Mast-Cell Disruption and I^{131} Distribution in the Rat*

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The alteration of I^{131} distribution in tumor-bearing animals has been described by Scott *et al.* (18, 19, 21, 22). This phenomenon, which results in increased I^{131} uptake in skin and gastrointestinal tract and lower than normal thyroid uptake and urinary I^{131} excretion, has been called "iodide trapping." The altered I^{131} distribution was shown to occur locally in the skin adjacent to the tumor implant and was detected when the tumor mass weighed as little as 50 mg. As tumor growth proceeded, the entire skin took up more I^{131} than normal, and finally the gastrointestinal tract and muscle showed elevated levels. The iodide trapping syndrome can also be elicited in normal rats by the administration of a polypeptide fraction obtained from the tumor (19). Its occurrence in animals bearing transmissible or spontaneous tumors has not been adequately explained.

It has been shown that tumor growth or the administration of tumor polypeptide caused a pronounced disruption of mast cells in the rat, as observed in mesenteric spreads taken from these animals (20). The alteration in the mesenteric mast cell population occurs during the period of tumor growth which has been shown previously to cause widespread alterations in the I^{131} distribution of the host. In order to further the understanding of the possible relationship between mast cell disruption and iodide trapping in the tumor-bearing animal, we have investigated the effect of mast cell disrupting agents upon I^{131} distribution in the rat.

The effect of three of the components of the mast cell upon I^{131} distribution in the rat was studied. These were histamine (17), 5-hydroxytryptamine (5-HT or serotonin) (1), and heparin (11). The effect of reserpine, which releases 5-HT from the body (2–4,) was also studied in this respect.

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MATERIALS AND METHODS

Inbred Slonaker rats weighing approximately 150 gm. were used in this study. Control and treated animals were of similar age, sex, and weight, and the variation of weight in separate experiments was limited to ± 5 gm. The tumor polypeptide was prepared from frozen solid tumors obtained from rats of the same strain by a method described earlier (19). This tumor, classified as a fibrosarcoma, has been described previously (18).

The agents used to disrupt mast cells were distilled water, as described by Fawcett (9); polymyxin B, as reported by Norton and de Beer (12), and Bushby and Green (5); compound 48/80, the action of which upon mast cells has been extensively reviewed by Paton (16).

The histamine was administered as the phosphate and the 5-HT as the creatinine sulfate complex. Amounts shown in the tables refer to the amount of free base given per rat in isotonic saline. Polymyxin B in isotonic saline and reserpine were given on a mg/kg basis. The above compounds were given by intraperitoneal injection except as noted. Heparin, as the sodium salt in isotonic saline, was injected subcutaneously at a dosage level of 1000 U.S.P. units per rat.

Each rat received 20 μc. of I^{131} intraperitoneally. This was given by separate injection immediately following administration of the agent being tested for its effect upon I^{131} distribution. This amount of I^{131} does not appreciably expand the iodide pool of the animal, since it corresponds to only 2×10^{-4} μg. of iodine. At the intervals shown in the tables, the rats were killed with ether. Wet specimens from these animals were assayed with a scintillation counter composed of a thallium-activated sodium iodide crystal and a RCA 5819 photomultiplier tube. The counting accuracy was $\pm$ 1.6 per cent or better. The values are expressed as per cent of the administered dose except for those for skin and remains, which are given as per cent of dose per gram. The data have been expressed, where possible, as the mean of three rats $\pm$ standard error, with the use of $\sqrt{\frac{\Sigma \text{ dev}^2}{(n \times n - 1)}}$.

RESULTS

The data shown in Group I of Table 1 illustrate the effect of histamine administration upon the 4-hour I^{131} distribution in the rat. A dose of 0.25 mg. resulted in a significant increase in skin uptake ($P = .02$), thyroid uptake ($P = .05$), and a decrease in urinary I^{131} excretion to 42 per cent of normal. No significant increase in the gastrointestinal tract uptake occurred at this dosage level, but administration of 0.55 mg. of histamine resulted in a greater increase ($P = .03$). At the latter dose no significant difference was observed in skin ($P = .08$) or thyroid uptake ($P = .05$).

