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# Effects of Boron Neutron Capture Therapy Using Borocaptate Sodium in Combination with a Tumor-selective Vasoactive Agent in Mice

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**Boron neutron capture therapy (BNCT) destroys tumor cells by means of α particles and recoil protons emitted by $^{10}B(n,\alpha)^{7}Li$ reaction. For BNCT to be effective, the tumor/normal tissue concentration ratio of $^{10}B$ must be larger than 1.0, because neutron distribution is not selective. We examined the combination of $^{10}B$-enriched borocaptate sodium (BSH) with flavone acetic acid (FAA) as a model compound which causes vascular collapse in squamous cell carcinoma in mice (SCCVII tumors) and would increase the tumor/normal tissue concentration ratio of $^{10}B$. FAA (200 mg/kg, i.p.) was injected, and 5 min later BSH (75 mg/kg, i.v.) was administered, followed 15 to 180 min later by irradiation with thermal neutrons. The $^{10}B$ concentrations were measured by prompt gamma ray spectrometry. Without FAA, tumor $^{10}B$ concentrations were less than or equal to normal tissue concentrations at all time intervals, except that the concentrations were 1.7- to 2.7-fold greater in tumor than muscle at 15 and 180 min after injection of BSH. With FAA, $^{10}B$ concentrations 2.1- to 6.9-fold greater in tumor than in muscle were achieved at all intervals tested. For blood and skin, significant differential accumulations were found in tumors at 120 and 180 min. Tumor/liver ratios were less than 1 at all times. Cell survival was determined by *in vivo*/*in vitro* colony assay, and increasing radiosensitization correlated with increasing tumor $^{10}B$ concentrations, whether or not they were achieved with FAA. Tumor control rates, determined at 180 days after BNCT, similarly appeared to depend only on $^{10}B$ levels at the time of irradiation. Because $^{10}B$ levels correlate with the radiation response of tissues, a therapeutic gain would be expected whenever the tumor levels exceed normal tissue levels, such as in tumors located in muscle irradiated at 15–180 min after FAA+BSH, or in those in skin irradiated at 120 and 180 min.**

Key words: BNCT — Borocaptate sodium — Flavone acetic acid

Boron neutron capture therapy (BNCT) utilizes α particles and recoil protons emitted by $^{10}B(n,\alpha)^{7}Li$ reaction to kill tumor cells. These particles exhibit high linear energy transfer and have high relative biological effectiveness. These characteristics are desirable to treat radioresistant tumors such as malignant glioma or malignant melanoma. For BNCT to be effective, the tumor/normal tissue concentration ratio of $^{10}B$ must be larger than 1.0 because neutron distribution is not selective, and the larger the ratio, the better the expected outcome.

$^{10}B$-Enriched borocaptate sodium ($Na_2B_{12}H_{11}SH$: BSH) has been used in clinical BNCT for malignant glioma since 1968.[1)] BSH distributions in various tissues depend upon both the concentration gradient between the blood and the tissue, and compartmentalization. Tumor-to-blood ratios of 1.3 to 1.46 have been reported for malignant glioma.[2, 3)] BSH does not cross the blood brain barrier (BBB) into the normal brain, but accumulates in malignant gliomas because of their defective BBB. However, in tumors in other organs, BSH distributions are not selective[4)] because of the lack of a mechanism such as the BBB.[5)] We used as a model vasoactive agent flavone acetic acid (FAA), which causes vascular collapse in murine tumors,[6, 7)] postulating that it might cause entrapment of BSH in tumors, but not in normal tissues. FAA is more cytotoxic to endothelial cells than tumor cells *in vitro*, and also increases the permeability of endothelial cells.[8)] Thus, FAA induces vascular damage and hemorrhagic necrosis within tumors. If irradiation were given after an appropriate time interval, when the $^{10}B$ level in the tumor exceeds those in normal tissues, a therapeutic gain might be achieved. We investigated the changes in pharmacokinetics of $^{10}B$ following administration of BSH alone and in combination with FAA in tumors and normal tissues. We also evaluated the effects of BSH alone and in combination with FAA on the response of murine tumors to irradiation with thermal neutrons.

