Emerging molecular targets

Anesthesia and α_{2A} adrenergic receptors

The ideal anesthetic would have a well defined and highly selective site of action in the brain that promotes a rapid loss of consciousness with no other actions on the major organs of the body. Also, it would work at a molecular site where the effect of the anesthetic could be readily reversed with a second agent to allow the patient to quickly regain consciousness with no lingering side effects.

Unfortunately, such an anesthetic does not exist. Even though surgeons have used various chemicals to induce anesthesia for the past 150 years, little is known about the precise mechanism of action of most of the anesthesia-inducing compounds. The drugs used to induce anesthesia are not highly specific, and the patient must wait for the anesthetic agent to be naturally dispersed from the site of action or metabolized before regaining consciousness. As a result, great skill is needed by the anesthesiologist to provide just the right amount of drug to maintain an unconscious state, while at the same time managing potentially life-threatening side effects associated with the anesthetic.

An important step in developing an ideal anesthetic has now been taken by Dr Mervyn Maze and coworkers at the Stanford University Medical Center (Palo Alto, CA, USA). They used antisense technology to reveal that in rats the anesthetic dexmedetomidine (Dex) induces anesthesia by acting on the α_{2A} subtype of the α-adrenergic receptor in the locus ceruleus of the brain [*J. Clin. Invest.* (1996) 98, 1076–1080]. Maze's group injected antisense oligonucleotides directly into the locus ceruleus to specifically inhibit by 30–40% the expression of the various subtypes of the α-receptor. They then administered a dose of Dex, placed the rats on their backs, and determined how long it took for the rats to regain consciousness and right themselves. When the antisense specific for the α_{2A}-adrenergic receptor was used, the rats righted themselves much more quickly than when antisense for the other subtypes of the α-adrenergic receptor or a scrambled oligonucleotide was administered.

The fact that Dex induces anesthesia through action on an α-adrenergic receptor has been known for some time, and its inability to discriminate between the different subtypes of this receptor is thought to be responsible for its cardiovascular and other side effects. The new knowledge that it induces anesthesia by acting on the α_{2A} subtype of the receptor provides a rationale for the discovery of more specific anesthetics that will more closely approximate the ideal.

Chloride ion efflux and human neutrophil function

The discovery of compounds to inhibit or modulate neutrophil activation remains an important goal of pharmaceutical research. The key to finding such compounds may await the identification of novel molecular targets.

Recently, the role of chloride ion efflux during neutrophil activation has been the focus of research by several groups. This is because resting neutrophils have an unusually high level of intracellular chloride ions and one of the earliest steps observed upon neutrophil activation is a massive efflux of chloride ions. However, it has not been clear if the efflux of chloride ions is essential for neutrophil activation or simply a by-product of the activation process. Now, Dr Renzo Menegazzi and coworkers from the University of Trieste (Trieste, Italy) report that chloride ion efflux is an essential step that is required to activate the adherence, spreading and respiratory burst of human neutrophils that is triggered by tumor necrosis factor α (TNFα) [*J. Cell Biol.* (1996) 135, 511–522].

Within five minutes of addition of TNF to a preparation of human neutrophils resting on a fibronectin-coated surface, Menegazzi and coworkers consistently observed a massive efflux of chloride ion from the neutrophils. They used three different chloride transport inhibitors – furosemide, ethacrynic acid, and *o*-[(3-hydroxymercuri-2-methoxypropyl)carbamoyl]phenoxyacetic acid – to evaluate the importance of the chloride ion efflux upon neutrophil activation. All three inhibitors were effective in blocking chloride ion efflux as well as the adherence, spreading and respiratory burst reactions. Moreover, they observed that the same sequence of neutrophil reactions could be achieved in the absence of TNF by simply exposing the neutrophils to a chloride-free medium, a maneuver that also triggers a rapid efflux of chloride ion from the neutrophil. The researchers believe this latter experiment strongly supports the results with the chloride transport inhibitors that suggest that chloride ion efflux is an essential step in the activation of human neutrophils by TNF.

The mechanism by which TNF triggers the efflux of chloride ions from neutrophils remains to be determined as well as the role that chloride ion efflux plays in the signal-transduction process leading to neutrophil activation. However, if the observations of Menegazzi and coworkers turn out to be correct, drug discovery groups may do well to include the search for inhibitors of neutrophil-specific chloride ion transport in their repertoire of assays for the discovery of compounds to block neutrophil function.

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New ligands for peptide receptors

In spite of recent innovations in peptide delivery systems aiming to make peptides available as therapeutic agents, the design of metabolically stable small molecule ligands that mimic bioactive peptides remains an important area of pharmaceutical research.

In *Recent Advances in the Development of Peptide Receptor Ligands,* a special issue of *Regulatory Peptides*, many of the major aspects of the design and discovery of ligands for peptide receptors are discussed. Studies highlighting new developments in neuropeptide Y, opioid, bradykinin and bombesin receptor ligand design are included, as well as reviews of research in more mature areas, such as CCK and tachykinin receptor ligand design. [*Regul. Pept.* (1996), 65, 1–100]. For more information contact Elsevier Science, fax: +31 20 485 3264, e-mail: F.KLINKENBERG@elsevier.co.nl.

The 2nd Joint Winter Meeting of the European Peptide Club (ENC) and the Winter Neuropeptide Conference takes place in Kitzbühel, Austria, on 8–11 February 1997. This year's meeting is entitled *Neuropeptides in Sensory and Other Brain Systems.* Information on the meeting is available from Dr Alois Saria, fax: +43 512 504 3716, e-mail: alois.saria@uibk.ac.at.

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