Blood and Tissue Histamine in Mice, Rats, Hamsters, and Guinea Pigs. Comparative Study (34233)

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The histamine contained in mammalian tissue is endogenous in origin. It is formed by intracellular decarboxylation of histidine (1). Histidine decarboxylase (HD) is the enzyme responsible for histamine formation. The enzymic activity of HD can be inhibited by α-methylhistidine but not by α-methyl-DOPA, and pyridoxal phosphate is required as a cofactor (2). The elevation of the tissue histamine-forming capacity (HFC) appears to be a part of the mechanism-sustaining homeostasis. High HFC has been found in certain types of normal and "pathological" tissues. Tissues of various organs and of various species differ significantly regarding HFC and the content in endogenous histamine (2). Mammalian mast cells are particularly rich in histamine and consequently tissues rich in mast cells, as some portions of skin contain large amounts of histamine (3). In mast cell tissues the histamine content depends on the lifetime and the number of cells rather than on HFC. In non-mast cell tissue, as the gastrointestinal mucosa or lung, the actual histamine content represents the balance between HFC and the rate of removal of histamine. Tissue histamine is continuously discharged into the blood and partly excreted (2, 3).

The literature on tissue and blood histamine in animals, does not contain satisfactory information on histamine levels of normal, common laboratory rodents. The purpose of the present study was to compare tissue and blood histamine of mice, rats, hamsters, and guinea pigs under uniform experimental conditions. Histamine was determined by a fluorometric method in fasting and fed animals.

Methods. The following male rodents were used in this study: (i) Swiss albino mice, av body wt 25 g (range 21–30 g); (ii) Sprague-Dawley rats, av body wt 165 g (range 151–200 g); (iii) Syrian golden hamsters, av body wt 95 g (range 79–106 g); (iv) Guinea pigs, av body wt 442 g (range 340–540 g).

The animals were adapted to the laboratory conditions for at least 4 weeks prior to this study. Purina rat chow (USA) was fed to mice, rats, and hamsters. Guinea pigs were fed with Purina guinea pig chow (USA), containing stabilized Vitamin C. Food and drinking water were given as desired. Only clinically healthy animals, checked by a veterinarian, were used for the present study. When used as "fasting animals" they were deprived of food for 48 hr. Fed animals were sacrificed 4 hr following a feeding. Blood was taken from the aorta into heparinized tubes under light ether anaesthesia. Lung, liver (without gallbladder), stomach, small intestine, and large intestine, were then dissected. The stomach was isolated between cardia and pylorus and opened along the great curvature. The intestines were opened along the mesenteric attachment. The total gastrointestinal tract was cleaned of fat and mesentery and washed twice with chilled normal saline to remove digestion residuum. All organs studied were washed in chilled saline immediately after the dissection, and dried gently with topper sponges. They were then weighed (wet weight), minced, diluted in the proportion of 1 g to 10 ml of 0.4 perchloric acid and homogenized at 4° for 20 min, at 60,000 rpm, in a Virtis homogenizer. The homogenates were left in the flasks for 10 min, to complete the extraction, and then centrifuged for 10 min, at 2,000 rpm. We found that the supernatant can be stored in a freezer (−20°) for 3–4 weeks without any change in histamine content.

TABLE I. Histamine in Blood (μg/100 ml) and in Tissues (μg/g of wet tissue) of Mice, Rats, Hamsters, and Guinea Pigs after 48 hr of Fasting (av and SD).

Group	Animals	No. of animals	Blood	Lung	Liver	Stomach	Small intestine	Large intestine
1	Mice	20	13.9 ± 3.9	1.2 ± 0.2	0.5 ± 0.07	14.1 ± 4.2	1.0 ± 0.2	1.2 ± 0.4
2	Rats	20	16.7 ± 3.8	8.5 ± 3.2	1.7 ± 0.5	20.2 ± 5.7	9.8 ± 3.3	10.5 ± 5.6
3	Hamsters	20	21.7 ± 7.4	4.3 ± 1.7	1.0 ± 0.1	16.2 ± 3.1	19.9 ± 8.2	6.2 ± 1.8
4	Guinea pigs	20	20.6 ± 7.0	17.0 ± 6.9	1.9 ± 0.6	23.3 ± 5.2	12.6 ± 4.6	4.8 ± 1.6
	p		<0.01[a]	<0.01[b]	<0.01[c]	<0.01[d]	<0.01[e]	<0.01[b]

[a] First versus third and fourth groups; second versus third group.
[b] Each group versus all other groups.
[c] First versus all other groups; second versus fourth group; fourth versus all other groups.
[d] First versus second and fourth group; third versus all other groups.
[e] First versus all other groups; third versus all other groups.

