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EXPERT REVIEWS

Found in translation: integrated approaches to drug development

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2010 Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists Annual Scientific Meeting

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The 44th Annual Scientific Meeting of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; 'Found in translation: integrated approaches to drug development', was held in Melbourne, Australia, from 28 November to 1 December 2010. This was a wide-ranging conference that included some discussion of new drugs and new targets for drug development. The new drugs included dynamin inhibitors, Xen2174, an oxytocin receptor agonist and annexin-A12–26. The new targets included B7-dependent costimulation, chemoattractant receptors, granulocyte–macrophage colony-stimulating factor and glutathione peroxidases.

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Annual Scientific Meeting brings together academics and/or researchers from Australia and New Zealand to discuss their research in experimental and clinical pharmacology and toxicology. At the 2010 meeting, there were symposia entitled 'Exploiting novel drug discovery paradigms'; 'Current challenges facing pharmacogenomics'; 'Immunopharmacology in diseases of the cardiovascular, respiratory, and central nervous system'; 'Antivenom treatment'; and 'Medication safety'. There were also oral and poster presentations. Some of the new drugs and targets discussed at ASCEPT 2010 are the subject of this article.

New drugs

Dynamin inhibitors

Synaptic vesicle recycling in nerve terminals is essential for the maintenance of neurotransmission and this recycling involves the enzyme dynamin I. Thus, following exocytosis, synaptic vesicles are reformed from the plasma membrane by endocytosis, and this endocytosis requires dynamin I. Inhibition of dynamin I will lead to a reduction in neurotransmitter recycling, which may be useful in the treatment of epilepsy. The antipsychotic drug chlorpromazine inhibits dynamin I, so it has been suggested that inhibitors of dynamin I may have potential use as antipsychotic drugs.

Adam MClusky (University of Newcastle, NSW, Australia) is developing small molecules that inhibit dynamin I. By screening a number of compound libraries, the bisindolylmeleimides were initially identified as inhibitors of the GTPase activity of dynamin I, with the concentration that causes 50% inhibition (IC_{50}) values of approximately 100 µM, but these were thought to have structures that were too complex. Thus, the indole structure of the bisindolylmeleimides was used as a scaffold to develop simpler structures and these indole-based dynamin inhibitors were called dynoles [1]. The best dynole was 2-cyano-3-(1-[2-(dimethylamino)-ethyl]-1*H*-indol-3-yl)-*N*-octylacrylamide with an IC_{50} of 1.3 µM [1]. This dynole inhibited receptor-mediated endocytosis in U_2OS cells. As receptor-mediated endocytosis is mediated by dynamin II, this shows that the dynoles are not selective for dynamin I.

The next group of dynamin inhibitors developed by McClusky were the iminochromene inhibitors [2]. The most potent of these was *N,N*-(ethane-1,2-diyl)bis(7,8-dihydroxy-2-iminochromene-3-carboxamide), which inhibited dynamin I and II with IC_{50} values of

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200–300 nM [2]. One of the other iminochromene inhibitors, *N,N*-(ethane-1,2-diyl)-bis(7,8-dihydroxy-2-iminochromene-3-carboxamide), inhibited dynamin II receptor-mediated endocytosis and dynamin I-mediated synaptic vesicle endocytosis with IC_{50} values of 11 and 100 µM, respectively [2].

Recently, McCluskey and colleagues have identified some dynamin inhibitors that show a fivefold selectivity for dynamin I over dynamin II [3]. To do this, the group used a homology model for the GTP-binding domain of human dynamin I, which led to the development of the pthaladyns [3]. 4-chloro-2-([2-(3-nitrophenyl)-1,3-dioxo-2,3-dihydro-1*H*-iso-indole-5-carbonyl]-amino)-benzoic acid (compound 23), inhibited dynamin I and II GTPase activity with IC_{50} values of 17 and 63 µM, respectively [3]. The most interesting finding with this series of inhibitors was that compound 23 inhibited synaptic vesicle endocytosis with an IC_{50} of 13 µM, but was not active against receptor-mediated endocytosis [3], which suggests that the group is now successfully making small molecules that are selective for dynamin I over II.

