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^{111}In (III) uptake by inflammatory and normal tissues

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Tissue distributions of ^{111}In (III) in the rats bearing granuloma, inflammatory tissue induced by turpentine oil, were compared with those of ^{67}Ga. The results showed that indium-111 resembles ^{67}Ga in the manner of uptake by inflammatory and normal soft tissues. The effect of cold-$InCl_3$ on ^{111}In (III) uptake showed that transferrin is not involved in the uptake of ^{111}In (III) into inflammatory tissues but is involved in the uptake into liver and spleen.

Key words: ^{111}In (III) uptake, Inflammatory tissue, Transferrin

INTRODUCTION

BECAUSE ^{111}In(III) is taken up by malignant tissues, it has been widely used for tumor-imaging.[1] Ever since the observation of ^{67}Ga accumulation in tumors,[2] ^{67}Ga has also been used for the detection of various tumors.[3] It has been reported, however, that the distribution of ^{111}In(III) differs from that of ^{67}Ga(III) in tumor-bearing mice.[4] In the blood ^{111}In(III) is present in a transferrin-bound form,[5,6] and ^{67}Ga(III) is also exclusively bound with transferrin both *in vitro* and *in vivo*.[7–9] Hara[10] reported that the binding affinity of indium for transferrin was stronger than that of gallium. Ando et al.[11] reported that ^{111}In(III) and ^{67}Ga(III) were remarkably taken up by inflammatory tissue adjacent to areas of tumor tissues. We have recently reported that the uptake of ^{67}Ga(III) into normal soft tissues, such as liver and spleen, occurs in a transferrin-bound form, but into inflammatory tissue, such as granuloma, in an unbound form.[12] In the present study, we have investigated whether or not the distribution of ^{111}In(III) differs from that of ^{67}Ga(III) differ from each other in inflammatory tissues and whether or not transferrin is involved in the uptake of ^{111}In(III).

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MATERIALS AND METHODS

Animals

Male Wistar rats weighing 150–200 g were purchased from Shizuoka Laboratory Animal Center (Hamamatsu, Japan), and were housed in wire mesh cages at a room temperature of 23±1°C and in relative humidity of 55±5%.

Production of inflammatory tissue

The production of an inflammatory tissue, granuloma, was carried out by the method described in the previous report[13] as follows. A paper pellet (size 8 mm) was dipped in turpentine oil and implanted bilaterally in the subcutaneous tissues of the abdomen in each animal.

^{111}In and ^{67}Ga solutions

Indium-111 chloride and Gallium-67 citrate (kindly supplied by Nihon Mediphysics Co. Ltd., Takarazuka, Japan) were diluted with saline to 185 kBq (5 μCi)/ml.

Administration of ^{111}In and ^{67}Ga

Each rat, at 6 days after the administration of turpentine oil, was intraveneously injected with ^{111}In or ^{67}Ga solution in a dose of 37 kBq (200 μl).

Administration of cold-$InCl_3$

Each rat, at 6 days after the administration of turpentine oil, was intravenously injected with $InCl_3$

(1.25 and 2.50 μmole/ml saline) in a dose of 100 μl 5 min before the administration of ^{111}In.

Removal of granuloma and other tissues

At 4 h or 24 h after the administration of ^{111}In and ^{67}Ga solution, rats were anesthetized with urethane (1.5 g/kg, i.p.) and immediately perfused with cold saline. The inflammatory lesion and other tissues were then removed. The granuloma tissue was obtained from the inflammatory lesion with complete removal of the implanted paper pellet and abscess.

Determination of radioactivity

The radioactivity of the removed tissues was determined with a well-type NaI-scintillation counter (Aloka, ARC-300). The uptake ratios of ^{111}In in various tissues were expressed in the following formula:

$$\text{Uptake ratio} = \frac{\dfrac{\text{Sample radioactivity (cpm)}}{\text{Sample weight (g)}}}{\dfrac{\text{Total radioactivity administered (cpm)}}{\text{Body weight of rat (g)}}}$$

RESULTS

Time course of ^{111}In(III) uptake by inflammatory and normal tissues

Twenty-four hour tissue distributions of ^{111}In(III) at 3, 6, and 9 days after the administration of turpentine oil are shown in Fig. 1. The uptake ratios of ^{111}In(III) in liver and spleen reached a maximum at 6 days after the administration of turpentine oil. On the other hand, in granuloma the uptake ratios at 3 and 6 days after the administration of turpentine oil were nearly the same as each other, whereas at 9 days after the uptake ratio decreased.

