Highlights from the 34th Annual Meeting of the Australasian Neuroscience Society, held in January 28-31, 2014, in Adelaide, Australia

Vol: 2; Issue: 3

Update on cognitive disorders: pathophysiology and therapeutic managements

Anil Kumar* and Puneet Rinwa

Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, INDIA

Date Received:	Date of Accepted:	Date Published:
11TH Feb 2014	28th Feb 2014	01-Mar-2014

Summary:
The 34th Annual Meeting of the Australasian Neuroscience Society (ANS-2014) was held in Adelaide, Australia, from January 28-31, 2014. The conference was held in the spacious, modern and centrally-located Adelaide Convention Centre in Australia's most livable city, Adelaide. The primary objectives of the meeting were to define and describe contributions of cognitive neuroscience, the relevance of synaptic plasticity to neuropsychiatry and to facilitate the worldwide advancement of neurochemistry and related neuroscience. The present brief report highlights a comprehensive outlook and addresses some of the cellular and molecular aspects, recent developments and challenges in the field of cognitive disorders. The conference was made up of the familiar mix of lectures, symposia, oral and poster presentations and socio-cultural programs.

Introduction

The 34th Annual Meeting of the Australasian Neuroscience Society (ANS-2014) was held in Adelaide, Australia, from January 28-31, 2014. The meeting was organized by the Australasian Neuroscience Society (ANS), which was founded in 1971 as an informal collection of interested Australian neuroscientists. ANS-2014 meeting was one of the largest meetings of neuroscientists in the Australasian region. It began with delivery of the Overseas Plenary lecture by Moses Chao of the Skirball Institute of Biomolecular Medicine, USA. Dr. Perry Bartlett (Queensland Brain Institute, Australia), Dr. Marcello Costa (Flinders University, Australia) and Dr. Trevor Kilpatrick (University of Melbourne, Australia) also delivered other plenaries during the course of the meeting covering various topics of neuroscience interest. Many oral presentations were also organized parallelly covering various areas of neuroscience. There were also the extended periods for poster presentation and discussion. The meeting served as a platform to discuss the advancements of neuroscience made in the areas of neurodegenerative research involving Alzheimer's disease, synaptic plasticity and related cognitive disorders etc. This report briefly addresses cellular and molecular aspects and recent developments. ANS 2014 tried to highlight the current research on cognitive neuroscience. In the present meeting report, authors have tried to summarize the various scientific activities and their key discussion in the areas of cognitive neuroscience.

Welcome remarks and Moses Chao Lecture

The meeting's welcome address was presented by Dr. Moses Chao from Skirball Institute of Biomolecular Medicine, USA. Prof. Chao has delivered a lecture on "The future of neurotrophic factors". Prof Chao's presentation has been focused on the implications of abnormal glucocorticoid and neurotrophin signaling in numerous psychiatric disorders. His laboratory has recently examined an impact of brain-derived neurotrophic factor (BDNF) signaling on the glucocorticoid receptor (GR) transcriptional regulatory functioning by using gene expression profiling in primary rat cortical neurons stimulated with the selective GR agonist dexamethasone (Dex) and BDNF, alone or in combination. Simultaneous treatment with BDNF and Dex elicited a unique set of GR-responsive genes associated with neuronal growth and differentiation and also enhanced the induction of a large number of Dex-sensitive genes. BDNF via its receptor TrkB enhanced the transcriptional activity of a synthetic GR reporter, suggesting a direct effect of BDNF signaling on GR function. Indeed, BDNF treatment induced the phosphorylation of GR at serine 155 (S155) and serine 287 (S287). Expression of a nonphosphorylatable mutant (GR S155A/S287A) impaired the induction of a subset of BDNF- and Dex-regulated genes. Mechanistically, BDNF-induced GR phosphorylation increased GR occupancy and cofactor recruitment at the promoter of a BDNF-enhanced gene. GR phosphorylation in vivo is sensitive to changes in the levels of BDNF and TrkB as well as stress. Therefore, Prof. Chao suggested that BDNF signaling specifies and amplifies the GR transcriptome through a coordinated GR phosphorylation-dependent detection mechanism [1]. Prof. Chao's laboratory has also discovered and defined the genes encoding the NGF receptor. His research interests are to define the mechanisms used by trophic factors to change synaptic plasticity in cognitive disorders.

