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The chemotherapy for malignant glioma has made great progress, however, there still remains many limitations. It is mandatory to develop the more effective chemotherapeutic administration method to increase the drug delivery into the brain tumor selectively without causing major side effects. It has been pointed out that a functional characteristic of tumor vessels was the lack of autoregulation. In the present study, the uptake of ACNU (1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride) in the experimental brain tumor and the effect of induced hypertension were investigated from the view points of this lack of autoregulation in the brain tumor.

Materials and Method

KEG-1 cells (1×10^6) were implanted semistereotaxically into the brains of WKA rats weighing 200 gm around. About 10 days later, under the sodium pentobarbital anesthesia, canuli were introduced into the femoral artery and vein, and blood pressure was continuously monitored. Rats were immobilized with pancuronium bromide and artificially ventilated. Body temperature, PH, PaO_2 and $PaCO_2$ were maintained within physiological range throughout the experiment. Ten μCi of ethylene-^{14}C-ACNU (specific activity: 26.1 μCi/mg) was administered intravenously following the continuous elevation of blood pressure by angiotensin II. Rats were decapitated at 10, 20 and 30 minutes after the injection of ethylene-^{14}C-ACNU, and the tumor tissue together with contralateral brain tissue were sampled. These samples were burned with sample oxidizer (Aloka ASC-113) and the radioactivity of ^{14}C was counted with liquid scintillation counter (Aloka LSC-903).

Results

In four rats of the non-hypertensive control group, which were decapitated at 10 minutes following the injection of ethylene-^{14}C-ACNU, the uptake of ^{14}C-ACNU in the brain tumor was 0.53±0.10 %dose/g tissue (mean ± SE) (Fig. 1). On the other hand, in four rats of the induced hypertension group, decapitated at 10 minutes as well, it was 1.12±0.14 %dose/g tissue ($p<0.01$). In the four rats of induced hypertension group sacrificed at 20 or 30 minutes, the uptake of ^{14}C-ACNU was almost the same as that of the non-hypertensive

control group. Also the uptake of ^{14}C-ACNU in the contralateral brain tissue of the two groups did not show any statistically significant difference throughout the experiment (Fig. 2).

Discussion

Recently many attempts have been made to administer high dose of antitumoral agent to patients.[1] However, there still remains unsolved problems, most importantly, suppression of side effects due to the high dose load. This experiment was designed to clarify the enhancement effect of induced hypertension on the selective drug delivery into the brain tumor, and thus to give an answer to these problems.

One of the characteristics of tumor vessels has been reported as the lack of autoregulation[2], which suggests that the microcirculation in brain tumors may be dependent on perfusion pressure. As a fact, it has already been reported that elevation of blood pressure produced a several fold increase in blood flow in transplanted AH109A tumor selectively.[3] On the basis of these theoretical background, the effect of induced hypertension was investigated using the experimental brain tumors which has been reported to have low blood flow.[4]

ACNU has been widely used mainly for malignant glioma patients because of its high affinity to lipid, although it is known to be a water-soluble drug.[5] The antitumor mechanism of ACNU is considered principally by the alkylating moiety, because ACNU dose not demonstrate carbamoylating activity.[6] The main reason to choose ethylene-^{14}C-ACNU in this study is due to the fact that ^{14}C is labelled in the active site of ACNU. Therefore, the uptake of ^{14}C in the experimental brain tumor following the administration of ethylene-^{14}C-ACNU is considered to reflect the accumulation of effective ACNU derivatives. Also ACNU has been known to have rather short biological half life of about only 12 minutes in rat plasma.[5] These facts indicate that the evaluation even at a short period following the administration of ACNU, the accumulation of this drug can be considered meaningful observation as an antitumoral agent.

In the induced hypertension group of rats decapitated at 10 minutes following the administration of ACNU, the uptake of ^{14}C in the experimental brain tumor was about twice as that of the non-hypertensive control group. Moreover, the uptake of ^{14}C in the contralateral brain tissue did not differ between the two groups. These results clearly demonstrated that the uptake of ^{14}C was succeeded to increase selectively in the brain tumor by induced hypertension for only a short period of time, while it was remained unelevated in the contralateral normal brain tissue.

The method of induced hypertension for only 10 minutes we tried in this study seems easy to apply also clinically. This induced hypertension chemotherapy will be effective for the management of malignant glioma patient without causing any additional side effects.

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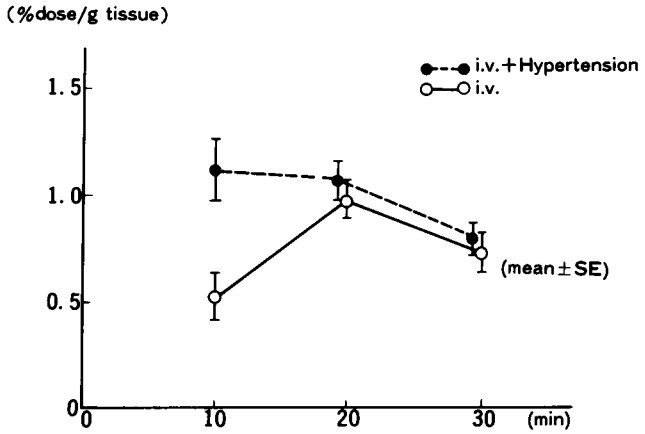

Fig. 1. The accumulation of ^{14}C-ACNU in the experimental brain tumor.

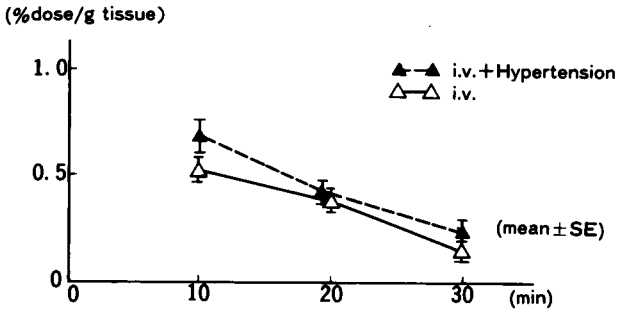

Fig. 2. The accumulation of ^{14}C-ACNU in the contralateral cortex.