CONTROLLING PAIN IN THE 21ST CENTURY

Report on the Society for Medicines Research meeting held at Charing Cross and Westminster Medical School, London on Thursday July 10th, 1997.

A one day symposium entitled "Controlling Pain in the 21st Century" was held on 10th July 1997 at Charing Cross and Westminster Medical School, London. This meeting which was organised by the Society for Medicines Research was well attended assembling Society members and visitors from academia and the pharmaceutical industry. It provided the participants with an informed view of pain treatment covering a range of topics including those pains not currently treated satisfactorily and prospects for designing new analgesics, new potential analgesics in development and a focus on neuropathic pain. The eight speakers generated considerable interest as evidenced by the ensuring questions and discussions.

"Overview Controlling Pain in the 21st Century" Professor Wall, (St Thomas Hospital, London), opened the meeting setting a high standard which never faltered. "Where are we now" and "What is wrong", were the questions posed and to answer these, past successes and failures were reviewed. Successes include post opertive and labour pain as well as most cancers followed by partial successes in treating chronic inflammation and osteoarthritic pain. Unfortunately, pain associated with nerve damage, diseases with no pathology (for example low back pain), and trigeminal neuralgia are notable failures. Current work on the analysis of inflammatory conditions is particularly exciting - inflammation involves a coordinated series of changes in the region of tissue damage which involves every type of cell in the region including nerve fibres and also changes distant systems, such as the immune, endocine and central nervous systems. Nerve growth factor, bradykinins and many other factors are involved in the signalling of the damage but intervention at the level of one factor is not the answer as they all contribute to the pain experienced.

The nervous system is plastic and reacts both to the presence of nerve impulses and to novel chemicals which are transported within the nervous system. The largest contemporary group of intractable pains involve damage to the peripheral and /or central nervous system. Nerve cell firing is influenced by both C-fibres with excitatory interneurons and A-fibres with inhibitory interneurons. These involve numerous neurotransmitters and receptors and all contribute in their own way to the intensity and type of pain experienced.

Sensory perception involves not simply activity in a specialised neural pathway but the setting of the entire brain in its ability to register input signals and in its tendency to react. Pain, particulary chronic pain, necessarily involves a resetting of central activity as well as peripheral events. Pain intervention therefore has to accommodate this complex interplay if it is to be successful.

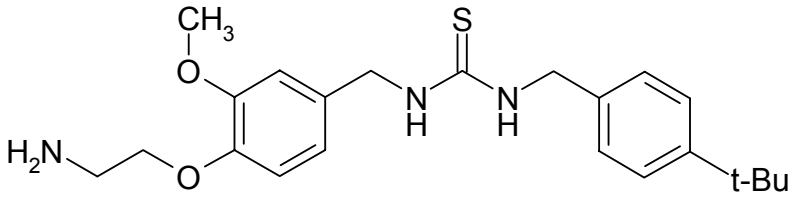
Many agents have been tried in treating neuropathic pain without much success; the opiates exemplified by morphine generaly do not work because the receptors are lost in this situation. Some success has been experienced with tricylic antidepressants and this could be as a result of their combined action on serotonin and adrenaline transmitter systems. Although antiepileptics work against trigeminal neuralgia, which involves spasmodic pain with trigger zones, the reasons why are not understood. Ultimately surgery can cure but overall the treatment is pragmatic.

Low back pain effects many people yet a great number of sufferers receive no pain treatment which reflects the lack of available therapies.

As a conclusion, two ways of curing pain were considered which do not involve the use of analgesics. "Emergency cure" involves shifting the sufferers attention away from the pain yet does this involve a natural pharmacology? Similarly the "placebo reaction" which involves a persons expectation - is this expectation built into the nervous system involving an attention controlling mechanism and is there a physiology and pharmacology involvement?

