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Calcium fructoborate: plant-based dietary boron as potential medicine for cancer therapy

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1. ABSTRACT

It was predicted that more B-containing molecules will be discovered that will prove useful in applications involving cell surface signaling, but insufficient progress was made in this general direction. The main objective of this review is to reveal other promising research directions for B-chemoprevention and chemotherapy using Calcium Fructoborate (CF). Targets include breast cancer, prostate cancer, lung cancer and cervical cancer. CF has been identified as Ca $(C_6H_{10}O_6)_2B)_2 \bullet 4H_2O$ and 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. CF showed inhibitory effects on MDA-MB-231 breast cancer cells as well, and enters the cell (most likely) by a co-transport mechanism via a sugar transporter. Inside cells CF acts as an antioxidant and induces the overexpression of apoptosis-related proteins and eventually apoptosis.

2. INTRODUCTION

Numerous biological functions of B compounds are known. Boron is present in bacterial antibiotics such as tartrolon, borophycin, boromycin and aplasmomycin (1-3) and in the bacterial quorum sensing molecule *auto-inducer AI-2 (*4). Plants need B for growth, blooming, seed formation, and extract borate from soil using specialized transporters such as BOR1 (5). 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 (6, 7). Borate ions activate the mitogen-activated protein kinase pathway and stimulate the growth and proliferation of human embryonic kidney 293 cells (8, 9). The B-transporter NaBC1 controls plasma borate levels in human kidney cells (8). 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 creates the formation of anionic tetravalent compounds with tetrahedral structure, which behave as nucleophiles (10). Various types of B-containing molecules exist or are presently investigated as therapeutic agents. They include B-containing analogues of natural biomolecules (11), the antibacterial and antimalarial agent diazaborine (12), antibacterial oxazaborolidines (13, 14), antibacterial diphenyl borinic esters (15), the antifungal agent benzoxaborole AN2690 (16), and a B-N bond containing estrogen receptor modulator (17). Except for the drug Bortezomib, the major current use of B-compounds in the treatment of cancer is in neutron capture therapy (BNCT), (18, 19). It was predicted that more B-containing molecules will be discovered that will prove useful in applications involving cell surface signaling (20, 21), but insufficient progress was made in this general direction. The main objective of this review is to reveal other promising research directions for B-chemoprevention, chemotherapy and ^{10}Boron Neutron Capture Therapy (^{10}BNCT) using CF. Targets include breast cancer, prostate cancer, lung cancer and cervical cancer.

3. DIETARY BORON AND CANCER RISKS

3.1. 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 (22). Dietary B is inversely correlated with prostate cancer (23, 24), 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 (24). High correlation (r = 0.63) was found between the concentration of B from subsurface water and the distribution of prostate cancer in Texas (25). Increased uptake of boric acid (BA) decreased the incidence of prostate tumors in mice, and reduced the levels of Immunoglobulin F (IgF) from tissue and prostate specific antigen (PSA) from plasma (26). Broader understanding of the cellular mechanisms involving B was gained form the work of Barranco *et al.* (27) who showed that BA inhibited the growth of prostate cancer cell through decreased expression of A-E cyclin, though 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 steroid hormones (particularly androgens); androgens are putatively involved in prostate carcinogenesis (28, 29). The fact that high estradiol levels correlate with low prostate cancer risks is also known (28). The supplementation 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 (28). Increased dietary B in women led to increased levels of estrogen indicating a connection between B and estrogen expression (29, 30). 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 (31). BA decreased the expression of five major cyclin proteins (A, B1, C, D1 and E), which have significant roles in the cell cycle (32), 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). No correlation with prostate cancer frequency was observed when the B consumption was maximum 1.17 mg d-1 (34).

