

Effect of L-¹⁰B-*p*-Boronophenylalanine-fructose and the Boron Neutron Capture Reaction on Mouse Brain Dopaminergic Neurons¹

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ABSTRACT

Radiation damage to the dopamine tracts caused by enriched L-¹⁰B-*p*-boronophenylalanine (L-¹⁰BPA)-fructose and the boron neutron capture reaction was investigated using the mouse model. Following various treatments with L-¹⁰BPA and neutron irradiation of the head, the brain was perfusion fixed and removed; 50- μ m frozen sections were cut. Dopaminergic neurons were visualized using immunohistochemistry for tyrosine hydroxylase. The administration of L-¹⁰BPA had no permanent effect on dopaminergic tracts. Neutron capture therapy with L-¹⁰BPA caused a reduction in tyrosine hydroxylase immunohistochemical activity within 4 h of irradiation, but by 48 h, this reduction reversed. No damage was observed at 120 h postirradiation.

INTRODUCTION

BNCT³ is a binary treatment for cancer which combines neutron irradiation with a tumor-seeking, boron-containing drug in an attempt to kill tumor cells without serious damage to normal cells. The amino acid melanin precursor analogue, BPA, has been tested previously in melanoma-bearing animals (1, 2) and used in a clinical trial of BNCT (3). In the case of melanoma, it is a rational biochemical approach to load the tumor with this precursor analogue, since melanin is synthesized from the amino acid phenylalanine. However, it has been found that BPA can selectively accumulate in tumors other than melanoma, *e.g.*, in a murine mammary adenocarcinoma, rat glioma, and a xenografted human glioma (4). The use of BPA has, therefore, been proposed for BNCT of high-grade brain cancer, since it can penetrate the BBB, so that it is possible to load the required concentration of boron into the tumor cells. Pharmacokinetic studies of D,L-BPA-fructose have been performed in human patients with melanoma or glioma, and uptake into these cerebral tumors was found to be adequate (5). Before human trials of BNCT can be commenced, an important safety consideration should be resolved in that BPA may also be a precursor for the catecholamine neurotransmitters. Therefore, it is important to determine whether BPA will accumulate in the catecholamine-containing neurons in the brain. If this does occur, unwanted radiation side effects could arise when the concentration of ¹⁰B in the nervous system is of the same order of magnitude as that in the cancer site.

Catecholamines were first localized in specific brain pathways in 1964 (6). The organization of the central dopaminergic system is considerably more complex than the main central noradrenergic system, which largely emanates from a small cell cluster. Not only are there many more dopaminergic neurons in the brain, but there are also several major regions containing dopaminergic neurons. These separate neuronal populations specialize in a diverse range of important

brain functions including emotional behavior, motor coordination, and the secretion of various hypothalamic and pituitary hormones.

Dopamine synthesis, like that of all catecholamines in the nervous system, originates from the amino acid precursors phenylalanine and tyrosine, which must be transported across the BBB into the neuron. The rate-limiting step in catecholamine synthesis is the conversion of L-tyrosine to L-dihydroxyphenylalanine by the enzyme tyrosine hydroxylase (TH) (7). This step could be affected by BPA and BNCT.

To test the hypothesis that BPA accumulates in central catecholaminergic neurons which would then be affected by the neutron capture reaction, a two-phase study was initiated. Phase I was an investigation of the effect of L-¹⁰BPA on central dopaminergic neurons and fibers, and Phase II was an investigation of the effect of L-¹⁰BPA and BNCT on central dopaminergic neurons and fibers. In addition, histochemistry was used to evaluate the effects of such treatments on central myelination and on the BBB.

MATERIALS AND METHODS

All chemicals used were of analytical grade, and reagent solutions were prepared in Millipore-filtered water. L-BPA 95% enriched in ¹⁰B (Boron Biologicals, Inc.) was added to 0.3 M fructose and titrated with 5 M NaOH to obtain a solution of L-¹⁰BPA-fructose at pH 8, with final concentrations 12 mg/ml or 32 mg/ml in terms of L-¹⁰BPA. A 1% (w/v) washing solution of NaNO₂ in 0.1 M phosphate buffer (pH 7.4) and a 4% (v/v) fixative solution of formaldehyde in 0.1 M phosphate buffer (pH 7.4) was prepared. For immunohistochemistry, normal horse serum was obtained from CSL Ltd., Australia, and the antibody to tyrosine hydroxylase was purchased from Incstar Corp., Australia. Biotinylated anti-mouse IgG and Vectastain ABC kit was purchased from Vector Laboratories, Inc., and 3,3'-diaminobenzidine tetrahydrochloride was obtained from Sigma Chemical Co. The standard histochemical stains, Luxol fast blue and hematoxylin and eosin, were purchased from Gurr Chemicals. This study was approved by the animal ethics committee of the University of Sydney.

