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Mast cell stabilizing agents in nasal allergy

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The symptomatology of allergic rhinitis is initiated by the release of pharmacological substances derived from mast cells and possibly also from basophiles. If a compound preventing this degranulation and reaching all these cells was available, the treatment of type I-hypersensitivity manifestations would become a child's play. Because this presumption is still an irreality, our treatment is still depending upon compounds only reaching a part of the mast cells involved or compounds inhibiting the activity of the released mediators.

THE PROCESS OF MAST CELL DEGRANULATION

Numerous stimuli may induce the degranulation of a mast cell. They all have their specific receptor on the surface of this cell. The immunologically determined degranulation is the best known reaction. It is the result of an interaction between an antigen and an antibody. The antigen, also called "allergen" in this kind of reaction, reacts with the Fab-fragment of two adjacent IgE molecules, bound at the mast cell membrane. IgG STS (Short-Term-Sensitizing Antibodies) also possess the capability of binding to the mast cell membrane, but in a lesser extent (Parish, 1970).

However, there are also non-immunologic factors, causing degranulation.

Once the mast cell or basophile is triggered by the immunological or non-immunological mechanisms, biochemical modifications of the mast cell membrane are noted. These modifications may allow the entrance of calcium into the cell (Austen, 1979; Lichtenstein, 1975). This is the first step of a chain of enzymatic reactions, including depression of intracellular cyclic AMP.

The endstage of degranulation is the effusion of the granular membrane with the cellular membrane.

Degranulation of mast cells and basophiles depends on the cAMP-cGMP ratio. Substances causing an augmentation of cAMP inhibit the process of degranulation, while substances causing augmentation of the intra-cellular cGMP stimulate the degranulation (Figure 1).

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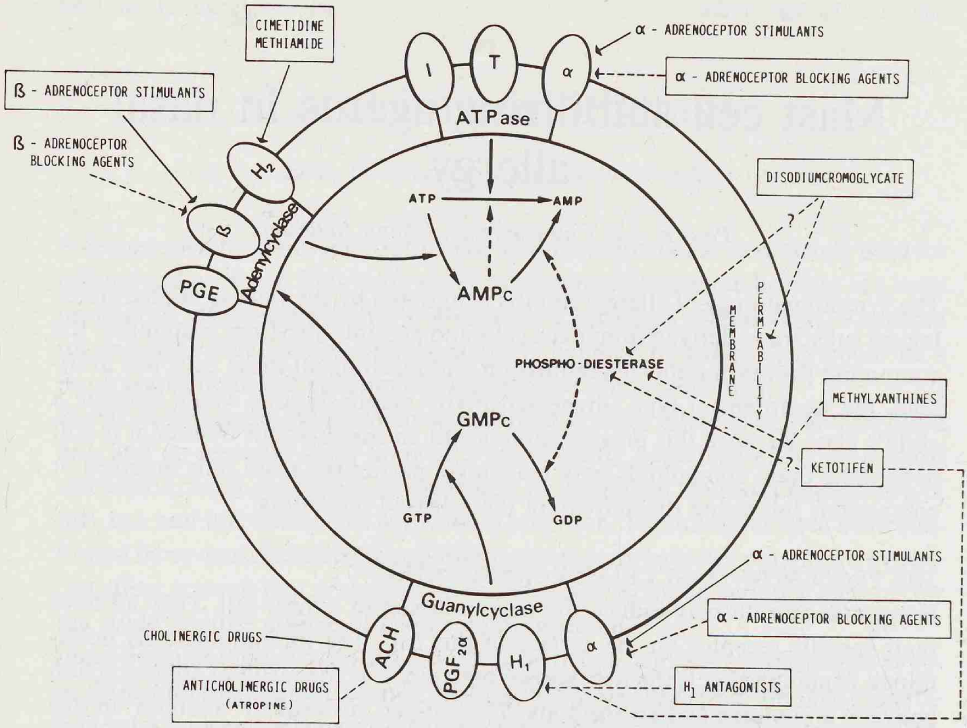

Figure 1. Modulation of the cyclic nucleotides by different pharmacological agents and hormones. Mast cell stabilizing agents are put in a square (modified after Michel, 1981).

cAMP is formed from ATP under the influence of adenylcyclase, which is situated in the cellular membrane. cGMP is formed from GTP under influence of guanylcyclase. This enzyme is located in the cellular membrane or in the cytoplasm or in both. cAMP and cGMP are degraded by the action of phosphodiesterase via a kind of feed-back mechanism.

