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The influence of selenium and selenoproteins on immune responses of poultry and pigs

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ABSTRACT

Selenium is an essential nutrient for poultry and pigs, and is important for a number of physiological processes including regulation and function of the immune system. Through its incorporation into selenoproteins, Se is involved in the regulation of oxidative stress, redox mechanisms, and other crucial cellular processes involved in innate and adaptive immune response.

This review provides current knowledge on the mechanisms by which selenium can modulate the resilience to infectious diseases, and how this micronutrient can influence the capacity of the bird or the pig to maintain its productivity during an infectious challenge. In relation to the most frequent and economically important infectious diseases in poultry and pig production, the present paper considers the influence of different selenium sources (organic *vs.* inorganic Se) as well as dietary concentrations on the immune responses of poultry and pigs with major emphasis on the potential beneficial impact on animal resilience to common infectious diseases.

1. Introduction

1.1. Is Se deficiency a problem?

As an essential trace element, selenium (Se) is an integral part of selenoproteins which participate in a number of physiological processes in production animals. With the discovery of the first selenoprotein glutathione peroxidase (GPX1) (Rotruck et al., 1973), the specific biological importance of Se became clear, and the subsequent discovery of at least 25 genes coding for selenoproteins has formed the basis for the studies of Se in relation to human health and disease prevention (Papp et al., 2007). Selenoproteins are responsible for the diverse biological functions and molecular pathways of Se, and they all contain at least one selenocysteine (Labunskyy et al., 2014; Roman et al., 2014). In mammals there are eight gluthathione peroxidases (GPXs), five of them being selenocysteine enzymes (GPX1, GPX2, GPX3, GPX4 and GPX6), whereas the other three (GPX5, GPX7 and GPX8) have a cysteine at their catalytic site. The GPXs are involved in the hydrogen peroxide (H_2O_2) signalling, detoxification of hydroperoxides, and maintaining cellular redox homeostasis, and GPX1 is the most abundant selenoprotein in mammals working as a potent antioxidant in the cell scavenging toxic H_2O_2 as reviewed by Lubos et al. (2011). This protection of cells from oxidative damage by degrading toxic H_2O_2 has received much attention in relation to human health and disease prevention.

Synthesis of selenoproteins is regulated by the availability of Se, and when Se availability is limited, it is supplied for synthesis of certain selenoproteins at the expense of others (Howard et al., 2013; Seyedali and Berry, 2014). Research in animal models such as

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knockout or overexpressing mice for specific selenoproteins has improved the knowledge on the biological action of Se, however, uncertainty rises when these results are extrapolated to human health. As far as monogastric livestock is concerned, older research has focused on the physiological role of Se, as Se-deficient pigs were seen to suffer from *e.g.* myopathy and mulberry heart disease and chickens from liver necrosis and muscular dystrophy (Koller and Exon, 1986). Later, considering the mechanism by which dietary selenium modulates immunity and health of poultry and pigs, major attention has been given to GPXs and their function in antioxidant activity, inflammation and respiratory burst. A considerable number of experimental results are available suggesting that Se primarily in the form of selenomethionine and selenocysteine is present in tissues and cells of the immune system in humans and animals (Roman et al., 2014). Methods for extraction and measurement of these two amino acids has been recently published in fish tissues (Jagtap et al., 2016), and a method has been developed to discriminate the contribution of selenoproteins (containing selenocysteine) and other Se containing proteins (containing selenomethionine) in tissues of animals during supplementation studies (Bierla et al., 2012). A recent meta-analysis integrating results of 40 selenium supplementation experiments in chickens showed that the tissue Se concentration was correlated to the concentration of Se added to the feed and to the activity of GPX, but GPX activity was not correlated with dietary Se concentrations (Zoidis et al., 2014). Several severe and common diseases in poultry and pig production are of infectious origin, and there are a number of ways by which nutrition may influence the exclusion of pathogens through modulation of the immune system (Klasing, 1998). This review focusses on the role of selenium herein, and will describe the mechanisms by which selenium can modulate the resistance and resilience to infectious diseases, *i.e.* how this micronutrient can influence the capacity of the bird or the pig to maintain its productivity during an infectious challenge. Hence, in relation to the most frequent and economically important infectious diseases in the poultry and pig production, the aim of the present paper is to study the influence of the dietary sources and content of selenium on the immune responses of poultry and pigs with major emphasis on the potential beneficial impact on animal resilience to common infectious diseases.

1.2. Sources of selenium

Originally, animals have access to Se through plants or grains they consume. Selenium is not an essential element for plants and fungi (including yeast) but they are able to convert mineral forms of Se present in the soil into various organic forms (mainly selenomethionine and metylselenocysteine) as a strategy of adaptation (White, 2016). The Se content of plants varies to a great extent depending on the selenium concentration of the soil, and its availability. However, the Se requirement of the animal is often higher than the endogenous level, and Se is therefore added to the diet on regular basis. In human nutrition a few chemical forms (selenomethionine, selenocysteine, selenate, and selenite) account for almost all Se in diets (Burk and Hill, 2015).In nutrition of livestock, feed sources of Se are also differentiated into either inorganic (selenite, selenate), or organic selenium (selenomethionine from Se-yeasts, pure selenomethionine and analogues) feed ingredients. All these forms are absorbed without regulation, and all have high bioavailability (Burk and Hill, 2015).

