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EFFECTS OF SELENIUM ON ANIMAL HEALTH

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Abstract

Selenium is an essential trace element in the diet of humans and domesticated animals. It is a component of more than 30 selenoproteins, which play a significant role in the body. Selenoproteins protect cells from damage inflicted by free radicals, the cause of many chronic diseases. They also participate in the metabolism of thyroid hormones, control reproductive functions and exert neuroprotective effects. In addition to its anti-proliferative and anti-inflammatory properties, selenium stimulates the immune system. The role of selenium is aided by vitamin E and sulfur-containing amino acids. Selenium deficiency contributes to pathological changes in farm animals, which incur large financial losses each year. Low selenium levels can lead to the development of nutritional muscular dystrophy, also known as white muscle disease, in lambs, kids, foals, calves and poultry from birth to 3 months of age. Selenium deficiency may also cause exudative diathesis in poultry as well as dietary necrotic liver degeneration and mulberry heart disease in pigs. Parturition problems resulting from reduced tension of the muscular layer of the uterus, postparturient paraplegia, placental retention and purulent inflammations of the uterine lining are also attributed to low selenium levels. Selenium deficiency contributes to the formation of ovarian cysts and increased embryonic mortality in the first 3-4 weeks after insemination. Selenium and vitamin E facilitate neutrophil migration to the mammary gland, and they enhance the bactericidal effects of neutrophils, thus shortening and alleviating the symptoms of clinical mastitis. Selenium poisoning is rarely encountered, and it most often results from an overdose of selenium supplements. The most common forms of selenosis are chronic selenosis, referred to as alkali disease, and acute selenosis, popularly known as blind staggers.

Key words: selenium deficiency, selenoproteins, animals.

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SELEN I JEGO WPŁYW NA ZDROWIE ZWIERZĄT

Abstrakt

Selen jest niezbędnym składnikiem diety nie tylko ludzi, ale również zwierząt domowych. Wchodzi w skład ponad 30 białek zwanych selenoproteinami, które pełnią różnorodne funkcje, m.in.: pomagają zapobiegać uszkodzeniu komórek przez wolne rodniki, które uważa się za czynnik etiologiczny rozwoju przewlekłych chorób, uczestniczą w metabolizmie hormonów tarczycy, warunkują prawidłowy przebieg funkcji rozrodczych oraz działają neuroprotekcyjnie. Selen wykazuje działanie antyproliferacyjne i przeciwzapalne oraz stymuluje układ odpornościowy. Działanie tego pierwiastka jest ściśle powiązane z witaminą E i aminokwasami siarkowymi. Niedobór selenu odpowiedzialny jest za powstawanie wielu patologicznych stanów w organizmie zwierząt gospodarskich, co każdego roku generuje znaczne straty ekonomiczne. Schorzeniem powodowanym przez zbyt niski poziom selenu jest pokarmowa dystrofia mięśni (PDM), zwana też chorobą białych mięśni, występująca u jagniąt, koźląt, źrebiąt, cieląt oraz drobiu do 3. miesiąca życia. Do innych chorób uwarunkowanych niedoborem tego biopierwiastka należą: skaza wysiękowa drobiu, pokarmowe zwyrodnienie wątroby i choroba morwowego serca u świń. Niedoborom selenu przypisuje się również wpływ na trudne porody związane ze słabym napięciem mięśniówki macicy, zaleganie poporodowe, zatrzymanie łożyska oraz powstawanie ropnych zapaleń błony śluzowej macicy. Zbyt niski poziom tego pierwiastka może być przyczyną tworzenia się cyst na jajnikach i zwiększonej zamieralności zarodków w czasie 3-4 tygodni od inseminacji. Selen wraz z witaminą E usprawnia migrację neutrofili do gruczołu mlekowego oraz zwiększa ich zdolność do zabijania bakterii, co skraca czas trwania klinicznego zapalenia gruczołu mlekowego oraz łagodzi jego przebieg. Obecnie zatrucie selenem występuje rzadko, głównie jest związane z przedawkowaniem preparatów selenowych. Najczęściej opisywane są dwie postacie selenozy: przewlekła, zwana chorobą alkaliczną, i ostra, zwana ślepą kołowacizną.