Boron Analysis in Brain Samples

Animals. Three adult BALB/c mice (6-8 weeks) weighing 25-30 g were given an i.p. injection (1 ml) of L-¹⁰BPA-fructose (12 mg of L-¹⁰BPA/mouse). The mice were sacrificed 1.5 h after administration of the drug, and the brains were dissected out for boron analysis.

Boron Analysis. Gross boron analysis in brain samples were performed by inductively coupled plasma-atomic emission spectroscopy after tissue digestion in perchloric acid/hydrogen peroxide, according to the method described previously (9). Specific boron localization in the brain was analyzed with neutron capture radiography as described (10).

Immunohistochemistry

In this study, central dopaminergic neurons were visualized using the indirect ABC avidin-biotin immunohistochemical method (8).

Tissue Preparation. The mice were deeply anaesthetized by an i.p. injection of sodium pentobarbitone (20 mg/kg). After sedation, the chest cavity was opened, and a catheter was inserted into the left ventricle of the heart. Following washing out of the blood, fixative was perfused through the body for 30 min. Drainage occurred through the cut right atrium. The head was removed, and the brain was dissected. The brains were stored in fixative solution at 4°C until histological examination.

Received 10/28/94; accepted 12/19/94.

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¹ This work was supported in part by the Australian Institute of Nuclear Science and Engineering, the Government Employees Assistance to Medical Research Fund, the National Health & Medical Research Council, and the Australian Research Council.

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³ The abbreviations used are: BNCT, boron neutron capture therapy; BBB, blood brain barrier; BPA, *p*-boronophenylalanine; H&E, hematoxylin and eosin; LFB, Luxol fast blue; NCT, neutron capture therapy; TH, tyrosine hydroxylase; THIR, TH-immunoreactive.

Staining Protocol. Brains were cryoprotected in 30% sucrose in 0.1 M Tris-phosphate buffer (pH 7.4) for 24 h prior to cutting at 50 μ m on a Leitz freezing microtome. Sequential sections were allocated into three pots. The first series of sections were stained with Luxol fast blue (LFB) for myelin. The second series were stained with H&E for histopathology. The third series of sections were stained immunohistochemically with antibodies to tyrosine hydroxylase (the rate-limiting enzyme for catecholamine synthesis). Briefly, the immunohistochemical protocol was as follows. Sections were washed in 50% ethanol, then with 3% H₂O₂ in 50% ethanol to quench endogenous peroxidase activity, prior to incubation in 10% normal horse serum for 1 h to absorb nonspecific binding sites. Sections were incubated in the antibody for tyrosine hydroxylase for 24 h at 4°C. The next day, sections were incubated successively in biotinylated anti-mouse IgG for 1 h and Vectastain ABC for 1 h, with washing in buffer between incubations. Specific staining was visualized with 3,3'-diaminobenzidine tetrahydrochloride and H₂O₂. As a negative control, in one case the primary antibody was omitted, with no resultant staining of tissue.

Phase I

Animals. Adult male BALB/c mice (6–8 weeks) weighing 25–30 g were randomly allocated into three groups. Group A (three mice) was an untreated control group. Groups B and C (three mice/group) were each given an i.p. injection of L-¹⁰BPA-fructose (32 mg of L-¹⁰BPA/mouse). The mice were anaesthetized and perfused at either 4 h (groups A and B) or 48 h (group C) after administration of the drug.

Phase II

Animals. Adult BALB/c mice (6–8 weeks) weighing 25–30 g were separated into five groups of six (groups D–H). In each group, three mice were given an i.p. injection (1 ml) of L-¹⁰BPA-fructose (12 mg of L-¹⁰BPA/mouse), while the other three were given i.p. 1 ml of saline solution.