3.2. 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 (35). Negative correlation was also found between the amount of B intake and the incidence of lung cancer, though the underlying mechanism remains unclear (36). Experimental evidence showed that nutrition with some B-compounds (such as BA, borax, and CF) had antioxidant or anti-inflammatory consequences (37-42). Correlation exists between some lung cancers and 17-beta -estradiol and treatments includes 17-beta-estradiol-based hormone replacement therapy (HRT) (43). It was shown that dietary supplementation with B increases the concentration of 17-beta-estradiol (44), mimics the effect of HRT and, in postmenopausal women may be used to decrease cancer risks associated with low estrogen levels. Low dietary B (alone or jointly with HRT) was correlated with increased lung cancer risks in women (43). 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 (44). Women with high dietary B intakes, as well as HRT users, may show higher hormone levels competing with cigarette smoke carcinogens for estrogen receptors (45). 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 (45).

3.3. 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 (46). 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 (47-49). According to one hypothesis the low incidence of cervical cancer in Turkey is correlated with its B-enriched soil (50, 51). Indeed, the ingestion of B via drinking water is negatively correlated with risks of cervical cancer (52). 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 (52). It was found that serine protease inhibitors reduce the immortalizing and transforming capacity of the HPV E7 oncogene (53), and that the plasminogen activator inhibitor-1 (also a serine protease inhibitor) reduces the invasive capacity of cancer cells (54). 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 (52).

4. STUDIES ON THE MECHANISM OF ACTION OF CALCIUM FRUCTOBORATE

4.1. Molecular compositions

CF, dietary supplement produced by the FutureCeuticals Company (proprietary name, FruiteX-B®), with potential use in chemotherapy of diseases, was investigated by thermal analysis and by X-ray diffraction (55, 56). Results of measurements performed in air show that FruiteX-B® is identical with the natural CF. FruitexB loses water of crystallization up to 150°C and then degrades in six stages, more exactly one endothermic and five exothermic. By thermal analysis (TA), the molecular formula Ca ($(C_6H_{10}O_6)_2B)_2 \cdot 4H_2O$ has been established (56). X-rays diffraction (XRD) indicates a weak crystallinity of CF. Thermal analysis of FruitexB and of BA and calcium carbonate showed that there are no similarities between their thermo analytical curves. Only with fructose, similarities appear, but shifted to higher temperatures as a result of the bonding influences in the calcium fructoborate complex. Mass loss is of 8.5 % up to 152°C, when the experiment is performed in air. This loss is due to the crystallization water of the compound. By correlation of the results of thermo gravimetric analysis with the elemental analysis, no precursors traces were found and the molecular formula of FruitexB has been identified as Ca ($(C_6H_{10}O_6)_2B)_2 \bullet 4H_2O$. Above 152 °C, the decomposition in air occurs in six stages: first stage is weakly endothermic, the second is weakly exothermic, and the following four are exothermic. For the last 4 stages, the exchanged heat was determined as well. Gravimetric effects of the last six stages are due to decomposition of fructose from the complex with a mass loss of 77.8 ±1 %, compared to the 76.6 % (calculated on the basis of the proposed formula). Residue of 13.7±1 % is calcium borate (theoretical 14.8 %). XRD results show a weak crystallinity of calcium fructoborate and confirmed the thermal analysis results when no evidence of fructose, boric acid and calcium carbonate were found (56). FruitexB comes therefore as the calcium fructoborate found in natural products.