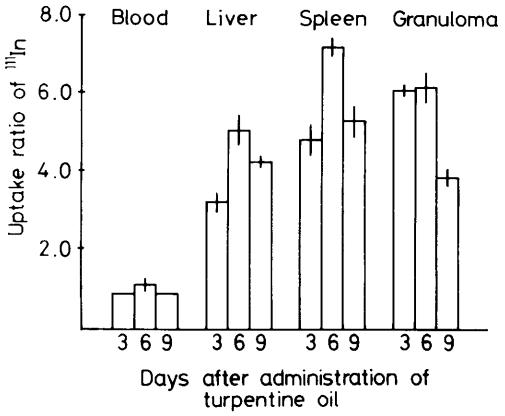

Fig. 1 Twenty-four hour tissue distributions of ^{111}In in rats at 3, 6 and 9 days after the administration of turpentine oil. Each value represents the mean and SEM for five rats.

Difference of tissue distributions of ^{111}In(III) and ^{67}Ga(III)

Tissue distributions of ^{111}In(III) and ^{67}Ga(III) at 4 and 24 h after injection into rats bearing granuloma induced by turpentine oil are shown in Fig. 2. At 4 h after the injection, the retention of ^{111}In(III) in the blood was considerably higher than that of ^{67}Ga, whereas only small difference in the uptake of ^{111}In(III) and ^{67}Ga(III) was found in the granuloma, liver, and spleen. On the other hand, at 24 h after the injection, not only was there greater blood retention of ^{111}In(III) than ^{67}Ga(III) but also greater uptake of ^{111}In(III) by granuloma, liver, and spleen. Particularly noteworthy was the uptake of ^{111}In(III) into liver and spleen, in comparison with that of ^{67}Ga(III).

The effect of cold-InCl$_3$ on the uptake of ^{111}In(III) by inflammatory and normal tissues

To investigate the effect of cold-InCl$_3$ on the reten-

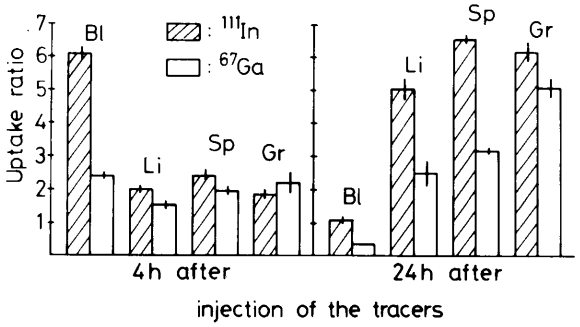

Fig. 2 Tissue distribution of ^{111}In and ^{67}Ga at 4 and 24 h after the injection into rats at 6 days after the administration of turpentine oil. Bl: Blood, Li: Liver, Sp: Spleen, Gr: Granuloma. Each value represents the mean and SEM for five rats.

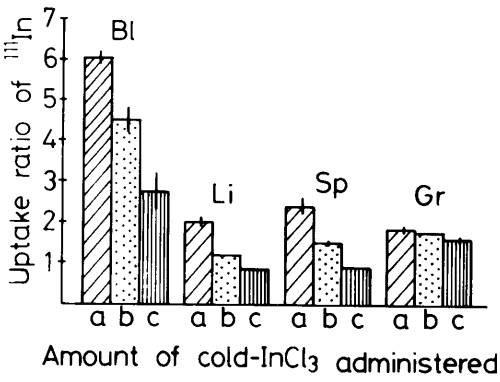

Fig. 3 Effect of cold-InCl$_3$ on the 4 h tissue distribution of ^{111}In in rats at 6 days after the administration of turpentine oil. Each value represents the mean and SEM for five rats. Amount of cold-InCl$_3$ administered; a: 0 μmole/rat (control), b: 1.25 μmole/rat, c: 2.50 μmole/rat. Bl: Blood, Li: Liver, Sp: Spleen, Gr: Granuloma.

