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Boron uptake in melanoma, cerebrum and blood from $Na_2B_{12}H_{11}SH$ and $Na_4B_{24}H_{22}S_2$ administered to mice

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The nuclear reaction $^{10}B(n, \alpha\gamma)^7Li$ [1] has been used in boron neutron capture therapy (BNCT*) [2] to cure malignant gliosarcomas implanted in the hind legs of mice [3, 4] and spontaneous malignant melanomas in pigs [5]. The sulfhydryl borane monomer $[B_{12}H_{11}SH]^{2-}$ (BSH) [6, 7] is used as a ^{10}B carrier for BNCT of malignant human brain tumors [8, 9]. It has been suggested that its disulfide dimer, $[B_{24}H_{22}S_2]^{4-}$ (BSSB) [10, 11], and its disulfide monoxide dimer [12] may also have favorable properties as carriers of ^{10}B for BNCT. We now report that Na_4BSSB yields higher tumor–blood and tumor–cerebrum boron concentration differences than does Na_2BSH when each is infused to deliver the same dose of boron (~200 μg B/g body wt) very slowly (~1 μg B/g body wt hr) into tumor-bearing mice. This observation may have implications for BNCT of human brain tumors such as malignant gliomas, which have an imperfect blood–brain barrier and which, therefore, are more accessible to Na_4BSSB or to Na_2BSH than are normal brain tissues.

Methods and results

Cs_4BSSB was synthesized by oxidation of Cs_2BSH (Callery Chemical Co., Callery, PA) using *o*-iodosobenzoic acid as described by Wellum *et al.* [11]. The sparsely soluble cesium salts of these two boranes were converted to their highly soluble sodium salts as follows. One hundred milligrams of the cesium salt was dissolved in 15 ml of warm water with stirring and then passed through an ion-exchange column (1.5 × 1.0 cm) containing 0.6 g of 100–200 mesh Dowex 50 W-X8. Recovery efficiency of the column, as judged by prompt gamma analysis of boron [13] in aliquots of column inflow and outflow, was >90%. X-ray fluorescence analysis [14] of the sodium salt of BSH failed to reveal residual cesium.

Thin-layer chromatography (TLC) with 3 M aqueous NH_4NO_3–acetonitrile (2:1) on DEAE cellulose plates (Brinkmann, Westbury, NY) [15] was used to detect contamination of Na_4BSSB ($R_f = 0.23$) by Na_2BSH ($R_f = 0.56$). The visible spectrum of the blue, non-degassed solution of 2.3×10^{-4} M Cs_4BSSB in the colourless solvent, 5.0×10^{-3} M trifluoroacetic acid in dimethylformamide, had one broad absorbance band which was maximum at 628 nm. The 628 nm absorbance of the solution decreased slowly with a half-life of ~66 days, much longer than that reported originally (~8 days) [11]. The initial absorbance of the solution, 0.71, was only two-thirds of the expected [11] absorbance.

ESR of the blue solution of Cs_4BSSB in the acidified dimethylformamide solvent was performed with a Varian E-line X-band spectrometer calibrated for field sweep with an aqueous solution of Fremy's salt, $K_2(SO_3)_2NO$, and for measurements of g values with a solution of perylene in concentrated sulfuric acid. A single peak was found at $g = 2.023$. The previously reported value was 2.019 [11]. The peak-to-peak width of the first derivative of the signal was 18.6 G. The signal width at half-maximum intensity was 26.0 G, more than the reported [11] value of 19.3 G. The 628 nm absorbance and the intensity of the ESR signal of the blue solution decreased with time, but a constant arithmetic ratio of these quantities to each other was maintained meanwhile. Other observations which show that Na_4BSSB was the principal solute in the indicated (Tables 1–3) mouse infusions were the exact correspondence of the principal infrared absorption bands of the cesium salt of our preparation with those of Cs_4BSSB [11] and the absence of significant contamination of our Na_4BSSB preparations by Na_2BSH when they were tested by TLC.

