MEETING REPORT

The Third International Conference on Neurodegeneration in Alzheimer’s Disease, Parkinson’s Disease, and Acute Stroke, Princeton, NJ, July 26 – 27, 1999

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This conference was organized by the Strategic Research Institute, New York, NY and attended by approximately 120 scientists, mostly from the pharmaceutical industry. The conference was held at the Hyatt Hotel in Princeton, NJ and chaired by A. L. Sabb (Wyeth-Ayerst Laboratories, Princeton, NJ), R. Tanzi (Harvard Univ. and Massachusetts General Hospital, Boston, MA) and J. P. Steiner (Guilford Pharmaceuticals, Baltimore, MD). It consisted of three sessions dealing with basic aspects of neurodegeneration and experimental, as well as clinical studies of neuroprotective drugs. Eighteen 35-minute lectures and three posters were presented. Most speakers represented laboratories that are actively involved in research on neurodegeneration and/or development of new neuroprotective drugs.

Approaches to the therapy of Alzheimer’s disease (AD) were extensively discussed at the conference. Selective inhibitors of Aβ protein production (γ-secretase inhibitors) were discovered at Bristol-Myers Squibb, but their structures were not yet released. Some general aspects of their program were discussed by P. Molinoff. D. Falb (Praecis Pharmaceuticals, Boston, MA) reported that small fractions of Aβ protein inhibit its aggregation in vitro. K. Duff (Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY) reviewed murine models of neurodegenerative diseases. PS/APP mice are behaviorally impaired and develop cognitive deficits. Crossing of two strains (PSIMI46v and TG 2576) resulted in mice with an early (at the age of 3 months) development of amyloidosis.

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S. G. Younkin (Mayo Clinic, Jacksonville, FL) discussed the diagnostic and prognostic value as well as limitations of Aβ protein measurements in patients with late-onset AD. In at least 50% of these patients, the elevation of Aβ₄₂ is genetically determined. Mutations of APP, PS₁, and PS₂ genes lead to elevation of Aβ₄₂ in plasma and cerebrospinal fluid. Aβ₄₂ and Aβ₄₀ levels also increase with age. In patients with late-onset AD, plasma Aβ₄₂ is significantly increased but tends to decline with the progression of the disease. This decline may be associated with the increased deposition of the protein. Currently available techniques do not measure all Aβ proteins.

R. Tanzi and his associates (Massachusetts General Hospital, Boston, MA) are interested in presenilins that may function as γ-secretases. Tanzi’s associate, T.-W. Kim, observed that an increased expression of mutant presenilins is associated with a disturbance of calcium homeostasis and lowering of intracellular calcium due to inhibition of capacitance-controlled calcium entry. The channels controlling this type of calcium entry are not voltage dependent and are conceivable targets for novel drugs.

J. Shen (Harvard Univ. and Brigham and Women’s Hospital, Boston, MA) is developing transgenic mice that express mutated human α-synuclein gene. These mice are expected to serve as models of Parkinson’s disease. Eight mutations of this gene were identified. The mutated gene leads to formation of Lewy bodies and nigral degeneration.

D. Schenk (Elan Pharmaceuticals, Menlo Park, CA) described a transgenic mouse model (PD-APP mouse) that overexpresses the V717F form of APP and is being used in the development of the Alzheimer’s vaccine. In addition to amyloid deposits these mice exhibit neuronal loss and some cognitive decline. Vaccination with Aβ₄₂ (AN 1792) not only prevents but also reduces amyloid deposits. The mechanism of action is not clear. Only a tiny fraction of it enters brain. It is conceivable that the mechanism of action involves stimulation of phagocytosis. Aβ₄₀ produces similar effects.

J. P. Steiner (Guilford Pharmaceuticals, Baltimore, MD) discussed neuroimmunophils and the development of GPI 1046 [3-(3-pyridyl)-1-propyl(2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate]. The neuroprotective activity of neuroimmunophilin ligands appears to be independent of their immunosuppressant activity. The goal of the program at Guilford is to separate the two activities and to develop a neuroprotective compound free of immunosuppressant activity.

At 10 mg/kg, s.c., once daily for 1 week or 1 month, GPI 1046 promoted recovery of rats with 6-hydroxydopamine (6-OHDA)-induced lesions. It restored dopamine transport activity in striatum and had antiparkinsonian activity in animal models. Other investigators (Harper et al. Neuroscience 1999;88:257–267) reported, however, that GPI 1046 has only marginal effect on neurite outgrowth and Steiner stated that it has undesirable pharmacokinetic characteristics. GPI 1046 is not a clinical candidate.

B. S. Slusher (Guilford Pharmaceuticals, Baltimore, MD) discussed inhibition of N-acetylated alpha-linked acidic dipeptidase (NAALADase) as an approach to neuroprotection. This enzyme forms glutamate from N-acetyl-aspartyl-glutamate (NAAG). She used dissociated cortical neuronal cultures made ischemic with metabolic inhibitors and studied the effects of NAALADase inhibitors on the release of lactic dehydrogenase (LDH). The leading NAALADase inhibitor is GPI 5000: it reduces brain injury in the MCAO model, is neuroprotective in the spinal cord injury model, and reverses hyperalgesia in rats subjected to sciatic nerve constriction. It also enhances nerve conduction in streptozotocin diabetic rats.
The role of nuclear factor kB (Nf-kB) in drug-induced neuroprotection was the subject of the presentation by S. P. Little (Lilly Research Laboratories, Indianapolis, IN). Most of the material she presented was previously published (Stroke 1998;29:677–682 and Brain Res 1997;776:222–229). It appears that the transient activation of Nf-kB may induce the formation of protective factors in neurons, whereas persistent activation of NF-kB in hippocampal neurons leads to neuronal death in the CA1 area. The antioxidant LY 231617 [2,6-bis(1,1-dimethylethyl)-4-[[(1-ethyl)amino)methyl]phenol hydrochloride] at 50 mg/kg p.o. or 1 mg/kg i.v. bolus followed by infusion at 1 to 5 mg/kg/h, had neuroprotective activity and prevented Nf-kB activation at 72 hours after ischemia.

