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Histamine and histaminergic ligands; a playground for medicinal chemists

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It is about hundred years ago that in the chemical literature the compound 4-β aminoethylimidazole appeared for the first time; no relationships with biological activities were mentioned. About 5 years later, the compound was found to be identical with a component isolated from animal tissue: decarboxylated 1-histidine. From that time on, the name histamine is used, from histos, tissue. As the compound was considered to be 'just' a degradation product from proteins, from 1-histidine, no attention was paid to the biological role for histamine initially.

In the late twenties of the previous century, histamine got much attention when it was found that the compound was the same as the compound H1, which was considered to play a major role in allergic reactions. Obviously, the chemically very simple histamine played a major role in physiology and in pathology.

When the role of histamine in allergy was generally accepted, the interest for anti-histaminics emerged. The first useful anti-histaminics appeared on the market during the 1940s; antergan, diphenhydramine. The compounds were not as successful as anti-allergies as has been hoped and even expected. The main reasons for the limited rate of success were twofold. First, in allergy, histamine is one of the mediators only, so an anti-histaminic blocks the allergic reactions only in part. The other reason is the high incidence of side effects caused by these compounds: anti-cholinergic, anti-adrenergic, anti-serotoninergic, local-anaesthetic and especially the induction of sedation or even sleep.

Paradoxically, it has been these side effects which prompted interest of many medicinal chemists in anti-histaminics. From the original structure of these ligands, several therapeutic classes were entered; anti-depressants, anti-psychotics, anti-Parkinson therapeutics, sleeping pills.

During the 1970s, the histamine field was divided into the H1- and the H2-system. The H2 receptors have physiological functions especially in the production of gastric acid. The H1 receptors are found, e.g. on smooth muscles (contraction airways, edema formation). The H2-blockers became a blockbusting success in the treatment of gastric ulcers. The H2 ligands, chemically derived from the histamine molecule, showed that it was possible to reach high receptor selectivity. Subsequently new H1 blockers, the second generation of anti-allergic anti-histamines, were developed: receptor (H1) selective, no brain penetration and, therefore, a much reduced incidence of sedation. During the 1980s the existence of a third class (H3) of histamine receptors was detected, followed by a fourth (H4) in the early 2000s. Whereas for the H1 and H2 receptors no sub-classes have been found, at least three H3 receptor types have already been published. So far no H3 (or H4) ligand has resulted in an useful therapeutic agent. Research in the histamine field has not only resulted in new medicinal agents, it has also contributed very much in very general ways to understanding drug action and, therefore, in developing new approaches in drug design.

As early as in the 1960s Nauta and his co-workers proposed that receptors—and he used the histamine receptor as his tool, at that time no differentiation H1-H2 had been reached—would be proteins in a helix shape. He used his phantasy to propose individual aminoacids as binding anchors for both histamine agonists and antagonists. Nauta's phantasy was not far from our current reality!

Another nice example of using histamine ligands for very general problems is found in the work of Ganellin and co-workers. The histamine H2 antagonists such as cimetidine, ranitidine and famotidine, do not penetrate the brain. As H2-receptors are found in the CNS, it was attractive to develop brain penetrating H2 antagonist.

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Ganellin c.s. showed that the simple lipophicity approach (low lipophilicity should mean no penetration, high lipophilicity on the other hand promote passage of the blood–brain barrier) does not work. They used the so-called Δ log P approach to design brain penetrating H2-antagonists. The Δ log P principle may be generally applicable in designing brain penetrating (or the reverse) compounds; the non-sedating H1 antagonists may be a matter in case.

As we know now the primary structure of many receptors, including the G-protein coupled receptors (GPCR) and as molecular biology techniques do allow the synthesis of mutant receptors, we are now able to obtain detailed information on molecular aspects of ligand–receptor interactions. And again the histamine receptors are of great help. In recent years, our group has been able to show that ligands, both agonists and antagonists, may react in different ways with one and the same receptor leading to the same effect though, such may even occur for chemically closely related ligands. These findings may have a meaning for SAR-studies!

Another appealing development concerns the concept of inverse agonism and constitutively active receptors. Also in this case histamine receptors have been very helpful in re-defining ligands of receptors: agonists, inverse agonists and neutral antagonists. In this reviewing presentation, attention will be paid to

– milestones in histamine research;
– histamine and histamine receptors as tools in medicinal chemistry research.

Finally some recent developments in histamine H3 and H4 research will be briefly reviewed.

Further reading list

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