Gallium-67 Uptake by Hepatoma: Studies in Cell Cultures, Perfused Livers, and Intact Rats

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In this investigation, the effect of transferrin on ^{67}Ga uptake by rat hepatoma was studied at three levels: (a) at the level of individual tumor cells in culture; (b) at the level of isolated, perfused livers with implanted intrahepatic tumors; and (c) in intact animals bearing intrahepatic tumors. This approach was possible using H-4-II-E hepatoma cells which grew into discrete tumors when implanted intrahepatically. Transferrin at low concentrations (0.05–0.5 mg/ml) stimulated, while at a higher concentration (1.0 mg/ml) it inhibited ^{67}Ga uptake by tumor cells in culture. In contrast, in isolated, perfused livers with intrahepatic tumors, transferrin at concentration levels of 0.05 and 0.1 mg/ml had no effect, while at 0.25–1.0 mg/ml transferrin inhibited ^{67}Ga uptake by intact tumors. Administration of transferrin which markedly enhanced the serum unsaturated iron binding capacity, had no effect on ^{67}Ga accumulation in the intrahepatic tumors in vivo. These results indicate that, although transferrin at low concentration promotes the uptake of ^{67}Ga by individual tumor cells in culture, it does not do so in intact tumors in isolated rat liver preparations or in tumor bearing rats. We conclude that the mechanism of ^{67}Ga uptake by intact tumors is different from that of tumor cells growing in culture.

J Nucl Med 26:1438–1444, 1985

Studies of gallium-67 (^{67}Ga) uptake by tumor cells in culture have demonstrated that transferrin enhances ^{67}Ga accumulation by tumor cells *(1-5)*. This observation leads to the hypothesis that ^{67}Ga accumulation in tumors in vivo is due to transferrin-mediated uptake by tumor cells *(1-3)*. However, in vivo studies of ^{67}Ga uptake by tumors are contradictory in regard to support of this hypothesis. Bradley et al. *(6,7)* found a decrease in ^{67}Ga tumor uptake in rats bearing subcutaneous Walker 256 carcinosarcoma with decreased unsaturated iron-binding capacity (UIBC) and no change in tumor uptake in iron-deficient anemic rats with elevated UIBC. Hayes et al. *(8)* observed no change in ^{67}Ga uptake in rats bearing intramuscular Morris 5123C hepatoma at decreased UIBC levels, but a significantly reduced tumor uptake in iron-deficient anemic rats and animals with increased UIBC following injection of apotransferrin. According to their in vivo observations, Hayes et al. suggested that ^{67}Ga entry into tumor is independent of ^{67}Ga binding to transferrin *(8)*.

The status of iron-saturation of plasma transferrin profoundly affects the plasma level, body retention, and organ distribution of intravenously injected ^{67}Ga *(6-9)*. This complicates the interpretation of in vivo studies of ^{67}Ga tumor uptake. Our further understanding of the mechanism of ^{67}Ga tumor uptake is hampered by the lack of a tumor model suitable for studying the various possible factors which may affect the tumor uptake of ^{67}Ga in intact animals.

In this study, ^{67}Ga uptake by H-4-II-E rat hepatoma was investigated. The H-4-II-E tumor cells when implanted into rat liver grew into a discrete intrahepatic tumor. This allowed the study of tumor ^{67}Ga uptake at three levels: (a) at the cellular level using tissue culture; (b) at the organ level using isolated, perfused rat livers with implanted intrahepatic tumors; and (c) in intact animals bearing intrahepatic or intramuscular tumors.

Received Dec. 10, 1984; revision accepted Aug. 28, 1985.

