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The Sites of Action of some Histamin-Releasing Substances in the Dog

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Abstract

1. The rates of histamine release from the liver, skin and muscle by four kinds of histamine-releasing substances, sinomenine, compound 48/80, tween 20 and polyvinylpyrrolidone (PVP), were compared by intravenous injection in dogs, each in a dosage to cause a fall of approximately 80 per cent in the arterial blood pressure. 2. By compound 48/80, the rates were especially marked from the liver and muscle and only slight from the skin, while those by sinomenine, tween 20 and PVP were largest from the skin, followed by those from the liver and muscle, in that order. The rate of histamine release from the skin by PVP was characteristic in that it was far larger than that by other releasers. 3. On direct application of the drug solutions to the excised tissues of the liver and skin the rates of release of histamine differed only slightly by the tissue in any of these releasers 4. Some considerations were given on the reason for the different ratios by the organ of in vivo histamine release though as yet no definite conclusion could be drawn.

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THE SITES OF ACTION OF SOME HISTAMINE-RELEASING SUBSTANCES IN THE DOG[1,2]

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Since ALAM *et al.*[1] discovered the action of curare in releasing histamine from the skeletal muscle, numerous reports have been made on the release of histamine from mammalian tissues by many organic chemical substances including basic compounds, large molecules and surface-active agents. These substances seem not to release histamine in the same ratio from any of the tissues. It is known that curare liberates histamine from the skeletal muscle in perfusion but not to a detectable amount from the lung[1]. MACINTOSH and PATON[2] reported that licheniformin as well as a large number of related compounds with the structure of an organic base liberate histamine from the skin and muscle of a cat but not from the liver. According to HALPERN[3], in rats receiving several injections of dextran and no longer capable of releasing histamine by this substance, another releaser, compound 48/80, was still able to cause a typical anaphylactic response.

Formerly, it had been our belief that the chief source of histamine liberated in dogs is the liver, for it is known that the liver is the richest organ in histamine in this animal and that the large amount of histamine is liberated from this organ during anaphylactic[4,5] and peptone shock[6]. A more recent study of MACINTOSH and PATON[2] suggests that the same thing may be said of the action of numerous other basic organic compounds. However, MAYEDA[7,8] in our laboratory, having found the histamine-releasing activity of sinomenine, an alkaloid of *Sinomenium acutum* Rehd., demonstrated that this liberates histamine in a much higher rate from the skin rather than from the liver when injected intravenously in this animal. These observations suggest that it would be interesting to study the main sites of histamine release, yet to be known, of other powerful histamine releasers.

In the present experiments, compound 48/80 (organic base)[9], tween

1) Aided by a grant for Fundamental Scientific Research from the Ministry of Education.

2) Preliminary note in Folia pharmacol. japon. 53, 74 §, 1957.

20 (surface-active agent)[10, 11] and polyvinylpyrrolidone (large molecular compound)[12, 13, 14] and also sinomenine were injected intravenously in dogs and the rates of histamine release from the liver, skin and skeletal muscle were quantitatively examined, and these results were compared with that of the *in vitro* study of histamine release from the liver and the skin tissues.

METHODS

Adult dogs weighing 7—12 kg. were anesthetized by an intravenous injection of 40 mg./kg. of amytal sodium for the experiments. The releasers, sinomenine hydrochloride[3], compound 48/80[4] (condensation product of *p*-methoxyphenethylmethylamine with formaldehyde), tween 20 and polyvinylpyrrolidone[5] (PVP, mol. wt., 25, 000—35, 000), were all injected into the femoral vein respective dosage of 3, 0.7, 10 and 350 mg./kg., which were determined to be necessary for causing about 80 per cent fall of the arterial blood pressure. These substances were dissolved in 0.9% saline solution to the concentration of 3, 0.1, 10 and 35 per cent, respectively, and injected within 30 seconds, except PVP which was given within 5 minutes.