"What are the Prospects of Designing New Molecules as Analgesics" - Dr Bevan (Novartis, London) opened by reviewing currently available analgesics highlighting the disadvantages to all the classes of compounds in terms of side effects and variability of response. Recent studies however in nociception and analgesia research have identified potential new sites for therapeutic intervention particularly in chronic inflammatory and neuropathic pain conditions which involve phenotypic changes in sensory pathways. New approaches to drug discovery have also increased the probability of identifying drugs with novel mechanism of actions. Molecular biological techniques have provided powerful ways to examine the changes in gene expression in models of chronic pain and have provided human cloned target molecules for use in assays. New high-throughput assay systems have also been developed which can support the screening of large compound libraries in order to idenftify lead compounds for drug discovery programes. Additionally combinatorial and parallel chemical synthesis programmes have accelerted the lead optimisation procedures. New animal pain models for persistant pain, chronic inflammation and neuropathies have been developed and interspecies differences (eg animals vs humans) are now better understood.

Examples of potential new analgesics include capsaicin analogues, eg SDZ-249,482, neurokinin and bradykinin receptor antagonists, while molecular and cell biological studies have identified potential new soduim channel targets.



SDZ-249,482

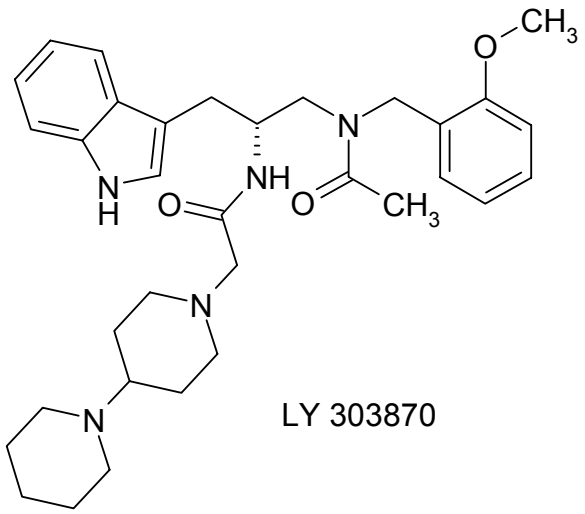
SDZ-249,482 a capsaicin agonist is orally active, more potent than opiates and NSAIDS and is effective in a number of acute and persistant models of pain yet has less side effects than capsaicin itself. It also works topically.

Bradykinins are formed at sites of tissue injury and clearly have a role in pain. Antagonists at the two receptors are available, des Arg^9 Leu^8 Bk - B_1 antagonist and HOE 140 and FR 173657 - B_2 antagonist. These antagonists have potential in inflammatory hyperalgesia.

"3-Aryl-1,2-Diacetamidopropanes as Novel and Potent NK-1 Receptor Agonists - A New Generation of Analgesics?" Dr Hipskind (Eli Lilly,USA) described how Lilly scientists

using classical medicinal chemistry approaches, improved antagonism against the target enzyme by more than 3000 fold over the original lead. The stimulus for this research was the role of Substance P (SP), a member of the neuropeptide family that exert their effects through neurokinin (NK) receptors, SP itself being a neuromodulater of pain acting primarily at NK-1 receptors stimulating smooth muscle contraction, vasodilation, plasma extravasation and the release of inflammatory mediators.

Directed screening driven by the hypothesised importance of the Phe^7 - Phe^8 substrucure of SP for NK-1 receptor binding, identified compounds with an IC_{50} of approximately 5μM at the NK-1 receptor in human IM-9 lymphoblasts. LY 303870, possessing an IC_{50} of 0.25mM; IM-9, was discovered during a comprehensive medicinal chemistry programme. While exhibiting high affinity for human and guinea pig (0.31mM) NK-1, LY303870 had a 15-30 fold lower affinity for rat and mouse brain NK-1 receptors. It was also found to be highly selective for NK-1 receptors vs other NK and multiple non-NK systems. Several *in vitro* assays have shown LY 303870 to be a potent and fully functional antagonist whilst *ex vivo* binding studies in guinea pigs revealed that it potently blocked central NK-1 receptors labelled by ^{125}I-SP (ED_{50} 25ng/kg p.o.) with a long duration of action (>24hrs at 10mg/kg p.o.)



