Nutritional modulation of the antioxidant capacities in poultry: the case of vitamin E

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ABSTRACT Commercial poultry production is associated with a range of stresses, including environmental, technological, nutritional, and internal/biological ones, responsible for decreased productive and reproductive performance of poultry. At the molecular level, most of them are associated with oxidative stress and damages to important biological molecules. Poultry feed contains a range of feed-derived and supplemented antioxidants and, among them, vitamin E is considered as the "headquarters" of the antioxidant defense network. It is well-established that dietary supplementation of selenium, vitamin E, and carotenoids can modulate antioxidant defenses in poultry. The aim of the present paper is to present evidence related to modulation of the antioxidant capacities in poultry by vitamin E. Using 3 model systems including poultry breeders/males, semen, and chicken embryo/postnatal chickens, the possibility of modulation of the antioxidant defense mechanisms has been clearly demonstrated. It was shown that increased vitamin E supplementation in the breeder's or cockerel's diet increased their resistance to various stresses, including high polyunsaturated fatty acids (**PUFA**), mycotoxin, or heat stress. Increased vitamin E supplementation of poultry males was shown to be associated with significant increases in α-tocopherol level in semen associated with an increased resistance to oxidative stress imposed by various external stressors. Similarly, increased vitamin E concentration in the egg yolk due to dietary supplementation was shown to be associated with increased α-tocopherol concentration in the tissues of the developing embryos and newly hatched chicks resulting in increased antioxidant defenses and decreased lipid peroxidation. Furthermore, increased vitamin E transfer from the feed to egg yolk and further to the developing embryo was shown to be associated with upregulation of antioxidant enzymes reflecting antioxidant system regulation and adaptation. The role of vitamin E in cell signaling and gene expression as well as in interaction with microbiota and maintaining gut health in poultry awaits further investigation.

Key words: nutritional modulation, antioxidant, vitamin E, oxidative stress, poultry

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INTRODUCTION

Commercial poultry production is associated with a range of stresses, including environmental, technological (Surai and Fisinin, 2016a), nutritional, and internal/biological (Surai and Fisinin, 2016b) ones. It is believed that these stresses are responsible for decreased productive and reproductive performance of poultry (Surai, 2002), and, at the molecular level, most stresses are associated with oxidative stress and damage to important biological molecules (Surai, 2018). Therefore, poultry feed contains a range of feed-derived and supplemented antioxidants. Among them, vitamin E is considered as the "headquarters" of antioxidant defense network. It is well established that dietary supplementation of selenium, vitamin E, and carotenoids (Surai, 2002, 2018) can modulate antioxidant defenses in poultry. In a previous review paper, the importance of selenium in antioxidant defense mechanisms in poultry was described (Surai and Kochish, 2018a). The aim of the present paper is to present evidence related to modulation of the antioxidant capacities in poultry by vitamin E.

Choice of a Model System to Address Antioxidant System Modulation

To address the nutritional modulation of the antioxidant capacities in poultry by vitamin E, a