Measurement of in vivo histamine release from the skin, muscle and liver. Liver sample was removed from the terminal lobes, skin from the outer sides of the femur and also from the ears in a part of experiments, and muscle from m. glutaeus maximus, all in an amount necessary to provide for a 3g. sample, from the left side prior to the injection of the releasers and from the corresponding right side portion 30 minutes after the injection. Of the skin pieces, hair and the subcutaneous tissues were removed as much as possible. Cares were taken to arrest bleeding during and also after resection of these tissues. The excised tissues were washed with 0.9% saline solution, gross moisture was wiped off with a piece of filter paper, and weighed.

For extraction of histamine, 3g. of finely cut tissues were boiled with 10 c. c. of N-hydrochloric acid for 10 minutes in a water bath, ground with quartz sand, centrifuged, and the supernatant (extract) was separated. In a part of experiments the CODE method[15] was adopted for same

3) Sinomenine hydrochloride was generously supplied by the Shionogi Research Laboratories, Imafuku 192, Amagasaki.

4) Compound 48/80 was obtained through the kindness of Dr. EDWIN J. DE BEER, the Wellcome Research Laboratories, Tuskahoe 7, New York.

5) Polyvinylpyrrolidone was obtained through the courtesy of the Ono Pharmaceutical Industries, Doshomachi 2, Osaka.

purpose. The extract solutions were then neutralized with N-sodium hydroxide and assayed for histamine with a piece of guinea pig ileum suspended in a bath of Tyrode solution containing 0.05 μg./c. c. of atropine sulfate. The fact that the effect of an active substance was suppressed by neoantergan to the same degree as that of equiactive histamine served for identification of histamine action. The amount of the other components (including K^+) in the extract effecting contraction in the presence of neoantergan, was quite small enough to be negligible for the present purpose of histamine assay. For the calculation of the total amount of histamine released from the whole organ, dimension of the skin of whole body was roughly computed by the RUBNER method[16]. Total weight of the skeletal muscle was calculated as 39 per cent of body weight; this percentage was based on actual measurements of three dogs similar in stature to the animals used for the present experiment. In spite of the evidences pointing differences in contents of histamine in various regions of the skin, the value of femoral skin was used as a basis of calculation for the reason that it is representative content in comparatively wide range of the skin[17]. The weight of the liver was measured after removing as much blood as possible.

Measurement of in vitro histamine release from excised tissues. The skin, removed of hair and subcutaneous tissue, was stretched on a cork board, pinned to the original size, and cut into strips of 0.7 mm. width with a mincer made by fixing several safety razor blades placed in parallel with the same spacings. The liver was cut into flat pieces of about 1.5 mm. in thickness with two parallel blades and again cut into strips of 1.5 mm. width in the same manner as with the skin. Several divisions of 100—200 mg. of minced tissues, obtained from the same tissue, were used for each experiment. Flat-bottomed test tubes, each containing 0.9% saline solution with test substance, tissue piece and a glass bead of 3 mm. diameter for agitating this mixture, were shaken 100 rounds per minute for a distance of 5 cm. in a bath of 37°C for 60 minutes. The quantity of histamine diffusing out in the medium was determined with a piece of guinea pig ileum. In order to make accurate assay of histamine, the amount of the releasers contained in the test solution was added into the bath together with the standard histamine solution. The rate of histamine release by each releasers was calculated by the following equation:

$$\text{Rate of histamine release (\%)} = \frac{\text{Total amt. released} - \text{spontaneous release}}{\text{Residual amt. in the tissue} + \text{total amt. released}} \times 100$$

Measurement of arterial blood pressure. In experiments on *in vivo* histamine release, the pressure of femoral artery was also recorded kymographically through a mercury manometer. The maximum rate of hypotension was indicated in the records for 30 minutes after the injection.