LY 303870

In *in vivo*_studies LY 303870 blocked the characteristic nociceptive behavoural response elicited by intrathecal administration of a selective NK-1 agonist in conscious mice and the potentiation of the tail flick response in the rat. The long duration of action was confirmed in a guinea pig model of inflamation (ED_{50} = 91 ng/kg p.o.; 100% effective at 24hrs, 100μg / kg p.o. and 100% effective at 8 hrs, 1 mg/kg p.o.). LY 303870 also blocked the pain-related behaviour in the second phase of the formalin test (model of persitent neciceptive activation induced by tissue injury) in a dose dependant manner, ED_{50} 4mg/kg i.p. and 10mg/kg p.o. The oral administration resulted in blockade for at least 24 hours.

LY 303870 has shown no neurological or motor side effects nor does tolerance develop. Although it does work in a migraine model (Moskvitch) this has not been reproduced in the clinic in acute migraines. The compound is curently undergoing Phase II clinical evaluation for analgesia.

"Fish-Killer to Pain Killer: The Calcium Channel-Blocking Conopeptide, SNX-111, as an Analgesic". Dr Miljanich (Neurex Corp. USA) presented an exciting new prospect in SNX-111 which is derived from the venom of fish-eating snails, and is the first of a new class of analgesics directed at the N-type neuronal voltage-sensitve calcium channel.

CKGKGAKCSRLMYDCCTGSCRSGKC

SNX-III

Two general classes of omega conopeptides have emerged, those blocking N-type calcium channels (SNX-111) and those blocking P/Q-type channels (SNX-230). Inhibition of neurotransmitter release by SNX-111 and 230 reveals that presynaptic N-type and / or P/Q-type channels mediate release at most synapses and, in many cases, both channel types co-exist on the same terminal. However, the relative distribution of N channels in the CNS not only defines the therapeutic efficacy of N-type channel blockers but also underlies the favourable safety profile of these compounds. Autoradiographic studies have shown that N channels are highly localised to spinal dorsal horn layers receiving dense input from sensory afferent nociceptors. Thus intrathecally administered SNX-111 potently suppresses evoked pain behaviour in rat models of acute or persistent nociceptive pain. It is more potent than morphine and unlike opiates, chronic administration does not elicit tolerance. Encouragingly, SNX-111 is also anti-nociceptive in neuropathic pain models where opiates are much less effective.

Phase I / II clinical evaluation of SNX-111 has been completed in the treatment of severe, chronic pain unresponsive to opiate treatment with 84% of evaluable patients experiencing significant reduction or elimination of their otherwise intractable pain. Two phase III studies employing implantable pumps for chronic inthathecal infusion are in progress for neuropathic pain associated either with cancer and AIDs or from less malignant pathologies. A phase II study of epidural SNX-III for peri-operative pain is also underway.

Small molecule N-channel blockers with properties superior to those of peptides have the potential to broaden analgesic and anti-inflammatory applications of this emerging class. Structure activity analysis is ongoing and key features of SNX-111s channel-binding pharmacophore have been identified. This could lead to the successful development of a second generation non-peptide N-channel blocker.

"Neurotrophines, Pain and the Management of Peripheral Neuropathies". Dr Malcangio, (Queen Mary and Westfield College, London), discussed the three topics neurotrophins, their potential role in pain, and management of peripheral neuropathies. The neurotrophins are a family of proteins that influence neuronal phenotype and cosist of four members, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5). These exert their effects on responding neurones through activation of specific receptor tyrosine kinases of the trk family, trkA, trkB and trkC for NGF, BDNF / NT-4/5 and NT-3 respectively.

NGF may play a role in pain mechanisms in the adult rat - unmyelinated and thinly myelinated (nociceptive) primary affferent fibres (C and Aδ), which contain nociceptive transmitters in their central and peripheral terminals, express trkA receptors. Single systemic injection of NGF induces thermal and mechanical hyperalgesia in rodents and humans which is likely to occur through sensitisation of nociceptive fibre terminals in the periphery. However, NGF can induce new synthesis of the nociceptive peptide substance P(SP) and increased release of SP from central terminals in the spinal cord may explain delayed NGF-induced hyperalgesia.

