PLENARY LECTURES

PLE-TUE-01

ANS OVERSEAS LECTURE

Sponsored by Neuroscience Research Australia

OPTOGENETICS: DEVELOPMENT AND APPLICATION

Deisseroth, K.
Department of Bioengineering, Stanford University, Stanford, CA 94305 USA

Abstract not available.

PLE-MON-02

ANS PLENARY LECTURE

Sponsored by The University of Queensland

GENERATING ENTERIC NEURONS DURING DEVELOPMENT AND FOR CELL THERAPY

Young H.M.
University of Melbourne.

Migration of neural precursors plays a crucial role in the development of the nervous system. The enteric nervous system forms from the migration of neural crest cells from the caudal hindbrain (vagal level). Enteric neural crest-derived cells (ENCCs) undertake the longest migration of any embryonic cell population as the gut grows rapidly during ENCC colonization. Our research is focused on the mechanisms controlling the migration and differentiation of ENCCs during development, and on the potential of enteric neural stem/progenitor cells to treat diseases of the enteric nervous system. Migration of ENCCs is influenced by molecules expressed by the gut mesenchyme, such as GDNF, as well as by molecules expressed on the cell surface of ENCCs, such as L1. We have visualised ENCCs as they colonize explants of embryonic gut and shown that they migrate as chains of cells. While the migration of ENCCs is predictable at the population level, the behavior of individual cells remains unpredictable. Live imaging studies have also revealed how ENCCs colonize the gut. It had been assumed that each region of the gut is colonized by cells that cease to migrate, but our imaging studies have shown that the key change in behaviour is a loss of directional migration. A previously unreported element influencing ENCC migration are the neurites of early differentiating neurons, which project along the same pathway and in the same direction as ENCCs migrate. The anally directed neurites act as substrates for migrating ENCCs. We have examined the development of electrical behaviour of the enteric neural network. Calcium imaging studies revealed that the early neurons show spontaneous Ca^{2+} transients, and respond to electrical field stimulation and some neurotransmitters. Patch clamp studies showed that the early neurons are also capable of firing action potentials. While blocking neural activity in cultured explants did not affect ENCC migration, it did influence the rate of differentiation of some sub-types of enteric neurons. We are also investigating the potential for cell therapy for treating enteric neuropathies. Our studies to date have shown that enteric neural stem/progenitor cells can be successfully isolated and cultured and that they are capable of migrating and differentiating into neurons with the appropriate electrophysiological properties following transplantation into the colon of post-natal mice in vivo. Ongoing experiments on animal models of Hirschsprung disease and other enteric neuropathies will establish whether normal gut function can be restored using cell transplantation.

PLE-TUE-03

LAWRIE AUSTIN LECTURE

A BRIEF HISTORY OF THE NIGRAL DOPAMINERGIC NEURONE, L-DOPA AND TRPM2 CHANNEL: CONSIDERATIONS FOR PARKINSON'S DISEASE

Lipski J.
Department of Physiology and Centre for Brain Research, Faculty of Medical and Health Sciences, University of Auckland, New Zealand.

Since their first in vivo electrophysiological identification by A Grace, B Bunney, G Aghajanian and colleagues in the 1970's, dopaminergic neurons in the Substantia Nigra pars compacta (SNc) have become a focus of attention of a wider neuroscience community due to two main reasons: their importance in motor control and reward-related behaviour, and their crucial involvement in the pathogenesis of Parkinson's disease (PD). In the first part of my lecture I will concentrate on intrinsic properties of these neurons, as some of these properties may be associated with their relatively selective degeneration in PD. In particular, I will present evidence obtained in our laboratory that SNc neurons express the Transient Receptor Potential Melastatin 2 (TRPM2) channel, a member of a large superfamily of TRP channels that is permeable to Ca2+ and Na+, and could be activated in vitro by membrane-permeable oxidant H2O2, intracellular adenosine diphosphate ribose (ADP-ribose), and indirectly by rotenone (a mitochondrial toxin used to produce models of PD in rodents). As TRPM2 channels are also positively modulated by intracellular Ca2+, they may provide an important link between oxidative stress, calcium dysregulation and cell damage due to calcium overload. In the second part of my lecture I will present our data on the exogenous effects of L-DOPA (3,4-dihydroxyphenylalanine; levodopa) on dopaminergic SNc neurons and adjacent non-dopaminergic neurons. Apart from the well-documented inhibitory action of the drug on dopaminergic neurons mediated by D2 receptors and GIRK channels, we have identified an excitatory effect mediated by both glutamate (mainly AMPA/kainate) receptors and non-glutamatergic (oxidative stress-dependent) mechanisms. These results will be presented in the context of clinical observations that use of L-DOPA, a drug which remains the gold-standard in symptomatic treatment of PD, often leads to serious motor (dyskinesia) and non-motor side-effects, and of the hypothesis that the drug may contribute to accelerated degeneration of dopaminergic SNc neurons in PD.

PLE-TUE-04

ECCLES LECTURE

ELUCIDATING THE PATHOPHYSIOLOGY OF SYRINGOMYELIA

Stoodley M.A.
Macquarie University.

Purpose. Syringomyelia is a condition where expanding cysts form in the spinal cord in association with spinal cord injury, cranio-vertebral junction abnormalities, arachnoiditis, and spinal tumours. These cysts may cause spinal cord damage, resulting in pain, sensory loss, paralysis, or even death. The origin of syringomyelia fluid is one of the greatest enigmas in neuroscience. Often considered to simply contain CSF, syringomyelia pathophysiology must be more complex because syrinx pressure must exceed CSF pressure for syrinx expansion to occur. Treatment of syringomyelia is unsatisfactory and improved treatment is unlikely to be developed without a greater understanding of syrinx pathogenesis. **Methods**. A series of experiments has been conducted using rodent and ovine models of syringomyelia. These experiments have examined CSF flow in the subarachnoid space and spinal cord, and the cellular and molecular conditions in the cord tissue around syrinx cavities. In addition, computational modelling has been used to explore CSF dynamics and the effects of perturbations of CSF flow in the subarachnoid space. MRI was used to study CSF flow in patients with syringomyelia and cranio-cervical junction abnormalities. **Results**. A normal flow of CSF from the subarachnoid space to the spinal cord central canal was demonstrated. This flow is mainly via the perivascular spaces. Pulsations in the subarachnoid space are necessary for this flow to occur. Obstruction of CSF flow in the subarachnoid space by arachnoiditis increases local subarachnoid pulse pressure and may increase flow in the perivascular spaces. In addition, the timing of pulse transmission through the subarachnoid space may have a crucial effect on perivascular flow. In animal models of syringomyelia the perivascular flow continues, even when there is evidence of raised syrinx pressure. The blood-spinal cord barrier remains structurally and functionally disrupted around syrinx cavities, with evidence of fluid flow from vessels in the cord in to the cord substance. There is an increase in aquaporin-4 channel formation in astrocytes around syrinx cavities. Fluid flows out of syrinx cavities in to the surrounding extracellular space with a preferential flow in to the central grey matter and central canal. **Conclusion**. Advances have been made in the understanding of CSF physiology in the subarachnoid space and spinal cord and in the pathogenesis of syringomyelia. These advances are impacting surgical decision-making. There is a possibility that further advances will result in pharmacological treatments for this disabling condition.