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The Nutritional and Metabolic Effects of Boron in Humans and Animals

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ABSTRACT

We have undertaken studies in humans and animals that aimed to obtain further information about the intake and excretion of boron (B) as well as its effects on markers of coronary heart disease. In humans, we have shown that the intake of B is 2.2 mg/d; its urinary excretion is 1.9 mg/d, and there appears to be little intraindividual variation. Supplementation with 10 mg of B/d resulted in the recovery of 84% of the dose in the urine and a significant increase in plasma estradiol concentration, but no effect on plasma lipoproteins. In rats, increasing the intake of B through the drinking water is reflected in the tissue concentrations, results in an increase in plasma testosterone and vitamin D, and results in a decrease in HDL cholesterol. It is clear that B has the potential to impact significantly on a number of metabolic processes.

Index Entries: Boron; dietary intake; steroid hormones; lipids; urinary excretion; humans; rats.

INTRODUCTION

Boron (B) is the only nonmetal of the group IIIA elements in the periodic table. The B atom is small, with only three valence electrons. It acts as a Lewis acid, accepting hydroxyl ions, and thus leaving an excess of protons. B complexes with organic compounds containing hydroxyl groups, and those with more than two hydroxyl groups react more strongly. Thus, B is capable of interacting with substances of biological interest, including polysaccharides, pyridoxine, riboflavin, dehydroascorbic acid, and pyridine nucleotides. B was accepted as being essential for

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plants in 1923, and recently evidence has accumulated indicating that it may be an essential nutrient for animals *(1)*.

B occurs in high concentrations in sedimentary rocks and in clay-rich marine sediment owing to the relatively high concentration of B in seawater (4.5 ppm). Deposits of B are found in association with volcanic activity, and where marches or lakes have evaporated under arid conditions. The concentration of B in soil is influenced also by the presence of other minerals, soil pH, and texture *(1,2)*.

DIETARY B

The concentration of B in plants varies considerably from one species to another and also depends on the stage of growth. Furthermore, the extent of absorption by plants is influenced by the moisture content and temperature of the soil *(1,2)*. The geological influences, in addition to variations in the analytical methods used for the determination of B concentrations, result in the reporting of a wide range of B content of the same food. The B content of some foods has been published from a number of countries *(3–8)*. Consistently, foods of plant origin are rich sources of B.

What Is the Intake of B in a Group of Healthy Subjects?

To determine the magnitude of B consumption in a group of healthy free-living adults, we undertook a dietary study *(3)* in which subjects were provided with portable scales, and instructed to weigh where possible all food and liquids consumed for seven consecutive days. Analyses of energy, protein, fat, carbohydrate, dietary fiber, and alcohol content were performed using the NUTTAB database of Australian foods and the DIET 1 computer software (version 3.3, 1992, Xyris software Pty. Ltd., Highgate Hill, Queensland, Australia). The Australian database does not include analyses of B in foods. However, since a strong concordance was noted between the B content of the foods analyzed in our laboratory *(3)* and those listed in the more comprehensive Finnish Tables *(4)*, which employed a similar method of analysis, the latter were used to analyze the B content in the food records.

The analyses of the 7-d weighed records are shown in Table 1. The values represent the mean ± SD for a total of 210 d (males: 119, females: 91 d). The dietary intake of energy, protein, fat, and carbohydrate for the study population met national recommendations, except mean energy intake for the females was below the recommended range. The B intake in male and female subjects was similar, 2.28 ± 1.3 mg/d and 2.16 ± 1.1 mg/d respectively. Because wine contributes appreciable amounts of B, the values with and without wine consumption were analyzed. In the wine

Table 1
Mean Nutrient Intakes of Male and Female Subjects*

	Males	Females	All subjects
n	17	15	32
Total energy (MJ)	10.5 ± 3.8	6.9 ± 1.8	8.9 ± 3.6
Protein (% en)	17.2 ± 2.2	16.5 ± 2.1	16.9 ± 2.1
Fat (% en)	32.3 ± 4.5	28.7 ± 5.0	30.6 ±5.0
Carbohydrate (% en)	46.9 ± 4.3	53.5 ± 4.9	50.0 ± 5.6
Dietary Fibre (g)	31.7 ± 14	21.8 ± 6.6	27.4 ± 12.6
Alcohol (% en)	3.4 ± 3.1	1.5 ± 2.0	2.5 ± 2.8
Boron (mg)	2.3 ± 1.3	2.2 ± 1.1	2.2 ± 1.2

*Values shown as mean ± SD.

drinkers, wine contributed an average of 1.00 ± 0.65 mg/d in males (n = 6) and 0.67 ± 0.37 mg/d (n = 5) among the females. B intake correlated positively with energy (r = 0.34, $P < 0.0001$), dietary fiber (r = 0.31, $P < 0.0001$), and plant protein (r = 0.27, $P < 0.0001$), but not with carbohydrate intake.