The supplementation of animal feed with the mineral form of Se, also named the inorganic form of Se, has some disadvantages, which are related to an interaction with other minerals, relative high toxicity, low transfer efficiency to milk and eggs and inability to build and maintain Se reserves in the body. Considering all mentioned aspects, the use of organic Se sources, such as selenomethionine has been shown to be superior to that of inorganic sources (Schrauzer, 2000; Surai and Fisinin, 2014, 2016). In their meta-analysis of Se accumulation in tissues (liver, kidney, breast and leg muscle), of chickens, Zoidis et al. (2014) concluded that Se source did not affect tissue Se concentration significantly (overall, $P > 0.05$) when data of Se source were pooled. However, certain inorganic sources (calcium selenite, sodium selenite) and organic sources (Se-proteinate, Se-yeast, Se-malt, Se-enriched cabbage and Se-enriched garlic) as well as the background Se concentration derived from feed ingredients were found to significantly affect tissue Se concentration (Zoidis et al., 2014). In addition, other minor organic forms derived from plants or yeast metabolisms such as methylselenol, selenohomocysteine, and selenoadiosine have been reported due to the progress in analytical methodology of analysing Se-species (Bierla et al., 2012). More recently, a feed additive as, hydroxy-selenomethionine, (2-hydroxy-4-metylselenobutanoic acid or HMSeBA) was indicated to be more bioavailable than selenite and Se-yeast in monogastrics (Briens et al., 2013; Jlali et al., 2014; Zhao et al., 2017, 2014).

1.3. Assessment of Se-status

Selenomethionine is the natural dietary form in human and animal diets, and once ingested, it is absorbed *via* intestinal methionine transporters and enters the methionine pool of the body. The other major fate of this Se form is its metabolism, which occurs mostly in the liver, *via* methionine cycle and transsulfuration pathway yielding selenocysteine as a transient form quickly converted to selenide available for selenoprotein synthesis in animals, (Burk and Hill, 2015). When considering the comparison of organic versus inorganic Se forms in terms of Se bioavailability for livestock, most focus has been given to selenomethionine as the organic Se form. It represents the major form of the unspecific pool of Se with only known function to be a safe storage form of Se for the animal that can be released in case of limitation (Schrauzer, 2003; Burk and Hill, 2015). On the contrary, selenocysteine represents the specific pool of Se when incorporated into selenoproteins. However, all dietary forms of Se must be converted into the unique intermediate selenide before *de novo* synthesis of selenocysteine to be incorporated into selenoproteins (Rayman, 2008). In other words, dietary selenocysteine cannot be directly used for selenoprotein synthesis. Once converted to selenide, Se can enter the specific and dedicated selenoprotein translation pathway, a complex machinery able to deal with the high reactivity of Se and ensure specific selenocysteine synthesis and encoding (Larsen and Tollersrud, 1981; Allmang et al., 2009; Labunskyy et al., 2014). For this reason, selenocysteine is recognised as the 21st amino acid (Arner, 2010). Organic forms of Se and selenite are readily absorbed with

an overall efficiency close to complete (70–90%) at normal physiological dietary levels; whereas selenite has a lower efficiency because its direct absorption does not exceed 60%. Very high intake of selenomethionine results in accumulation of selenomethionine in tissues that can be much higher than the selenocysteine from selenoproteins. The selenium status of an animal or human is, however, often assessed by measurement of the Se concentration in whole blood or blood fractions (plasma, serum). Total selenium is measured using atom absorption spectrophotometry or better even Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Plasma or serum concentrations will reflect changes in Se status within a short period, whereas whole blood concentration is considered as a better indicator of the selenium intake on the longer term. Analysis of the activity of selenium dependent glutathione peroxidase (Se-GPX) is a frequently used biomarker of selenium status in many animal studies. The activity of Se-GPX is dependent on the presence of selenium, but the relationship between dietary selenium supplementation and the activity of Se-GPX is not simple, especially when the variation of selenium intake is small. A recent meta-analysis of experiments with chickens showed tissue Se concentration to be correlated with the dietary Se content and with GPX activity, the latter not being correlated with the dietary Se level (Zoidis et al., 2014). However, in studies with a higher variation in selenium intake, GPX activity is considered a good biomarker of selenium intake. In humans, the Se-GPX activity in plasma will be saturated at an intake of around 40–50 μg Se/day, whereas the enzyme activity in thrombocytes is a more sensitive marker and will be changing at intakes up to 200–300 μg Se/day. Comparison of various plasma status biomarkers (Selenoprotein P (SELENOP), GPX and Se) revealed that the SELENOP concentration was the best biomarker studied for assessing optimal expression of all selenoproteins, because its optimization required a larger intake of Se than did GPX activity (Xia et al., 2010). This study furthermore showed that the SELENOP concentration was optimised at 40 weeks by a 35 ug supplement, whereas GPX was optimised by 21 ug at the same total ingestion (35 ug Se/day), but the Se concentration showed no tendency to become optimised (Xia et al., 2010). Similarly, in chickens it was recently confirmed that Se requirements may be higher than previously estimated (Li and Sunde, 2016). However, considerations about the dietary Se form and animal health status are often neglected when assessing Se requirements. In an acute phase response to invading pathogens, the blood concentration of many trace elements will decrease (McKenzie et al., 1998). Maehira and co-workers showed that an acute phase response in rats induced by injection of lipopolysaccharides (LPS) significantly decreased Se content in plasma and liver and increased the content in muscle, kidney, lung, spleen, heart, and thymus (Maehira et al., 2002).

