

Evaluation of novel boron compound for boron neutron capture therapy using rat brain tumor model

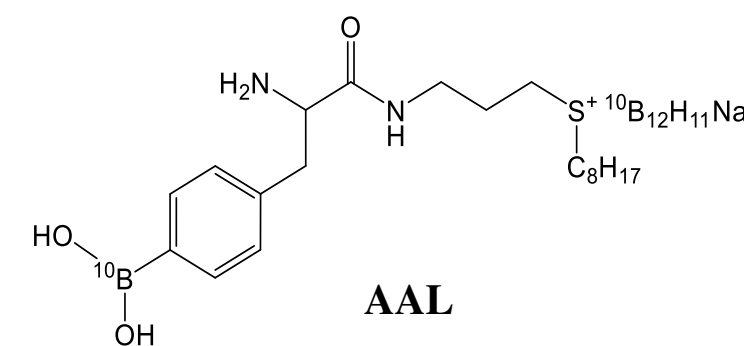
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【Introduction】

Glioblastoma (GBM) is resistant to all currently available therapies, including surgery, radiotherapy, and chemotherapy, has a median survival time of less than 2 years. Because malignant glioma cells are highly infiltrated into the normal brain parenchyma.

Boron Neutron Capture Therapy (BNCT) is expected as a therapeutic method to selectively destroy tumor cells. Although BNCT demonstrates high therapeutic effect when applied with the existing drugs (boronophenylalanine; BPA, borocaptate sodium; BSH), it is not yet satisfactory. We developed new boron compound (**AAL**) that combines the characteristics of BPA and BSH, which has a boron cluster in its structure and targets an amino acid transporter.

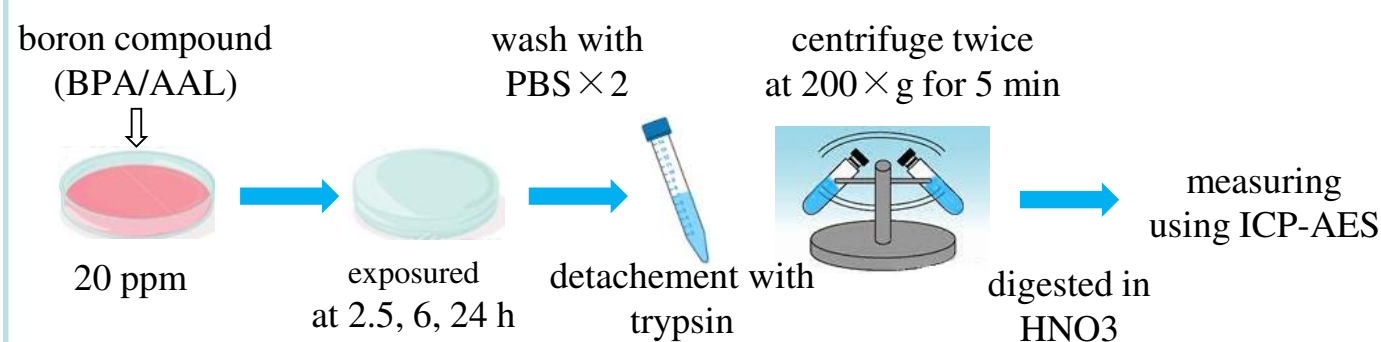


【Material & Methods】

In vitro

• Intracellular uptake of ¹⁰B in F98 glioma cells

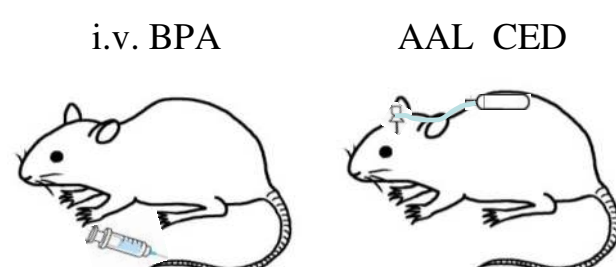
After F98 rat glioma cells incubation for 72 h, the medium was exchanged for boron compounds containing 5 μg ¹⁰B/mL of BPA, AAL in the culture medium, and the cells were cultured for 2.5, 6, and 24 h.