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## MATERIALS AND METHODS

**Tumors** The murine squamous cell carcinoma SCCVII was used in these studies. Tumor cells, exponentially proliferating in Eagle's minimum essential medium supplemented with 292 mg/liter L-glutamine and 12.5% fetal calf serum were inoculated ($5\times10^4$ cells) into the thigh of the right hind leg of syngeneic 8- to 10-week-old male C3H/He mice. About 7 and 14 days later, the tumors reached mean diameters of 5 mm (suitable for tumor control assay) and 10 mm (suitable for *vivo/vitro* colony formation assay), respectively.

**Compounds and measurement of boron concentration** BSH (Boron Biologicals, Inc., Raleigh, NC) and FAA were dissolved in physiological saline at concentrations of 6 mg/ml and 10 mg/ml, respectively. FAA (200 mg/kg body weight, i.p.) and BSH (75 mg/kg body weight, i.v. via tail vein) were administered as reported previously.[9, 10] This dose of FAA has been found to reduce the blood flow in SCCVII tumors to approximately 40% of the control by 60 min after FAA injection.[11] Because the $T_{1/2}$ of BSH clearance from blood is nearly 30 min,[9] when both FAA and BSH were given, BSH was injected 5 min after FAA administration to allow BSH to distribute freely in tumor tissues before vascular collapse. Mice were killed by cervical dislocation 15 to 180 min after drug administration, and tumor, liver, skin, muscle and blood samples were collected. The blood sample for $^{10}B$ measurement was collected by heart puncture from anesthetized mice. The $^{10}B$ concentrations in these tissues were measured by prompt gamma ray spectrometry using a thermal neutron guide tube installed at Kyoto University Reactor.[12]

**Thermal neutron irradiation** A thermal neutron beam with a negligible component of fast neutrons and gamma rays was used.[13] Mice were anesthetized and restrained in a LiF thermoplastic box holding three mice with the tumor-bearing legs pulled through a narrow slit in the front side. The legs were fixed with adhesive tape. Thermal neutron irradiation was started at 30, 60, or 180 min after the completion of the drug injections, and continued for a maximum of 40 min. Neutron fluences and core plus capture gamma ray doses were measured by using radioactivation of gold foil (3 mm diameter, 0.05 mm thick) and thermoluminescent dosimeters, respectively. The thermal neutron flux and gamma ray dose rate were $7.52\times10^9$ n/cm$^2$s and 0.002 Gy/s at 5 megawatts, respectively. The core gamma ray dose rate was 0.0004 Gy/s.

**Colony formation and tumor control assay** In the colony formation assay, the mice were killed immediately after irradiation. The tumors were removed and minced with scissors. A single cell suspension was then made by digesting tumor fragments with a mixture of 0.05% trypsin and 0.02% EDTA at 37°C for 15 min. An appropriate number of tumor cells to form 50 to 100 colonies was inoculated onto 60 mm diameter Petri dishes containing complete medium. After incubation for 10 days, the colonies were fixed with ethanol, stained with crystal violet, and counted macroscopically. The plating efficiency (PE) of the cells in control tumors was about 40%. The surviving cell fraction (SF) was obtained by dividing the PE of the treated group by that of the control. The best-