Słowa kluczowe: selen, niedobór, selenoproteiny, zwierzęta.

INTRODUCTION

Selenium was discovered in 1818 by the Swedish chemist Berzelius, while he was producing sulfuric acid. The element was named after the Greek moon goddess, Selene (Lenz, Lens 2009). Selenium, sulfur and tellurium belong to group 6 (chalcogens) in the periodic table of the elements. Selenium rarely occurs in its elemental state in nature. It is a trace element with an estimated 0.00008% content of the earth's crust (Bednarek, Bik 1994a). Selenium concentrations in soil and the entire food chain vary considerably. In some countries, mainly in China and Brazil, very low (<0.1 mg kg^{-1}) as well as very high selenium soil levels (>0.5 mg Se kg^{-1}) are noted in areas distant only 20 km from one another (Dhillon, Dhillon 2003). In the United States, Ireland and India, the selenium content of soils may be as high as 100 mg Se kg^{-1} (Lenz, Lens 2009). In Poland, the most selenium-deficient areas are the southern parts of the country as well as the regions of Pomerania and Masuria (Bednarek, Bik 1994b). Our knowledge about the effects of selenium on living organisms has evolved significantly in the past

decades. Perceived mostly as a toxic element in the past, selenium has been recognized as a vital contributor to human and animal health.

SELENOPROTEINS

Selenium is a vital component of various metabolic pathways in animals, and its role is complemented by vitamin E and sulfur-containing amino acids. Selenium is not accumulated in bodily organs or tissues. When ingested, it is incorporated into the functionally important group of selenoproteins, where, in combination with cysteine, a sulfur-containing amino acid, it is present mostly in the form of selenocysteine. The biological role of selenium as a component of glutathione peroxidase (GSH-Px) was first implied in 1973. Since then, more than 30 selenium-containing proteins, mostly enzymes, have been identified (Hefnawy, Tortora-Perez 2010). To date, scientists have been successful in describing detailed biological functions of only 10 selenoproteins from the above group. GSH-Px is one of the key selenoenzymes that has been characterized in detail. GSH-Px protects hemoglobin and fatty acids from oxidation, and it scavenges free radicals. The substrates for GSH-Px include reduced glutathione and, subject to enzyme specificity, hydrogen peroxide or phospholipid hydroperoxide. Four isoforms of the enzyme have been identified in mammals. They are: classic GSH-Px, also known as cytoplasmic peroxidase, which is found in all bodily tissues, plasma GSH-Px, an extracellular enzyme determined mostly in the kidneys and liver, gastrointestinal GSH-Px, and phospholipid-hydroperoxide GSH-Px which protects cell membrane phospholipids against oxidation and participates in the synthesis of prostaglandins and catecholamines (Arthur 2000). The first three GSH-Px isoforms are tetramers, whereas the latter is a monomer.

Iodothyronine deiodinases are also an important group of selenoenzymes which regulate the conversion of thyroxine (T_4) into 3,5,3'-triiodothyronine (T_3), a metabolically active thyroid hormone, or into reverse 3,5',3'-triiodothyronine (rT_3), an inactive hormone. Type 1 5'-iodotyronine deiodinase is present in the liver and kidneys, which, like the thyroid gland, produce hormone T_3. Its presence was also noted in the brain and in pituitary glands in ruminants. Type 2 5'-iodotyronine deiodinase is present in the brain and pituitary glands of all animal species. It catalyzes the transformation of T4 into T3 in tissues that are unable to capture the circulating T3. Type 3 5'-iodotyronine deiodinase converts T4 into rT3, and T3 – into diiodothyronine. It has been determined in the brain, skin and placenta, and it is responsible for inactivating thyroid hormones (Arthur 1997, Chadio et al. 2006). Selenium deficiency can obstruct the above conversion process, which suggests that low levels of the investigated element can affect thyroid functions (Hess, Zimmermann 2004).