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chain, including breeder—egg—newly hatched chick—posthatch chick was chosen as a model system and characterized in detail earlier (Surai and Kochish, 2018a). In addition, another model, based on poultry male nutrition and semen quality, was also used. Avian spermatozoa are highly specialized cells consisting of various membrane structures and their functional integrity determines vital physiological functions, including motility and fertilizing ability. In this respect, the lipid composition of chicken semen is considered to be an important determinant of its quality (Cerolini et al., 1997). In fact, avian spermatozoa are characterized by high concentrations of C20 and C22 polyunsaturated fatty acids (**PUFA**), in particular, arachidonic (20:4) and docosatetraenoic (22:4) acids (Surai et al., 1997a, 1998a,b, 2000a,b) predisposing them for the oxidative damage within spermatozoa membranes causing male subfertility (Surai, 2002). It has been shown that H_2O_2 and organic hydroperoxides have toxic effects on cockerel's sperm motility. For example, a 0.3 mM concentration of H_2O_2 caused a 50% reduction in motility of chicken spermatozoa within 8.5 min of the start of the sperm incubation at 37°C (Surai et al., 1998b). Furthermore, H_2O_2 and hydroxyl radicals sharply reduced egg fertility (Rui et al., 2017), and the susceptibility of chicken spermatozoa to H_2O_2 toxicity was shown to be much higher (5 to 100-fold) than that in mammalian (human, mouse, rabbit, dog, and ram) spermatozoa (Wales et al., 1959). Therefore, an efficient antioxidant system is required to protect sperm membranes against peroxidative damage (Surai, 1999a, 2002). The antioxidant system of avian semen includes the natural antioxidants: vitamin E (Surai, 1989a; Surai and Ionov, 1992a; Surai et al, 1997a; Surai et al., 1998b, 2000b), vitamin C, and glutathione (**GSH**) (Surai et al., 1998b), as well as antioxidant enzymes, glutathione peroxidase (**GSH-Px**) and superoxide dismutase (**SOD**) (Surai et al., 1998a,d). Of these, vitamin E by acting as a fat-soluble antioxidant within membranes plays a central role in the protection of spermatozoa PUFA against peroxidation (Surai, 1999a, 2002).

Modulating Effects of Dietary Vitamin E

The purpose of this section is to consider the modulating effects of vitamin E on antioxidant defenses at the level of breeders/cockerels, semen and egg—developing embryo—newly hatched chicks.

Cockerels and Breeders Our research on the modulation of the antioxidant defenses of poultry started in early 1980 (Surai, 1983a, 1991), when protective effects of increased vitamin E levels in the diet of turkey, chicken, goose, and duck males and females were shown. In particular, it was shown that vitamin E concentrations in tissues (liver, kidney, testicles, and adrenals) of poultry males (turkey, chicken, duck, and goose) significantly decreased from the beginning to the end of the reproduction period (Surai, 1982b, 1988a, 1991, 1992). In our later study, cockerel diet containing 12 mg/kg feed-derived α-tocopherol was supplemented with 4 different levels of vitamin E (0, 20, 200, and 1000 mg/kg) and α-tocopherol concentrations in the liver (7.1, 9.0, 26.4, and 51.9 mg/kg) and testes (4.2, 5.9, 14.7, and 24.2 mg/kg) significantly increased and led to decreasing lipid peroxidation in the tissues (Surai et al., 1997a). Furthermore, when a comparison was made between cockerels fed on diets with a different level of vitamin E supplementation (0, 20, and 200 mg/kg), it was found that vitamin E in the liver (6.9, 9.1, and 28.9 mg/kg) and testes (4.9, 7.1, and 16.8 mg/kg) was significantly elevated (Surai et al., 1998d). This was associated with improved antioxidant defenses leading to a significantly increased resistance of the tissues to lipid peroxidation. Similarly, when vitamin E level in the cockerel diet increased by 4 times (from 40 to 160 mg/kg), the highest increase in vitamin E concentration was observed in the liver (3.2-fold) and testes (2.9-fold), and the lowest increase was found in cerebellum (1.5-fold) and internal fat (1.7-fold). When susceptibility to lipid peroxidation was assessed in the same tissues, the biggest decrease due to elevated vitamin E concentration was observed in testes (by 74%), and the lowest response was seen in the cerebellum (by 25%) and cerebrum (by 31%) (Surai and Sparks, 2000). Similarly, a significant increase in vitamin E concentrations in all the tissues studied including liver, lung, heart, kidney, testes, plasma, and whole semen was observed in cockerels fed on diets enriched with PUFA and increased (200 vs. 40 mg/kg) vitamin E supplementation (Surai et al., 2000a).

In a later study, it was found that due to dietary tocopherol mix ($\alpha + \gamma + \delta$) supplementation of layers, the enhancement of total tocopherols in the different tissues were as follows: egg yolk > liver > adipose tissue > dark meat > white meat (Cherian et al., 1996). Furthermore, laying hens were fed on high vitamin E diet (250 mg/kg) for 8 wk and a comparison was made with birds fed on a low vitamin E diet (15 mg/kg). As expected, there was a significant increase in vitamin E concentration in all 12 tissues studied due to increased vitamin E dietary supplementation (Surai, 1999a). Therefore, high vitamin E supplementation was proven to be an effective way to increase antioxidant defenses of major tissues.

