Further studies have shown that the sympathomimetic amines can inhibit the antigen-induced histamine release in both actively and passively sensitized guinea-pig lung; they seemed less effective in actively sensitized than in passively sensitized lung (Table 1).

TABLE 1. *Inhibition by isoprenaline of antigen-induced histamine release*

	Passively sensitized human lung			Passively sensitized guinea-pig lung			Actively sensitized guinea-pig lung		
Isoprenaline concentration (M)	No. of experiments	Histamine release (%)	% inhibition	No. of experiments	Histamine release (%)	% inhibition	No. of experiments	Histamine release (%)	% inhibition
	6	12–40		11	15–26		7	10–15	
10^{-9}			80–93			12–64			13–29
10^{-8}			85–100			80–95			45–65

Histamine release by antigen in terms of % tissue content.

Inhibition of histamine release expressed as $\frac{\text{uninhibited release} - \text{inhibited release}}{\text{uninhibited release} - \text{blank release}} \times 100$

The methylxanthines theophylline and caffeine were also found to be capable of inhibiting antigen-induced histamine release from passively sensitized human lung, and from both actively and passively sensitized guinea-pig lung, but they were less potent than the sympathomimetic amines and their dose response curves were irregular. Theophylline produced significant inhibition in a concentration range of 10^{-7} to 10^{-6}M.

The actions of sympathomimetic amines and methylxanthines may be related to their effect on the 3′,5′-cyclic adenosine monophosphate system.

E. S. K. A. is a Wellcome Research Fellow.

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An amino-acid receptor in the guinea-pig ileum

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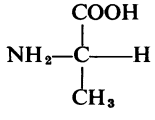
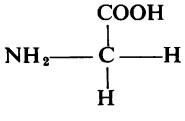
During an investigation of the quantity of histamine in different layers of human skin, aqueous extracts of an acetone powder of the stratum corneum were found to cause a histamine-like contraction of the guinea-pig ileum which, however, was not reduced by concentrations of mepyramine sufficient to abolish the response of the tissue to histamine (Lewis, Rosenthal & Trahan, 1959).

The products responsible for most of this activity were isolated by ion exchange chromatography and identified as the amino-acids L-serine and L-alanine. Usually these compounds contract the guinea-pig ileum at concentrations of 10–20 μg/ml, although a few preparations were almost completely insensitive. A large amount of L-serine is present in the stratum corneum (10 mg/g) and when assayed on the guinea-pig ileum this would be equivalent to a histamine concentration of 1 μg/g.

In order to see whether the activity of the amino-acids on the guinea-pig ileum was related to their structure, the common amino-acids and a number of closely related compounds were tested. Each compound was assayed in the order of a 2×2 Latin square against L-alanine as standard because it had the greatest relative molar potency. The activity of the least active compounds was estimated simply by matching responses. All compounds with appreciable activity gave a log dose/response slope similar to that of L-alanine.



Alanine



Glycine

The following results indicate a relationship between structure and activity in the α-amino-acids and derivatives so far examined.

1. $-CH_3$ is optimal since replacement by H or by larger groups resulted in a reduction of activity.

2. A free α-H in an L-amino-acid appears to be optimal since replacement by a methyl group reduced activity to 20%. In addition, the D-amino-acids retained 5% or less of activity.

Owing to the limited availability of derivatives, the effect of modifying the carboxylic and amino groups was investigated using only analogues of glycine, which itself possessed 15–20% of the activity of L-alanine.

3. $-COOH$ is an essential group because activity was reduced at least 10-fold when it was replaced by phosphonic or sulphonic acid groups or converted to the amide.

4. An amino group appears to be necessary because activity was reduced to less than 10% of that of glycine when it was converted to guanidino or acetylated. The tri-methyl ammonium derivative (betaine) retained 20% and the mono-methyl ammonium derivative (sarcosine) retained full activity.

These findings indicate that the four α-carbon substituents of L-alanine combine to give optimal activity. In addition, it appears to be necessary that the $-COOH$ and $-NH_2$ groups are attached to the same carbon atom since β-alanine has almost negligible activity.

These results raise the question—does the guinea-pig ileum contain a specific α-amino-acid receptor?

REFERENCE

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