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MEETING REPORT

NEURODEGENERATIVE DISORDERS: AN UPDATE

HIGHLIGHTS OF THE 23RD BIENNIAL MEETING OF ISN-ESN 2011, AUGUST 28-SEPTEMBER 1, 2011, ATHENS, GREECE

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SUMMARY

The 23rd Biennial Meeting of the ISN-ESN was held in Athens, Greece, from August 28th to September 1st, 2011. The meeting was organized by the International Society for Neurochemistry (ISN) jointly with the European Society for Neurochemistry (ESN). ISN-ESN's main mission is to facilitate the worldwide advancement of neurochemistry and related neuroscience, as well as promote cellular and molecular neuroscience. The present brief report highlights various cellular and molecular aspects discussed in the areas of neurodegenerative disorders. The report provides a comprehensive outlook and addresses some of the cellular and molecular aspects, recent developments and challenges in the field of neurodegenerative disorders.

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INTRODUCTION

The 23rd Biennial Meeting of the ISN-ESN was held at Megaron Athens International Conference Centre, Athens, Greece, from August 28th to September 1st, 2011. The meeting was organized jointly with the European Society for Neurochemistry (ESN). ISN-ESN's main mission is to facilitate the worldwide advancement of neurochemistry and related neuroscience disciplines, as well as to promote cellular and molecular neuroscience among neurochemists. It also serves as a platform to discuss the advancements of neuroscience made in the areas of neurodegenerative research involving Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), etc. This report briefly addresses cellular and molecular aspects and recent developments, and highlights the gap in the current research on neurodegenerative disorders.

The meeting was opened by a speech by Dr. Mangoura, Chair of the Local Organizing Committee, and Dr. Shirao, Chair of the Program Committee. Their speech highlighted the overview of the entire meeting program, which consisted of symposia, workshops, young investigator colloquia, young scientist lectures and multiple poster sessions ranging from genetic architecture to brain circuits and from synaptic plasticity to neuropsychological diseases. A total of 2,300 scientists from 65 countries attended the meeting. The present reports highlights the key issues discussed in the areas of neurodegenerative disorders, particularly AD, PD and HD.

EPIGENETICS AND HISTONE DEACETYLASES IN NEURODEGENERATIVE DISEASE

Neurodegenerative diseases, such as polyglutamine-related diseases, amyotrophic lateral sclerosis and AD, are accompanied by

transcriptional dysfunctions, leading to neuronal death. It is becoming more evident that the chromatin acetylation status is impaired during the lifetime of neurons by a common mechanism related to the loss of function of histone acetyltransferase (HAT) activity. Notably, the HAT termed CREB-binding protein (CBP) has been shown to display neuroprotective functions (1). Histone deacetylases (HDACs) are a family of proteins that play an important role in regulating transcription, as well as several cellular processes (2). Several HATs have now been shown to participate in basic but vital neuronal functions. Dr. Boutillier of the Centre National de Recherches Scientifiques (CNRS) nicely elaborated the status of acetylation during neurodegenerative processes and memory functions, and suggested the use of epigenetic modulators in AD. Furthermore, Dr. Boutillier's data pointed out the use of molecules inducing a histone hyperacetylated state as therapeutic tools, potentially able to increase memory-related transcription programs and reactivate synaptic plasticity. Dr. D'Mello of the University of Texas at Dallas described the potential of HDAC inhibitors for neurodegeneration. Administration of pharmacological inhibitors prevents neuronal loss and improves behavioral outcome in a variety of tissue culture and in vivo models of neurodegenerative disease. Furthermore, HDAC inhibitors block the activities of all HDACs efficiently, as well as identifying the HDAC(s) responsible for neurodegeneration. Dr. D'Mello further provided hope that HDAC inhibitors could be developed in the near future. He also reviewed the role of individual HDAC proteins in the regulation of neuronal survival and death, and described HDAC class members, including HD9, HD4 and HD7, which protect neurons from death. It was further highlighted that pharmacological inhibitors designed to specifically target neurotoxic HDACs may be of great value in the treatment of neurodegenerative diseases. In addition, it appears essential to envisage direct stimulation of the acetyltransferase function as a new therapeutic tool in neurodegenerative disease.