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MATERIALS AND METHODS

Culture and implantation of H-4-II-E hepatoma cells

H-4-II-E hepatoma cells were cultured according to Kovacs et al. *(10)* in modified Swim's 77 medium* containing 2m*M* L-glutamine and supplemented with 20% horse and 5% heat-inactivated fetal calf serum (complete Swim's medium). The cells were subcultured weekly by a 5-min exposure to 0.25% trypsin and subsequent seeding in T-75 flasks. After three passages, 1×10^6 cells in 0.1 ml complete Swim's medium were implanted either intramuscularly into the thigh of a hindleg or into the liver of male ACI rats† weighing between 180–200 g. For implantation into the liver, the abdomen of anesthetized rats was opened using sterile techniques. The cell suspension was injected slowly into the middle lobe of the liver. The animals were studied 10 to 14 days after the implantation of tumor cells. At this time, the tumors, intramuscular or intrahepatic, were small, but clearly defined. The average weight of intramuscular tumors was 1.08 ± 0.16 g (mean $\pm$ s.e.m., n=8), and that of intrahepatic tumors was 0.79 ± 0.09 g (n=47).

Biodistribution studies

Rats bearing hepatoma were given 5 μCi of carrier-free [^{67}Ga]citrate intravenously through the tail vein. In addition, 5 μCi of technetium-99m (^{99m}Tc) sulfur colloid‡ was administered intravenously at 1 hr before the animals were killed. At 6, 24, and 48 hr after ^{67}Ga administration, the animals were anesthetized with intraperitoneal pentobarbital. The abdominal and thoracic cavities were then opened and the rats exsanguinated by cardiac puncture. Samples of blood, tumor, liver, and other major organs including muscle were obtained, weighed and counted along with appropriate standards, in an auto-gamma scintillation counter§. The counting error was kept below 3%. Radioisotope cross-over contribution was corrected using a computer stripping program. The results were expressed as percent injected dose per gram tissue. The radioactivity in the blood was estimated by using a blood volume of 7% of the body weight.

For the study of the effect of transferrin, essentially iron-free human transferrin at a dose level of 140 mg/kg body weight was injected intravenously 15 min before ^{67}Ga was administered. For the study of the effect of iron, iron dextran (ferric hydroxide dextran complex)¶ was injected intramuscularly at a dose of 125 mg iron/kg body weight at 7 and 13 days before ^{67}Ga administration.

Gallium-67 uptake by H-4-II-E hepatoma cells

Tumor cell monolayers were formed by incubating 2.5×10^6 cells in complete Swim's 77 tissue culture medium in 60×15 mm disposable petri dishes at 37°C in a humidified 5% CO_2/95% air atmosphere for 24 hr. Gallium-67 uptake was initiated by replacing the culture medium with 5 ml Williams' E medium* supplemented with 2% globulin-free bovine albumin, 0.01*M* Hepes (pH 7.2), 1 μCi/ml [^{67}Ga]citrate and varying amounts of human apotransferrin ranging from 0-1.0 mg/ml. After incubation for 3 hr at 37°C, the media were transferred to disposable test tubes. Cell monolayers were washed twice with 2 ml phosphate buffered saline (PBS). Using a plastic spatula, the cells were scraped from the petri dishes and transferred to test tubes. The radioactivities in the incubation media, washes and cells were then determined. The results were expressed as the percents of total ^{67}Ga added which were taken up by the cells. The viability of the cells was determined by plating efficiency, e.g., the percentage of cells seeded which formed colonies. The plating efficiency under our experimental conditions was 60% at time zero and did not change after 3 hr of incubation.

Gallium-67 uptake by isolated, perfused rat livers with implanted, intrahepatic tumors

This was done using a recirculating isolated perfused liver preparation as described previously *(11)*. Briefly, rats were anesthetized with sodium pentobarbital (50 mg/kg). The bile duct, portal vein and thoracic vena cava were cannulated, and the inferior vena cava was then tied off. Blood was removed from the liver by an initial perfusion with 5 ml heparinized isotonic saline, followed by 50 ml oxygenated perfusion buffer. After separation from its donor, the liver was immediately transferred to the perfusion chamber. The perfusion medium (initial volume = 50 ml) consisted of an oxygenated Krebs-Ringer bicarbonate buffer, supplemented with 40 mg dextrose, 2 g bovine serum albumin (fraction V) and 500 units heparin. The system was maintained at 37°C, and the pH of the perfusion medium was kept between 7.35 and 7.45 with periodic addition of sodium bicarbonate. The perfusion flow was adjusted to 20 ml/min. The functional integrity of the isolated, perfused livers was demonstrated by measuring (a) uptake of [^{99m}Tc]sulfur colloid; (b) uptake and clearance of [^{99m}Tc]disofenin; (c) production of bile; and (d) the activity of glutamic oxaloacetic transaminase in the perfusion medium *(11)*.

