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Effects of Boron on Selected Aspects of Swine Health Related to Calcium and Phosphorus Metabolism

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EFFECTS OF BORON ON SELECTED ASPECTS OF SWINE HEALTH RELATED TO CALCIUM AND PHOSPHORUS METABOLISM

by

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INTRODUCTION

Boron has been under ever-growing, pressing concern regarding its nutritional impact in swine systems. Particularly, its influence on the metabolism of calcium and phosphorus has been a point of interest for some time that has still not been thoroughly studied. While data has supported its physiological vitality to botanical systems, with boron being shown to be a necessary element for vascular growth in plants (Warrington, 1923), a concrete role for boron in animal health at large has not yet been established. Rather, it has been speculated that it serves some physiological importance outside of plant biology as well (Nielsen, 1997). With boron being vital to plant health, it then is reasonable that an increase in boron intake can be achieved when pursuing forage dieting for livestock, and hence this is a factor to consider for farmers when structuring nutritional programs for their animals. With a diet focused on feeds, increasing incorporated boron beyond using more plant-based food would then have to be done artificially. The use of boron in nutritional programs in swine systems specifically has been under heavy scrutiny for some time due to its suspected, yet undetermined potential for toxicity to pigs (Khaliq et al., 2018). Combined with some positive effects of boron that have been demonstrated in various studies (Armstrong et al., 2001; Nielsen et. al., 1987; Nielsen, 1994; Rossi et al., 1993; Wilson and Ruszler, 1997, 1998), however, it is for this reason that the implications of boron in swine health have been and continue to be of particular interest.

Experiments with boron incorporated into swine models have supported various overarching effects of boron. Although a large collection of research has not been amassed on the topic, a few experiments have been completed involving such effects in different areas of swine health. One such study by Armstrong and Spears (2001) investigated different measures of bone quality in growing barrows and demonstrated several positive results of boron supplementation to these animals' diet. Concurrently, this specific study also focused on effects of the supplement on utilization of calcium and phosphorus in the test subjects, producing some positive data in this regard as well for the incorporation of boron into these animals' systems, but with less clear implications. However, knowing the positive correlation observed between boron supplementation and different bone measurements—along with the absence of negative interactions between supplemented boron and calcium or phosphorus metabolism—and the involvement with calcium specifically in bone growth and health, the study could indicate a positive effect of boron on at least calcium utilization within pigs. There have also been studies in other animal systems that suggested boron supplementation may be able to increase the retention of phosphorus (as well as calcium), displaying at least some trending effect of boron on these other two micronutrients as they are implemented in biological systems. As a result, combined with the concern over possible toxicity in pigs with boron supplementation, this is a topic that could certainly be researched further. The aim of this paper is to analyze the current findings to date surrounding boron's impact on calcium and phosphorus metabolism in pigs, addressing some of the more specific areas where additional boron research on this topic would be beneficial, and establishing connections and drawing inferences on the suspected effects from boron research in other organisms.

HEADING 2

BROADER INFLUENCES OF BORON RELATED TO CALCIUM AND PHOSPHORUS

Boron is a mineral that has been supported with data from research spanning many decades to impact animal health, ranging across various species. Multiple studies have demonstrated it being essential for at least plant health. Animal models used in some of these studies analyzing the effects of boron supplementation have been both micromolecular and macromolecular, with some of the involved species including zebrafish, frogs, cattle, fowls, rodents, and pigs. To begin with, in swine, supplementing boron to growing and nursing barrows on low-boron diets showed an increase in average daily feed intake and growth (average daily gain), although no effect on feed efficiency (Armstrong and Spears, 2001). Additionally, boron deficiency caused decreased survivability and growth in zebrafish and trout embryos (Eckhert, 1998; Rowe and Eckhert, 1999), respectively, as well as decreased development of rat and frog embryos (Fort et al., 1999). Bacteria have also been used, with one study displaying data for a reverse relationship from the one in focus presently—this specific study supported compensation for boron deficiency in cyanobacteria through an increase in calcium levels (Bolanos et al., 1993; 2002), displaying an effect of calcium on boron levels in the organism. Again, although this may be somewhat of a reverse to the relationship being investigated in this review, it does still provide evidence for an interaction between these two minerals physiologically. Likewise, and more in line with the original relationship in question, boron deficiency in plant models has been shown to decrease the amount of calcium bound to membranes (Mühling et al., 1998; Wimmer and Goldbach 1999). In lambs, boron supplemented in a low calcium diet caused a variety of downstream effects, including restored (relative to control group with normal calcium levels) growth rate (average daily gain), humoral immune response, total antioxidant activity, and degenerative changes in kidney and liver tissues. Expressions of SOD1 mRNA and gene were enhanced also, and while overall gene expression in the normal group was enhanced as well, these specific changes to superoxide dismutase (SOD) were not present in erythrocytes (Bhasker et al., 2017).