4.2. Calcium Fructoborate and Oxidativ stress

Despite the fact that there has been remarkable progress regarding the beneficial effects of supplementing human and animal diet with B compounds, especially in their natural forms, their mechanisms of action have not been elucidated yet. Our studies were inspired by research that showed that borate protects the skin and facilitates the healing of profound wounds through its action on some compounds of the extracellular matrix of the conjunctive tissue (57). Keratinocyte cultures have been chosen as the study model because these cells are the major constituents of the epidermis, actively involved in skin wound healing by their capacity to proliferate and differentiate into cells forming the skin barrier. The response of keratinocytes to different agents is of particular interest because these cells take part in cutaneous immunological reactions that involve the release of pro-inflammatory cytokines (58). There is evidence to support the hypothesis that dietary B helps control the normal inflammatory process by serving as a suppressive signal that down regulates specific enzymatic activities at the inflammation site that are typically elevated during inflammation (59,60). Our studies demonstrated that the incubation of keratinocytes with CF did not generate an oxidative stress and its antioxidant effect after the exogenous exposure of the cells to H_2O_2. The inhibiting effect of the CF on pyrogallol auto-oxidation suggests its possible role as a scavenger for superoxide radicals. The antioxidant effect of a soluble carbohydrate compound of B (CF), represents a new challenge for the natural antioxidant world and shows a very important physiological role of B in life processes. Based on our results, we support the hypothesis that the soluble carbohydrate compounds of B, formed by the complexation of boric acid with free sugars , glycolipids, and glycoproteins, buffer the reactive species of oxygen by developing organic peroxyborates. Our results suggest a hypothetical mechanism of influence of the CF as scavenger for the reactive species of oxygen. In this paper (40) we have taken into account the balance between the actively metabolic mono-dentate carbohydrate complex and the bi-dentate carbohydrate complex of CF. We suppose that the mono-dentate complex is capable of react with the superoxide radical , generating a organic peroxyborate radical , accompanied by the release of hydrogen peroxide. The peroxyborate radical might have a longer lifetime than the common oxygen reactive species, being able to react with a hydrogen donor (DH_2) which it oxidized with the reconstruction of the mnon-dentate complex. This path can be catalyzed by an enzyme with peroxidase capacity. The fact that CF in high concentrations increases the intracellular oxidant power of the keratinocites might suggest that at higher organic peroxyborate radical concentration, the capacity of the cellular peroxidase activity is exceeded. The validity of this mechanism might explain several effects of B and its derivates, (e.g., CF) as well as the implication of these compounds in the cellular signalization mechanisms, supplementing the types of reactive species with derivates of B (40).

4.3. Calcium fructoborate and anti-inflammatory processes

Our *in vitro* studies show that CF has profound effects on human PMN cells related to its concentration (41). Thus, the treatment with CF of fMLP-stimulated PMN, for 24 h, resulted in a decrease of respiratory burst, in a dose-dependent manner. The decrease of ROS level was evident even when non-cytotoxic doses were used (for example, by 50% at 450 μM CF), which underlies the fact that CF is a superoxide anion scavenger and may have anti-inflammatory effects. These data must be interpreted

considering the previous observations that neutrophils stimulation with fMLP results in an increase of superoxide anion generation and apoptosis level (61). It is possible that CF inhibits activation of the enzymatic complex NADPH-oxidase that directly reduces molecular oxygen to generate superoxide anion, which is later converted into other reactive intermediates. It is worth mentioning that this action is due to CF and not to calcium ions or borate residue from its composition). Actually, Granfeldt *et al.* (62) showed that an increase in (Ca2+) mediated through binding of fMLF to its receptor is part of a signaling cascade that activates the plasma membrane-localized oxidase. At this moment, it is difficult to propose a mechanism by which CF inhibits NADPH-oxidase function because this membrane-bound enzyme complex is comprised of both integral membrane and cytosolic proteins, and it is subjected to a complex control. A better understanding of the mechanisms used by the CF to inhibit the NADPH-oxydase will allow developing a new therapeutic approach to deal with the phenomenon. Hunt (63) proposed an essential role of boron as a regulator of respiratory burst by suppression of serine proteases released by inflammation-activated white blood cells, inhibition of leukotriene synthesis, reduction of reactive oxygen species generated during the neutrophil's respiratory burst, and suppression of T-cell activity and antibody concentrations. Investigation of CF effects on the intracellular level of superoxide anions in unstimulated PMN cells strengthens the idea of the antioxidant activity exerted by CF, previously proposed by us (40), according to which CF is a scavenger for superoxide anions. The superoxide dismutase (SOD) protects the PMN contents against oxidizing activity by destroying superoxide anions (O^{-2}); SOD reduces both the oxidative stress and the activation of mediators of inflammatory response (64). In our study, we pointed out a low level of superoxide anions at the cytotoxic dose of CF as a result of an increase in SOD activity. Low superoxide dismutase activity in PMN cells may explain the small discrepancies between the data regarding the superoxide anions and SOD activity. These data suggest that PMN cells apoptosis and CF-induced cytotoxicity is not mediated by the superoxide release.