The liver was perfused for a 1 hr equilibration period; 5 μCi carrier-free [^{67}Ga]citrate was then added to the perfusate. Apotransferrin, when used, was introduced into the system 10 min before the addition of ^{67}Ga. The livers were perfused with ^{67}Ga for 4 hr. At the end of perfusion, the original perfusate was disconnected and the liver flushed with 100 ml of fresh medium to remove intravascular ^{67}Ga. The radioactivity in the perfusate, wash medium, bile, and liver was determined as described previously *(11)*. The results were expressed as percent of the dose originally introduced into the perfusion medium.

Other studies

Serum total iron-binding capacity (TIBC) and unsaturated iron-binding capacity (UIBC) were assayed using a commercial kit.** Rat transferrin was isolated from ACI

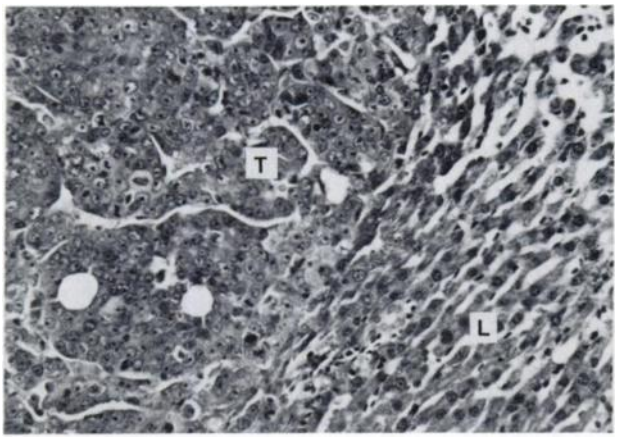

FIGURE 1
Histological section (X420) of H-4-II-E intrahepatic tumor. (T) Tumor, (L) Liver

rat serum as described previously *(11)*. Statistically significant differences were determined using Student's t-test for independent means *(12)*.

RESULTS

Gallium-67 uptake by intrahepatic and intramuscular hepatoma in vivo

H-4-II-E hepatoma cells when implanted into rat liver or muscle grew into a discrete tumor. Figure 1 shows the histological section of such an intrahepatic tumor. A clear differentiation between normal liver tissue and tumor was observed. To determine the validity of using this tumor model, a study of the distribution of intravenously administered carrier-free [^{67}Ga]citrate and [^{99m}Tc]sulfur colloid in rats bearing intrahepatic or intramuscular tumors was initiated.

Table 1 shows the results of ^{67}Ga and [^{99m}Tc]sulfur colloid uptake in livers and intrahepatic tumors. Gallium-67 was taken up by the tumor avidly. At 6 hr after injection, the tumor to liver ratio was 1.82 ± 0.15 (mean ± s.e.m., n=5). This ratio remained nearly constant up to 48 hours. In contrast, very little [^{99m}Tc] sulfur colloid was taken up by the tumor. The tumor to liver ratio for [^{99m}Tc]sulfur colloid was only 0.10 ± 0.03 (n=7). These findings, namely significant tumor ^{67}Ga uptake but little or no uptake of [^{99m}Tc]sulfur colloid, are consistent with clinical observations in patients with hepatoma *(13)*.

Table 2 shows the results of ^{67}Ga distribution in rats bearing intramuscular hepatoma. Gallium-67 tumor uptake at 24 or 48 hr after injection was not significantly different from that in intrahepatic tumors ($p > 0.1$). The tumor to liver ratio at 48 hr was statistically not different from that at 24 hr. The tumor to muscle ratio was high (about 25) because of the low muscle ^{67}Ga uptake.