Plenary lectures- Dr. Trevor Kilpatrick from the University of Melbourne, Australia delivered his talk on unraveling the neurobiology of multiple sclerosis. Early markers of axonal and clinical outcomes are required for early phase testing of putative neuroprotective therapies for multiple sclerosis (MS). The recent study from Dr. Kilpatrick's laboratory also suggests that acute demyelinating optic neuritis normalise optic nerve axial diffusivity and could also promote axon survival and improve visual outcomes. Another plenary lecture by Dr. Marcello Costa from the Flinders University, Australia was focused on neurogastroenterology. Contractions and relaxations of the muscle layers within the digestive tract alter the external diameter and the internal pressures. These changes in diameter and pressure move digesting food and waste products. Defining these complex relationships is a fundamental step for neurogastroenterologists to be able defines normal and abnormal gut motility. In another session of plenary lecture of Dr. Perry Bartlett (Queensland Brain Institute, Australia) who discussed about the production of new neurons in the adult brain and their regulations. Microglia positively affects neural progenitor cell physiology through the release of inflammatory mediators or trophic factors. Dr. Bartlett demonstrated previously that reactive microglia foster K(ATP) - channel expression and that blocking this channel using glibenclamide administration enhances striatal neurogenesis after stroke.

Symposiums- Several symposia were organized on different aspects of neuroscience such as social cognition, receptor, synapses and memory and microRNAs in Alzheimer's disease etc.
Symposium on 'social cognition' was delivered by Dr. David Skuse from Behavioural and Brain Sciences Unit, Institute of Child Health, University College, London. Dr. Skuse urged that successful social interactions are required to observe and monitor other people's behaviour in relation to ourselves, and to respond appropriately. Social understanding, language and imitation are probably learned through neural systems that respond both during our own actions and when we see others behaving in a similar way. The development of social cognition involves the co- action of a network of cortical loci, often known as the 'social brain'. In certain neurodevelopmental disorders, coordination of this multiplicity of neural systems is inefficient. Paradigmatic among such conditions are autism spectrum disorders (ASD): recent research suggests autism is in essence a 'neural connectivity disorder'. In order to understand the biological basis of social cognition, we need to map the relationship between functionally relevant anatomic areas and neurochemical pathways.

In recent years, animal models of social reward have been studied intensively. New evidence is emerging about how and where a range of critical neuropeptides, including oxytocin and vasopressin, interacts with dopaminergic 'reward' circuits in those model systems. One aspect of this complex neural system, which has been subject to extensive research in human and animal models, underpins social recognition. Most of us find social encounters rewarding but those with ASD seem not to share those feelings to the same extent; they are less able to recognize emotions and remember unfamiliar faces. The inter-relationship between genetic influences on neuropeptide function and dopaminergic-mediated social reward could contribute to individual differences in the social brain's functioning, and hence the neural basis of neurodevelopmental disorders in which social cognition is impaired.

Dr. Huganir from the Department of Neuroscience, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, USA, discussed that neurotransmitter receptors are known to mediate signal transduction at synaptic connections between neurons in the brain. Several studies report the regulation of glutamate receptors, the major excitatory receptors in the central nervous system, and examine the modulation of receptor function by protein phosphorylation and the regulation of subcellular targeting of glutamate receptors to synapses. Studies in Dr. Huganir's laboratory have found that glutamate receptors are multiply phosphorylated by a variety of protein kinases. Phosphorylation regulates several properties of these receptors including ion channel properties and membrane targeting. Recent studies in Dr. Huganir's lab have demonstrated that the phosphorylation of glutamate receptors is regulated during cellular models of learning and memory such as long-term potentiation (LTP) and long-term depression (LTD). Moreover, phosphorylation of the glutamate receptor GluA1 subunit is required for the expression of these forms of plasticity, for the retention of spatial memory and also regulates emotional memory formation and fear erasure. Dr. Huganir have also identified a variety of proteins, including the PDZ-domain containing proteins GRIP1/2 and PICK1, that directly interact with glutamate receptors and are critical for their proper subcellular trafficking [2]. Dr. Huganir have shown that the PDZ-domain based complex is required for cerebellar LTD and is critical for hippocampal LTP and LTD and spatial learning. These studies indicate that the modulation of receptor function is a major mechanism for the regulation of synaptic transmission and is a critical determinant of animal behavior. Importantly, recent evidence has implicated the mis-regulation of glutamate receptors in several neurological and psychiatric disorders including Alzheimer's, schizophrenia, and autism.