Of all elements, selenium has one of the narrowest ranges between dietary deficiency (< 40 μg/day) and toxic levels (> 400 μg/day) (WHO, 1996) which makes it necessary to carefully control intakes in both humans and animals. Insufficient dietary selenium supplementation leads to deficiency symptoms depending on the severity of deficiency and on the specific animal species. Classical selenium deficiency symptoms in production animals, *i.e.* myodegenerative disorder called “white muscle disease” in calves and lambs, myopathy and mulberry heart disease in pigs, exudative diathesis and muscular dystrophy in poultry, are only rarely seen (Koller and Exon, 1986) as animal feed is usually supplemented with selenite to provide a safety margin to avoid selenium deficiency condition. However, as noted by Mahan (2000), the mulberry heart condition in young pigs, attributable to a vitamin E and Se deficiency still prevails in some swine herds. In humans, selenium deficiency has been implicated in a number of conditions including cancer (Papp et al., 2007), heart disease, dysfunction of the immune system and reproduction. Recent evidence suggests that selenium intake in most parts of Europe and Middle Eastern countries is decreasing and is low when compared with the recommend intakes (Rayman, 2000; Stoffaneller and Morse, 2015). Declining intakes in the last three decades have mainly been attributed to a change of the wheat source for bread and cereal products, from wheat deriving predominantly from North America (high selenium content) to wheat of European origin (low selenium content) (Nohr and Biesalski, 2007). This will also influence the natural Se content of feed crops for chickens and pigs, although the Se supplementation *via* premixes usually neglects the natural Se content of feed ingredients.

Excessive intake of selenium can result in toxicity, and selenium toxicity problems in livestock have been recorded for hundreds of years although the cause was unknown. Symptoms of selenium intoxication (selenosis) of the livestock are hair loss, hoof deformities and reduced productivity. Sudden exposure to high Se intake will result in deaths from respiratory failure (Lee et al., 1999).

The bioavailability and distribution of Se in the body is influenced by a number of factors including chemical form of Se, other dietary compounds, selenium status, physiological status, and animal species. Recent advances in Se biochemistry have provided a deeper understanding of the principal differences in the metabolism of organic and inorganic Se-sources. In pig research, major attention has been given to the periods where Se deficiency is likely to occur which is in the neonate, at weaning, and during the reproductive period. These are also the critical phases of vitamin E status in pigs. In poultry, it seems less clear whether there still are situations of selenium (and vitamin E) deficiency. The interest in Se supplementation of poultry has been directed to the possibility of enrichment of poultry products (meat, eggs) to meet the recommended dietary Se allowance of the consumers, in poor soil Se regions and in particular that of population subgroups known to have low Se intakes, *e.g.* elderly people > 65 years (Thane and Bates, 2001). Several reports show the possibility of increasing the Se content in table eggs by supplementing the layer diet with organic Se additive (Surai et al., 2007; Fisinin et al., 2009; Bennett and Cheng, 2010; Jlali et al., 2013).

2. The role of selenium in the immunity of poultry and swine

2.1. General immunomodulatory properties of selenium

Selenoproteins influences immunity through many mechanisms (Huang et al., 2012). In general, there are a number of ways by which nutrition may influence the exclusion of pathogens through modulation of the immune system. Chronically severe deficiencies of micronutrients are more debilitating to the development of the immune system than deficiencies of dietary energy and protein (Klasing, 1998). Although deficiencies of specific fatty acids, vitamin A and D, iron and several of the B-vitamins are especially

damaging to the development of the immune system, this review will focus only on Se in relation to infectious diseases. However, given the tight biological interaction between selenium and vitamin E, the function of this vitamin will be described when scientific studies encompass both Se and vitamin E.

Through its incorporation into selenoproteins, Se is involved in regulating oxidative stress, redox, and other crucial cellular processes in nearly all tissues and cell types, including those involved in innate and adaptive immune responses. For a review, (Spallholz et al., 1990) Spallholz included a total of 82 papers but only 4 studies (1972–1989) were extracted focussing on the role of Se in relation to immunity in pigs and chicken, whereas the remaining addressed other animal species (rat, mouse, human, ruminants). Since then, the number of papers on Se in relation to porcine/avian immunity has increased, although the information is still scarce. Also, conflicting results are published due to difficulties in comparing different animal studies as many confounding factors *e.g.* sex, age, pathogen strain, dose and the major histocompatibility complex (MHC) influence the immune/disease parameters. However, reviews have recently been published, summarizing findings on the biochemistry of active Se species in humans and the link between Se intake, selenoproteins functionality and health or disease including inflammation and immunity (Labunskyy et al., 2014; Roman et al., 2014).

Early findings suggested that the enzymes, glutathione peroxidase 1 (GPX1) and glutathione peroxidase 2 (GPX2) contained selenium (Flohe et al., 1973; Rotruck et al., 1973; Ursini et al., 1982; Ursini et al., 1985). These two enzymes are key elements in our knowledge of the biological function of Se. One of the first findings associated with immunity was the discovery that patients suffering from chronic granulomatous disease showed decreased activity of the GPX2 enzyme (Holmes et al., 1970). Later, the thioredoxin reductases (TXNRD's) selenoenzymes were described (Nakamura, 2004). So far twenty-five selenoproteins have been identified in humans, but only few of them have been functionally characterized (Roman et al., 2014). GPX's and TXNRD's play complementary roles where equilibrium is a key factor in the modulation of the immune response.

Today we know that the biological effects of Se are exerted through the amino acid selenocysteine. In the body, Se was shown to be present in many of the major immunological organs; bone marrow, thymus, liver, spleen and lymph nodes (Behne and Wolters, 1983; Huang et al., 2012). At cellular level, Se is found in lymphocytes, granulocytes and monocyte/macrophages. An overview of the tissue distribution of the human selenoproteins and their subcellular location can be obtained from Roman et al. (2014). Some selenoproteins are involved in cellular activation and differentiation hence being of importance for innate and adaptive immune responses. Macrophages utilize the redox control during cellular activation by stimulating expression and activity of methionine-R-sulfoxide reductase B1 (MSRB1) (Lee et al., 2013), which is a protein responsible for the reconversion of methionine residues from their oxidized form (methionine sulfoxide), and present in the cytoplasma and the nucleus. The study of Lee et al. (2013) shows that proteins can be regulated by reversible site-specific methionine-R-sulfoxidation, and that it regulates actin disassembly and re-assembly by targeted oxidation and reduction of methionine, hence having a crucial role in regulating the innate immune response through the redox control of actin.