Epigenetics at the level of protein post-translation modifications has emerged as a critical modifier of numerous cellular processes, including transcriptional control. Protein modification has also taken on a growing importance in human disease. HD is a devastating autosomal dominant disease that strikes in mid-life, for which no disease-modifying treatments are available. It is caused by a polyglutamine repeat tract within the huntingtin (*HTT*) protein encoded by a CAG repeat within the *HD* gene. Furthermore, Dr. Thompson of the University of California, Irvine, described the basic mechanism for exploiting drug targets for the therapeutic treatment of HD. He began with data showing that huntingtin interacts with key transcriptional regulatory proteins and inhibits in vitro protein acetylation, and that the presence of the mutation causes reproducible and early transcriptional dysregulation. Dr. Thompson explored the therapeutic potential of HDAC inhibitors and suggested great promise in multiple models of polyglutamine diseases. He further extended his presentation to highlight the role of protein modification of the huntingtin protein itself, and SUMOylation, acetylation and phosphorylation have all been suggested as critical modifications that contribute to subcellular localization, transcriptional regulation and protein turnover. Furthermore, epigenetic mechanisms underlying gene expression changes have been shown to specifically modulate histone methyltransferases in the brain.

PD GENE, PROTEIN DEGRADATION AND MITOCHONDRIAL QUALITY CONTROL

Accumulation of aggregate α-synuclein is a characteristic feature of PD and other α-synucleinopathies. Cellular accumulation of misfolded proteins is often associated with activation of the endoplasmic reticulum (ER) stress pathway. Dr. Lee of Johns Hopkins University in Baltimore showed that transgenic (Tg) mice overexpressing mutant human (Hu) α-synuclein exhibit ER stress with onset of neurodegeneration. A53T Hu α-synuclein Tg mice with the disease exhibit increased levels of ER chaperones (BiP/GRP-78, GRP-94 and PDI) and activation of the ER stress-related transcription factors ATF-6 and XBP-1. However, the induction of ER chaperones occurred in the absence of the expected increase in the phosphorylation of eIF-2A. This abnormal ER stress response in A53T Hu α-synuclein Tg mice was associated with increased levels of cleaved caspase-12, an ER stress-related caspase in mice, and increased activation of caspase-9, a downstream target of cleaved caspase-12. The above signs of an unfolded protein response coincided with the disease and were not seen in areas that were not affected by α-synucleinopathy. Thus, ER stress and activation of caspase-12 and caspase-9 are selectively associated with a synucleinopathy. Furthermore, Dr. Lee hypothesized that accumulation of misfolded/aggregated α-synuclein in the ER of A53T Hu α-synuclein Tg mice causes ER stress, an abnormal unfolded protein response and contributes to neurodegeneration.

Dr. Fon of the Montreal Neurological Institute at McGill University discussed E3 ubiquitin-protein ligase parkin-mediated ubiquitination and regulation of synaptic proteins. Mutation of the *PARK2* gene causes an autosomal recessive juvenile-onset form of PD that accounts for a large fraction of familial cases. Ubiquitination targets substrates to different cellular pathways depending on the length and architecture of the ubiquitin chain. Dr. Fon showed that E3 ubiquitin-protein ligase parkin regulates cell-surface receptor trafficking and kinase signaling pathways through monoubiquitination of adaptor proteins such as epidermal growth factor receptor substrate 15 (protein Eps15) and PRKCA-binding protein (*PICK1*). Furthermore, Dr. Fon highlighted that his group explored the role of the *N*-terminal E3 ubiquitin-protein ligase parkin-like domain as a versatile interaction module, connecting E3 ubiquitin-protein ligase parkin to proteins involved in ubiquitination and trafficking. Dr. Fon's group identified the SH3 domain within proteins such as endophilin-A as a novel E3 ubiquitin-protein ligase parkin-interacting module.

The etiology of PD remains unknown, although clinical and experimental evidence implicates the involvement of mitochondrial dysfunction and oxidative stress. Mutations in the mitochondrial serine/threonine-protein kinase PINK1 cause recessive inherited early-onset PD. The enzyme's role in apoptosis, abnormal mitochondrial morphology, impaired dopamine release and motor deficits has been well documented. Dr. Morais of the Centre for Human Genetics, Katholieke Universiteit Leuven, showed that PINK1 deficiency impacts on the function of complex I of the mitochondrial respiratory chain, resulting in mitochondrial depolarization and increased sensitivity to apoptotic stress in mammalian cells and tissues. Furthermore, Dr. Morais explained that deficiency of PINK1 affects synaptic function in *Drosophila* neurons as a reserve pool of synaptic

vesicles is not mobilized during rapid stimulation. In addition, the work provides a clear proof of concept that complex I deficiency underlies the pathogenesis of hereditary forms of PD.