Gallium-67 uptake by H-4-II-E tumor cells in culture

To further investigate the mechanism of ^{67}Ga uptake, the effect of transferrin on ^{67}Ga uptake by H-4-II-E tumor cells in culture was studied. As shown in Fig. 2, after a 3-hr incubation, 0.9% of the added ^{67}Ga was taken up by 6×10^6 hepatoma cells in the absence of transferrin. Transferrin at 0.01 mg/ml had no effect, while at concentrations of 0.05 and 0.1 mg/ml, transferrin stimulated ^{67}Ga uptake by hepatoma cells almost 60%. In contrast, transferrin at a concentration of 1.0 mg/ml inhibited ^{67}Ga uptake by hepatoma cells by 30%. These results are similar to those previously described for other tumor cell lines *(3-5,14)*.

Gallium-67 uptake by isolated perfused livers with implanted intrahepatic tumors

To determine whether the above observed effect of

TABLE 1
In Vivo Distribution of ^{67}Ga and [^{99m}Tc]Sulfur Colloid in Rats with Intrahepatic Tumors*

Time postinjection	Uptake (% dose/g tissue)			p value
	Liver	Tumor	Tumor/liver	(Liver vs. tumor)
[^{67}Ga]citrate (n = 5)				
6 hr	1.04 ± 0.10	1.87 ± 0.15	1.82 ± 0.15†	<0.005
24 hr	1.14 ± 0.09	2.04 ± 0.19	1.71 ± 0.11†	<0.005
48 hr	1.32 ± 0.04	2.12 ± 0.27	1.63 ± 0.22†	<0.025
[^{99m}Tc]sulfur colloid (n = 7)				
1 hr	15.84 ± 0.69	1.48 ± 0.39	0.10 ± 0.03	<0.001

*Rats with intrahepatic tumors were injected with [^{67}Ga]citrate (5 μCi) or [^{99m}Tc]sulfur colloid (5 μCi). At various intervals after injection, rats were killed and radioactivity in liver and tumor was determined. Results were expressed as percent dose injected per g tissue (mean ± s.e.m.).

†These ratios are not significantly different ($p > 0.5$) from each other.

TABLE 2
In Vivo Distribution of ^{67}Ga in Rats with Intramuscular Tumors*

Time postinjection	^{67}Ga uptake (% dose/g tissue)				
	Liver	Muscle	Tumor	Tumor/liver	Tumor/muscle
24 hr (n = 3)	1.22 (1.14–1.33)	0.07 (0.05–0.14)	1.42 (0.90–1.72)	1.15 (0.79–1.38)	25.4 (11.7–44.6)
48 hr (n = 5)	1.58 ± 0.08	0.07 ± 0.02	1.48 ± 0.36	0.94 ± 0.24	24.8 ± 6.7

*Rats with intramuscular tumors were injected with 5 μCi [^{67}Ga]citrate. At 24 or 48 hr after injection, animals were killed and radioactivities in liver, muscle, and tumor were determined. Results were expressed as percent dose injected per g tissue (mean ± s.e.m. or range).

transferrin on ^{67}Ga uptake by hepatoma cells in culture is applicable to intact tumors, the following experiments were carried out to study ^{67}Ga uptake by isolated perfused livers with implanted intrahepatic tumors. This model is particularly suitable because it can be used to study the effect of transferrin on ^{67}Ga uptake by hepatoma without the various complicating factors found in in vivo systems.

Human apotransferrin or rat transferrin was added to the perfusion medium at concentrations of 0.05–1.0 mg/ml, similar to those applied in the study of ^{67}Ga uptake by hepatoma cells in culture. As shown in Table 3, at 4 hr after perfusion, the liver uptake of ^{67}Ga in the absence of transferrin was 1.65 ± 0.16% dose/g tissue, while the tumor uptake was 0.47 ± 0.03% dose/g (mean ± s.e.m., n=5). While at concentrations of 0.25 and 1.0 mg/ml, human apotransferrin inhibited liver and tumor uptake of ^{67}Ga, at 0.05 and 0.1 mg/ml it had no effect on either liver or tumor uptake of ^{67}Ga. Similar results were obtained using rat transferrin at concentrations of 0.1 and 1.0 mg/ml. These findings suggest that the observation made in tumor cells growing in tissue culture, namely that transferrin at low concentrations promotes ^{67}Ga uptake, cannot be extrapolated to intact tumors.

