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Selenium, selenoproteins and oxidative stress in small ruminants. Review.

Selenio, selenoproteínas y estrés oxidativo en pequeños rumiantes. Revisión.

Díaz-Sánchez Víctor[1], Olazábal-Fenochio Alan[1], César Ibarra-Gudiño[2]

[1]National Autonomous University of Mexico, Faculty of Higher Studies Cuautitlán, Mexico. [2]Faculty of Veterinary Medicine and Zootechnics of the Autonomous University of Nayarit; Nayarit, Mexico.*Correspondence author and responsible: Díaz-Sánchez Víctor. National Autonomous University of Mexico. Cuautitlán School of Higher Education. Multidisciplinary Research Unit. Cuautitlán Izcalli, Mexico State, Mexico. C.P. 54714. victorm_diazs@comunidad.unam.mx, cesaroctavio76@hotmail.com.

ABSTRACT

Animal production conditioned by multiple factors, within these, the most important is nutrition. Some of the most common nutritional problems in production are to the geographical characteristics and properties of soils directly related, in different areas of grazing and forage production, an example of this is observed in the poor natural distribution of selenium in soils throughout the world, a deficiency that affects the production, products and by-products of small ruminants. Minerals, and within these, microminerals such as selenium have an important role in the nutrition of small ruminants, since, although they do not provide energy, they are essential for the synthesis of nutrients, participating in numerous metabolic activities as cofactors, maintaining the physiological effect balance in the body. Selenoproteins are mainly enzymes with antioxidant capacity, which participate in the oxidative balance, eliminating free radicals that could damage cells, causing diseases that affect metabolic function in the animal organism, with a detriment in animal production, so that deficiency through supplementation must be corrected.

Keywords: selenium, selenoproteins, oxidative stress, small ruminants.

RESUMEN

La producción animal está condicionada por múltiples factores, dentro de estos, el más importante es la nutrición. Algunos de los problemas nutricionales más comunes en la producción están directamente relacionados con las características geográficas y las propiedades de los suelos en diferentes áreas de pastoreo y producción de forraje, un ejemplo de esto se observa en la pobre distribución natural de selenio en suelos de todo el mundo; una deficiencia que afecta a la producción, productos y subproductos de pequeños rumiantes. Los minerales, y específicamente, los microminerales como el selenio tienen un papel importante en la nutrición de los pequeños rumiantes, ya que, aunque no proporcionan energía, son esenciales para la síntesis de nutrientes, participando en numerosas actividades metabólicas como cofactores, manteniendo el efecto fisiológico y el equilibrio en el organismo. Las selenoproteínas son principalmente enzimas con capacidad antioxidante, que participan en el equilibrio oxidativo, eliminando los radicales libres que podrían dañar las células; causando enfermedades que afectan la función metabólica en el organismo animal, con un detrimento en la producción animal, por lo que la deficiencia debe ser corregida a través de la suplementación.

Palabras clave: selenio, selenoproteínas, estrés oxidativo, pequeños rumiantes.

INTRODUCTION

Selenium (Se) is an essential trace element to maintain physiological balance in animals. It acts through proteins with enzymatic capacity, which mainly have antioxidant properties

in the body (Marek *et al*., 2013; Kruzhel *et al*., 2014). Sheep and goats obtain the mineral through the diet (Tapiero *et al*., 2003; Slavica y Cepelak, 2004), it is important to mention that the Se content in the soil below 0.010 mg/kg of dry matter may cause signs of deficiency in ruminants. Nevertheless, amounts <0.5 mg/kg in soils or <0.1 ng/kg in plants are considered insufficient for the production of selenoproteins in the organism (Ramírez-Bribiesca *et al*., 2001; Hefnawy y Tórtora-Pérez, 2010; Kruzhel *et al*., 2014); causing metabolic disorders and diseases related to Se deficiency.