RESULTS

Immediately after the injection of sinomenine or compound 48/80, arterial blood pressure showed a sudden fall after a slight rise for 20—30 seconds, reached the minimum in 1—2 minutes where it stayed for some time, then gradually tended to recovery. The maximum fall of blood pressure during 30 minutes after the injection was about the same degree in the two releasers in the present doses, i. e. 83 (80—87) per cent by sinomenine and 83 (78—85) per cent by compound 48/80. The delayed depressor effect, a characteristic of histamine-releasing action[2] was observed by these relcasers. The latent period until the fall of blood pressure seemed to be slightly shorter in compound 48/80 than in sinomenine. With the injection of tween 20 and PVP, there was no transitory rise of blood pressure. It began to fall by the end of injection of tween 20. How-

Table 1. The rate of histamine release by sinomenine from the liver, skin and muscle in dogs, with maximal fall of blood pressure.

Exp. dog	Organ	Before Sinom.	After Sinom.	Difference	% hist. release	Hist. released from the whole organ	Max. fall of B.P. within 30 min.
		(μg./g.)	(μg./g.)	(μg./g.)		(mg.)	(%)
I	Liver	44.2	34.0	10.2	23.0	3.4	
9.0 kg. ♀	Skin	12.2	8.8	3.4	27.8	1.8	87
	Muscle	2.2	2.2	0	0	0	
						Total 5.2	
II	Liver	61.2	47.6	13.6	22.2	4.0	
7.0 kg. ♀	Skin	10.9	8.2	2.7	25.0	1.2	80
	Muscle	2.0	2.0	0	0	0	
						Total 5.2	
III	Liver	68.0	61.2	6.8	10.0	1.9	
7.0 kg. ♂	Skin	12.1	8.1	4.0	33.3	1.7	82
	Muscle	2.1	1.9	0.16	7.8	0.44	
						Total 4.0	
Average	Liver	57.8	47.6	10.2	18.4	3.1	
	Skin	11.8	8.4	3.1	28.7	1.6	83
	Muscle	2.1	2.0	0.05	3.6	0.15	
						Total 4.9	

ever, this initial fall was slight and either it stopped or showed a slight temporary rise before going to a profound fall, reaching the maximum of 81 (79—85) per cent fall in 2—4 minutes after the end of injection. The earlier onset of the fall of blood pressure by tween 20 may not be due to liberated histamine but probably due to the action of this substance itself. With PVP, a more gradual fall than the foregoing three substances began 1—3 minutes after beginning of the injection, the blood pressure reaching the minimum after 4—5 minutes, and returned to normal in a comparatively short time. The rate of maximum fall of blood pressure was rather smaller than that of the others, being 73 (69—79) per cent. This comparatively mild fall of blood pressure may have some bearing on the slow

Table 2. The rate of histamine release of compound 48/80 from the liver, skin and muscle in dogs, with maximal fall of blood pressure.

Exp. dog	Organ	Before 48/80	After 48/80	Difference	% hist. release	Hist. released from the whole organ	Max. fall of B.P. within 30 min.
		(μg./g.)	(μg./g.)	(μg./g.)		(mg.)	(%)
I	Liver	40.8	25.8	15.0	36.7	5.5	
	Skin	6.1 (27.2)	6.1 (24.5)	0.68 (2.7)	11.1 (10.0)	0.4	83
11.0 kg. ♀	Muscle	2.2	1.7	0.56	25.0	2.4	
						Total 8.3	
II	Liver	68.0	46.2	21.8	32.0	7.7	
	Skin	8.8 (40.8)	8.2 (29.9)	0.68 (10.9)	7.7 (26.7)	0.25	85
10.0 kg. ♂	Muscle	2.0	1.1	0.84	42.9	3.3	
						Total 11.3	
III*	Liver	34.0	20.4	13.6	40.0	4.7	
	Skin	6.1	4.8	1.4	22.2	0.79	78
10.5 kg. ♀	Muscle	1.4	1.0	0.42	30.0	1.7	
						Total 7.2	
IV*	Liver	54.4	37.4	17.0	31.3	4.9	
	Skin	6.8	5.8	1.0	15.0	0.51	85
9.0 kg. ♀	Muscle	1.7	1.1	0.56	33.3	2.0	
						Total 7.4	
Average	Liver	49.3	32.5	16.8	35.0	5.7	
	Skin	7.0 (34.0)	6.6 (27.2)	0.94 (6.8)	14.1 (18.3)	0.49	83
	Muscle	1.8	1.2	0.60	32.8	2.3	
						Total 8.5	

Values in parentheses refer to histamine content of the aural skin.
* CODE's method for histamine extraction.

speed of injection.

