CIBA FOUNDATION SYMPOSIUM

Jointly with

THE PHYSIOLOGICAL SOCIETY

and

THE BRITISH PHARMACOLOGICAL SOCIETY

on

HISTAMINE

in honour of

SIR HENRY DALE, *O.M., G.B.E.*,
M.D., F.R.C.P., F.R.S.

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SYMPOSIUM OF THE PHYSIOLOGICAL AND PHARMACOLOGICAL SOCIETIES AT THE WELLCOME FOUNDATION

CHAIRMAN'S OPENING REMARKS

W. FELDBERG

National Institute for Medical Research, Mill Hill, London

IT IS most gratifying to see that the idea of a symposium on histamine has been so well received and that so many have come. As Chairman of the opening session it is my pleasant duty to welcome you. We are delighted that so many of our colleagues from abroad could come, and I would like to extend a special welcome to all those who have come from overseas—from South America, Canada and the States—to those who have come from the Continent, and naturally also to those who came from Scotland.

The idea of a symposium on histamine was suggested at a meeting of the Biological Council's Co-ordinating Committee for Symposia on Drug Action held in July 1953. The Chairman of the Committee, Sir Charles Harington, undertook to bring the suggestion to the notice of the British Physiological and Pharmacological Societies.

The suggestion was welcomed by these Societies, who appointed a joint sub-committee to organize the symposium. It consisted of Prof. Gaddum, Prof. Paton, Dr. Schild, Dr. Wood and myself and had at least one bright idea, although it was actually not a very original one, namely that of getting Dr. Wolstenholme from the Ciba Foundation interested in the matter. The result was that we now have two symposia, that the contents of both will be published by the Ciba Foundation, and that many more guests from abroad could be invited. On behalf of the organizing Committee I should like to express our thanks to the Ciba Foundation and to Dr. Wolstenholme personally, who has probably more experience in arranging symposia than anyone else in this country and on whose help and advice, I can assure you, we

could always rely. The meeting should also know that we are greatly indebted to Dr. Schild who cheerfully carried the main burden of organizing this symposium. Finally, on behalf of the organizing Committee—and I think you would wish me to do so also on your behalf—I should like to express our most sincere thanks to the Wellcome Foundation for their hospitality. We are fortunate that we can meet here in this fine hall for our symposium on histamine and, as mentioned by Mr. Perrin, the Chairman of the Wellcome Foundation, in his speech at the reception lunch party, this is indeed the most appropriate place, because it was in the Wellcome Research Laboratories that Sir Henry Dale carried out his pioneer work on histamine, and we are proud and glad to have him with us today.

DISTRIBUTION OF HISTAMINE IN THE BODY

W. FELDBERG

National Institute for Medical Research, Mill Hill, London

IF I HAD to shorten my contribution to the utmost, I could just say: histamine is very widely distributed in the body. In fact, if we look up its distribution in the book by Guggenheim (1951), we find there is scarcely any organ which does not contain at least some histamine. It occurs in the skin, in the subcutaneous tissue, in skeletal muscle, in all the viscera so far examined, and in the peripheral and central nervous systems. There are two tissues which, as far as I know, have not yet been examined: bone and cartilage, so I do not know if they contain histamine. Histamine occurs also in tumours and not only in those consisting of mast cells. It has been found in sarcoma of mice and rats but not in the Rous sarcoma of chicken, and histamine also appears to be absent in carcinoma, or to be present in these tumours in traces only (Rosenthal, 1949).

Histamine occurs, further, in many physiological and pathological body fluids: in blood, plasma, bile, gastric juice, urine, in the secretion of the nose, in blister fluid, sputum, and pus, but it has not been found in pancreatic juice and is usually absent in saliva, although Ungar and Pocoulé (1937) detected minute quantities occasionally.

Mention might be made that histamine is also a naturally occurring constituent of various plants such as nettles, spinach, tomatoes, Chenopodia and others, and it is sometimes present in plant tissues in extremely high concentrations. Werle and Raub (1948) found, in growing seeds of spinach, concentrations of nearly 0·5 mg./g. fresh tissue, and even higher values in the flowers of the spinach plant

which had survived the winter. In one specimen a value of 1·34 mg./g. was found.

