Conference Report

The Myriad Pathways of Neurodegeneration Discussed at NEUROCON 2015

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NEUROCON 2015, the fourth Neurocon meeting, was organized by the Department of Biochemistry, ICARE Institute of Medical Sciences & Research, Haldia, Department of Biochemistry, Institute of Post-graduate Medical Education & Research, Kolkata and Cell Biology and Physiology Division, CSIR-Indian Institute of Chemical Biology, Kolkata from January 7-10, 2014 at Haldia, a tiny port-city of West Bengal in India. The Neurocon meeting was attended by delegates from several countries, such as Australia, Germany, India, Italy, Sweden, UK and the USA. Since its inception in 2009, Neurocon meeting has been held every alternate year and primarily focused on brain aging, neurodegenerative and neurodevelopmental disorders. This year's theme of the conference was 'Development, Degeneration and Regeneration of Neurons: Neurochemistry to Clinical Neurology'. The theme and format of the conference allowed active and intense participation of an energetic and receptive audience comprising invited senior speakers and young students or budding neuroscientists. Some notable features of the format of Neurocon meeting are worthy of mentioning. The symposium had two types of presentations. For example, each 'Original Work' presentation was followed by 'Panel Discussion' by a group of pre-selected students; and a 'Review Presentation' or a 'Memorial Lecture' was subjected to 'Rapid Fire' by a select group of senior scientists soon after the lecture. Both the 'Panel Discussion' and 'Rapid Fire' sessions were found to be highly stimulating, primarily because the questions were pre-planned after proper home work. In addition, the typical 'Question & Answer' from the audience was maintained. While the invited speakers consumed thirteen hours altogether for delivering their respective lectures, three and a half hours were utilized by the participants in discussing the implication of lectures. Further, this format specially allowed an active involvement of student-participants with conference proceedings. The post-dinner round-table discussion was also an innovative approach. It was organized not as an informal discussion within a gathering over a drink, but as a regular session with pre-fixed scientists' meeting with pre-selected students sitting over round tables, and everyone had to participate in a constructive manner.

The symposium discussed many aspects that intersect neurodegeneration, brain aging and neuroinflammation. In particular the cross-talks among molecular pathogenesis, population genetics, clinical neurology and therapeutic approaches in relation to Alzheimer's disease (AD), Parkinson's disease (PD) and normal non-pathological brain aging have been well covered. Among the 34 invited lectures by senior scientists, 20 were devoted to these three main topics: brain aging, neurodegeneration, and neuroinflammation. Major findings of the presentations are summarized below.

The "Amyloid Cascade" hypothesis as the cause of neurodegeneration, synaptic loss and cognitive decline in AD still remains the dominant hypothesis, and both animal and cell culture based research findings were presented to strengthen this hypothesis. In primary culture of cortical and hippocampal neurons, oligomeric Aβ42 was shown to activate the transcription factor FoxO which migrated to nucleus and induced the pro-apoptotic genes like PUMA, Bim, Bax etc. triggering neuronal death (S.C. Biswas, CSIR-Indian institute of Chemical Biology, Kolkata, India). FoxO was also shown to regulate a cell cycle protein phosphatase which activated a pro-apoptotic pathway in neurons. Martin Hallbeck (Linköping University, Linköping, Sweden) demonstrated neuron-to-neuron transfer of oligomeric amyloid-beta peptide in a cell culture based model utilizing neuronally differentiated SHSY5Y cells or human induced pluripotent stem cells. The receiving cells in turn manifested toxic consequences of oligomeric amyloid-beta peptide, and the investigator suggested that the spread of AD pathogenesis in brain could take place at least partly on neuron-to-neuron transfer of misfolded oligomeric amyloid-beta through neuritic connections. In human primary brain cell culture and human brain tissue, D.K. Lahiri (Indiana University School of Medicine, Indianapolis, USA) showed identification of novel microRNAs that regulate levels of APP and beta-secretase or BACE1 proteins, and he discussed the translational implication of this work. Two species of microRNA *e.g.* miR-101 and miR-153 downregulate APP expression post-transcriptionally, but miR-346 significantly activates APP expression by acting near IRE site at 5'-UTR of APP mRNA. Thus miR-346 may be further investigated as a potential drug target for decreasing the amyloid-beta load. In another significant study, D.K. Lahiri showed the anti-amyloidogenic effect of rivastigmine, a widely used anticholinesterase drug for AD patients, and proposed model of activation *via* the α-secretase pathway. Lahiri and colleagues have shown that rivastigmine caused increased levels of sAPP-α in the brain of AD triple transgenic mice as well as in samples from AD patients. This is an interesting finding, and other cholinesterase inhibitors used in AD cases could also be tested in a similar way.

