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Several effects of boron are induced by uncoupling steroid hormones from their transporters in blood

Martiniano Bello[a], Concepción Guadarrama-García[a,b], Luz M. Velasco-Silveyra[b], Eunice D. Farfán-García[b], Marvin A. Soriano-Ursúa[b,*]

[a] Laboratorio de Modelado Molecular y Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón s/n, 11340 México City, Mexico

[b] Departamento de Fisiología y Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón s/n, 11340 México City, Mexico

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ABSTRACT

Boron is increasingly added to food supplements due to multiple effects that have been reported in mammals after boric acid administration. Among these effects are inflammatory process control, bone and muscle strength enhancement, protein expression regulation, and a decreased risk of developing some pathologies in which these processes are key, such as osteoporosis, dermatological inflammatory non-infectious maladies and diseases affecting the central nervous system. Experimental data have suggested that steroid hormone levels in plasma change after boric acid administration, but a clear mechanism behind these variations has not been established. We analyzed possibilities for these changes and hypothesized that boric acid disrupts the interactions between steroid hormones and several carriers in plasma. In particular, we proposed that there is an uncoupling of the interactions between sex hormone binding globulin (SHBG) and estrogens and testosterone and that there are alterations in the binding of hydrophobic ligands by other carrier proteins in plasma. Further experimental and computational studies are required to support the hypothesis that boric acid and probably other boron-containing compounds can displace steroid hormones from their plasma carriers. If such phenomena are confirmed, boron administration with a clear mechanism could be employed as a therapeutic agent in several diseases or physiological events that require modulation of steroid hormone levels in plasma.

Introduction

Boron is an element that is widely distributed in the environment (soil, water, etc.), and it is also found in plants, seeds and several organs from some animal species, although its abundance is low in comparison to other elements [1,2]. Currently, boron is added to many new synthetic molecules that are being tested as potential drugs [3,4].

Although historic data suggest boron (as boric acid and borates) has been used by humans for biomedical purposes for thousands of years [4–6], boron has only been widely used as an antiseptic and food preservative from 1870 until World War II [5]. Its use was then limited or avoided due to the development of more selective and safe antimicrobials.

However, in the recent years, people have begun taking boron supplements as a preventive or therapeutic agent [1,4,6]. Currently, boron is added (commonly as boric acid) to supplements to build strong bones, treat osteoarthritis, aid in building muscles and increasing testosterone levels, treat painful menstruation, and improve thinking skills and muscle coordination [7,8].

Some observed effects after boron-containing compounds (BCCs) administration

Some experimental data support these effects [8,9]; however, there is not enough evidence to support its regular employment [10]. For instance, boron deprivation disrupts bone developmental stages in mice [11], and its administration induces bone mineralization and tooth mineral composition [12,13]. Additionally, boric acid administration induces many physiological changes (some linked to boron-induced toxicity [2,14]), and among these changes are changes in bone, muscle, inflammatory responses and hormone plasma levels [1,7]. Moreover, effects of boric acid administration have been often reported but its mechanism of action remains unclear [14].

Although most of the biological studies employed boric acid or borax, some other natural BCCs have been reported to have attractive biological activities for the development of therapeutic compounds. For

* Corresponding author at: Departamento de Fisiología, Escuela Superior de Medicina, Plan de San Luis y Díaz Mirón, México, D.F. 11340, Mexico.
E-mail address: msoriano@ipn.mx (M.A. Soriano-Ursúa).

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example, boromycin isolated from *Streptomyces antibioticus* is a potent antimicrobial agent [15], and fructoborates found in some plants are regulators of inflammatory processes [9,16].

Additionally, in the last few decades, substituting a single boron atom (BCC) or multiple boron atoms (boron clusters) in organic molecules has been used to reach specific biological targets, yielding compounds that have been introduced for human use [17]. However, although BCCs and boron clusters have made important contributions to the development of new drugs, the former have made greater progression in introducing new drugs to the market, such as bortezomib (Velcade) and tavaborole (Kerydin), and bortezomib was approved as an anticancer drug in 2003 and tavaborole as a topical antifungal agent in 2014 [18–20].

Hypotheses

We hypothesize that boric acid, and probably other structurally related BCCs, modifies interactions of sexual steroid hormones with several carriers in plasma. Particularly, we suggest that it induces uncoupling of estrogens and testosterone interactions from sexual hormone binding globulin, but other alterations of hydrophobic hormones with proteins that act as carriers in plasma can be included in the observed effects after boric acid administration.

Evidential support of the hypothesis

Biological effects of boron on the plasma levels of steroid-hormones

Experimentally, a boron deficiency in a mammalian diet can influence several functions, the most relevant of which are the modulation of bone growth, immunological responses, and some mental functions [20,21]. It is well documented that BCCs influence enzymatic activity, the metabolism of steroid hormones, and the metabolism and activity of other micronutrients such as calcium (Ca^{2+}) and magnesium (Mg^{2+}) [21,22]. Therefore, some BCCs could be used as therapeutic tools for arthritis, metabolic diseases, central nervous system disorders and various infectious diseases [4,21].

