Effect of Histamine H$_2$-Receptor and β-Receptor Blockade on Histamine-, Orciprenaline- and Prostaglandin-Stimulated Frequency of the Isolated Guinea-Pig Atrium$^{1}$)

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Abstract

For the oxyntic cell of the stomach the hypothesis was forwarded by Grossmann and Konturek [1] that, if one of its three receptors is blocked, the physico-chemical properties of the two others are changed in such a way that they respond less sensitively to their specific stimulation. This hypothesis was tested for the heart by studying the effect of histamine-H$_2$-receptor- and β-receptor-blockade on the orciprenaline-, histamine-, and prostaglandin E$_1$-stimulated frequency of the spontaneously beating isolated guinea-pig atrium.

Therefore cumulative dose response curves were established for orciprenaline, histamine and prostaglandin E$_1$ (PGE$_1$) alone or in the presence of metiamide or pindolol. (1) The β-blocker pindolol inhibited the effect of orciprenaline in a competitive manner, without having an effect on histamine- and PGE$_1$-stimulation. (2) The histamine H$_2$-receptor blocker metiamide inhibited the histamine response competitively. (3) In contrast to pindolol, metiamide inhibited the PGE$_1$-stimulated rise in atrial frequency, most obviously non- or uncompetitively.

From these results it is evident that in the heart the particular inhibitors, at least at the receptor site, act rather specifically without affecting neighbouring receptors and that metiamide influences the PGE$_1$-response in a way different from the receptor site.

Introduction

In 1974, Grossman and Konturek [1] studied the effect of atropine and the H$_2$-receptor antagonist metiamide on the gastric acid response to histamine, pentagastrin, 2-desoxy-D-glucose and food. Metiamide inhibited all gastric acid stimulants. Atropine also inhibited the acid response to the stimulants except histamine. From these results the authors drew the following conclusion which they forwarded as a hypothesis:

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Effect of Histamine Receptor Blockade on the Isolated Guinea-Pig Atrium

GASTRIC MUCOSA

Stim: CHOLINERGICS
Inhib: ATROPINE

Stim: HISTAMINE
Inhib: H₂ BLOCKERS

Stim: GASTRIN
Inhib: ?

HEART

Stim: CATECHOLAMINES
Inhib: β- BLOCKERS

Stim: HISTAMINE
Inhib: H₂ BLOCKERS

Stim: PROSTAGLANDINS
Inhib: ?

Figure 1
Models of stimulatory mechanisms of the heart and gastric mucosa and their possibilities of inhibition.

The atria (50-70 mg w.w.) were allowed to beat spontaneously. Resting tension was adjusted to 0.5 g and maintained at that level for the whole experiment. The frequency was recorded by a ratemeter measuring the reciprocal value of the distance between two contraction cycles.

A 60 minutes equilibration period was allowed in each experiments before addition of any drug [2].

Cumulative dose response curves were established using the 1/2 log 10 interval as described by Van Rossum [3]. Each preparation was used only for one dose-response curve. The results are expressed as rise in frequency above the unstimulated level.

Histamine dihydrochloride (Merck, Darmstadt); Metiamide (Smith, Kline & French Ltd., Welwyn Garden City); Pindolol (Visken® (Sandoz, Basel); prostaglandin E₂) (The Upjohn Comp. Kalamazoo, Michigan).

Results
Influence of β- and H₂-receptor blockers on the orciprenaline effect (Fig. 2)

Orciprenaline in the range of 10⁻⁸–10⁻⁶ M produced a dose-dependent rise in atrial frequency with an ED₅₀ of 5 x 10⁻⁸ M. In the presence of 8 x 10⁻⁸ M pindolol, the dose response curve is shifted towards the right so that the ED₅₀ was now 5 x 10⁻⁶ M (a shift of two log units to the right) but leaving the maximal response unchanged.

The H₂-receptor antagonist metiamide in a dose, which undoubtedly inhibits histamine stimulated atrial frequency, but having no inhibitory effect on the spontaneous frequency, did not reduce the orciprenaline driven atrial frequency, indicating that H₂-receptor blockade does not affect the efficiency of the adrenergic

Figure 2
Effect of 8 x 10⁻⁸ M pindolol and 5 x 10⁻⁴ M metiamide on orciprenaline stimulated frequency of the isolated guinea-pig atrium.

Abscissa: log dose; ordinate: change in frequency above the unstimulated level.

Each curve is made from the mean of 5 experiments ± S.E.M.

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