MICROBIAL DISEASE

Part three of the anthrax trilogy

Knowledge of the structure of the proteins that make up 'anthrax toxin' should be valuable in the design of new drugs to counteract its lethal effects. Two of the three toxin components, protective antigen and lethal factor, had their structures determined in 1997 and 2001, respectively. In the 24 January issue of *Nature*, Drum *et al.* now complete the story by elucidating the structure of the third component, oedema factor (EF), with and without calmodulin (CaM), the protein that activates EF after entry into the host cell.

Like many infectious organisms, the anthrax bacteria disrupts intracellular signalling pathways by increasing the concentration of a key signalling molecule — cyclic AMP — in infected cells, thus inhibiting the immune response against the bacteria. On binding to calmodulin, a ubiquitous intracellular modulator, the conformation of EF is considerably altered, creating a site that can catalyse the formation of cAMP from ATP, but at a rate 1,000-fold higher than that of the adenylyl-cyclase–CaM complex that has this role in normal cells. Moreover, in the EF–CaM complex, CaM is locked into a conformation that cannot modulate other signalling proteins, as it would normally.

Whether or not EF represents a good drug target remains to be seen; however, its active site is a deep, narrow pocket that should be amenable to blocking with a small molecule, and also differs considerably from the active site of mammalian adenylyl cyclase, reducing the risk of adverse interference with this key enzyme. Further research could also have benefits beyond the potential for anthrax therapies, as EF-like adenylyl-cyclase toxins are found in pathogens that cause whooping cough and common hospital-acquired infections.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Drum, C. L. *et al*. Structural basis for the activation of anthrax adenlyl cyclase exotoxin by calmodulin. *Nature* **415**, 317–402 (2002)

FURTHER READING Petosa, C. *et al*. Crystal structure of the anthrax toxin protective antigen. *Nature* **385**, 833–838 (1997) | Pannifer, A. D. *et al*. Crystal structure of the anthrax lethal factor. *Nature* **414**, 229–233 (2001)

ANALGESIA

Ecstatic about RAVE

We are all naturally dependent on opioids for our emotional health, and some of us indulge in their recreational use. Both internally generated endorphins and drugs exert their action by interacting with specific membrane receptor proteins on neurons. Opioid painkillers, such as morphine, also exert their effect through the μ-opioid receptor (MOR). Use of morphine is hindered in the long-term by the development of tolerance to the painkilling effects of the drug. In contrast to the prevailing view, Whistler and colleagues provide *in vivo* evidence that endocytosis of MOR can reduce, rather than increase, the development of tolerance to morphine.

Opioid receptors belong to the large superfamily of G-protein-coupled receptors (GPCRs). The mechanisms for mediating the development of tolerance and dependence to morphine are controversial. The ability of MOR agonists to promote endocytosis of MOR is not related linearly to the agonist activity. The net amount of a signal that is transmitted to the cell is a function of both processes, a relationship termed 'relative activity versus endocytosis', or RAVE. Morphine has a high RAVE value because of an inability to promote endocytosis. Endorphins and other opiate drugs have similar signalling efficacies, but have lower RAVE values because they induce endocytosis.

Whistler and colleagues reasoned that if prolonged signalling at MOR contributes to the development of tolerance, then lowering the RAVE value by reducing that prolonged signalling would reduce the unwanted side effects. Consistent with this hypothesis, they showed that rats treated chronically with morphine plus the enkephalin, DAMGO (D-Ala^2-MePhe^4-Gly^5-ol), which facilitates MOR endocytosis, had reduced development of analgesic tolerance compared with rats treated with morphine alone. The present study shows that MOR can dimerize, as seen with other GPCRs, and proposes that this dimerization is mechanistically important in influencing the endocytic properties of the receptor, thereby reducing the development of tolerance to morphine.

The current view that endocytosis of MOR contributes directly to tolerance by decreasing the number of functional receptors on the cell surface has discouraged drug discovery programmes from investigating new agonists to promote endocytosis. However, this study indicates that agonists that promote endocytosis of MOR might provide analgesics with improved tolerance profiles. In the meantime, administration of drugs that promote endocytosis of MOR with morphine might produce less tolerance than morphine alone.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER He, L. *et al*. Regulation of opioid receptor trafficking and morphine tolerance by receptor oligomerization. *Cell* **108**, 271–282 (2002)

FURTHER READING Williams, J. T. *et al.* Cellular and synaptic adaptations mediating opioid dependence. *Physiol. Rev.* **81**, 299–343 (2001)

WEB SITES Whistler's laboratory: http://www.egcrc.org/pis/whistler-r.htm

Encyclopedia of Life Sciences: http://www.els.net opiates | opiate receptors