METABOLIC EFFECTS OF B

Anionic trace elements, such as B, are usually absorbed from the gastrointestinal tract with high efficiency. Boric acid is also absorbed through open wounds and serous cavities. Excretion through the urine, bile, sweat, and breath is the major mechanism for maintaining homeostasis *(1)*.

How Useful Are Measurements of Urinary B in Humans?

We obtained 24-h urine samples on two different occasions at three weekly intervals from 18 healthy male subjects and measured the concentration of B *(9)*. The results obtained show that in subjects maintaining their habitual diet, the mean concentrations of urinary B in samples obtained on two different occasions were 1.87 ± 0.15 (mean ± SE) and 1.90 ± 0.23 (range: 0.35–3.53) mg B/day. In a second study, subjects were supplemented with 10 mg B for 4 wk. This resulted in a significant increase in urinary B excretion accounting for 84% of the ingested dose (from 1.6 ± 0.3 to 10.16 ± 0.92 mg/d). This suggests that the urinary excretion of B is a reflection of intake.

Table 2
Tissue Concentration of B (ppm) in Male Rats Receiving B in Their Drinking Water (2, 12.5, and 25 mg/rat/d) for 6 wk[a]

Tissue	estimated daily boron intake (mg)		
	2	12.5	25
Heart	1.15 ± 0.17	11.30 ± 1.06	20.28 ± 3.17
Lung	1.14 ± 0.15	10.91 ± 0.72	21.43 ± 4.5
Liver	1.13 ± 0.19	11.40 ± 1.65	19.36 ± 2.88
Kidney	3.04 ± 0.60	20.20 ± 3.64	32.32 ± 7.18
Spleen	1.20 ± 0.16	10.90 ± 0.90	23.63 ± 4.80
Testes	1.07 ± 0.20	11.27 ± 1.13	23.02 ± 2.70
Plasma	1.05 ± 0.11	11.19 ± 0.83	19.80 ± 2.54

[a]All values are expressed in ppm as mean ± SD for 5 rats in all groups. Concentrations shown for tissues obtained from animals fed the 2-mg dose are significantly different from those fed the 12.5 and 25 mg, and the 12.5-mg dose from 25 mg by two-way of ANOVA followed by Duncan's multiple-range test, $P < 0.05$.

B CONCENTRATIONS IN TISSUES

The estimated B content of humans is 3–20 mg *(1)*. Based on tissues obtained from two human cadavers, the total amount of B in different tissues and organs is reported to be (mg B/organ or tissue): skin, 7.8; skeleton, 2.1; liver, 7.8; heart, 0.2; spleen, 0.1; and kidney, 0.1 *(10)*. The plasma B concentration of neonates measured immediately after birth are higher than those recorded after 4–5 d of breast-feeding *(11)*.

We determined the response in rats to three levels of B intake during an experimental period of 6 wk *(12)*. B was added to the drinking water as boric acid to provide 2, 12.5, and 25 mg B/rat/d. Overall, the B concentration in tissues increased with dose, and among the organs examined, the kidney showed the highest concentration of B (Table 2).

EFFECT OF B ON PLASMA STEROID HORMONES AND PLASMA LIPIDS

B intake has a marked effect on the plasma testosterone concentration *(12,13)*. Increasing the intake of B from 2 to 12.5 and 25 mg