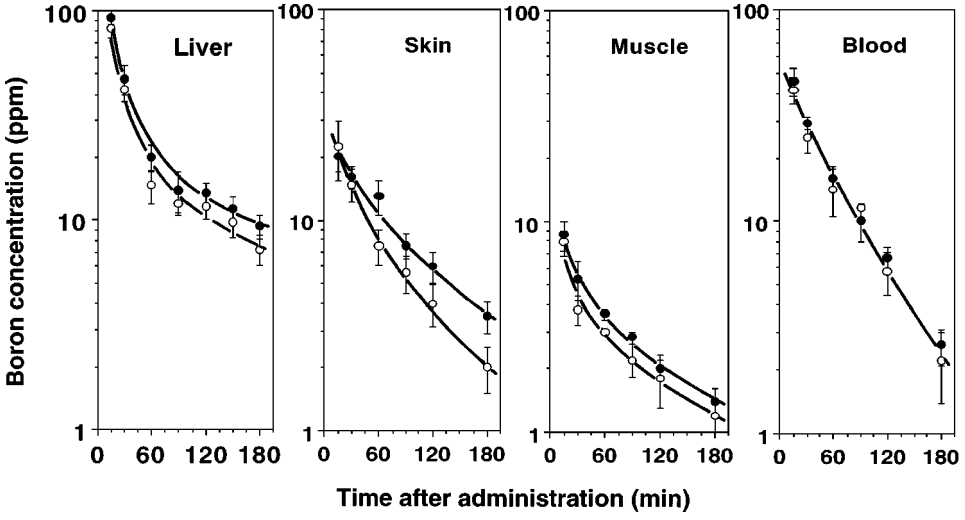


Fig. 1. Boron ($^{10}B$) concentrations (ppm) in the liver, skin, muscle and blood as a function of time after BSH at 75 mg/kg body weight (○) and BSH+FAA at 200 mg/kg body weight (●). Each data point with vertical line represents the mean value and standard deviation in eight mice.

fitted lines in plots of the neutron fluence versus SF were determined by the least-squares method. In the tumor control assay, the tumor-bearing legs of mice were observed twice a week after treatment. The tumor control rate was defined as the proportion of tumors which regressed completely and did not regrow within 180 days after treatment. The neutron fluence required to achieve 50% tumor cure ($TCD_{50}$) was determined by logit analysis.

## RESULTS

**Pharmacokinetics of boron compound** The clearance curves of $^{10}B$ from normal tissues and tumors are presented in Figs. 1 and 2, respectively. Pharmacokinetic parameters are shown in Table I. The mean $^{10}B$ concentrations at 15 min after BSH injection were highest in liver (83.0±8.0 ppm), followed by blood (41.6±6.0 ppm), skin (23.0±7.0 ppm), tumor (13.7±0.7 ppm), and muscle (7.9±1.1 ppm). This order was maintained at least until 180 min after BSH injection. The clearance curves of $^{10}B$ from the tissues were biphasic except for the blood, which showed a nearly monophasic curve. The initial phase of the clearance curves was steepest in the liver ($T_{1/2}$=18.2±1.1 min). FAA slightly decreased the rate of clearance of $^{10}B$ in most tissues except the blood. The $T_{1/2}$ in the tumor increased from 36.3±0.6 to 61.3±2.6 min, and in the skin, from 29.3±1.8 to 73.9±15.1 min. However, no effects on the $T_{1/2}$ were observed in the other tissues. The $T_{1/2}$ of the second phase was increased in the tumor, but not in any other tissues. The mean $^{10}B$ concen-

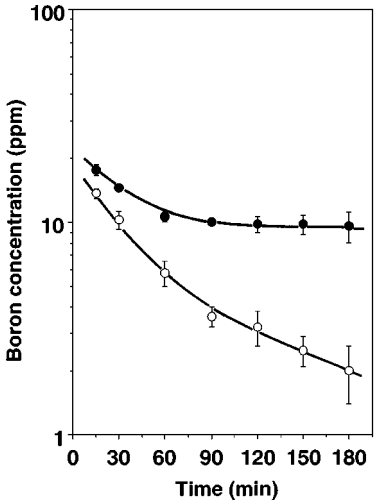


Fig. 2. Boron ($^{10}B$) concentrations (ppm) in SCCVII tumors as a function of time after BSH at 75 mg/kg body weight (○) and BSH+FAA at 200 mg/kg body weight (●). Each data point with vertical line represents the mean value and standard deviation in eight tumors.

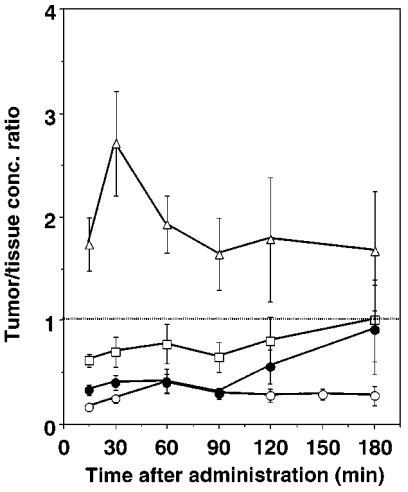


Fig. 3. Tumor/tissue concentration ratio of $^{10}B$ as a function of time after BSH administration in various tissues. Each data point with vertical line represents the mean value and standard deviation. ○ liver, □ skin, △ muscle, ● blood.