Se deficiency, in association with vitamin E, causes "white muscle" disease. The requirements of Se for sheep depends on the amount of vitamin E in the diet; The level of Selenium suggested for sheep is 0.1 mg Se / kg DM. The experiences obtained in Mexico suggest using a dose of 0.25 mg Se in seemingly healthy lambs and 0.5 mg dose in lambs with sign of nutritional muscular dystrophy or white muscle disease (Carbajal *et al.,* 2013).

Therefore, it is necessary to perform a supplementation in animals lacking the mineral to avoid these pathologies related to the deficiency. The objective of this work was to combine the most relevant information regarding Se, the function of the most important selenoproteins and their relationship with the oxidative balance.

Absorption, distribution, metabolism and excretion of selenium

The absorption of Se in ruminants through diet can vary from 11 to 35% on average (Lescure *et al*., 2009; Hefnawy y Tórtora-Pérez, 2010; Kruzhel *et al*., 2014), because the rumen due to their pH and microbiota characteristics, they can transform the mineral mainly to selenides. They are chemical forms of Se that the animal cannot absorb for the production of selenoproteins, (Ghany-Hefnawy *et al*., 2007; Galbraith *et al*., 2015).

The mineral that passes the rumen, reaches the small intestine, where the absorption of Se occurs, mainly in the duodenum and the ileum. Selenoamino acids, such as selenomethionine are absorbed through the same route used by methionine; through active transport, selenocysteine can be absorbed in the same way, or it can be absorbed bound to proteins; finally, the inorganic salts of Se are absorbed by passive diffusion in the gastrointestinal tract (Juniper *et al*., 2009a; Rosen y Liu, 2009).

The metabolism of selenate and/or selenite in the animal organism differ from each other. The selenate at the rumen level can be reduced to selenite, due to the ruminal environment, or continue through the gastrointestinal tract to be absorbed in the small intestine by passive diffusion. On the other hand, selenite can also be reduced in the rumen, but unlike selenate, it is directly reduced to selenides, which neither the animal nor the ruminal microbiota can use for its metabolic functions.

It is important to note that both selenate and selenite can be used by the ruminal microbiota to synthesize selenomethionine or selenocysteine, which can be used by the animal through digestion (Ghany-Hefnawy *et al*., 2007; Juniper *et al*., 2009a; Gresakova *et al*., 2013).

After absorption, Se can be used for the synthesis of selenoproteins, stored in the form of selenomethionine, and thus inserted into different proteins in the animal organism; or also be excreted in different ways (Juniper *et al*., 2009a). Se, transported through plasma incorporated into cells such as erythrocytes and leukocytes; as well as proteins and enzymes such as myoglobin, nucleoproteins and myosin. Through the system it is transported to the liver, where a fraction of the mineral is maintained within the hepatocytes, the rest are transferred by circulation to different organs, where they are stored as selenomethionine, which can be incorporated into proteins instead of methionine, but without antioxidant enzyme activity (Gresakova *et al*., 2013). Within the organism, the distribution of Se has a hierarchy, being the highest concentration in kidneys, followed by the liver, heart and skeletal muscle esquelético (Berry, 2005; Qin *et al*., 2007; Juniper *et al*., 2009b; Birben *et al*., 2012).

Selenoproteins are within nucleated cells formed from organic and inorganic compounds. Regardless of their origin, they must become selenides, since it is the central chemical form for the formation of selenocysteine, the only selenoamino acid that can be inserted into selenoproteins for its proper function. From this selenide, there may be two routes, one of which is its methylation for subsequent excretion of the organism, or its incorporation for the formation of selenocysteine in the formation of the different selenoproteins will be inserted (Letavayová *et al*., 2006).

Both the organic and inorganic source of selenium are into hydrogen selenide (H_2Se) transformed, a central compound in the formation of selenoproteins. In the case of selenate, it must first be to selenite and later reduced to selenide through glutathione reduced. In the case of selenomethionine will be transformed into hydrogen selenide by an enzyme-lyase and then it is incorporated into proteins such as selenomethionine or it will be transformed into selenocysteine by transulfurization, which will be transformed into hydrogen selenide by the enzyme-lyase.