Since mitochondrial dysfunction is thought to be a major damage mechanism of normal brain aging as well as AD, several published studies have attempted to improve mitochondrial functions indirectly. In a novel approach, I.G. Onyango (Gencia Biotech, Charlottesville, VA, USA) and his co-workers systemically injected aged mice with recombinant TFAM (mitochondrial transcription factor A) and observed improvement in mitochondrial biogenesis, mtDNA gene expression, mitochondrial ATP synthesis and respiration in brain along with improved performance of these animals in Morris water maze test. This has obvious implication in preventing cognitive deficits associated with normal aging and AD. Mitochondrial dysfunction as a possible cause of cognitive deficit in aging and AD was suggested by W.E. Müller (University of Frankfurt/M, Biocenter, Frankfurt, Germany and University of Erlangen, Erlangen, Germany) and his co-workers. Their study showed that levetiracetam, an anti-epileptic drug that diminished neuronal hyperexcitability and cognitive deficits in animal models of AD, also prevented the impairment of mitochondrial dynamics (fusion-fission balance) and some bioenergetic functions in a cell based model of aging and AD. S. Chakrabarti (ICARE Institute of Medical Sciences and Research, Haldia, India) demonstrated that a combination of N-acetylcysteine, α-lipoic acid and α-tocopherol when given with the diet over a prolonged period (4-5 months) could prevent multiple age-related changes in rat brain such as increased levels of APP, Aβ42 and BACE1 as well as a decreased activity of amyloid-beta peptide degrading enzyme neprilysin. The combination of drugs also improved the reference memory and working memory impairment in aged rats. Since these drugs are marketed products used for different medical conditions, the results have obvious beneficial implications. The epidemiology of post-stroke dementia in a large community-based study in Kolkata (S.K. Das, Burdwan Medical College, Burdwan, India), the first report from India, showed that the prevalence of dementia and depression in stroke survivors was similar to that reported from the West. Another interesting clinical presentation on early onset dementia of various etiologies (A.K. Biswas, Bangur Institute of Neurosciences, Kolkata, India) raised an important issue, based on his clinical experience and the records of the local hospital, that various neurodegenerative disorders including AD appear nearly one decade earlier in Indian population. The speaker reasoned that this could be due to exposure to environmental risk factors, such as chemicals and pesticides. This is an important issue which needs further explorations, and in my view specific nutritional deprivation, gene polymorphism and chronic subclinical infections may also play a role here.