Table I. Pharmacokinetics of BSH in Tumors and Normal Tissues

| Tissue | $^{10}B$ Concentration at 15 min (ppm) | $T_{1/2}$ (min) | | | |
|---|---|---|---|---|---|
| | | without FAA | | with FAA | |
| | | Init. phase | 2nd phase | Init. phase | 2nd phase |
| Liver | 83.0±8.0 | 18.2±1.1 | 118±14.1 | 20.8±2.6 | 112±18.1 |
| Skin | 23.9±7.0 | 28±1.8[a)] | 62±7.2[b)] | 73.9±15.1[a)] | 81.1±3.5[b)] |
| Muscle | 7.9±1.1 | 35.4±18.3 | 93.0±6.8 | 37.6±9.8 | 87.4±8.5 |
| Blood | 41.6±6.0 | 40.6±2.5 | — | 41.3±2.2 | — |
| Tumor | 13.7±0.7 | 36.3±0.6[c)] | 103.5±10.2 | 61.3±2.6[c)] | not determined |

*a*), *b*) $P<0.05$, *c*) $P<0.01$.
Mean±SD.

tration in the tumor was constant (10.6±0.6 to 9.6±1.6 ppm) from 60 to 180 min. Thus, the administration of FAA improved the $^{10}B$ concentration ratios of tumor to blood, skin and muscle (Fig. 3 vs. Fig. 4). At 180 min after FAA+BSH administration, the ratios reached 2.7±0.7, 3.7±0.9 and 6.9±1.5 for skin, blood and muscle, respectively (Fig. 4).

**Colony formation assay** BSH and FAA alone or in combination did not affect the PE of the tumor cells. The SF as a function of neutron fluence and parameters of cell survival curves are presented in Fig. 5 and Table II. The SF decreased exponentially with neutron fluence. The cell-killing effect of NCT was enhanced by BSH given 30 or 60 min before irradiation, but not 180 min before. The addition of FAA to the treatment further enhanced the cell killing effect, for both the 60 min and 180 min intervals. That these differences can be accounted for by the differences in boron concentration in the tumor at the time of irradiation is shown in Fig. 2. The cell-killing effect of BNCT evaluated in terms of the neutron fluence required to produce a surviving fraction of 10% depends only upon the $^{10}B$ level in the tumor (Fig. 6).

**Tumor control assay** Tumor control rates as a function

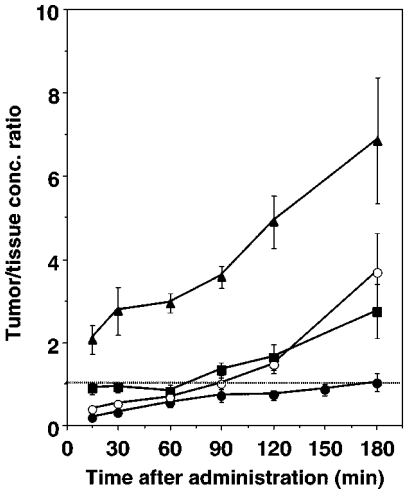


Fig. 4. Tumor/tissue concentration ratio of $^{10}B$ as a function of time after FAA+BSH administration in various tissues. Each data point with vertical line represents the mean value and standard deviation. ● liver, ■ skin, ▲ muscle, ○ blood.

