

new developments in ANALGESIA

Novel therapies for pain and headache are major medical needs and constitute a continued opportunity. Novel treatments are likely to arise from a better understanding of both the pathophysiology of clinical pain conditions and the pharmacology of existing therapies. Triptans and COX-2 inhibitors are the most successful current novel treatments for pain and headache and represent major advances over pre-existing therapies. Future treatments for pain and headache are likely to arise from genomic studies, although the challenge will be to identify those gene products with the greatest utility as drug discovery targets.

Improvement in basic knowledge of the physiology of pain perception has yet to deliver its full potential for improvement in pain therapeutics. Patients who suffer chronic pain are not satisfied with the treatments they are offered with up to 52% claiming that prescription medication is ineffective, 80% believing that 'pain was something you had to live with' and up to 30% feeling that their pain is so severe and debilitating that they cannot function as normal people. Perhaps the most worrying statistic is that up to 57% of patients are often in pain at the end of their lives although they consider that freedom from pain at this time is the most important factor in their medical care. Neuropathic pain is sometimes refractory to conventional analgesic drugs and although some progress has been made with classifying responses to drugs in a variety of nerve damage models in animals, in the clinic responses are less predictable probably because patients have pain arising from a variety of mechanisms and thus treatment has to be empirical¹. Reports in the medical literature suggests pain may be becoming more prevalent, especially for chronic conditions such as low back pain, although this may be in part due to an increased willingness of patients to complain about ineffective therapy². Current NIH estimates are that pain is responsible for \$100 billion worth of healthcare and lost productivity costs each year. It is therefore,

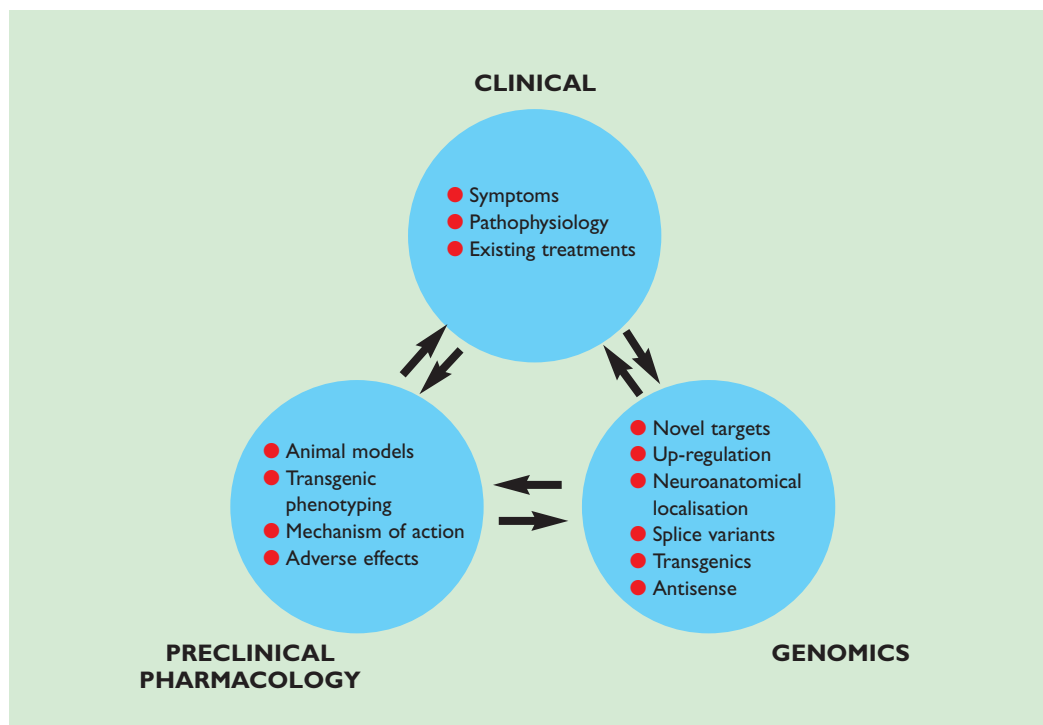
imperative that new analgesics are designed and developed to meet this need.