Similarly, in terms of some of these broader health benefits, another work suggested boron participates as an enzyme cofactor in antioxidant processes and acts as an immunomodulatory (by showing anti-inflammatory and Ig-stimulant characteristics) in enhancing resistance to mycotoxins in weaned pigs (Taranu et al., 2010). Boron supplementation has been shown to increase activity of superoxide dismutase dependent on calcium and zinc (and selenium-dependent glutathione) (Griffith et al., 1978; Nielsen, 1994; 1997), an enzyme important for its antioxidant properties, modulating superoxide free radicals to either oxygen gas or hydrogen peroxide (Docampo and Moreno, 2017). The elevated enzymatic activity then shows some possible disinterest in boron to compete with calcium physiologically (e.g. for a binding site to this specific enzyme), and in fact, an ability to enhance this calcium activity. Boron has also been shown through differential display polymerase chain reaction to increase mRNA of superoxide dismutase (Luo and Eckhert, 2000). Enhancement of gene and mRNA expressions specifically has been supported elsewhere as well, with boron supplementation to rat diets showing a decrease in DNA damage in a study by Kaneshima et al. (1966), the relevant forms here being boric acid and borax. Boron caused an increase in total mRNA for tumor necrosis factor (TNF)-alpha in cultured human fibroblasts (Benderdour et al., 1998) too, a finding that translates to pigs particularly well; a comparable effect from boron was observed in pigs with increases to TNF-alpha and interferon-gamma, by decreasing hydrogen peroxide production through enzymatic activity in the respiratory burst cascade. The increase observed in the two proteins was in response to stress, and hence occurred through increased production of cytokines. Similarly, boron was shown to decrease the inflammatory response caused by intradermal injections of phytohemagglutinin into pigs (Armstrong and Spears, 2003). Treatment of boron (boric acid) to human placental nuclei and wheat germ extract showed an increase in mRNA transcription and protein (VEGF and TGF-beta—factors important in angiogenesis and wound healing) translation (Dzondo-Gadet et al., 2002), and a lack of boron in unexpected root formation showed an increase in ribonuclease activity, hence decreasing RNA levels as well. Such increase in ribonuclease activity during boron deficiency was thought to be through cytokinesis, due to boron's effect on RNA metabolism (Ali and Jarvis, 1988). These data on boron's influence in nucleic acid biology suggest it may support phosphorus functionality in pigs, although the form of boron seems relevant, as competition has been suggested specifically between the borate and phosphate ions (Pfeiffer et al., 1945).

HEADING 3

SPECIFIC INHIBITORY ACTIVITY OF BORON RELATED TO CALCIUM AND PHOSPHORUS

While boron has been shown to benefit organisms in some fashion across several physiological pathways, some studies have shown some inhibitory implications as well. This again is a contributing, important factor to the continuing uncertainty surrounding boron's commercial use as a nutrient additive. The mineral was shown in laying hens, for example, at 400 mg boron/kg diet supplementation to decrease egg production, consumption of food and live weight (Rossi et al., 1993; Wilson and Ruszler, 1996; 1998; Kurtoğlu et al., 2002; Eren et al., 2004). Likewise, and specifically related to calcium and phosphorus, Wilson and Ruszler (1998) demonstrated additions of 50, 100, 200, and 400 mg boron/kg diet to laying hens decreased bone levels of calcium and phosphorus, and an inverse relationship between concentrations of phosphorus and boron has been observed in the brain and liver of guinea pigs (Akagi et al., 1963a).

Boron has also displayed negative regulation in reference to proteases. More specifically, boric acid and its n-alkylboronic acids have exhibited reversible, inhibitory binding to alpha-chymotrypsin, and in purified enzyme systems, inhibition of serine protease activity. This activity has displayed some dependence on pH, however, with these n-alkylboronic acids' inhibition showing a decline at pH less than 7, due to changes in the ionogenic groups of the enzyme's binding site. N-alkylboronic and boric acid were in fact found through two-component inhibition to compete for the same binding site in boric acid-specific inhibition of alpha-chymotrypsin, the site again being the ionogenic group, which more specifically is a catalytically active imidazole of the histidine-57 residue. These same competitive and inhibitory properties were displayed between boric acid and n-alkylboronic acids with chains up to 3 carbons, but with chain lengths greater than 3 and up to 6, n-alkylboronic acids are shown to become bifunctional inhibitors by interacting with the hydrophobic aspect of the enzyme's active site as well (Antonov and Ivanina, 1970).

