PLENARY LECTURES

PLE-WED-01

OVERSEAS PLENARY LECTURE

SEQUENTIAL EVENT MEMORY FORMATION AND REACTIVATION IN THE HIPPOCAMPUS AND BEYOND

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Research in our laboratory has focused on the manner in which memory representations in the brain are formed, maintained, and used during behavior. By introducing arrays of microelectrodes into hippocampal and neocortical areas of freely behaving rodents we have been able to examine the coordinated activity of ensembles of large numbers of individual neurons and relate this ensemble activity to behavioral performance and memory. By monitoring neural activity during sleep we have begun to examine the nature of offline memory processing and consolidation. One of our fundamental working hypotheses is that experience leads to plastic changes in the hippocampus that preserve both the content and the temporal linkage of events that constitute episodic memory. Long-term neocortical memory may be formed through interactions with deep memory structures such as the hippocampus, and memory reactivation during sleep may play a critical role in this consolidation process. Previous work found that temporal sequences of neural ensemble activity generated during awake experience spanning several minutes were reproduced during REM episodes at equivalent timescales (Louie and Wilson, 2001). We further identified evidence of memory replay of brief episodes of experience during non-REM sleep that occurred at an accelerated rate with several seconds of recent experience being replayed in brief bursts, a fraction of a second in duration (Lee and Wilson, 2002). Similar temporal replay of recent experience has also been found to occur during periods of quiet wakefulness in the context of ongoing behavioral tasks in time-reversed form (Foster and Wilson, 2006). These novel reactivation events may reflect the processing of sequential experience during active learning. Sequential memory reactivation has now also been seen in primary visual cortex (Ji and Wilson, 2007) pointing to a critical role for slow oscillations in coordinating hippocampal-neocortical interactions during sleep. These results, characterizing the interactions between the hippocampus the neocortex during behavioral tasks and sleep, the possible role of temporal replay of recent experience in learning and the formation of memory, and more recent results extending these findings will be discussed.

PLE-WED-02

LAURIE AUSTIN LECTURE

ADVENTURES IN NEUROCHEMISTRY: PEOPLE, PLACES AND PUZZLES

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Lawrie Austin is well known to have played a key role in the establishment of the Australian Neuroscience Society, but he was foremost an eminent neurochemist recognised internationally for his diverse contributions. Lawrie had a distinguished association with the International Society for Neurochemistry (ISN) and the Asia Pacific Society for Neurochemistry (APSN). Indeed many Australian neuroscientists, just like Lawrie Austin, have served ISN and APSN with distinction, and fostered the field of neurochemistry through these societies and/or its related journals, *Journal of Neurochemistry*, *Neurochemistry International* and *Neurochemical Research*. While my own work has addressed the neurochemical aspects of various neurotransmitters, the neurobiology of L-glutamate (Glu) has been my continuing passion involving many Australian and international colleagues. Although now well established as the key excitatory transmitter, during the 1970/80s there was still much scepticism as its central pathways were poorly delineated and receptor antagonists did not exist. At that time, we used discrete excitotoxic lesions and retrograde mapping techniques to establish the patterns of organization of glutamatergic neurons in the forebrain and limbic system. A key study from this period is one of the few that defines a glutamatergic pathway both anatomically and electrophysiologically. Over this period we made some of the initial pharmacological observations on competitive and non-competitive NMDA receptor antagonists, described the axonal transport of Glu receptors and defined the structure-activity relationships of various classes of NMDA receptor ligands. Computer-assisted molecular modelling and establishment of primary neuronal cultures for drug screening underpinned a translational programme focused on the development of polyfunctional neuroprotectives. One molecule, AM-36, acted at multiple targets and was an effective neuroprotective agent both *in vitro* and *in vivo*. Basic studies of injury induced by excitotoxic and other insults revealed neuronal injury occurred across an apoptotic-necrotic continuum. Use of genetic mouse models and potential therapeutics provided insights relevant to “death” signalling and cytoprotection in neuropathologies. Most recently, we have explored aspects of programmed cell death and how mitochondria determine caspase-dependent and -independent neuronal injury, which are recruited differentially dependent upon stressor and neuronal phenotype. Other efforts have focused on the biology of astrocytes and their Glu transporters, which prevent excitotoxicity - functional relationships exist between transporter activity and astrocyte phenotype. Indeed we described recently an homeostatic “defensive” response of Glu transporters to stressors implicated in the pathology of motoneurone disease.

PLE-THU-03

ANS PLENARY LECTURE

THE ACTION POTENTIAL

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The action potential is the fundamental electrical signal used by the brain for communication. In my lecture I will review recent work on action potentials, including their site of generation, their modulation by subthreshold synaptic input, and their role in synaptic plasticity.

PLE-THU-04

ECCLES LECTURE

NEUROTRAUMA MANAGEMENT– PREVENTION, PROTECTION AND REPAIR

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The framework for the present management of traumatic brain injury was established in the 1970s. Lundberg introduced continuous intracranial pressure monitoring. The CT scan revealed the gross morphology of brain injury and neuropathological studies showed the great importance of raised intracranial pressure and ischaemia in fatal head injuries. Since then clinical management of patients with severe head injury in Intensive Care Units has focused on increasing brain oxygenation and reducing intracranial pressure. Research has focused on cerebral blood flow, autoregulation and the genesis of brain swelling. Clinically head injury is conceived as having two components, the primary injury which is the direct effect of impact and secondary injury due to post impact factors particularly hypotension, hypoxia, blood clots and brain swelling. Treatment protocols aim at preventing these secondary events through pre-hospital retrieval systems and by clinical management based by Evidence Based Guidelines. This general approach has lead to a steady fall in the mortality of patients with severe head injury however it is limited. Treatment protocols are usually “one size fits all’ and do not take into account the marked heterogeneity of brain injury. Furthermore primary brain injury is no longer conceived as a single irreversible event. Rather impact initiates complex injury responses which develop over hours and days. Components of the evolving injury include axonal disconnection, cytotoxic cascades, neuropeptide release and inflammatory reactions. During this early post injury period the final burden of neuronal death may be decided and may potentially be reduced. Elements of the evolving injury can be blocked in experimental models but so far the neuroprotective agents developed experimentally have failed in clinical trials. Reasons for these failures include inadequate preclinical testing, inappropriate animal models and the logistical complexity of international multicentre trials. The present search for clinically effective neuroprotection has two principle goals 1. To increase oxygenation in vulnerable brain regions such as the penumbra of brain contusions. 2. To reduce brain swelling The primary impact injury also initiates reparative mechanisms. Present and future directions in brain injury research include the identification and possible augmentation of intrinsic repair mechanisms, the role of intrinsic stem cells and a greater understanding of neuroplasticity. SUMMARY Clinical management is based on preventing secondary injury according to principles set down thirty years. Neuroprotection is the main focus of present research and aims to develop treatments which can be targeted to specific components of injury. The capacity of the brain for recovery and regeneration are becoming better understood. The future management of head injury will include all three approaches – prevention, neuroprotection and promoting repair and regeneration.