Thus atropine and promethazine have different effects on the gastrin mechanism. Atropine blocks the effects of both endogenous[2,6] and exogenous gastrin, while promethazine blocks only endogenous gastrin. In other words, this antihistamine seems to work by inhibiting the release of gastrin from its cell of origin, but, once gastrin is circulating, its secretory effect is unaltered by the promethazine.

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Histamine Binding Capacity related to the Supply of Histamine

Earlier results[1] have indicated that an increase in the capacity to bind histamine can be regarded as an important factor in histamine desensitization. In these experiments, a large amount of bound histamine was found in the tissues of mice after repeated injections of histamine. It was therefore interesting to look for a relationship between the supply of histamine to the tissues and their capacity to bind this substance.

Experiments were carried out with male albino mice weighing 26–40 g. An intraperitoneal infusion of histamine labelled with carbon-14 was given over 24 h. Fine polyethylene tubing, long enough to allow the mouse access to food and water, as well as freedom of movement in the cage, was inserted into the peritoneal cavity. Histamine doses of 0·1, 1·0, 10 and 100 μg/g of mouse (containing 2–5 nc. of labelled histamine) were prepared in 1·3 ml. of saline, this being the volume infused over 24 h by means of a syringe driven by a motor. The mice were then kept for 2 days in normal conditions to allow unbound histamine to be removed in urine and faeces. Forty-eight hours after the end of the infusion, each mouse was homogenized in a Waring blender with 200 ml. of 10 per cent trichloroacetic acid and 2 ml. of histamine–histidine carrier (containing 66·4 mg of histamine dihydrochloric acid and 40 mg of histidine hydrochloride/ml.). Labelled histamine was determined according to the method of Waton[2]. The histamine content of untreated mice was measured biologically, as described by Parratt and West[3]. Briefly, each mouse was homogenized in 10 per cent trichloroacetic acid and allowed to stand for not less than 24 h. The trichloroacetic acid extract was filtered, the excess acid removed by ether and the solution assayed on the isolated atropinized guinea-pig ileum. Specificity for histamine was confirmed by the mepyramine test[4]. All values of histamine refer to the base.

The behaviour of the mice during the infusion did not seem to be influenced by the histamine, but a toxic effect was not expected, because the LD_{50} of histamine given to mice intraperitoneally, according to Angelakos and Loew[5], is 2,056 mg/kg of body weight. The values for labelled histamine found 48 h after the end of the infusion are given in Table 1. These show that for the smaller doses (0·1, 1·0 and 10 μg/g of mouse) the percentage of histamine taken up in relation to the histamine supplied is similar in each case. For the larger dose (100 μg/g mouse) the value obtained is approximately seven times greater.

Table 1

No. of mice used	^{14}C-Histamine infused (dose/g of mouse/24 h)	^{14}C-Histamine bound, values/g of mouse with standard error of the mean	Percentage of histamine taken up in relation to histamine supplied	Percentage of histamine taken up in relation to the original histamine content (0·8 μg/g)
13	0·1 μg	0·033 ng ± 0·002	0·033	$3·4 \times 10^{-4}$
12	1·0 μg	0·38 ng ± 0·05	0·038	$3·9 \times 10^{-3}$
9	10 μg	3·5 ng ± 0·38	0·035	$3·6 \times 10^{-2}$
13	100 μg	258 ng ± 58	0·258	2·6

In order to compare the amounts of bound histamine with histamine already present in the mouse, the histamine content of untreated mice was determined. The mean value for twelve mice was 9·8 μg/g of mouse with a standard error of the mean of 0·6 μg/g. The uptake of histamine in each dose was expressed as a percentage of the original histamine content of the mice (Table 1).

These experiments do not indicate in which tissue of the mouse the histamine is bound. According to Beaumariage[6], the skin of the mouse contains a large amount of histamine. Schayer[7] has shown that when ^{14}C-histidine was injected into the mouse, histamine was formed and bound largely in the skin. Binding therefore probably took place chiefly in the skin.

The present results demonstrate that the binding of histamine is related to the supply of histamine. For a wide range of doses (0·1–10 μg of histamine/g) this relationship was consistent. When the dose of histamine was greater than the content of histamine already present in the mouse (9·8 μg/g) this relationship changed, and the percentage of bound histamine increased. These results indicate that new histamine binding sites were formed after stimulation by the increased supply of histamine. If there was only a limited number of binding sites available, the percentage of bound histamine would decrease as more histamine was administered. These results, however, do not support such an assumption.

The data for histamine binding agree with earlier results[1]. In these experiments, 10 μg of ^{14}C-histamine/g of mouse was injected daily over 28 days. Three days after the end of the treatment, 109 ng of histamine/g of mouse was found; this value of daily histamine uptake (3·5 ng/g) was similar to that now obtained by the 24 h infusion of 10 μg of ^{14}C-histamine/g of mouse.

Thus the provision of new histamine binding sites where the body can store histamine in a non-toxic, bound form may be regarded as an important factor in the mechanism of histamine desensitization.

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