POSSIBLE ALTERATION OF THE BLOOD–BRAIN BARRIER BY BORON-NEUTRON CAPTURE THERAPY

H. HATANAKA, M. MORITANI and M. CAMILLO

Abstract

In the course of re-assessment of boron-neutron capture therapy (BNCT) for malignant brain tumors, fractionation of neutron irradiation has been proposed. The authors have used BNCT with a single fraction technique during the past 21 years and now decided to study some effects of fractionation. Twenty-two healthy mouse brains were irradiated with thermal neutrons after boron-10 injection (mercaptoundecahydrododecaborate). A second dose of boron-10 was administered and its uptake in the boron-neutron-capture-irradiated brains was determined. A tendency towards increased boron uptake in the moderately BNCT-treated brains was noticed, which may result in increased brain damage if fractionated neutron irradiation is used.

Key words: Neutron capture therapy, mice, brain, blood–brain barrier, fractionated irradiation, boron-10 uptake.

An ideal therapy for tumors should destroy tumor tissues selectively without causing damage to the normal tissues surrounding the tumor. Boron-neutron capture therapy (BNCT) has theoretically been considered to be one of the best methods to achieve this goal. BNCT is expected to deliver heavy particle radiation only to the tumor cells (1). The most important feature of BNCT is the selective exclusion of the non-radioactive boron-10 in the normal tissue that adjoins the malignant cells. In brain tumor treatment, slow neutrons are delivered to the brain matter. Some of these neutrons will be captured by boron-10 in tumor cells and produce secondary heavy particle radiation by neutron capture reactions.

BNCT was tried in two institutes between 1951 and 1961 but was then totally discarded until one of the authors (Hatanaka) in 1968 took up the method again, using a new technique (2, 3). Despite a few interruptions due to shortage of boron-10 compound or to close-down of the two reactors which were available for this therapy, Hatanaka et al. have, during the past 22 years, treated 105 cases (4, 5). Approximately half of these patients had recurrent brain tumors already treated by conventional radiotherapy. Among 38 grade III-IV astrocytomas, treated solely by BNCT up to 1985, the 5-year survival rate of patients with superficially located tumors (to which theoretically sufficient neutron fluence could be delivered) was 58%. As of July, 1990, four of the long-surviving patients with malignant gliomas have reached a follow-up of 9, 11, 13, and 18 years. (Among the 18 autopsied patients, three were found at autopsy to be free from residual tumor (6)).

In view of the encouraging results in this clinical series, BNCT is being re-assessed, and the International Society for Neutron Capture Therapy was founded in 1984. Meetings have been held in Cambridge (Massachusetts), Tokyo (7), and Bremen (8), and the 4th meeting of the society will take place in Sydney in 1990. European and American projects are going on with financial aid from the European Common Community and the U.S. Government. Workshops have been held in Brookhaven, Annapolis, Oxford, Cambridge (Mass.), Amsterdam, and Lausanne. Some participants in these meetings have proposed a fractionated irradiation schedule in BNCT with the hope of enhancing a recovery of the normal brain matter (8, 9).

The present experiment was designed to evaluate the influence of neutron capture irradiation upon the blood–brain barrier (BBB) (10) which is crucial in preserving the advantage of BNCT, namely the exclusion of the normal brain matrix from exposure to secondary heavy particle radiation.

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Material and Methods

Experiment I. In the first experiment, nine 8-week-old IV-CS-strain male mice weighing 25–29 g were used. They were divided into 3 groups of 3 animals. Two groups to be irradiated received an intramuscular injection of 0.1 ml of 0.1N Na$_2$B$_6$H$_{12}$SH (96%-enriched $^{10}$B-sodium mercaptoundecahydrododecaborate, supplied by Shionogi Research Laboratories) 3.5 h before irradiation. Before irradiation, each mouse was encased in a boron-containing rubber-sheet cylinder to shield the body against neutrons. The vault of the animal’s head was exposed through a hole (1.5 x 1.3 cm). Three control animals were not irradiated. The irradiation was carried out at the thermal neutron medical port of the reactor of Musashi Institute of Technology (a modified TRIGA-II, 100 kW). In order to measure neutron flux, gold foils (thickness 0.02 mm and 2.8 mg) were attached to the head surface.

The irradiation time was one hour for group IA and two hours for group IB. Just before and after the irradiation, blood samples were collected from tail veins. The volume of blood specimens ranged between 0.04–0.2 ml.

Another intramuscular injection of the boron solution (0.2 ml) was given 24 h after irradiation in all 3 groups of animals. After another 24 h, blood and brain specimens were obtained as described in Experiment I, and were irradiated for 30 min (IIIA) or 1 h (IIIB).

Results and Discussion

The neutron flux (in n/cm$^2$ s) was $1.06 	imes 10^9$ for Experiment I, $0.99 	imes 10^9$ for Experiment II, and $1.01 	imes 10^9$ for Experiment III, and the fluence was $3.8 	imes 10^{12}$ and $7.7 	imes 10^{12}$ for groups IA and IB, $5.3 	imes 10^{12}$ and $9.5 	imes 10^{12}$ for groups IIA and IIB, and $1.8 	imes 10^{12}$ and $3.6 	imes 10^{12}$ for groups IIIA and IIIB respectively.

Tables 1–3 show the results of boron analyses for the three experiments. In Experiment I, boron in blood could not be detected and the concentration is given as zero in Table 1. It is clear from the 3 tables that the brains of the control animals which had not been irradiated still contained a certain minimum amount of boron (0.24–0.37 µg $^{10}$B/g). We therefore assumed that the boron concentration in the brain should exceed 0.37 in order to suggest an alteration of the BBB. It is noted that the BBB of the animals of group IB, group IIB and perhaps group IIA may have been affected by the BNCT, although the limited number of animals does not allow an adequate statistical evaluation.

In clinical practice the authors have allowed a much higher blood concentration of boron-10 (12) and a much higher neutron fluence to the patients’ brain surface (~15 µg $^{10}$B in blood and ~1.0 x 10$^{13}$ neutron in neutron velocity time) (4, 6). The dose of boron-neutron capture radiation delivered in the present animal experiments was less than one-tenth of the dose for our patients. Nevertheless, the boron-10 concentration in the animal brain was higher after BNCT than in the control group. This

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<td><strong>Experiment I</strong></td>
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<td>Boron-10 in blood</td>
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suggests that the initial BNCT altered the BBB, which means that the advantage of BNCT could be jeopardized if fractionated neutron irradiation is used.

The total number of animals studied is still small and the present type of experiment should be repeated in larger series and with more varied schedules. However, our preliminary results strongly suggest that even low-dose BNCT can affect the BBB and that this might reduce the advantage of BNCT if it is carried out with fractionated neutron irradiation.

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**REFERENCES**