S31. Alzheimer's Disease: from molecular biology to clinical therapy

Chairs: F Müller-Spahn (CH), C Haass (D)

S31-1
EPIDEMIOLOGY AND RISK FACTORS FOR ALZHEIMER'S DISEASE

Albert Hofman. *Dept. of Epidemiology & Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands*

This presentation addresses the possibilities of prevention of Alzheimer's disease by prevention of vascular diseases and by treatment of risk factors for vascular diseases. The evidence for a causal link between vascular factors and Alzheimer's disease will be presented. As an example data obtained in the Rotterdam Study will be shown. Vascular factors to be discussed include blood pressure and smoking. Atherosclerosis and thrombogenesis will be addressed, as well as vascular diseases, including stroke and co-morbid vascular diseases, including diabetes mellitus and atrial fibrillation. For each of these factors the individual attributable risk (etiologic fraction) for Alzheimer's disease will be assessed. In addition, the overall population's attributable risk of vascular factors and diseases for Alzheimer's disease will be estimated. This presentation will, finally, address the potential for prevention of Alzheimer's disease and associated neurologic diseases by intervention of vascular factors and vascular disease.

S31-2
THE PATHOLOGICAL FUNCTION OF PRESENILIN AND βAPP IN ALZHEIMER'S DISEASE

Christian Haass. *Central Institute for Mental Health, Department of Molecular Biology, 68159 Mannheim, Germany*

Alzheimer's disease (AD) associated mutations have been identified in three genes. Point mutations within the βAPP gene are located close to the cleavage sites of the three secretases and influence their activity in a pathological manner by overproducing the highly neurotoxic 42 residue Aβ (Aβ42). Mutations in the Presenilin genes (PS-1 and PS-2) are the most common cause of early onset familial AD. PS proteins undergo proteolytic processing. The fragments generated occur as a heterodimer which binds to another unknown protein to form a 100–150 kDa complex. Besides this major processing pathway two additional proteolytic mechanisms involving the proteasome and caspases are utilized to degrade PS proteins in highly regulated manner. Presenilin mutations are known to cause the enhanced production of Aβ42 by a so far unknown mechanism. We will present data demonstrating that Aβ40 and Aβ42 are generated by two distinct cellular mechanisms. PS genes are homologous to the sel-12 gene of Caenorhabditis elegans which has been postulated to function in the facilitated signaling by lin-12 and gpl-1. We introduced the human PS-1 cDNA into sel-12 mutant animals and found that human PS-1 fully complements the sel-12 phenotype. Moreover, we demonstrate that two AD mutations, C410Y and A246E exhibit a strongly reduced rescuing activity.

S31-3
EARLY DIAGNOSIS AND BIOLOGICAL MARKERS IN ALZHEIMER'S DISEAE (AD) PATIENTS

C. Hock[1]. [1]*Department of Psychiatry (PUK), University of Basel, Wilhelm-Klein-Str. 27, CH-4025 Basel, Switzerland*

Several biochemical measures showed significant alterations in AD patients versus controls, such as cerebrospinal fluid (CSF) levels of amyloid precursor protein (APPs), amyloid β-peptide $(A\beta)_{1-42}$, and Tau protein, intracellular calcium level regulation by potassium channels in blood cells, and serum p97 levels. Some of these measures may change with progression of the disease (total Aβ, Tau protein). Although some of these measures were significantly altered in AD when mean levels were compared to levels in control groups, there was still substantial overlap so that these measures were not considered to be sensitive enough to serve as a biological marker. However, if the assumption is true that the specific histopathology precedes the clinical manifestation of AD for years, or even decades, then a significant portion of the age-matched controls might be preclinical AD patients. Therefore, considerable overlap of a potential marker between AD patients and *age-matched* controls does not definitely exclude that the measure might be a sensitive and specific tool. New research designs for a biological marker of sporadic AD have to be developed that include not only healthy age-matched controls, but cover the whole age-range of healthy subjects in order to differentiate age-effects from effects of a beginning AD pathology (sensitivity). Further control groups should include other neurodegenerative, neurological and psychiatric disorders (e.g. major depression) (specificity).