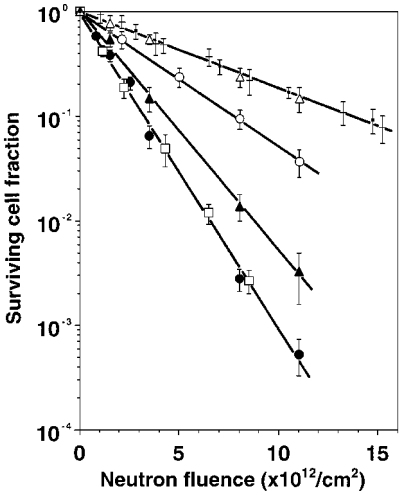


Fig. 5. Surviving cell fractions as a function of neutron fluence. ● 60 min after FAA (200 mg/kg) + BSH (75 mg/kg), ○ 60 min after BSH (75), □ 30 min after BSH (75), ▲ 180 min after FAA (200)+BSH (75), △ 180 min after BSH (75), ■ 60 min after FAA (200), +NCT alone. FAA was injected 5 min before BSH administration. Each data point with vertical line represents the mean value and standard deviation in eight tumors in two independent experiments. The cell survival curves of 60 min after FAA+BSH and 30 min after BSH groups are presented as a single line because these two lines are considered to be identical (see Table II). The curves of 180 min after BSH, 60 min after FAA and NCT alone are in a similar situation.

Table II. Parameters of Cell Survival Curves of SCCVII Tumors Following BNCT

| Treatment groups | $-\ln SF = C + \alpha\Phi$ | | |
|---|---|---|---|
| | $C$ | $\alpha$ ($\times 10^{-12}$) | |
| FAA+BSH-60 min-Neutrons | 0.000337 | 0.704±0.021 | NS |
| BSH-30 min-Neutrons | 0.0748 | 0.682±0.011 | NS, * |
| FAA+BSH-180 min-Neutrons | –0.0395 | 0.529±0.012 | * |
| BSH-60 min-Neutrons | –0.0215 | 0.299±0.005 | * |
| BSH-180 min-Neutrons | 0.000313 | 0.175±0.002 | * |
| Neutron alone | –0.0378 | 0.171±0.005 | NS |
| FAA-60 min-Neutrons | 0.00737 | 0.164±0.011 | NS |

Mean±SD. * $P<0.001$.
$\Phi$ : Neutron fluence.

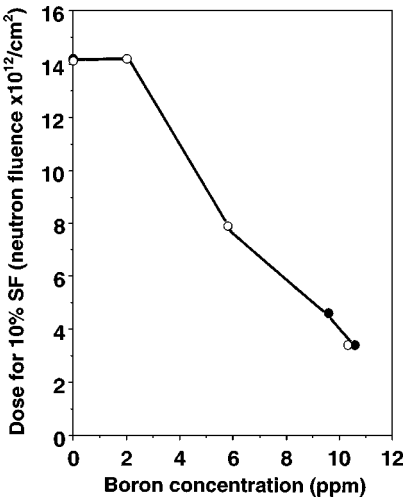


Fig. 6. Neutron fluence ($\times 10^{12}$/cm$^2$) for 10% surviving fraction (SF) as a function of boron ($^{10}$B) concentration. ○ BSH alone, ● FAA (200) + BSH.

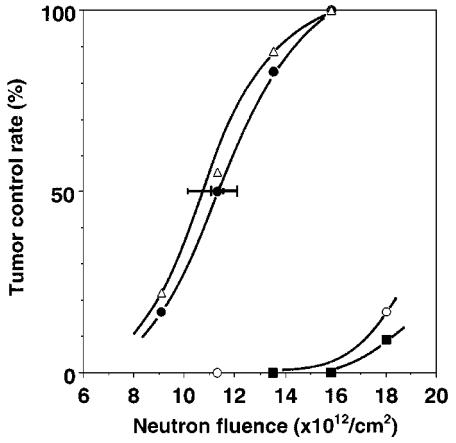


Fig. 7. Tumor control rate as a function of neutron fluence. ● 60 min after FAA (200) + BSH (75), ■ 60 min after FAA (200), ○ 60 min after BSH (75), △ 30 min after BSH (75). FAA was injected 5 min before BSH administration. Each data point corresponds to 9 to 20 tumors and the horizontal line represent the 95% confidence limits of $TCD_{50}$.

of neutron fluences in various treatment protocols are presented in Fig. 7. A $TCD_{50}$ could not be achieved by neutron exposure at 60 min after BSH or FAA injection due to lethal whole-body gamma doses. However, when neutrons were delivered to tumors 60 min after FAA+BSH, the $TCD_{50}$ was $11.4\pm0.5\times10^{12}$ n/cm$^2$. A similar $TCD_{50}$, $10.8\pm0.8\times10^{12}$ n/cm$^2$, was obtained in tumors irradiated 30 min after BSH alone, when the $^{10}$B concentrations in the tumors were similar. Although tumor control was only 17% at the neutron dose of $18\times10^{12}$/cm$^2$ given 60 min after BSH, the same control rate was achieved by $9.1\times10^{12}$/cm$^2$ of neutrons with the combination of FAA and BSH, suggesting enhancement by FAA by a factor of about 2.0.