Irradiation. Thermal neutron irradiations were undertaken at the BNCT facility of the 100 kW Argonaut reactor (Moata) Lucas Height Research Laboratories, operated by the Australian Nuclear Science and Technology Organisation. Irradiations with thermal neutrons were commenced at 1.5 h after the drug (or saline) was administered to the mice. The reactor facility and neutron dosimetry has been reported previously (1). The animal irradiation capsule described formerly for mouse leg irradiation was modified so that only the head of the mouse received the full thermal neutron radiation dose. All mice were anaesthetized using ketamine and xylazine before loading into the irradiation capsule. The first three groups (groups D, E, and F) were given a single dose of L-¹⁰BPA-fructose and a single dose of neutron radiation at a nominal fluence of 10¹³ n/cm² (irradiation time, 22 min). They were anaesthetized and perfused at 4 (group D), 48 (group E), and 120 h (group F), respectively, after the radiation. Groups G and H were given two and four doses of L-¹⁰BPA-fructose, followed by neutron irradiations with 24-h intervals between irradiations. The mice were anaesthetized and perfused at 4 h after the last radiation treatment.

RESULTS

Boron Analysis and Neutron Dosimetry. Gross boron concentration in the brain measured by the inductively coupled plasma-atomic emission spectroscopy method (9) was found to be 4.6 \pm 1.3 ppm. In order to examine whether there was any specific localization of L-¹⁰BPA into dopaminergic neurons, neutron capture radiography (10) was used. It was found that this concentration of boron could not be detected with the methodology used. The absorbed radiation dose in the brain from ¹⁰B(n, α)⁷Li reaction, based on the dosimetry calculation of Allen *et al.* (1), is 0.883 Gy/ppm ¹⁰B/10¹³ n/cm², and for an average ¹⁰B concentration of 4.6 ppm, the dose is equal to 4.0 Gy. In addition, there is concomitant radiation from hydrogen ¹H(n, γ) and nitrogen ¹⁴N(n,p) neutron capture reactions, as well as the reactor γ -ray component. The BNCT facility in the Moata reactor, for one irradiation in this experiment with no boron in the tissue, gives a radiation dose of 4.4 Gy. The total radiation dose to the brain is the

sum of non-boron and boron doses, *i.e.*, 4.4 Gy + 4.0 Gy = 8.4 Gy. BNCT with this average boron concentration was sufficient to cause the transient changes identified.

Phase I: Effect of L-¹⁰BPA-fructose. L-¹⁰BPA did not affect the normal architecture of the brain as evidenced in myelin and H&E stains. No behavioral abnormalities were noted in animals injected with L-¹⁰BPA-fructose. The outcome of the histological staining of the mouse brain sections is summarized in Table 1. There were no significant differences with respect to cell count and staining intensity in the appearance of THIR neurons after dosing mice with 32 mg of L-¹⁰BPA, compared with untreated controls. In addition, no histopathological changes were observed in either group using LFB and H&E. However, changes were identified in the terminal fields of the THIR neurons, in that THIR fiber staining was absent in the olfactory tubercle, and only light staining was observed in the accumbens nucleus of group B mice compared with groups A or C. Therefore, staining was perturbed at 4 h after injection but recovered by 48 h. In contrast, the hippocampus and arcuate nucleus appeared more densely innervated in group B, compared with groups A and C.

Phase II: Effect of L-¹⁰BPA-fructose and the Boron Neutron Capture Reaction. Table 2 summarizes the histological response to BNCT. There was no histological evidence of radiation-induced damage to the nervous tissue, myelin, or blood vessels in the brain sections. Mice behaved normally throughout the experiment period, except for the first one h after irradiation when they were under the influence of anaesthesia or under the influence of a syndrome characterized by depression of neural function (11, 12). There was a reduced cell count and staining intensity of THIR neurons in groups D, G, and H. Therefore, 4 h after single or multiple doses of L-¹⁰BPA and irradiation there was a significant reduction in THIR of the dopaminergic neurons. In contrast, THIR neurons in groups E and F mice had no decrease in THIR of the dopaminergic neurons. Therefore, the BNCT effect is reversible by 48 h. Fig. 1 shows THIR cell bodies within the midbrain of mice from groups D and F.