In vivo

• ¹⁰B biodistribution study in F98 glioma bearing rats

After 12 days of tumor implantation, F98 glioma-bearing rats were administered with each of the boron compounds (i.v. BPA or AAL(CED: Convection Enhanced Delivery)).

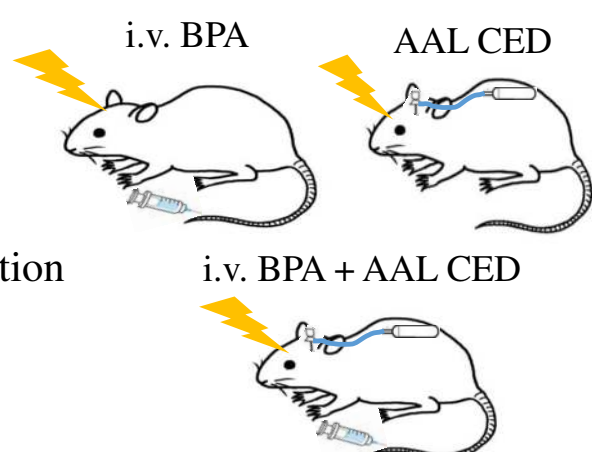


• BNCT study

F98 glioma bearing rats were irradiated (at 1 MW for 1 h) at 14 days after the implantation of 10³ F98 glioma cells.

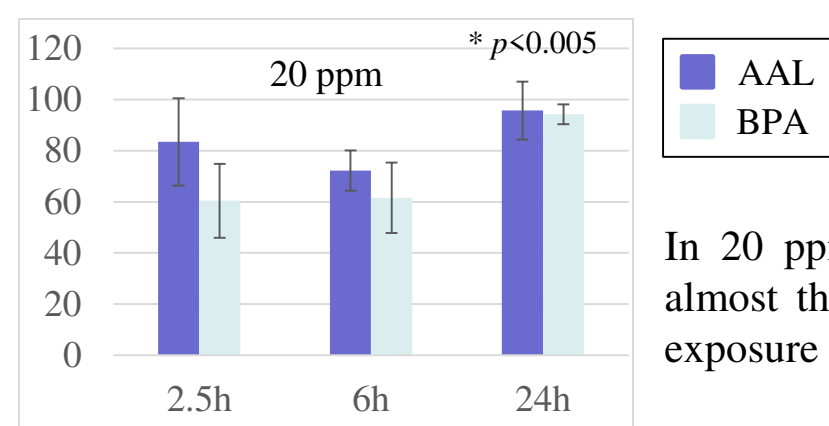
The therapeutic effect was evaluated in terms of the survival time for all rats.

- ① untreated controls
- ② irradiation controls
- ③ AAL CED controls
- ④ i.v. BPA 2h + irradiation
- ⑤ AAL CED 6h + irradiation
- ⑥ AAL CED 6h + i.v. BPA 2h + irradiation



