Localizing Ability of [48V] Vanadyl(IV)-Pheophorbide into Tumor

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Introduction

We had synthesized [^{48}V] vanadyl(IV)-pheophorbide chelate (^{48}V(IV)O-Pheo), and reported that this compound was able to depict tumor distinctly[1]. Pheophorbide (Pheo), which is one of the decomposed products from chlorophyll, is produced by elimination of phytyl and magnesium. Pheo is known to have strong photodynamic actions and as well as affinity to tumor[2), 3)].

In this paper we synthesized [^{48}V]vanadyl(IV)-tetraphenylporphyrin (^{48}V(IV)O-TPP), as a vanadium porphyrin chelate, for the purpose of enhancing the utility of ^{48}V(IV)O-Pheo. And we examined the relation of Pheo as a ligand to the localizing ability of ^{48}V(IV)O-Pheo into tumor.

Materials and Methods

^{48}V was produced by the reaction of ^{48}Ti(p,n)^{48}V with 18 MeV protons. Procedure for the purification of ^{48}V and the synthesis of ^{48}V(IV)O-Pheo were followed by the methods described previously[1]. ^{48}V(IV)O-TPP was synthesized according to the method of Bencosme et al[4].

[^{14}C]-Pheo was prepared by hydrolysis of [^{14}C]-Chlorophyll with 30 % hydrochloric acid, and then extracted with ether[2]. [^{14}C]-Chlorophyll was extracted from [^{14}C]-Algae (ICN Radiochemicals, U.S.A.) with acetone.

We used three kinds of tumors. Male C3H/He mice bearing subcutaneously transplantable mammary carcinoma (FM3A), hepatoma (MH 134) and male ddY mice bearing transplantable sarcoma (S 180) were injected with each compound through a lateral tail vein. Prior to injection, these compounds were emulsified into liposome. The mice were sacrificed by cervical dislocation at various time after injection. The tissue uptake was expressed as the percentage of dose per gram of tissue.

Results and Discussion

Figure 1 presents the structures of V(IV)O-Pheo and V(IV)O-TPP. The distribution of ^{48}V(IV)O-TPP and ^{48}V(IV)O-Pheo in mice bearing FM3A tumor was shown in Figure 2. The high uptake of ^{48}V(IV)O-TPP was observed in kidney. The concentration in each tissue was less than that of ^{48}V(IV)O-Pheo, so it was suggested that ^{48}V(IV)O-TPP was excreted smoothly from body. Tumor uptake of ^{48}V(IV)O-Pheo was increased with the time after injection, but the level of ^{48}V(IV)O-TPP was invariable and low.

Tumor to skeletal muscle ratio of each ^{48}V-compound was shwon in Table 1. Prophyrin chelate of ^{48}V accumulated into tumor more than inorganic ^{48}V. These results indicated that $^{48}V(IV)O$-Pheo had high localizing ability into FM3A tumor, so we examined the localization of $^{48}V(IV)O$-Pheo into other tumors. Table 2 presents FM3A, MH 134 and S 180 tumor uptakes of $^{48}V(IV)O$-Pheo. The concentration of $^{48}V(IV)O$-Pheo in each tumor increased with time, and the localizing ability did not depend on the kind of tumor.

For the purpose of making sure that the localization of $^{48}V(IV)O$-Pheo into tumor was dependent on the affinty of Pheo to tumor, the distribution of ^{14}C-labelled Pheo in mice bearing FM3A tumor was examined. As shown in Table 3, high concentration of [^{14}C]-Pheo was observed in liver and spleen at 2 hr after injection, and these values decreased with the time after injection. On the contrary, tumor uptake of [^{14}C]-Pheo increased with time, which was in agreement with the behavior of $^{48}V(IV)O$-Pheo. On the other hand, high activity of ^{14}C was detected in the intestinal contents, which suggested that Pheo was degraded into one of bile pigments with the ring open and excreated into feces.

In conclusion $^{48}V(IV)O$-Pheo was metabolized mainly in liver, and separated ^{48}V and Pheo were excreted via different pathways: ^{48}V was excreted from kidney into urine, and Pheo was degraded into bile pigments and excreted into feces.

References

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3) Iwai K., Horigome M. and Kimura S., Photomed. Photobiol. 8 (1986) 25.
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Table 1. The ratio of FM3A tumor/skeletal muscle uptake of ^{48}V-compounds.

^{48}V-compound	Ratio		
	2 hr	12 hr	24 hr
$^{48}V(IV)O$-Pheo	1.98 ± 0.05	4.47 ± 0.28	5.45 ± 0.24
$^{48}V(IV)O$-TPP	2.73 ± 0.16	3.82 ± 0.15	3.25 ± 0.11
$^{48}V(IV)O$-SO_4	1.27 ± 0.08	2.13 ± 0.15	1.86 ± 0.07
$^{48}V(IV)O$-AsA	2.27 ± 0.14	2.24 ± 0.10	2.08 ± 0.07
$^{48}V(IV)$	1.89 ± 0.09	1.90 ± 0.29	1.82 ± 0.09
$^{48}V(V)$	1.88 ± 0.10	2.11 ± 0.08	2.03 ± 0.08

Values are means SE of four mice.