Aqueous solutions of Na_2BSH or Na_4BSSB were infused slowly intraperitoneally (Osmotic pump, model 2001, Alza Corp., Palo Alto, CA) or were injected intraperitoneally promptly into 15–20 g female BALB/cJ mice bearing subcutaneously implanted Harding–Passey (HP) melanomas [16].

All borane solutions loaded into osmotic pumps were in water except in mouse group L (Table 2) where 5.3×10^{-3} M sodium metabisulfite ($Na_2S_2O_5$) was added to retard oxidation of BSH. Mice were deeply anesthetized with ether and killed by exsanguination from the heart at the times specified in the tables. These osmotic pumps were designed to function for 219 ± 6 hr, but the precise duration of infusion in each mouse varied, either because the mouse was killed before the scheduled cessation of pump function or perhaps because some of the pumps were used several years after their manufacture and therefore pumped more slowly or more rapidly than expected. Focal hepatic necrosis and fibrosis which were observed in some mice bearing the rigid cylindrical (3.0 × 0.7 cm) osmotic pumps for 8–10 days may have been due to direct pressure on the liver or its vasculature.

Tissue and blood specimens in quartz test tubes, with sufficient H_2O added to bring each sample to a total weight of 1.00 g, were analyzed for boron by counting 478 keV gamma photons from the $^{10}B(n, \alpha\gamma)^7Li$ reaction during irradiation by slow neutrons [13]. The results of boron analyses of HP melanomas, whole blood and cerebra are shown in Tables 1–3.

Variations of boron doses to individual mice were due mainly to special experimental conditions. Mice were selected for infusion or injection on the basis of tumor size rather than body weight. Moreover, the volumes of individual

* Abbreviations: BNCT, boron neutron capture therapy; ESR, electron spin resonance; BSH, $(B_{12}H_{11}SH)^{2-}$; BSSB, $(B_{12}H_{11}S—SB_{12}H_{11})^{4-}$ or $(B_{24}H_{22}S_2)^{4-}$; and LET, linear energy transfer.

Table 1. Comparison of boron concentrations in mouse blood, cerebrum and melanoma after prompt intraperitoneal injection of a sulfhydryl borane or its disulfide dimer

Mouse group	Time after injection (hr)	Mouse number	Injected boron dose (μg/g body wt)	Boron concentration (μg/g wet wt)		
				Cerebrum†	Blood	Melanoma
			Sulfhydryl borane: $Na_2(B_{12}H_4SH)$			
A	6	1	34	6.5 [6.4]	4.9 [5.0]	19.5 [20.1]
		2	37	" "	0 [0]	6.5 [6.1]
		3	36	8.1 [7.9]	6.5 [6.3]	0 [0]
B	12	1	38	3.2 [3.2]	0 [0]	8.1 [7.5]
		2	33	" "	2.7 [2.9]	8.4 [8.9]
		3	36	9.7 [9.4]	0 [0]	0 [0]
C	24	1	36	5.4 [5.4]	3.2 [3.1]	8.6 [8.4]
		2	34	" "	9.2 [9.5]	5.9 [6.1]
		3	34	3.2 [3.3]	2.2 [2.3]	4.3 [4.4]
			Disulfide borane: $Na_4(B_{12}H_{11}S—SB_{12}H_{11})$			
D	6	1	36	1.3 [1.3]	10.4 [10.1]	10.0 [9.7]
		2	36	" "	10.4 [10.1]	8.4 [8.2]
		3	36	1.1 [1.1]	11.3 [11.0]	10.9 [10.6]
		4	36	" "	12.4 [12.1]	10.9 [10.6]
		5	36	2.1 [2.0]	13.9 [13.5]	12.8 [12.4]
		6	36	" "	12.5 [12.2]	—
		7	36	1.4 [1.4]	14.4 [14.0]	—
		8	36	" "	11.6 [11.3]	—
E	12	1	36	1.5 [1.5]	4.4 [4.3]	13.3 [12.9]
		2	36	" "	4.7 [4.6]	9.4 [9.1]
		3	36	0.6 [0.6]	6.1 [5.9]	14.3 [13.9]
		4	36	" "	4.7 [4.6]	7.4 [7.2]
		5	36	0.4 [0.4]	4.4 [4.3]	12.1 [11.8]
		6	36	" "	—	15.8 [15.4]
F	12	1	30	5.9 [7.1]	0 [0]	3.2 [3.7]
		2	28	" "	2.7 [3.4]	10.0 [12.5]
		3	32	1.6 [1.8]	10.3 [11.3]	5.9 [6.4]
G	24	1	36	0.9 [0.9]	2.5 [2.4]	7.1 [6.9]
		2	36	" "	2.3 [2.2]	7.3 [7.1]
		3	36	1.7 [1.7]	3.2 [3.1]	8.8 [8.6]
		4	36	" "	3.2 [3.1]	12.8 [12.4]
H	24	1	29	8.1 [9.3]	3.2 [3.9]	9.0 [10.9]
		2	32	" "	0 [0]	7.0 [7.7]
		3	32	0 [0]	1.6 [1.8]	13.5 [14.8]