Selenide (H_2Se) will be by the enzyme selenophosphate synthetase transformed into selenophosphate for the subsequent synthesis of selenocysteine, which is in its t-RNA synthesized, which is initially aminoacylated with serine, through the serine synthetase, forming Ser-t-RNASec. This serine residue provides the carbon skeleton of selenocysteine; Ser-t-RNASec phosphorylaphosphoryl-t-RNASec, through the enzyme PSTK (phosphoseryl-t-RNASec kinase); then in a reaction that involves the addition of selenophosphate in the presence of selenocysteine synthetase; Phosphoseryl-t-RNASec becomes a Sec-t -RNASec, which will be incorporated into selenoproteins through a UGA codon (Silva *et al*., 2000; Berry, 2005; Ohta y Suzuki, 2008).

Excretion of Se can be by lungs, feces and urine, depending on the route of administration and tissue levels. The administration of Se orally has as its main route of excretion through feces; In case of ingestion of high levels of the mineral, volatile forms will be through the lungs exhaled. Parenteral injection of Se will be primarily through the urine excreted. Finally, it is known that the amount of mineral expelled through the bile is small (Silva *et al*., 2000; Berry, 2005; Ohta y Suzuki, 2008).

Selenium Functions

The functions of this mineral are carried out through selenoproteins, which act in a general way in oxidation-reduction reactions, with the aim of maintaining oxidative balance (Köhrle, 2004; Lescure *et al*., 2009; Rahmanto y Davies, 2012; Kruzhel *et al*., 2014). In this way, the participates in the immune response, spermatogenesis, growth and development processes, the defense against oxidative damage and the regulation of thyroid hormones; as well as indirectly in the regulation and efficiency of production processes (Ramírez-Bribiesca *et al*., 2004; Revilla-Vázquez, *et al*., 2008; Kumar *et al*., 2009). On the contrary, low concentrations of Se are related to productive and reproductive problems in small ruminants (Celi, 2010; Mahmoud *et al*., 2013). The deficiency in small ruminants can be due to a restriction in the diet or a low absorption in the gastrointestinal tract. Se deficiency is the main cause of several diseases. Example of these are: nutritional muscular dystrophy, anemia, mastitis, infertility associated with low seminal quality, retention of placenta or products and abortions, low immunity, weak animals, and lower weight gains, production of milk and wool (Forman y Torres 2002; Sobiech y Kuleta 2002; Arthur *et al*., 2003; Gill y Walker, 2008; Lekatz *et al*., 2010; Haenlein y Anke, 2011; Karami *et al*., 2011; Pavlata *et al*., 2012; Stefanowicz *et al*., 2013).

Nutritional muscular dystrophy or white muscle disease

It is the main sign caused by Se deficiency, a consequence of damage to myocyte membranes. It can occur in most animals, although more frequently in young animals, whose mothers consumed a ration lacking Se during pregnancy (Ramírez-Bribiesca *et al*., 2001; Sobiech y Kuleta, 2002). In selenodeficient animals, myocyte membrane phospholipids undergo peroxidation, causing damage and malfunction to membrane proteins. The main consequence of cell injury is the increase in calcium permeability, which accumulates causing damage, and therefore, loss of muscle functionality (Karami *et al*., 2011).

Muscular dystrophy can manifest itself acutely or chronically. The acute form is characterized by death of the animal in a few hours. Commonly observed signs are abnormalities when walking, tremor and decreased muscle tone and cardiac abnormalities. In areas with selenodeficiency is considered the main cause of death in small ruminants (Ramírez-Bribiesca *et al*., 2001).