Table 2. Uptake of $^{48}V(IV)O$-Pheo into FM3A, MH 134 and S 180 tumors.

Tumor	% Dose / g tumor			
	2 hr	8 hr	16 hr	24 hr
FM3A	3.82 ± 0.22	4.47 ± 0.21	4.72 ± 0.23	5.42 ± 0.23
MH 134	3.23 ± 0.29	4.21 ± 0.32	4.78 ± 0.49	5.21 ± 0.28
S 180	2.48 ± 0.16	3.20 ± 0.21	4.10 ± 0.14	4.92 ± 0.31

Values are means SE of four mice.

Table 3. Tissue distribution of [^{14}C]-Pheo in C3H mice bearing FM3A tumor.

Tissue	% Dose / g tissue		
	2 hr	12 hr	24 hr
FM3A tumor	0.71 ± 0.09	2.09 ± 0.08	2.51 ± 0.16
Blood	4.78 ± 0.17	1.69 ± 0.15	1.06 ± 0.10
Liver	6.74 ± 0.26	4.54 ± 0.25	2.50 ± 0.20
Kidney	1.91 ± 0.15	2.66 ± 0.12	2.34 ± 0.13
Spleen	7.04 ± 0.30	3.65 ± 0.25	2.22 ± 0.22
Lung	2.19 ± 0.22	1.54 ± 0.08	1.26 ± 0.14
Skeletal muscle	0.39 ± 0.09	0.27 ± 0.01	0.23 ± 0.01
Stomach	1.46 ± 0.13	1.30 ± 0.11	1.20 ± 0.06
Intestinal contents	2.80 ± 0.23	6.51 ± 0.31	7.66 ± 0.46

Values means ±SE of four mice.

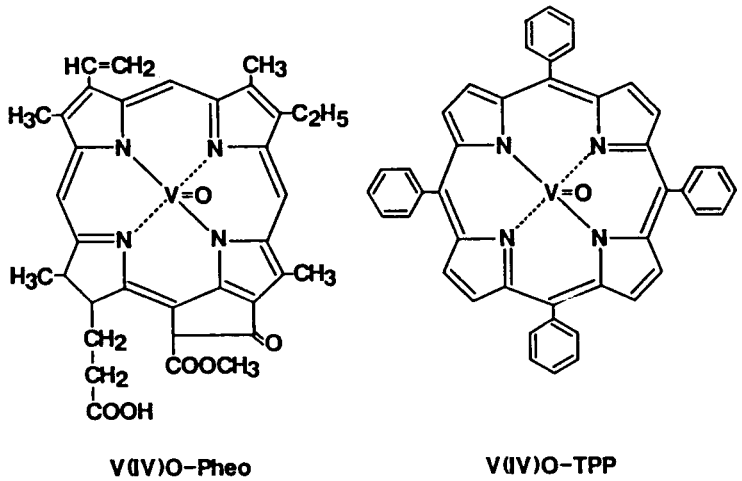

Fig. 1. Structures of vanadyl(IV)-pheophorbide (V(IV)O-Pheo) and vanadyl(IV)-tetraphenylporphyrin (V(IV)O-TPP).

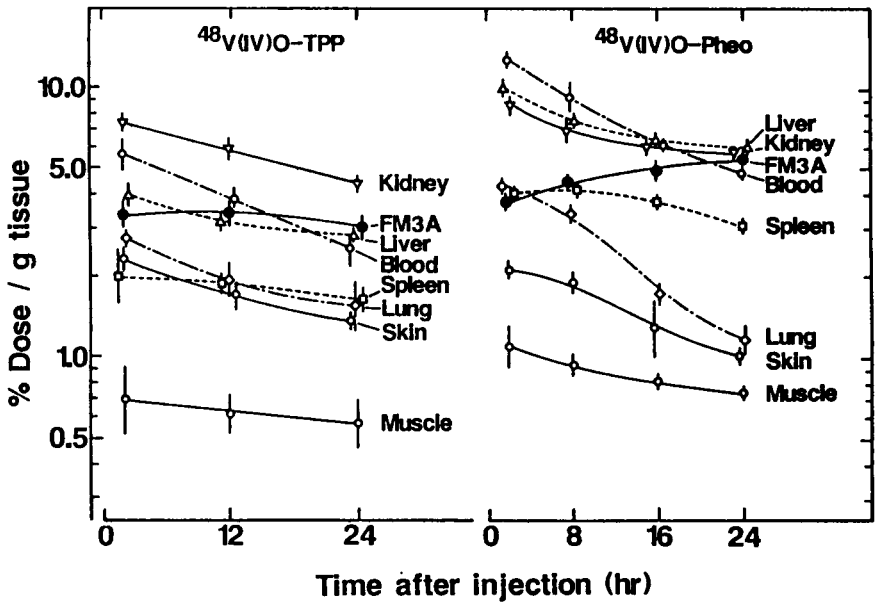

Fig. 2. Tissue distribution of ^{48}V(IV)O-TPP and ^{48}V(IV)O-Pheo in C3H mice bearing FM3A tumor.
Bars, SE of four mice.