Boron-Containing Compounds as Preventive and Chemotherapeutic Agents for Cancer

Romulus I. Scorei[1] and Radu Popa[2,*]

[1]*Dept. Biochemistry, University of Craiova, A.I. Cuza Street, no.13, Craiova, 200585, Romania;* [2]*Portland State University, 1719 SW, 10th Avenue, SB2 Room 246 Portland, OR, 97201, USA*

Abstract: In the last few years boron (B) compounds became increasingly frequent in the chemotherapy of some forms of cancer with high malignancy and of inoperable cancers. As more B-based therapy chemicals are developed it is necessary to review the correlation between B and the incidence of different forms of cancer, the biochemical and molecular mechanisms influenced by B and to explore the relevance of B in the chemoprevention of cancer. This minireview analyzes dietary and therapeuptic principles based on the chemistry of B compounds. We summarize studies correlating B-rich diets or B-rich environments with regional risks of specific forms of cancers, and studies about the utilization of natural and synthetic B-containing compounds as anticancer agents. We review mechanisms where B-containing compounds interfere with the physiology and reproduction of cancer cells. Types of cancers most frequently impacted by B-containing compounds include prostate, breast, cervical and lung cancer. Mechanisms involving B activity on cancer cells are based on the inhibition of a variety of enzymatic activities, including serine proteases, NAD-dehydrogenases, mRNA splicing and cell division, but also receptor binding mimicry, and the induction of apoptosis. Boron-enriched diets resulted in significant decrease in the risk for prostate and cervical cancer, and decrease in lung cancer in smoking women. Boron-based compounds show promising effects for the chemotheraphy of specific forms of cancer, but due to specific benefits should also be included in cancer chemopreventive strategies.

Keywords: Boron, cancer, chemotherapy, chemoprevention, diet.

INTRODUCTION

Boron (B) has well established biochemical and nutritional functions [1-3]. In the last few years B also became increasingly more frequent in some specific anticancer processes [4-6]. Uncertainty remains about using B-based chemicals as anticancer agents. Some recent reports advise against using some B-containing chemicals such as boric acid (BA) for the treatment of specific forms of cancer [7-10]. Numerous biological functions of B compounds are known. Boron is present in bacterial antibiotics such as tartrolon, borophycin, boromycin and aplasmomycin [11-13] and in the bacterial quorum sensing molecule *auto-inducer AI-2* [14]. Plants need B for growth, blooming, seed formation, and extract borate from soil using specialized transporters such as BOR1 [15]. In plants the rigidity of the cell wall depends in part on the formation of a rhamnogalacturonan II complex (RG-II), a pectic polysaccharide covalently linked through cis-diol bonds to apiosil residues of borate-esters [16, 17]. Borate ions activate the mitogen-activated protein kinase pathway and stimulate the growth and proliferation of human embryonic kidney 293 cells [18, 19]. The B-transporter NaBC1 controls plasma borate levels in human kidney cells [18]. Whether cells can manage B independently of the expression and activity of B transporters remains unclear.

The fact that B has such a broad spread of physiological functions is not surprising. The electronic structure of B and its position in the periodic table (adjacent to carbon) make B-containing molecules electrophilic with trigonal planar structures that are neutral yet isoelectronic relative to carbocations. The formation of additional bonds with B alows the formation of anionic tetravalent compounds with tetrahedral structure, which behave as nucleophiles [20]. Various types of B-containing molecules exist or are presently investigated as therapeutic agents. They include B-containing analogues of natural biomolecules [21], the antibacterial and antimalarial agent diazaborine [22], antibacterial oxazaborolidines [23, 24], antibacterial diphenyl borinic esters [25], the antifungal agent benzoxaborole AN2690 [26], and a B-N bond containing estrogen receptor modulator [27].

*Address correspondence to this author at the Portland State University, 1719 SW, 10th Avenue, SB2 Room 246 Portland, OR, 97201, USA; Fax: 503 725 3888; Tel: 503 725 9503; E-mail: rpopa@pdx.edu

Except for the drug Bortezomib, the major current use of B-compounds in the treatment of cancer is in neutron capture therapy (BNCT), [28, 29]. It was predicted that more B-containing molecules will be discovered that will prove useful in applications involving cell surface signaling [30, 31], but insufficient progress was made in this general direction. The main objective of this review is to reveal other promising research directions for chemoprevention and chemotherapy using B-based chemicals. Targets include breast cancer, prostate cancer and lung cancer.