Results on histamine release from the liver, skin and skeletal muscle by the intravenous injection of these four substances are shown in Tables 1—4.

Of the data for the skin, the values in parentheses are those obtained with the skin of the ear lobe, which contains high amount of histamine. The histamine contents in the liver, skin and muscle of normal dogs had been ascertained as being approximately the same at corresponding positions on the left and right sides by preliminary experiment with two dogs.

Table 3. The rate of histamine release by tween 20 from the liver, skin and muscle in dogs, with maximal fall of blood pressure.

Exp. dog	Organ	Before Tween 20	After Tween 20	Difference	% hist. release	Hist. released from the whole organ	Max. fall of B.P. within 30 min.
		(μg./g.)	(μg./g.)	(μg./g.)		(mg.)	(%)
I	Liver	44.8	36.4	8.4	18.8	2.8	
	Skin	12.9 (36.4)	8.2 (14.6)	4.8 (21.8)	36.8 (59.9)	2.1	80
8.0 kg. ♂	Muscle	2.8	2.5	0.28	10.0	0.87	
						Total 5.8	
II	Liver	47.6	39.2	8.4	17.7	3.5	
	Skin	10.9 (38.4)	6.1 (19.6)	4.8 (18.8)	44.1 (49.0)	2.4	79
9.0 kg. ♀	Muscle	5.0	4.8	0.28	5.6	0.98	
						Total 6.9	
III*	Liver	47.6	40.8	6.8	14.3	2.6	
	Skin	6.8	2.7	4.1	60.3	2.7	85
12.0 kg. ♀	Muscle	1.4	1.3	0.14	10.0	0.66	
						Total 6.0	
Average	Liver	46.7	38.8	7.9	16.9	3.0	
	Skin	10.2 (37.4)	5.7 (17.1)	4.5 (20.3)	47.1 (54.4)	2.4	81
	Muscle	3.1	2.6	0.23	8.5	0.84	
						Total 6.2	

Values in parentheses refer to histamine content of the aural skin.
*** CODE's method for histamine extraction.**

The percentage rate of release of histamine by sinomenine was largest in the skin among the three organs but the total amount of histamine released from each whole organ was largest in the liver, followed by the skin and muscle in that order. Histamine release from the muscle was smallest in the present experiment, differing from the report of MAYEDA[8].

Table 4. The rate of histamine release by PVP from the liver, skin and muscle in dogs, with maximal fall of blood pressure.

Exp. dog	Organ	Before PVP	After PVP	Difference	% hist. release	Hist. released from the whole organ	Max. fall of B. P. within 30 min.
		(μg./g.)	(μg./g.)	(μg./g.)		(mg.)	(%)
I	Liver	67.4	60.6	6.8	10.1	2.2	
	Skin	13.5	7.4	6.1	45.0	3.6	69
9.9 kg. ♂	Muscle	1.7	1.5	0.14	8.3	0.54	
						Total 6.3	
II	Liver	74.8	68.0	6.8	9.1	2.3	
	Skin	10.9	5.4	5.4	50.0	3.2	69
10.0 kg. ♂	Muscle	1.8	1.8	0.07	3.8	0.27	
						Total 5.8	
III*	Liver	30.8	25.2	5.6	18.2	1.9	
	Skin	9.4	4.7	4.7	49.9	2.6	82
10.0 kg. ♂	Muscle	1.5	1.5	0.08	5.2	0.31	
						Total 4.8	
Average	Liver	57.7	51.3	6.4	12.5	2.2	
	Skin	11.3	5.9	5.4	48.3	3.1	73
	Muscle	1.7	1.6	0.10	5.8	0.37	
						Total 5.7	

* CODE's method for histamine extraction.