S31-4
ALZHEIMER'S DISEASE: POTENTIAL OF IMAGING AND SPECTROSCOPIC TECHNIQUES: PET, SPECT, DCS-MRI, MRI, MRS AND FMRI. AN OVERVIEW

J.-F.J. Nedelec*, N.R. Bolo, Y. Hodé, J.-P. Macher. *FORENAP, MR Centre, Centre Hospitalier, Rouffach 68250, France*

Reduced Cerebral blood flow, Neural loss, Brain atrophies, abnormalities of membrane phospholipds and metabolic variations are involved in the pathophysiology of Alzheimer's disease (AD). Imaging Techniques such as PET SPECT use radioactive water to evaluate deficits in regional cerebral blood flow (rCBF). An alternative can be Dynamic Susceptibility Contrast MR Imaging which uses contrast agents instead of radionuclides to evaluate rCBF. MRI has been largely applied to determine the extent of global and regional brain atrophy. Magnetic Resonance Spectroscopy (Proton-, Phosphorus-, Carbon-MRS) provides, in a noninvasive way, insights into in vivo brain metabolism for a number of metabolites. Proton MRS (1H) provides information mainly on N-acetyl-containing molecules with N-acetylaspartate as the major contributor, choline containing compounds (glycerophosphocholine and phosphocholine), creatine and phosphocreatine, inositol, glucose, glutamate and glutamine. Phosphorus-MRS provides information on phospholipid metabolism (phosphomonoesters and phosphodiseters) and on energy metabolism (ATP, phosphocreatine, inorganic phosphate). Carbon-MRS, with specifically 13C labelled precursor such as glucose, highlights the Krebs Cycle trunover. Significant but heterogeneous metabolic variations are reported by different groups worldwide in patients with mild to moderate AD. Based on our experience these data will be presented and discussed. These studies can also be correlated with neurocognitive rates. FMRI, which provides activation maps reflecting significant regional cere-

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bral blood flow variations occurring during neurocognitive tasks can also be performed with AD patients.

S31-5

CHOLINERGIC TREATMENT STRATEGIES IN ALZHEIMER'S DISEASE

E. Giacobini. *Department of Geriatrics, Institutions Universitaires de Geneve, Route de Mon-Idee, 1226 Thonex-Geneva, Switzerland*

Two major pharmacological principles are utilized in cholinomimetic therapy of Alzheimer Disease (AD): the first is direct stimulation of nicotinic or muscarinic receptors with selective agonists, the second is a reduction of acetylcholine hydrolysis by means of cholinesterase inhibition. The cognitive and behavioral effects achieved with the two approaches are different and therefore one can envision either combination or alternative use of these drugs. Cholinesterase inhibitors (ChEI) have been mostly used. The results of therapy with ChEI pose several questions:

1. Do all ChEI act in the same way? What makes the difference in clinical efficacy? 2. Is selectivity for AChE important? 3. Is there a "brain selective" ChEI? 4. Do ChEI produce tolerance? 5. Is there an interaction of cholinergic and non-cholinergic effects?. 6. Is there an effect of cholinergic stimulation on APP release which could be of therapeutic relevance?

If basic principles of pharmacology are applied to the results obtained in the patient one can expect to improve magnitude and duration of effects.