The role of selenoproteins in the protection of host cells against damage caused by oxidative stress is well-described. GPX1 is the most abundant selenoprotein in mammals, and is an enzyme present in the cytosol and mitochondria that catalyzes GSH-dependent reduction of H_2O_2 to water. GPX2 is primarily found in the epithelium of the gastrointestinal tract, whereas GPX3 is excreted primarily from the kidney and is the major GPX form in plasma. GPX4 is expressed in a wide range of cell types and tissues, and GPX6 is only found in olfactory epithelium and during embryonic development (Labunskyy et al., 2014). Many phagocytic cells rely on the production of ROS in their bactericidal activities during inflammation, and antioxidant systems are crucial to prevent host-cell damage (McKenzie et al., 1998). Hence, ROS production would have positive effects in combatting invading pathogenes, but if the oxidation is uncontrolled due to overleaking of electrons from mitochondria, the reactive oxygen products may induce damage to the host epithelium. GPX1 has been considered as one of the major antioxidant enzymes, and appears to play a protective role under conditions of oxidative stress. However, compared to its family members, GPX1 expression is more sensitive to changes in both Se status and oxidative stress conditions. It appears that global protein synthesis is reduced under conditions of stress as a means of reserving cellular resources, and that GPX1 recovers more rapidly compared to other selenoproteins (Papp et al., 2007). However, this may of course depend on the Se-status of the individual.

Se deficiency may lead to a less responsive immune system. This may be a major disadvantage in viral infections and in mice it was shown that coxsackievirus is more prone to mutate into a virulent cardiotoxic form in Se deficient hosts (Beck et al., 1995). Interestingly, in humans virulent strains of influenza virus are observed to evolve in areas of Se-deficiency in China and some hypothesize that simian immunodeficiency viruses (SIVs) naturally infecting African non-human primates may have crossed the species barrier to humans in Se-deficient areas of Africa (McKenzie et al., 1998). Adequacy and moderate supplementation is generally considered to support the normal fully functional immune system and the effect of extensive Se supplementation is debatable Some authors hypothesize that supplementation may potentially "boost" cellular immunity as Se may increase expression of IL-2R on T cells and enhance T cell responses (Kiremidjianschumacher et al., 1994; McKenzie et al., 1998). The so-called "boosting" effect may be beneficial to the immune system in elderly or virally infected hosts. It is, however, controversial whether Se supplementation is an advantage for immunity in cases of parasitic infections or allergy in humans.

2.2. Innate immunity

Selenium, in the form of selenoproteins, plays a pivotal role in anti-inflammatory responses as well as the antioxidant defense system. The survival of host cells is dependent on biochemical and physiologic factors. Cell and tissue protection requires oxidative balance, *i.e.* balance between production of reactive oxygen and nitrogen species (ROS, RNS) and the counteracting antioxidant defense systems. Under physiological conditions, such as stress due to *e.g.* infection, ROS production participates in the activation and

signalling of various endogenous systems (Vladimirov and Proskurnina, 2009).

Macrophages are important professional scavenger cells of the innate immune system. They can phagocytose microorganisms by various mechanisms mediated by Fc receptors and or complement opsonisation. Macrophages produce as part of their pathogen elimination mechanism nitric oxide ($NO^{\cdot}$) and ROS during phagocytosis and in response to pathogen associated molecular patterns (PAMP) interaction with pattern recognition receptors (PRRs) (reviewed by Gordon and Martinez-Pomares, 2017). Particularly in relation to macrophage responses, selenoproteins act as major antioxidants to mitigate the cytotoxic effects of ROS (Vunta et al., 2008), actin regulation (Lee et al., 2013) and limit pathogen replication (Markley et al., 2017). In chickens, it was shown that a diet deficient in both vitamin E and Se had negative impact on macrophage numbers as well as their phagocytic potential (Dietert et al., 1990).

Another important cell type producing ROS are neutrophils, the predominant phagocyte population in peripheral blood. Apart from production of ROS, neutrophils are efficient in phagocytosis and production of extracellular traps (Deniset and Kubes, 2016). Few studies describe the effect of Se deficiency alone on neutrophil function, but a number of studies address the subject in Se and vitamin E deficient animals. In general, Se deficiency does not necessarily affect neutrophil numbers but rather different aspects of neutrophil function.

The chicken heterophils are the polymorphonuclear (PMN) leukocytes, which perform functions comparable to mammalian neutrophils. Dietert and co-workers showed decreased ability of heterophils to phagocytose *S. typhimurium* in Se/Vitamin E double deficient chickens (Dietert et al., 1983). Impaired neutrophil function has also been reported in Se deficient pigs. Thus, the ability of peripheral blood PMN to phagocytose yeast, *in vitro*, was shown to be impaired when pigs suffered from vitamin E and Se deficiencies (Wuryastuti et al., 1993).

Low Se content may also affect intestinal mucosal immunity and in commercial broilers, deficiency was shown to reduce soluble IgA amounts in the duodenal mucosa and increase levels of pro-inflammatory cytokines interleukin-1β (IL-1β), IL-17A and interferon gamma (IFN-γ). In contrast, anti-inflammatory cytokines, such as TGF-β1 and IL-10, were significantly suppressed (Liu et al., 2016).

While Se deficiency appears to have negative impacts on innate immunity, the effect of Se supplementation varies and is highly influenced by the source and dose of dietary Se. *In vitro* studies on human neutrophils delineate the problems associated with studies of Se supplementation. Hence, Urban and Jarstrand studied the *in vitro* effect of sodium selenite on neutrophil chemotactic migration, phagocytosis and intracellular killing of staphylococci. They found that the phagocytic and bactericidal potential increased with dietary Se supplementation but at high concentration Se had no or even negative effect (Urban and Jarstrand, 1986).