Several interesting presentations on Parkinson's disease pathogenesis, genetics and treatment are worth mentioning in this report. S.V. Kalivendi (CSIR-Indian Institute of Chemical Technology, Hyderabad, India) showed that oxidative stress and increased intracellular iron in dopaminergic neurons enhanced the transcription and aggregation of an isoform of α-synuclein (112-syn) with slightly lower mol. wt. which could have pathological implications. They carried out interesting biophysical experiments to show that 112-syn was more susceptible to fibril formation and had less chaperone activity. Lisa Chakrabarti (University of Nottingham, Nottingham, UK) showed the presence of hemoglobin in mitochondrial inner membrane and inner membrane space, and then further documented the accumulation of hemoglobin in mitochondria in large nigral dopaminergic neurons in PD subjects by post-mortem analysis. However, neither the function of hemoglobin in mitochondria, nor its role in PD pathogenesis was conclusive from her studies. K.P. Mohanakumar (CSIR-Indian institute of Chemical Biology, Kolkata, India) presented a detailed review of melatonin functions in CNS and also showed data indicating protective effect of this drug in experimental PD models. Jharna Ray (S.N. Pradhan Centre for Neurosciences, University of Calcutta, Kolkata, India) produced data on the prevalence of different gene mutations *e.g. Parkin*, *DJ-1*, *PINK 1* in PD patients from Eastern India; however, the patient population under her study was diagnosed as sporadic PD. Several speakers working on various alterations during brain aging made very informative contributions in the symposium. M.K. Thakur (Banaras Hindu University, Varanasi, India) analyzed the role of neuropsin, a serine protease implicated in synaptic plasticity and hippocampal long-term potentiation in scopolamine induced amnesia in mice in relation to synaptic adhesion molecule L1CAM and MAP2c dependent neurite outgrowth. His group's work showed that neuropsin expression pattern in brain changed during aging, was correlated with L1CAM cleavage and MAP2c level and reversed by a leaf extract from the plant *Aswagandha*, a medicinal plant mentioned in ancient Indian system of medicine. Apparently, neuropsin could be a drug target in amnesia associated with aging or other diseases. In another study, using electrophysiology and patch-clamping, F. Sesti (Rutgers University, Robert Wood Johnson Medical School, New Jersey, USA) explained that oxidative modification of delayed rectifier potassium channel and Ca2+ and voltage-dependent K+ channel could result in altered excitability of neurons in brain aging and neurodegenerative disorders. Neurodegeneration and glial changes with aging in autopsied human mid-brain samples were analyzed by histopathology as well as immunohistochemistry and densitometry of various markers by P.A. Alladi (National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India) and her co-workers. The changes were moderate indicating sub-threshold neurodegeneration and glial activation in the nigra of Asian-Indian population. The author tended to suggest that their findings could provide some clues to epidemiological studies that indicated less vulnerability of Asian-Indian to PD.

Other discrete studies presented by the invited speakers covered a wide range of topics *e.g.* environmental neurotoxicology (organochlorine pesticides and microwaves as triggers for neurodegenerative diseases), the anti-aggregation effect toward amyloid-beta peptide of hypothalamic neuroendocrine precursor like proSAAS-derived peptide, model of spinocerebellar ataxia neurodegeneration in drosophila, IL-1β mediated inflammatory response in microglia and dihydroxystilbene cytotoxicity against neuroblastoma cell line. Some presentations in this category appeared quite exciting. Roberto Cappai (Molecular Science and BioTechnology Institute, The University of Melbourne, Victoria, Australia) presented data to explain the protective action of exogenously administered APP in preventing cognitive and motor deficits of traumatic brain injury. In his study, APP knock-out animals were more susceptible to traumatic brain injury. This raises the question, suggested by others earlier, that increased APP in AD brain is a cellular defense response to neurodegenerative changes. B.S.S. Rao and co-workers (National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India) demonstrated that depression was associated with cognitive deficits, morphological changes in amygdala and dentate gyrus as also impairment of LTP in hippocampus in experimental rats. Interestingly, sub-therapeutic doses of anti-depressants along with exposure to enriched environment reversed all the depression related alterations. This obviously needs further study and has implication in the therapeutic management of major depression. Another significant study was presented by Barbara Viviani (Università degli Studi di Milano, Milan, Italy) who showed that early life stress in the form of maternal deprivation on post-natal day 9 in rats caused long-lasting change observed in post-natal day 45 in the hippocampal synapses. These changes observed in male pups only and included high levels of IL-1β receptor type 1 and of their associations with NMDA receptor subunits. This study should be explored further to extrapolate its significance in human conditions. In an in-depth review, Georg Reiser (Medizinische Fakultät der Otto-von-Guericke Universität Magdeburg, Magdeburg, Germany) explained how ABCD1 knock-out mice could be a model for X-linked adrenoleukodystrophy. ABCD1 is a transport protein which carries very long-chain fatty acids in to peroxisomes for oxidation. In X-linked adrenoleukodystrophy, a severe neurodegeneration occurs as a result of defective ABCD1 transport system. The data showed that astrocytes from ABCD1 knock-out mice were more vulnerable to supra-physiological doses of very long-chain fatty acids. The presentation also highlighted the importance of peroxisome proliferator-activated receptor (PPAR) family in regulating the ROS load and ROS signaling in the brain. Given the critical role of ROS in neurodegenerative processes, the PPARs could be a therapeutic target. In another presentation, an interacting partner of PPARα known as nuclear receptor binding factor 2 (NRBF2) was shown to be a major regulator of autophagy using a conditional knock-out mouse (presented by Jianhua Zhang, University of Alabama at Birmingham, Alabama, USA). The conditional knock-out of NRBF2 in such mice resulted in decreased levels of autophagy related proteins and increased accumulation of protein aggregates.