Table 1 Summary of histological staining outcomes for animals treated with L-¹⁰BPA-fructose^a

Animal group	L- ¹⁰ BPA (mg/mouse)	Perfusion time (h after L- ¹⁰ BPA)	Anti-TH on cell-body	Anti-TH on cell-terminal	H&E	LFB
A	0	4	+++	+++	+++	+++
B	32	4	+++	+	+++	+++
C	32	48	+++	+++	+++	+++

^a The qualitative cell count and staining intensity in the samples is shown based on +++ as the normal or control response.

Table 2 Summary of histological staining outcomes for animals treated with L-¹⁰BPA-fructose and neutron irradiation^a

Animal group	L- ¹⁰ BPA (mg/mouse)	No. of irradiation exposures	Perfusion time (h after irradiation)	Anti-TH on cell-body	Anti-TH on cell-terminal	H&E	LFB
D	12	1	4	+	+++	+++	+++
	0	1	4	+++	+++	+++	+++
E	12	1	48	+++	+++	+++	+++
	0	1	48	+++	+++	+++	+++
F	12	1	120	+++	+++	+++	+++
	0	1	120	+++	+++	+++	+++
G	2 \times 12	2	4	+	+++	+++	+++
	0	2	4	+++	+++	+++	+++
H	4 \times 12	4	4	+	+++	+++	+++
	0	4	4	+++	+++	+++	+++

^a The qualitative cell count and staining intensity in the samples is shown based on +++ as the normal or control response.

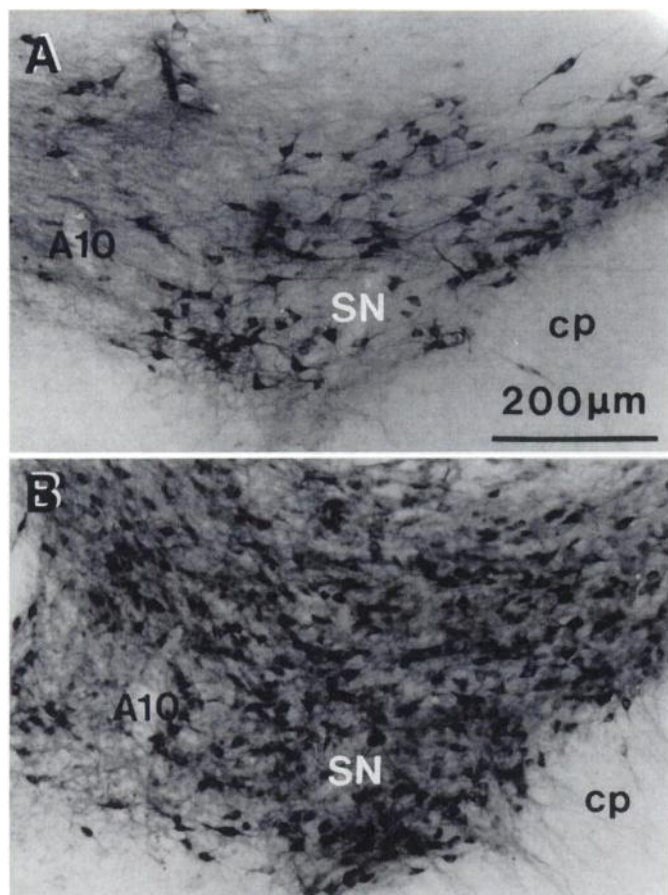


Fig. 1. THIR cell bodies within the midbrain of mice dosed with L - 10 BPA-fructose and irradiated with neutrons. A, 4 h after irradiation (group D). B, 120 h after irradiation (group F). A10, A10 group of dopaminergic cells; SN, substantia nigra; cp, cerebellar peduncle. The scale bar is equivalent for both A and B.

DISCUSSION

Our results suggest that L - 10 BPA crosses the BBB and transiently affects catecholamine-synthesizing pathways in the brain. There was no overt sign of radiation damage in the mice treated with the BNCT procedure. Irradiation induces programmed cell death, or apoptosis, a process which develops 3 to 96 h postirradiation and is characterized by typical cell morphology and fragmentation of chromatin (13, 14). Therefore, while our investigations covered only the short period of 4 to 120 h postirradiation, damage to dopaminergic structures would be expected to become evident within this time. Indeed, such effects, albeit reversible, are observed at 4 h with administration of a high dose of L - 10 BPA-fructose (32 mg L - 10 BPA/mouse) alone and also with the combination 12 mg/mouse L - 10 BPA-fructose and neutron irradiation.