2.3. Adaptive immunity

Antibodies (immunoglobulins) represent an important diverse family of proteins produced by B lymphocytes. The specific binding of antibodies to their cognate antigen constitutes an important immune mechanism and especially neutralizing antibodies are important to prevent pathogen entry/spread and reduce toxicity of pathogen products. In addition, binding of antibodies to pathogen surfaces renders them more susceptible to phagocytosis by innate immune cells and certain isotypes of antibodies are involved in complement activation which leads to efficient pathogen destruction. Hence the ability of an animal to produce specific antibodies is a key element in the response to both vaccines and primary infections and therefore essential for immune protection (Moser and Leo, 2010).

In general there is little evidence of an effect of Se deficiency in relation to impaired humoral immunity in poultry and pigs. A few studies report a beneficial effect of dietary Se supplementation in chickens on the induction of specific antibodies by Infectious bursal disease virus vaccines (Arshad et al., 2005; Shekaro et al., 2012). In contrast, when the influence of Se on broiler immunity was studied by feed supplementation of various concentrations (0, 100, 200, 300, or 400 μg/kg diet) of organic Se, no effect was found on the production of antibodies specific for Newcastle disease virus vaccine (Rao et al., 2013).

Similarly, supplementation with Se has failed to show an effect on specific antibody responses in pigs. Thus Blodgett and co-workers studied six groups of 16 pigs which were fed diets supplemented with sodium selenite (0–1.5 mg/kg). Whole blood concentrations of Se linearly increased as dietary Se increased, but no effect was observed on antibody responses in terms of IgG titres to lysozyme and ribonuclease (Blodgett et al., 1986). However, more detailed studies are needed for understanding the potential effect of Se on humoral immune responses in both poultry and pigs. Effects of supplementation would not necessarily affect IgG and IgM levels in an identical way. Also different effects may be expected on antibody responses directed against T-dependent antigens *vs.* T-independent antigens.

T lymphocytes are able to respond to an antigen-specific stimulation through their T cell receptors (TCR) which *e.g.* induce production of soluble molecules with various pathogen eliminating effects. Various T cell subsets exist but studies in relation to Se mainly comprise the two following broadly defined subsets. Classical cytotoxic T cells (CTLs) express in addition to the pan-T cell marker CD3 also the co-receptor CD8 on their surface (CD8+ T cells). CTLs recognize *e.g.* virally infected or otherwise damaged/dysfunctional (*e.g.* tumour) cells and induce apoptotic cell death *via* secretion of perforin and granzyme. T helper cells (Th) which in addition to CD3 express the co-receptor CD4 (CD4+) are able to secrete a variety of cytokines which provide “help” to other immune cells which negatively affects pathogen survival (Moser and Leo, 2010).

Selenium deficiency was shown to impair thymus development in broilers. Chickens fed a diet low in Se concentration were observed to have reduced CD3 + CD8+ T cell frequencies in peripheral blood (Peng et al., 2011). Likewise, Chang and co-workers reported that chickens from an inbred Cornell line showed slightly decreased frequencies of peripheral T cells when fed a diet low in Se and vitamin E (Chang et al., 1994).

In the Se study by Rao and co-workers, organic Se in various concentrations did not affect leukocyte counts or relative weight of

lymphoid organs in commercial broilers. However, cell mediated immunity assessed by *ex vivo* proliferation capacity increased with Se concentration (Rao et al., 2013). In another study with broilers and dietary selenised yeast (Se-yeast), Levkut and co-workers identified increased numbers of both CD4+ and CD8+ cells in peripheral blood when the diet was supplemented with Se (Levkut et al., 2009).

A number of studies describe the potential effect of Se and vitamin E on lymphocyte functions by assessing the response to non-specific mitogenic stimulation *in vitro*. In contrast, to human and mouse research, immunological studies of domestic animals have been hampered by the lack of reagents to study phenotypes of T cells subsets and functional output like cytokine production. Hence, older studies suffer from the fact that entire lymphocyte populations were studied in bulk. Deficiency of Se and vitamin E was shown to hamper mitogenic responses to *e.g.* Concanavalin A (ConA) and phytohaemagglutinin (PHA) in both chickens and pigs (Marsh et al., 1981; Wuryastuti et al., 1993; Chang et al., 1994). Interestingly, studies showed that lymphocytes from pigs fed a diet deficient in Se and Vitamin E show lower response to mitogenic stimulations than lymphocytes from pigs fed a supplemented diet but only in the presence of autologous serum and not when foetal calf serum was added to the culture (Lessard et al., 1991).

Larsen and co-workers assessed the dietary supplementation of vitamin E in combination with Se on PHA responses of peripheral pig lymphocytes and found a positive effect (Larsen and Tollersrud, 1981). A more recent *in vitro* study showed nicely that the experimental setup for studying the effect of Se on cellular immune responses should be carefully evaluated. Hence, it was shown that porcine splenocytes treated with different mitogens in the presence of 0.5–4 mmol/L sodium selenite varied in response. Se promoted anti-CD3 (T-cell receptor induced) or ConA-induced T-cell proliferation and IL-2 production but had no effect on T-cell responses to PHA (Ren et al., 2012).

The cellular response to mitogen does not necessarily represent the immunological events taking place during infection *in vivo*. In fact, antigen-induced T cell activation and differentiation may be far more relevant to study. However, as only a small percentage of the large T cell repertoire will respond to a particular antigen, quantification of antigen-specific T cells is more difficult than bulk studies of the whole T cell pool. Hence, more detailed studies of vaccine-induced T cell activation are needed for understanding the potential effect of Se on *e.g.* vaccine induced disease protection in poultry and pigs and methods are now available (Gerner et al., 2015; Dalgaard et al., 2016).