## DISCUSSION

The concentration of $^{10}$B in the liver was higher than that in the blood (Fig. 1), as has been reported previously.[2] This may be associated with higher levels of glutathione in the liver than in the skin, muscle and blood.[14–16] BSH might be trapped in the liver by covalent mixed disulfide bonding between glutathione and BSH.[17] This could also account for the higher $^{10}$B concentration achieved in the murine fibrosarcoma NFSa 60 min after BSH injection (Ono, unpublished data). NFSa contains more GSH than SCCVII tumors (2.1 vs. 1.1 mmole/kg).[18, 19]

The selective effect of FAA on the pharmacokinetics of BSH in tumors (Figs. 1 and 2) can be explained by the selective effects of FAA on the tumor vasculature.[10] However, the effect of FAA depends on the type of tumor,[11] so the effects of FAA on BSH clearance may also be dependent on tumor type. FAA does not produce vascular collapse in human tumors.[20] Therefore, a different agent would have to be used clinically, even though FAA was used as a model in this study.

In BNCT, a larger radiation dose to the tumor than to surrounding normal tissue can be delivered only when the tumor/normal tissue ratio of $^{10}$B concentrations is >1.0, because otherwise selective delivery of neutrons to the tumor site is impossible. Higher tumor/normal tissue ratios of $^{10}$B (Figs. 3 vs. 4) may provide a larger therapeutic benefit with BNCT. Namely, they may facilitate delivery of curative doses to tumors located in deeper sites without increasing the radiation doses to superficial and surrounding normal tissues.

The high LET particles emitted by the boron neutron capture reaction have very limited tracks (<10 $\mu$m), i.e., they do not exceed approximately one cell diameter.[21] Therefore, if the microdistribution of $^{10}$B is altered by FAA, the cell-killing effects could be changed even though the mean $^{10}$B levels in tumors are the same.[9] However, it appears that gross boron concentrations in the tumor account for the tumor response to neutron irradiation, independently of whether FAA was used to achieve them (Fig. 6).

Macroscopic hemorrhage was observed in tumors treated with FAA when the tumors were removed from mice for the colony formation assay. FAA itself induces a growth delay in SCCVII tumors.[19] However, FAA alone

did not modify the PE and tumor cell survival curves when neutrons were delivered 60 min after FAA injection, and no additional cytotoxicity or sensitization was observed in tumors irradiated 180 min after FAA+BSH as compared with those irradiated 60 min after FAA+BSH (Fig. 5). It is likely that the duration of oxygen deprivation and other FAA-induced stresses was insufficient to kill a significant proportion of tumor cells in these experiments. An antitumor effect of FAA could not be demonstrated in the tumor control assay, even though the tumor cells remained *in situ*, and were thus subject to maximum exposure to the effects of FAA (Fig. 7). The effect of FAA on the $TCD_{50}$ in the absence of BSH could not be determined because gamma-ray scatter from the neutron beam was lethal to the mice at the higher doses required to achieve 50% tumor cure. However, similar $TCD_{50}$ values were obtained in two groups irradiated when the $^{10}B$ concentrations in the tumors were similar, namely, in the group irradiated 30 min after BSH, and in the group irradiated 60 min after FAA+BSH (Fig. 7). This suggests that FAA itself had no significant effect on tumor control.

FAA inhibited the clearance of BSH from SCCVII tumors but had little or no effect on clearance from normal tissue. Maintenance of high tumor levels of $^{10}B$ correlated with maintenance of enhanced sensitivity to thermal neutron irradiation. FAA itself did not have a measurable effect on tumor cure by neutrons. If enhancement of both early and late effects in normal tissues is correlated with $^{10}B$ concentration, as is the case with tumors, a therapeutic gain could be realized through BNCT with the use of FAA or some other selective inhibitor of tumor blood flow.

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