(1) Giacobini. E. Jap. J. Pharmacol. 1997.74. 225–241

S31-6

ANTI-INFLAMMATORY AND ANTIOXIDANT THERAPEUTIC STRATEGIES IN AD

Hannes B. Stähelin. *Geriatric University Clinic University Hospital CH-4031 Basel, Switzerland*

Accumulating evidence has implicated free radical production and resultant oxidative damage as a major contributing factor in brain aging and cognitive decline. Aβ-induced NO production by microglial cells is one mechanism of the neuronal death in Alzheimer's disease (AD). There is also evidence for cytochrome oxidase dysfunction with oxidative stress and damage in the brains of patients with AD. One additional mechanism of oxidative damage is the nitration of tyrosine residues in proteins e.g. in neurofibrillary tangles of AD but not in controls. Inflammatory processes contribute to the aetiopathology of AD. Interleukin-6 (IL-6), a proinflammatory cytokine, is found in the brains of AD patients, but not in brains of normal control persons. These results support the hypothesis that antioxidant or antiinflammatory compounds could prevent or slow down the course of AD. Several epidemiological studies are in support of a protective effect of antioxidants and anti-inflammatory compounds. In the Prospective Basel Study in people aged 65 and older, higher ascorbic acid and beta-carotene plasma level are associated with better memory performance. Similarly in the EURONUT-Seneca study higher plasma levels of certain vitamins and carotenoids appear to be associated with lower risk of developing dementia. Studies in experimental animals are scarce but in one study chronic PBN (an antioxidant) treatment improved the cognitive performance of aged rats in several tasks. In humans In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alpha-tocopherol slows the progression of disease. Similarly for anti-inflammatory compounds the onset of AD was inversely associated with prior use of corticosteroids or ACTH. Similar but weaker trends were present for history of arthritis or for prior daily use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin. A history of arthritis resulted in a low risk of AD (OR = 0.54; 95% CI, 0.36 to 0.81), as did a history of use of NSAID. In one study the relative risk (RR) for AD was of 0.38 (0.15 to 0.95) when comparing NSAID users (n = 365) to NSAID non-users (n = 5,893). These results not only provide a direct linkage between free radicals/oxidative damage and cognitive performance in old age, but also suggest that synthetic brain antioxidants could be developed to treat or prevent age-associated cognitive impairment and Alzheimer's disease. The results of experimental and epidemiological studies consistently show the close interplay between oxidative stress and inflammatory mechanism in AD. The results indicate the important role played by antioxidants and anti-inflammatory agents in brain aging and may have implications for prevention of progressive cognitive impairments.

S32. Social phobia: developmental risks and impairments

Chairs: JP Lepine (F), H-U Wittchen (D)

S32-1

PREVALENCE, INCIDENCE AND SYNDROME STABILITY OF GENERALIZED AND NON-GENERALIZED SOCIAL PHOBIA IN ADOLESCENTS AND ADULTS

H.U. Wittchen[1] *, J.P. Lépine[2]. [1]*Max Planck Institute of Psychiatry, Clinical Psychology and Epidemiology Unit, Munich, Germany* [2]*Hôpital Fernand Widal, Paris, France*

It is frequently assumed that social phobia is a persistent chronic disorder starting early in life with more or less slowly accumulating disabilities and impairments. In a more recent prospective longitudinal epidemiological sample of 3,021 subjects, we recently investigated prevalence and incidence of generalized and non-generalized social phobia. The baseline findings suggest a lifetime cumulative incidence of about 7%, with women having slightly higher prevalence estimates than men. The 1-year follow-up investigation showed a relatively high incidence. At the same time partial or full remission of previous social phobia was quite high as well, suggesting overall a low stability of social phobia among adolescents. The paper will discuss risk factors for first onset as well as predictors for remission and non-remission and suggests by presenting differential profiles of associated features and complications that generalized social phobia is of primary clinical importance, whereas non-generalized phobia might be a transient disorder with no substantial longterm risks.

S32-2

PSYCHOSOCIAL IMPAIRMENTS AND QUALITY OF LIFE IN SOCIAL PHOBIA

H. Katschnig. *Department of Psychiatry, University of Vienna, Austria*

It seems that social phobia is one of the most neglected psychiatric disorders, both in terms of its prevalence and the amount of suffering and disability it creates. Recent estimates from epidemiological surveys suggested that the life time prevalence may be as high as 13.3%, if intensive questioning is carried out. Superficial