Phylogenetical Persistence of the Non-Mast Cell Histamine Stores of the Digestive Tract: A Comparison with Mast Cell Histamine

The main locations for storage of histamine in the mammalian body are the mast cells and the mucosal layer of the digestive tract[1,2]. A previous report raised the question of histamine content in the mast cells of lower vertebrates, and presented evidence that they were deficient in this substance[3]. Among tissues which in spite of numerous mast cells showed low levels of histamine (0.08–0.77 μg/g) were the swimbladder of a teleost (*Rutilus rutilus*) and the tongue and the peritoneum of an amphibian (*Rana temporaria*). Additional evidence for absence of histamine in the mast cells of amphibians has later been presented by others, studying *Rana catesbeiana*[4].

During the last 4 years I have performed further and more systematic studies, including one or more species from every subclass of living lower vertebrates[5]. The results support the view that the mast cells of teleosts and amphibians are devoid of histamine[3,4]. However, through the use of both chemical and histochemical methods[6,7], it was clearly demonstrated that high concentrations of histamine are present in mast cells and blood basophils of turtles, snakes, lizards and crocodilians. Large species differences explain why previous experiments[3] – which moreover were performed during spring and summer, when tissue mast cells in reptiles seem to be most scarce – indicated that the histamine levels in reptilian tissues were low.

The present work utilizes the information summarized above in an attempt to study the non-mast cell histamine of the digestive tract in species where it is not intermingled with mast cell histamine. Observations were made in several species of fish, amphibians and reptiles (5–12 specimens from each species). The tissue samples were dissected out shortly after the animals had been killed. Histamine was assayed spectrofluorometrically, as described previously[3,6], and tissue levels were calculated as μg histamine base/g wet tissue.

The histamine content of different parts of the digestive tract of 2 species of stomachless teleosts, where acid secreting cells are absent[8,9], are listed in Table I. The total digestive tract, divided into 3 parts, was assayed, and as can be seen from the Table, showed rather low levels of histamine. Similar histamine levels are previously found in the gut of the cyclostome *Myxine glutinosa*[3] which phylogenetically represents a stage where stomach has apparently not yet evolved.

Table II lists tissue histamine levels in the digestive tract of teleosts, amphibians and reptiles, which all have a stomach. It is evident that the histamine levels of intestinal tissues are low or moderate, whereas those of the stomach, although displaying wide variations, are always high. The whole stomach was included in the assay, except in reptiles, in which small amounts of tissue had been removed for observation on mast cells. In a few large specimens of *Gadus morhua*, *Brosmius brosme* and *Testudo graeca* (not included in Table II), tissues from the stomach were split into mucosal and muscular layers before being assayed. The histamine levels of the mucosal layer were about twice as high as those listed in Table II for the whole stomach of the same species, whereas the muscular layer showed levels similar to or lower than the intestine. Assay of histamine in the stomach from a single specimen of cartilaginous fish (*Squalus acanthias*) gave values of 26.1 μg/g and 1.8 μg/g for the mucosal and the muscular layer, respectively.

Among the species studied, absence of mast cell histamine has been demonstrated, as already mentioned, in *Rutilus rutilus*[3]. During the present work, small tissue samples from the swimbladder of *Salmo irideus* and the mesentery of *Bufo bufo* were stained in alcoholic thionin (0.1%) for microscopy of mast cells. Adjacent samples were used for assay of histamine. Despite the presence of numerous mast cells in all preparations studied, the histamine levels were only 0.2–0.5 μg/g (swimbladder) and 0.1–0.2 μg/g (mesentery). A histochemical method[7] also failed to provide evidence for the presence of hista-

Table I. Tissue histamine levels in the digestive tract of teleostean fish with reduced stomach

Species	Part of digestive tract	Histamine content (μg/g)
Rutilus rutilus	anterior	1.0–1.4
	middle	0.7–1.6
	posterior	0.9–1.5
Labrus berggylta	anterior	0.3–0.8
	middle	0.4–0.7
	posterior	0.4–0.9

Table II. Tissue histamine levels in stomach and intestine of fish (teleosts), amphibians and reptiles with normal stomach functions