In the case of compound 48/80, the rate of release of histamine was marked from both the liver and muscle, that from the skin being slight. With the organ as a whole, the amount released was overwhelmingly large from the liver. Total amount of histamine released from the three organs was larger than that in the case of sinomenine.

The percentage rate of release of histamine by tween 20 was larger from the skin than from the other organs and the amount released from the skin was far larger than that by sinomenine. The rate of release was larger from the aural skin than from that of the thigh. The latter result agrees with KUME's finding[17] with sinomenine in the dog.

The effect of PVP was similar to that of tween 20 but only difference was that with PVP the release from the skin is by far greater than that from the liver or muscle as compared with the case of the latter releaser. The total amount of histamine released from these three organs by PVP was rather smaller than that by the other substances.

Table 5 shows the rate of *in vitro* histamine release from the liver and skin by these four kinds of substances, measured by the method

Table 5. The rate of *in vitro* histamine release by some releasers from minced tissues of the dog's liver and skin.

Tissue	No. of exp.	Histamine release (%)						
		Sinomenine HCl		Compound 48/80		Tween 20		PVP
		0.2%	1.0%	0.02%	0.1%	0.5%	3.0%	3.5%
Liver	5	10.4 (8.1-12.5)	15.0 (12.8-16.1)	9.4 (8.1-10.8)	16.6 (15.3-17.5)	23.8 (14.8-27.0)	29.0 (17.6-32.4)	27.1 (14.3-31.5)
Skin	5	13.2 (9.6-15.1)	18.3 (13.5-20.2)	7.8 (6.3-9.1)	11.1 (7.3-14.6)	24.1 (15.2-27.5)	30.7 (16.9-34.8)	28.7 (14.6-33.1)

Table 6. Histamine contents and percentages of spontaneous histamine release of the tissues used in the experiments in Table 5.

Tissue	Histamine content (μg./g. tissue)	Spontaneous histamine release (%)
Liver	45.2 (25.1—70.3)	3.4 (2.2—4.1)
Skin	11.7 (6.4—17.3)	7.1 (4.1—10.2)

described above. Histamine contents and the spontaneous release of these tissues are shown in Table 6. The concentration of releasers, with the exception of PVP, was selected by the ratio of dosages causing about the same degree of hypotension. The action of these substances was examined with the two organs of each dog at the same time. All the values listed are obtained with five dogs. The ratio of release differs with each substance but there is no marked difference from the liver and skin by any of these substances. This could not have been anticipated in the result of the *in vivo* experiment.

DISCUSSION

The results of the present experiments have indicated that the rates of release of histamine from different organs are not necessarily the same by any histamine-releasing substance given intravenously. The rate of release by sinomenine was found to be greatest from the skin, followed by that from the liver, as was reported by MAYEDA[8], but the total amount released from each organ was greater from the liver, differing from his result. This may be due to the fact that in the present experiment weight

of the liver of the dogs was greater than that used by MAYEDA[8], probably owing to the difference in nutrition, as may be imagined from the weight ratio of the whole muscles.

Release of histamine by compound 48/80 was largest from the liver and smallest from the skin, and this was approximately the same as the results obtained by MAYEDA[8] with peptone. NISHIYAMA[18] indicated that the release of histamine from the liver was greater than that from the skin during anaphylactic shock in dogs. Both tween 20 and PVP effected a greater release of histamine from the skin than from other two organs, and this difference was especially marked in PVP.

