

# PLENARY LECTURES



PLE-MON-01

**ANS/AuPS OVERSEAS LECTURE***Sponsored by the Prince of Wales Medical Research Institute***CIRCUITS AND DYNAMICS FOR OLFACTORY CODING****Laurent G.**

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Olfaction is a complex synthetic sense subserved by shallow circuits. By synthetic I mean that natural odors are usually complex blends; yet the perception of these chemical objects is generally singular (e.g., coffee, jasmine, sweat, etc.). By shallow, I mean that contrary to what is seen in the visual, somatosensory or auditory systems, odorant signals reach olfactory cortex, the presumed site of associations and learning, with reduced preprocessing: the shortest path to cortex from olfactory receptors comprises only two synapses. Understanding olfactory processing, while interesting in its own right, thus also offers general relevance (perception of complex natural objects) and the practical advantage of comparatively simple circuits. In this talk, I will summarize our attempts to understand some of the computational and mechanistic features of olfactory processing using insect model systems, with much emphasis placed on connectivity and dynamics.

## PLE-MON-02

## AuPS INVITED LECTURE

## ANALGESIC CONOTOXINS MODULATING PAIN PATHWAYS

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The small and highly structured peptides found in the venom of marine cone snails target a wide variety of membrane receptors and ion channels in normal and diseased states. A number of these peptides (conotoxins) have shown efficacy *in vivo* including inhibitors of voltage-gated sodium ( $\text{Na}_v$ ) and calcium ( $\text{Ca}_v$ ) channels and nicotinic acetylcholine receptors (nAChRs) which are in preclinical development for the treatment of chronic and neuropathic pain. A number of structurally related  $\omega$ -conotoxins bind directly to and selectively inhibit N-type calcium channels of pain-sensing primary nociceptors. Among these,  $\omega$ -conotoxin MVIIA (Prialt) still maintains its orphan drug status as a valuable alternative intrathecal analgesic for the management of chronic intractable pain, especially in patients refractory to opioids. Newly discovered  $\omega$ -conotoxins from *Conus catus* are more potent and selective for N-type ( $\text{Ca}_v2.2$ ) calcium channels over other  $\text{Ca}_v$ s (Berecki G. et al., *Mol. Pharmacol.*, 2010). Furthermore, in spinal cord slices, these peptides reversibly inhibited excitatory monosynaptic transmission between primary afferents and dorsal horn superficial lamina neurons. In the rat partial sciatic nerve ligation model of neuropathic pain,  $\omega$ -conotoxins CVIE and CVIF significantly reduced allodynic behaviour. Another potential target for conotoxins is the tetrodotoxin (TTX)-resistant voltage-gated sodium channel  $\text{Na}_v1.8$  which is selectively expressed in small sensory neurons and has a major role in nociception associated with inflammatory pain. The modulation of these channels by the  $\mu\text{O}$ -conotoxins, MrVIA and MrVIB isolated from *Conus marmoreus*, has been examined on native and cloned  $\text{Na}_v1.8$  channels expressed in *Xenopus* oocytes (Daly N.L. et al., *J. Biol. Chem.*, 2004). These  $\mu\text{O}$ -conotoxins are more potent on TTX-resistant than TTX-sensitive  $\text{Na}^+$  currents in rat dorsal root ganglia and MrVIB is 10–30-fold more selective for  $\text{Na}_v1.8$  than other  $\text{Na}_v$ s. In neuropathic and chronic inflammatory pain models, allodynia and hyperalgesia were both reduced by intrathecal infusion of MrVIB (0.03-30 nM), whereas motor side-effects occurred only at 30-fold higher doses (Ekberg J. et al., *PNAS*, 2006). A third family of conotoxins, the  $\alpha$ -conotoxins, competitively inhibit nAChRs and bind at the interface between specific subunits allowing them to discriminate among different nAChR subtypes.  $\alpha$ -Conotoxins Vc1.1 (ACV1) and RglA are small disulfide bonded peptides currently in development as a treatment for neuropathic pain (Vincler M. et al., *PNAS*, 2006). Recently it was proposed that the primary target of Vc1.1 and RglA is the  $\alpha9\alpha10$  neuronal nAChRs. Surprisingly, however, we found that Vc1.1 and RglA more potently inhibit the N-type ( $\text{Ca}_v2.2$ )  $\text{Ca}^{2+}$  channel currents in rat sensory neurons via a G protein-coupled receptor mechanism (Callaghan B. et al., *J. Neurosci.*, 2008). This is the first demonstration of  $\alpha$ -conotoxins acting as via G protein-coupled  $\text{GABA}_B$  receptors modulating native  $\text{Ca}_v2.2$  channels. The prevailing view has been that  $\alpha$ -conotoxins primarily target nAChRs, so our current findings have the potential to introduce a paradigm shift in thinking about the targets of  $\alpha$ -conotoxins.  $\text{GABA}_B$  receptors may play a critical role in pain pathways and are a clear therapeutic target for these and novel “designer” conotoxins.