Vitamin E concentration in plasma, various tissues, and egg yolk was significantly increased with increasing dietary vitamin E supplementation (from 0 up to 20,000 mg/kg). In this study, the egg yolk was characterized by the highest vitamin E concentration, followed by liver and muscles (Sünder and Flachowsky, 2001). When breeder's diet was supplemented with increasing vitamin E doses (0, 40, 80, 120, and 160 mg/kg), breeder's plasma α-tocopherol concentration significantly increased showing the following values 0.84, 3.25, 5.68, 8.25, and 10.88 mg/kg, respectively (Lin et al., 2005a). However, only vitamin E supplementation at 120 mg/kg was shown to increase GSH-Px activity in plasma, while at 160 mg/kg

vitamin E supplementation was associated with decreased malondialdehyde (**MDA**) and reactive oxygen species (**ROS**) in plasma measured fluorometrically by using 2′,7′-Dichlorofluorescin Diacetate as a reactive agent (Lin et al., 2005b). Furthermore, increased dietary vitamin E levels (from 30 to 60 mg/kg) for 10 wk was shown to be responsible for significant increase in antioxidant defense indexes evidenced by increased serum α-tocopherol concentrations, SOD activity, and the antioxidant capacity of serum measured by FRAP assay based on reduction of Fe^{3+} to Fe^{2+} by antioxidants present in the serum with the following formation of a colored complex with 2,4,6 tripyridyltriazine present in the solution (Zduńczyk et al., 2013). Similarly, supplementation of vitamin E at 125 to 250 mg per kg diet (vs. 25 or 5 mg/kg) significantly reduced the concentration of lipid peroxide (MDA) and increased GSH-Px activity in serum and catalase activity in erythrocytes of heat stressed laying hen (Panda et al., 2007). Under tropical summer conditions, increased (125 vs. 25 mg/kg) vitamin E supplementation of White Leghorn layers was associated with a significant increase in GSH-Px, glutathione reductase (**GR**), and catalase activities and decreased lipid peroxidation in layer erythrocytes (Panda et al., 2008).

Taken together, these data provide evidence that dietary vitamin E can increase antioxidant defenses of breeder birds directly by increasing vitamin E level in tissues or indirectly by enhancing activities of antioxidant enzymes, including SOD, GSH-Px, GR, and catalase. This could decrease oxidative stress, reduce lipid peroxidation, and bring some benefits in terms of productive and reproductive performance of birds. However, there have been many contradictory reports on whether increased vitamin E supplementation can improve productive and reproductive performance of breeding poultry. Indeed, effects of increased vitamin E supplementation on poultry breeders depend on the age of breeders, presence, levels and form of other antioxidants in the diet (e.g., Se, carotenoids, etc.), levels and form of PAFAs (e.g., omega-3/omega-6 ratio), and level of commercially-relevant stresses (Surai, 2002).

Avian Semen The antioxidant system of semen plays an important role in maintaining fertility. On the one hand, effective defense against peroxidation is vital to maintain structural integrity of the spermatozoa during semen manipulation, including semen collection, dilution, liquid storage, cryopreservation, etc. On the other hand, prevention of lipid peroxidation would arrest reduction in the levels of the functionally important C20–22 PUFA of avian spermatozoa (Surai et al., 2001b; Surai, 2002). In particular, the proportions of omega-6 long chain PUFA (20:4n-6 and 22:4n-6), phosphatidyl ethanolamine (**PE**), and phosphatidyl serine (**PS**) significantly decreased in turkey semen after 1 h of in vitro incubation in the presence of Fe^{2+} at 37°C. Adding vitamin E (200 mg/kg) to incubation medium was shown to prevent the loss of PUFA, PE, and PS due to induced peroxidation (Maldjian et al., 1998). Lipid peroxidation is considered to be a significant factor decreasing the fertilizing ability of stored turkey sperm (Long and Kramer, 2003). It has been demonstrated that peroxidative damage to avian sperm can occur during in vitro incubation leading to accumulation of the toxic end-product (MDA) of lipid peroxidation (for review see Surai et al., 2001b; Surai, 2002).

