From demons to darlings: drugs from venoms

Drugs from venoms was the theme of a recent conference held on Heron Island, Queensland, Australia (16–21 August 1998). Unlikely as this premise might seem, there are some important examples of toxins or venom components being developed for pharmaceutical use. The arrow poison tubocurarine has been used in anaesthetic practice as a muscle relaxant for over 40 years, and most modern muscle relaxants were designed with an understanding of the structures of the curare alkaloids. Captopril, the first angiotensin converting enzyme (ACE) inhibitor in clinical use, was developed as an analogue of the bradykinin potentiating peptides from the venom of the Brazilian snake *Bothrops jararaca*, and even one of the most lethal toxins known, botulinum toxin, has found a use in treating uncontrollable muscle spasms.

The main themes explored during the conference were the benefits gained from the exquisite selectivity of toxins, the structure-based design of new agents from an understanding of the SAR of toxins, and the use of toxins as tools to probe potential therapeutic targets at the molecular and functional levels.

From fish killer to pain killer

George Miljanich (Neurex Corporation, California, USA) described progress with the development of the calcium channel blocker ω-conotoxin MVIIA (SNX-111, ziconotide) as an agent for treating intractable pain. This particular conotoxin, from the marine snail *Conus magus*, is highly specific for N-type Ca^{2+} channels, and it has been demonstrated that such channels are the major contributor to the calcium current involved in the release of neurotransmitters from nociceptive neurones in the spinal cord. Other reflexes appear to involve transmitter release triggered by activation of P/Q channels, and they are not affected by ziconotide. Miljanich described the clinical trials involving the intrathecal administration of ziconotide to patients with intractable neuropathic or cancer-related pain. The outcomes of Phase II trials were impressive, and results from two extensive Phase III studies are currently being analysed. Neurex plan to request FDA approval soon for what will be another clear example of going from venom to drug.

Ziconotide is ω-conotoxin MVIIA, which is just one of dozens of active peptides that have been isolated from *Conus* venoms. The development of this aspect of venom research was outlined by the principal pioneer in the area, Baldomero Olivera (University of Utah, Salt Lake City, UT, USA). He emphasized how the conotoxins acted synergistically in nature by having groups of toxins that acted on different functional components. At the neuromuscular junction, for example, ω-conotoxins block Ca^{2+} channels and reduce acetylcholine release, α-conotoxins block acetylcholine receptors, and μ-conotoxins block Na^{+} channels, especially preventing conduction of muscle action potentials. Olivera described recent work that is exploring the potential of conantokins, which block NMDA receptors, in treating epilepsy. So far, the development of drugs acting on NMDA receptors has been disappointing, principally because of side effects. The conantokins are highly selective for one subtype of NMDA receptor, and it is hoped that this selectivity will translate into a useful therapeutic ratio.

With ~500 species of cone snails and ~100 different peptides in each venom, this source must be expected to provide additional toxins with the potential to be developed into therapeutic agents.

Molecular scaffolds and structure-based drug design

The advent of high-field NMR spectroscopy has enabled the three-dimensional structures of small peptides, such as the conotoxins, to be determined relatively easily. Several speakers from Australia [Ray Norton and Paul Pallaghy, Biomolecular Research Institute, Melbourne; Glenn King, Sydney University; Kathy Nielsen and John Gehrmann, Centre for Drug Design and Development (CDDD), Brisbane] provided new information about structures of α- and ω-conotoxins and spider toxins. However, no matter how good the resolution of the structure, there can always be questions about conformational changes of the toxin under physiological conditions and on binding to the target. Some of the pitfalls of relying on NMR-derived structures were shown by Michael Rafferty (Parke-Davis, Ann Arbor, MI, USA). Using a benzodiazepine nucleus as a template, functional side chains were added to mimic the predicted geometry of the active residues of ω-conotoxin MVIIA in attempts to find low molecular weight analogues of this Ca^{2+} channel blocker. The lack of success was subsequently ascribed to a conformational change in the toxin at physiological pH. By contrast, a more conventional high-throughput screening approach has provided lead compounds of low molecular weight.