Alterations in autophagy regulation have been implicated in neurodegeneration associated with PD and related diseases, including familial parkinsonism caused by mutations in the *PINK1* gene and in leucine-rich repeat serine/threonine-protein kinase 2 (*LRRK2*). Loss of endogenous *PINK1* function adversely affects mitochondrial function and structure, promoting selective mitophagy. Dr. Chu of the University of Pittsburgh School of Medicine discussed *PINK1* and autophagy in mitochondrial and neuritic quality control (3). Dr. Chu explained that overexpression of *PINK1* reverses mitochondrial pathology and autophagic neurite degeneration. *PINK1* regulates mitochondrial quality control and neurite/synaptic health through multiple mechanisms.

NANOTECHNOLOGY, NANOMEDICINE AND BIOMEDICAL TARGETS IN NEUROGENERATIVE DISEASES WORKSHOP

AD is a neurodegenerative disorder characterized by progressive loss of cognitive function and the formation of extracellular β-amyloid (Aβ) peptide aggregates. Despite all scientific efforts, no adequate treatment is currently available. Dr. Andrieux of the Université Paris-Sud highlighted the role of nanoparticles in AD. Dr. Andrieux demonstrated the high stability as well as the ability to reach the CNS of poly(methoxypolyethyleneglycol cyanoacrylate-co-*n*-hexadecyl cyanoacrylate) (PEG-PHDCA) nanoparticles. Dr. Whiteley of the Department of Biochemistry, Rhodes University, South Africa, showed that platinum, gold and silver nanoparticles interact strongly and inhibit nitric oxide synthase, superoxide dismutase (SOD) and acetylcholinesterase (AChE), which are associated with the metabolism of arginine (4). Arginine accumulates in AD patients, indicating a metabolic disturbance of enzymes that metabolize this amino acid, while SOD is involved in oxidative stress leading to the formation of reactive oxygen species (ROS) such as peroxynitrite. AChE activity has also been shown to be influenced by arginine. However, Dr. Ali of the Division of Neurotoxicology, National Center for Toxicological Research (NCTR), explored the role of microvessel endothelial cells that comprise the blood–brain barrier in brain inflammation and neurotoxicity associated with colloidal metallic nanoparticle-like silver, gold and copper. Dr. Ali highlighted the interactions of nanoparticles with brain microvessel endothelial cells, which produce a cascade of proinflammatory mediators involved in brain inflammation and neurotoxicity. The increasing use of nanomaterials is likely to result in their release into the environment. Dr. Chen of the National Centre for Nanoscience and Technology, Beijing, China, highlighted the analytical methods to detect and characterize nanomaterials in the brain and the assessment of central nervous system (CNS) exposure to nanoparticles. Dr. Chen has also shown that intranasally instilled copper nanoparticles could be transported into the murine CNS and accumulate in the brain.

Dr. Philbert from the University of Michigan at Ann Arbor discussed polymer nanoparticles for biological sensing and brain tumor therapy (5). PEBBLE nanoplatforms are self-assembled, fluorescent probes with conserved cores that contain multiple elements for the selective localization and measurement of single analytes in a living cell. Biocompatible matrices are hydrophobic or hydrophilic and include plasticized polyvinyl chloride, decyl methacrylate, polyacrylamide or sol-gel with diameters of 20% AD 200 nm. Elements that may be embedded within the copolymer matrix include a fluorescent sensing molecule, enzyme sensitizers and antioxidant dendrimeric antenna supermolecules. These possible combinations provide a wide variety of probe functions in a range of biological specimens. PEBBLE and other related nanoscale optical sensors provide for analysis of physiological processes in living cells and biological media in real time. Dr. Philbert explained the recent advancement in PEBBLE nanoplatforms (Dynamics Nano Platforms %AD DNPs) that enabled magnetic resonance imaging of orthotopic experimental brain tumors and enhancement of visual contrast for neurosurgical resection.

D-SERINE IN THE BRAIN: FROM NEUROTRANSMISSION TO NEURODEGENERATION

A common form of synaptic memory, hippocampal long-term potentiation, depends on Ca^{2+} influx through postsynaptic NMDA receptors (NMDA-R). Astroglia can regulate activation of these receptors by releasing the NMDA-R co-agonist D-serine in a Ca^{2+}-dependent manner. However, Ca^{2+} signals in astrocytes have been associated with the release of other signaling molecules, such as glutamate, ATP and TNF-α. In addition, neurons themselves represent an important source of D-serine. Dr. Rusakov of the UCL Institute of Neurology, London, discussed how long-term potentiation relies on D-serine released from neighboring astrocytes. Dr. Rusakov demonstrated the suppression of endogenous Ca signaling in individual CA1 astrocytes by clamping their internal Ca concentration and found that this procedure blocks long-term potentiation (LTP) induction at nearby CA3–CA1 excitatory synapses. This LTP blockade can be reversed by exogenous D-serine or glycine, whereas depletion of D-serine or inhibition of exocytosis in individual astrocytes blocks LTP at local synapses. The underlying mechanism involves the reduced occupancy of the ionotropic glutamate NMDA-R co-agonist site.