Thioredoxin reductase is an enzyme and a selenoprotein that is found in all mammals. In the presence of electrons taken from NADPH, it catalyzes the reduction of oxidized thioredoxin and transfers the redox capacity of thioredoxin to cell proteins (Lu et al. 2009). Our knowledge of the physiological functions of thioredoxin reductase continues to grow. Thioredoxins can donate electrons to redox enzymes, including ribonucleotide reductase and thioredoxin peroxidase. The discussed enzyme probably participates in DNA transcription and binding. Thioredoxins also act as growth factors, apoptosis inhibitors and hydroperoxidase reducers (Arner, Holmgren 2000).

Selenoprotein P also plays an important role in the body. Selenoprotein P and plasma GSH-Px are the only identified plasma selenoproteins. The presence of selenoprotein P has been determined in the blood, liver, heart, kidneys and testes (Brown, Arthur 2001). Until recently, researchers were of the opinion that selenoprotein P is an antioxidant responsible for selenium transport. The above observations were formulated based on high selenium concentrations in the discussed protein and its extracellular location. The proposed role of selenoprotein P is often questioned (Daniels 1996). Selenoprotein P binds heparin proteoglycans in cells and the intercellular matrix, and it is also capable of binding metal ions. For this reason, selenoprotein P could also protect endothelial cells against oxidants (Persson-Moschos 2000). Selenoprotein P concentrations decrease less rapidly in a selenium deficiency compared with GSH-Px (Hill et al. 1996).

Selenoprotein W, first isolated from rat muscle tissue, is one of the most recently identified selenoproteins (Whanger 2000). It was determined mostly in muscles, spleen, testes, heart and brain. Its functions have not yet been fully investigated, but it has been suggested that selenoprotein W participates in muscle differentiation and development by protecting myoblasts against oxidative stress (Loflin et al. 2006).

The protein found in sperm mitochondria is a specific selenoprotein that determines the integrity of sperm tails. In selenium deficiency, its concentrations decrease significantly, sperm motility is weakened and spermatogenesis is impaired (Ursini et al. 1999, Pfeifer et al. 2001).

The group of selenium-containing proteins is also inclusive of selenoprotein K, an antioxidant in cardiomyocytes (Lu et al. 2006), selenoproteins M and H which demonstrate neuroprotective activity (Zhang et al. 2010), selenoprotein N which promotes muscle function (Lescure et al. 2009), selenoprotein S whose deficiency could contribute to colorectal cancer in humans (Sutherland et al. 2010), as well as proteins with less known functions, including selenoproteins T, O and I (Lopez-Heras et al. 2011).

EFFECT OF SELENIUM ON THE IMMUNE SYSTEM

Selenium affects the immune system, and selenium compounds influence humoral immunity mechanisms and increase the levels of type M immunoglobulins (Maggini et al. 2007). Selenium supplementation of animal feed increases antibody levels, enhances the phagocytic activity of neutrophil granulocytes and macrophages and, when stimulated with myogens, increases T lymphocyte counts (Hoffman 2007, Kamada et al. 2007). Selenium is indispensable in the production of the lymphocyte migration inhibition factor and interleukin 2 (Wintergerst et al. 2007), which accelerates the proliferation, maturation and activity of T lymphocytes (Shrimali et al. 2008). T cells are particularly sensitive to Se deficiency because their cell membrane contains lipids that are more readily oxidized than the membrane lipids of B lymphocytes (Arthur et al. 2003). Selenium deficiency lowers the count and cytotoxic activity of T lymphocytes, an effect which is accompanied by decreased lymphotoxin production (Hawkes et al. 2001). A study on cows (Cao et al. 1992) has demonstrated significantly lower levels of lymphocyte proliferation (stimulated with concavalin A) in animals suffering from selenium deficiency than in the control group. In cows whose immunity was impaired due to a decrease in T lymphocyte counts, the administration of selenium supplements had an immunostimulating effect. Selenium supplementation intensified blastic transformation of splenic lymphocytes and prevented a decrease in lymphocyte proliferation (Ghany-Hefnawy, Tortora-Perez 2010).