Interestingly, mouse and human research point to the fact that a variety of selenoproteins may be of importance in T cell regulation; being expressed at low levels in naïve T cells and at higher levels in activated and memory T cells (Huang et al., 2012). T cell responses are of particular importance in viral infections. Selenoproteins regulate cellular redox balance and interestingly the establishment and progression of viral infections are influenced by the redox state of the host cell (Nencioni et al., 2011). Hence, Se may beneficially influence vaccine-induced immunity to viral vaccines and in particular live attenuated vaccines used *e.g.* in livestock production.

A study focussing on influenza vaccination of humans (older adults with marginal Se status) receiving diets containing selenomethionine in a yeast matrix (SeY) or Se-enriched onions (SeO) containing methylselenocysteine showed that moderate doses of Se increased frequencies of flu-specific T cells 11–12 weeks after vaccination (Ivory et al., 2017). Another study reported similar effects of sodium selenite on immune responses to live attenuated polio vaccine in adults with marginal Se status; increased production Th1 cytokines, earlier peak in antigen-specific T cell proliferation, and an increase in the frequency of T helper cells (Broome et al., 2004). In conclusion, more research is needed especially of Se in relation to vaccination/infection with RNA viruses (*e.g.* the coronaviruses) causing problems in pig and poultry production. These viruses are characterized by their ability to easily mutate into more virulent stains. Se is hypothesized to support Th1-type host protective immunity and impede evolution of more virulent strains of RNA virus in pigs and poultry but detailed studies are still lacking.

Only little information is available regarding the comparative effect of inorganic and organic selenium on the immune system of animals. The results of da Silva et al. (2010) from a feeding experiment with broilers vaccinated against infectious bursal disease (IBD) or immunised with sheep red blood cells (SRBC) showed, that birds receiving 0.3 mg/kg feed of an organic selenium source (Sel-Plex™, providing at least 50% of its selenium under the form selenomethionine) had a higher feed intake and a higher H/L ratio than birds receiving the inorganic selenium source (sodium selenite). On the other hand, birds supplied with sodium selenite had higher antibody titres against IBD and SRBC.

3. Selenium and infectious disease in poultry and pigs

3.1. Poultry diseases

Positive effects of selenium supplementations in amounts exceeding the nutritional requirements have been observed for coccidiosis, necrotic enteritis and avian pathogenic *E. coli* (APEC) in poultry, where supplemental selenium seems to increase disease resistance and/or alleviates symptoms associated with the disease (Larsen et al., 1997; Mahmoud and Edens, 2005; Wunderlich et al., 2014; Lee et al., 2014a; Lee et al., 2014b; Xu et al., 2015).

Coccidiosis is one of the most significant poultry diseases worldwide. The global economic impact of coccidiosis has been estimated to exceed 3 billion USD annually which is attributed to production losses, control measures and treatment (Blake and Tomley, 2014). Coccidiosis is caused by a single-celled spore forming parasite belonging to the Genus Eimeria with several species being prevalent in poultry, *e.g. E. tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. necatrix*. The parasites undergo an asexual and a sexual reproduction cycle in the intestinal tract of the host and are responsible for the damage of the mucosal cell lining and the underlying tissue. The disease is characterized by oxidative stress, inflammation, nutrient malabsorption, diarrhea, fluid loss and dehydration. Oxidative stress is a critical initial event in Eimeria infections (Pohanka, 2013; Wunderlich et al., 2014). Epithelial host cells activate

membrane-bound NADPH oxidases to form superoxide radicals and hydrogen peroxide. Neutrophils and macrophages recruited to the parasite invasion site produce superoxide by NADPH oxidases inside the phagosome and nitric oxide by nitric oxide synthases in the cytoplasm. Superoxide and nitric oxide radicals form peroxynitrite that counteracts parasites invading the epithelial cell (Wunderlich et al., 2014).

Necrotic enteritis is a severe intestinal disease associated with toxin producing *Clostridium perfringens* Type A occurring primarily in broilers. Coccidiosis is known as a predisposing factor for the disease. Once the mucosal lining is injured by Eimeria, *Clostridium perfringens* colonizes the intestine. The net B toxin of *Clostridium perfringens* has been shown to trigger the disease, which is characterized by typical intestinal lesions primarily in the region of the jejunum and duodenum. The mucosa is destroyed and gets necrotic, which significantly reduces nutrient absorption and thereby weight gain. In acute clinical cases, high mortality can be observed, whereas in subclinical cases, the disease is characterized primarily by reduced weight gain and intestinal lesions. In broilers, the disease occurs usually in the period from 20 to 28 days of age. Dietary supplementation of antibiotics and ionophore anticoccidials can be used in the prevention of the disease. The withdrawal of antibiotic growth promoters is supposed to have contributed to a new emergence of the disease.

Lee et al. (2014a) use a necrotic enteritis disease model involving both an oral inoculation of *E. maxima* (day 14) and *Clostridium perfringens* (day 18) to evaluate whether sodium selenite (up to 20 μg/egg) given as *in ovo* injection on day 18 of broiler embryonic development offers disease protection. The *in ovo* injection of sodium selenite increased bird weight, reduced intestinal lesions and oocyst production and increased the levels of transcripts for interleukins (IL1-beta, IL6 and IL8), the serum antibodies against alpha toxin and NetB toxin. *In ovo* injection of Se incorporated into hydrolysed soybean protein (B-taxim) showed similar results with respect to the protection against necrotic enteritis (Lee et al., 2014b). Compared to the results obtained from *in ovo* injection, dietary supplementation of B-taxim over a period of 24 h was less effective. However, 0.50 mg selenium/kg feed alleviated the body weight reduction associated with necrotic enteritis, reduced intestinal lesions and increased antibody production against NetB-toxin (Xu et al., 2015).