Vitamin E was first detected in turkey semen in 1981 (Surai, 1981), and most α-tocopherol (85%) was shown to be located in the cells with only a very small proportion of this vitamin found in the seminal plasma (Surai, 1981; Surai, 1989a; Surai, 1992; Surai and Ionov, 1992a). A similar distribution of vitamin E was described for chicken semen with about 88% of the semen's vitamin E to be located in the spermatozoa (Surai et al., 1998b). It is important to mention that there are species-specific differences in vitamin E concentration in avian semen. For example, in duck spermatozoa, vitamin E concentration was shown to be about 3 times lower compared to chickens (Surai et al., 2000b). Similar to other species, in duck semen, most vitamin E was associated with spermatozoa.

Vitamin E concentration in spermatozoa depends on its dietary provision. For example, increase in vitamin E supplementation of the turkey diet (from 20 to 80 mg/kg) was shown to significantly elevate α-tocopherol concentration in spermatozoa (Surai, 1983a,b; Surai and Ionov, 1992a). On the whole, depending on dietary supplementation, vitamin E concentration in chicken semen varied more than 2-fold: from 0.46 μg/mL (12 mg/kg feed-derived α-tocopherol, without vitamin E supplementation) up to 1.04 μg/mL (12 mg/kg feed-derived α-tocopherol + vitamin E dietary supplementation at 200 mg/kg) (Surai et al., 1997a). Similarly, increased vitamin E supplementation (150 vs. 25 mg/kg) of quail male diet caused a significant increase in α-tocopherol concentration in semen associated with a significant (>3-fold) reduction of lipid peroxidation and improvement of semen quality as indicated by increased semen volume and motility, decreased percentage of dead, and abnormal spermatozoa (Golzar Adabi et al., 2011). Increasing the α-tocopherol content of the spermatozoa membrane was shown to make spermatozoa more resistant to the "unnatural" stresses incurred during artificial insemination, short-term sperm storage, and cryopreservation (Surai, 1983b, 1991, 1992, 2002).

Generally, vitamin E is implicated as an important natural stabilizer of spermatozoa membranes. To validate this hypothesis, 2 main approaches were used. First, the release of aspartate aminotransferase (**AST**) from spermatozoa during sperm manipulation was used as a marker of sperm membrane integrity. In particular, during in vitro sperm storage, the AST activity increased in the medium/diluent and simultaneously decreased in the spermatozoa (Surai and Ionov, 1981; Surai, 1989b). Similar changes in AST activity were also observed in chicken spermatozoa during a freeze-thaw procedure (Matsomoto et al., 1985), and a

highly significant ($r = 0.99$) correlation between AST activity in seminal plasma and the percentage of dead spermatozoa was shown (Bilgili et al., 1985). The second approach employed low concentrations of detergent (Triton X-100) in the sperm storage medium/diluent to induce sperm membrane damage. This treatment was shown to significantly increase the release of AST from spermatozoa (Surai, 1989b). Thus, AST leakage from spermatozoa during sperm storage in vitro and sperm treatment by low concentrations of a detergent were used to confirm a membrane stabilizing effect of vitamin E. Therefore, stabilizing effect of increased vitamin E concentration in turkey spermatozoa was shown (Surai, 1982a) with increased semen resistance to lipid peroxidation, measures as MDA formation during semen storage (Surai, 1984; Surai et al., 1997a). Increased antioxidant defenses of turkey semen was shown to be beneficial during sperm storage and cryopreservation (Surai, 1988b) with vitamin E incorporated into spermatozoa membranes to be much more effective than added directly into the diluent (Surai, 1991).

