Some recollections of early swine research with selenium and vitamin E[1]

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ABSTRACT: Despite the much-publicized finding of protective effects of selenium against myopathies in young ruminants (white muscle disease), the earliest discovery of the health benefits of selenium was made with swine in 1957. Because the body fat of pigs more closely resembles the fat in their diets than does that of ruminants, swine were useful subject animals for the investigation of dietary antioxidants, and much has been learned from them concerning the metabolic functions of both selenium and vitamin E. Swine research also played an important role in establishing nutrient essentiality status for selenium and in gaining approval from regulatory agencies (FDA) for its supplementary addition to livestock diets. These findings added significantly to the developing knowledge of the role of selenium in animal nutrition and subsequently to the acceptance of selenium supplementation as a production practice with various species of farm animals worldwide. This paper will examine some steps in the assembly of information concerning dietary antioxidants, including, more recently, implications for human nutrition and disease control.

Key Words: Pigs, Selenium, Vitamin E

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Introduction

The lively interest that has arisen over the last few years concerning the potential health benefits of antioxidant substances in the human diet makes it timely to review our knowledge of selenium and vitamin E, two important members of the antioxidant family. Swine have played an important part in this research, partly to improve their health and production efficiency, but also as a suitable animal model for the development of knowledge applicable to humans. In this paper, some of the early research findings related to selenium and vitamin E gained through studies with swine will be discussed.

Selenium

Much of the early interest in selenium was directed toward its protective effect against myopathies, such as the one commonly known as “white muscle disease.” However, it is interesting to recall that the earliest published reference to selenium’s role as an essential nutrient for domestic animals was generated with swine as the subject animal (Eggert et al., 1957). The predominant lesion indicative of selenium deficiency in swine was hepatosis dietetica, often accompanied by mulberry heart (Pellegrini, 1958).

To begin with, it was difficult to change from regarding selenium as a toxin or even as a carcinogen, to now thinking of it as an essential micronutrient. Kubota et al. (1967) and Ku et al. (1972) published useful surveys of selenium status in the United States and established the direct relationship between dietary and animal tissue selenium. Areas of selenium toxicity have been mapped around the world, as have, more recently, those of selenium deficiency (Oldfield, 1999), and it is significant that the latter are much more extensive than the former.

Because selenium and vitamin E often appeared to work together, it was questioned early on whether selenium was in fact an essential nutrient in its own right or merely an adjuvant to vitamin E. Swine research contributed to the evidence that selenium was an essential nutrient when it was shown that high levels of vitamin E did not eliminate the need for selenium (Ewan et al., 1969). This was confirmed with reference to reproduction when a single, subcutaneous 2.5-mg dose of Se as selenite given to sows just before mating resulted in a significant increase in farrowing percentages in Australian piggeries (Levander, 1986). The diet fed these sows was considered adequate in vitamin E.

One of the perplexing things that delayed the practical application of selenium supplementation in the United States was the FDA’s refusal to authorize its use because of fears that it might be a carcinogen. When this concern was removed, research, again conducted

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with swine (Meyer et al., 1981), allowed the FDA to recognize selenium as an essential nutrient, and it approved the addition of up to 0.3 ppm of Se to prestarter and starter diets for pigs (Ullrey, 1992) in 1982.

Reilly (1996), who has chronicled the selenium scene for many years, has estimated that selenium has generated over 100,000 papers in the scientific literature. In spite of the tremendous amount of research that selenium has attracted, investigations with it continue to generate new understandings—many of them involving swine. For example, research at Ohio State University has shown that low-Se diets fed to boars caused abnormal mitochondria to occur in their sperm, along with a 25% lower ATP concentration (Marin-Guzman et al., 2000), and the authors suggested that selenium might enhance the maturation of sperm in the epididymis. There was no benefit, however, from adding selenium to semen extenders in terms of sperm motility.

The benefits conveyed by selenium to animal health and productivity stimulated a research effort into the most effective form of selenium to use. Much of the attention was focused on comparisons of organic vs. inorganic sources; the organic form was frequently supplied by selenized yeast and the inorganic forms were the sodium salts. Apparently, different forms of selenium perform differently at varying levels in the diet. Cary et al. (1973) and Mahan and Moxon (1978) found no differences in the effects of organic or inorganic selenium in pigs when given at levels below 0.1 ppm in the diet using tissue retention as the criterion. In contrast, when the selenium content of the feed exceeded 0.1 ppm, organic forms of selenium were clearly better utilized. Interestingly, the availability of inorganic selenium proved higher than that of organic forms for the seleno-enzyme, glutathione peroxidase (Goehring et al., 1984). In Finland, inorganic selenium (sodium selenate) has been added to fertilizers and converted to organic forms by crops that are then fed to livestock, thereby raising the selenium content of meats and benefiting human consumers (Hartikainen and Ekholm, 2001).

Vitamin E

Although the fat-soluble dietary factor that was to become known as vitamin E was discovered in 1922, deficiency symptoms in swine were not described until more than a quarter-century later (Adamstone et al., 1949). Vitamin E has proven to be a multistructured compound, and during the four decades since its original discovery, eight structurally similar, naturally occurring compounds have shared its vitamin status. When selenium's status as an essential micronutrient was being established, it became evident that the two substances, vitamin E and selenium, acted synergistically. Hoekstra (1975) proposed that their synergism related to the process of antioxidation, wherein tocopherols tended to prevent oxidative damage to polyunsaturated fats in cell membranes, whereas selenium, as part of seleno-enzyme glutathione peroxidase, catalyzed the destruction of lipid hydroperoxides. This explains how these two nutrients play separate but interrelated roles in the cellular defense system against oxidative damage.