Group II of Table 1 shows the I^{131} distribution resulting from the administration of varying doses of 5-HT. When 0.087 mg. was given, the G.I. tract had a highly significant increase in I^{131} uptake (P = .001). While the skin and thyroid did not show significant changes, the urinary I^{131} excretion was only 56 per cent of normal. More pronounced iodide trapping occurred when 2.18 mg. of 5-HT was given. The I^{131} uptake in the G.I. tract was significantly higher (P = .001), as was the uptake in the skin (P = .03), and the urinary I^{131} excretion was reduced to 19 per cent of normal.

When histamine and 5-HT were administered simultaneously, a similar alteration was observed. These data are presented in Group I of Table 2. While a slight effect upon I^{131} distribution was seen when 0.1 mg. of each amine was given, administration of 5-HT (0.65 mg.) and histamine (0.55 mg.) produced the characteristic iodide trapping syndrome. At this dosage level the G.I. uptake was significantly increased (P = .03), as was the skin uptake (P = .05). No significant decrease in thryoid uptake was detected, but the urinary I^{131} excretion was reduced to 16 per cent of normal. Higher doses likewise produced a lowered urinary I^{131} excretion. When 1.3 mg. of 5-HT and 1.1 mg. of histamine were given, the G.I. tract uptake was higher (P = .01), but no significant increase in the skin uptake was observed (P = .07). When 2.0 mg. of each amine was given, skin uptake was increased (P = .04), but no real increase in the G.I. tract uptake was seen (P = .4).

As shown in Group II of Table 2 the administration of 1000 units of heparin did not cause iodide trapping. It also had no action upon the characteristic alterations produced by 5-HT and histamine when these three compounds were given simultaneously by subcutaneous injection.

Group I of Table 3 shows the effect of tumor poly-

TABLE 1

I^{131} DISTRIBUTION IN THE RAT 4 HOURS AFTER THE ADMINISTRATION OF HISTAMINE OR 5-HYDROXYTRYPTAMINE

Three rats per group

Group	Treatment	Dosage (mg.)	Per cent of I^{131} found: G.I. tract	Skin (per cent/gm)	Thyroid	Remains (per cent/gm)	Urine
I	Histamine	.25	24.2± 4.7	0.66±.03	10.1±2.8	0.28	21.4
	"	.55	26.7± 2.8	0.63±.05	6.4± .29	0.21	30.4
	"	1.1	34.6±11.3	0.57±.08	6.5± .59	0.19	23.5
	"	5.0	22.7± 7.4	0.88±.14	8.2±1.4	0.33	11.8
	Controls	*	13.8± 2.7	0.50±.03	6.8± .37	0.16	51.1
II	5-HT	.087	25.0± .62	0.59±.06	8.4± .77	0.24	28.0
	"	.87	23.7± 7.2	0.67±.07	8.7±2.4	0.27	16.7
	"	2.18	30.6± 1.7	0.78±.09	8.3±1.7	0.30	9.2
	Controls	*	14.8± .58	0.40±.08	8.7± .68	0.13	49.8

* Controls received saline.

TABLE 2

I^{131} DISTRIBUTION IN THE RAT 4 HOURS AFTER THE ADMINISTRATION OF VARIOUS COMBINATIONS OF 5-HT, HISTAMINE, AND HEPARIN

Three rats per group

Group	Treatment and Dosage*	Per cent of I^{131} found: G.I. tract	Skin (per cent/gm)	Thyroid	Remains (per cent/gm)	Urine
I	5-HT 0.1 +Hist. 0.1	23.5±0.9	0.98±.15	6.5± .96	0.25	27.8
	" 0.5 + " 0.5	31.1±3.5	0.95±.02	8.6± .58	0.28	16.5
	" 0.65+ " 0.55	37.3±5.3	0.75±.02	6.2±1.2	0.28	6.8
	" 1.3 + " 1.1	38.7±2.4	0.78±.07	7.6±1.6	0.24	7.3
	" 2.0 + " 2.0	26.9±4.5	0.97±.10	5.9± .23	0.38	7.7
	Controls, 0	17.8±3.5	0.59±.02	6.8± .97	0.17	41.7
	Controls, 0	21.8±1.7	0.67±.05	7.4± .97	0.22	39.2
II†	Heparin, 1000	22.5± .93	0.74±.06	7.7±1.2	0.22	37.4
	Heparin+5-HT+Hist. 1000 0.65 0.55	32.9±1.8	1.19±.01	6.5±1.4	0.32	8.8
	Controls, 0	24.1±1.9	0.91±.11	7.5±1.7	0.22	33.3

* Dosage of 5-HT and histamine given in mg. per rat and heparin in U.S.P. units. Controls received saline.