Dr. Hynd from School of Chemistry and Molecular Biosciences, University of Queensland, Australia, discussed about the synaptic profiling of MicroRNAs in Alzheimer's disease. MicroRNAs (miRNAs) are small non-coding RNA molecule present in virtually all animals and plants. miRNAs are ~20-25 nucleotides long and affect gene expression by interacting with messenger RNAs. In contrast to short-interfering RNA (siRNAs), miRNAs are encoded in the human genome and function as endogenous in vivo regulators of gene expression. To date, over 1,500 miRNAs have been identified to be encoded within the human genome and comprise approximately 2% of all mammalian genes. It has been hypothesized that deregulation of miRNA expression in the brain may be involved in neurological dysfunction and/or neurodegenerative processes [3]. Recently, it has been suggested that Alzheimer's disease (AD) is primarily a disease of synaptic dysfunction. Mounting evidence suggests that the loss of synapses is the best pathological correlate for the cognitive decline observed in AD. One of the major neuropathological findings in the brains of individuals with AD is the loss of synaptic contacts in areas of the brain known to be affected in AD. Dr. Hynd discussed the differential expression of both mRNA's and miRNA's localized to the synaptic terminal and their involvement in the pathogenesis of AD. Whole tissue and synaptosomal fractions were taken from control and AD cases. Transcripts analysed included Neuroligin, Synaptophysin, Setptin 8, Neurexin, Tau, and the Vesicular Glutamate transporter 1. Based on the results from this study, molecular profiling of miRNA's may have potential for the therapeutic amelioration of AD.

Oral sessions- Simultaneously, several oral as well as poster sessions were organized on different

aspects. Some of the major areas of poster sessions have been highlighted below. Drug addiction involves loss of control over drug-related behaviors. Psychostimulants have been show to lead to early habitual control over behaviors not restricted to drugs suggesting that the changes in decision-making capacity may be quite general. N-acetylcysteine (NAC) has been shown to restore glutamate homeostasis and reduce relapse to cocaine seeking [4]. Dr. Corbit from School of Psychology at the University of Sydney, Australia examined that exposure to cocaine accelerates habit learning and the effect could be prevented by co-administration of NAC. In addition, Dr. Corbit used in-vitro electrophysiology to investigate the effects of cocaine on measures of synaptic plasticity and the ability of NAC to normalize these effects in brain regions critical for goal-directed learning. These data indicate that NAC normalizes glutamatergic activity in the dorsal striatum following cocaine exposure and prevents unusually rapid habitual control of performance. Dr. Vukovic from Queensland Brain Institute at the University of Queensland, Brisbane, Australia studied how new nerve cells contribute to the maintenance of learning and memory. A primary brain structure involved in memory processing is the hippocampus, where regulated production of new neurons (neurogenesis) underpins learning and memory [5]. With ageing, there is a reduction in hippocampal neurogenesis, which accompanies diminished performance in behavioural tasks designed to test memory. To address the functional significance of newly born neurons, recently, Dr. Vukovic have developed a transgenic mouse model that allows to specifically and reversibly delete these cells in the hippocampus and to discover the relationship between neurogenesis and cognition.