By contrast, trkC receptors for NT-3 are expressed by non-nociceptive myelinated primary afferent fibres (Aα,β). Neuropathies involving these large fibres are reversed by systemic treatment with NT-3. Surprisingly NT-3 inhibits SP release from the spinal cord - this inhibition is reversed by Naloxone suggesting the involvement of enkephalins.

Streptozotocin (STZ)-induced diabetes in the rat is associated with persistent hyperalgesia, reduced neurotrophic support, reduced SP release from the spinal cord and reduced content in peripheral nerves. The hyperalgesia is relatively insensitive to morphine and baclofen. NK-1 antagonists do not reverse the STZ induced hyperalgesia but the NMDA antagonist MK801, at 0.1mg/kg, b.i.d. for 6 days, does reverse the activation of NMDA receptors, probably through increased release of glutamate. STZ induced pain may provide a good model of neuropathic pain.

"Can Patterns of Immediate Early Gene Expression Provide New Opportunites for Treating Neuropathic Pain". Dr Munglani, (Addenbrookes Hospital, Cambridge), discussed the understanding of c-fos in acute and chronic pain. There are many families of immediate early genes. The observation that physiologically relevant levels of predominantly noxious stimuli caused expression of some of these genes in the spinal cord nuerones has helped understanding the plastic nature of the CNS; how it learns and forms memories. Particular focus has been given to one immediate early gene, c-fos. C-fos expression in spinal cord shows distinct distribution, concentrated in laminae I, II and V. The magnitude of this expression is directly proportional to the magnitude of the noxious stimuli. C-fos is expressed in the same neurones as GABA, and the use of antisense technology has shown that inhibiting c-fos expression causes increased pain behaviour and decreased production of dynorphin, an analgesic opioid within the spinal cord and perhaps other peptides such as NPY. The amount of c-fos correlates with the intensity of the stimulus. As c-fos disappears in superficial levels in the dorsal horn, it increase in deeper laminae. Thus the pattern of c-fos expression in the spinal cord may help us to understand the adaptive responses to pain.

In the rat model of neuropathic pain (chronic constrictive injury following ligation of the sciatic nerve), hyperalgesia develops over 2-3 week period. C-fos expression increases in laminae 3 and 4 of the dorsal horn, with a good relationship to measures of hyperalgesia. Treatment with MK-801 prevented c-fos expression and hyperalgesia. Sham controls also had high c-fos expression but no hyperalgesia and therefore there was no relationship between c-fos and hyperalgesia in sham animals. C-fos expression in laminae I and II was not increased in this chronic pain model, probably because of activation of descending inhibitory systems in chronic pain.

"Encapsulated Bovine Chromaffin Cell Transplants in the Management of Neuropathic Pain". Dr Buchser, (Hospital Morges, Switzerland), described the successful exploitation of an emerging therapeutic strategy relying on transplantation of naturally occurring or genetically modified cells as a continuous source of biologically active cell secretions. Chromaffin cells from the adrenal gland secrete a mixture of compounds that have a strong analgesic effect especially when administered intrathecally - studies in animal models have shown that these cells can survive and have biological effects when transplanted within a semipermeable membrane capsule. The antinociceptive substances released by chromaffin cells include noradrenaline, enkephalins, endorphins, neurotensin, somatostatin and neuropeptide Y.

Implantation of encapsulated bovine chromaffin cells produced long lasting analgesic effects in an ischaemic model of spinal cord injury. Allodynia produced was clearly decreased whereas a sham implantation had no effect. A human scale implant was developed which contains up to 1.5million cells in a flexible tube about 0.7mm in diameter and 5cm long. This device, which is retrievable, is implanted into the cerebrospinal fluid (CSF) among the spinal roots of the *cauda equina* with minimal invasive surgery. Local anaesthesia is required but no pharmacologic immunosupression.

