283P HISTAMINE H_3 RECEPTORS AND THEIR LIGANDS: FROM FUNCTIONAL ASPECTS TO THERAPEUTIC APPLICATIONS

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The histamine H_3 receptor was initially identified as an autoreceptor control-ling histamine synthesis and release in CNS neurons (Arrang *et al.*, 1983) and its pharmacological identity established with the design of the first selective ligands (Arrang *et al.*, 1987). Since then the H_3 receptor has been shown to control the presynaptic release of several amines, aminoacids and neuropeptides in the CNS or PNS.

A large number of agonists, partial agonists and antagonists were designed with the aim of developing novel classes of drugs for the treatment of inflammatory and psychiatric diseases. With the recent cloning of the human receptor (Lovenburg *et al.*, 1999), molecular studies could be undertaken.

Arrang *et al.* (1983) *Nature* **302**: 832-837

Arrang *et al.* (1987) *Nature* **327**: 117-123

Lovenburg *et al.* (1999) *Mol Pharmacol* **56**: 1101-1107

284P HOTTING UP: THE VANILLOID RECEPTOR STORY SO FAR

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Capsaicin, the pungent substance in chili peppers, has been known for many years to act with remarkable selectivity as an excitant of nociceptive sensory nerve terminals. Over the last decade increasing evidence emerged to suggest that its action was mediated by a specific receptor and this was finally cloned two year ago (Caterina *at el.*, 1997). The receptor (VR1) has the typical structure of a ligand-gated ion channel. When expressed in a line, VR1 confers sensitivity, not only to capsaicin but also to heat in the noxious range (>45 °C) and to protons, suggesting that it could account for the sensitivity of nociceptive neurons to a variety of painful stimuli, both chemical and physical.

Studies on the thermosensitivity of sensory neurons, down to the single channel level, confirm the close similarity of the membrane responses to heat and capsaicin, but show that distinct individual channels respond to either type of stimulus, suggesting that post-translational modifications of VR1 may control its responsiveness to particular stimuli.

The trail of the long-postulated, but hitherto elusive, endogenous ligand for the capsaicin receptor recently took a surprising turn with the demonstration by Zygmunt *et al.* (1999) that the endogenous cannabinoid anandamide is a potent agonist at the vanilloid receptor – an action unrelated to its effect on cannabinoid receptors.

Thus, in a few years, capsaicin has changed in status from a relatively obscure pharmacological curiosity, to being the proud owner of a physiological role, and with a good chance of being the harbinger of a new role for lipid mediators related to anandamide.

Caterina M J *et al* (1997) *Nature* **389** 816-822

Zygmunt PM *et al* (1999) *Nature* **400** 452-457

285P ORPHAN RECEPTORS AND THE DISCOVERY OF OREXINS, A FAMILY OF HYPOTHALAMIC NEUROPEPTIDES INVOLVED IN REGULATING FEEDING AND AROUSAL

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The superfamily of G-protein-coupled receptors (GPCRs) is one of the largest family of genes yet identified, and has a proven history of being an excellent source of drug targets. Recent advances in DNA, sequencing technologies has allowed the identification of a plethora of sequences encoding 'orphan' GPCRs – putative receptors whose cognate ligand remains to be discovered.

In most cases, the level of sequence homology with known receptors is insufficient to classify orphans into particular receptor sub-families. Consequently, reverse molecular approaches are being employed to identify the natural ligand and physiological function of such receptors.

The identification of a number of orphan receptor ligands will be described, focusing on the discovery of the orexins, two novel neuropeptides encoded by the same gene which activate two closely related (previously orphan) receptors. The orexins are expressed predominantly in the lateral hypothalamus, although their neurones project throughout the brain. Consistent with these sites of projection, orexin-A stimulates feeding, increases arousal and has effects on neuroendocrine function.

286P ALZHEIMER'S DISEASE: TREATING THE ILLNESS RATHER THAN THE SYMPTOMS

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The 1990's witnessed great advances in the understanding of the molecular pathology of Alzheimer's disease with the discovery of a number of risk-factor genes. These advances have focused attention on the deposition of beta-amyloid and abnormally phosphorylated tau as key events in the progress of the illness.

This in turn has offered many potential targets for drug discovery, with the aim of developing treatments that interfere with the disease process, rather than merely treating the symptoms.

287P PHARMACOLOGY *IN SILICO*: REDUCTION TO PRACTICE?

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Our understanding of pharmacology will be revolutionised by advances in genomics, computation structural biology and new processes for handling this tidal wave of information. When the giant robot sequencers have completed their task and all of the human genome has been catalogued, pharmacologists will be left with the task of making sense of the data so that it can be utilised for new approaches to desirable therapies.

Single nucleotide polymorphisms (SNPs) offer the promise of tailoring therapies to patient genotypes. SNP databases will become much larger than the simple human genome collection. The challenge will be to identify the role of SNPs in disease and account for their influence on clinical trials. Current estimates suggest that at the moment there are around 300 molecular targets available for drug design; over the next three years, the number of targets is expected to rise 10-fold.

Clearly, new technologies for structure determination and drug design are needed to keep up with the data that will come onstream. The development of gene expression microarrays, whereby it is possible to put the genome on a chip, herald a new form of large-scale, highly parallel experiments to monitor gene expression, even in a single cell.

Complex gene expression networks are now being identified by reverse engineering using signalling network theory. Where a time element is present in the analysis, we have, in principle, the capability of understanding the dynamics of pharmacogenomics on single cells, tissues and the body.

288P ABC TRANSPORTERS, CHANNELS, CHANNEL REGULATORS AND DRUG RESISTANCE

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The ABC superfamily of transporters and channels includes over 100 examples from bacteria, protozoa, fungi, insects, plants and man. ABC transporters play a wide variety of physiological roles and many are of consideable medical relevance, including the cystic fibrosis gene product CFTR, the pfmdr protein which contributes to chloroquine resistance of the malaria parasite, and P-glycoprotein and MRP which confer resistance of tumours to chemotherapeutic drugs.

The substrates handled by ABC transporters can vary from small molecules such as ions, amino acids and sugars, to large molecules such as polysaccharides and proteins. It has recently become apparent that several ABC proteins, in addition to their intrinsic transporter/channel activity, have regulatory functions modulating the activity of heterologous ion channels.

The structure and function of one ABC transporter, the multidrug resistance P-glycoprotein, will be described. This protein is responsible for the resistance of many cells and tumours to chemotherapy. Recently we have obtained the first structural data, through electron microscopy, of P-gp. The mechanisms by which it acts as a transporter, and by which it modulates cell volume-regulated chloride channels will be discussed.

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