DIETARY BORON AND CANCER RISKS

In this section we discuss cancer dietary risks associated with B and the use of B-based chemicals in chemoprevention. It was found that low B diet leads to a number of general health problems and increased cancer risks [32-34]. Most common symptoms of B deficiency include arthritis [35, 36], memory loss [37, 38], osteoporosis [39], degenerative and soft cartilage diseases [40], hormonal disequilibria and drop in libido [41]. The daily uptake of B varies depending on food selection, the use of some specific personal products and the B content of water. Reported values for the overall B uptake vary: 0.8-1.9 mg d^{-1} in the European Union; 1.7-7 mg d^{-1} in the United States, ~0.93 mg d^{-1} in Koreea, 2.16-2.28 mg d^{-1} in Australia, 1.75-2.12 mg d^{-1} in Mexico and 1.8-1.95 mg d^{-1} in Kenia [42-45]. These dissimilarities may be correlated with regional differences in the abundance of high energy food and in food products rich in fiber and plant proteins. A diverse diet should allow an uptake of ~1.5-3 mg B d^{-1} [43, 46, 47]. The actual B requirements for the human body remain unclear; knowing this will require more knowledge about the biological functions of B and the regulation of its exchange [48]. It was suggested that humans need at least 0.2 mg B d^{-1} and that the ingested food has to contain ~1-2 mg B d^{-1} [49]. The Tolerable Upper Intake Level (UL) of B for adults of ~18 yrs in age is ~20 mg B d^{-1} [50].

Due mainly to their increased solubility borate salts are common in animal and plant tissues, though they are generally more concentrated in plants. On average, the total amount of B in plants and animals is ~30-50 ppm, but may range widely from < 0.07 ppm in animal liver to 248 ppm in some seaweed [51]. In tissue and bodily fluids most B is in the form of BA. The human blood contains 15.3-79.5 ng B ml^{-1}, of which 98.4 % as BA and 1.6 % as borate anion. The high variability of B among different organs indi-

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cates different functions and deposits in different tissues and organs rather than cellular B management. It was estimated that the total B content in the human body varies between 3 and 20 mg, with 0.06 ppm in blood, 0.02 ppm in plasma, 0.75 ppm in urine and highest concentrations (4.3-17.9 ppm) in bones, nails and hair. Differences in B content were also found depending on the health of the individual; for example B was 3 ppm in arthritic bones relative to 56 ppm in healthy bones [52].

DIETARY BORON AND PROSTATE CANCER

Prostate cancer is the most common cancer in men in USA and it is one of the eight highest causes of mortality in men [53]. Dietary B is inversely correlated with prostate cancer [32, 54], though the source of this correlation remains unclear. The risk of prostate cancer was one third smaller in men ingesting >1.8 mg B d^{-1} through food relative to 0.9 mg B d^{-1}. High B content in food however, did no offer protection against other forms of cancers [32, 54]. High correlation (r = 0.63) was found between the concentration of B from subsurface water and the distribution of prostate cancer in Texas [6]. Increased uptake of BA decreased the incidence of prostate tumors in mice, and reduced the levels of Imunoglobuline F (IgF) from tissue and prostate specific antigene (PSA) from plasma [4]. Broader understanding of the cellular mechanisms involving B was gained form the work of Barranco *et al*. [55] who showed that BA inhibited the growh of prostate cancer cell through decreased expression of A-E cyclin, thugh B did not induce cell death. Furthermore, cells treated with BA showed decreased adhesion and migration, indicating lower metastatic potential. It was hypothesized that B produces effects on prostate cancers through its influence on steroidic hormones (particularly androgens); androgens are putatively involved in prostate carcinogenesis [56, 57]. The fact that high estradiol levels correlate with low prostate cancer risks is also known [56]. The supplimentation of food with 10 mg of B twice a week had effect on plasma testosterone levels in four weeks, but significant changes (from 52 to 74 pmol l^{-1}) in estradiol levels [57]. Increased dietary B in women led to increased levels of estrogen indicating a connection between B and estrogen expression [58].

