioxidant status in comparison to subjects consuming diets poor in fruits and vegetables, but the impact on cognitive performance is unclear. Healthy community dwellers (45 to 102 years old, n=193) underwent cognitive testing and blood withdrawal for the measurement of antioxidant micronutrients and biomarkers of oxidative stress as well as administration of a food frequency questionnaire to assess the daily intake of fruits and vegetables (high intake HI, low intake LI). Ninety-four subjects of the HI group had significantly higher cognitive test scores, higher levels of carotenoids, a- and ?-tocopherol as well as lower levels of F2a isoprostanes than the 99 subjects of the LI group. Cognitive scores were directly correlated with blood levels of a-tocopherol and lycopene and negatively correlated with F2a isoprostanes and protein carbonyls. The results were independent of age, gender, body mass index, education, total cholesterol, LDL- and HDL-cholesterol, triglycerides, and albumin. Healthy subjects of any age with a high daily intake of fruits and vegetables have higher antioxidant levels, lower levels of biomarkers of oxidative stress, and better cognitive performance than healthy subjects of any age consuming low amounts of fruits and vegetables. Modification of nutritional habits aimed at increasing intake of fruits and vegetables should be encouraged to lower prevalence of cognitive impairment in later life.

JOURNAL OF ALZHEIMER'S DISEASE Volume 17, Number 4, August 2009, Pages 921-927

Interactions Between Glycogen Synthase Kinase 3ß, Protein Kinase B, and Protein Phosphatase 2A in Tau Phosphorylation in Mouse N2a Neuroblastoma Cells

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Abstract: In this study, we investigated how tau phosphorylation is regulated by protein kinase glycogen synthase kinase 3ß (GSK3ß), protein kinase B (PKB), and protein phosphatase 2A (PP2A) in mouse N2a neuroblastoma cells. Results showed that GSK3ß overexpression significantly increased PKB phosphorylation at the S473 site but not the T308 site. Neither GSK3ß nor PKB overexpression could reduce the PP2AC phosphorylation at the Y307 site. In contrast, either PKB or GSK3ß knockdown could increase PP2A phosphorylation at the Y307 site. PP2AC knockdown increased GSK3ß phosphorylation at the S9 site but not

at the Y216 site, and PKB phosphorylation at the T308 site but not at the S473 site. Tau phosphorylation at the S396 site was increased by GSK3ß or PKB overexpression. Tau phosphorylation at the S214 site was only induced by PKB overexpression in the study. While GSK3ß knockdown decreased tau phosphorylation at the S396 site, PKB knockdown increased tau phosphorylation at both the S396 and S214 sites. PP2AC knockdown decreased tau phosphorylation at the S396 and S214 sites. These findings suggested that tau phosphorylation at the S396 and S214 sites is differentially regulated by GSK3ß, PKB, and PP2A in N2a cells. The end phosphorylation state of tau is possibly caused by the synergic action of the three enzymes.

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