The molecular mechanisms involved in the effect of selenium on the immune system have not been fully elucidated. Selenium could exert its effect aided by selenoenzymes – glutathione peroxidase and thioredoxin reductase. Those selenoenzymes are responsible for maintaining thiol groups on the surface of lymphocyte membranes in a reduced state, which significantly enhances the lymphocyte proliferative response to myogens, increases immunoglobulin production and boosts the killing activity of lymphocytes (Akyol et al. 2007). Selenates increase the levels of reduced glutathione inside cells and maintain thiol groups in a reduced state (Qin et al. 2007). Selenium deficiency can aggravate an inflammatory process in the body, depressing the activity of selenoenzymes, which inhibit excessive synthesis of arachidic acid from linoleic acid (Reinhard et al. 2007). At normal concentrations of selenium, GSH-Px inhibits phospholipase A_2 and lowers the levels of arachidonic acid and its metabolites, the products for eicosanoid synthesis, in particular leukotriene B4. The synthesis of prostacyclin from arachidonate is intensified, and it inhibits the lipoxygenase metabolic pathway (Johnson et al. 2000). The effect of selenium on the immune system could also be produced via a different pathway. The use of sodium selenate as an immunostimulator influences the expression of α and β subunits of interleukin 2 on the surface of activated T and B lymphocytes, natural killer

(NK) cells and lymphokine-activated killer (LAK) cells, but it does not affect the endogenous concentrations of interleukin 1 (IL-1), interleukin 2 (IL-2) or interferon γ (IFN-γ). By binding to IL-2 receptors, IL-1 is internalized, and it induces the signal for the transition of activated cells from phase G1 (postmitotic) to phase S (DNA synthesis) of the cell cycle (JOZSEF, FILEP 2003).

Selenium deficiency inhibits neutrophil migration and disrupts the distribution of receptors on the neutrophil surface. The above can most probably be attributed to the oxidation of tubulin by excess H_2O_2 and the resulting damage to neutrophil microtubules (HADDAD et al. 2002). Neutrophils sampled from selenium-deficient animals were also characterized by impaired ability to produce and release free radicals for the extermination of foreign cells (YANG et al. 2004). Interestingly, high selenium doses also attenuate the immune response. In an *in vivo* study, excessive selenium concentrations inhibited the growth of cells in S and G2 phases of the cell cycle and decreased the synthesis of antibody proteins and prostaglandins (ZAGRODZKI 2004).

SELENIUM AND CANCER

Selenium is a key trace element with anti-neoplastic properties. Decreased Se blood concentration are often observed in cancer patients. The incidence of neoplastic diseases is significantly elevated in areas with low selenium concentrations in the soil (SANZ ALAEJOS et al. 2000). Several mechanisms of the anti-neoplastic action of selenium have been described. One of them is related to its antioxidant effect, namely the redox-dependent modulation of transcription factor functions which inhibits cell growth (SPYROU et al. 1995). Subject to the applied dose, selenium has a stimulatory or an inhibitory effect on the growth of animal tumors which are sensitive to the cytotoxic action of NK cells (KOLLER et al. 1986). Selenium also stimulates the production of anti-neoplastic metabolites; it inhibits angiogenesis and induces the apoptosis of cancer cells (COMBS, GRAY 1998).