In a recent study (65), we showed that treatment of LPS-stimulated RAW264.7macrophage cells with CF induced an inhibition of the IL-1β, IL-6 and NO release in the culture media, an increase of TNF-α production, and had no effects on LPS-induced COX-2 protein expression. The pro-inflammatory cytokine IL-1β is synthesized by activated monocytes and macrophages as a 31-kDa, biologically inactive precursor that is proteolytically processed to the biologically active 17-kDa mature molecule by the IL-1β converting enzyme. Studies on LPS-stimulated cultured macrophages, showed that induction of apoptosis but not necrosis effectively induced conversion of the IL-1β precursor to its mature form and resulted in the concomitant release of the mature cytokine from the cell (66). Our data suggest that CF affects the post-translational activation of biologically inactive IL-1β precursor. Considering the absence of pro-apoptotic effects of CF treatment (data not shown) we came to the conclusion that this compound could uncouple IL-1 β processing and apoptosis. The effects of CF treatment on IL-6 synthesis by RAW 264.7 macrophages might be explained by the fact that IL-6 is a secondary cytokine whose expression can be stimulated by primary cytokines like IL-1, whose post-translational activation seems to be inhibited by this borate derivative. These studies provide evidence to support the view that CF can be an effective, safe anti-inflammatory agent. Our results regarding CF effects on LPS-stimulated macrophage TNF-α production are contradictory because TNF-α plays a major role in regulating inflammation, mostly through the induction of inflammatory cytokines, including IL-1β and IL-6. Cao *et al.* (67) studied LPS-induced TNF-α formation in THP-1 cells and noticed the inhibitory effect exhibited by boric acid. Interestingly, when Armstrong and Spears (68) examined the effect of boron supplementation of pig diets they found a decreased inflammatory response following a phytohemmaglutinin intradermal injection. They also noticed an increased level of TNF-α in serum as well as in peripheral blood monocytes isolated from pigs that received the B-supplemented diet and cultured in the presence of LPS. These data could not explain the reduction in localized inflammation following an antigen challenge in pigs. Other studies showed that boron increased TNF-α release by cultured human fibroblasts and chick embryo cartilage (69,70). The complex regulation of TNF-α synthesis, at the level of transcription, translation, and secretion, makes difficult to explain the high levels of this cytokine at the same time with the decrease in other inflammatory mediators (71-73) In addition, the signaling pathways involved in cytokine release from RAW 264.7 macrophages are now under investigation (74). Moreover, the involvement of different pro- and anti-inflammatory mediators in a sequential and concerted manner and regulation of cytokine induction can occur after a variable pattern in different cell types and depends on the nature of the stimulatory ligand. These mediators can act at the level of cell surface, cell membrane, cytosol, or nucleus. There is continuing interest in the effects of long-chain n–3 polyunsaturated fatty acids (PUFAs) on human immune function and inflammatory processes (75, 76). In previous studies (77, 78) it was shown that increasing dietary (n–3) to (n–6) fatty acid ratio from 0 to 1 resulted in a dose-response increase in TNF production by LPS-stimulated resident peritoneal macrophages. On the other hand, some experimental data suggested that boron had essential function similar to (n–3) fatty acids (79). Consequently, macrophage CF treatment might induce a replacement of n–6 PUFA with n–3 PUFA in cell membranes generating a decreased cellular response to inflammatory stimuli.