Marine natural products to Xen2174 for pain

Marine natural products are an important source of new chemical diversity for drug discovery. Richard Lewis (Xenome Ltd.; the Institute of Molecular Biosciences, University of Queensland, Brisbane, Australia) uses the venom of *Conus* (marine cone snails) as his source of new pharmacologically active compounds. Conotoxins are highly specific for their evolved target. One of the ω-conotoxin family, MVIIA (ziconitide), is already on the market for chronic pain. Xenome has developed a synthetic conopeptide library from derived venom peptide sequences as a discovery platform for novel drug lead discovery.

Noradrenaline amplifies descending pain inhibition and the levels of noradrenaline can be increased by inhibiting the noradrenaline transporter. This transporter is inhibited by the χ-conotoxins, and one of the analogs of this, χ-MrIA, also reverses allodynia in a rat model of neuropathic pain [4]. From this basis, Xen2174 was developed for superior chemical stability [4]. Xen2174 inhibits the noradrenaline transporter [4], and has been shown to be safe in a Phase I clinical trial where it was used intrathecally to treat severe and unmanageable pain in cancer. Lewis reported that Xen2174 was going to be clinically tested in postsurgical pain.

Oxytocin receptor agonist

Oxytocin receptors in the CNS modulate anxiety and social behavior. However, the endogenous ligand (oxytocin) has limited ability to cross the blood–brain barrier. William Jorgensen (Brain and Mind Research Institute, University of Sydney, NSW, Australia) is involved in nonpeptidic oxytocin receptor agonist development. Compound 1 is a piperazine that produces a similar pattern of neuronal activation to oxytocins – that is, pronounced Fos expression in the paraventricular and supraoptic nuclei of the hypothalamus and in the medial amygdala. After intraperitoneal injection in rats, compound 1 crossed the blood–brain barrier and was active as an anxiolytic and prosocial. Jorgensen is using compound 1 as a lead for the development of clinically relevant nonpeptidic oxytocin receptor agonists for use in the treatment of anxiety.

Annexin-A1$_{2–26}$

Annexin-A1 (ANX-A1; also known as lipocortin-1) is a member of the annexin protein superfamily. The expression of ANX-A1 is upregulated by ischemia/reperfusion and glucocorticoids. Rebecca Ritchie (Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia) has previously shown that the N-terminal-derived peptide ANX-A1$_{2–26}$ preserves the viability of cardiomyocytes subjected to metabolic inhibition *in vitro*. In intact hearts of mice and rats subjected to ischemia-reperfusion injury, ANX-A1$_{2–26}$ accelerated and improved the recovery of left ventricular developed pressure. ANX-A1$_{2–26}$ cardioprotection was associated with attenuated cardiac enzyme release and increased Akt phosphorylation. Thus, ANX-A1-based therapies may be a novel approach for the prevention and treatment of reperfusion injury.

New targets

B7-dependent costimulation

Recently it has been demonstrated that both innate and adaptive immunity contribute to hypertension. In hypertension, inflammatory cells (i.e., macrophages and T cells) accumulate in the blood vessel wall and kidney of hypertensive animals. Mice lacking lymphocytes are resistant to the development of hypertension, and in these mice the introduction of T cells can restore hypertensive responses to angiotensin II and to deoxycorticosterone salt challenge. T-cell activation requires T-cell receptor ligation and costimulation. This costimulation often involves interaction between B7 ligands (CD80 and CD86) on antigen-presenting cells with the T-cell coreceptor CD28.

David Harrison (Emory University School of Medicine, Atlanta, GA, USA) has recently shown that angiotensin II-induced hypertension in mice increased the presence of activated dendritic cells in secondary lymphatic tissues [5]. Furthermore, blockade of B7-dependent costimulation with cytotoxic T-lymphocyte antigen (CTLA)-Ig reduced both angiotensin II and deoxycorticosterone salt-induced hypertension [5]. CTLA-Ig also reduced the activation of circulating T cells, T-cell cytokine production and vascular T-cell accumulation [5]. This research suggests blockade of B7-dependent costimulation as a new target for the treatment of hypertension.