Anemia

In selenodeficient animals, anemia and Heinz bodies associated with the low activity of the erythrocyte antioxidant enzymes and the consequent cell destruction have been observed (Stefanowicz *et al*., 2013).

Mastitis

Se deficiency and low activity of selenoenzyme glutathione peroxidase, condition the phagocytic activity of leukocytes in diseases such as mastitis, causing bacterial proliferation and damage to the mammary gland. It has been shown that supplementation with this micronutrient increases the efficacy of phagocytosis by neutrophils and macrophages, effectively eliminating the pathogens that invade the mammary gland (Sánchez *et al*., 2006).

Placental retention

Selenium-deficiency can lead to an increase in placental retention. Normally the placental tissue exerts a strong chemotactic activity on leukocytes, which have to do with the separation of the placenta after delivery. If the chemotactic activity on leukocytes is deficient or delayed, placental retention will occur, which contributes to the infection of the uterus, damaging the gestation capacity (Lekatz *et al*., 2010).

Compromised immune response

Se deficiency is for depressing both the humoral immune response and the cellular response well known. The increase in calostral IgG observed in supplemented ruminants, as well as an increase in antibody response in pups supplemented with Se (Rose *et al*., 2012). Kumar *et al*., found that by supplementing sheep with Se and then exposing them to a bacterial agent, the humoral immune response increased significantly with respect to the control group Kumar *et al*., 2009).

Phagocytes contain glutathione peroxidase (GSHPx) in lysosomes. A nutritional deficit of the decline in the activity of GSHPx in these cells, and therefore in the ability to destroy the phagocyte antigen (Forman y Torres, 2002; Hoffmann y Berry, 2008; Avery y Hoffmann, 2018).

Selenium functions and oxidative balance

Selenium is mainly to oxidative balance related, since most selenoproteins have an antioxidant function in the body (Hawkes y Alkan, 2010). When there is an increase in free radicals that cannot be regulated by enzyme systems and antioxidant molecules, they attack cell membranes, altering their function and viability. The imbalance between oxidants and antioxidants in favor of the former is "oxidative stress" called, due to the high production of reactive oxygen species (ROS), which in high concentrations can damage cellular functioning. Factors such as pollution, radiation, medications, infections and

inflammation, generate oxidative stress; causing an excess of ROS in the body (Hawkes y Alkan, 2010). They specifically damage the structures of carbohydrates, nucleic acids, lipids and proteins; altering its function and causing damage to the cellular structure, which will have an impact on the correct function of the organs and the homeostasis of the organism (Grotto *et al*., 2009; Rahmanto y Davies, 2012; Birben *et al*., 2012).

To counteract ROS, there are different lines of defense in the body, which are controlled by a system that includes low molecular weight oxidant radical scavengers, enzymes and non-enzymatic defenses (Rahmanto y Davies, 2012). Currently, approximately 30 selenoproteins are known in mammals, within which most have antioxidant functions. See table 1. (Haenlein y Anke, 2011).