A phase I study has been completed in patients suffering intractable pain not satisfactorily treated with currently available analgesics; 8 severe cancer pain and 2 denervation pain sufferers. Individual patients generally shared pain relief with a decrease in its intensity and reduction in morphine intake. Survival of the cells was confirmed with good biocompatibility in 8 out of 8 retrieved devices. Increased catecholamine release in 3 out of 4 retrieved devices was evident. The only notable complication or side effect to arise from the study is headache in about a third of patients. This study represents the first successful trial of encapsulated cells in humans and justifies further investigations. Superior implant devices are being developed and a randomised, double blind Phase II study is to be initiated in some 30 patients.

"New Perspectives on Neuropathic Pain and Opioids" Dr McCormack (Drug Research Group, McCormack Ltd, Leighton Buzzard) opened by discussing the modulation of synaptic function by opioids and neurotrophic factors posing a number of questions such as "How are opioids, neurotrophic factors and K_{ATP} channels connected? Why do neurotrophic factors demonstrate naloxone-sensitive antinociception? Why do K_{ATP} openers demonstrate naloxone-sensitive antinociception?" This lead to a review of the convergence of the effects of opioids and neurotrophic factors on for example the "effectors", nociception, ion channel conductance, neurotransmitter release (both potentiation and attenuation), K_{ATP} agents, phosphorylation of synapsin I and MAP kinase activity.

Human neuropathic pain syndromes are caused by trauma or disease-evoked damage to peripheral nerves, dorsal roots, spinal cord, or to certain regions in the brain. By comparison with inflammatory pains, reduction of neuropathic pain parameters is generally less responsive to the effects of opioids. Whereas infusions of opioids have achieved adequate analgesia in neuropathic pain patients, dose-response curves may have been "shifted to the right" possibly beyond the normal therapeutic range resulting in an unacceptable ratio of benefit to harm. It

remains a considerable challenge to translate such knowledge into clinical practice. However, we propose that final common pathways of intrinsic neuronal reparation and analgesia are shaped by opioid and neurotrophic factor signalling, and that such convergence may provide new opportunities for managing difficult-to-treat neuropathic pains. Significantly, this hypothesis also emphasises the role of neurotrophic factors as modulators of synaptic efficacy through effects upon presynaptic release of neurotransmitters.

Although it is well documented that it is the βγ (Gβγ) subunit of the heterotrimeric GTP-binding protein (G protein) that is the messenger by which opioids 'talk' to neurotrophic factor (NT)-mediated signalling pathways, until recently, the mechanism of this cross-talk remained unclear. The emerging picture however that free Gβγ (ie, the messenger) recruits phosphoinositide 3-kinase (PI-K) (ie, the message template) to the plasma membrane, enhancing the activity of an Src-like kinase, which in turn leads to the activation of the Shc-Grb2-Sos-Ras pathway, resulting in increased mitogen-activated protein kinase (MAPK) activity (with subsequent changes in gene expression and ultimately neuronal phenotype). "Traditional opioids" signalling is through the Gα protein and to test the model on opiate to act through the Gβγ dimer protein involving the K_{ATP} sensitive channel is required - such an opioid appears to be buprenorphine.

Formulating such data into the 'convergence' hypothesis allows an evaluation of the functional significance of reports that SH2 domain-containing protein tyrosine phosphatases associate with the P85 subunit of P1-3K and Shc proteins, following stimulation by neurotrophins, for example. One function of the convergence of opioid and NT signalling upon P1-3K and Shc could be to promote the relocation of protein tyrosine phosphatases to/within the cell membrane with a resultant increase in the open probability of the STP-sensitive potassium (K_{ATP}) channel. As a model for future research the hypothesis distinguishes some opioids as notable candidates for further investigation. What, for example, are the clinical implications of reports that morphine's antinociception is uncoupled by pretreatment with pertussis toxin whereas buprenorphine is relatively unaffected and that the analgesic activity of buprenorphine but not fentanyl, is superadditively augmented by the addition of K_{ATP} channel openers. It remains an exciting challenge to see if such interactions can be exploited/manipulated as a tool for regulating NT-mediated signalling