Strategies to develop new therapies can arise from our understanding of the pathophysiology of clinical pain conditions and the pharmacology of existing drugs, to novel gene targets identified using molecular biological techniques or taking a mechanistic approach or interactions of two or more of these approaches (Figure 1). Most analgesics in current use were discovered empirically. The cost benefit analysis for each of these strategies is different. Refinement of existing drugs provides the greatest probability for success but there comes a time when the improvement is so small that the drug will not recoup its cost of development. Progress in molecular neurobiology has generated a stream of new putative targets, however, this approach has yet to deliver an analgesic to the clinic (Figure 2). Phenotyping of transgenic mice in pain and inflammation assays can provide early target validation, and adoption of such targets is a high risk strategy which could provide high returns. Identifying receptor or ion channel targets that are altered in different types of human pain could provide analgesics for pain syndromes which are refractory to existing analgesics. Here we report on several case studies, highlighting the value and problems of each of the strategies

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Therapeutics

Figure 1



Refinement of existing analgesics

Triptans: The triptans were the first mechanism-based agents developed to treat migraine and can be considered refinements of existing drugs. The vasoconstrictor action of ergotamine on the cranial vasculature was proposed as early as 1938 as a possible mechanism for its anti-migraine efficacy. Ergotamine remained the only acute treatment specific to migraine until the launch of sumatriptan (Imigran[®]; Glaxo) in 1991, the first of a new class of what were subsequently shown to be 5-HT agonists as a novel treatment for migraine. Using classical *in-vitro* pharmacological studies Humphrey and colleagues (Glaxo) demonstrated that sumatriptan could produce the selective contraction of some but not all 5-HT receptor bearing blood vessels. These data supported the hypothesis that it was possible to contract cranial blood vessels while having a minimal effect on other major blood vessels. Following cloning and pharmacological characterisation of the 5-HT receptor family, it was subsequently demonstrated that like ergotamine, sumatriptan has high affinity at 5-HT_{1D} and _{1B} receptors, but in contrast to ergotamine it has only moderate affinity at 5-HT_{1A} receptors and lacks activity at other 5-HT, adrenergic and dopamine receptors. Its clinical efficacy and tolerability is superior to that of ergotamine. The discovery of sumatriptan triggered continued studies in this area by several of the other major pharmaceutical companies to produce 'sec-

ond generation triptans' (eg rizatriptan, Maxalt[®], Merck; naratriptan, Naramig[®], Glaxo; zolmitriptan, Zomig[®], AstraZeneca) with improved pharmacokinetics. Rizatriptan, for example, has faster onset after oral administration and better bioavailability than sumatriptan³. The side-effect profile of rizatriptan is similar to that of sumatriptan. Maxalt-MLT[®] (Merck), is a further refinement and is the first anti-migraine medicine available as orally disintegrating tablets, thus allowing it to be taken without water making it more convenient for the patient. The therapeutic action of the triptans is thought to be three-fold; (1) direct vasoconstriction of excessively dilated cranial blood vessels (a 5HT_{1B} receptor mediated response), (2) inhibition of the release of vasoactive neuropeptides (eg calcitonin-gene related peptide, CGRP) from peripheral terminals of trigeminal sensory fibres within the meninges (5-HT_{1D} receptor mediated response), and (3) inhibition of neuropeptide release (eg CGRP) in central terminals in the nucleus trigeminal caudalis (5-HT_{1D} receptor mediated response). The major theoretical limitation in therapeutic use of the triptans is the potential cardiovascular liability in patients with coronary heart disease due to the vasoconstrictor action. This inhibits the more widespread prescription of these agents by clinicians despite their effectiveness and good safety profile. Anti-migraine agents lacking a vasoconstrictor action would have a clear advantage over the 'triptans'. LY334370