Neurons are highly radiation insensitive because they do not undergo mitosis (15). The threshold for irreversible intracellular disruption during interphase is 50 Gy for the nucleus and 250 Gy for the cytoplasm (16), which exceeds the nominal maximum absorbed dose of 4×8.4 Gy applied in these experiments. Capillaries and oligodendrocytes are the dose-limiting organs of the brain, causing delayed tissue necrosis and demyelination of axons at single doses of 15–20 Gy. While these effects are important in radiation therapy, the objective of this work was to determine whether additional damage would be caused to central dopaminergic systems as a result of the use of L - 10 BPA in BNCT of brain tumors. The effects of BNCT on capillary damage is the subject of another investigation in our laboratories (17).

No other type of histological damage was observed in the brain sections stained with LFB or H&E, confirming previous reports. Morris *et al.* (18) reported no long-term effect in the spinal cord of rats after i.v. injections of 10 B-enriched sodium mercaptoundecahydrocloso-dodecaborate with neutron irradiation. Minimal histopathological changes were found following i.p. injections of L - 10 BPA-fructose to nude rats and a radiation dose sufficient to eradicate intracerebral melanoma (19).

The results of the Phase I study demonstrate that 32 mg L - 10 BPA-fructose caused a transient change in some terminal fields on THIR neurons in the mouse. THIR neurons within the olfactory tubercle and nucleus accumbens became nonimmunoreactive, but THIR neurons increased within the hippocampus and arcuate nucleus, although such changes appear reversible within 48 h. These effects were not observed within the neuronal somata and suggests that L - 10 BPA affects the proportion of insoluble to soluble TH in the terminal fields (20). In the second phase of the experiment, the L - 10 BPA dose was reduced to 12 mg/mouse, which eliminated this effect.

No effect on brain tissue was observed if neutron radiation was given without L - 10 BPA administration. However, in groups given both L - 10 BPA and neutron radiation, transient changes were observed. At 4 h after the irradiation, THIR neurons had a reduced staining intensity, which reverted to control levels by 48 h and remained normal until at least 120 h postirradiation. In the groups which were given two and four doses of L - 10 BPA and neutron radiation, it was found that the reduction in THIR neurons was more severe than if only a single dose was administered. These results suggest that L - 10 BPA combined with neutron irradiation directly affects catecholamine synthesis within central dopaminergic neurons. Using extraction and iodine oxidation of catecholamine from brain homogenate followed by spectrofluorimetry, Afonin *et al.* (21) revealed a 25–40% inhibition of TH activity in rat brain after 100 Gy electron radiation. Changes in brain enzyme activity with different qualities of ionizing radiation have also been documented (22, 23). Radiation rich in neutrons increased monoamine oxidase activity, but radiation rich in γ rays decreased this enzyme. Unlike monoamine oxidase activity, it appears that TH activity is not affected by the quality of radiation. Both high LET radiation (boron neutron capture reaction in this project) and low LET electron radiation (21) decrease TH activity, confirming past studies where altered motor behavior was also observed (12).

Conclusion. The administration of L - 10 BPA had no permanent effect on central dopaminergic neurons. Neutron capture therapy with L - 10 BPA caused a reduction in THIR within 4 h of irradiation. This reduction was reversed after 48 h and did not reappear up to 120 h. The possibility of longer term effects have not been investigated.

The time frame in these experiments are adequate for apoptosis to be manifest (10, 11); therefore, damage to dopaminergic structures should have become evident within this time. However, for blood boron concentrations and thermal neutron fluence at a level adequate for the control of s.c. melanoma by NCT, no evidence of specific damage to catecholaminergic pathways was found. Furthermore, for doses up to 4 times the therapeutic dose given over 4 days, no evidence of sustained damage to these pathways was observed. Thus, neutron capture therapy with L - 10 BPA appears to be a safe procedure in the mouse brain model.

ACKNOWLEDGMENTS

The assistance of Julia Mallesch, Haider Meriaty, and Martin Carolan is gratefully acknowledged.

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Cancer Res 1995;55:874-877.

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