A cardinal feature of pathological over-eating, is that although the individual can describe the negative consequences of their behaviour, they have great difficulty intervening and changing their behaviour. Indeed, many overweight individuals express a desire to limit their food consumption, yet struggle to control their intake. As such pathological overeating has the capacity to resemble an addictive disorder. Dr. Brown from Department of Neurosciences, Medical University of South Carolina, Charleston, USA carried out a study to establish whether rats prone to obesity would show addiction-like impairments in behavior and synaptic plasticity. Collectively, the results of the study support the concept of that, akin to drugs of abuse, highly palatable food can be considered 'addictive' and provides evidence that strategies used to treat drug addiction may also have utility in treatment of the pathological overeating which often underlies obesity. Brain-derived neurotrophic factor (BDNF) supports many neurotransmitter systems implicated in Alzheimer's disease, and its expression is reduced in the prefrontal cortex of Alzheimer's disease patients. Dr. Van den Buuse from Behavioural neuroscience laboratory, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia have previously shown in mice that forebrain BDNF expression correlates significantly with the pubertal rise in testosterone [6]. Despite their confluences, interactions between BDNF and androgens are understudied in Alzheimer's disease, particularly at the crux adolescent period. Dr. Buuse therefore examined the effects of pre-pubescent hormone manipulation in a BDNF heterozygous (het) mouse model of Alzheimer's disease. TNF-α is shown to be essential for cognitive development and plays a role in anxiety-like behaviour, partially through modulating neurotrophin expression. In young mice (3 month old) lack of TNF-α and its receptors did not affect exploratory or depression-like behaviour, it is unclear whether this role changes with ageing. Dr. Camara from Discipline of Psychiatry, University of Adelaide, Australia studied the effects of lack of TNF-α and its receptors on mood-like behaviour and neurotrophin expression in older mice. Dr. Camara found a lack of TNF-α and TNF-R2 in older mice and appeared protective against depression-like behaviour. This could be due to enhanced signalling of TNF-R1 or by chronic activation of TNF-α through TNF-R2 binding, but more work is needed to validate this.

Acetylcholine (ACh) is a neurotransmitter widely distributed in the central nervous system that plays a critical role in regulating several aspects of behaviour and cognition. Considerable evidence suggests that a number of cholinergic systems undergo degenerative changes during ageing and dementia, resulting in cholinergic hypofunction at specific brain areas. Dr. Matamales from Centre for Ageing Dementia Research, Queensland Brain Institute, University of Queensland, Australia found that these alterations in cholinergic transmission have been related to the progressive cognitive

impairment observed in both Alzheimer's disease patients and healthy, elderly subjects, and can be ameliorated with anticholinesterase agents, which increase ACh in synapses. Interestingly, the brain structure with the highest content of ACh and ACh-receptors is the striatum, a subcortical nucleus that is crucial for the acquisition of goal-directed behaviours. Despite that, whether age affects cholinergic transmission in the striatum is poorly understood. Importantly, it has been proposed that dysfunction of striatal circuitry may be responsible for the diminished goal-directed behaviours of aged individuals which could be a major predisposing factor for the development of neuropsychiatric disorders, such as apathy. Moreover, Dr. Matamales assessed the behaviour of aged mice through striatal-dependent paradigms and found alterations in their performances. These results suggest that an impaired striatal cholinergic transmission may contribute to the deficits in the cognitive control of actions that are characteristic of ageing and dementia.

Poster sessions- Similarly, different researchers showcase their research and related findings in the form of poster. Exercise is known to result in beneficial effects on cognition and aspects of mood including anxiety and depression however the effects of varied parameters of exercise on these factors are less well understood. Dr. Ayliffe from the Psychiatric Neuroscience Laboratory, University of Adelaide, Adelaide, investigated the effects of voluntary exercise on indicators of cognition, anxiety and mood in C57BL/6 mice and found that exercise resulted in the significant improvements in cognition, anxiety, or depression-like behaviors in young adult rodents. Similarly, Dr. Blackmore from Queensland Brain Institute, The University of Queensland, Brisbane, Australia also investigated that 24-month-old mice retains a population of neural precursor cells in the dentate gyrus of the hippocampus that can be activated after physical exercise. They also found out that activating these endogenous latent precursor cells correlates to increased neurogenesis and improved cognitive ability.