Increase in the α-tocopherol concentration of semen by dietary manipulation did result in a significant reduction in the susceptibility of the semen to lipid peroxidation. In fact, the susceptibility of semen to peroxidation showed a very high negative correlation ($r = -0.998$) with the α-tocopherol content of the semen. Furthermore, the resistance of testes homogenates to in vitro peroxidation also increased due to the dietary supplementation with α-tocopherol (Surai et al., 1998d). In a similar manner, vitamin E supplementation (200 mg/kg vs. no supplementation) reduced the lipid peroxidation of rooster sperm (Safari et al., 2018). Furthermore, during semen storage, the susceptibility of spermatozoa to lipid peroxidation significantly increased, as a result of initiation of spontaneous lipid peroxidation (Cecil and Bakst, 1993). In such conditions, the protective effect of vitamin E in the spermatozoa has been clearly demonstrated (Surai et al., 1998b; Breque et al., 2003). It seems likely that only "physiological" levels of vitamin E in the chicken diet could be beneficial for semen quality and protective effects of vitamin E have some species-specific differences. For example, the α-tocopherol concentration in chicken semen increased significantly due to high (100 to 20,000 mg/kg) vitamin E supplementation, whereas lipid peroxidation in the semen samples substantially decreased due to increased vitamin E supplementation. However, the reproductive performance of cockerels was negatively influenced by very high (1,000 to 20,000 mg/kg) doses of vitamin E (Danikowski et al., 2002). The authors suggested several possible explanations for the negative effect of high vitamin E supplementation on the cockerel reproduction, including pro-oxidant properties of high vitamin dosages; however, decreased lipid peroxidation in semen samples contradicts this suggestion. Negative effects of high vitamin E dosage on vitamin D metabolism and membrane structure were also considered by the authors. It seems likely that vitamin E excess can negatively affect cell signaling (Zingg, 2018) in testicles leading to deterioration in semen quality. Furthermore, effects of vitamin E access on expression of various transcription factors, including Nrf2 and NF-κB, and gene expression await further investigation.

Furthermore, lipid manipulation and various stress factors can substantially increase semen susceptibility to lipid peroxidation and protective effect of vitamin E would be much more pronounced. In the early 1970, it was shown that inclusion of a high level (10%) of safflower oil into the cockerel diet without vitamin E supplementation decreased fertility down to 11%, while dietary vitamin E provision (32.4 mg/kg) was associated with fertility maintenance at 69% (Tinsley et al., 1971). In the case of lipid manipulation of the cockerel semen by increasing proportion on n-3 PUFA, dietary vitamin E supplementation at 200 mg/kg was shown to be effective in decreasing lipid peroxidation and improving sperm membrane integrity, viability, and motility by enhancing antioxidant status (Safari et al., 2018). The diet supplemented with tuna oil and 40 mg vitamin E/kg diet markedly depleted vitamin E from the tissues of the birds and decreased the concentration of vitamin E in the semen associated with increased semen susceptibility to lipid peroxidation. Interestingly, these negative effects of omega-3 PUFA were largely prevented by the higher (200 mg/kg) vitamin E supplementation (Surai et al., 2000a). Therefore, increased vitamin E concentration in chicken semen was associated with a significant (>3-fold) decrease in lipid peroxidation, which was initially elevated by inclusion of high levels of PUFA. The best sperm quality was found in cockerels fed on the control diet rich in omega-6 PUFA supplemented with vitamin E at 200 mg/kg, while enrichment of the diet with omega-3 PUFA increased vitamin E requirement to 300 mg/kg (Cerolini et al., 2006). Increased vitamin E supplementation (300 vs. 100 mg/kg) was associated with improved semen antioxidant defenses as indicated by decreased lipid peroxidation, increased spermatozoa concentration, and motility. Similarly, chicken sperm concentration was decreased in the fish oil supplemented cockerels fed on the diet containing moderate level (40 mg/kg) of vitamin E and such an effect was prevented by increasing the vitamin E to 200 mg/kg (Cerolini et al., 2005). Replacing omega-6 fatty acids in the turkey male diet by omega-3 fatty acids simultaneously with increased (120 vs. 60 mg/kg) vitamin E supplementation was associated with improved semen antioxidant defenses, as indicated by a significant (more than double) increase in vitamin E concentration and decrease in semen lipid peroxidation. The changes in antioxidant defenses were also associated with improved semen quality (Zaniboni et al., 2006; Zaniboni and Cerolini, 2009). Under heat stress conditions (daily temperature 33 to 36°C and relative humidity 60 to 70%), inclusion of high level of vitamin E (200 mg/kg) in the diets containing 6 mg/kg feed-derived vitamin E enhanced the semen

quality parameters, including the spermatozoa count and motility, and reduced the percentage of dead spermatozoa. Dietary vitamin E also increased GSH-Px activity, total antioxidant potential, and decreased lipid peroxidation in seminal plasma (Ebeid, 2012).