Table 1. Main selenoproteins and their function

Selenoprotein	Tissue distribution	Functions
Glutathione peroxidase family (GPx1, GPx2, GPx3, GPx4, GPx6; snGPx-4)	Obicua (GPx1, GPx4), gastrointestinal (GPx2), Kidney and plasma (GPx3), Olfactory epithelium, Bowman gland (GPx6), testis, Sperm (snGPx4)	Antioxidant, lipoxygenous modulation, redox signal transduction
Thioredoxin reductase family (TRx1,2,3; TGR)	All body cells	Redox regulation, drug metabolism, signal transduction
Family of Deiodinases	Expression and regulation in specific tissues, mainly in thyroid, liver, kidney and pituitary	Catalyze the conversion of T4 to T3 and the degradation of rT3 (DIO1 and DIO2) as well as T4 and T3 (DIO1 and DIO3)
Selenophosphate synthetase 2 (SPS2)	Various tissues	Catalyzes the production of selenophosphate, it is required for the incorporation of selenocysteine into selenoproteins
Selenoproteins of 15 and 18 kDa (Sell5, Sell8)	Various tissues, brain	Unknown
Selenoprotein M (SelM)	Various tissues, brain	Proliferation and regeneration
Selenoprotein N (SelN)	Skeletal muscles, liver, kidney, heart, stomach	Mutations leading to rigid spine and muscular dystrophy
Selenoprotein P (SelP)	The liver is the main source of SelP; Obicua	Transport of selenium, antioxidant
Selenoprotein R (SelR, MsrB)	Various tissues	Reductase sulfoxide R-methionine
Selenoprotein T (SelT)	Skeletal muscle, heart muscle, brain, testis and liver	Antioxidant
Selenoprotein W (SelW)	Skeletal muscle, heart muscle, brain, testis and liver	Unknown
Selenoprotein H, K, M, O, S, V, Y, Z	Various tissues	Unknown
Selenoprotein I	Various tissues	Hypothetical phosphatidyl transferase CDP-alcohol

(Modified of Holben y Smith, 1999; Köhrle, 2004; Kumar and Priyadarsini, 2014)

Selenium supplementation methods

Due to the conditions of the soil throughout the world and the physiological characteristics of ruminants, it is possible that there is a deficiency of Se in sheep and goats, so it will be necessary to perform a supplementation to avoid problems. Supplementation in small ruminants has multiple benefits in animal production. This is done through organic or inorganic mineral salts, which can be incorporated into the diet, water, mineral mixing blocks, injectable solutions or prolonged-release forms such as intraruminal boluses (Hall

et al., 2009; López-Arellano *et al*., 2015). The mineral supplementation will be reflected in the organism, where blood Se levels can be an indicator of the correct supplementation of this element in ruminants (intravitally), as well as the measurement of selenoprotein activity, or levels in the organs. Deficient, adequate and toxic levels of Se are in tissues established of small ruminants, see table 2.

Table 2. Selenium levels in blood, liver, kidney, muscle and milk in small ruminants

	Blood	Liver	Kidney	Muscle	Milk
Poor	0.003-0.040	0.01-0.10	0.05-0.60	0.01-0.03	0.002-0.020
Marginal	0.040-0.080	0.15-0.25	0.70-1.10	0.03-0.09	0.020-0.030
Suitable	0.150-0.500	0.25-1.50	0.90-3.00	0.09-0.40	0.025-0.250
High	-	2.00-10.0	4.00-6.00	0.40-0.60	-
Toxic	-	15.0-30.00	6.00-15.00	0.60-20.00	-

ppm wet weight Puls, 1988.

A preventive therapeutic dose of 0.25 mg/kg of live weight is considered parenterally (Ramírez-Bribiesca *et al*., 2005). To supplement males and females 3-4 weeks before the mating season and 3-4 weeks before delivery is recommended. In the same way, it is recommended to supplement the lambs and kids at birth, at weaning and at the beginning of fattening. In the case of dietary supplementation, to make a dose of 1-3 ppm is recommended according to the federal drug administration of the *Food and Drug Administration* (FDA, 2007).

Signs of toxicity by ingested selenium

If the dose of Se required by the animal is exceeded, there may be a risk of poisoning. The main signs of moderate intoxication are anorexia, grinding of the teeth, secretion of mucus from the nose and cyanotic mucous membranes. In acute poisoning, the animal will have disseminated hemorrhages in the body and sudden death (Revilla-Vázquez *et al*., 2008).

CONCLUSIONS

Selenium is essential for all animals, allowing maintaining the oxidative balance through selenoproteins, distributed in the body. There are soils with deficiency of this mineral in the world, so supplementation is important, mainly in ruminants since these absorb proportionally smaller amounts of the mineral, unlike non-ruminant animals. Supplementation can be through different routes, taking into account the recommended doses to avoid animal poisoning.

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