(Lilly Research Labs) is a selective 5-HT_{1F} agonist which lacks vasoconstrictor action and has been reported to be effective in reducing headache pain intensity in migraineurs⁴. Although development of LY334370 has been discontinued, 5-HT_{1F} agonists would appear worth pursuing as a novel approach to treatment of migraine. Evidence suggests that the vasodilatation of cranial blood vessels during a migraine attack underlies the pathophysiology of migraine and this vasodilatation may be at least partly due to the release of the vasoactive peptide calcitonin gene related peptide (CGRP) from the endings of trigeminal sensory afferents. Other potential targets therefore include an antagonist acting at the receptors for CGRP. BIBN4096BS (Boehringer Ingelheim), a non-peptide CGRP receptor antagonist, is currently in phase IIa clinical trials for migraine although no data are yet available. It will be interesting to see if these third-generation agents will be as effective as the triptans against migraine, although it is likely they will have fewer side effects.

COX-2 inhibitors: Like the triptans, the recently introduced selective cyclooxygenase 2 inhibitors are refinements of existing analgesics. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin (acetylsalicylic acid), are the most widely prescribed and self-medicated drugs in the world. They have a long and fascinating history, stretching back several

centuries where extract of willow bark was used for the treatment of fever and acute rheumatism. Acetylsalicylic acid was synthesised in 1897 by Felix Hoffman and shown to have analgesic and anti-inflammatory activity in animals and marketed as an analgesic. The most commonly used agents include diclofenac, piroxicam, naproxen, ibuprofen and indomethacin. These agents inhibit the activity of the enzyme (cyclo-oxygenase) responsible for converting arachidonic acid to prostanoids. The major limitations in clinical use of NSAIDs are the side-effects on the gastrointestinal (GI) tract including ulceration and haemorrhage. GI toxicity may occur in up to 50% of patients treated chronically with NSAIDs for rheumatoid arthritis. In the late 1980s, two isoforms of cyclo-oxygenase were identified: COX-1, which is expressed constitutively in most cell types and was thought to be involved in cytoprotection of the gastric mucosa, and COX-2, which is expressed at very low levels under normal conditions (except in brain, kidney and ovaries/testes where it is constitutively expressed), but is rapidly induced by pro-inflammatory stimuli. The recognition of such differences in expression offered a potential breakthrough in the development of safer NSAIDs via selective COX-2 inhibition thus avoiding the gastrointestinal problems attributable to inhibition of COX-1. A key question was whether selective inhibition of COX-2 would provide the same analgesic efficacy as the mixed COX-1/COX-2 inhibitors. Preclinical studies with the