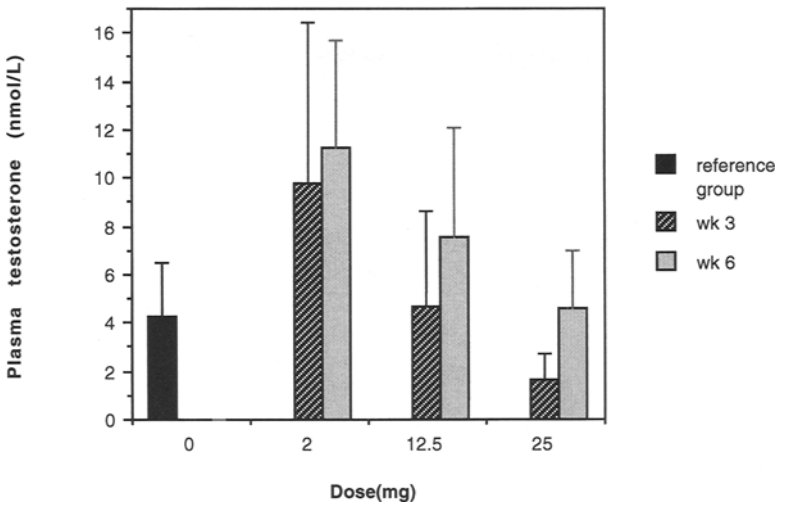

Fig. 1 The effect of three doses of B in drinking water in adult male rats on the concentration of plasma testosterone. Each bar represents mean ± SD, $n = 5$/treatment group and $n = 4$ in the reference group. The plasma testosterone concentration in animals fed the 2-mg dose is significantly higher than in those fed 12.5 and 25 mg, as determined by two-way ANOVA followed by Duncan's multiple-range test, $P < 0.05$.

resulted in lower plasma testosterone concentrations, which tended to increase (or partially rebound) by 6 wk of treatment (Fig. 1). The effect of B on the plasma testosterone concentration was paralleled by the testicular testosterone concentration (as shown by a significant and strong correlation, $r = 0.86$, $P < 0.0001$) *(12)*. In subsequent studies *(13)*, we showed that an intake of 2 mg of B/d resulted in transient effects on plasma lipids and a significant reduction in HDL_3-cholesterol (Table 3). Based on the results obtained in rats, the potentially favorable effects of B need to be balanced against the reduction in HDL_3-cholesterol.

It has been hypothesized *(14)* that B is required for the synthesis of these steroid hormones as well as others, such as vitamin D. An experiment was performed to determine the specificity of the effect of B on steroid hormones and to determine the subsequent impact on plasma lipids in rats over a 4-wk study period *(13)*. The addition of boric acid to the drinking water, equivalent to 2 mg B/rat/d, resulted in a rise in the plasma 1,25-dihydroxyvitamin D and testosterone concentrations relative to the control group. The increase in the concentrations of two unrelated steroid hormones supports the hypothesis that B stimulates the hydroxylation-related processes of the cholesterol nucleus.

Table 3
The Effect of Boric Acid Intake (Equivalent to 2 mg B/Rat/D) for 4 wk on Plasma Lipids and Lipoproteins (mmol/L) in Adult Male Rats[a]

	Control	Treatment
triacylglycerol	1.14 ± 0.22	0.99 ± 0.16
cholesterol	2.00 ± 0.14	1.96 ± 0.12
HDL-cholesterol	1.30 ± 0.12	1.24 ± 0.05
HDL_2-cholesterol	0.98 ± 0.1	1.01 ± 0.06
HDL_3-cholesterol	0.32 ± 0.03	0.23 ± 0.05*

[a]Values are shown as mean ± SD, $n = 6$ in the control group and $n = 8$ in the treatment group.
*$P < 0.002$.

What Is the Impact on Risk Factors for Coronary Heart Disease (CHD) when B Supplements Are Consumed?

Postmenopausal women supplemented with about 3 mg of B/d have a twofold increase in 17-β estradiol, which is equivalent to the levels found in women on estrogen-replacement therapy, and the levels of testosterone, the precursor of estradiol, also increased *(14)*. Although this observation was not confirmed in another study *(15)*, the possibility that B could impact on plasma steroid hormones and CHD risk factors warranted further investigation.

It is well recognized that diets high in plant foods lower the risk of CHD by reducing plasma lipids and oxidation of lipoproteins. The possibility that this effect is owing to the minor dietary factors in plants has not been widely explored. A diet rich in fruits and vegetables as well as nuts and legumes is rich in B, which in turn is reported to have a role in steroidogenesis. Gonadal hormones influence plasma lipoprotein metabolism and therefore may affect cardiovascular risk by affecting the plasma lipoprotein profile. This led us to investigate the effect of B supplementation on plasma lipids and lipoprotein oxidation *(13)* in 8 normolipidaemic male subjects (age 28.0 ± 7.6 yr; weight 75 ± 6.6 kg; body mass index (BMI) [kg/m^2] 24.7 ± 1.7). They were supplemented with 10 mg B/d for 4 wk in a placebo-controlled, randomized crossover trial (Fig. 2). Conjugated dienes and malondialdehyde (MDA) formed by Cu-catalyzed oxidation of LDL were measured to estimate the effect of B on its oxidative susceptibility.

