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Introduction

Glucose metabolism in tumors is quite active as found in the brain or the heart, and the increased uptake of glucose into these tissues is observed. Deoxy-glucose is a non-physiological glucose analog and there have been many reports[1-6] on the use of 2-deoxy-2-fluoro[^{18}F]-D-glucose (^{18}FDG) which is quite similar to glucose uptake into tumors, as a tracer for diagnosing cancers using its active uptake into tumors. It is conceivable that the increased uptake of ^{18}FDG into tumors may be due to active glucose metabolism by viable tumor cells and the decrease in the number of viable tumor cells may cause the decreased uptake of ^{18}FDG into tumor tissues.

We have been exploring the possibility of utilizing the change in ^{18}FDG uptake as means for evaluating efficacy of cancer chemotherapy. We succeeded in devising a satisfactory experimental model for this purpose. We report a part of results obtained by investigating the relationship between the morphological change of tumors and ^{18}FDG uptake change under cancer chemotherapy using this model.

Materials and Methods

Male Donryu (Suzuki A) rats were used in this experiment. Hepatoma(AH272) cells were subcutaneously implanted in the backs of the rats. Anticancer drugs were injected into the tail veins of the rats. The area of the tumors was measured from outside at designated intervals and expressed at the unit of mm^2 in the long axis × the longest diameter vertical to the long axis. ^{18}FDG(20-30 μci/body) supplied by the Cyclotron and Radioisotope Center, Tohoku University, was intravenously injected into the rats, which were sacrificed by cervical dislocation one hour after the administration. The excised tumors were weighed, the area of tumors was measured directly and the radioactivity of tumor was counted by an automated NaI well counter. The uptake of ^{18}FDG into tumors was expressed as % injected dose/g tissue.

Experiment 1: About 5×10^6 tumor cells were implanted in rats weighing 200-300 g. The area and weight of tumors, and the ^{18}FDG uptake into the tumors were measured at the specified intervals of 6, 9, 12 and 15 days after

implantation, respectively.

Experiment 2: On the 9th day after implantation of 5×10^6 tumor cells 4.0 mg/kg of Adriamycin(ADR) or 2.5 mg/kg of Mitomycin C(MMC) was administered to rats weighing 80-120 g at single doses, respectively. 1.25 mg/kg of MMC was administered to rats on the 9th and 15th days after the implantation. The area of tumors was measured at designated intervals. In this experiment the appropriate dose of MMC for Hepatome(AH272) bearing rats was investigated.

Experiment 3: On the 9th day after implanting 5.4×10^6 tumor cells in rats weighing 80-120 g, single doses of 4.0 mg/kg of ADR, and of 0.15, 0.25, 0.5 or 0.75 mg/kg of MMC were administered, respectively. The area and the weight of tumors, and the ^{18}FDG uptake into tumors were measured on the 15th day after implantation (on the 6th day after the anticancer drug administration).

Experiment 4: On the 9th day after implanting 6.6×10^6 tumor cells, single doses of 4.0 mg/kg of ADR, and of 1.25 or 2.5 mg/kg of MMC were administered. On the 15th day after implantation (on the 6th day after the anticancer drug administration), the area and the weight of tumors, and the ^{18}FDG uptake into tumors were measured.

Results

Experiment 1: The area and the weight of the tumors increased gradually till the 12th day and rapidly increased on the 15th day after implantation. However, the increased uptake of ^{18}FDG into tumors from 6 to 15 days after implantation was not observed (Chart 1, Fig. 1).

Experiment 2: The area of the tumors was distinctively measured on the 7th day after implantation. As shown in Fig. 2, the area of tumors reduced in the groups treated with MMC at any dose although that in the control and the ADR administered groups extended.

Experiment 3: The area and the weight of tumors decreased in dose of MMC dependent manner. Regarding the group of 0.5 mg/kg of MMC, the area and the weight of tumors decreased to 37% and 17% of those of the control group, respectively. In the group of 0.75 mg/kg of MMC, the area and the weight of tumors decreased to 31% and 19% of those of the control group.

Compared to the ^{18}FDG uptake into tumors in the control group, that in the ADR group as well as in the groups of 0.15 mg/kg and 0.25 mg/kg of MMC did not decrease, while that in the groups of 0.5 mg/kg and 0.75 mg/kg of MMC reduced to 82% and 41% of that of the control group. The area and the weight of tumors in the group of 4.0 mg/kg of ADR decreased to 78% and 48% of those of the control group, while the ^{18}FDG uptake into tumors increased by 44% of that of the control group.