The question as to what caused the difference in the degree of histamine release from these organs by these substances cannot be answered fully with our present knowledge on the mode of binding of histamine in the cells and on the mechanism of its release. There is no similarity in the chemical structure of compound 48/80 and of sinomenine but they may be of the same category in that they are both basic compounds. Although there is a difference that sinomenine releases a larger amount of skin histamine than compound 48/80, these two substances are powerful releasers of liver histamine. This seems to be also true with licheniformin, and also other diamines, diamidines, diguanidines, bis-quaternary bases, as well as benzamidine derivatives[2]. MONGAR and SCHILD[19] called attention, in their studies on *in vitro* histamine release from various organs of guinea pigs, to some similarity of compound 48/80 or D-tubocurarine and anaphylaxis in their action. KAMIMURA[20] observed that the action of sinomenine was also similar to these compounds on this point. It has been suggested by ELDRIDGE and PATON[21] that the histamine-releasing action of peptone is at least partly due to basic amino acids, arginine and lysine contained in it. Would it not be possible, then, to explain such common characteristics of action of these substances by the hypothesis that these substances replace histamine by binding with acidic residues in the tissue?

Compound 48/80 abundantly releases histamine from mast cells but does not seem to release histamine from other tissues[22]. Dog liver is especially rich in mast cells, which are found around the fine blood vessels and in the wall of sinusoids[23], easily accessible by the circulating chemical substances. It follows, therefore, that a series of histamine-releasing substances having strong affinity to these cells can readily liberate histamine from the liver. YAMASAKI and KAWAMOTO[24] have observed that intravenously injected peptone disrupts only a few mast cells of the skin but tween 20 and PVP effect strong change of these cells in the skin rather than in the liver, in proportion to the intensity of their histamine releasing

action iu our present study. Therefore, difference in the site of histamine release can not be explained only by the affinity of certain substances to mast cells.

The most simple explanation may be the one based on the hypothesis that such difference is produced by a variety in local concentration of the chemicals distributed after injection but yet there is no experimental evidence to support such a belief. MACINTOSH[25] tried to explain the differences of *in vitro* and *in vivo* effects of some basic compounds in connection with their binding power with hematocytes, plasma proteins, or heparin *in vivo*. According to the hypothesis that the activity of an enzyme is involved in the action of histamine-releasing substances[26, 27], differences in the tissue element taking part in protease activation may give different effects on histamine releasing effect of such substances, but it is impossible to detemine at present whether or not protease activation has any causal relation to the histamine release.

In contrast with such non-uniformity of histamine release from tissues *in vivo*, the *in vitro* experiment showed no marked difference in the rates of release of histamine from the liver and skin pieces by any of these substances. This suggests that there are some differences in the mechanism of histamine release under these two kinds of experimental conditions. In one, the releasers reach the tissue via the blood, while in the other, they penetrate into the tissue cells directly from their surface. The fact that histamine is not released from the lung of a guinea pig by intravenous injection or perfusion of compound 48/80[28, 29] or sinomenine[30] but a large amount of it is released on direct application of the drug solutions on the excised tissue pieces of this animal[20, 31] may also be explained similarly. A similar ratio of the *in vitro* liberation of histamine from different tissues (such as the skin and liver) may be due to the fact that the action of releasers is manifested chiefly through its action on the surface membrane of histamine-containing cells, as PATON[32] has suggested.

The difference in the site of action of histamine-releasing substances *in vivo* seems to be fundamentally related to the mechanism of histamine release, as is also true with differences in effects according to the differences in species of animals; therefore more extensive studies are desired for clarifying the reason for these phenomena.

SUMMARY

1. The rates of histamine release from the liver, skin and muscle by four kinds of histamine-releasing substances, sinomenine, compound 48/80, tween 20 and polyvinylpyrrolidone (PVP), were compared by in-

travenous injection in dogs, each in a dosage to cause a fall of approximately 80 per cent in the arterial blood pressure.

2. By compound 48/80, the rates were especially marked from the liver and muscle and only slight from the skin, while those by sinomenine, tween 20 and PVP were largest from the skin, followed by those from the liver and muscle, in that order. The rate of histamine release from the skin by PVP was characteristic in that it was far larger than that by other releasers.

3. On direct application of the drug solutions to the excised tissues of the liver and skin the rates of release of histamine differed only slightly by the tissue in any of these releasers

4. Some considerations were given on the reason for the different ratios by the organ of *in vivo* histamine release though as yet no definite conclusion could be drawn.

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