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Selenium deficiency associated porcine and human cardiomyopathies

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ABSTRACT

Selenium (Se) is a trace element playing an important role in animal and human physiological homeostasis. It is a key component in selenoproteins (SeP) exerting multiple actions on endocrine, immune, inflammatory and reproductive processes. The SeP family of glutathione peroxidases (GSH-Px) inactivates peroxides and thereby maintains physiological muscle function in humans and animals. Animals with high feed conversion efficiency and substantial muscle mass have shown susceptibility to Se deficiency related diseases since nutritional requirements of the organism may not be covered. Mulberry Heart Disease (MHD) in pigs is an important manifestation of Se deficiency often implicating acute heart failure and sudden death without prior clinical signs. Post-mortem findings include hemorrhagic and pale myocardial areas accompanied by fluid accumulation in the pericardial sac and pleural cavity. Challenges in MHD are emerging in various parts of the world.

Se is of fundamental importance also to human health. In the 1930s the Se deficiency associated cardiomyopathy named Keshan Disease (KD) was described for the first time in China. Various manifestations, such as cardiogenic shock, enlarged heart, congestive heart failure, and cardiac arrhythmias are common. Multifocal necrosis and fibrous replacement of myocardium are characteristic findings. Pathological findings in MD and KD show striking similarities.

Introduction

Selenium (Se) was established as a dietary indispensable trace element after demonstrating preventive effects on torula yeast (*Candida utilis*) induced rat liver necrosis [1]. It is a constituent of numerous selenoproteins (SeP) that play critical roles in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection [2–7]. Vitamin E (vit E), along with SeP, is a nutrient with potential antioxidant catalytic activity [8,9].

Se deficiency involvement in fatal cardiomyopathy is well known in pigs [10–13] and in humans [14–17]. These conditions are called Mulberry Heart Disease (MHD) [10] and Keshan Disease (KD) [18], respectively. MHD was described for the first time in 1967 [19]. Nutritional, environmental and genetic factors may influence the prevalence of MHD at marginal or deficient Se and/or vit E supply [11]. In 1935, an outbreak of fatal cardiomyopathy was reported in the Keshan and nearby counties in the North East of China [20,21]. Enteroviral [22–25] and mycotoxin influence [26] as well as chronic pollutant poisoning [27,28] have been discussed as risk factors for KD pathogenesis.

Elevated dietary polyunsaturated fatty acid (PUFA) levels combined with low vit E levels have been discussed as possible interacting factors in progression of both MHD and KD [24,29,30]. This review will pinpoint important issues regarding Se requirements, sources, metabolism, and deficiency consequences across species with particular focus on pathology in the porcine and human cardiac muscle.

Se requirements in animals

Most of Se in ordinary feeds and forages is protein-bound SeMet, accounting for 55–65% of the Se in cereals and more in protein concentrates [5]. Providing adequate dietary Se supply to livestock is complicated due to variations in Se concentrations in feeds and forages [31]. Kappel et al. [32] could demonstrate variations in Se concentrations in various forages sampled from the same farm in Louisiana (US) ranging from 57 to 295 μg/kg DM throughout the year. Increased oxidative stress imply higher Se requirements [31], like e.g. high levels of dietary PUFAs in feeds which are vulnerable to

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oxidation [33,34]. Oxidative destruction of PUFAs within cell membranes is an important mechanism of free radical-mediated cellular injury [35].

A "hierarchy" of requirements for livestock have been stated for different stages of production, ranging from 0.02 to 0.2 mg/kg dry matter (DM), taking into consideration various vit E and PUFA levels, temperature stress and field circumstances [31]. The National Research Council (US) indicates that the dietary requirement in pigs ranges from 0.3 mg/kg for weanling pigs to 0.15 mg/kg for finishing pigs and sows [36]. There is no general agreement on limits between adequate, marginal and deficient blood levels in pigs, neither for vit E nor for Se. Radostits and co-worker [37] indicate 0.07–0.09 and 0.18–0.22 mg/L as normal serum values for neonate and adult pigs, respectively. Such low normal Se levels in piglet's blood plasma with increment after weaning, as well as considerably higher levels in adult sows were also shown in a study of Norwegian pig herds [38].

Se is regarded as the most toxic essential trace elements [31]. The European Commission has set upper limit values for inorganic Se to 0.5 mg/kg and organic Se (Se yeast, L-SeMet) to 0.2 mg/kg complete animal feed to prevent selenosis [39].

Se requirements in humans

The intake requirement of Se for *optimal human health* has not been established [40]. Uncertainty regarding the definition of optimal Se status has resulted in different dietary Se recommendations [41], and no accepted reference ranges exist due to variations in Se status between countries [42].

Current daily Se intake recommendations are based on levels that maximize the activity of glutathione peroxidase (GSH-Px) in plasma, since this is a well described functional protein in humans [42,43]. Recommendations range from 40 to 75 μg/day in men and women in the United States [44], while several European Countries recommend Se supply from 25 to 70 μg/day [45–47]. In Australia and New Zealand, recommended daily Se intake ranges from 40 to 70 μg/day [48]. For children, recommendations range between 5 and 50 μg/day depending on age and country [45–49]. Recommended daily Se intake for pregnant women ranges from 30 to 70 μg/day, while during lactation, 30–75 μg/day are recommended [45–49]. Country dependent recommendations are summarized in Table 1.