The control on the synthesis of adenylcyclase and guanylcyclase resides in hormonal and pharmacological receptors at the membrane of the mast cell and basophile. This is also valid for the synthesis of ATP-ase, which degrades ATP into AMP and which is also localized in the mast cell membrane.

Till now three receptors are described for adenylcyclase: one for prostaglandine E, one beta-receptor and one H_2-receptor. Compounds stimulating the receptors for adenylcyclase will increase the activity of adenylcyclase which results in an increase of intracellular cAMP, which in turn inhibits mast cell degranulation. These compounds can be considered as inhibitors of mast cell degranulation. So, cimetidine - which is a H_2-receptor stimulant - beta-adrenoceptor stimulants and prostaglandine E are inhibitors of the degranulation. On the contrary, beta-adre-

noceptor blocking agents have an action in favour of degranulation.
For guanylcyclase, there are acetylcholine-receptors, receptors for prostaglandine F2α, H_1-receptors and probably also α-receptors. Compounds activating these receptors will increase the activity of guanylcyclase and result in an increase of the level of cGMP, which favours degranulation. So, cholinergic drugs, prostaglandine F2α, histamine and α-receptor stimulants can be considered as activating the process of degranulation. On the other hand, anti-cholinergic drugs (atropine), H_1-antagonists and α-adrenoceptor blocking agents will inhibit the degranulation.
There are α-receptors and receptors for insuline and thyroxine regulating the activity of ATP-ase. Stimulation of these receptors will result in an increase of the activity of ATP-ase, which degrades ATP into AMP and decreases the avaibility of ATP to be transformed into cAMP. This decrease in cAMP will result in an inhibition of mast cell degranulation. On the contrary, α-adrenoceptor blocking agents can be considered as inhibitors of the process of degranulation.
Methylxanthines have an inhibitory effect on the phosphodiesterases and augment the intracellular level of cAMP (Hadden et al., 1977). Consequently, they also inhibit the degranulation mechanisms.
The first compound that was shown to possess a mast cell stabilizing activity, was disodium cromoglycate (Altounyan, 1967). The mode of action of this compound, although many pharmacological and clinical studies proved its beneficial effect in allergic diseases, remains unknown. It is postulated that disodium cromoglycate is influencing the membrane permeability for calcium ions, in this way preventing the first reaction in the whole mechanism of degranulation. An other hypothesis is that cromoglycate is inhibiting phosphodiesterases that degrade cAMP (Pauwels and Van Der Straeten, 1979). Consequently, the level of intracellular cAMP remains high, which has an inhibitory effect on the mechanism of degranulation.
All H_1-antihistamines inhibit the degranulation of mast cells and basophiles, because they inhibit – via H_1-receptors at the mast cell membrane – the activity of guanylcyclase, and thus of cGMP.
Ketotifen, an H_1-antihistamine, which has also an activity against other mediators, will inhibit the mast cell degranulation in this way. In addition, it has been shown that it has an other mode of action in inhibiting the process of degranulation (Lichtenstein and Gillespie, 1975). It was suggested that, like for cromoglycate this could be an inhibition of phosphodiesterase, resulting in a lesser degradation of cAMP.
The list of compounds, inhibiting or stimulating degranulation, is certainly not exhaustive. In the future, many substances will certainly be added to this list. And who knows that some day it will be shown that every molecule has a certain effect on the degranulation of mast cells and basophiles...

