G-PROTEIN-COUPLED RECEPTORS

Orphan's pain

'Orphan' G-protein-coupled receptors (GPCRs) — receptors that have been identified by genomic techniques, but whose function and ligands are unknown — are proving to be fertile ground for researchers who are looking for potential new drug targets. Writing in *Nature Neuroscience*, Lembo *et al.* describe how they have reunited one group of orphan GPCRs with their ligands, and uncovered a new receptor system that might be important as a potential target for analgesia.

The family of GPCRs that are described by Lembo and colleagues is expressed only in small sensory neurons in the dorsal root ganglia and trigeminal ganglia in rats and humans, which led the researchers to name these GPCRs the sensory-neuron-specific receptors (SNSRs). The neurons in which the SNSRs are expressed are involved in the transmission of pain signals. When the researchers searched for ligands for the SNSRs by expressing them in cultured cells and testing a panel of candidates, they discovered that the receptors were activated by a range of opioid-related peptides.

The most potent ligand was bovine adrenal-medulla peptide 22 (BAM22), which is produced by cleavage of the opioid peptide precursor proenkephalin A. BAM22 is expressed in the rat dorsal root ganglion and the dorsal horn of the spinal cord. It has been implicated in nociception, and can bind to all the known opioid receptors, but its function is unclear.

When Lembo *et al.* compared the abilities of different opioid-related peptides to activate the SNSRs, they found that the structural requirements for activation of SNSRs were different from the requirements of opioid receptors. They also found that, unlike opioid receptors, the SNSRs could not be blocked by naloxone or other opioid-receptor antagonists. They propose that the SNSRs represent a new family of GPCRs — distinct from the opioid receptors — that are likely to be involved in nociception.

Recently, Dong *et al.* described a family of mouse GPCRs, called MRGs (*mas*-related genes), and Lembo *et al.* report that these are identical to the SNSRs. However, Dong *et al.* found that the neural MRGs, which were also expressed in a specific subset of sensory neurons, were most potently activated by peptides such as neuropeptide FF (NPFF), which has also been implicated in pain systems, but which activates the SNSRs only weakly. As there are many MRGs, it is possible that their sensitivities to NPFF and BAM22 vary.

The discovery of a family of receptors that is expressed only in nociceptive neurons, and which recognizes an opioid-type ligand through a non-opioid mechanism, might provide a new target for analgesic therapies. In particular, as the authors point out, the very specific localization of the SNSRs to the nociceptive neurons might indicate that drugs that target these receptors will have fewer side effects than compounds that target opioid receptors, which are widely expressed in the brain.

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Nature Reviews Neuroscience

References and links

ORIGINAL RESEARCH PAPER Lembo, P. M. C. *et al*. Proenkephalin A gene products activate a new family of sensory neuron-specific GPCRs. *Nature Neurosci*. **5**, 201–209 (2002)

FURTHER READING Dong, X. *et al*. A diverse family of GPCRs expressed in specific subsets of nociceptive sensory neurons. *Cell* **106**, 619–632 (2001)

WEB SITES Encyclopedia of Life Sciences: http://www.els.net/
G protein-coupled receptors | opiate receptors

IN BRIEF

NEURODEGENERATIVE DISEASE

Neurotoxin-induced degeneration of dopamine neurons in *Caenorhabditis elegans*.

Nass, R. *et al. Proc. Natl Acad. Sci. USA* **99**, 3264–3269 (2002)

The molecular basis of dopamine-neuron vulnerability and cell death in Parkinson's disease is poorly understood. Nass *et al.* report that exposure of *C. elegans* to the neurotoxin 6-hydroxydopamine causes selective degeneration of dopamine neurons, as visualized by fluorescent-protein tagging. The model system that was established could be a powerful tool for studying the molecular mechanisms that underlie the degeneration of dopamine neurons in Parkinson's disease, and might also be valuable in screening for neuroprotective agents.

CANCER

Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukaemia.

Kantarjian, H. *et al. N. Engl. J. Med.* **346**, 645–652 (2002)

Chronic myelogenous leukaemia (CML) is caused by the BCR–ABL kinase. Imatinib mesylate (Gleevec), a selective inhibitor of this kinase, was approved for the treatment of CML in 2001. Kantarjian *et al.* assessed the effects of Gleevec in patients with late–chronic-phase CML in whom therapy with interferon-α had failed, and found that it induced high rates of cytogenetic and haematological responses, and prevented disease progression in ~90% of patients.

VIRAL INFECTION

Inhibition of cyclooxygenase 2 blocks human cytomegalovirus replication.

Zhu, H. *et al. Proc. Natl Acad. Sci. USA* **99**, 3932–3937 (2002)

Prostaglandins such as PGE_2 elicit a wide range of physiological responses. Zhu *et al.* show that levels of cyclooxygenase 2 (COX2), a key enzyme in the pathway that synthesizes PGE_2, are markedly increased in human cells after infection with human cytomegalovirus (HCMV). Treatment of cells with a selective COX2 inhibitor reduced the production of infectious virus by a factor of >100, and virus replication was substantially restored when drug-blocked cultures were supplemented with PGE_2. These findings indicate that induction of COX2 and synthesis of PGE_2 are essential for efficient HCMV replication in human cells.

CANCER

The *CLN3* gene is a novel molecular target for cancer drug discovery.

Rylova, S. N. *et al. Cancer Res.* **62**, 801–808 (2002)

Defects in the *CLN3* gene cause juvenile Batten disease, a neurodegenerative disorder characterized by accelerated apoptotic death of photoreceptors and neurons. By contrast, resistance of tumour cells to apoptosis is a key feature of cancer development. Rylova *et al.* show that *CLN3* is overexpressed in several cancer cell lines and that blocking *CLN3* expression using an antisense approach inhibits cancer-cell growth and viability.