Nitric oxide is synthesized from L-arginine by L-arginine NO pathway and is converted to nitrite and nitrate in oxygenated solutions. A family of enzymes, termed the NO synthases (NOS), catalyze the formation of NO and citrulline from L-arginine, O2, and NADPH. The constitutive NOS isoforms (NOS-1 and NOS-3) produce low levels of NO as a consequence of increased intracellular Ca2+. By contrast, the inducible isoform of NOS (NOS-2 or iNOS) generates large amounts of NO through a Ca2+-independent pathway (80). Some pro-inflammatory agents, such as endotoxin, TNF-α and IL-1 induce NOS-2 activity. High levels of NO induce changes

suggestive of apoptosis in RAW 264.7 mouse macrophage cell line (81). It is possible for CF to inhibit NO production by blocking iNOS expression in RAW 264.7 macrophages. Due to the critical role that NO release plays in mediating inflammatory responses, our data suggest that CF could represent a useful anti-inflammatory agent. Jeon *et al.* (82) showed that the p38 MAPK pathway is specifically involved in LPS-induced iNOS expression in LPS-stimulated RAW 264.7 cells. The p38 MAPK also regulates LPS-induced TNF-α and IL-1 production by monocytes (83, 84). In a study focused on the effects of NO on TNF synthesis in the RAW 264.7 cell line (85) a suppression of LPS-induced TNF synthesis by exogenous addition of NO-releasing agents was found. The finding of an increased TNF production in the presence of two NO synthase inhibitors, indicated a negative feedback by endogenous NO on TNF synthesis *in vitro*. Cyclooxygenase-2, the enzyme primarily responsible for induced prostaglandin synthesis, represents the product of an immediate early gene induced by endotoxin in macrophages. Secreted prostaglandins promote inflammation by increasing vascular permeability and vasodilatation and by directing cellular migration into the site of inflammation through the production and release of pro-inflammatory cytokines such as interleukin-6 (86). Our data suggest that CF does not affect COX-2 protein expression level in LPS-stimulated macrophages and, consequently, neither the prostaglandin synthesis, which might sustain the anti-inflammatory properties of this boron derivative. Since CF complex is characterized by a high boron–fructose association constant (about 6,000) (87) we consider that *in vitro* response of LPS-stimulated macrophages is due to the entire molecule. There are studies demonstrating that various boron-containing compounds displayed anti-inflammatory properties (88, 89). In a comparative study concerning the effects of CF and sodium borate on fMLP-stimulated PMN we found that CF exhibited superior anti-inflammatory and antioxidant properties (40). Moreover, we demonstrated that while both boric acid and CF inhibited the growth of MDA-MB-231 breast tumor cells, only CF induced the apoptosis (90). This study demonstrated that CF treatment of LPS-stimulated RAW 264.7 macrophages induced an up-regulation of TNF-α protein level in culture medium, no significant changes in the level of LPS-induced COX-2 protein expression and a decrease in NO production as well as in IL-1β and IL-6 release. Although we can conclude that CF might affect macrophage production of inflammatory mediators, these studies have to be completed with further research aiming to establish whether CF treatment can be beneficial for suppression of pro-inflammatory cytokine production and against progression of endotoxin-associated diseases. We also intend to elucidate the mechanism of CF effects and its efficacy as an anti-inflammatory agent comparing to drugs with well established anti-inflammatory action.

