PAR2 antagonists—the next generation of anti-inflammatories?

Abi Berger *BMJ*

New understanding of how sensory nerve cells transmit their signals to the central nervous system has been reached by researchers at the University of California in San Francisco.

Nigel Bunnett, professor of surgery and physiology, and his team have shown that tryptase—a degradatory enzyme known to be involved in triggering the inflammatory process—works by activating a new class of receptor called PAR2 (proteinase activated 2 receptors).

Professor Bunnett's work suggests that substances that block these receptors could make good candidates for new anti-inflammatory drugs (*Nature Medicine* 2000;6:151-8).

When sensory nerve cells are activated, calcium levels

inside these cells rise and the neuropeptides, such as substance P and calcitonin gene related peptide (CGRP) are released. Both of these are important in the formation of inflammatory oedema.

Mast cells sit in the vicinity of sensory nerve endings in both animals and humans. When mast cells degranulate they release tryptase, in addition to histamine and prostaglandins. It has been shown that tryptase activates PAR2 receptors, which are located on sensory neurons.

Professor Bunnett and his colleagues wanted to find out if the release of neuropeptides from neurons is mediated by tryptase activated PAR2 receptors. "We wanted to establish whether the mast cells were

'talking' to neurons via tryptase," explained Professor Bunnett.

They first examined rat sensory nerves to see if they expressed PAR2 receptors and found that 63% of them did. Up to 40% of them also expressed substance P and CGRP.

The researchers then cultured sensory nerve cells and measured the level of intracellular calcium, as a measure of nerve cell excitation. When they then introduced pure human tryptase and trypsin (a PAR2 agonist), the intracellular calcium level went up, indicating excitation had occurred.

"We then wanted to see whether tryptase stimulated the release of substance P and CGRP from nerves," said Professor Bunnett. They did this by taking pieces of rat tissue, perfusing them with buffer, and adding tryptase and specific PAR2 agonists. Both substance P and CGRP were released.

In the final experiment, the team took a single rat paw and injected a PAR2 agonist into the pad. After six hours the paw had become swollen, and the amount of oedema was measured.

The team repeated this procedure in animals that had been pretreated with antagonists of the substance P and CGRP receptors or with capsaicin—a neurotoxin that ablates sensory nerves. When the researchers then introduced PAR2 agonists, very little oedema was produced.

"This confirmed to us that PAR2 receptors on sensory nerves are critical to the inflammatory process," said Professor Bunnett, "and substances that specifically block PAR2 receptors should make good anti-inflammatory agents." □

Drug company issues warning about flu drug

Gavin Yamey *BMJ*

GlaxoWellcome issued a warning letter to doctors across Europe last week that its drug for treating influenza, zanamivir (Relenza), could cause bronchospasm and serious respiratory deterioration.

The company now advises doctors to use special caution in prescribing the drug to patients with underlying asthma or chronic obstructive pulmonary disease. Such patients, it suggests, should be informed of the risk of bronchospasm and should ensure that a fast acting bronchodilator is available.

Over 500 000 prescriptions of the drug have been issued in Europe and the United States during the current flu season.

In the United States, the Food and Drug Administration sent out a "public health advisory" notice on the safe and appropriate use of flu drugs, including zanamivir and a second new drug, oseltamivir (Tamiflu).

Laura Bradbard, spokeswoman for the administration, said: "As of January 12, there were five deaths of people with influenza who were treated with Relenza. Two died of bacterial infection, in two there was an underlying disease contributing to the death, such as diabetes or respiratory disease, and one had complicated influenza."

The advisory notice warns doctors that "anti-viral products have no activity against bacterial infections" and advises them to be suspicious of primary or concomitant bacterial infection in patients with flu-like symptoms.

The National Institute for Clinical Excellence (NICE) ruled last year that doctors in England and Wales should not prescribe zanamivir (16 October, p 1024). It made its ruling partly because no clear evidence exists for its safety and efficacy in patients with serious respiratory or cardiac disease, as these patients have been excluded from clinical trials (11 September, p 659). □

A nerve cell releases neuropeptides, triggered by tryptase activated PAR2 receptor

UK lifts ban on frozen eggs

Jacqui Wise *London*

The UK Human Fertilisation and Embryology Authority has decided to allow frozen eggs to be used in infertility treatment following a report showing that the procedure is sufficiently safe.

Until now, infertility clinics in the United Kingdom were allowed to freeze and store human eggs, but they could not be thawed and used in infertility

treatment. British infertility clinics have been campaigning vigorously for the ban to be lifted and had threatened to launch a judicial review of the authority's ruling. The technique is widely used elsewhere in the world, particularly in the United States.

The authority decided to lift the ban after commissioning an independent report from Dr Sharon Paynter, lecturer in the department of obstetrics and gynaecology at University of Wales College of Medicine, Cardiff.

The report concludes: "Whilst this technique is not without risk,

recent results are very encouraging. Any patient wishing to undertake this option should be fully informed of the risks involved and the chance of success."

The main risk is that the eggs will not survive the freezing and thawing process. Dr Paynter said that one of the main determining factors of success is the quality of the eggs that are collected. For best results, mature oocytes should be frozen within eight hours of collection. The use of frozen eggs, however, carries a much lower success rate than conventional in vitro fertilisation (1-10% compared with 17%). □