Boron concentrations in square brackets are the observed concentrations multiplied by a normalization factor based on linear extrapolation to the average injected dose of 35 μg/g body wt. The normalization factor is [35/boron dose].

* Ditto marks in the "Boron Concentration—Cerebrum" column indicate that the concentration was measured by combining the cerebra of two mice.

osmotic pumps varied slightly and only became known gravimetrically, by tare, after each pump had been filled completely and sealed. Since the sodium salts of BSH and BSSB are hydroscopic, the exact boron content of a lyophilized batch of Na_4BSSB or Na_2BSH was determined only after the borane was dissolved in water and measured by prompt gamma spectroscopy at the Brookhaven National Laboratory Medical Research Reactor. The residual boron in each pump was measured by prompt gamma spectroscopy of a 1-ml aliquot from 4 ml of water with which each used pump was slowly equilibrated after removal from the peritoneal cavity of the mouse. Calibration of the prompt gamma analytical system for ^{10}B determinations was performed on each day of measurement at the Brookhaven Medical Research Reactor using U.S. National Bureau of Standards ^{10}B-enriched boric acid.

Discussion

In mouse groups A–H (Table 1), the dose of boron in Na_4BSSB and in Na_2BSH was chosen so as to be below the maximum tolerable dose of boron in Na_2BSH which can be administered rapidly to mammals [7]. It was reasoned that prompt injection of higher doses of boron as Na_2BSH or as Na_4BSSB might entail a risk of toxicity. Slow infusion of Na_4BSSB (Tables 2 and 3) may provide a better prospect than does rapid injection (Table 1) for obtaining sufficiently large concentrations of boron in tumor (>20 μg B/g) and sufficiently large [17] tumor–blood and tumor–cerebrum boron concentration differences for BNCT. The summary of statistical analyses in Table 4 shows that Na_4BSSB yielded larger tumor–blood boron concentration differences than did Na_2BSH when each was administered at

Table 2. Comparison of boron concentrations in mouse blood, cerebrum and melanoma from slow intraperitoneal infusion of a sulfhydryl borane or its disulfide dimer