Tissue and blood histamine were determined following the method of Shore *et al.* (4) and the results were expressed in micrograms per gram of wet tissue or per 100 ml of total blood. The Turner model 110 fluorometer was used for measurement of fluorescence. The biochemical results were evaluated statistically by Student's t test.

Results. Table I summarizes the results of the histamine determinations in fasting animals. The significance of differences between the four species studied is recorded in the footnotes to Table I. It may be noted that the histamine content of the tissues of mice is much lower than that found in the three other species. The other rodents, however, also differ significantly from each other in the histamine content of certain tissues. Table II gives both fasting and postprandial values of histamine in blood and tissues. It is apparent from Table II that feeding did not produce a significant alteration of histamine levels under the conditions of this experiment.

Discussion. The organs selected in this study for the determination of histamine content, are known to play an important role in the synthesis and/or metabolism of histamine.

Lung. Histamine is partly inactivated in

TABLE II. Fasting (F) and Postprandial (Pp) Levels of Histamine in Blood and Tissues of Rodents.[a]

Animals	Condition	No. of animals	Blood	Lung	Liver	Stomach	Small intestine	Large intestine
Mice	F	20	13.9 ± 3.9	1.2 ± 0.2	0.5 ± 0.07	14.1 ± 4.2	1.0 ± 0.2	1.2 ± 0.4
	Pp	20	12.4 ± 2.3	1.3 ± 0.2	0.5 ± 0.1	13.4 ± 3.4	1.1 ± 0.6	1.1 ± 0.6
	p		NS[b]	NS	NS	NS	NS	NS
Rats	F	20	16.7 ± 3.8	8.5 ± 3.2	1.7 ± 0.5	20.2 ± 5.7	9.8 ± 3.3	10.5 ± 5.6
	Pp	20	16.0 ± 8.5	8.7 ± 3.3	1.8 ± 0.3	19.6 ± 4.2	12.6 ± 4.9	10.9 ± 4.4
	p		NS	NS	NS	NS	<0.05	NS
Hamsters	F	20	21.7 ± 7.4	4.3 ± 1.7	1.0 ± 0.1	16.2 ± 3.1	19.9 ± 8.2	6.2 ± 1.8
	Pp	20	26.4 ±10.4	3.8 ± 1.7	0.9 ± 0.2	13.1 ± 3.4	17.3 ± 8.3	5.3 ± 1.6
	p		NS	NS	NS	<0.05	NS	NS
Guinea pigs	F	20	20.6 ± 7.0	17.0 ± 6.9	1.9 ± 0.6	23.3 ± 5.2	12.6 ± 4.6	4.8 ± 1.6
	Pp	20	21.7 ± 7.7	16.3 ± 7.0	1.6 ± 0.4	22.8 ± 4.9	12.3 ± 4.6	4.3 ± 1.2
	p		NS	NS	NS	NS	NS	NS

[a] Fasting lasted 48 hr; when fed, animals received food after 48 hr fasting and were sacrificed 4 hr later; av and SD.
[b] NS = $p > 0.05$.

the lung. The mechanism of this enzymatic action has been studied in rats and in guinea pigs. In rats, the major histamine-metabolizing enzyme of the lung is diamine oxidase; guinea pig lungs contain imidazole-*N*-methyl-transferase, which is responsible for most of the histamine-metabolizing activity (5). Nothing is known regarding the inactivation of histamine in the lungs of mice and hamsters. In the present study, all four species differed significantly from each other, regarding lung tissue histamine.

Liver. The liver plays a primary role in the metabolism of endogenous histamine. Portal blood contains more histamine than other vessels (6). Portal venous bypass or liver damage can result in gastric hypersecretion, considered by some to be due to endogenous histamine, noninactivated in hepatic tissue (7). The high histamine content of portal blood is evidently a result of histamine formation in the gastrointestinal tract. In the rodents studied, the histamine content of the liver was manyfold lower than the histamine content of the stomach. The differences between four species studied were less marked (Table I) in the case of blood and liver histamine than in the lung. It may be interesting to note, for example, that the lung histamine level in guinea pigs was about 14 times higher than lung histamine in mice. However, blood histamine in guinea pigs was less than twice the blood histamine level of mice. Similar comparisons can be made between mice and other rodents, regarding blood, liver, and lung histamine.