Dr. Genevra Hart from Brain & Mind Research Institute, University of Sydney, also explained about the role of fronto-striatal pathway in executive functions, particularly in decision-making involving goal-directed actions. The changes in this pathway have been linked to the cognitive symptoms associated with various forms of psychiatric disorder, neurodegenerative conditions and addiction. By examining pathway-specific activity using tract tracing coupled with immunohistochemistry, Dr. Genevra also found direct evidence that a circuit linking prelimbic prefrontal cortex and a posterior region of dorsomedial striatum mediates the acquisition and consolidation of goal-directed actions.

Recently, studies have shown that pentacyclic triterpenes have anti-inflammatory effects in the brains of obese mice; a disease where inflammation contributes to energy balance deregulation, and cognitive impairment. Bardoxolone Methyl (BM) is a compound synthetically modified from the pentacyclic triterpene, oleanolic acid. Dr. Camer from the Centre for Translational Neuroscience, University of Wollongong, Wollongong, Australia found that BM treatment in 12 week old C57B1/6 male mice fed a high fat diet (HFD) for 21 weeks significantly prevented body weight gain, and reduced visceral fat, liver weight and liver lipid content compared with untreated mice. Furthermore, analysis of BM treated mouse liver tissue revealed significantly reduced levels of PTP1B, an inflammatory mediator, compared to the HFD control group.

Recent animal experiments have demonstrated that adult vitamin D (AVD) deficiency is associated with altered behavior and neurochemistry. Epidemiological evidence links low vitamin D with cognitive decline; therefore there is a need to explore the impact of this common exposure on more specific neurobiological processes. Dr. Groves from the Queensland Brain Institute, The University of Queensland, St Lucia, Australia explained that AVD deficiency impacts on hippocampal neurogenesis and that this may be sex-specific [7]. Both estradiol and Brain-Derived Neurotrophic Factor (BDNF) have neuroprotective properties, particularly with respect to cognition. Dr. Wu from the Behavioural Neuroscience Laboratory, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia determined the effects of pre-pubescent ovariectomy (OVX) and estradiol replacement on spatial memory (assessed in the Y-maze) and hippocampal BDNF protein expression (measured

by Western blot) in young adult wild-type mice (WT) and BDNF heterozygous mice (+/-). The results confirmed the neuroprotective role for estradiol in spatial memory and suggested that BDNF may mediate this effect in WT mice.

Dr. Jawahar from the Discipline of Psychiatry, The University of Adelaide, Adelaide explained about the association between early life stress (ELS) events such as childhood maltreatment with the increased inflammation leading to cognitive deficits in adulthood. Maternal separation (MS) stress, an animal model of ELS has been implicated in behavioural and neurobiological alterations leading to cognitive loss in adulthood [8]. However, the neuro-immune interaction effects of MS on adult behaviour and biology are unclear. Dr. Jawahar and his lab discovered that neuro-immune interactions post MS are dependent on the type of MS and may have a role in long-term effects of MS in adulthood. Also that a second stress treatment in adolescence or adulthood may be needed for better neuro-immune interaction response.
Oxidative stress and neuroinflammation, the prominent features of mild traumatic brain injury (mTBI), progressively evolves over time and are known to be the major contributors to cognitive deficits [9]. Dr. Kumar and Rinwa from Panjab University, Chandigarh demonstrated the study on interaction of Panax ginseng (PG) against cognitive deficits and neuroinflammation associated with mTBI and the probable role of nitric oxide pathway in this effect. Their findings suggested that modulation of nitric oxide signalling cascade might be involved in the protective effects of PG against head trauma-induced cognitive impairment and neuroinflammation.