5. FRUCTOBORATE AS POTENTIAL ANTICANCER AGENT

5.1. Breast cancer and 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 (40, 41, 42). CF showed inhibitory effects on MDA-MB-231 breast cancer cells as well (90, 91), and enters the cell (most likely) by a co-transport mechanism via a sugar transporter (42). Inside cells CF acts as an antioxidant and induces the overexpression of apoptosis-related proteins and eventually apoptosis (40, 90). In the recent study, we demonstrated that CF and BA inhibited the proliferation of breast cancer cells MDA-MB-231 in a dose-dependent manner (90). As revealed by different experiments (TUNEL, Bcl-2 and pro-caspase-3 protein expression, and cytochrome c caspase-3 activities), it appeared that the anti-proliferative effect of CF in breast cancer cells MDA-MB-231 is mediated by induction of apoptosis. On the other hand, BA induced a cell death-independent proliferative inhibition of breast cancer cells. In a previous study, Barranco and Eckhert (92), using DU-145 prostate cancer cells, showed that BA inhibited cell proliferation without inducing apoptosis. They demonstrated that BA induces conversion to a senescent-like cellular phenotype and also causes a dose-dependent reduction in cyclins A–E, as well as mitogen-activated protein kinase proteins, suggesting their contribution to proliferative inhibition (93). Unlike BA, the mechanism underlying the antiproliferative activity of CF has not been elucidated. When MDA-MB-231 cells were treated with 0.45 mM CF, for 24 h, no effects on cell viability, Bcl-2, caspase-3, and p53 protein expression were observed. Cytotoxic effects and an increase in caspase-3 activity were seen in MDA-MB-231 cells treated with CF doses higher than 2.25 mM. Therefore, the treatment of tumor cells with CF resulted in a rapid release of cytochrome c from the mitochondria, which preceded caspase 3 activation. At CF concentrations greater than or equal to 5 mM CF, the cytotoxic effects became stronger, and repression of Bcl-2 protein expression was seen. The mechanism of the noticed downregulation of Bcl-2 by CF remains to be delineated. This may occur at the transcription level and/or post-transcription level and may also involve reduced Bcl-2 messenger ribonucleic acid stability, leading to a decrease in Bcl-2 expression. Taking into account the central role of p53 in the regulation of apoptosis, it is of great interest to study p53 involvement in the apoptosis induction by different potential chemotherapeutic agents. In this context, we investigated the relationship between p53 tumor suppressor protein immunoreactivity and CF action upon MDA-MB-231 cells and found out a down regulation of p53 protein expression at doses greater than or equal to 5 mM. An explanation of this finding might be that higher doses of CF stimulated degradation of p53 mediated by cytoplasmic 26S proteasomes (94, 95) and that in MDA-MB-231 cells the apoptotic process is p53 independent. Based on these results, we conclude that while both BA and CF inhibit the growth of breast cancer cells, only CF induces apoptosis. Further studies will be needed to determine if BA and CF will be suitable for clinical application in breast cancer patients.

5.2. Fructoborate and 10B-Neutron Capture Therapy-a vision for future

^{10}BNCT was initially proposed as a means to selectively kill cancer cells without affecting normal cells

(96). The present days BNCT uses a number of ^{10}B-containing compounds that preferentially concentrate in tumor cells. The tumor area is then irradiated by a neutron beam; neutrons interact with ^{10}B and yield highly energetic $_2$He^4 and recoiling $_3$Li^7 nuclei along with kinetic energy and γ-radiation (97).

$$^{10}_{5}B+_{0}n^{1} \rightarrow \left[^{11}_{5}B\right] \rightarrow ^{4}_{2}He+^{7}_{3}Li+\gamma-radiation.(2.4MeV)$$

This allows delivering high radiation dosage to the cancer cells with limited effects on normal cells. Modern BNCT is actually a combination of chemo- and radiotherapy and is used in the treatment of high grade glioma. In order for BNCT to be therapeutically useful ^{10}B-chemicals have to show some specific properties: i) Good water solubility so they can be administered intravenously; ii) Low toxicity; iii) High selectivity by tumor cells; and iv) Accumulation in large concentrations in cancer cells. The larger challenge of BNCT was and remains biasing the retention of B toward cancer cells.