D-Serine is a co-agonist at the glycine site of the ionotropic glutamate NMDA-R. About 90% of endogenous brain D-serine is directly produced from L-serine by serine racemase. Dr. Mori of the Department of Molecular Neuroscience at the University of Toyama in Japan demonstrated reduced neurotoxicity with NMDA and $Aβ_{1-42}$ peptide injections into the forebrain of serine racemase knockout mice. Dr. Mori's presentation further demonstrated that the duration of tonic–clonic seizure, proto-oncogene c-Fos expression in the cortex and astrogliosis in the dentate gyrus of the hippocampus are attenuated in serine racemase knockout mice in the pentylenetetrazol model of epilepsy. Dr. Mori further stressed that these results suggest that D-serine may be involved in controlling the extent of NMDA-R-mediated excitotoxic insults. Furthermore, Dr. Mori suggested that control of serine racemase activity and D-serine levels in the brain could be a novel strategy for neuroprotection against various excitotoxic diseases.

D-Serine is a transmitter-like molecule that physiologically activates NMDA-R in the brain. Recently, reports indicate that neurons are the main source for D-serine synthesis in most brain areas. The synthesis of D-serine is carried out by serine racemase, an enzyme that is predominantly expressed in neurons and converts L- to D-serine. Dr. Wolosker of the Technion-Israel Institute of Technology found that D-serine is released by neurons through depolarization and hetero-

exchange catalyzed by the neuronal D-serine transporter Asc-1 both in vitro and in vivo. Functional studies indicate that neuronal D-serine is also involved in synaptic plasticity and NMDA-R neurotoxicity. The data can be conceptualized by the serine shuttle model, whereby D-serine synthesized and released by neurons can be further taken up by astrocytes for storage and activity-dependent release. Astrocytes express little serine racemase and are likely to export L-serine required for D-serine synthesis by the predominantly neuronal serine racemase. The serine shuttle constitutes a new type of neuron–glia crosstalk that plays a role in NMDA-R transmission and may be a therapeutic target in neurodegenerative diseases in which NMAD-R dysfunction plays a pathological role.

PUFA AND DERIVATIVES: BRAIN NEUROPROTECTIVE AGENTS FOR SENESCENCE

Age-related deficits in neuronal function and synaptic plasticity have been reported by several groups, and in animals these deficits are characterized by impairments in learning performance and memory tasks and in the ability of aged animals to sustain LTP in the hippocampus. One of the factors that contributes to the age-related deficit in LTP is a decrease in the concentration of polyunsaturated fatty acids, particularly docosahexaenoic acid in the hippocampus. Dr. Lynch of Trinity College Dublin described a study demonstrating the effect of docosapentaenoic acid (DPA), a precursor of eicosapentaenoic acid (EPA), for its ability to modulate age-related and Aβ-induced changes in the rat. Chronic DPA treatment significantly attenuated the age-related increase in microglial activation, as well as restoring spatial memory dysfunction.

Long-term supplemented arachidonic acid (AA) preserves hippocampal cognitive activity in senescent rodents, as discussed by Dr. Sakakibara of the Department of Biological Science and Technology at Tokai University. He further elaborated that long-term administration of AA to senescent rats might help to preserve membrane fluidity and maintain hippocampal plasticity.

Protein kinase C (PKC) has been shown to be a central component of memory storage in mollusks, rodents and humans. The PKC-Φ isoform may be particularly important for memory because it is relatively brain-specific and plays an important role in synapse maturation. Therefore, isoform-specific PKC activators may be useful as therapeutic agents for the treatment of AD. Dr. Nelson of the Blanchette Rockefeller Neurosciences Institute at West Virginia University developed several Φ-specific PKC activators made by cyclopropanation of polyunsaturated fatty acids. These compounds (AA-CP4, EPA-CP5, DHA-CP6) activate PKC in a dose-dependent manner. These new activators produced sustained activation of PKC and no indication of downregulation as with other PKC activators, such as bryostatin and phorbol esters. Furthermore, Dr. Nelson reported that these activators did not show any evidence of toxicity or tumorigenicity and they were suggested to be useful candidates for the treatment of AD.