† Subcutaneous injections.

peptide upon the distribution of I^{131}. Iodide trapping was elicited with an amount derived from 5 gm. of rat sarcoma. Gastrointestinal tract uptake was increased (P = .02), but no significant changes occurred in the skin (P = .2) or thyroid. The administration of 25 gm. equivalents of tumor polypeptide resulted in more pronounced effects with significantly higher uptakes in the gastrointestinal tract (P = .02) and skin (P = .02) and a significantly lower value for the thyroid (P = .02) when compared with effects in animals given normal saline. The urinary excretion of I^{131} was reduced to 35 per cent of normal. These data are similar to those reported previously (19).

When 2.5 mg/kg of polymyxin B was administered, a pronounced alteration in the I^{131} distribution was observed, as shown in Group II of Table 3. Higher than normal I^{131} uptakes occurred in the skin (P = .02) and G.I. tract (P = .06). No significant decrease was observed with thyroid uptake, but urinary I^{131} excretion was reduced to 7 per cent of that seen in control animals.

The data presented in Group III of Table 3 show the effect of compound 48/80 on I^{131} distribution. Gastrointestinal tract uptake of I^{131} was greater than in controls, and the values obtained at dosages of 500 and 1000 μg/kg suggest a real increase (P = .05). Skin levels, while higher, were not significantly increased with these amounts of compound 48/80 (P = .3–.5), and thyroid uptake was not appreciably depressed when compared with that in animals receiving isotonic saline. However, urinary I^{131} excretion was reduced to approximately 60 per cent of normal at these three dosage levels.

Table 4 illustrates the effect of distilled water administration upon I^{131} distribution. The iodide trapping syndrome was elicited with as little as 2 ml. of distilled water. Administration of 8 ml. of distilled water resulted in higher I^{131} uptakes in the G.I. tract (P = .01) and skin (P = .01). While no significant alteration in thyroid uptake occurred, the urinary I^{131} excretion was reduced to 17 per cent of normal. Administration of 15 cc. of water gave significantly higher values for gastrointestinal tract (P = .05) and skin (P = .001). Thyroid uptake at these time periods was significantly lower (P = .01), and the urinary I^{131} excretion was 16 per cent of normal.

Bhattacharya and Lewis reported that the administration of reserpine caused a release of stored 5-HT but caused only slight histamine release (2–4). This finding has been substantiated by Parratt and West (15).

TABLE 3

I^{131} DISTRIBUTION IN THE RAT 4 HOURS AFTER THE ADMINISTRATION OF TUMOR POLYPEPTIDE, POLYMYXIN B, OR COMPOUND 48/80

Three rats per group

Group	Treatment	Dosage*	Per cent of I^{131} found: G.I. tract	Skin (per cent/gm)	Thyroid	Remains (per cent/gm)	Urine
I	Tumor polypetide	5	20.1± .88	0.74± .09	6.3± .88	0.19	37.0
	" "	10	21.1±2.2	0.69± .05	4.4± .83	0.21	36.3
	" "	25	31.0±4.7	1.08± .11	3.0± .75	0.27	18.2
	Controls	0	14.2±1.2	0.52± .08	5.6± .16	0.17	51.9
II	Polymyxin B	2.5	29.6±1.4	1.34± .18	3.0± .44	0.36	3.2
	Controls	0	22.0±2.7	0.72± .08	4.3± .50	0.18	43.4
III	Compound 48/80	100	27.5±3.2	1.03± .06	6.3± .24	0.30	19.6
	" "	500	27.7±1.3	1.06± .11	5.8± .42	0.28	17.9
	" "	1000	27.1±1.2	0.95± .12	5.9± .72	0.31	18.5
	Controls	0	17.3±3.5	0.79± .17	7.6±2.1	0.27	31.1

* Tumor polypetide given in gm. equiv./rat, Polymyxin B in mg/kg, 48/80 in μg/kg. Controls received saline.