Normal sleep-wake cycle ensures the balance of synaptic potentiation and depression which called total synaptic strength. Sleep deprivation significantly impairs the basal synaptic strength. A large body of evidence suggests that chronic caffeine treatment significantly improves synaptic plasticity during stress, including sleep deprivation. Dr. Sahu from Neurophysiology Division of DIPAS, India investigated that caffeine administration preserved basal synaptic strength and facilitated cognitive performance during 48h sleep deprivation. Exposure to cognitive enrichment (CE) has been shown to have distinct beneficial effects on the neurobiology and behaviour of animals. Such animals were observed to be more responsive and display diverse behaviour with improved cognitive performance [10]. However, little is known about the effects of short-term CE on cognition, anxiety- and depression-like behaviour. Dr. Singhal from Psychiatric Neuroscience Lab of the University of Adelaide, Australia conducted experiments on C57BL/6 mice to measure the alterations in different behaviours in response to short-term CE with novel objects, toys and accessories. Three months old mice were reared in a cognitively stimulating enriched environment for four weeks followed by an assessment of a range of behaviors using an established battery of behavioral tests. The results of the study suggested that CE may play a role in memory; however no broad effects on various behaviors were observed at this young age of animals.

Concluding remarks- The present report has been focused on various recent developments in the area of cognitive disorders, particularly on the pathogenesis and their therapeutic interventions. Alzheimer's disease and cerebrovascular disease are the quantitatively most important causes of cognitive impairment in adults. Other similar disorders, such as Lewy body disease and fronto-temporal dementia, were also discussed at different symposia. In addition, oral and poster presentations, lectures and invited talks on diverse areas of cognitive neuroscience were also organized during the conference.

References

1. Lambert WM, Xu CF, Neubert TA, Chao MV, Garabedian MJ, Jeanneteau FD. Brain-derived neurotrophic factor signaling rewrites the glucocorticoid transcriptome via glucocorticoid receptor phosphorylation. Mol Cell Biol. 2013 Sep; 33(18):3700-14.
2. Jenkins MA, Wells G, Bachman J, Snyder JP, Jenkins A, Huganir RL, Oswald RE, Traynelis SF. Regulation of GluA1 AMPA Receptor Function by Protein Kinase C at Serine-818 and Threonine-840. Mol Pharmacol. 2014 Jan 22. [Epub ahead of print]
3. Srinivasan S, Selvan ST, Archunan G, Gulyas B, Padmanabhan P. MicroRNAs -

the Next Generation Therapeutic Targets in Human Diseases. Theranostics. 2013 29;3(12):930-942.

4. Schmaal L, Veltman DJ, Nederveen A, van denBrink W, Goudriaan AE N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: a randomized crossover magnetic resonance spectroscopy study.. Neuropsychopharmacology. 2012 Aug;37(9):2143-52.
5. Jevtić P, Edens LJ, Vuković LD, Levy DL. Sizing and shaping the nucleus: mechanisms and significance.. Curr Opin Cell Biol. 2014 Feb 3;28C:16-27.
6. Manning EE, van den Buuse M. BDNF deficiency and young-adult methamphetamine induce sex-specific effects on prepulse inhibition regulation. Front Cell Neurosci. 2013 Jun 12;7:92.
7. Groves JO, Leslie I, Huang GJ, McHugh SB, Taylor A, Mott R, Munafò M, Bannerman DM, Flint J. Ablating adult neurogenesis in the rat has no effect on spatial processing: evidence from a novel pharmacogenetic model. PLoS Genet. 2013;9(9):e1003718.
8. Harrison EL, Jaehne EJ, Jawahar MC, Corrigan F, Baune BT. Maternal separation modifies behavioural and neuroendocrine responses to stress in CCR7 deficient mice.. Behav Brain Res. 2014 Feb 3. pii: S0166-4328(14)00050-3.
9. Kumar A, Rinwa P, Dhar H. Microglial inhibitory effect of ginseng ameliorates cognitive deficits and neuroinflammation following traumatic head injury in rats. Inflammopharmacology. 2013 Sep 20. [Epub ahead of print]
10. Sahu S, Kauser H, Ray K, Kishore K, Kumar S, Panjwani U. Caffeine and modafinil promote adult neuronal cell proliferation during 48 h of total sleep deprivation in rat dentate gyrus.. Exp Neurol. 2013 Oct;248:470-81.