CLINICAL EFFICACY OF MAST CELL STABILIZING COMPOUNDS

Cromones

Since Roger Altounyan in 1967, postulated that inhalation of disodium cromoglycate (DSCG) prevented asthma attacks by a kind of stabilization of the mast cell membrane, the pharmacological concept on the mode of action of cromoglycate underwent remarkable changes. It is not only shown that DSCG is a mast cell stabilizer, but also that it has a beneficial effect in bronchial hyperreactivity, preventing bronchoconstriction induced by several stimuli, probably by inhibiting the afferent pathway of the reflex mechanism (Chung and Jones, 1979). By analogy, DSCG is also postulated to have an inhibitory effect on the receptors of the sensible nerve-endings in the nasal mucosa. If this hypothesis is true, DSCG would have two very important ways of action:

1. preventing mast cell degranulation and liberation of mediators;
2. inhibiting the triggering of the sensible receptors by the already released mediators or by non-specific stimuli.

There are numerous clinical trials published about the activity of cromoglycate in allergic rhinopathy, as well in hay fever as in perennial forms. When concentrating only at the double-blind cross-over trials with a placebo, we see that most authors report a beneficial effect, notably patients preferring the active compound above the placebo. In most trials, there is a statistically significant difference between the two therapeutical regimens. However, the results are not uniform, and in some studies the beneficial effect is not striking. The best results are noted in patients with symptoms of sneezing and watery rhinorrhea, while nasal obstruction is usually less influenced.

In long-lasting cases of allergic rhinopathy, the results are poor, contrary to what is seen in patients with seasonal allergic rhinitis (Van Cauwenberge, 1978).

A weak point in the activity of DSCG may be that it is not stabilizing the basophiles, which are shown by Okuda (1977) to be very important in the initiation of the chain of reactions.

In addition, and this is valid for all topically administered compounds in the nose, it is impossible to reach the whole nasal mucosa with a nasal spray, especially in cases where the mucous membranes are edematous. It would therefore be an enormous advantage to possess an active and safe oral cromone.

Many pharmaceutical laboratories were or still are working in this field, but until now there is no effective and safe compound commercially available yet. Some of the promising new compounds with a good in-vitro activity prove to be less active when used in allergic patients; other compounds were eliminated because of toxic or carcinogenetic side effects.

Till now, five clinical trials comparing the clinical activity of topically administered disodium cromoglycate and a corticosteroid are published. The conclusion

of these comparative trials is that the topical application of cromoglycate and a nasal corticosteroid has an equal efficiency (Chatterjee et al., 1974; Haguenauer, 1981) or that the nasal corticosteroid gives better results than disodium cromoglycate (Frankland et al., 1975; Tandon and Strahan, 1980; Brown et al., 1981).

Ketotifen

Ketotifen inhibits the liberation of mediators, especially of SRSA. It also neutralizes in vivo the effect of SRSA at the target cells, notably bronchi. It is also a calcium antagonist and an H_1-antihistamine. The clinical trials in which ketotifen was used in nasal allergy, are not convincing yet.

The conclusion drawn from the clinical trials with ketotifen is that, until now, it is not proven that ketotifen has a superior activity than a pure H_1-antihistamine in controlling nasal symptoms in allergic rhinitis (Martin-du-Pan, 1978; Phillips et al., 1980; Tarab and Varonier, 1981; Warner and Goldsworthy, 1982).

CONCLUSION

Till now there is only one topical nasal mast cell stabilizing compound available for the practitioner. This compound is disodium cromoglycate. It has a similar or less pronounced activity against nasal allergy symptoms than the topically applied nasal corticosteroids.

There is a compound available with a proven mast cell stabilizing activity, namely ketotifen. Till now, the clinical results with ketotifen in controlling nasal allergy symptoms are not convincing.

When we only concentrate on mast cell stabilizing products, we have to wait for a safe and clinically effective oral cromone to improve the results of the actually available topical cromoglycate.

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