APEC infections occur as acute fatal septicemia or subacute pericarditis, airsacculitis, and salpingitis, are common and of significant economic importance in poultry production (broilers and layers) and is observed worldwide (Larsen et al., 1997; Mahmoud and Edens, 2005; Guabiraba and Schouler, 2015). The tendency to more extensive rearing systems with access to outdoor areas (free range and organic production) has contributed to increasing problems with *E.coli* infections in poultry production (Guabiraba and Schouler, 2015). Larsen et al. (1997) found that an inorganic selenium source added at a dietary supplemental dose of 0.4 mg/kg (total selenium content of 0.45 mg/kg feed) reduced bird mortality and air sac lesions, when white leghorn type chickens were inoculated with *E. coli* (serotype O1:K1) in the lower abdominal air sac. Mahmoud and Edens (2005) reported that broilers receiving an additional dietary selenium supplementation of 0.2 mg/kg feed (total feed selenium content of 0.48 mg Se/kg) were significantly heavier compared to non-supplemented birds when exposed to heat stress and an intranasal challenge with an enteropathogenic *E. coli* (serotype O1; EPEC).

A single report suggests a potential beneficial effect of Se added at levels of 1 mg/kg to a basal diet providing 0.15 mg/kg Se on the immune response of broilers challenged at day 5 with *Salmonella* Typhimurium. The supplemented birds showed higher serum agglutination titres compared to the non-supplemented control (Hegazy and Adachi, 2000).

3.2. Pig diseases

In the review performed by Spallholz et al. (1990) entitled 'Advances in understanding selenium's role in the immune system' only two studies on pigs were included, *i.e.* the supplementation studies of Blodgett et al. (1986) and Larsen and Tollersrud (1981) on the effect of dietary vitamin E and Se on phytohaemaglutinin response of pig lymphocytes. The latter study showed an increased phytohaemaglutinin response by lymphocytes. Since that time, immunological related studies have focused on the perspective of the importance of Se for disease resistance in weanling pigs, and hence transfer of Se from sow to the progeny was primarily studied.

Mahan and Parrett (1996) demonstrated that colostrum and milk Se and vitamin E concentrations declined with advancing age. Consequently, older high-producing sows were considered more likely to produce progeny with low vitamin E and Se status at birth and weaning than younger sows; and postweaning pigs were considered to encounter deficiency more quickly if their vitamin E and Se status was compromised prior to weaning. Further, studies have found that transfer of Se from sows to piglets is limited (Mahan et al., 1977) and that plasma Se concentrations in weaned piglets are highly dependent on Se levels in the post-weaning diet (Mahan and Peters, 2004). In order to increase the Se status of dams and the progeny by dietary means, a number of studies have been conducted on the comparison of inorganic (selenite) and organic (Se-yeast) Se supplementation at different levels (0.15 and 0.3 mg/kg Se). Mahan (2000) concluded that inorganic Se was more biologically available for sow serum GPX activity, whereas organic Se was more effectively incorporated into milk. Sows fed the organic Se source had a greater transfer of Se to the neonate, colostrum, milk, weaned pig, and sow tissues than sows fed inorganic Se (Mahan and Peters, 2004). Furthermore, pigs born by sows fed with an organic Se (Se-yeast) had greater serum Se content at birth than sows supplemented with inorganic Se (Yoon and McMillan, 2006). Also, in a study over six parities of sows and progenies, Se concentration in colostrum and piglets at birth was greater when the organic form of Se was fed (Peters et al., 2010). A more recent study showed that greater Se accumulation in both natal and foetal tissues was associated with organic Se (Ma et al., 2014). In addition, the organic Se source hydroxy-selenomethionine, (2-hydroxy-4-methylselenobutanoic acid or HMSeBA) when supplementated to growing pigs showed a higher deposition of Se in muscle compared to selenized yeast (Jlali et al., 2014). Likewise, in laying hens, the provision of HMSeBA increased Se deposition in eggs and breast muscle compared with other Se sources (sodium selenite and selenized yeast) (Jlali et al., 2013).

Of specific interest in relation to Se and immunity of pigs is that organic Se increased milk Se content more than did inorganic Se

and increased suckling piglets' serum Se content. Inorganic Se affected the sow serum GPX activity more than organic Se, but the latter was biologically more available to be incorporated into colostrum and milk (Surai and Fisinin, 2016). However, a recent study (Chen et al., 2016a, 2016b) on multiparous sows showed that sows antioxidant status (assessed as concentration of α-tocopherol, GPX, superoxide dismutase (SOD), GSH) and Se level increased when sows were fed organic Se (Se-yeast) compared with sodium selenite. In addition, Se status and antioxidant status (measured as total antioxidant capacity, activities of superoxide dismutase, glutathione peroxidase, and glutathione content) in the progeny including newly-born and 21 d old nursery piglets were improved when Se was added as organic Se instead of in organic Se to the diet of sows. However, it should be noted that in this study (Chen et al., 2016b), the activity of GPX in piglets was not affected by dietary Se source offered to the sows, but the concentration of Se in heart, pancreas, thymus gland, thyroid and loin was increased in 21 d old piglets from sows fed the organic Se source. The studies included the interaction with dietary vitamin E at concentrations of 30 and 90 IU/kg (Chen et al., 2016a, 2016b), but the measured parameters were less affected by this interaction. Using another form of Se, the selenomethionine, Hu et al. (2011) showed increased Se deposition in sow and progeny from birth to weaning and antioxidant status (increase in GPX, SOD, GSH) in tissues of piglets.