Experiment 4: The area of tumors in the groups of 1.25 mg/kg and 2.5 mg/kg of MMC reduced to 71% and 53% of that of the control group and the weight of tumors in these groups reduced to 39% and 19% of that of the control group, respectively. In these groups, the ^{18}FDG uptake into tumors decreased

to 37% and 38% of the control group, respectively. The weight of tumors in the group of 4.0 mg/kg of ADR increased by 44% of that of the control group, and the area and the ^{18}FDG uptake into tumors did not differ from those of the control group.

Discussion

On the basis of the fact that the ^{18}FDG uptake into tumors is higher than any other tissue, ^{18}FDG-PET images have been used for the detection of cancers. From the results of the present study, ^{18}FDG-PET images of various cancer patients on cancer chemotherapy were considered to be useful to evaluate the efficacy of cancer chemotherapy and to predict prognosis by recognizing changes of tumors by chemotherapy not only as their morphological change but also as the change of cell viability in tumor tissues.

From the results investigated[7] the effects of anticancer drugs on ascitic tumors, the most necessary experimental models to analyse clinical results were those with subcutaneously implanted tumors as well as with intravenously injected anticancer drugs and those with distinctive reduction of tumors caused by anticancer drugs. In fact, there were few appropriate models available for this purpose. K. Sato, one of the co-authors, succeeded in devising a fairly satisfactoryy model using subcutaneously implanted hepatomas(AH272) and intravenously injected MMC. This report illustrates the relationship between the change of ^{18}FDG uptake into tumors and the evaluation of cancer chemotherapy and the possibility of clinical application of the results is explored using the experimental model by him.

The weight of subcutaneously implanted hepatomas(AH272) rapidly increased on the 15th day after implantation, but ^{18}FDG uptake into the tumors did not change between the 6th day and the 15th day of implantation. Since the ^{18}FDG uptake per gram of tumor tissue did not change, there was no change in the cell viability and the components of the tumors during this period. If anticancer drugs are administered under this circumstance, the observed change in ^{18}FDG uptake into tumor tissues may be caused by anticancer drug. As shown in Fig. 2, the tumor area was reduced by administering 1.25 mg/kg $\times$ 2 and 2.5 mg/kg of MMC. From these results, the experiments shown in Chart 2 and 3 were conducted. Significant correlation between the tumor area and the tumor weight was detected ($r=0.97$, $p<0.01$). The tumor weight decreased even in relatively small MMC dosage, but the ^{18}FDG uptake into tumors did not always lower and distinctive decrease (-59%) of the ^{18}FDG uptake was seen with the 0.75 mg/kg of MMC. With more MMC dosage (1.25 and 2.5 mg/kg) the ^{18}FDG uptake decreased to 37 and 38% of that in the control group, respectively, which was accompanied by the decrease of the tumor weight. In the 4.0 mg/kg ADR group, no reduction of the tumor weight was observed and the ^{18}FDG uptake into tumors remained unchanged.

Conclusion

In the investigation of the relationship between the morphological changes of tumors and the change in ^{18}FDG uptake into tumors by anticancer drugs, although the change in the area or the weight of rat hepatoma was found to be more sensitive to anticancer drugs than that of ^{18}FDG uptake, the decrease in ^{18}FDG uptake in hepatoma was observed when sufficinent dose of effective drug such as MMC was given.

From the results, it was suggested that ^{18}FDG-PET imaging is a promising method for the evaluation of anticancer activity of drugs.

Further experimental studies on this imaging system will contribute to a substantial progress in this field.

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Table 1. ^{18}FDG uptake in s.c. implanted hepatoma (AH272) in rats. Mean ± S.D. Tumor cells ($4.6\text{-}5.4\times10^6$) were inoculated in the backs of male Donryu (Suzuki A) rats.

Days after implantation	No. of rats	Tumor		
		Area·mm²	Weight·g	^{18}FDG uptake· % injected dose/g tissue
6	6	187±78	0.17±0.13	4.84±1.11
9	6	338±73	0.55±0.36	5.53±2.13
12	6	353±98	0.73±0.48	5.78±1.00
15	5	835±120	3.07±1.15	5.13±0.41

Table 2. ^{18}FDG uptake in s.c. implanted hepatoma (AH272) in rats following anticancer drug administration. Mean ± S.D. Tumor cells (5.4×10^6) were inoculated in the backs of male Donryu (Suzuki A) rats. ADR: Doxorubicin, MMC: Mitomycin C.