The effect of reserpine upon I^{131} distribution is shown in Table 5. Animals receiving 2.5 mg reserpine/kg showed no significant change of I^{131} uptake in the G.I. tract during the time period tested. Skin uptake was increased at 4 hours (P = .01) and 24 hours (P = .01). The data show that urinary I^{131} excretion was reduced at all time intervals, e.g., the 4-hour value for the reserpine-treated animals was only 31 per cent of normal.

DISCUSSION

Previous studies have suggested that a polypeptide fraction obtained from rat sarcoma was responsible for iodide trapping, since the alteration in I^{131} distribution observed in tumor-bearing animals could be elicited in normal animals by the administration of the tumor polypeptide (19). We have recently demonstrated that the tumor polypeptide causes the disruption of mesenteric

mast cells in amounts which produce significant alterations in the I^{131} distribution (20). The results in the present study indicate that two of the mast cell components, histamine and 5-HT, also produce the iodide trapping syndrome when administered to normal animals. However, heparin, also a mast cell component, had no effect upon I^{131} distribution and did not alter the trapping caused by histamine and 5-HT.

Parratt and West (14) and West (24) reported that, while rat mast cells do contain 5-HT, a considerable amount of the total body 5-HT may be located outside these cells. The tumor polypeptide, by virtue of its ability to disrupt mesenteric mast cells, caused the release of that amount of 5-HT contained within them. The ability of tumor polypeptide to bring about the release of 5-HT has been shown in studies involving the determination of urinary 5-hydroxyindoleacetic acid, a metabolic product of 5-HT (6–8, 23).These showed that the administration of 25-gm. equivalents of tumor polypeptide results in nearly a twofold increase in the amount of this compound in the urine.[1] The administration of reserpine to preferentially release 5-HT from the body stores caused a moderate degree of iodide trapping which suggests that 5-HT from sites other than the mast cell may be involved to some extent in the altered I^{131} distribution. However, these studies did not show whether tumor polypeptide administration or the growth of a tumor acts on 5-HT from areas other than the mesenteric mast cell.

Paton's recent review presents a large amount of evidence that compound 48/80 is capable of mast cell destruction and release of their contents (16). A similar action for polymyxin B has been reported by Norton and de Beer (12) and Bushby and Green (5). Fawcett has demonstrated that distilled water, when injected intraperitoneally, results in widespread destruction of mast cells in the serous membranes of the peritoneal cavity (9). The results of the present study demonstrate

TABLE 4

I^{131} DISTRIBUTION IN THE RAT 4 HOURS AFTER THE INTRAPERITONEAL ADMINISTRATION OF VARIOUS AMOUNTS OF DISTILLED WATER

Three rats per group

Liquid*	Amount (cc/rat)	Per cent of I^{131} found: G.I. tract	Skin (per cent/gm)	Thyroid	Remains (per cent/gm)	Urine
Distilled water	2	26.9±2.0	0.85± .01	10.1± .77	0.25	16.9
" "	8	34.2±1.4	0.98± .09	8.6±1.4	0.25	7.4
" "	15	46.7±4.4	0.82± .07	4.7± .40	0.24	5.1
" "	20	40.0±5.5	0.90± .59	3.4± .45	0.29	1.7
Controls, saline	5	19.7±2.3	0.56± .06	10.0±1.5	0.18	38.3
" "	8	14.5±1.5	0.55± .03	9.2±1.5	0.17	43.2
" "	15	28.0±4.9	0.38± .01	9.1± .95	0.18	32.3

* Administered intraperitoneally.

TABLE 5

I^{131} DISTRIBUTION IN CONTROL AND RESERPINE-TREATED RATS AT VARIOUS TIME PERIODS

Three rats per group

Time period (hours)	Treatment*	Per cent of I^{131} found: G.I. tract	Skin (per cent/gm)	Thyroid	Remains (per cent/gm)	Urine
1	Reserpine	31.2±3.2	0.85± .03	1.7± .01	0.39	3.1
	Controls	33.7±2.5	0.82± .20	2.4± .20	0.33	9.1
2	Reserpine	31.0±1.4	0.77± .01	3.0± .62	0.37	5.1
	Controls	38.0±8.3	0.57± .09	4.6±1.1	0.25	14.5
4	Reserpine	17.6±2.0	1.09± .07	7.3± .18	0.38	8.9
	Controls	24.1±3.1	0.58± .04	7.5±1.4	0.23	29.2
7	Reserpine	14.0±3.0	0.63± .09	13.2±1.8	0.27	27.6
	Controls	11.9±2.6	0.51± .06	13.8±2.2	0.25	35.5
24	Reserpine	2.6± .39	0.23± .002	19.6± .72	0.09	64.2
	Controls	1.5± .91	0.09± .02	19.7± .78	0.027	73.8

* Reserpine-treated rats received 2.5 mg/kg I.P. Controls received saline.