Stomach. The stomach contains a large quantity of histamine (8). There is, for example, enough histamine activity present in human gastric mucosa to allow local and humoral stimulation of parietal cells (9). The gastric mucosa of laboratory animals is rich in histidine decarboxylase. In the rats, about half of the whole body histamine formation takes place in the stomach wall. In the rat, mouse, and cat, gastric mucosal HFC is higher than in other tissues (2). It is known that histamine, released from the gastric mucosa and other tissues, may act as a stimulant of gastric secretion (10, 11) and it is considered possible that endogenous histamine, locally produced, is a physiological stimulant of parietal cells and therefore a true gastric hormone (8). In the rat, stomach histamine is localized at the base of the gastric glands and in the few submucosal mast cells (12). Histamine being a free, diffusible agent, when formed in close proximity to the parietal cell, is obviously bound to stimulate these cells (8). The fact that the gastric mucosa lacks mechanisms for effective inactivation of histamine (13) may contribute to the secretory action of endogenous histamine on the parietal cell. In the four species studied, gastric tissue was found to be rich in histamine. The differences between histamine levels of gastric tissue of the four species were less marked than differences between the histamine levels of lung or intestine.

An interesting observation has also been made of the ratio of the histamine levels. Despite marked differences between the lung and intestine levels between the four species, the "blood/stomach" ratio was similar in these rodents.

Feeding. Does feeding stimulate the synthesis or metabolism of gastric histamine? Because both parasympathetic stimulation and gastrin release histamine from glandular stomachs (14), postprandial changes in gastric histamine would be expected. Histamine has been found to increase in pyloric and fundic mucosa of dogs 1–2 hr after feeding (15). Feeding does not alter gastric tissue histamine in cats (16). Feeding of fasted rats and mice caused a mobilization of histamine and an acceleration of the rate of histamine formation in the region of mucosa containing parietal cells (2). Under the conditions of the present study, feeding did not significantly alter the levels of blood and tissue histamine. Perhaps the postprandial sampling was performed too late after the beginning of feeding. However, it might be expected that after 48 hr of fasting, feeding *ad libitum* will affect at least gastric and/or intestinal histamine. Only in rats was the postprandial histamine of the small intestine higher than "fasting" histamine. The fact that different animals were used, for necessary technical reasons, for the study of fasting and postprandial histamine levels, makes the evaluation of

Table II difficult. Only highly significant differences would be considered relevant under the conditions of the present study.

Intestines. The distribution of histamine in the other parts of the gastrointestinal tract has been studied in dogs (17). It was found that the overall histamine content of the mucosa and submucosa decreased in passing from the stomach to the colon. However, the mucosal glands retain a relatively high histamine content throughout the gut (17). There is no reliable information on distribution of histamine in rodent intestine. In the present study, the overall histamine content of both parts of rodent intestine was lower than histamine content of the stomach. In mice, histamine levels of both intestines were very low as compared with other rodents. In mice the ratio of gastric to intestinal histamine was about 10; in the other species studied it was not more than three (Table I). These are some of the many significant differences in tissue histamine levels between mice and other rodents.

It is possible that more precise results might be obtained regarding the histamine levels in the gastrointestinal tract of rodents, by the study of isolated mucosa of various segments of the gut. Such a study presents some technical difficulties and was omitted in the present preliminary work.

Summary. Available data on blood and tissue histamine in laboratory rodents do not give reliable information on "normal values" for histamine levels. To obtain this information, the fasting and postprandial histamine of blood, lung, liver, stomach, small and large intestine, was determined in mice, rats, hamsters, and guinea pigs under uniform experimental conditions, using a fluorometric method. The results were analyzed statistically. It was found that all four species studied differed from each other regarding the content of histamine in blood and certain tissues. The differences were most marked between mice and other rodents. There was no experimental evidence that feeding, after a prolonged fast, significantly affected the levels of blood or tissue histamine in the rodents studied.

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