SELENIUM TOXICITY

Selenium is a bioelement that plays key physiological functions, but the difference between what is considered an adequate dose of selenium and a toxic one is relatively small. Toxic effect of selenium on animals was first reported in the 1930s in South Dakota, where animals grazed on pastures rich in selenium and developed alkali disease and blind staggers due to acute or chronic selenium poisoning. The first mention about selenium toxicity

was made by Marco Polo during his journey to China in 1295. He described symptoms of hoof rot disease in horses, which is contemporarily known as selenosis (Tinggi 2003). Selenosis or alkali disease affects horses, cattle, pigs and poultry. It is caused by high selenium concentrations in the soil, and by the consumption of plants growing in areas with elevated levels of alkaline compounds. In such environments, plants easily accumulate readily soluble and available selenium compounds. Plants that easily absorb selenium from the soil, thus posing a potential risk to grazing animals, include members of the families Leguminosae, Cruciferae and Compositae. They are referred to as selenophilic, selenium-bearing or selenium indicator plants. Plants which can absorb moderate or relatively high amounts of selenium without adverse consequences to consumers include wheat, barley, oats and maize (Bednarek, Bik 1994a). In animals, selenosis is observed in two clinical forms: chronic, known as alkali disease, and acute, referred to as blind staggers. Chronic selenosis leads to the loss of vitality, weight loss, hair loss, rough hair coat, hoof deformations, hoof necrosis, joint stiffness, myocardial atrophy, cirrhosis and anemia. In cattle, chronic selenosis lowers fertility by supporting the growth of ovarian cysts and prolonging anoestrus. Acute forms of selenosis are rarely diagnosed, and they result mainly from selenium overdose. In most cases, the disease affects the central nervous system, and the most common symptoms are dementia, unsteady gait, grinding of the teeth, salivation, colic and loss of vision (Koller, Exon 1986). The last stage of the disease is manifested by dyspnea and limb paralysis, and death usually results from respiratory failure (Tinggi 2003). Selenium is readily transferable through the placenta and it is secreted to milk, which is why symptoms of selenosis may be observed already in suckling animals (Guyot et al. 2007). A single selenium dose of 1-6 mg kg^{-1} BW is lethal for most animal species (Hogue 1970, Whanger et al. 1996). Feed with a selenium content higher than 20-30 ppm leads to acute selenosis, and doses below 3-5 ppm cause chronic and subacute selenium poisoning (Panter, James 1990, Nuttal 2006).

SELENIUM DEFICIENCY

In 1957, Schwarz and Foltz demonstrated that selenium plays a positive role in animal health. They noted that selenium supplementation of diets prevented liver necrosis in rats (Schwartz, Foltz 1957). The selenium content of animal feed reflects concentrations of this trace element in soils on which crops are grown for green fodder, as well as the level of selenium availability to plants. Selenium availability is determined by the amount and type of selenium compounds present in the soil, plant species, climatic conditions, soil pH and the content of selenium antagonists, such as arsenic, sulfur and lead. Diseases caused by deficiency of selenium occur mostly