Drug	Dose· mg/kg	No. of rats	Tumor		
			Area·mm²	Weight·g	^{18}FDG uptake· %injected dose/g tissue
Control		7	481±329	2.18±2.01	3.21±1.46
ADR	4.0	6	375±111	1.04±0.68	4.61±0.87
MMC	0.15	6	308±205	1.46±1.92	4.06±0.65
MMC	0.25	6	285±122	1.04±0.54	5.23±0.82
MMC	0.50	6	177±108	0.37±0.38	2.64±1.27
MMC	0.75	6	150±99	0.42±0.28	1.32±0.84

Table 3. ^{18}FDG uptake in s.c. implanted hepatoma (AH272) in rats following anticancer drug administration. Mean ± S.D. Tumor cells (6.6×10^4) were inoculated in the backs of male Donryu (Suzuki A) rats.

Drug	Dose· mg/kg	No. of rats	Tumor		
			Area·mm²	Weight·g	^{18}FDG uptake· %injected dose/g tissue
Control		7	389±67	1.08±0.65	5.57±1.24
ADR	4.0	7	421±84	1.56±0.71	5.15±1.07
MMC	1.25	6	277±105	0.42±0.13	2.07±0.15
MMC	2.5	7	205±130	0.21±0.09	2.14±0.88

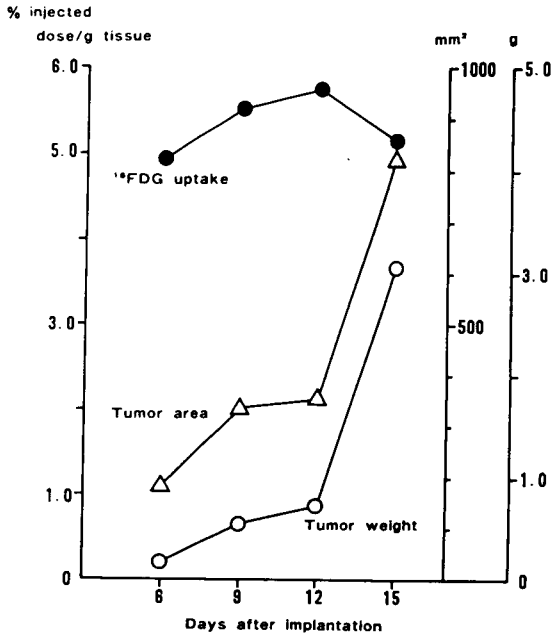

Fig. 1. Changes of tumor area, weight and ^{18}FDG uptake in s.c. implanted hepatoma(AH272) in rats. Tumor cells (4.6×10^{6}) were inoculated in the backs of male Donryu (Suzuki A) rats.

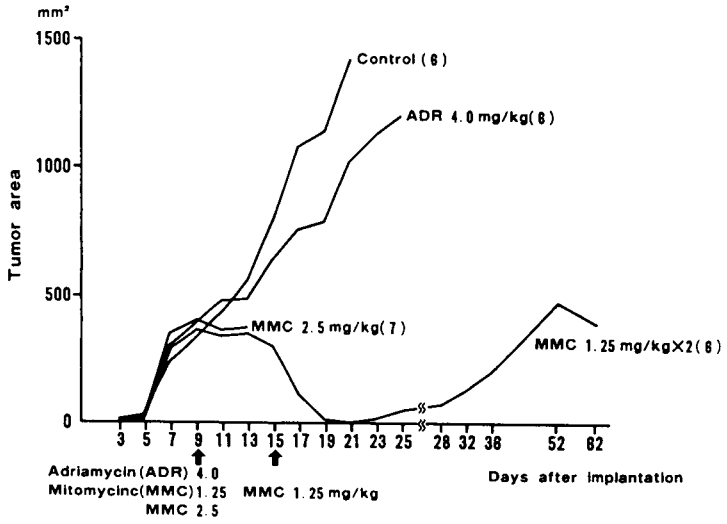

Fig. 2. Changes of tumor area of s.c. implanted hepatome(AH272) in rats following anticancer drug administration. Tumor cells (5×10^{6}) were inoculated in the backs of male Donryu (Suzuki A) rats. Nos. in parentheses indicate Nos. of rats.