Three research directions can be used to study the relationship between B and prostate cancer risks: regulation of steroid hormones, anticancer metabolites and cell proliferation. Several potential BA binding sites may be involved in prostate cancer. For example Prostate Serum Antigen (PSA), a serine protease, is a potential site for direct boration [59]. Boric acid decreased the expression of five major cyclin proteins (A, B1, C, D1 and E), which have significant roles in the cell cycle [5], and inhibited the release of Ca(II) stored by the NAD^+ cADPR system, which may explain the effects of B on prostate cancer cells [33, 55]. No correlation with prostate cancer frequency was observed when the B consumption was ≤ 1.17 mg d^{-1} [60].

DIETARY BORON AND LUNG CANCER

Along with many other factors, cigarette smoking is the highest risk factor in lung cancer. Higher lung cancer-related mortality was seen in man than women [61]. Negative correlation was also found between the amount of B intake and the incidence of lung cancer, though the underlying mechanism remains unclear [62]. Experimental evidence showed that nutrition with some B-compounds (such as BA, borax, and calcium fructoborate) had antioxidant or antiinflammatory consequences [63-68]. Correlation exists between some lung cancers and 17β-estradiol and treatments includes 17β-estradiol-based hormone replacement therapy (HRT) [69]. It was shown that dietary supplementation with B increases the concentration of 17β-estradiol [57, 58, 70], mimics the effect of HRT and, in postmenopausal women may be used to decrease cancer risks associated with low estrogen levels [52]. Low dietary B (alone or jointly with HRT) was correlated with increased lung cancer risks in women [34]. It was proposed that reduction in lung cancer risks may be due to estrogen receptors binding substrates other than estrogen, including carcinogenic polycyclic aromatic hydrocarbons (PAHs) from the cigarette smoke condensate [71]. Women with high dietary B intakes, as well as HRT users, may show higher hormone levels competing with cigarette smoke carcinogens for estrogen receptors [34]. If this model is correct, then increasing the B intake during HRT will also limit the carcinogenic potential of PAHs from cigarette smoke. It was recently confirmed that the highest quartile of B intake was associated with the lowest lung cancer risks in smokers, while the highest risk existed in smokers with low dietary B and no HRT [34].

DIETARY BORON AND CERVICAL CANCER

Cervical cancer is the second most frequent cancer in women worldwide, yet in countries such as Turkey it only ranks the 7th [72]. The cause of this discrepancy is unclear and may involve a combination of environmental, genetic, social and infectious factors. For example, Human papillomaviruses (HPV) are the main cause of cervical cancer; HPV 16 and HPV 18 cause ~95% of all cervical cancers. Many other factors are also correlated with the incidence of cervical cancer [73-75]. According to one hypothesis the low incidence of cervical cancer in Turkey is correlated with its B-enriched soil [76-77]. Indeed, the ingestion of B via drinking water is negatively correlated with risks of cervical cancer [78]. It was suggested that this effect may be due to the interference of B chemistry in the life cycle of HPVs, but no such correlation was found with the incidence of oral cancers also induced by HPVs [78]. It was found that serine protease inhibitors reduce the immortalizing and transforming capacity of the HPV E7 oncogene [79], and that the plasminogen activator inhibitor-1 (also a serine protease inhibitor) reduces the invasive capacity of cancer cells [80]. Because B exists in the human body mostly in the form of BA, (which is an inhibitor of serine proteases), it was hypothesized that ingestion of higher amounts of B through drinking water will inhibit HPV transformation, thus reducing the incidence of cervical cancer [78].

BORON COMPOUNDS IN THE CHEMOPREVENTION AND CHEMOTHERAPY OF CANCER

Numerous medical applications exist for B-based compounds, including chemical therapy in osteoartritis, ostheoporosis, viral and bacterial infections, as well as treating cancer with the drug Bortezomib, and B-radiotherapy (BNCT), [1, 3, 7, 81-83].