Species	Histamine content (μg/g)	
	Stomach	Intestine
Fish		
Salmo irideus	11.5–19.8	0.3–0.9
Gadus morhua	6.5–14.4	0.6–1.7
Gadus virens	7.1– 9.2	1.2–2.0
Brosmius brosme	5.5– 8.3	1.2–2.8
Trigla gurnardus	9.8–13.6	1.1–2.3
Pleuronectes microcephalus	6.9– 9.8	0.2–0.4
Amphibians		
Rana esculenta	5.4– 8.7	0.2–0.3
Bufo bufo	4.6–12.5	0.3–0.6
Reptiles		
Testudo graeca	10.5–16.0	0.1–0.2
Vipera berus	5.2–11.6	0.3–0.5

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mine in the mast cells of these species. The cheek pouch of the hamster, which showed a mast cell density similar to that of the swimbladder of *Salmo irideus*, was studied for comparison. The histamine content of the cheek pouch was 19.8–30.5 μg/g, and histamine could easily be histochemically localized in the mast cells. In the reptilian specimens, chosen from 2 species which compared to other reptiles generally have very low levels of histamine in their tissues[3,5], mast cells were searched for in tissue from mesentery, intestine and stomach (after staining with alcoholic thionin). Occasionally, a single or a few of these cells were encountered, but in most preparations they seemed to be completely absent. There is good reason to believe, therefore, that the histamine content of tissues from the digestive tract of all studied species of fish, amphibians and reptiles (Tables I and II) represents non-mast cell histamine.

The present study indicates that whereas the presence of histamine in the mast cells in confined to rather limited groups of vertebrates, the presence of high tissue levels of non-mast cell histamine in the digestive tract, and specifically in the gastric mucosa, is a general feature. The results support the view that non-mast cell histamine is intimately linked to the gastric secretory process, actively or passively.

Résumé. La teneur en histamine des divers segments du tube digestif a été mesurée chez les poissons, les batraciens et les reptiles. Les résultats indiquent la présence de dépôts d'histamine dans la muqueuse gastrique de tous les vertébrés, tandis que l'histamine de mastocytes n'existe que chez des groupes limitées de vertébrés.

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Site of Formation of Cx-Reactive Protein

The appearance of C-reactive protein (CRP) in human serum has been recognized for years as a common non-specific response to infection and other pathological processes. For this reason tests for its presence have joined the host of other laboratory aids used clinically for the evaluation of the status of patients. Interpretation of the human response is based on a body of empirical observation, since the function of the protein is unknown and its source is not established beyond some dispute.

MONTELLA and WOOD[1] showed that blockade of the reticuloendothelial system with ThO_2 severely depressed the ability of the rabbit to produce the analogous Cx-reactive protein (CxRP) and suggested it might arise from this cellular compartment. KUSHNER and KAPLAN[2] and KUSHNER et al.[3] found CxRP in necrotic muscle tissue but not in normal tissue following experimental injury. CxRP was detected by immunohistochemical methods. They interpreted their results to indicate CxRP arises as a product of tissue degeneration. GOTTLIEB[4], on the basis of labelling experiments with ^{14}C-glycine was led to the view that CxRP exists in some form in tissue prior to breakdown of a precursor molecule to give circulating CxRP. Finally, HURLIMANN et al.[5], using tissue culture technics, demonstrated CRP production by liver slices of man, monkey and rabbit, but not by kidney, lung, lymph node, intestine, salivary gland, mammary gland, bone marrow, spleen and peripheral leucocytes of Rhesus monkeys. We report here the behavior of CxRP in rabbits following total surgical removal of their livers to supplement the earlier observations on the source of CxRP.

New Zealand female rabbits were totally hepatectomized by a 2 stage procedure, to be described in detail elsewhere, based on the procedure first described by DRURY[6]. Briefly, the vena cava and the portal vein are partially occluded and some weeks later when collateral circulation has been established the liver is removed surgically. Rabbits were maintained subsequently by parenteral administration of glucose until death intervened. Serum CxRP levels were determined by the titration procedure of SWIFT et al.[7] using specific guinea-pig CxRP antiserum (CxRPA) of our own preparation[8].

Summary of CxRP responses before and after total hepatectomy

Rabbits studied during first stage preparatory surgery

Serum sample	No.	Serum CxRP	Mean titer
Preoperative	16	16/16 negative	–
Postoperative (24 h)	16	16/16 positive	1:11
Postoperative (48 h)	16	16/16 positive	1:16

Rabbits studied during second stage, total hepactectomy, which survived longer than 8 h

Serum sample	No.	Serum CxRP	Mean titer
Preoperative	15	11/15 positive	1:8
		4/15 negative	–
Terminal posthepatectomy			
Positive preoperative rabbits	11	6/11 negative	–
		5/11 positive	1:5
Negative preoperative rabbits	4	4/4 negative	–

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