AMYLOID PRECURSOR PROTEIN (APP) AND PRION PROTEIN METABOLOMES: INTERACTION, MECHANISM AND NEURODEGENERATION

The importance of the Aβ peptide and its oligomers in AD pathology and disease progression is well established. However, understanding the physiology and functions of APP has been highly influenced by an amyloid-centric perspective of the protein, despite the heterogeneity of its expression and its processing into multiple metabolites in different cellular compartments. Hence, the overall complexity of the APP metabolic network and its regulation has been rarely addressed fully. Metabolism of APP contributes to the pathogenesis of AD. The consequent processing of APP by β- and γ-secretases generates a soluble ectodomain, the Aβ peptide and the APP intracellular domain. Current therapeutic strategies have focused on preventing Aβ formation or enhancing its clearance. Dr. Turner of the Institute of Molecular and Cellular Biology at the University of Leeds showed that transcriptional upregulation involves direct binding of APP intracellular domain (AICD) to the neprilysin (NEP) promoters competitively with the histone deacetylase HD1 in a neuronally specific manner. The alternative and predominant α-secretase pathway of APP metabolism generates a larger ectodomain, which precludes the formation of Aβ but could allow formation of AICD. Dr. Turner further highlighted the molecular mechanism underlying the differential compartmentalization of α- and β-secretase-mediated pathways of APP metabolism, their modulation by protein–protein interactions and the molecular basis of the transcriptional regulation. Furthermore, Dr. Xu of the Neurodegenerative Disease Research Program at the Sanford-Burnham Medical Research Institute recently identified an AICD-interacting mitochondrial solute carrier family protein (designated as appoptosin) that induces ROS release and intrinsic caspase-dependent apoptosis. The physiological function of apoptosis is to transport/exchange glycine/D-alanine across the mitochondrial membrane for heme synthesis. The APP/AICD–appoptosin interaction modulates appoptosin-induced apoptosis. Dr. Xu further explained that appoptosin is a crucial player in apoptosis and a novel proapoptotic protein involved in neuronal cell death, providing a possible new therapeutic target for neurodegenerative disorders and cancer.

APP generates multiple smaller peptides, including Aβ and AICD. Although Aβ is known to play a pivotal role in AD pathology, there is growing evidence that amyloid-independent mechanisms also contribute to AD pathogenesis. AICD exerts significant biological effects by regulating intracellular signaling pathways and modulating gene expression. Dr. Pimplikar of the Cleveland Clinic, Department of Neuroscience, Lerner Research Institute, showed data from transgenic mice that overexpress AICD in the forebrain and hippocampal neurons and demonstrated that these mice recapitulate AD pathologies, including memory deficits, in an age-dependent manner. AICD activates inflammatory pathways and neuroinflammation is the earliest pathological feature observed in these animals. Dr. Pimplikar suggested a model in which an environment of chronic low-grade neuroinflammation triggered by factors such as AICD, Aβ, aging, stroke, etc., plays a causative role in the pathogenesis of AD.

PRION PROTEIN: BEYOND PRION DISEASE

Prion protein is a highly conserved glycosylphosphatidylinositol (GPI)-anchored cell-surface protein expressed mainly in the nervous and immune systems. Although abnormal conformers of PrP^C are associated with neurodegenerative disorders, the cellular content of the normal protein affects not only neural activity and integrity, but

also innate and acquired immunity. Dr. Linden from the Instituto de Biofisica da Universidade Federal do Rio de Janeiro, Brazil, proposed the hypothesis that the prion protein is a dynamic cell-surface platform, or scaffold, for the assembly of signaling modules, based on which selective interactions with many ligands and transmembrane signaling pathways translate into a wide range of consequences upon both physiology and behavior. Dr. Linden showed that the interaction of PrP^C with its ligand Hop/STI1 entails reciprocal remodeling that may be involved in the propagation of signals mediated by PrP^C.

There is evidence that alteration in the normal physiological activity of PrP^C contributes to prion-induced neurotoxicity. This mechanism has been difficult to investigate, however, because the normal function of PrP^C has remained obscure, and there are no assays available to measure it. Dr. Harris of the Boston University School of Medicine, Department of Biochemistry, showed that cells expressing deletion or disease-associated point mutations in the conserved, central region of PrP exhibit spontaneous ionic currents and hypersensitivity to certain classes of cationic drugs. He further highlighted that the toxic activity of these mutant PrP molecules requires localization to the plasma membrane and depends on the presence of a polybasic amino acid segment at the *N*-terminus (residues 23-31).