【Result】

Intracellular uptake of boron in F98 glioma cells



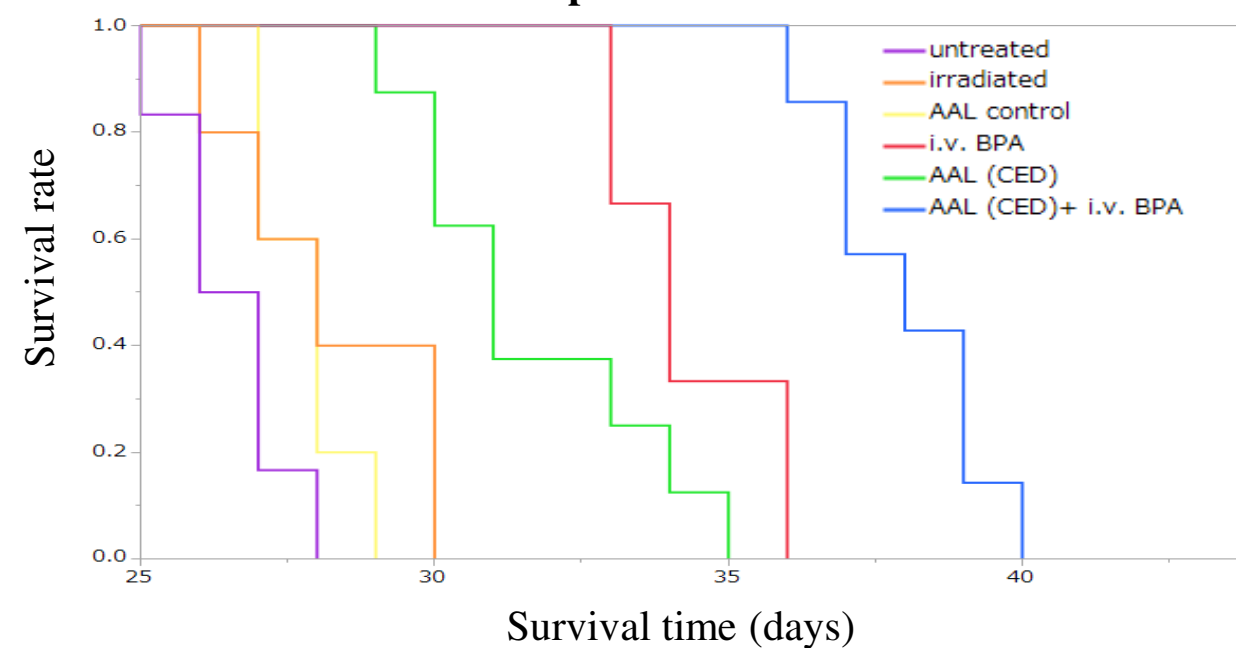
In 20 ppm, AAL and BPA showed almost the same concentration at all exposure times.

Boron Concentrations in brain tumors in F98 Glioma Bearing Rats

Time (h)	n	Boron concentrations ± SD (μg ¹⁰ B/g)				Ratios ^a		
		Tumor	Ipsilateral Brain	Contralateral Brain	Blood	T/Br	T/BI*	
AAL (1000ppm) CED (200μl/24h)	2	3	41.5 ± 13.2	1.4 ± 0.5	0.5 ± 0.3	0.6 ± 0.1	30.4	76.0
	6	2	59.9 ± 18.2	2.9 ± 0.5	1.3 ± 0.9	0.4 ± 0.1	20.9	162.5
	24	3	25.1 ± 26.6	0.9 ± 0.3	0.2 ± 0.1	0.2 ± 0.01	27.9	141.5
BPA (1000ppm) iv	2	3	19.9 ± 1.0	6.4 ± 1.4	4.7 ± 0.9	9.9 ± 3.2	3.1	2.0
	6	3	17.0 ± 1.3	4.8 ± 0.4	4.5 ± 1.0	7.0 ± 0.5	3.6	2.4

AAL CED group : 1.2 mg¹⁰B/kg b.w. ^aT/Br: the tumor to normal brain ratio, T/BI: the tumor to blood ratio
 i.v. BPA group : 12 mg¹⁰B/kg b.w.

Kaplan-Meier



Agent	Route	Time (h)	Physical dose (Gy)		Equivalent dose (Gy-eq)	
			Brain	Tumor	Brain	Tumor
BPA	i.v.	2	1.6	3.7	-	10.5

RBE: 3.0, CBE: 3.1

【Discussion】

AAL (CED) and i.v. BPA combined group had a significant survival prolongation compared with single agent group. It is thought that AAL irradiated by thermal neutron had cell killing effect on cells in which BPA was not taken up.

【Conclusion】

The combination use of AAL (CED) provides additional BNCT effects. The mechanism by which AAL is incorporated has not been clarified, and further experiments are needed.