Table 1 Granuloma-, liver- and spleen-to-blood ratios of ^{111}In distribution in rats treated with various amounts of cold $InCl_3$ 5 min before the injection of ^{111}In

Cold $InCl_3$ μmole/rat	Granuloma-	Liver-	Spleen-
	to -blood ratio		
0*	0.31	0.33	0.40
1.25	0.39	0.27	0.33
2.50	0.58	0.31	0.33

*^{111}In only injected.
Each value was calculated by using the respective mean of uptake ratio in Fig. 3.

tion of ^{111}In(III) in the blood and ^{111}In(III) uptake by inflammatory and normal tissues, *in vivo* experiments were performed (Fig. 3). Cold-$InCl_3$ dose-dependently reduced ^{111}In(III) retention in the blood. Similarly, the uptake of ^{111}In(III) by the liver and spleen was dose-dependently reduced. In contrast to this, cold-$InCl_3$ had little effect on the uptake of ^{111}In(III) into the inflammatory tissue, granuloma. Table 1 shows the granuloma, liver- and spleen-to -blood ratios of the ^{111}In(III) distribution in rats treated with various amounts of cold-$InCl_3$ 5 min before the injection of ^{111}In(III). Cold-$InCl_3$ dose dependently increased the granuloma to blood ratio, whereas the ratios of liver and spleen to blood were nearly constant.

DISCUSSION

We have reported that ^{67}Ga uptake can indicate the processes and/or stages of inflammation;[13] that is, both ^{67}Ga(III) uptake and granuloma weight reached a maximum at 6 days after the administration of turpentine oil. In the present study, however, ^{111}In(III) uptake by granuloma at 3 and 6 days after the administration was nearly the same; therefore, ^{111}In(III) uptake cannot indicate the processes and/or stages of inflammation. Additionally, ^{111}In(III) uptakes by liver and spleen at 6 days after the administration of turpentine oil were greater than at 3 and 9 days after, whereas ^{67}Ga(III) uptakes by liver and spleen at 6 days after the administration of turpentine oil were lowest among those at 2 to 12 days after that.[13] We think that these differences may be due to different affinities between ^{111}In(III) and ^{67}Ga(III) for transferrin,[10] but a final conclusion cannot yet be drawn. We have recently reported that ^{67}Ga(III) is exclusively bound with transferrin[9] and $FeCl_3$ decreases the ^{67}Ga(III) retention in blood.[12] Indium-111(III) is also present in a transferrin-bound form.[5,6] In the present study, it can be said that the much higher retention of ^{111}In(III) than ^{67}Ga(III) in blood is supported by the results, reported by Hara,[10] that the binding affinity of indium for transferrin was stronger than that of gallium. At 24 h after the injection, ^{111}In(III) uptake by liver and spleen were greater than ^{67}Ga(III) uptake. This result might also be due to the difference in the affinity of indium and gallium for transferrin. Moreover, ^{111}In(III) uptake by liver and spleen was remarkably decreased by cold-$InCl_3$. We think that ^{111}In(III) uptake, as well as ^{67}Ga(III) uptake, by liver and spleen also occurs in a transferrin-bound form. On the other hand, the results that the uptake of ^{111}In(III) and ^{67}Ga(III) by inflammatory tissue, granuloma, were nearly the same 4 hr and 24 h after the injection suggest that transferrin is not involved in ^{111}In(III) uptake by granuloma. Additionally, the fact that cold-$InCl_3$ did not inhibit ^{111}In(III) uptake by granuloma, but did inhibit that by liver and spleen also shows that transferrin is involved in the uptake by normal tissues, such as liver and spleen, but is not involved in the uptake by inflammatory tissue, granuloma. We have recently reported that transferrin is not involved in the uptake of ^{67}Ga into inflammatory tissue, granuloma.[12] Indium-111(III) resembles ^{67}Ga(III) in the manner of uptake by inflammatory and normal soft tissues. Higashi et al.[4] reported that ^{111}In(III) and ^{67}Ga(III) were uptaken differently by tumor and normal tissues despite the fact that they belong to the same group in the periodic table. They found that the uptake of ^{67}Ga(III) into tumor tissue was greater than that of ^{111}In(III), whereas ^{67}Ga uptake by the liver was less than that of ^{111}In(III).[4] We think that these differences are due to different affinities for transferrin, i.e., these results show that both ^{67}Ga(III) and ^{111}In(III) are taken up into tumor tissue in a transferrin-unbound form, whereas into the liver in a transferrin-bound form. Moreover, it has previously been reported that the uptake of ^{67}Ga(III) into tumor cells occurs in an unbound form.[14–17] We conclude that the uptake of ^{111}In(III), as well as that of ^{67}Ga, into inflammatory tissues, such as granuloma, may also be similar to that occurring in tumor tissues.

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