STI1–PrP^C as a potential therapeutic target in neurodegenerative disorders was discussed by Dr. Prado of the Robarts Research Institute at the University of Western Ontario. Dr. Prado proposed that PrP^C acts as a signaling scaffold in neurons and glia, allowing for distinct ligands to signal and modify neuronal function. STI1, a protein secreted from astrocytes, binds PrP^C in neurons, triggering an increase in intracellular calcium via $\alpha 7$ nicotinic acetylcholine receptors. This response is the upstream signal for an intracellular cascade that protects cells from death and helps them to differentiate. Dr. Prado's data suggest that the STI1–PrP^C complex may play an important role in protecting neuronal cells from the toxic effects of $A\beta$ oligomers.

MOLECULAR MEDIATORS OF PSYCHIATRIC AND COGNITIVE SYMPTOMS IN HD

HD is an autosomal dominant neurodegenerative disorder due to expanded CAG repeats in the huntingtin (*HTT*) gene. Although the resulting mutant huntingtin protein is already expressed in embryonic development, the disease usually manifests in the fourth decade of life. Dr. Chesselet of the University of California, Los Angeles, discussed the neuropathological and behavioral deficits in HD knock-in mice. The behavioral and neuropathological deficit was found to start from an early age in CAG140 knock-in mice in contrast to the CAG150 strain. Dr. Chesselet further explained that the strain back-crossed with CAG140 and CAG150 showed a difference in time course of motor phenotypes in terms of pole test, open field and running wheel test. He also explained that both models showed marked differences in aggregation of huntingtin protein, as detected with several antibodies, as CAG140 knock-in mice already showed diffuse nuclear staining, microaggregates, nuclear inclusions and neuropil aggregates in the striatum and cortex at 4 months of age, whereas these pathological hallmarks occur much later in $Hdh^{(CAG)150}$ mice. CAG140 knock-in mice also showed early (3 months of age) deficits in spontaneous alternation in the Y-maze, whereas $Hdh^{(CAG)150}$ mice were not impaired in this test at the same ages. However, novel object recognition performance was impaired in both lines by 4 months of age, as explained by Dr. Chesselet.

Dr. von Horsten of the Friedrich-Alexander University in Germany discussed how transgenic HD rats and mice were characterized by the identification of post-natal behavioral changes comprising reduced ultrasonic vocalization, loss of prepulse inhibition and increased risk taking. He highlighted that they provided the first evidence of reduced neuronal differentiation capacity in the subventricular zone of the post-natal rat brain. He also mentioned that low-dose treatment of this pre-HD-syndrome with HDAC inhibitors resulted in marked improvement of the behavioral changes in vivo, as well as a complete reversal of the aberrant neuronal differentiation capacity in vitro. Finally, Dr. von Horsten concluded that the phenotypic observations, along with successful intervention by low-dose non-specific HDAC inhibitors, are indicative of very early transcriptional dysregulation in HD.

Dr. Alberch of the University of Barcelona, Spain, highlighted that cognitive deficits are one of the clinical features of HD that are present in early stages, when motor symptoms are not yet evident. He indicated that they have analyzed the onset and progression of cognitive dysfunction and the underlying molecular mechanisms in transgenic exon-1 and knock-in full-length HD mouse models. From the biochemical analysis, they found dysfunctional activation of two important pathways involved in memory consolidation: the cAMP-dependent protein kinase (PKA) and the CREB/CBP pathways. He indicated the role of PKA and CBP in cognitive deficits in HD, as administration of either PKA or HDAC inhibitors rescues recognition memory deficits in HD mouse models.

Dr. Hannan of the Florey Neuroscience Institute in Australia discussed their findings which suggest that disruption of specific neuromodulatory systems occurs early in particular brain regions of HD mice, and may be involved in the affective and cognitive endophenotypes. In a transgenic mouse model of HD (R6/1 line), they characterized motor deficits followed by progressive onset of affective (depression-like) and cognitive endophenotypes. He highlighted that environmental enrichment (which enhances sensory stimulation, cognitive activity and physical exercise) can delay the onset of these endophenotypes. Their investigation on molecular mechanisms mediating affective and cognitive symptoms in HD, and their modulation by environmental stimuli, was also described. Microarray analysis indicated that early gene expression changes occur in multiple brain regions of the HD mice, including the hippocampus and neocortex, associated with the onset of the cognitive and affective signs. He discussed how even at an early pre-motor symptomatic age, gene expression was deregulated, with regional and sex-specific differences.

POSTER SESSIONS

Several poster sessions were organized in the areas of neuroscience. The present report highlights the area of neurodegenerative disorders.