When discussing the distribution of histamine in the body, I must avoid as far as possible touching those aspects which are reviewed by the other speakers of this session and of the following, and this naturally imposes a restriction on the subject. My main object will therefore be to underline some of the striking and puzzling facts concerning the distribution of histamine in animal tissues.

First of all, we are not in the position to say that this or that organ has a high or low histamine content, because the distribution of histamine varies in different species. For instance, if we take the liver: in guinea pigs it contains usually only traces, in rats it has an average histamine content of less than 1 μg./g., whereas in dogs and horses values between 8 and 110 μg./g. histamine have been found. Similar species differences for the histamine content occur in other organs. Thus the organs which are rich in histamine vary in different species.

I said that the histamine content of liver varies in dogs and horses between 8 and 110 μg./g. I want to emphasize this wide range because it illustrates the tremendous individual variations which exist in the histamine content of so many organs. Anyone who wants to study changes in histamine content of organs and is not aware of these variations is apt to draw wrong conclusions. I myself once erred badly in this respect. The great individual variations make it difficult also to compare the histamine contents of different organs. I have tried to overcome this difficulty in Table I, by giving plus and minus signs instead of figures. The blank spaces do not mean that the organs contain no histamine but only that I did not find values in the papers I looked at.

The liver we have discussed. Another organ with a high histamine content in many species is the lung, except in rats. Skeletal muscle contains, in general, relatively small amounts of histamine except in rats.

When we consider the histamine content of skin, we have to consider not only species differences but also regional

Table I

DISTRIBUTION OF HISTAMINE

	Rat	G Pig	Rabbit	Cat	Dog	Cattle	Horse	Man
Liver	−	−	+++	− +	++	− +	+++	
Lungs	− +	+++		++	++	++++	++++	
Skeletal Muscle	+	− +	− +	− +	− +	− +	−	
Skin Body	+ +	− +	− +	++	− +			− +
Skin Ear		+	++	++++	++			
Skin Feet	++++	− +		++				
Stomach (mucosa)	− +	− +		++	++++			
Small intest (mucosa)	+	++		++	++++			++++
Aorta		+			−	− +	−	
Heart	− +	− +	− +		− +	+		
Spleen	−	+	− +		− +	− +	− +	
Nerves my		++		++	++	+		
Nerves n-my					++++	+++		
Symp gangl				− +	− +			
Brain		−		−	−	− +		
Hypothalamus				− +	− +			
Eminentia mediana				+	+			
Post pituitary				++	+			
Ant pituitary				++	+			

Code for histamine values

++++	often	40 − 100 µg/g or more
+++	"	20 − 40 µg/g
++	"	10 − 40 µg/g
+	"	10 − 20 µg/g
−+	"	1 − 10 µg/g
−	"	less than 1 µg/g

differences. The general level of skin histamine in different species is highest in rats, next come cats, then dogs and man; guinea pigs have a relatively low skin histamine. Independent of whether the general level of skin histamine is high or low,

ears, face and paws are normally the regions with the highest histamine values. Miles and I (1953) found that the skin of the cat's ear contains between 95 and 120 μg./g. The regional

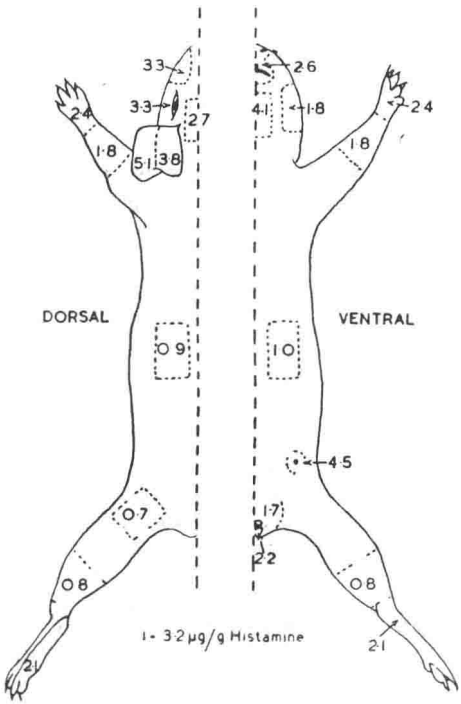

FIG. 1. Diagram of guinea pig's body surface to illustrate regional differences in histamine content of skin. The figures represent mean values for each region, the abdominal skin being taken as unity. (Feldberg and Miles, 1953.)