Tolerable upper Se intake level in humans including a safety margin has been set to 400 μg/day in adults and 45–280 μg/day in infants and children based on morphological changes in finger-nails as the main criterion for clinical diagnosis of selenosis [44,50].

Deficiency of Se in the human diet has been associated with the KD affecting the heart [14,18,24,25,51–53]. KD is a cardiomyopathy characterized by heart failure, cardiac enlargement and cardiac shock [14]. Reports show higher prevalence among children and women of child-bearing age living in areas with Se poor soil [54].

Se sources, uptake and metabolism

Se is a semi-metallic, naturally occurring trace element occurring in four different inorganic chemical forms; (selenide (Se^{2-}), elemental selenium (Se^{0}), selenite (Se^{4+}), and selenate (Se^{6+})). Se competes with sulphur (S) in biochemical pathways, and is incorporated into the S-containing amino acids, cysteine (Cys) and methionine (Met) [55] forming organic Se compounds like SeCys and selenomethionine (SeMet) [56].

Se availability depends on the concentration of Se in the soil, the parent rock, weathering, pH and soil texture. Se deficient soil regions are found in e.g. New Zealand, China, the Scandinavian and Balkan countries, and the Atlantic Region of Canada [14,57–59]. A recently published cohort study indicates common marginal Se deficiency within certain socioeconomic groups living in the South East of the United States [60].

The retention of organic Se forms is higher than that of inorganic forms [41]. Price differences have, however, given preference to usage of Se salts in animal feed [61]. The most prevalent Se supplements typically consumed by livestock are the inorganic Se sources Na_2SeO_3 and sodium selenate (Na_2SeO_4). Se supplements for humans exist in numerous forms including SeMet, Na_2SeO_3 and Na_2SeO_4 [62].

Since 2006, organic Se has been allowed as a feed additive. Today, Se yeast is the leading source of organic Se supplements in animal and human nutrition [63]. It contains 94 ± 5% of the total Se in the form of SeMet [63]. In May 2013 and February 2014, two organic SeMet sources were given market authorization by the EU [64]. A hydroxy-analog of SeMet (R,S-2-hydroxy-4-methylselenobutanoic acid, HMSeBA) and L-SeMet are two pure sources of SeMet [63]. HMSeBA has shown greater relative Se bioavailability compared to Se yeast in broiler chickens [65] and pigs [66].

Nano-elemental Se has gained substantial attention due to its therapeutic effects on cancer cells [67] and formulations are being investigated to ensure high-dose delivery to target cells [68]. Nano-elemental Se produced by chemical [69], physical [70] or biological [69] techniques has drawn much attention due to its relatively high absorption rate and bioavailability [71–73]. Bioavailability and toxicity of Se nanoparticles depend on size [72] and thermo-stability [73]. Nano-Se has shown a 7-fold lower acute toxicity than Na_2SeO_3 in mice (LD50 113 and 15 mg Se/kg body weight respectively) [67]. However, results by Li et al. [74] show that toxicity differences between species must be taken into consideration when applying nano-elemental Se. Nano-Se exhibit strong toxicity for Medaka (*Oryzias latipes*), most likely due to hyper-accumulation of nano-elemental Se in the liver.

Selenate shares sodium-mediated carrier transport mechanism with S while selenite is absorbed through passive diffusion [103]. SeMet and SeCys follow the sodium-dependent, carrier-mediated routes of the amino acids Met and Cys across the small intestinal mucosa and are absorbed as intact molecules [104]. A documented route of uptake for both nano-and micro-particles is via the M-cell rich layer of Peyer's Patches by active transport [105].

Generally, the dietary form and the Se status of the individual determinates the metabolic fate [35,106]. Different Se sources can convert to the precursor selenide for SeP synthesis [107] or selenosugars [102]. Selenite is reduced to selenide by the glutathione/glutaredoxin and thioredoxin systems in the liver [81,82]. The exact mechanism of selenate reduction is not yet clear. Selenide may also be generated from dietary SeMet and SeCys by lyase action [83]. Selenide has three main conversion routes dependent on the current Se status of the organism. Firstly, selenide is transformed to Se-cysteyl tRNA for insertion of SeCys in SeP. At moderate levels of intake, excess selenide not used in SeP synthesis is converted into selenosugars for excretion via urine. At high intake levels, methyltransferases add a methyl group to selenide, resulting in dimethylselenide (excreted via breath and feces) and trimethyl selenonium (excretion via urine) [102,111,112].

SeMet provides a slow-release reserve pool from normal protein turnover [86]. It can be randomly incorporated into proteins instead of Met [87] and its contribution to plasma Se depends largely on the amount of SeMet ingested [88]. This can lead to high Se levels in tissue and blood proteins. SeMet containing proteins can be more sensitive to oxidation than natural proteins [89,90] and can therefore act as targets of immune response. The Panel on Food Additives and Nutrient Sources, European Food Safety Authority (EFSA) has noted that at high dose levels, L-SeMet influences the immune system. Additionally, there are possible endocrine disrupting effects [91].