Mechanism of neuroprotection

Mr. Chen of Tzu Chi University, Taiwan, presented the restorative effect of acetyl-L-carnitine against methamphetamine-induced

neurotoxicity. Acetyl-L-carnitine (30 or 100 mg/kg i.p.) significantly restored cognitive deficits, social withdrawal and lower levels of tyrosine hydroxylase in the striatum and reduced glial cell line-derived neurotrophic factor (GDNF) expression in the hippocampus. He concluded that acetyl-L-carnitine has therapeutic potential for the treatment of behavioral abnormalities in methamphetamine abusers. Dr. Cimarosti of the University of Reading, U.K., presented data showing that post-translational modification by small ubiquitin-related modifier (SUMO) proteins is essential for the integrity of eukaryotic cells. He demonstrated that metabolic stress caused by oxygen and glucose deprivation leads to increases in SUMO-1 and SUMO-2/3 conjugation in cultured rat neurons. Mr. Foskolou of the Biomedical Research Foundation Academy of Athens discussed how *PROX1* is a candidate gene with a critical role in modulating Notch 1 signaling and could be involved in suppressing malignant transformation. *PROX1* is expressed in higher amounts in human neuroblastomas with a favorable prognosis, while Notch 1 expression shows exactly the opposite correlation. He provided evidence that *PROX1* blocks the proliferation and promotes the differentiation of human and mouse neuroblastoma cells. Bromodeoxyuridine (BrdU) incorporation assays and phospho-histone H3 immunostaining showed that *PROX1* exerts a strong antiproliferative effect on Neuro-2a, SH-SY5Y and primary neural precursor cells. Clonal analysis, TUNEL assays and FACS-based analysis demonstrated that *PROX1* has an antiapoptotic effect. Most importantly, the repressive function of *PROX1* on Notch 1 cannot fully explain its antiproliferative effect on neuroblastoma cells.

Dr. Goh of the University of Melbourne, Australia, explained that genetic manipulation of NEDD4 family-interacting protein 1 (*NDFIP1*) expression would be expected to modify the animal response to brain injury, as this enzyme is an important player in the ubiquitination and degradation of target proteins through the NEDD4 ligase pathway. He found a significant increase in cortical lesion volume in *Ndfip1* head-injured heterozygous mice as compared to their wild-type littermates.

Cellular mechanism of AD

Dr. Bomfim from the Instituto de Bioquimica Medica da Universidade Federal do Rio de Janeiro, Brazil, reported that serine phosphorylation of insulin receptor substrate 1 (IRS-1; IRS-1pSer) is a common denominator in AD due to elevated IRS-1pSer636/639. Insulin and exendin-4, a novel antidiabetic drug, prevented oligomer-induced neuronal pathologies. Exendin-4 further rescued IRS-1pSer and phospho-JNK (c-Jun *N*-terminal kinase) levels in transgenic mouse hippocampi, which establish molecular links between dysregulated insulin signaling in AD and diabetes. Dr. Chauhan of the University of Illinois at Chicago highlighted that AD brains without diabetes had 32-36% more plaques, while AD brains with diabetes had 46-48% more plaques, indicating an additional increase of ~10-12% in plaque load in AD brains with diabetes, as confirmed by semiquantitative immunocytochemistry using 6E10 and 4G8 antibodies for detecting Aβ plaques. Dr. Chauhan concluded that diabetes appears to be a strong predisposing co-morbid trigger for developing sporadic AD. Dr. Chong from the Department of Microbiology, School of Medicine, Ewha Medical Research Institute, Ewha Womans University, South Korea, highlighted that norepinephrine (NE) reduces Aβ-mediated cytotoxicity and C-C motif chemokine 2 (MCP-1, *CCL2*) production but enhances Aβ-induced IL-1β production. Dr. Chong concluded that NE differentially modulates the innate inflammatory response by Aβ challenge by acting on β-adrenoceptors in human THP-1 macrophages. Dr. Chong also suggested that NE provides a protective effect against an Aβ insult independent of downregulation of phosphatidylinositol 3-kinase (PI3K)/serine/threonine-protein kinase Akt or NADPH oxidase. Dr. de Ceballos from the Department of Cellular, Molecular and Developmental Neuroscience, and CIBERNED, Cajal Institute, CSIC, Madrid, Spain, highlighted the effects of cannabinoid agonists on vascular dysfunction in AD. Dr. de Ceballos confirmed and extended the existence of altered vascular responses in Tg APP- and Aβ-treated isolated vessels. Tg APP displayed decreased vasodilation to two pharmacologically different cannabinoid agonists, which were able to prevent decreased acetylcholine vasodilation in the presence of Aβ. This suggests that treatment with cannabinoids may ameliorate the vascular responses in AD-type pathology. Dr. Dulovic from the University of Belgrade, Faculty of Medicine, Institute of Medical and Clinical Biochemistry, compared the cerebrospinal (CSF) levels of $A\beta_{1\text{-}42}$, total tau (T-tau) and tau phosphorylated at threonine 181 (P-tau181) among AD patients with different ages of onset of the disease and controls. Dr. Dulovic suggested that CSF biomarkers may have an important role as a supportive diagnostic tool in the diagnosis of AD in routine clinical practice. Dr. Elda Alejandra from the Centre for Biotechnological Studies (CEBiot) at the Universidad Politecnica de Nicaragua (UPOLI) presented mathematical modeling of changes in copper, iron, ceruloplasmin and ferritin in AD. Dr. Elda Alejandra highlighted that the differential increase in copper and iron levels in serum samples in early and severe AD was associated with an increased level of ceruloplasmin, but not ferritin.