A different approach to structure-based drug design was described by André Ménez (CEN Saclay, France). His group has successfully transferred functions of large proteins (such as metal binding properties) to the much smaller framework typical of scorpion toxins

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like charybdotoxin. The ability to mimic the CD4 binding activity of gp120 in a relatively small peptide is impressive, and there may be some therapeutic potential in AIDS.

Toxins to probe therapeutic targets

Toxins can be very useful as probes of potential therapeutic targets. They can be used at the molecular level to reveal differences between different subtypes of receptors or ion channels. This approach was demonstrated on actions of brevetoxins and ciguatoxins on different types of Na^+ channels by presentations by Richard Lewis (CDDD) and David Adams (University of Queensland, Brisbane, Australia). As well as providing a better understanding of the properties of tetrodotoxin-sensitive and -resistant Na^+ channels, this work explores the therapeutic potential of agents that might act selectively on different types of Na^+ channels.

The ability of dendrotoxins from mamba snake venoms to distinguish different subtypes within the Kv1 family of K^+ channels was used in a study by Alan Harvey and colleagues (Strathclyde University, Glasgow, UK) aimed at localizing different K^+ channels in the brain and looking for selective changes with ageing and in Alzheimer's disease. Use of the toxins revealed changes in subunit expression in different conditions, leading to speculation that there may be scope for therapeutic intervention to improve cognitive function by targeting particular subtypes within the Kv1 family of K^+ channels.

Future prospects

The conference highlighted the rapid progress being made in understanding the structure and the pharmacological effects of some known toxins. Many contributions indicated the scope for finding additional toxins with novel structures and potentially useful activity. However, the conference also emphasized the considerable amount of work and the long time required to go from venom to drug. There is hope that ziconotide will be rapidly approved for therapeutic use so that it will act as a catalyst for other projects in the area of 'venoms to drugs'.

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Conquering airway inflammation in the 21st century

Inflammation of the lower airways is central to the pathophysiology of several severe lung diseases, in particular asthma and chronic obstructive pulmonary disease (COPD). The first meeting, held last year, on *Conquering Airway Inflammation in the 21st Century* focused upon airway inflammation, asthma and current therapy (β_2-adrenoceptor agonists, glucocorticosteroids and theophylline), and introduced several new therapeutic targets and 'anti-inflammatory' molecules [Rogers, D.F. and Giembycz, M.A. (1998) *Trends Pharmacol. Sci.* 19, 160–164]. This year's meeting, held at the National Heart & Lung Institute (London, UK) on the 14–16 September 1998, extended discussion of inflammation to airways remodelling, and had an increased emphasis on new targets and molecules.

In several instances, pharmaceutical moieties, which last year had demonstrated encouraging effects in preclinical evaluation, had now entered clinical trial. It was interesting to note that airways remodelling, although critical to development of the irreversible component of impaired lung function in asthma and COPD, was not an endpoint target for evaluation of drug efficacy. This is understandable, as remodelling is not an easy parameter to quantify. However, inhibition and/or reversal of airways remodelling may affect the overall value of any therapy for asthma and COPD. The following account focuses upon the newer targets and molecules discussed at the meeting, in particular where chemical structures and clinical data were presented.

Phosphodiesterase inhibitors

Elevation of cyclic AMP, either by β_2-adrenoceptor agonists or as a result of one of the possible mechanisms of action of theophylline, is a central therapeutic recommendation in guidelines on the management of asthma. Cyclic AMP can also be elevated by inhibiting the enzyme(s), termed phosphodiesterase (PDE), that degrade it. Although PDEs comprise a ten-member superfamily, it is PDE4 that is the predominant isoenzyme in immune and pro-inflammatory cells, and it is a major contributor to cyclic AMP metabolism in airways smooth muscle.

First generation PDE4 inhibitors such as rolipram are active across a broad spectrum of disease models. However, their therapeutic utility is limited by unwanted side effects, predominantly nausea, vomiting and gastric acid secretion. Fortunately, there are currently two options to reduce side effects. The first is development of compounds that are selective for one of the four gene families (PDE4A, B, C or D), which may selectively promote the desirable, rather than the deleterious, effects of PDE

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