Lyons et al. (2007) concluded on basis of their review that sodium selenite should be replaced by organic selenium in premixes for pigs and sows because organic forms of Se are more bioavailable than inorganic (sodium selenite). However, although there seems to be convincing scientific literature showing advantages of organic selenium for sows and suckling piglets, very few studies are available on the effect on the piglets post-weaning. Quesnel et al. (2008) compared the effect of organic (Se yeast) and inorganic Se (sodium selenite) at 0.3 mg/kg in sow diets on colostrum production and piglet response to a poor sanitary environment after weaning. According to the studies mentioned above, organic Se fed to the dam was better transferred to colostrum and milk, and consequently to piglets, but the source of Se did not influence immunoglobulin concentration in colostrum and milk, haptoglobin concentration or performance of pigs post weaning.

A more recent study from Norway concluded that vitamin E and selenium supplementation to piglets in Norway may still be suboptimal, but that the two nutrients partially compensate for each other in the weaning period (Sivertsen et al., 2007). Another clear proof of the interplay between vitamin E and selenoprotein systems was obtained by Wortmann et al. (2013). Indeed, early death was observed in their conditional GPX4 knock out mouse model unless vitamin E was supplemented. However, whereas it is well-documented how selenium status may be increased in piglets at weaning by using especially organic Se rather than inorganic selenium sources, there is a lack of knowledge on the influence of antioxidants in general (*i.e.*, selenium and vitamin E status) on the immune responses of piglets upon an infectious challenge post weaning. Some studies have investigated the effect of dietary Se supplementation in relation to infection with porcine circovirus type 2 (PCV2) associated with Post Weaning Multisystemic Wasting Syndrome (PMWS). In a mice study, dietary Se yeast supplementation attenuated the PCV2 infection through altering systemic inflammation and maintaining the normal organ morphology The effect of PCV2 vaccination in pigs post weaning, and treatment with heat stress and dietary antioxidant concentration (extra supplementation of vitamin E and Se and an SOD-rich melon supplement *vs.* NRC (2012) norms of vitamin E and Se) on various blood oxidative stress markers, was determined by Royer et al. (2016). The authors observed that vaccination decreased GPX activity and higher concentrations of haptoglobin and lipid peroxides, and that the oxidative stress biomarkers were associated with each specific stress inducer. Chen et al. (2012) concluded that differences in morbidity and severity of PMWS observed in different pig farms may be related to variation in oxidative stress and that selenium has a potential role in the control of PCV2 infection. Furthermore, dietary Se and vitamin E mitigated the impacts of heat stress on intestinal barrier integrity, associated with a reduction in oxidative stress in growing female pigs (Liu et al., 2016). On the other hand, after a bacterial induced acute-phase reaction using *Actinobacillus pleuropneumonia*, Humann-Ziehank et al. (2014) concluded that Se status was only marginally affected by the infection, and GPX activity in blood and liver remained unaffected. Lauridsen (2010) showed a 30% reduction in the liver vitamin E concentration after challenge of piglets post-weaning with *E. coli*, but did not look for Se or GPX in that study. However, according to the authors' knowledge, no data are available on the influence of the selenium status of piglets in relation to immune responses and disease prevention after enteric infectious challenge. Feeding a Se-enriched probiotic preparation comprising two strains of microorganisms, *Lactobacillus acidophilus* and *Saccharomyces cerevisiae*, increased beneficial bacteria (lactobacillus), and reduced *E. coli* numbers of in feacal samples post weaning compared to sodium selenite (Lv et al., 2015).

In vitro studies with primary splenocytes isolated from healthy pigs showed that selenomethionine diminished aflatoxin–B-1-induced immune toxicity, and selenomethionine enhanced mRNA and protein expression ofGPX1 and selenoprotein S, and thioredoxin reductase 1 without and with aflatoxin-treatments (Hao et al., 2016).

4. General discussion and conclusion

According to findings from a variety of studies and reviews involving Se and immunity mainly based on other animal species and humans, it can be concluded that there is considerable evidence supporting that Se through selenoproteins affects different types of immune responses in various ways. The major functions of Se are carried out by Se-enzymes, and their important mechanisms for immunity involve antioxidant and anti-inflammatory activities. We have provided an overview of current knowledge of the influence of Se on immune responses in poultry and pigs and the relationship to infectious diseases in these species. From human research is has been concluded that available evidence suggests that boosting Se levels in individuals with a moderate or low Se status may have more immune enhancing effects than supplementing an individual with adequate status. In pig research addressing the role of Se, major focus has been given to periods where Se deficiency is more likely to occur, which is in the neonate, at weaning, and during the reproductive period. These are also the critical phases of vitamin E status in pigs, and both micronutrients have been of special interest regarding their protective effect against myopathies. In poultry, it seems less clear if there are situations of selenium (and vitamin E) deficiency, but there are several demonstrations of potential positive effects of selenium supplementation to increase bird

resistance against major pathogens or alleviate consequences of environmental stresses. Further work is still needed to elucidate mechanisms and determine the effect of sub-optimal doses of selenium.

Recent advances in Se biochemistry have provided a deeper understanding of the principal differences in metabolism of the organic and inorganic Se-sources. The bioavailability and distribution of Se in the body is influenced by a number of factors among those the chemical form of Se. It seems well documented that organic sources of Se are more bioavailable than inorganic Se sources, thus providing a more efficient transfer of Se *via* colostrum to the off-spring. However, scientific documentation is lacking whether an enhanced bioavailability of Se and hence improved Se status of the sow would be beneficial for immunity and robustness of her piglets. Considering the increased use of antibiotics and pharmacological levels of zinc oxide for treatment of *E. coli* diarrhea in pig production, it is however of major interest to study, how nutritional immunology of pigs can be used as a tool, and in this context how dietary levels and sources of Se can modulate the resistance to this infectious disease. Furthermore, when adding to the mounting evidence that Se can inhibit the pathogenicity of certain viruses, the potential usefulness of dietary Se forms and concentrations becomes of major interest in both chicken and swine nutrition.

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