W. M. Welch (Pfizer Inc., Groton, CT) spoke about the discovery of potent and selective noncompetitive AMPA antagonists. The drugs were screened using cell cultures and calcium signalling. The first lead compound among the quinazolinones was CP-15,396. Attempts to optimize its activity led to mixed results. Another lead was discovered in a series of aminoaalkyl derivatives, CP-392,110. One of its atropoisomers, CP-462,022, was highly potent; its IC<sub>50</sub> in calcium uptake assay was 36 nM. It antagonized pentylentetrazole-induced convulsions in mice with an ED<sub>50</sub> of 4 mg/kg. The other atropoisomer was considerably less potent.

Cholinergic approaches to cognition activation were the subject of three presentations. J.-M. Vernier (SIBIA, La Jolla, CA) discussed nicotinic receptor activators. In their search for nicotinic agonists, they are using cell lines with transfected human nicotinic receptors and measure calcium entry using Fura-2. They search for subunit-selective compounds. One of the first leads was SIB-1469. Another lead was SIB-1553A: it is receptor-subtype selective (α<sub>4</sub>β<sub>4</sub>) and enhances hippocampal acetylcholine release. In rats with a cholinergic deficit, SIB-1553A reverses spatial working memory deficits. In mice it reverses scopolamine-induced memory deficits. Unlike nicotine, SIB-1553A reverses working and reference memory deficits in lesioned animals. The therapeutic ratio of...
SIB-1553A is 30 times that of nicotine. Phase I studies have been completed. The drug is well tolerated, enters the brain, and appears to improve attention and short-term memory in normal individuals.

A. L. Sabb (Wyeth-Ayerst Laboratories, Princeton, NJ) discussed the discovery and development of WAY-132983, a selective muscarinic M₁ agonist. This drug enhances cognition in animals, has a large therapeutic ratio (dose producing cognitive effect/dose causing side effects) and reduces β amyloid production in vitro. The compound appeared promising in the laboratory and had no serious toxicological problems.

J. J. Buccafusco (Medical College of Georgia, Augusta, GA) discussed the use of cholinergic activators to enhance memory and performance in aging primates. The drugs are evaluated in Delayed Match-to-Sample Task (DMTS) in 20- to 30-year-old primates. Thirty animals can be used daily for testing. Buccafusco tested muscarinic as well as nicotinic receptor agonists. He obtained beneficial results with ABT-418, SIB-1553A, and 3-(2,4-dimethoxybenzylidene)-anabaseine dihydrochloride (GTS-21). Surprisingly he obtained positive results with the nicotinic antagonist mecamylamine. He suggested that it may act as a partial agonist. The efficacy of nicotinic receptor agonists in acute phase of DMTS performance differs from that in the protracted phase. ABT-418 is more effective in the acute, while GTS-21 is more effective in the protracted phase. He also mentioned that the cholinesterase inhibitor [1-(methyl-3-(N,N-dimethylcarbamoyloxy)-2-pyridylmethylene)-4-(4-phenyl) diazinecarboxamide chloride], MHP–133 was effective in his test.

R. Bhat (Zeneca Pharmaceuticals, Wilmington, DE) proposed that glycogen synthase kinase 3β (GSK 3β) may represent another target for drugs to treat AD. It is a key enzyme in glycogen synthesis and is highly expressed in brain. It is a member of a multiprotein complex that is linked to neurodegeneration, τ phosphorylation, and the function of presenilins. The enzyme is also involved in apoptosis and is known to regulate β-catenin levels. In AD β-catenin levels are reduced. Inhibition of GSK 3β pathway promotes cell survival for up to 24 h after nerve growth factor withdrawal. Lithium, valproate, and insulin mimetics inhibit GSK 3β. In the middle cerebral artery occlusion model (MCAO) GSK 3β phosphorylation is increased.
A. J. Glasky (Neotherapeutics, Irvine, CA) reviewed the current status of AIT-082 (Neotrophin, leteprinim). This compound is now in phase II studies in patients with AD. There were no serious adverse effects at daily doses up to 500 mg. Glasky reported improvement in memory and behavioral function, although the number of patients was too small to show any statistical significance.

G. E. Ringheim (Hoechst Marion Roussel, Bridgewater, NJ) reviewed the pharmacological properties and the current status of propentofylline. According to him, the major mechanism of propentofylline action is inhibition of microglial functions. It also inhibits adenosine reuptake and phosphodiesterases I, II, and IV. Propentofylline inhibits microglial proliferation and their transformation into macrophages. It also inhibits the release of free oxygen radicals and cytokines (TNFα, IL-1β). It improves learning and memory in rats with forebrain lesions as well as in spontaneously hypertensive rats. The clinical studies suggest that propentofylline can slow the progression of dementia. The clinical data were, however, not sufficiently convincing to gain approval in any country. Further clinical studies are ongoing and a revised NDA is being prepared.

R. F. Mervis (Neuro-Cognitive Research Laboratories, Columbus, OH) evaluated patterns of dendritic changes in the hippocampus of PD-APP mice for Elan Pharmaceuticals and concluded that amyloid deposition contributes to neuronal damage and supports the use of these animals as a model of AD.