Increased levels of sex steroids have been shown in both men and women after boric acid supplementation [20–22]. Nielsen et al. [1] reported that dietary boron consumption for several weeks in postmenopausal women significantly increased their serum estradiol (E2) and testosterone levels. Their E2 levels almost doubled, and their testosterone levels more than doubled. An increased level of E2 was also reported by Naghii et al. [22] for healthy men after several weeks of dietary supplementation with boron.

Moreover, Naghii et al. [22] found changes in healthy men after only one week of boron supplementation (6 mg/day); they found an increase in free testosterone, but a significant decrease in E2 and inflammatory biomarkers. Levels of dihydrotestosterone, cortisol, and vitamin D increased slightly. Considering these effects, it has been suggested that boric acid has androgen amplifier effects, probably through a higher rate of conversion of total testosterone to free testosterone by modifying the testosterone metabolic pathways (which additionally may have an effect on the half-life of steroid hormones) [21].

Due to the increased level of estrogens that has been reported in postmenopausal women receiving hormone replacement therapy, it has been suggested that a reduction in E_2 catabolism, rather than increased E_2 synthesis, is the responsible mechanism. Each of the major routes of E_2 catabolism involve hydroxylations (in the vicinal hydroxyl groups of 17β-estradiol).

Additionally, boron has been shown to increase the levels of 25-hydroxyvitamin D_3 (25[OH]D_3) in the serum in animal and human studies [1,20,24]. In humans, boron supplementation (3 mg/d as sodium borate over 49 days) increases its concentration by 39%. Similar results were seen after boron supplementation of 6 mg/d over 60 days using calcium fructoborate, $Ca([C_6H_{10}O_6]_2B)_2{\cdot}4H_2O$, a boron-containing complex naturally existent in fruits [24]. Although the mechanism of action is unclear, it has been suggested that boron increases the half-life and bioavailability of E_2 and vitamin D [21].

In addition, Miljkovic et al. [22] hypothesized that boron suppresses the catabolic activity of 24-hydroxylase on 25(OH)D_3. Moreover, Pizzorno [21] suggested that nutritional boron can inhibit a range of microsomal enzymes that insert hydroxyl groups vicinal to existing hydroxyls in steroids, which include enzymes that catabolize 17β-estradiol, 25(OH)D_3, and 1α,25-dihydroxyvitamin D_3(1α,25[OH]$_2D_3$) [25]. They suggest BCCs (those with the ability to act as Lewis acids) readily form covalent complexes with cis-vicinal dihydroxy compounds due to the ability of boronic acids to form reversible covalent complexes with molecules containing vicinal hydroxyl groups. Therefore, it is suggested that the resulting boron-containing complexes interact with and inhibit the enzymes involved in catabolism [21,22].

However, it is well-known that the formation of covalent bonds between boric or boronic acid with diols systems is eased in alkaline conditions (pH ≥ 9), distinct to those found in most biological compartments of mammals [26–28], and the formation of these complexes is poor in neutral aqueous solutions [27–29]. In contrast, even unstable interactions of diols in the sidechains of residues in the active site of target proteins may be strong enough to inhibit some enzymatic systems (see the next section) [26]. Whatever the mechanism of action of BCCs in the disruption of steroid hormone levels, additional studies are required to analyze the impact of the boron source, time of boron supplementation and dose-dependence of the effects.

Without discarding the possible effects of boron on metabolic pathways, we suggest the possibility of boric acid inducing this free-steroid hormones increase by disruption of interactions of such hormones with molecules that act as transporters or avoid its action on steroid receptors. In this sense, it is well known that approximately 98% of testosterone molecules are bound to proteins in the blood, principally to sex hormone binding globulin (SHBG), and they are not bioavailable due to this binding that prevents it from exiting the capillaries [30,31].

Chemical features of boron, boric acid, boronic acids and boro-esters and their interactions with proteins

Because of the ability of a boron atom to replace carbon, it is widely used in synthetic chemistry [26]. Although boron is formally trivalent, its empty *p*-orbital makes it act as a strong Lewis acid that quickly accepts electrons from a Lewis base, such that when a boron atom accepts a pair of electrons from a Lewis base, it adopts a tetrahedral configuration (sp^3) that has a chemical configuration comparable to carbon. Consequently, boronic acids can easily be transformed from trigonal planar sp^2 to an anionic tetrahedral sp^3 at a higher pH than that found at physiological conditions [4,26], a chemical feature that makes boronic acid suitable as an enzyme inhibitor since the tetrahedral sp^3 adduct mimics the deacylation transition state for proteolysis [32,33]. However, among BCCs, some exceptions have been described for this condition (the requirement of alkaline media for tetracoordinated boron); for example, both trigonal non-covalent and tetragonal covalent forms were found to coexist as a mixture at pH 7.4 for benzoxaborole (pKa = 7.34) on the carbonic anhydrase II, while at pH 8.7 only the tetragonal form was found [26].

The interactions in a complex between a protein and BCCs, where the boron atom in the BCC is localized close to an electron donor present in the protein, consist of both electrostatic interactions and interactions through reversible covalent bonds that would produce potent biological activity [26]. For most of the 300 co-crystalized protein complexes available in the protein data bank (PDB), it can be observed that BCCs employ a range of diverse forms in their interactions with proteins [17,26]. BCCs are coordinated through the anionic tetrahedral by a variety of amino acid residues that have a nucleophilic side-chain, such as threonine, serine, lysine and histidine (PDB entries 3ZJV, 5JQT,