## PLE-TUE-03

## THE PHYSIOLOGICAL SOCIETY (UK) EXCHANGE LECTURE

**BRAIN POWER: HOW THE BRAIN'S ENERGY SUPPLY DETERMINES THE COMPUTATIONAL POWER OF NEURONS****Attwell D.**

University College London.

The brain comprises 2% of the body's mass, but uses 20% of its resting energy. This massive energy use is vital for neuronal computation: the energy is mainly used on pumping out the ions that enter during synaptic and action potentials. In this lecture I will first set the scene by reviewing how much energy the brain uses, and how the human body evolved to be able to use so much energy on neuronal information processing. I will then examine what subcellular processes the brain needs ATP for (such as synaptic currents, action potentials, maintaining the resting potential), and thereby demonstrate that energy use severely constrains the "design" of several features of neurons, including the affinity of AMPA receptors and the size of synaptic boutons. After reviewing how brain energy is generated, I will examine how the energy supply is regulated at the vascular level. Although the dogma is that this regulation is carried out by arterioles, I will focus on a recently discovered mechanism by which contractile cells called pericytes may control blood flow by regulating capillary diameter. I will then turn to how the energy supply is controlled at the level of individual neurons, examining how mitochondria are "parked" at active synapses to provide them with ATP. Finally I will describe how energetic failure, in conditions like stroke, spinal cord injury and cerebral palsy, leads to a reversal of glutamate transporters which release glutamate into the extracellular space and thus cause mental and physical impairment by damaging neurons and oligodendrocytes.

## PLE-TUE-04

## ANS PLENARY LECTURE

**THE ROLE OF NPY IN HEALTH AND DISEASE: INSIGHTS FROM TRANSGENIC AND KNOCKOUT MODELS****Herzog H.**

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Modern molecular biology technologies such as the generation of transgenic or gene-targeted rodent models have contributed tremendously to our understanding of the function of a large number of important genes including neuropeptide Y (NPY) and its corresponding Y-receptor genes. The analysis of the phenotypes of NPY related models has revealed significant and distinct roles of each gene in modulating, fertility, seizure susceptibility, pain perception, bone homeostasis, cardiovascular function, immune function, emotional behaviors and most importantly the control of energy homeostasis and feeding behavior. Many factors and pathways have been implicated in the regulation of appetite and energy homeostasis, however, none of them are as central and essential as the NPY system. NPY is a complex system consisting of 3 ligand genes NPY, peptide YY (PYY) and pancreatic polypeptide (PP) and at least 5 different receptors (Y1, Y2, Y4, Y5 and y6). Whereas central NPY is known to stimulate appetite and feeding behaviour, the mostly peripherally expressed family members PYY and PP have the opposite effect and have been identified as potent satiety factors. Negative energy balance, such as that which occurs during acute fasting or chronic food restriction, leads to increased hypothalamic NPY expression and the activation of appetite stimulatory pathways and other feeding related behaviours. However, NPY causes also neuroendocrine and metabolic changes which favour energy storage including decreased thermogenesis, hyperinsulinemia, insulin hyper-responsiveness in white adipose tissue, activation of the hypothalamo-pituitary-adrenal axis, and decreased activity of the hypothalamo-pituitary-thyrotropic, -somatotropic, and -gonadotropic axes. Peripheral injections of the other family members, PYY3-36 and PP, on the other hand induce satiety in humans and rodents particularly through activation of hypothalamic and brain stem Y2 and Y4 receptors thereby controlling body weight. Changes in bodyweight, however, needs also be matched with bone strength, eg larger body mass requires stronger bones. Recently, we have identified an important role for the neuropeptide Y receptor system in the regulation of bone formation with a significant elevation in bone formation and bone volume following germline or hypothalamus-specific deletion of neuropeptide Y2 receptors in mice. Subsequent studies in knockout mouse models now show that other members of the Y-receptor family are also playing a critical role in bone formation. New outcomes of the analysis of various germline and conditional knockout models from the NPY family in regards to the regulation of appetite, satiety and energy homeostasis with a particular focus on stress induced changes will be presented.