Boron has been implemented in multiple studies involving glycolysis and related substituents in particular, its suspected inhibitory features at different stages in the pathway being involved. In many of the studies, boron has been shown to inhibit aerobic and anaerobic glycolysis through enzyme interference (Akagi et al., 1963b; Misawa et al., 1966; Kaneshima et al., 1986), decreasing ATP production and downstream utilization of carbohydrates. In a separate study by Travis et al. (1971), the same glycolytic symptoms were induced through phosphorus deficiency. Boron in the borate form is known to be a competitive and reversible inhibitor of glyceraldehyde-3-phosphate (GAP) dehydrogenase, achieved by boration of nicotinamide adenine dinucleotide (NAD), a cofactor of the enzyme (Wu and Chapin, 1994). Boron also inhibited GAP dehydrogenase (verified with lower measured optical density of NADH) and caused buildup of fructose 6-phosphate and fructose 1,6-bisphosphate in liver homogenate from guinea pigs and rats (Misawa et al., 1966). Kaneshima et al. (1986) showed this effect of boron with lower measured optical density of NADH as well—here it caused accumulation of methemoglobin in the blood of guinea pigs. Additionally, boron binds strongly to the oxidized form of NAD (NAD+) (Ralston and Hunt, 2001) to influence a number of its downstream effects, one being the release of calcium from the endoplasmic reticulum through the ryanodine receptor (Henderson et al., 2009), which is helpful for a variety of processes including the immune response, bone formation, brain activity, and liver function (Khaliq et al., 2017). Other work has supported boron acting as a reversible inhibitor of the cyclic ADP-ribose (converted from NAD+) that binds to this receptor, and as a result boron was shown to decrease calcium release (Henderson et al., 2009). Esterase and acetylphosphatase activities of glyceraldehyde-3-phosphatase, an important intermediate in glycolysis, isolated from pig muscle were shown to be inhibited by borate in another study as well, through competitive inhibition with NAD; in the enzyme's esterase activity, the number of acetyl groups diminished slightly, so the effect of borate could be diacylation here as well (Wolny et al., 1977). Again, these data indicate a likely ability of boron to regulate energy metabolism pathways (e.g. glycolysis). In the study by Travis et al. (1971), lack of inorganic phosphate administered to human patients decreased ATP, glucose- and fructose-6-phosphate, and several other glycolytic substrates, with the major regulatory step thought to occur with GAP dehydrogenase (as ATP is a cofactor for GAP dehydrogenase). Compared to other studies on borate inhibition of glycolysis, this could suggest possible competition between borate and phosphate (and hence boron and phosphorus) for glycolysis regulation. A study conducted by Pfeiffer et al. (1945) actually surmised that these ions may be competing for the same site, observing that phosphate and boron ion levels were inversely related. This highlights the importance of boron's proposed effect on the pathway as it may be relevant to the physiological functionality of phosphorus, and specifically, how the two minerals may interact in a swine model.

HEADING 4

DIRECT EFFECTS OF BORON ON CALCIUM AND PHOSPHORUS

An earlier study by Nielsen (1994) showed that addition of boron can suppress increased calcium transport across the cell membrane resulting from a high potassium diet in rats, hence supporting that boron may be able to alter calcium transport across plasma membranes. The aforementioned author also asserted that boron and calcium both affect cell membrane characteristics and trans-membrane signaling in a human model specifically. Furthermore, later studies produced data suggesting boron may form boron ester complexes with phosphoinositides, glycoproteins and glycolipids in the cellular membrane to act as redox modifiers and calcium chelators (Goldbach et al., 2007), which affects membrane function and integrity, and in turn, transport or regulation of ions across the membrane (Wimmer et al., 2009). Boron is thought to be able to cross the plasma membrane by its ability to bind to cis diol groups and thereby bind to intracellular sugars. Such cis diol groups exist in the ribose that composes part of RNA, and this provides some insight into the transcriptional and translational regulation by boron referenced earlier (Dzondo-Gadet et al., 2002).