Boron compounds as anticancer agents

Boric acid (BA) is one of the best studied B-containing chemicals and was shown to control the proliferation of some types of cancer cells [55, 62, 84, 85]. Boric acid is an inhibitor of peptidases, proteases, proteasomes, arginase, nitric oxide synthase and transpeptidases [65, 86]. Inhibition of serine protease and dehydrogenase activity may be explained by the capacity of BA to bind OH groups from NAD and serine [59, 87]. The Prostatic Serum Antigen (PSA) is a serine protease, and a putative target for BA influence on the proliferation of androgen-sensitive cancer cells (Fig. **1**), [84]. Based on the inhibition of PSA the use of BA in the chemical therapy of prostate carcinoma was proposed [59]. The exact mechanism of BA-PSA inhibiton remains unclear however, because the treatment of mice having androgen-sensitive prostatic cancer cells (LNCaP) with BA led to both 25-38 % decrease in tumor growth and ~88 % reduction of PSA levels [4]. Inhibitory effects of BA were also seen in androgen-independent cell lines (DU-145 and PC-3l), suggesting that other (serine protease-independent) mechanisms may also exist [84]. Boric acid inhibited the control of the cell cycle control and the proliferation of DU-145 by inhibiting the agonist stimulated release of Ca^{2+} from ryanodine receptor sensitive cell stores [88]. In the case of melanoma cells BA slows down proliferation, possibly by inhibiting the second step of pre-mRNA splicing [89]. High dose of BA (12.5–50 mM) slowed cell replication and induced apoptosis in both melanoma cells and MDA231 breast

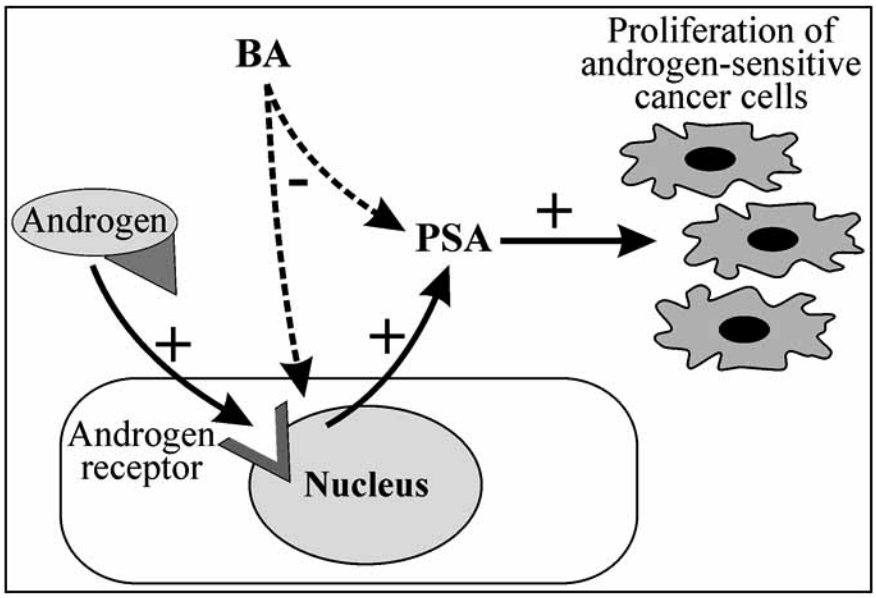

Fig. (1). The activity of androgen increases the expression of Prostatic Serum Antigen (PSA), which is a serine protease with positive effects on the proliferation of some cancer cells. The interference of BA in the proliferation of androgen-sensitive cancer cells may occur either via inhibition of the formation of PSA or inhibition of PSA activity.

cancer cells [85, 90]. Thus, the inhibition of cancer cells by BA may involve a diversity of cellular targets such as direct enzymatic inhibition, apoptosis, receptor binding and mRNA splicing.

Boronic acids are potent and selective inhibitors of the migration and viability of cancer cells. One potential mechanism of action is the inhibition of proteases. Because boronic acids interconvert with ease between the neutral sp2 (trigonal planar substituted) and the anionic sp3 (tetrahedral substituted) hybridization states, the B-OH unit replaces the C=O at a site where an acyl group transfer takes place [91]. The most efficient types of boronic acid derivatives acting as serine protease inhibitors are phenylboronic acid and diphenylboronic esters [92]. The drug Bortezomib (PS-341) is a boronic acid derivative, and a proteasome inhibitor (a novel target in cancer therapy), disrupts the regulation of cell cycle and induces apoptosis. Strong cytotoxic effects of PS-341 were seen on prostate cancer cells and MCF-7 and EMT-6 breast carcinoma cells [93]. In cell cultures, Bortezomib induced apoptosis in both hematologic and solid tumor malignancies, including myeloma [94], mantle cell lymphoma [95], cell lung cancer [96], ovarian cancer [97], pancreatic cancer [98, 99], prostate cancer [97, 100], and head and neck cancers [101].