Mouse group	Duration of infusion (hr)	Pump flow rate (μl/hr)	Mouse number	Total boron dose (μg/g body wt)	Boron concentration at end of infusion (μg/g wet wt)		
					Cerebrum*	Blood	Melanoma
				Sulfhydryl borane: $Na_2(B_{12}H_{11}SH)$			
I	219	1.04	1	225	0.5 [0.5]	1.6 [1.4]	3.8 [3.4]
		1.00	2	211	" "	7.8 [7.4]	10.9 [10.3]
		0.94	3	185	0.7 [0.7]	9.2 [10.0]	10.8 [11.7]
		1.04	4	194	" "	4.0 [4.1]	7.9 [8.1]
		0.99	5	190	2.4 [2.5]	4.9 [5.2]	9.2 [9.7]
J	234	1.01	1	271	3.2 [2.5]	14.1 [10.4]	13.0 [9.6]
		0.93	2	250	" "	3.8 [3.0]	— [—]
		0.99	3	265	3.2 [2.3]	4.9 [3.7]	14.1 [10.6]
		0.99	4	281	" "	8.1 [5.8]	15.1 [10.8]
K	190	0.99	1	208	— [—]	20.5 [19.7]	10.8 [10.4]
		0.99	2	190	— [—]	15.1 [15.9]	14.0 [14.7]
		0.91	3	169	7.0 [8.1]	11.9 [14.1]	11.4 [13.5]
		0.93	4	179	" "	5.4 [6.0]	14.1 [15.8]
L	219	0.95	1	187	0.7 [0.7]	6.0 [6.4]	6.5 [7.0]
		1.03	2	192	" "	4.2 [4.4]	6.8 [7.1]
		1.00	3	166	1.2 [1.3]	3.8 [4.6]	8.8 [10.6]
		1.04	4	201	" "	5.7 [5.7]	9.5 [9.5]
				Disulfide borane: $Na_4(B_{12}H_{11}S—SB_{12}H_{11})$			
M	216	1.01	1	302	2.3 [1.5]	5.3 [3.5]	23.3 [15.4]
		1.02	2	302	" "	3.2 [2.1]	20.4 [13.5]
		1.01	3	295	5.6 [4.0]	2.5 [1.7]	26.6 [18.0]
		1.00	4	261	" "	3.6 [2.8]	25.1 [19.2]
N	238	0.99	1	272	4.9 [3.6]	6.5 [4.8]	23.2 [17.1]
		0.98	2	269	" "	4.3 [3.2]	14.1 [10.5]
		0.97	3	267	5.4 [4.2]	3.2 [2.4]	30.3 [22.7]
		0.90	4	254	" "	3.8 [3.0]	26.5 [20.9]

Concentrations in square brackets are the observed concentrations multiplied by a normalization factor which extrapolates linearly the actual boron dose (listed in column 5) to a reference dose of 200 μg boron/g of body wt. The normalization factor is [200/boron dose].

* Ditto marks in the "Boron Concentration—Cerebrum" column indicate that the concentration was measured by combining the cerebra of two mice.

a standard whole body dose of boron. To our knowledge, such favorable boron concentrations as are listed in Tables 2 and 3 for Na_4BSSB have not been described to date for any other boronated substance injected or infused *in vivo* into mammals. Thus, Na_4BSSB might prove preferable to Na_2BSH (currently in clinical use [8, 9]) as a boron transport agent for BNCT of brain tumors if Na_4BSSB proves to be not excessively toxic to patients.

It should also be mentioned that the accumulation of boron from Na_4BSSB by normal tissues other than brain, notably by liver and kidney (data not shown), was substantial. It seems possible that uptake of Na_4BSSB may be a non-specific attribute of tumors and of a variety of normal tissues which lack a blood–brain barrier. Thus, the potential usefulness of this ^{10}B carrier for BNCT of extracranial neoplasms appears questionable. Preliminary study of Na_4BSSB infused into rats suggests that most of the resultant boron in blood is associated with plasma proteins rather than with blood cells. Thus, some type of plasma exchange might be done to lower the plasma boron concentration before Na_4BSSB-mediated BNCT of human malignant gliomas is performed. This would decrease substantially the inevitable radiation damage to normal brain endothelial cells that occurs during radiation therapy of a brain tumor.

Slow uptake of $Na_4B_{24}H_{22}S_2$ by a melanoma apparently is not followed by much loss of boron from the tumor during the first 3 days after infusion has ceased (Table 3). However, the blood concentration of boron seemed to decline during the same 3-day interval. This offers the potential benefit of using a low radiation dose rate to allow repair of damage from the poorly localized low LET radiations associated with BNCT [17]. Moreover, comparison of Table 1 with Tables 2 and 3 suggests that tumor–blood and tumor–cerebrum boron concentration differences are more favorable after $Na_4B_{24}H_{22}S_2$ is infused slowly than after it is injected rapidly.