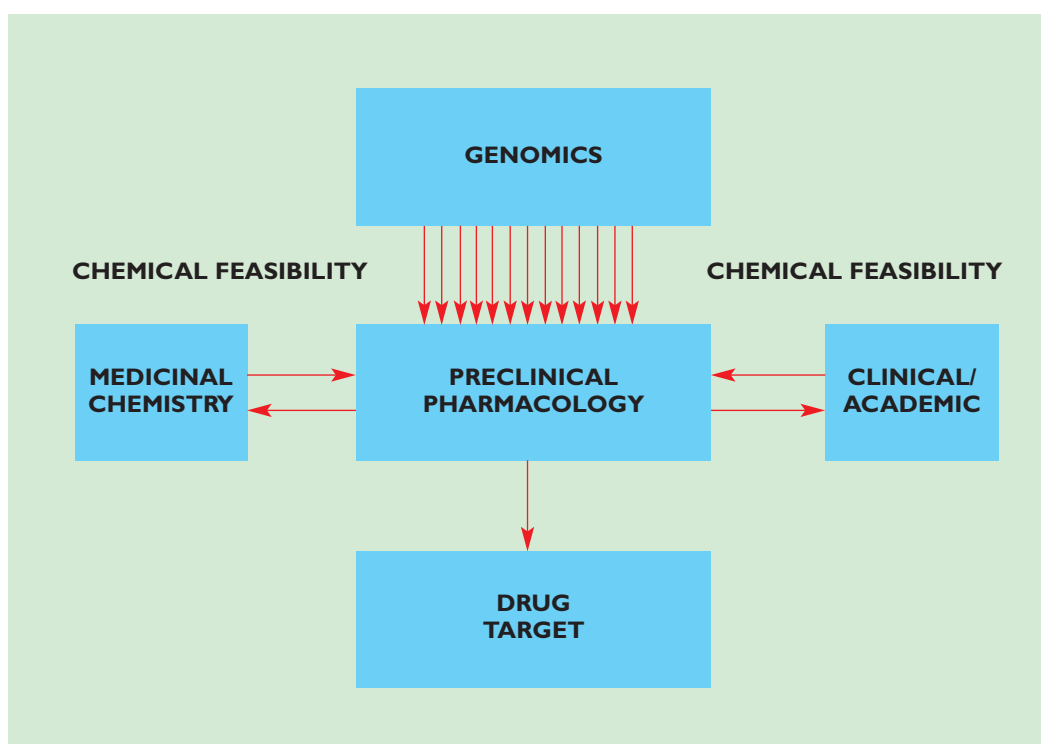


Figure 2

Therapeutics

highly selective COX-2 inhibitor, rofecoxib (Vioxx[®], Merck, Sharp and Dohme), were able to demonstrate comparable efficacy to indomethacin in rat inflammatory pain assays without affecting gastrointestinal integrity at up to 200mg/kg/day for five days (20 times the dose producing antinociception). Clinical studies with rofecoxib have now confirmed these observations in man, emphasising the predictiveness of the animal tests. In patients with postoperative dental pain, rofecoxib was administered orally (50mg). Rofecoxib had comparable analgesic efficacy to ibuprofen (400mg) although the duration of pain relief was longer. Rofecoxib also had similar efficacy to naproxen against rheumatoid arthritis but importantly was associated with significantly fewer upper gastrointestinal events⁵. The COX-2 inhibitors represent an important therapeutic advance.

Targeting physiological mechanisms arising from basic research

Substance P antagonists: Given that only so many refinements of existing analgesics can be cost effective, new approaches are needed. Understanding the physiology of pain is the first step. Based on this approach, substance P was a prime candidate and antagonists of substance P were developed for the treatment of migraine and pain. Substance P is expressed in the small sensory fibres that transmit pain signals to the spinal cord, it is released in response to intense painful stimuli, and when applied to the spinal cord of animals it causes pain-like behaviours. Substance P is also present in pain fibres that innervate the dura and release of SP can cause neurogenic inflammation which could lead to pain in the brainstem, and to migraine. Highly selective and high affinity antagonists of substance P (NK₁ receptor) were developed, but despite data from preclinical studies supporting an analgesic potential, clinical trials have not shown a convincing analgesic profile for NK₁ receptor antagonists in a range of pain conditions including migraine, dental pain, diabetic neuropathy and post-herpetic neuralgia (see review⁶). This set back has made scientists extremely cynical about the predictive value of the preclinical assays in which NK₁ receptor antagonists were effective. It needs to be remembered that these assays have been extremely good at predicting analgesic activity for other agents such as COX-2 inhibitors, gabapentin and NMDA antagonists. One possible explanation for the species discrepancy is that substance P may be a more important nociceptive neurotransmitter in small laboratory animals than it is in man. Secondly, it is possible that NK₁ receptor antagonists may have not been tested in most appropriate clinical pain conditions.

For example, there has been no major test of whether SP antagonists may be effective in chronic arthritic pain conditions. These agents are effective in animal arthritis models and increased expression of NK1 receptors is observed in the joints taken from patients with chronic arthritis.