[1] Scheline, R. R. The Relationship between Histamine and 5-Hydroxytryptamine Release, I^{131} Distribution and Sarcoma Growth in the Rat. Ph.D. Thesis, University of California, June, 1958.

that the administration of compound 48/80, polymyxin B, or distilled water produces an alteration in the I^{131} distribution similar to that observed in the tumor-bearing animal.

The various control data presented in the tables show some variability, especially in the case of gastrointestinal tract uptake. The G.I. tract level of I^{131} is presumably related to the secretory activity of the gastric mucosa during the time interval the experiment was conducted. It has been our experience that animals in the process of digesting stomach contents secrete more I^{131} than do fasting animals. In these studies we have noticed some variability in the amount of food remaining in the animals' stomachs. It is our opinion that this factor is responsible for the variation of G.I. tract I^{131} uptakes in the control animals.

We have shown that the growth of a subcutaneous tumor has a pronounced effect upon the population of mesenteric mast cells in the rat, since the number of intact mesenteric mast cells falls to 20 per cent or less of the value observed in normal rats (20). The changes seen in the mesenteric mast cell population occur at a period of tumor development which has been previously shown to bring about systemic alterations in the I^{131} distribution in the rat (19).

These results, considered together, indicate a relationship between tumor growth, alterations in the mast cell population, and the iodide trapping syndrome. They strongly suggest that the alterations in I^{131} distribution may be the result of histamine and 5-HT release from the mast cells, which are progressively disrupted during the growth of the sarcoma.

These data suggest that the iodide trapping syndrome in part may be a manifestation of the interplay between the tumor cell and the mast cells of the host. The local or systemic release of histamine and/or 5-HT, which can explain iodide trapping, has been demonstrated to be of value to the cancer cell, since rats depleted of histamine and/or 5-HT by distilled water, tumor polypeptide, or reserpine prior to tumor implantation supported tumor growth less adequately than did their controls (20). Conversely, if the host was given exogenous histamine and/or 5-HT by parenteral administration, tumor growth was favored (20).

Since the iodide trapping syndrome appears to be mediated through a pathway involving 5-HT, we now have a more rational basis for examining this phenomenon. In this connection, we are now studying the effects of 5-HT antagonists upon iodide trapping. Erspamer considers the function of 5-HT to be mainly that of an antidiuretic factor (6), and we are investigating the urinary output and its relationship, if any, to iodide trapping.

When considering these data one must keep in mind that the effects of tumor growth or tumor polypeptide have been shown only in one area, the mesenteric mast cells. The effect upon mast cells in other tissues is not known at this time. This factor precludes the statement that a cause-and-effect relationship exists between the mast cell disruption and iodide trapping observed in the tumor-bearing rat. We intend to study the effect of tumor growth upon mast cells in other areas of the rat, especially the skin, which has been shown to contain many mast cells (10, 13, 14). Since the iodide trapping syndrome first appears in the skin adjacent to the tumor implant, it will be of interest to see if the skin mast cells are disrupted in a manner which parallels the disturbance in I^{131} distribution.

SUMMARY

Disruption of mast cells by the administration of distilled water, polymyxin B, compound 48/80, or tumor polypeptide derived from rat sarcoma produced alterations in I^{131} distribution similar to those seen in a tumor-bearing animal. Injection of two of the known mast cell components, histamine and 5-HT, also caused this alteration, called iodide trapping. Heparin had no activity in this respect. Reserpine, because of its ability to release 5-HT from the body, produced the trapping syndrome.

These factors, together with the knowledge that growth of the tumor causes a progressive, widespread decrease in the number of intact mast cells, indicate that the release of histamine and/or 5-HT resulting from this disruption of mast cells may be responsible for the iodide trapping observed in the tumor-bearing animal.

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