The uptake of boron from $Na_4B_{24}H_{22}S_2$ into a subcutaneous transplanted mouse mammary carcinoma was comparable to the uptake of boron into the Harding–Passey melanoma when similar doses of the disulfide were administered via the Alza intraperitoneal osmotic pumps.* This suggests that the affinity of BSH and BSSB to melanoma may not necessarily be related to the presence of melanin in the tumor, which encourages further investigation of the affinity of sulfhydryl boranes to brain tumors.

* D. N. Slatkin, P. L. Micca, A. Forman, D. Gabel, L. Wielopolski and R. G. Fairchild, in *Proceedings of the Second International Symposium on Neutron Capture Therapy*, Teikyo University, Tokyo, Japan, Oct. 18–20, 1985 (to be published).

Table 3. Comparison of boron concentrations in mouse blood, cerebrum and melanoma, measured by prompt gamma spectroscopy from the $^{10}B(n, \alpha\gamma)^{7}Li$ reaction 6, 9 or 12 days after implantation of an intraperitoneal osmotic pump containing a sulfhydryl borane or its disulfide dimer

Mouse group	Time after implantation (hr)	Mouse number	Pump flow rate* (μl/hr)	Total boron dose (μg/g body wt)	Boron concentration at time after implantation (μg/g wet wt)		
					Cerebrum†	Blood	Melanoma
			Sulfhydryl borane: $Na_2(B_{12}H_{11}SH)$				
P	144	1	1.05	147	1.9 [2.6]	4.1 [5.6]	0 [0]
		2	1.03	145	" "	5.5 [7.6]	6.0 [8.3]
		3	0.99	131	0.6 [0.9]	5.5 [8.4]	6.6 [10.1]
		4	1.00	146	" "	7.4 [10.1]	9.7 [13.3]
		5	0.98	130	0 [0]	5.7 [8.8]	9.5 [14.6]
		Average concentrations:			0.8 [1.2]	5.6 [8]	6.4 [9.3]
Q	213	1	0.90	164	1.2 [1.5]	5.3 [6.5]	7.6 [9.3]
		2	0.87	159	" "	5.4 [6.8]	8.6 [10.8]
		3	1.08	188	1.7 [1.9]	3.3 [3.5]	8.2 [8.7]
		4	0.87	167	" "	4.6 [5.5]	11.7 [14.0]
		5	0.86	178	0 [0]	4.5 [5.1]	6.5 [7.3]
		Average concentrations:			1.0 [1.1]	4.6 [5.5]	8.5 [10.0]
R	288	1	—	231	2.8 [2.4]	0.5 [0.4]	7.6 [6.6]
		2	—	232	" "	0.3 [0.3]	6.3 [5.4]
		3	—	217	2.1 [1.8]	0 [0]	7.8 [7.2]
		4	—	258	" "	0 [0]	7.2 [5.6]
		5	—	222	0.3 [0.3]	0 [0]	7.2 [6.5]
		Average concentrations:			1.7 [1.5]	0.2 [0.1]	7.2 [6.3]
			Disulfide borane: $Na_4(B_2H_{11}S—SB_{12}H_{11})$				
S	144	1	1.05	144	0.6 [0.8]	3.6 [5.1]	12.4 [17.6]
		2	0.97	153	" "	5.3 [6.9]	12.0 [15.7]
		3	0.94	137	0 [0]	5.2 [7.6]	12.7 [18.5]
		4	1.06	153	" "	3.5 [4.6]	12.8 [16.7]
		5	0.96	137	2.9 [4.2]	2.6 [3.8]	6.6 [9.6]
		Average concentrations:			1.2 [1.7]	4.0 [5.6]	11.3 [15.6]
T	213	1	0.86	147	2.1 [2.5]	1.4 [1.9]	7.1 [9.7]
		2	0.88	184	" "	2.3 [2.5]	12.2 [13.3]
		3	1.06	201	1.7 [1.8]	5.4 [5.4]	—
		4	0.91	172	" "	3.7 [4.3]	12.8 [14.9]
		5	0.93	158	1.4 [1.8]	4.5 [5.7]	12.6 [16.0]
		Average concentrations:			1.7 [2.0]	3.5 [4.0]	11.2 [13.5]
U	288	1	—	236	4.0 [3.4]	0 [0]	15.8 [13.4]
		2	—	236	" "	0.4 [0.3]	9.5 [8.1]
		3	—	208	3.3 [3.1]	2.2 [2.1]	18.9 [18.2]
		4	—	221	" "	0 [0]	13.9 [12.6]
		5	—	234	1.1 [0.9]	0 [0]	13.1 [11.2]
		Average concentrations:			2.8 [2.5]	0.5 [0.5]	14.2 [12.7]