Effect of transferrin and iron on the distribution of ^{67}Ga in rats bearing intrahepatic tumors

The next studies were designed to determine the effect of transferrin and iron on the distribution of ^{67}Ga in rats bearing intrahepatic tumors. In these experiments, human apotransferrin at a dosage of 140 mg/kg body weight was administered intravenously 15 min before injection of [^{67}Ga]citrate. With this dosage, serum TIBC and UIBC increased markedly at 15 min after injection (Table 4). For studying the effect of iron, iron dextran at a dosage of 125 mg iron/kg body weight was injected intramuscularly at 7 and 13 days before the administration of [^{67}Ga]citrate. This dosage schedule markedly reduced the serum TIBC and UIBC (Table 4).

As shown in Table 4, administration of apotransferrin which markedly increased the serum iron-binding capacity, enhanced liver uptake of ^{67}Ga while it had no effect on tumor uptake. In contrast, administration of iron dextran which markedly reduced the serum iron-binding capacity, inhibited both liver and tumor uptake of ^{67}Ga.

DISCUSSION

Studies of the mechanism of ^{67}Ga accumulation in tumors are usually done in one of the following two systems: (a) in vitro, by measuring ^{67}Ga uptake by tumor cells in culture, and (b) in vivo, by studying ^{67}Ga uptake by tumors implanted subcutaneously or intramuscularly in animals. The in vitro system has the advantage of being simple and reproducible. However, since this in vitro condition is so different from the tumors in an in vivo situation, the observation made in a tissue culture system may not be applicable to the in vivo situation. On the other hand, the in vivo system has the disadvantage of being complex and the variables being studied are difficult to control. In addition, tumors are usually implanted subcutaneously or intramuscularly, which is not the origin of the tumor. Whether these implanted tumors represent the natural condition of tumors remains unclear.

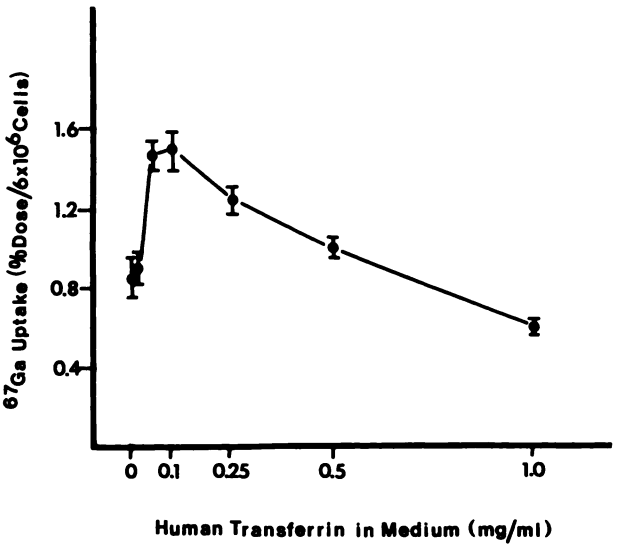

FIGURE 2
Gallium-67 uptake by hepatoma cells in culture. Monolayers of H-4-II-E tumor cells (6 × 10^6), were incubated with [^{67}Ga]citrate (5 Ci) in 5 ml Williams' E medium which contained 2% albumin and 0.01*M* Hepes and varying amounts of human apotransferrin. After 3 hr the cell-associated ^{67}Ga radioactivity was determined. Results were expressed as percent of ^{67}Ga dose added to cells (mean ± s.e.m., n=5)

TABLE 3
Effect of Transferrin on ^{67}Ga Uptake by Isolated Perfused Livers with Intrahepatic Tumors*

Item	n	^{67}Ga uptake (% dose/g tissue) Liver	Tumor	Tumor/liver
Control	5	1.65 ± 0.16	0.47 ± 0.03	0.29 ± 0.02
+ Human transferrin				
0.05 mg/ml	3	1.88 (1.76–2.04)	0.33 (0.24–0.47)	0.18 (0.13–0.27)
0.10mg/ml	6	1.87 ± 0.09	0.46 ± 0.05	0.25 ± 0.03
0.25 mg/ml	5	1.04 ± 0.07†	0.23 ± 0.03†	0.23 ± 0.02
1.00 mg/ml	5	0.87 ± 0.06†	0.31 ± 0.04†	0.34 ± 0.04
+ Rat transferrin				
0.10 mg/ml	5	1.28 ± 0.09	0.30 ± 0.08	0.24 ± 0.07
1.00 mg/ml	3	0.77 (0.50–1.12)†	0.18 (0.12–0.25)†	0.23 (0.17–0.31)