Chemoattractant receptors

The complement anaphylatoxin C5a is proinflammatory and probably contributes to sepsis. Charles Mackay (Monash University, Melbourne, VIC, Australia) has been using antibodies to the C5a receptors, C5ar and C512, to investigate the role of C5a in a mouse model of sepsis (cecal ligation and puncture), and showed that mid-grade sepsis was reduced by using antibodies to the receptors, or in knockout mice lacking C5ar or C512 [6]. However, in high-grade sepsis, it was necessary to block both C5ar and C512 to reduce the sepsis [6]. This shows that both C5ar and C512 are targets for inhibition in sepsis, and that this inhibition could be with antibodies or with small molecules.

MacKay has also been involved in research showing the relationship between the chemoattractant receptor GPR43 and ulcerative colitis. Normal intestinal microbiota may protect against the development of inflammatory diseases by fermenting dietary fiber

to produce short-chain fatty acids that stimulate the G-protein-coupled receptor 43 (GPCR43). Mice deficient in GPR43 show exacerbated or unresolving inflammation in models of colitis [7]. Thus, stimulation of the GPR43 may be important in resolving inflammation. In support of this, the GPR43 synthetic agonist phenylacetamide I was a potent chemoattractant for neutrophils [7]. This research suggests that agonists at GPR43 may have anti-inflammatory potential in inflammation of the gut.

In smoking-induced chronic obstructive pulmonary disease

Cigarette smoking is the major cause of chronic obstructive pulmonary disease (COPD). The drugs that are presently used to treat COPD (e.g., β-adrenoceptor agonists, muscarinic receptor antagonists and glucocorticoids) are not very effective. Ross Vlahos (University of Melbourne, VIC, Australia) has been exposing mice to cigarette smoke to determine the mediators involved in the resulting inflammation and how this inflammation can be reduced. The research has shown that granulocyte–macrophage colony-stimulating factor (GM-CSF) may have a role in this inflammation, and that an antibody to GM-CSF (22E9, an anti-GM-CSF monoclonal antibody [mAb]) reduced the macrophage and neutrophil levels in the bronchoalveolar lavage fluid, whole lung TNF-1 and macrophage inflammatory protein-2 [8]. The anti-GM-CSF mAb also decreased matrix metalloproteinase (MMP)-12 mRNA, but had no effect on MMP-9 and net gelatinase activity [8]. The mice treated with the anti-GM-CSF mAb also lost less weight when exposed to cigarette smoke compared with the untreated mice [8]. These results show that GM-CSF is a key mediator in smoke-induced airway inflammation and is a target for neutralization in diseases such as COPD.

Glutathione peroxidases are a family of antioxidant enzymes that catalyze the reduction of the damaging reactive oxygen species hydrogen peroxide and hydroperoxides to water and alcohols, respectively. Hydrogen peroxide is elevated in exhaled breath from subjects with COPD, and there is a depletion of glutathione peroxidise. Vlahos has shown that mice lacking glutathione peroxidise are susceptible to oxidative stress. When these mice were exposed to cigarette smoke they had enhanced neutrophils, macrophages and protolytic burden compared with wild-type mice [9]. The glutathione peroxidase mimetic ebselen inhibited smoke-induced increases in bronchoalveolar lavage fluid macrophages, neutrophils, proteolytic burden, and macrophage and neutrophil chemotactic factor expression when administered prophylactically [9]. This study shows that agents that mimic glutathione peroxidase, such as ebselen, may have therapeutic potential in the treatment of inflammatory conditions such as COPD.

Next year, the ASCEPT Annual Scientific Meeting is to be held in Perth, Western Australia, from 4 to 7 December, and the meeting will be in conjunction with the meetings of the Australian Physiological Society and the High Blood Pressure Council of Australia.

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