Vitamin E's antioxidant capabilities quickly found a practical application in commercial swine production. Tocopherols in the pigs' diets become a part of their tissue fats and inhibit the formation of oxidation products, which tend to reduce the acceptability of pork products in the human diet (Najman et al., 1976). Unlike ruminant animals, swine store a body fat that closely resembles the fat in their diet, and this may well have flavors and odors that are objectionable to consumers of their meat. Such flavor and odor compounds are most often the products of oxidation; if so, they will respond positively to the supplementary use of vitamin E and selenium, which improve the shelf life and quality of pork cuts.

Another of the persistent problems in swine husbandry has been that of iron deficiency anemia in baby pigs, for which a common treatment is giving iron, often as iron-dextran, by injection. It was noticed in Swedish studies that baby pigs that were deficient in vitamin E and selenium had a low tolerance to these iron-dextrose injections (Lannek et al., 1962). Pretreatment with vitamin E, selenium, or the commercially produced antioxidant, ethoxyquin, helped to prevent this intolerance. The literature has a number of reports linking baby pig anemia to vitamin E deficiency, but the relationship may not be causal (e.g., Nafstad, 1965). Canadian workers (Fontaine et al., 1977) concluded that vitamin E did not significantly influence erythropoiesis in growing pigs.

Ullrey (1981) has noted that not long ago, most nutritionists would have considered a vitamin E deficiency in swine to be unlikely, and recalled that the 1968 revision of the NRC's *Nutrient Requirements of Swine* stated that, "it is unlikely that practical swine diets would be deficient in vitamin E unless the diet contained excessive amounts of highly unsaturated fatty acids." With pigs raised in confinement, however, the commonly used corn-soybean diets of the Midwestern states could quite likely be deficient in both selenium and vitamin E. Beyond this, stress factors may act to increase pigs' requirements for both selenium and vitamin E. Common stresses are imposed by a cold, damp environment (Naftalin and Howie, 1969) and by infectious diseases (Keahy and Whitehair, 1966). Therefore, it appears that deficiencies of vitamin E and selenium can occur in commonly fed swine rations in this country. Indeed, Ohio studies (Mahan and Moxon, 1978) have reported losses and necropsy signs characteristic of vitamin E/selenium deficiency in pigs fed diets containing 22 IU of vitamin E and 0.1 mg of supplemental Se/kg.

Vitamin E functions, as does dietary selenium, to improve animals' immune response. Ellis and Vorhies (1976) have reported that increasing the vitamin E level of the swine diet over that generally considered adequate led to increased titers of serum antibodies to

Escherichia coli bacteria. Addition of 100,000 IU of vitamin E/t resulted in antibody titers 2 to 3 times higher than those of the pigs on the control diet.

The issue of vitamin E requirements is complicated by the fact that both the animals' needs and the nature of the diet must be considered. Swedish investigators recorded that, whereas a combination of 5 IU of vitamin E and 0.008 mg of Se/kg prevented deficiency signs in weanling pigs (Hakkarainen et al., 1978), the supplements were inadequate when given separately. Beyond the influence of unsaturated fats already mentioned, interactions may occur between vitamin E and some of the trace elements, including iron, copper, and zinc (Lannek et al., 1962). Ullrey (1981) recognized these interrelationships when he wrote, ". . . when Se supplements are restricted to 0.1 mg/kg, vitamin E supplements for corn-soybean diets should be at least 10 to 20 IU/kg. For problem herds, higher levels of vitamin E may be helpful, with the greatest benefit to be expected in the breeding herd and among young pigs. Supplements of 30 IU of vitamin E should be adequate under most circumstances. When diets contain considerable amounts of oxidized fat or the pigs are stressed by infection, even higher levels of vitamin E may be necessary."

What's Next?

Both selenium and vitamin E have been clearly established as essential nutrients, and there are many examples of a synergism of action between them. The two belong to a group of substances, along with vitamins A and C, that exert antioxidant powers that protect animals and humans from peroxide damage, and although this may be their major function, it is not the only one. Whereas much of the research reported herein has been directed toward improving the health and productivity of food-producing animals, recent evidence suggests that they may, particularly in the case of selenium, also provide benefits to human health. Their areas of activity include two of the most dreaded human ailments: cardiovascular diseases and cancer. Neve (1996) suggested that selenium protects against cardiovascular disease through the action of glutathione peroxidase against oxidation of lipids and subsequent reduced platelet aggregation. In men with cardiovascular disease, platelet aggregability is inversely related to selenium status (Neve, 1996). Peplowski et al. (1981) observed that supplemental selenium and vitamin E had a positive and additive effect in enhancing immune responses in weanling swine. The most widely cited study of selenium's protection against cancer is the one headed by Clark (1996) at the Arizona Cancer Center, in which 1,312 individuals with a history of nonmelanoma skin cancer were subjected to either dietary selenium supplementation (200 μg/day, as selenized yeast) or a placebo. The skin cancer did not respond, but there were striking effects on other cancers, including a 46% reduction in lung cancer, 58% reduction in colon cancer, and 63% fewer cancers of the prostate (Clark et al., 1996). An excellent review of the human health implications of selenium has been provided by Rayman (2000). The U.S. National Cancer Institute is now funding a 12-yr study in which 32,000 men will be given selenium and vitamin E to determine whether they are protective against prostate cancer. When one adds to this mounting evidence of health protection and the finding by Beck et al. (1994) that selenium will inhibit the pathogenicity of certain viruses, the potential usefulness of these substances becomes very great, indeed. And to the members of the American Society of Animal Science, it is especially noteworthy that much of the background research has been done with swine.

Implications

The antioxidants selenium and vitamin E are critical for both animal and human health and well being. Swine have been instrumental in the development of that understanding. Current research activity suggests that the understanding of the total contribution of these nutrients to health and well being will continue to grow.

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