Genes to drugs

Genomics impacts on almost every aspect of analgesic drug discovery from target identification and validation to lead evaluation. At the preclinical level many potential novel targets have been identified directly as a result of genomic studies. These studies have included the use of gene subtraction methods to determine changes in gene expression in pathological tissue following injury or inflammation. Genomic studies are likely to identify an increasing number of potential targets with the expectation that novel classes of analgesics will be realised. A major challenge will be to predict the physiological/pathophysiological relevance of novel targets and the potential efficacy versus adverse effects of compounds that act on the final protein products of these genes. The importance of this cannot be underestimated as there are likely to be more targets than can be viably exploited and success in developing novel analgesics is going to be increasingly dependent upon the judicious identification of the best potential targets. To achieve this potential targets need to be strictly reviewed in the context of evidence from both clinical and preclinical sources including using data from transgenic animals as well as evidence from available compounds (Figure 2).

In addition to helping to identify completely novel targets, information from genomic studies helps in the identification and evaluation of subtypes and/or splice variants of targets identified from clinical or preclinical studies. For example, some of the more effective treatments for neuropathic pain are compounds with sodium channel blocking properties such as carbamazepine, phenytoin, mexiletine and amitriptyline. The therapeutic utility of these compounds is, however, limited by their wide spectrum of pharmacological actions and importantly the non selective targeting of sodium channel subtypes which together result in a small therapeutic window. The cloning of a sensory neuron specific sodium channel (SNS/PN3) exclusively distributed in the small diameter nerve fibres associated with nociceptive transmission has led to the possibility of developing novel classes of sodium channel blockers with fewer of the CNS and cardiovascular side-effects of existing sodium channel blockers. In the absence of selective blockers for

SNS/PN3, a transgenic mouse has been generated and evaluated in nociceptive studies. Although studies with this gene deletion mutant were encouraging the antinociceptive phenotype of the mice was not as striking as expected. Electrophysiological data suggested this may be due to a compensatory upregulation of other sodium channels in small diameter sensory neurons of these mice. Therefore, in this case, while transgenic animals have helped validate SNS/PN3 as a potential analgesic target, studies with these animals may not be entirely predictive of the spectrum of activity of a selective small molecule blocker.

Another novel treatment that has been suggested for neuropathic pain conditions is a blocking drug which will target N-type calcium channels. The omega conotoxin peptide MVIIA (ziconotide, Elan®) blocks primary afferent neurotransmitter release in the spinal cord in a similar way to morphine and is effective when infused intrathecally in some patients with neuropathic pain. However, this therapy has limitations as patients reported a number of adverse events. These effects were possibly due to actions of the conotoxin on supraspinal N-type calcium channels. Recently, a number of splice variants of the N-type calcium channel have been identified, some of which have discrete localisation in either the peripheral nervous system or the central nervous system. It has been reported that certain omega conotoxins selectively block some splice variants. Although this is encouraging, it remains to be seen whether small molecules that target one or more splice variants can be developed and whether these can improve on the therapeutic window of ziconotide. The therapeutic utility is ultimately dependent upon the ability to deliver antinociceptive effects without affecting N-type calcium channels involved in sympathetic activity and other non-nociceptive neuronal functions. This is dependant upon an exclusive distribution and functionally important role for the splice variant in the target tissue; in this case the target tissue is the primary afferent nociceptors. Furthermore, to date toxins have proved disappointing leads for the development of small molecule ion channel blockers which tend to bind to a different distinct site on the large polypeptide multi-subunit ion channel complex.

Future developments in genomics will continue to impact on the development of novel analgesics. In particular, the development of conditional knockouts and the development of transgenic animals expressing the human ion channel or G protein coupled receptor target will help both in proof of concept studies as well as aiding the pharmacological realisation of novel analgesics.

Conclusions

The development of novel treatments for pain and headache is challenging and successes such as the triptans and COX-2 inhibitors are likely to be accompanied by failures. Strategies based upon strong clinical and preclinical evidence (Figure 1) are likely to reduce but not eliminate the risk of failures. Novel targets identified from genomic studies are likely to provide the greatest chances of developing analgesics with truly novel mechanisms of action which may consequently have a different therapeutic utility to existing analgesics. Targets identified from genomic studies are, however, also likely to have the weakest supporting evidence from existing clinical and preclinical studies and therefore have a high risk of failure. **DDW**

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