differences in the guinea pig's skin are illustrated diagrammatically in Fig. 1. The histamine content of the abdominal skin which is 3·2 μg./g. is taken in this diagram as unity. Skin from the ears contains five times as much histamine, and skin from many parts of the face and head and around the nipples has high histamine values; high histamine values

are also obtained from the skin of the feet. The large regional differences in skin histamine probably reflect regional differences in the mast cell content, and perhaps we shall hear more about this problem from Dr. West, and during the discussion.

Concerning the gastro-intestinal wall, I think it is not generally realized that the intestinal mucosa, in many species, has a very high histamine content, and to some extent this applies to the mucosa of the stomach as well. The distribution of histamine in the wall of the digestive tract of the dog is shown in Fig. 2. The wall of the oesophagus has a low

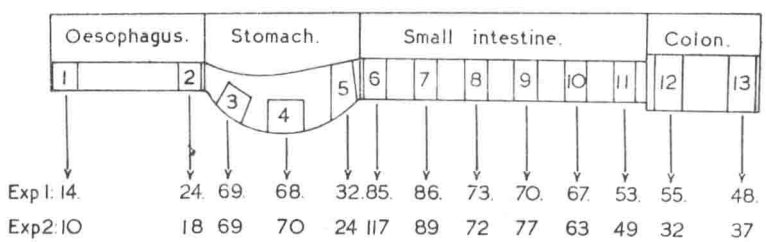

FIG. 2. Diagram of digestive tract to illustrate the position of pieces taken for extraction and histamine assay. The figures below the diagram are μg. histamine per g. of entire wall of the respective areas. (Douglas, Feldberg, Paton and Schachter, 1951.)

histamine content. In the stomach wall the histamine content is high, at least in the body ; in the pyloric region the value falls to half the level. When we come to the duodenum, the value becomes very high again and then there is a gradual decrease from duodenum to ileum and colon. The greater part of the histamine in the wall of the digestive tract resides in the mucosa; here the concentration of histamine is even higher than that given for the whole wall. For the gastric mucosa, values of over 100 μg./g. are often obtained for the body of the stomach and the values for the mucosa from the pyloric region are about half as high.

The mucosa of the digestive tract consists of many different cellular elements, and in order that these figures and differences, for instance the difference between the body and

pyloric region of the gastric mucosa should acquire a physiological meaning, we must know if the histamine is evenly distributed throughout the thickness of the mucosa or localized in certain parts. Such an attempt to localize the mucosal histamine in terms of histological structure was made by Harris and myself (1953).

Small flattened pieces of mucosa were frozen on the freezing microtome and cut in the horizontal plane in serial sections which were weighed, extracted, and assayed for histamine. In some experiments only alternate sections were used for such histamine assay and the others were stained and examined histologically. In other experiments an adjacent piece of mucosa was cut and used for histological control. From the results obtained, "histamine profiles" were constructed in which the ordinates represented histamine content of the sections, and the abscissae the position and thickness of the section. In Fig. 3 such histamine profiles are illustrated for the body and pyloric region of the gastric mucosa of the dog, and placed below are microphotographs of transverse sections through these regions. In the body the histamine profile shows two peaks: one is located in the region of the parietal cells, the other in the region of the muscularis mucosa. There is also some histamine in the connective tissue of the submucosa which probably resides here in mast cells, but I doubt that the peaks, particularly that in the region of the parietal cells, are of mast cell origin. In the pyloric region the mucosa has only one peak and it is located in the region of the pyloric glands. So it looks as if a large part of the mucosal histamine resides in the gland cells, and the difference in histamine content between the body and pyloric mucosa may be mainly due to the fact that gland cells do not spread over such a wide portion of the mucosa in the pyloric region. In fact, in some experiments the peak in the pyloric region was higher than either of the two peaks of the body mucosa.

The central nervous system has, in general, a very low histamine content, but there are certain small regions near the posterior pituitary, and the posterior pituitary itself