Bortezomib is presently used in cancer therapy of animal models and patients with prostate cancers that do not respond well to hormone-based therapy [93, 102]. This drug was studied extensively *in vitro* and *in vivo*, and anticancer activity was seen in cell and animal models with several solid tumor types, including prostate cancer. Preclinical studies of four human ovarian and three human prostate carcinoma cell lines showed highly efficienct bortezomib-induced apoptosis in spheroid and monolayer cell cultures. In some animals this drug led to complete regression of prostate cancer xenografts [103, 104]. Good correlation was seen between bortezomib dose, proteasome inhibition, and positive modulation of serum PSA. This indicated that bortezomib can be used efficiently in combination with radiation or chemotherapy for controlling androgen-independent prostate cancer [105].

Boromycin is a natural bacteriocidal polyether-macrolide antibiotic from *Streptomyces antibioticus.* Apart from its antibiotic activity against Gram-positive bacteria [106] boromycin selectively disrupts the cell cycle of a number of cancer cell types during G2 and renders them sensitive to a number of anticancer agents [107]. In bacteria, boromycin affects the cell membrane and leads to loss of intracellular potassium [106], yet, the mechanism of action in eukaryotic cells remains little understood.

Tartrolons are macrolides structurally related to boromycin and aplasmomycin [12]. Tartrolons, boromycin and aplasmomycin have identical B-binding areas, and bind B via covalent bonds with hydroxy groups. The antiviral and antineoplastic chemotherapeutic uses of these compounds were recently reviewed [13].

Borophycin is a polyketide extracted from species of *Nostoc* [108], have demonstrated effects on a number of cancer cell lines, and displayed promising antitumor activity against standard cancer cell lines (MIC = 0.066 mg/mL, for LoVo; and MIC = 3.3 mg/mL for KB), [13].

Calcium fructoborate (CF) is a natural product from plants (can be produced by chemical synthesis as well), and is efficient in the prevention and treatments (as adjuvant) of osteoporosis and osteoarthritis [67, 109]. Calcium fructoborate showed inhibitory effects on MDA-MB-231 breast cancer cells as well [90], and enters the cell (most likely) by a co-transport mechanism via a sugar transporter [68]. Inside cells CF acts as an antioxidant and induces the overexpression of apoptosis-related proteins and eventually apoptosis [66, 90].

Boranes are a large class of B-containing derivatives relevant in cancer treatments. Amine-carboxyboranes are efficient antineoplasic and cytotoxic agents with selective effects against unicellular tumors and leukemia-derived solid tumors, lymphoma, sarcoma and carcinoma [110]. Dicarba-closo-dodecaborane (carborane) is a novel class of androgen receptor antagonists, with a hydrophobic skeletal structure and possible antitumor activity [111]. Boron-betaine analogues showed antitumoral activity on Ehrlich ascites, on Walker 256 ascite carcinosarcoma and on Lewis lung carcinoma [112, 113]. Amine-boranes have cytotoxic activity and are of potential use in BNCT. These boron-containing compounds were shown to inhibit DNA synthesis; such inhibition was caused primarily by reducing the *de novo* purine biosynthesis via inhibition of PRPP amidotransferase, IMP dehydrogenase and dihydrofolate reductase activities [23]. Trimethylamine cyanoborane (TACB) inhibited DNA and proteins synthesis in Ehrlich ascite cells, gene regulation via chromatin phosphorylation and methylation and increased the cyclic-AMP levels [112]. TACB inhibits a number

of biochemical and molecular activities including DNA polymerization, thymidilate synthesis, S-adenosylmethyltransferase activity, non-histone chromatin methylation, DNAse, RNAse and catepsin [112] and are cytotoxic to cancer cells [110].

CONCLUSIONS

Two avenues with specific methodology exist when using B chemistry against cancer cells: diet-based chemoprevention and chemotherapy. Negative correlation was found to exist between B-supplemented nutrition and the incidence of some forms of cancer. Potential mechanisms regarding the activity of B-containing chemicals against cancer cells include the inhibition of numerous enzymatic processes, such as serine proteases, NAD-dehydrogenases, mRNA splicing, DNA polymerization, thymidilate synthesis, S-adenosylmethyltransferase, non-histone chromatin methylation, DNAse, RNAse, catepsin and others. Boron-containing chemicals also act by influencing Ca^{2+} receptors, by inhibiting cell division, nuclear receptor binding mimicry, and the induction of apoptosis. Because B has a small atomic mass and its chemistry includes neutrophilic and electrophilic reactivity, a wide array of B-based chemicals can be created and tested for chemoprevention and chemotherapy.

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