Continuing with support for boron's effect on calcium specifically in biological systems, in addition to impacting calcium activity through interactions with cellular plasma membranes, it has also portrayed a role in bone health in several studies, an area where calcium is known to be quite significant. Armstrong and Spears (2001) investigated different measures of bone quality in growing barrows and found that while increased boron (from 5 mg boron/kg diet to 15 mg boron/kg diet) did not affect bone mineralization, it still increased ultimate shear force of fibula in barrows. Therefore, this would be a great exploratory area to conduct further research on the mechanism of boron's strengthening effect here, as it is not affecting mineralization of the bone (e.g. increasing calcium deposits, a mineral known for bone strength). More definitively, they showed that supplementing boron did not affect calcium content in fat-free bone ash, indicating boron is not impacting calcium directly to influence bone strength. Phosphorus, however, was increased (compared to controls), although this did not impact fat-free bone ash percentage, and so the effect on phosphorus by boron is not definitive. The researchers further suggested that borate anion may interact with the molybate assay (used to calculate these ash mineral levels) to produce this perceived increase in phosphorus—due to similarity in configuration of borate and phosphate anions—or boron may simply be decreasing other minerals like magnesium, copper and zinc in the ash. Likewise, while boron has been shown to negatively affect laying hen eggs, supplementation at 30, 60, 90, 120, and 150 mg boron/kg diet to broilers showed no effect on bone calcium concentrations (Fassani et al., 2005). Some work also suggested boron supplementation (5 mg/kg of diet) in weanling barrows on a semi-purified diet can increase femur measures of extrinsic strength (Armstrong et al., 2000), and Armstrong et al. (2001) demonstrated earlier that supplementing boron to a low-boron diet can increase barrow bone mechanics measurements. Boron supplementation has been shown to have potential for increasing bone mechanical properties in rats (Chapin et al., 1997, 1998) and chickens (Rossi et al., 1993; Wilson and Ruszler, 1997, 1998) as well.

Finally, in terms of some of the most direct effects of boron on calcium and phosphorus metabolism, a few findings have been established to date. Boron appears to increase absorption of calcium in wethers (Brown et. al., 1989), and can treat and prevent milk fever (hypocalcemia) in cows during the periparturient phase (Kabu and Civelek, 2012). Boron was shown to enhance absorption and balance of calcium and phosphorus in vitamin D-deficient rats (Hegsted et al., 1991), as well as increase 1,25-hydroxyvitamin D in other rats (Samaan et al., 1998), and reduce calcium and phosphorus deficiency (and enhance growth) in broiler chickens (Cinar et al., 2015). When supplemented in water, boron also was shown to increase phosphorus retention in the body in heifers (shown by less excreted in the urine) and decrease plasma phosphate, though not to deficient levels (Green and Weeth, 1977). Also displayed by less excretion in the urine, boron supplementation was shown to increase calcium and phosphorus retention in the body in humans as well (Nielsen et. al., 1987). In pigs specifically, Armstrong and Spears (2001) showed it does not affect calcium and phosphorus retention or absorption in barrows, although it did show increased plasma phosphorus concentration after the nursing period for barrows. This indicates that their findings on the effects of boron on bone mechanical measurements can be induced without having to sacrifice significant alterations to metabolism of calcium or phosphorus, as while boron did not seem to enhance calcium or phosphorus functionality in the pigs, it did not appear to inhibit it either.

HEADING 5

SUMMARY

As mentioned previously, there are differing results for the overall impact of boron on the metabolism of calcium and phosphorus, and other minerals as a whole. Some studies have suggested that the activity of boron may actually be limited to organisms under some form of nutritional or other stress (Nielsen, 1991). Chicks have been shown to have increased plasma calcium and magnesium concentrations when supplied with boron, but this is also when they were first deficient in magnesium and cholecalciferol (Hunt, 1989), and nonruminant species supplemented with boron showed altered metabolism of calcium, phosphorus, and magnesium while under nutritional stress (Nielsen et al., 1987; Hegsted et al., 1991; Hunt et al., 1997). In addition, boron supplementation to post-menopausal women with low-magnesium diets caused less urinary excretion of calcium, magnesium and phosphorus (Nielsen et. al, 1987). This is supported in part by the findings discussed earlier as well, indicating boron can be impactful to pigs during an inflammatory response (Armstrong and Spears, 2003). Without many studies dedicated solely to this idea, further research on the matter would certainly help to provide a more complete picture of how boron is taking an effect on these important two minerals in the physiology of pigs—as well as perhaps many more minerals—and has other general effects in the species. Such findings could then provide insight into how boron may affect other species as well, particularly those most heavily involved in livestock, stimulating corresponding research in those species to garner support for the theories obtained with pigs. Moving forward, this would help in determining the most accurate benefits of boron additives to these animals' diets, helping agriculturists make more informative decisions between this and foraging (for example) in nutritional programs and better control the qualities in the animals they produce.

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