*Isolated livers with intrahepatic tumors were perfused with ^{67}Ga (5 μCi) in presence or absence of apotransferrin for 4 hr. At end of perfusion, radioactivities in liver and tumor were determined. Results were expressed as percent/g tissue (mean ± s.e.m.). Numbers in parenthesis: range.
†Significantly different from control values ($p < 0.05$).

Using the tissue culture system, Sephton and Harris *(1,2)* observed that human transferrin enhanced ^{67}Ga uptake by a number of tumor cell lines and proposed that ^{67}Ga accumulation in tumors was due to transferrin-mediated uptake by tumor cells. As an extension of this hypothesis, Larson and co-workers *(3)* proposed that there are transferrin receptors on tumor cells which are responsible for the uptake of the transferrin ^{67}Ga complex. However, as stated above, whether this in vitro observation is applicable to the in vivo situation is not clear. In all these in vitro experiments, transferrin stimulates ^{67}Ga uptake by tumor cells only at low concentrations. The concentration of transferrin in the interstitial fluid of tumors in vivo is not known. In vivo experiments using implanted tumors in animals have led to conflicting results: Increased plasma transferrin as determined by serum UIBC either reduced tumor ^{67}Ga uptake *(8)* or had no effect *(7)*. Similarly, a reduction of serum UIBC either reduced tumor ^{67}Ga uptake *(6)* or had no effect *(8)*. Conflicting results have also been reported for the effect of preincubation of ^{67}Ga with serum proteins on ^{67}Ga tumor uptake. Larson et al. *(15)* and Wong et al. *(16)* found enhanced ^{67}Ga uptake when ^{67}Ga was preincubated with serum *(15)* or human apotransferrin *(16)*. It was interpreted that binding of ^{67}Ga to transferrin played an important role in the in vivo tumor uptake of ^{67}Ga. Vallabhajosula et al. *(17)*, on the other hand, did not observe a difference in tumor uptake between ^{67}Ga preincubated with human transferrin and

TABLE 4
Effect of Transferrin and Iron on ^{67}Ga Distribution in Rats with Intrahepatic Tumors*

Item	Control	Transferrin†	Iron‡
^{67}Ga uptake (% dose/g tissue)			
Tumor	1.98 ± 0.13 (7)	2.16 ± 0.20 (5)	0.45 ± 0.03 (6)§
Liver	1.16 ± 0.07 (7)	1.49 ± 0.10 (5)§	0.46 ± 0.03 (6)§
Spleen	1.17 ± 0.06 (7)	1.32 ± 0.08 (5)	2.73 ± 0.36 (6)§
Blood	0.38 ± 0.02 (7)	0.37 ± 0.02 (5)	0.04 ± 0.00 (6)§
Kidney	0.99 ± 0.06 (7)	0.94 ± 0.04 (5)	0.86 ± 0.03 (6)
Muscle	0.08 ± 0.02 (7)	0.10 ± 0.01 (5)	0.02 ± 0.00 (6)§
Serum Iron-binding Capacity (μg/dl)			
TIBC	347 ± 17 (4)	522 ± 27 (4)§	257 ± 8 (6)§
UIBC	289 ± 12 (4)	426 ± 22 (4)§	77 ± 4 (6)§

*Rats with intrahepatic tumors were injected with 5 μCi [^{67}Ga]citrate. At 24 hr after injection, distribution of ^{67}Ga in various organs was determined. Results are mean ± s.e.m. Numbers in parentheses are number of experiments.
†Human transferrin at dosage of 140 mg/kg was given intravenously 15 min before injection of [^{67}Ga]citrate.
‡Iron dextran (125 mg iron/kg) was given intramuscularly at 7 and 13 days before injection of [^{67}Ga]citrate.
§Significantly different from control values ($p < 0.05$ or less).