Molecular mechanism of PD

Mr. Naved Ali of the Indian Institute of Chemical Biology in Calcutta, India, highlighted the production of q0 cells from SH-SY5Y cells and the use of these cells for the creation of normal and parkinsonian cybrids. Dr. Ali also described the expression of the proteins and their up- or downregulation with the help of immunoblot and 2-dimensional polyacrylamide gel electrophoresis (2-D PAGE). PD cybrids showed a significant decline in mitochondrial electron transport chain protein subunit expression (*ND4*, *ND5* and *ND6*) with respect to the control cybrids. Dr. Ali highlighted the newly generated cell lines as a reliable cellular model of PD and an invaluable tool for mitochondrial research on this disease, which has been achieved for the first time in this part of the world. Dr. Chadchankar from the School of Pharmacy at the University of Eastern Finland reported that methylphenidate (MPH) regulates dopamine overflow via an α-synuclein-specific presynaptic mechanism and hypothesized that MPH and α-synuclein share the same molecular targets. Dr. Chadchankar reported the effect of MPH on stimulated and basal extracellular dopamine levels in the dorsal striatum in wild-type and two murine lines lacking α-synuclein by in vivo voltammetry and in vivo microdialysis, respectively, and concluded that MPH and α-synuclein share the same pathways regulating dopamine overflow, which involve redistribution of vesicles in dopamine storage pools. Dr. Dickson from the Faculty of Health, School of Biomedical Sciences and Pharmacy, University of Newcastle and Hunter Medical Research Institute in Australia, highlighted the effect of tyrosine 3-hydroxylase

(TH) on α-synuclein aggregation. He concluded that the aggregation of α-synuclein may be influenced by the presence of TH, and therefore the aggregation process in TH-containing neurons may be different from that in other neurons. Dr. Emmanouilidou of the Biomedical Research Foundation, Academy of Athens, highlighted a novel, highly sensitive ELISA assay in conjugation with an in vivo microdialysis technique to measure α-synuclein in brain interstitial fluid. Dr. Finkelstein at the Mental Health Research Institute in Melbourne highlighted the efficacy of PBT-434, developed from a library of novel, redox-silencing, orally bioavailable, brain-penetrating compounds. Efficacy was assessed by stereological counts of nigral cells, TH expression and nigrostriatal terminal density and rotational behavior in response to amphetamine challenge (6-OHDA) or the pole test (MPTP). Dr. Finkelstein concluded that PBT-434 offers a differentiated therapeutic strategy that may treat a broad spectrum of patients, from those with early-onset to those with more advanced disease, including those on L-DOPA medication.

Neurodegenerative diseases

In terms of neurodegenerative disorders, several areas were covered by a number of investigators, such as the neuroprotective activity of endogenously expressed APP in traumatic brain injury, the cytotoxic effect of zinc on cholinergic SN56 neuroblastoma and C6 astrocytoma cells, the role of chaperone-mediated autophagy for the selective degradation of mutant huntingtin protein, the role of mitochondrial dysfunction in excitotoxic spinal motoneuron degeneration in vivo, etc.

CONCLUDING REMARKS

The present report has focused only on various updates in neurodegenerative disorders, particularly PD, HD, prion disease and AD, although various other areas of neuroscience, such as addiction, gene regulation, neuroimmunology, brain biogenetics, etc., were also discussed at different symposia. In addition, poster presentations, workshops, young investigator colloquia and young investigator lectures on diverse areas of neuroscience were also organized during the conference.

DISCLOSURES

The authors state no conflicts of interest.

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