There were also a few presentations pertaining to neurodevelopment or neuro-regeneration. Sumantra Das (CSIR-Indian Institute of Chemical Biology, Kolkata, India) showed that thyroid hormone induced astrocyte development, and the maturation was linked with upregulation of β-arrestin and subsequent endocytosis of β2-adrenergic receptors. Apart from this study related to neurodevelopment, Usha Rajamma (Manovikas Biomedical Research & Diagnostic Centre, Manovikas Kendra, Kolkata, India) presented a neurodevelopmental disease with the genetic association of MAOA (monoamine oxidase A) marker rs6323 displaying autism spectrum disorder with significant male bias in a case-control study. At the stem cell replacement therapy front, Akshay Anand (Post-graduate Institute of Medical Education & Research, Chandigarh, India) showed that NMDA induced apoptosis of retinal ganglion cells in mice could be prevented by transplantation of bone-marrow derived LIN-ve stem cells presumably by the release of neurotrophic factors. Future Neurocon meetings would continue to discuss further on aspects related to neurodevelopment and neuroregeneration.

The oral as well as the poster presentations by students, post-docs and young faculty members were extremely informative and appreciated; however, due to short of space it won't be possible to discuss each presentation separately within these few pages. In short, the pathogenesis of neurodegenerative diseases, through studies in cell based models (including cybrids) and experimental animal models, and the search for putative neuroprotective and anti-amyloidogenic agents have mostly dominated these presentations.

The 'Memorial Lectures' recalling the contributions of some of the notable Indian neuroscientist role models at the universities or research labs continued to represent a laudable tradition of the successive Neurocon meetings, which would certainly enthuse the younger scientists in India. The e-poster presentation was also a new and useful approach. A special session on the beneficial effects of tea against neurodegenerative diseases had attracted a great deal of attention right after the inaugural session of the symposium.

The aforementioned short report of the Neurocon-2015 meeting should complement the proceedings of the previous conference on Aging and Cancer published recently in "Current Aging Science" [1]. The processes of aging and age-related disorders, such as Alzheimer's disease, have become the subject of intense research; and it is, therefore, difficult to cover all these aspects in only one conference format such as Neurocon. Indeed, there are a number of journals specifically devoted in reporting advances in this area [2]. It is also appropriate to mention that a special issue of "Current Aging Science" has recently reviewed several mechanisms by which human lifespan can be extended [2]. Another thematic issue of "Current Aging Science" has thoughtfully captured various novel approaches on preventing and, perhaps at some far future date, eliminating aging [3]. Recently, Rose *et al.* stated that they were "optimistic about the eventual defeat of aging on a scale comparable to our present-day triumph over contagious disease" [4].

Overall, the Neurocon 2015 at Haldia was a great fest of Neuroscience combining excellent science, open discussions, scenic view and admirable physical comfort for the participants in the delightful ambience of a "Golden Retreat".

Finally, I would like to express my sincere thanks to all speakers and participants of Neurocon-2015, and above all the staff of "Current Aging Science" (Bentham) and its Editor-in-Chief for his advice, support and inviting me to write this report.

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