in areas where soils are acidic and characterized by selenium deficiency or excess levels of selenium in the form of poorly available compounds, such as selenium sulfide. Higher disease rates are reported after cold and wet summers, and in areas intensively fertilized with superphosphate and sulfur (Bednarek, Bik 1994b). In metabolic patterns, marked differences in selenium distribution are reported, subject to dietary levels of this trace element. In selenium-deficient diets, this element is first incorporated into specific proteins with vital bodily functions (selenoprotein P, thyronine 5'-deiodinase), and successive amounts of ingested selenium are combined with non-specific proteins. Variations are also noted in tissue distribution of selenium. The brain, endocrine glands and reproductive organs are priority pathways of selenium absorption, before the liver, heart, skeletal muscles and erythrocytes, which explains why the latter organs are more susceptible to deficiency of selenium (Floriańczyk 1999). Selenium deficiency contributes to pathological changes in farm animals, which incur vast financial losses each year. Although selenium deficiency affects all animal species, ruminants, mostly lambs and goats, seem to be particularly susceptible. The adverse effects of selenium deficiency on animals were first documented in 1957, when low levels of selenium and vitamin E were recognized as a potential cause of nutritional muscular dystrophy (NMD) (Muth et al. 1958). This condition, also known as white muscle disease, affects lambs, kids, foals, calves and poultry from birth to 3 months of age. NMD induces hyaline degeneration of skeletal muscle cells in various parts of the body, including the diaphragm, cardiac muscle and tongue (Beytut et al. 2002). The disease exists in two forms: acute, which affects the cardiac muscle, and subacute, which impairs mostly skeletal muscles. The clinical symptoms of acute NMD include tachycardia, arrhythmia, dyspnea at rest and cyanosis. In 60% of cases, acute NMD leads to sudden death. Chronic NMD is the most common form of the disease, and the affected animals have difficulty in standing up and maintaining a standing position. Changes in tongue muscles prevent suckling and swallowing, leading to milk discharge through the nostrils. Young animals affected by hyposelenosis are more susceptible to respiratory and gastric infections. Lower body gains are frequently reported (Aleman 2008). In adult individuals, selenium deficiency impairs fertility, contributes to the formation of ovarian cysts and increased embryonic mortality in the first 3-4 weeks after insemination (Ishii et al. 2002, Hemingway 2003, Palmieri, Szarek 2011). Placental retention is one of the most frequently encountered fertility disorders that accompany selenium deficiency. Selenium-dependent GSH-Px protects the placenta which undergoes rapid degeneration after parturition. The enzyme metabolizes peroxides into less biologically active forms to protect cell membranes against the adverse consequences of oxidation that can lead to physical and chemical changes. Neutrophil damage caused by reactive oxygen species is yet another selenium-related cause of placental retention (Rutigliano et al. 2008). Parturition problems resulting from reduced tension of the muscular layer of the uterus, postparturi-

ent paraplegia and purulent inflammations of the uterine lining are also attributed to low selenium levels. Selenium and vitamin E facilitate neutrophil migration to the mammary gland and enhance the bactericidal effects of neutrophils, thus shortening and alleviating the symptoms of clinical mastitis (Moeini et al. 2009). The mastitis-metritis-agalactia syndrome (MMA) in pigs has been found to be closely correlated with selenium deficiency (Hostetler, Kincaid 2004). Low selenium levels also contribute to dietary necrotic liver degeneration and mulberry heart disease. Dietary necrotic liver degeneration, also known as toxic liver necrosis, affects mostly young, fast growing and apparently healthy pigs. In young animals, mulberry heart disease may lead to sudden death due to acute heart failure. Numerous spots and smudges (foci of cardiomyocyte degeneration), separated by extravased regions, are observed in the affected heart (Sharp et al. 1970). Low levels of selenium and vitamin E may be a cause of exudative diathesis in poultry. The disease affects mostly chicks aged 3-6 weeks and, less frequently, young turkeys, ducks and quails. It is manifested by subcutaneous edema, mainly in the area of the abdomen, chest and neck. In swollen areas, the skin takes on a purple-red color, and it ultimately turns greenish-blue. The disease leads to loss of appetite, weight loss and massive deaths. In poultry, selenium deficiency decreases egg laying and hatchability, and it inhibits feather growth (Koller, Exon 1986, Surai 2002).

CONCLUSIONS

Selenium has a variety of functions. Owing to the antioxidant properties of glutathione peroxidase, selenium effectively neutralizes free radicals. This trace element is also essential to good health. The biological role of selenium-containing proteins needs to be explored in greater depth to validate positive health effects of selenium. Selenium is a promising element in prevention and treatment of various diseases, including cancer, but further work is needed to confirm the benefits of selenium supplementation in animals and humans.

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