Eggs, Embryos and Newly Hatched Chicks The antioxidant system of fresh egg includes vitamin E, carotenoids, GSH, and traces of coenzyme Q in the egg yolk (Gaal et al., 1995; Surai, 1999a, 2002; Karadas et al., 2011), and low levels of antioxidant enzymes, including SOD and GSH-Px, in the egg yolk and egg albumen (Gaal et al., 2005; Jiang et al., 2013; Rajashree et al., 2014). Indeed, the egg is protected by antioxidant systems to reduce the harmful effects of oxidative stress in embryogenesis, some of which may involve ferroptosis and lipid peroxidation (Conrad et al., 2018).

Vitamin E is delivered to the egg yolk during oocyte maturation and effectively transferred from the diet to the egg yolk (for review see Surai, 2002; Surai et al., 2016). The efficiency of vitamin E transfer to the egg yolk depends on many factors and substantially varies. For example, the transfer efficiency of vitamin E to egg yolk was shown to be 16 to 39% (12.6 to 30.0 mg Vit.E/kg feed, Naber, 1993), 26% (20 to 40 mg Vit.E/kg feed; Galobart et al., 2002), or 14 to 24% (10 or 260 mg Vit.E/kg; Irandoust and Ahn, 2015). Vitamin E in the egg yolk depends on the diet and includes tocopherols (α-tocopherol, 85.2 to 90%; β + γ-tocopherols, 7.9 to 11%) and tocotrienols (α-tocotrienol, 0.3 to 2%; β + γ-tocotrienols, 1.3 to 2.5%) (Table 1; Surai and Speake, 1998; Surai and Sparks, 2001). Interestingly, vitamin E composition of turkey egg yolk was shown to be more variable than in chicken yolk and includes α-tocopherol (57.0%), β + γ-tocopherols (24.6%), δ-tocopherol (1.7%), α-tocotrienol (5.7%), and β + γ-tocotrienols (11.0%). The proportion of the same vitamin E forms in turkey diet comprised 41.5, 18.2, 3.0, 7.2, and 30.1% total vitamin E, respectively (Surai et al., 1999c). Overall, the accumulation of α- and β + γ-tocopherols in the egg yolk was proportional to their concentrations in the diet. At the same time, tocotrienol transfer from the diet to the egg yolk was found to be much less effective compared to tocopherols (Surai et al., 1999c; Surai and Sparks, 2001). This was confirmed in a later study with chickens. Indeed, α-tocopherol was shown to be transferred to the chicken egg yolk more efficiently (21.19 to 49.17%) than γ-tocotrienol (0.50 to 0.96%) or δ-tocotrienol (0.74 to 0.93%) (Hansen et al., 2015), while α-tocotrienol transfer efficiency to egg yolk was shown to be only 4.32 to 6.75% (Walde et al., 2014). There are species-specific differences in efficiency of vitamin E transfer from feed to the egg yolk with laying hens to be more efficient than turkey, goose or duck (Surai et al., 1998c). However, mechanisms of such differences await further investigation.

