

Histamine and Cold Adaptation. (27939)

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Norepinephrine has a calorogenic action in cold-adapted animals(1,2). Cold adaptation also increases the cardiovascular responses to this amine(3). As this hypersensitivity develops a 6-fold increase in norepinephrine is observed during cold exposure(4,5). In the present investigation comparable studies were made on another biologically active amine. The excretion and systemic actions of histamine were investigated with relation to cold adaptation. Previous studies on mast cell distribution and on the hypothermic effect of histamine indicated indirectly that this amine might have some implication in cold adaptation(6,7).

Methods. Male rats weighing 200 g were placed in a cold room at 6°C and daily excretion of histamine in the urine was determined after 0, 1, 2, 7, 15 and 30 days. Histamine was assayed on guinea pig ileum suspended in oxygenated tyrode solution. The 24-hour urine samples were collected in 1 ml HCl · 1N and neutralized before determination of histamine. Guinea pigs, males 300 g, were tested for histamine sensitivity by exposing the animals to histamine aerosol at normal room temperature and observing respiratory symptoms such as dyspnea, convulsions, coma and apnea with death. The volume of the aerosol chamber was 3 cu ft. One control and one cold adapted animal were tested simultaneously. The cold adapted group had been exposed to cold (6°C) for one month. For each test 100 cc of water containing 500 mg of histamine phosphate were vaporized in the chamber over a period of 12 minutes.

Results. a) *Urinary histamine.* Fig. 1 indicates that cold exposure immediately increases urinary histamine in rats. After the second day this increase is 7 times above normal and these values are still high after 30 days of cold exposure. When results are expressed in $\gamma/100$ ml instead of $\gamma/24$ hr, the increase is still highly significant but of

smaller amplitude because of the increased urine volume due to cold.

b) *Histamine aerosol test.* Fig. 2 and Table I indicate that respiratory disorders observed in normal guinea pigs when exposed to an histamine aerosol, are much less severe and cause a lower mortality incidence if the animals are previously exposed to cold for one month.

Discussion. Adaptation to cold induces a rapid and sustained urinary excretion of histamine. We, and Heroux(8) have shown previously that mast cells, a source of histamine, decrease in the skin of the extremities of rats exposed to cold(6).

This increased excretion of histamine is accompanied by a decreased sensitivity to this amine as indicated by the lower incidence of respiratory troubles reported in Table I and Fig. 2 and by the smaller hypothermic effect of histamine in cold adapted animals(7). It is not known however whether the urinary increase of histamine reflects a larger secretion or a decreased destruction. There is a 6-fold increase in norepinephrine and histamine during cold adaptation accompanied by an increased sensitivity to norepinephrine and decreased sensitivity to histamine. Hormonal requirements above production levels incite hypersensitivity. Indeed the hyperactivity of thyroxine in myxedema, of insulin in diabetes and of epinephrine in denervated structures is well known. Should this be the case for norepinephrine it could be said that cold adapted animals become more sensitive to norepinephrine in spite of an increased secretion. This increased production would correspond to the upper limit of secretion permissible but would not fulfill the increased requirements occasioned by cold. Studies by Leduc suggest this interpretation(5). As for histamine it would seem that the decreased sensitivity in cold adapted animals would result from a secretion in excess of the requirements. This interpretation would find sup-

TABLE I. Responses of Guinea Pigs to Histamine Aerosol.

Normal					Cold-adapted (6°C for 1 mo)				
No.	Dyspnea	Convul-sions	Coma	Apnea with death	No.	Dyspnea	Convul-sions	Coma	Apnea with death
1	1.0*	1.2	1.5	1.7	1	1.3	1.7	1.9	2.00
2	.7	1.5	2.0	2.2	2	2.3	3.4	3.9	6.00
3	.8	1.5	2.7	4.0	3	1.8	2.2	—	—
4	1.1	1.8	3.5	4.6	4	1.7	—	—	—
5	1.6	3.0	5.0	7.1	5	3.0	—	—	—
6	1.5	4.0	5.7	—	6	—	—	—	—
7	1.7	3.1	6.1	—	7	—	—	—	—
8	1.7	2.0	—	—	8	—	—	—	—

* All values expressed in min.

port in a study where daily injections of histamine for a few weeks decreased the

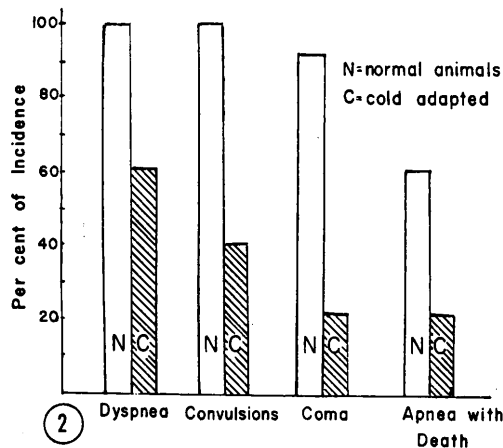
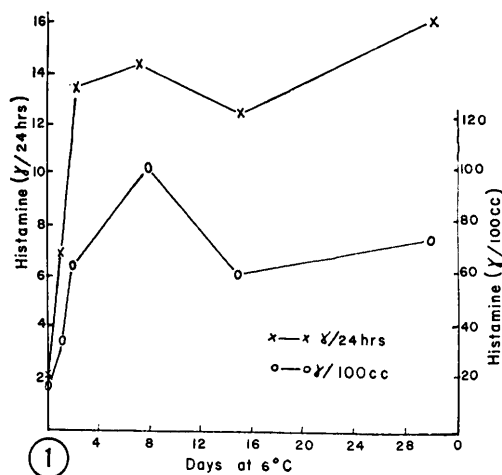


FIG. 1. Effect of cold exposure on urinary histamine (expressed in γ of the base) in rats.

FIG. 2. Effect of cold exposure (6°C for 1 mo) on incidence of respiratory symptoms in guinea pigs exposed to a histamine aerosol.

incidence of bronchospasm normally observed with histamine aerosols(9). There is some evidence that norepinephrine is involved in the process of cold adaptation(1 to 5). The role of histamine in normal physiology has not been clearly defined and similarly its importance in resistance and acclimatization to low temperatures is still a matter for speculation.

Summary. Rats exposed to cold (6°C) for one month show a very rapid and sustained increase in urinary histamine. At the end of this period animals develop a certain tolerance to histamine aerosols. This modification in histamine excretion in the cold possibly reflects mast cell changes and the decreased sensitivity to this amine in cold adapted animals would indicate levels of secretion above physiological requirements.

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