[^{67}Ga]citrate. Since after intravenous injection of [^{67}Ga]citrate 99% of the radioactive tracer is bound to plasma transferrin *(9,18)*, it seems unlikely that preincubation of ^{67}Ga with serum or transferrin before injection would substantially increase the binding of ^{67}Ga to serum transferrin to account for the observed effect.

In the current investigation, ^{67}Ga uptake by rat hepatoma was studied at three levels: (a) at the level of individual tumor cells in culture; (b) at the level of isolated, perfused livers with implanted intrahepatic tumors; and (c) in intact animals bearing intrahepatic or intramuscular tumors. This approach was made possible by using H-4-II-E hepatoma cells which grew into discrete tumors when implanted intrahepatically. Isolated liver perfusion has been extensively used for the study of the physiology of liver and bile formation *(19)*. In a previous publication, we have also used isolated rat liver perfusion to study hepatic ^{67}Ga uptake *(11)*.

Isolated, perfused livers with implanted intrahepatic tumors are particularly useful because they can be used to study ^{67}Ga uptake by intact tumors in a well controlled setting. In this study, we demonstrated that hepatomas accumulated ^{67}Ga in the absence of transferrin. Transferrin at low concentrations (0.05 and 0.1 mg/ml) had no effect on ^{67}Ga uptake by the tumor, while at higher concentrations (0.25 and 1.0 mg/ml) it inhibited ^{67}Ga uptake. This is in marked contrast to the tissue culture system. In the tissue culture system, transferrin at concentrations of 0.05 to 0.25 mg/ml promoted ^{67}Ga uptake by hepatoma cells.

Our observation that low concentrations of transferrin stimulated, while high concentrations of transferrin inhibited ^{67}Ga uptake by tumor cells in culture are consistent with those reported in the literature *(3,5,14)*. The difference in the effect of transferrin on ^{67}Ga uptake by intact tumors and tumor cells in culture observed in this study suggest that the mechanisms of ^{67}Ga uptake by intact tumors and tumor cells in culture are different. The observations are not surprising, since the physiology of tumor cells in intact tumors may be different from that in tissue culture. In addition, as summarized by Winchell *(20)*, a number of factors such as altered blood flow, neovascularization, increase in extracellular fluid and delayed efflux, all play significant roles in the localization of radiopharmaceuticals in neoplasms.

We also demonstrated that injection of transferrin, which enhanced serum UIBC, had no effect on ^{67}Ga uptake by intrahepatic tumors in vivo, while pretreatment with iron dextran, which reduced serum UIBC, inhibited ^{67}Ga uptake. These findings are consistent with those by Bradley et al. *(6)* and Vallabhajosula et al. *(17)*. However, since the status of serum UIBC profoundly affects the plasma level, retention and organ distribution of ^{67}Ga *(6-9)*, these in vivo observations are difficult to interpret.

Our results suggest that (a) the mechanism of ^{67}Ga uptake by intact tumors is different from that of tumor cells in culture and (b) the isolated, perfused liver with implanted intrahepatic tumor is a useful system to study the mechanism of ^{67}Ga uptake by hepatoma.

FOOTNOTES

*Gibco Laboratories, Grand Island, NY.
†Harlan, Walkersville, MD.
‡Squibb, New Brunswick, NJ.
§Packard Instrument Co., Inc., Downers Grove, IL.
¶Sigma Chemical Co., St. Louis, MO.
**Becton Dickinson Co., Orangeburg, NY.

ACKNOWLEDGMENTS

The authors thank Dr. C.J. Kovacs, University of South Alabama, for the H-4-II-E hepatoma cells.

This work was supported by a U.S. Public Health Service grant (CA-32845) and the Veterans Administration Research Service. The authors would like to express their sincere thanks to Dr. R.A. Rostock for his advice and to Suzanne M. Brown, Kenneth A. Kopher and James W. Sandoz for their assistance and maintenance of the tumor cell line. Ms. Mary Peplowski's secretarial assistance is very much appreciated.

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