Plasma estradiol concentrations increased significantly as a result of supplementation (Table 4), and there was a trend for plasma testosterone levels to be increased. The ratio of estradiol to testosterone increased

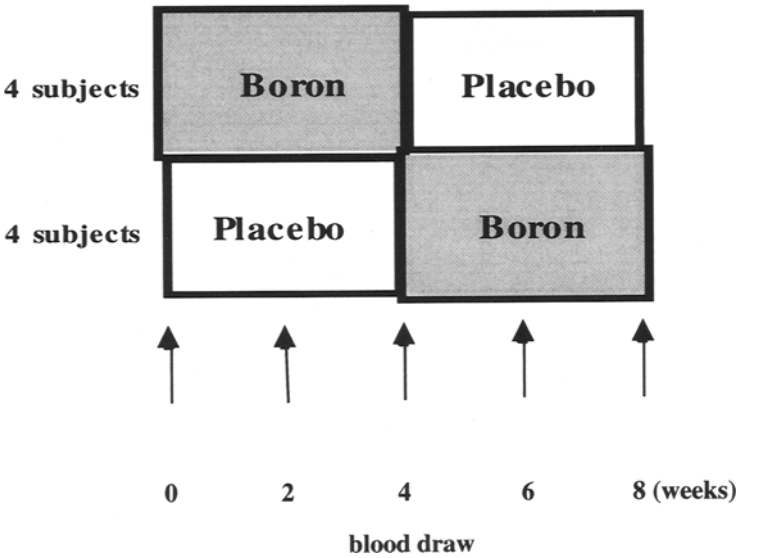

Fig. 2. Study design. Subjects were allocated randomly either to placebo or B supplements for 4 wk in each period.

Table 4
Effect of B Supplementation (10 mg/d for 4 Wk)
on Plasma Lipids, Oxidizability of Low-Density Lipoprotein
and Plasma Steroid Hormones in Healthy Volunteers

	Before Supplement	After Supplement
Lipids (mmol/l)		
Cholesterol	4.24 ± 1.02	4.39 ± 1.12
Triglycerides	1.38 ± 0.94	1.18 ± 0.52
HDL-cholesterol	1.18 ± 0.53	1.25 ± 0.67
LDL-cholesterol	2.44 ± 0.82	2.48 ± 1.17
LDL oxidation		
Lag time (min)	43.0 ± 7.0	42.8 ± 7.0
MDA(μM/50 μg protein)	6.61 ± 0.38	6.80 ± 1.16
Sex steroid hormones		
testosterone (nmol/L)	17.4 ± 3.5	19.4 ± 2.1*
oestradiol (pmol/l)	51.9 ± 21.4	73.9 ± 22.2**
oestradiol:testosterone	3.10 ± 1.2	3.96 ± 1.3***

Data shown as mean ± SD, $n = 8$.
*$P < 0.06$ (one-tail t-test); **$P < 0.004$ (paired t-test); ***$P < 0.01$ (paired t-test).

significantly after supplementation. Despite the effects on plasma steroid hormones, there was no difference in plasma lipids or lipoprotein levels, oxidation of LDL, and MDA formation after 4 wk (Table 4).

INTERACTIONS OF B WITH OTHER DIETARY CONSTITUENTS

A number of studies in humans and animals have considered the interaction between B and other nutrients. The balance of evidence suggests that B induces changes in Ca homeostasis by diverse mechanisms, including interaction with vitamin D and Mg metabolism. It is postulated that this is mediated by the influence of B on cell membranes *(1)*.

CONCLUSIONS

B appears to have a widespread role in biochemistry and nutrition, and there is some evidence to suggest that it may be an essential nutrient *(16)*. The variability in its natural distribution and variations in agricultural methods influence the B content of the food supply. Consequently, the intake of B depends on the soil geochemistry, the agricultural methods in use, and the food preference of the individual. B is absorbed easily, and tissue concentrations rise accordingly. High dietary doses are well tolerated and appear to interact favorably with Ca and vitamin D metabolism.

In a group of Australian adults, the intake of B is approx 2.2 mg/d, but its urinary excretion is approx 1.9 mg/d. Supplementation with 10 mg of B/d results in an increase in plasma estradiol and a tendency for an increase in testosterone. Despite these changes, plasma lipids are unaffected.

Interest is focused on phytochemicals in relation to disease prevention *(17,18)*. In view of the distribution of B in the food chain, it is possible that some of the biological effect of these minor dietary factors may be mediated via B. Further research will clarify these issues.

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