The small intestine regulates fructose absorption from dietary sources and, therefore, the availability of fructose to other tissues. It is also the organ system expressing the greatest amount of GLUT5 in human (98). After apical transport mediated by GLUT5, fructose is transported across the basolateral membrane by GLUT2. Recent work proposes that GLUT2 is also involved in the apical transport of fructose (99). After the small intestine, the kidney skeletal muscle and adipocytes expresses the most GLUT5 in human (100). In brain, GLUT5 has been identified in different cell types such as human microglia (101), cerebellar Purkinje cells in human fetus (102), mouse cerebellum (103), human blood-brain barrier (104), and rat hippocampus (105). Because the GLUT5 transporter is commonly found in tissues that metabolize fructose (106), these brain cells may be capable of utilizing fructose. GLUT5 mRNA and protein expression are affected by the development of tumors in certain organ systems. In general, oncogene-transformed cells that portray cancerous characteristics will also exhibit an increase in glucose transport by over expressing specifically sugar transporters like GLUT1 in breast, colorectal, lung, and ovarian carcinoma GLUT12 in breast cancer, or GLUT3 in lung, ovarian, and gastric cancers (100). This increase in glucose transport and metabolism may reflect a requirement by these rapidly growing cells for more sources of energy (107). Although GLUT5 is poorly expressed in normal mammary epithelial cells, the breast carcinoma cell lines MCF-7 and MDA-MB- 231 possess high amounts of GLUT5 mRNA and protein and exhibit high rates of fructose transport (108). In fact, GLUT5 knockdown by antisense oligonucleotide decreases rates of fructose uptake, thereby inhibiting the proliferation and the growth of MCF-7 and MDA-MB-231 cells, which are, respectively, models of early and late-stage breast cancer (109). A large-scale screening of the GLUT family of transporters in malignant vs. normal human tissues and cells showed that GLUT5 was highly over expressed in 27% of cancerous tissues tested, including tumors in brain, breast, colon, liver, lung, testis, and uterus (110). *In situ* RT-PCR and ultra structural immunohistochemistry confirmed GLUT5 expression in breast cancer. The extensive expression of the glucose/fructose transporter GLUT2, and the fact that in most of the tumor cells over expressing GLUT5 the rate of fructose uptake is exacerbated, indicate that fructose may be a preferred substrate providing energy required for the growth and proliferation of tumor cells. This increase of GLUT5 could indicate preferential utilization of fructose by cancer cells (100). In Caco2 cells and in highly proliferative cancer cells, GLUT5 expression is significant enough that it appears to be a good marker of malignancy or high proliferation rate. This suggests that cancerous cells lose the inhibitory factor (s) that blocks intensive GLUT5 expression in normal cells (100) and enriched ^{10}-Boron-Fructoborate (EBF) may become an important chemical challenger in the fight against some cancers. EBF transport inside cancerous cells induces a pro-apoptosis effect, as shown in our research (90), enhancing the BNCT effect.

6. SUMARY AND PERSPECTIVE

Three avenues with specific methodology exist when using B chemistry against cancer cells: diet-based chemoprevention, chemotherapy and 10B-BNTC. 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 Ca2+ 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.

CF is a natural product that can be very efficiently used as a boron food supplement in prevention and adjuvant treatment of osteoporosis and osteoarthritis. Our opinion is that more boron should be added to multivitamins especially in the organic form of these (CF). The CF form of boron is being found in some vegetables like celery and broccoli and fruits like grapes and plumes. At the same time, CF may also become a pharmaceutical ingredient with effects in oxidative metabolism and cell apoptosis. CF enters the cell by a “masked” transport and for cells with great affinity for sugars in physiological pathogenic states, CF could induce cell apoptosis. The prooxidant and antioxidant mechanisms are directly correlated to the molecular structure of CF. Compared to CF, the boric acid is transported into the cells using boron-specific transporter, NaBC1, while CF is transported using probably a sugar transporter. We believe that CF is highly reactive only toward the cells with over expressed sugar transporters, such as intestinal cells, adipose cells, muscle cells, and some cancerous cells.

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Abbreviations: CF**:** Calcium Fructoborate; MDA-MB-231: breast cancer cells; RG-II: rhamnogalacturonan II complex; NaBC1: Boron transporter; ^{10}BNCT: 10-boron neutron capture therapy; BA: boric acid; IgF: Imunoglobuline F; PSA: prostate specific antigene; HRT: hormone replacement therapy; PAHs: polycyclic aromatic hydrocarbons; HPV: Human papilloma viruses ; PMN; polymorfonuclear cells; SOD: superoxide dismutase; PUFAs: polyunsaturated fatty acids; EBF: ^{10}-Boron-Fructoborate.

Key Words: Calcium Fructoborate, Dietary Supplement, Prostate Cancer, Lung Cancer, Cervical Cancer, Breast Cancer, Apoptosis, Boron, GLUT-5, ^{10}BNCT. Enriched ^{10}-Boron-Fructoborate, Review

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