Concentrations in square brackets are the observed boron concentrations at the indicated times after implantation multiplied by a normalization factor which extrapolates the actual total boron dose (listed in column 5) to a reference dose of 200 μg boron/g of body wt. In this table, extrapolation is linear and the normalization factor is [200/boron dose].

* For groups R and U, pump flow rates were not measured individually. However, these pumps were from the same manufacturer's batch as were the pumps used for groups P, Q, S and T. The duration of flow from these pumps was about 9 days, but they were removed 12 days after their insertion into mice.

† Ditto marks in the "Boron Concentration—Cerebrum" column indicate that the concentration was measured by combining the cerebra of two mice.

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Table 4. Summary of statistical tests of data in Tables 1, 2 and 3

Hypothesis tested	Parametric test (Student's *t*-test)	Non-parametric test (Wilcoxon two-sample test)
[Data from Table 1]		
$d_{BSSB} > d_{BSH}$		
. . . . 6 hr after prompt intraperitoneal injection of either BSSB or BSH?	No	No
. . . . 12 hr after prompt intraperitoneal injection of either BSSB or BSH?	No	No
. . . . 24 hr after prompt intraperitoneal injection of either BSSB or BSH?	Yes, $P \leq 0.025$	Yes, $P \leq 0.05$
[Data from Table 2]		
9 ± 1 days after the start of continuous intraperitoneal infusion of either BSSB or BSH		
. . . . $d_{BSSB} > d_{BSH}$?	Yes, $P \leq 0.0005$	Yes, $P \leq 0.0005$
. . . . $d_{BSSB} - d_{BSH} \geq 8.5$ μg B/g?	Yes, $P \leq 0.025$	Yes, $P \leq 0.05$
[Data from Table 3]		
6 days after the start of continuous intraperitoneal infusion of either BSSB or BSH		
. . . . $d_{BSSB} > d_{BSH}$?	Yes, $P \leq 0.005$	Yes, $P \leq 0.025$
. . . . $(d_{BSSB} - d_{BSH}) \geq 4.6$ μg B/g?	Yes, $P \leq 0.05$	Yes, $P \leq 0.05$
9 days after the start of continuous intraperitoneal infusion of either BSSB or BSH		
. . . . $d_{BSSB} > d_{BSH}$?	Yes, $P \leq 0.005$	Yes, $P \leq 0.025$
. . . . $(d_{BSSB} - d_{BSH}) \geq 2.0$ μg B/g?	Yes, $P \leq 0.025$	Yes, $P \leq 0.05$
3 days after the end of a 9-day continuous intraperitoneal infusion of either BSSB or BSH		
. . . . $d_{BSSB} > d_{BSH}$?	Yes, $P \leq 0.005$	Yes, $P \leq 0.005$
. . . . $(d_{BSSB} - d_{BSH}) \leq 2.6$ μB/g?	Yes, $P \leq 0.025$	Yes, $P \leq 0.05$

Comparison of differences between normalized boron concentrations in tumor (C_t) and in blood (C_b) after administration of Na_2BSH ($d_{BSH} = C_t - C_b$) or of Na_4BSSB ($d_{BSSB} = C_t - C_b$). In the analyses of data from Tables 2 and 3, the significance of various positive values of the difference ($d_{BSSB} - d_{BSH}$) was tested repeatedly by the Wilcoxon two-sample test. The particular values of the difference which yielded a P value of 0.05 or less by a Wilcoxon test are listed as 8.5, 4.6, 2.0 or 2.6 μg B/g in the column named "Hypothesis tested".

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