PLENARY LECTURES

PLE-TUE-01

ANS OVERSEAS LECTURE

HOW ACTIVITY CHANGES SYNAPSES IN THE MAMMALIAN BRAIN

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One of the most fundamental properties of the brain is its ability to adapt rapidly to environmental changes. This is achieved mainly by changes in the connectivity between individual nerve cells. Synapses can be modulated in their strength by a variety of different mechanisms. We have investigated a number of these mechanisms, ranging from homeostatic control of synaptic efficacy to morphological manifestations of synaptic strengthening or weakening, on both excitatory and inhibitory cells. Yet, while we are beginning to understand the cellular mechanisms underlying synaptic changes, it is important to consider the functional implications of synaptic plasticity in the intact brain. We are therefore applying new imaging methods to investigate the effects of experience on synaptic changes in cortical circuits. In particular, in vivo two-photon microscopy has enabled us to study morphological as well as functional plasticity at the level of individual neurons in the neocortex. These experiments are beginning to close the gap between traditional cellular and systems studies, and they will enable us to obtain a much more comprehensive understanding of the phenomenon of synaptic plasticity and its role in cortical function and ultimately behavior.

PLE-TUE-02

LAWRIE AUSTIN LECTURE

CATECHOLAMINE SYNTHESIS IN RESPONSE TO STRESS: THE TIMING OF TYROSINE HYDROXYLASE PHOSPHORYLATION IS EVERYTHING

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The catecholamines, dopamine, noradrenaline and adrenaline, play a crucial role in the stress response. Basal levels of catecholamines are established in all catechaminergic neurons in the central and sympathetic nervous systems and in the adrenal medulla. Stress then leads to the secretion of these catecholamines, which are either lost by metabolism or removal by the blood stream, or recovered by reuptake. In order to maintain homeostasis the catecholaminergic cells always respond to stress by synthesising sufficient new catecholamines to maintain basal tissue levels. Catecholamine synthesis is therefore critical to the stress response and it is primarily controlled by the rate limiting enzyme tyrosine hydroxylase (TH). There are many mechanisms available to control TH activity including TH synthesis, feedback inhibition by the end products and protein phosphorylation. The focus of this talk will be the control of TH activity by protein phosphorylation. There are three phosphorylation sites on TH (Ser19, Ser31 and Ser40) that each increase TH activity via different mechanisms. It is established that the Ser40 phosphorylation increases TH activity by displacing bound catecholamines thereby relieving feedback inhibition. We have discovered that Ser19 and Ser31 can increase TH activity by facilitating TH phosphorylation at Ser40, which we call hierarchical phosphorylation. We have also discovered that in intact cells there are two mechanisms whereby TH is phosphorylated at Ser40 in response to different stressors; there is an acute mechanism which lasts for minutes and a sustained mechanism that lasts for days. Having established the basic mechanisms for control of TH activity by protein phosphorylation in model systems we have undertaken in vivo studies to investigate how: (i) TH phosphorylation is controlled under basal and pathological conditions using human postmortem tissue and (ii) stress modulates TH phosphorylation over time using animal models. Results from these studies will be presented.

PLE-WED-03

ECCLES LECTURE

NEW APPROACHES TO TREAT THE SACRED DISEASE

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Epilepsy has afflicted humanity since antiquity, and is currently the most common serious chronic neurological condition worldwide. Despite many new anti-epileptic drugs (AEDs) being introduced into practice over the past 15 years, the treatment outcomes remain unsatisfactory for many patients. There has been little reduction in the proportion of patients who are refractory to medical treatment, with approximately one third continuing to have seizures despite trials of treatment with multiple different AEDs. Furthermore all AEDs are symptomatic treatments, merely suppressing the occurrence of seizures without modifying the underlying epileptic condition or its comorbidities. There is no medical treatment that has been demonstrated to be effective at preventing the development of epilepsy after an epileptogenic insult, to prevent progression of the epilepsy or its comorbidities, or to cure the condition. A major challenge for translational researchers is to discover and develop new treatments that address these major treatment gaps. Advances in the understanding of the fundamental neurobiology of seizures and epileptogenesis have suggested new targeted approaches by which this may be achieved. Rigorous evaluation of these with studies using clinically relevant "true epilepsy" models is essential to provide the evidence base to select the most promising novel treatments to translate into clinical trials, and then to ultimately improve outcomes for patients with this disabling condition.

PLE-WED-04

ANS PLENARY LECTURE

MECHANISMS UNDERPINNING NEURON SURVIVAL FOLLOWING BRAIN INJURY

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How does the brain defend itself from cell death following injury? Are there intrinsic mechanisms that protect neurons during critical periods of ischemic and metabolic stress? If yes, what are these mechanisms and why are they inefficient? In this presentation, I will outline key discoveries from our laboratory demonstrating that the Ndfip1/Nedd4 ubiquitination pathway is a powerful mechanism for increasing neuron survival. This pathway is activated in neurons that survive traumatic brain injury and cerebral ischemia. To understand how this pathway is capable of protecting neurons, we used genetic, biochemical and cellular analyses of brain injury models. Our work shows that Ndfip1/Nedd4 mediates protein modification by addition of ubiquitin. This causes ubiquitinated proteins to be degraded, or trafficked to other cellular compartments, thereby altering the internal environment for shoring up cellular defence mechanisms. I will show how these mechanisms can improve neuronal well-being by minimizing toxic pathways while at the same time maximizing neuron survival pathways.