It seems likely that vitamin E metabolisms in non-domesticated birds could substantially differ from poultry. In particular, in zebra finches over 70% of the female's daily intake of α-tocopherol was shown to be deposited in egg yolk (Royle et al., 2003). The importance of vitamin E for embryo development can be shown by the determination of the level of vitamin E in egg yolk from wild birds. For example, the level of α-tocopherol in egg yolk from free living Canada geese was more than 4 times higher than that found in housed geese and almost 3-fold higher compared to that in free range geese (Speake et al., 1999). Similarly, α-tocopherol concentration in egg yolks of wild chukar partridges (*Alectoris chukar*) were significantly higher compared to yolks from farm-reared birds (Karadas et al., 2017). Furthermore, comparatively high vitamin E levels were detected in the egg yolk of wild gannets, pelicans, cormorants (Surai et al., 2001a), falcons (Barton et al., 2002), penguins, goldfinches, red bishops, and house sparrows (Garamszegi et al., 2007).

Vitamin E metabolism and interactions between dietary vitamin E and other nutrients, including carotenoids in wild birds need further investigation. On the one hand, dietary α-tocopherol was shown to enhance bioavailability of lutein and its transfer to the egg yolk (Islam et al., 2016). On the other hand, in another study, there was no effect of vitamin E dietary supplementation (0, 40, 100, or 200 mg/kg) on carotenoid concentration in egg yolk (Surai, 2000) and very high vitamin E doses (10,000 and 20,000 mg/kg diet) significantly decreased carotenoid concentration in the egg yolk (Sünder and Flachowsky, 2001). Interestingly, canthaxanthin supplementation of the maternal diet was associated with an increased $\propto$ -tocopherol concentration in the liver of 1-day-old chicks (Surai et al., 2003), while dietary lutein or lycopene did not affect vitamin E concentration in the egg yolk (Karadas et al., 2006). In contrast, in a free-living endangered passerine, the hihi supplementation of lutein and zeaxanthin led to decreased α-tocopherol concentration in nestling plasma (Ewen et al., 2006). In contrast, soon after the oxidative challenge, wild gull chicks supplemented with lutein showed the highest increase in plasma vitamin E levels (Lucas et al., 2014).

Increased vitamin E dietary supplementation improves antioxidant defenses in the egg by increasing vitamin E concentration in egg yolk and significantly decreasing lipid peroxidation as indicated by decreased MDA concentration (for review see Surai, 1999a, 2002; Surai et al., 2016). Protective effect of high vitamin E concentration in omega-3 enriched eggs was also shown (Surai et al., 2000c; Botsoglou et al., 2013). Dietary supplementation of the poultry breeders with high levels of vitamin E (200 mg/kg) was shown to improve antioxidant defenses of eggs as evidenced by decreased MDA and increased GSH-Px and SOD activity in the egg yolk and serum (Jiang et al., 2013).

The antioxidant system of the developing embryo and newly hatched chick was described in detail in our previous paper (Surai and Kochish, 2018a). In fact, our data, obtained for the last 20 yr clearly indicate that vitamin E has a special role in the antioxidant system

Table 1. Vitamin E distribution in the feed, egg yolk, and chick tissues, μg/g (adapted from Surai and Sparks, 2001).

	Wheat-based diet				Maize-based diet			
	α-toc.	B + γ-toc.	α-ttn.	B + γ-ttn.	α-toc.	B + γ-toc.	α-ttn.	B + γ-ttn.
Feed	120.5	37.7	7.1	54.1	114.8	55.6	7.7	30.1
Egg yolk	305.6	39.6	7.1	6.3	273.6	24.7	6.1	7.7
Tissues of day-old chicks								
Liver	2011.5	171.7	12.7	4.4	2117.1	244.9	15.4	2.0
Heart	45.1	4.1	0.8	0.3	55.0	5.2	0.9	0.4
Kidney	30.9	3.3	1.1	0.6	33.2	4.1	1.0	0.5
Lung	21.3	3.9	0.7	0.4	26.2	4.4	0.7	0.3
Leg muscle	35.3	2.1	0.4	0.2	35.0	2.5	0.5	0.3
Breast muscle	44.3	2.4	0.5	0.2	45.6	2.1	0.6	0.2
Adipose	44.4	2.0	1.9	0.6	51.8	2.5	1.8	0.5
Plasma	56.2	5.9	0.1	nd	68.8	6.6	0.1	nd
YSM	750.2	102.6	7.2	4.1	1219.5	149.8	14.0	3.2

toc.- tocopherol, ttn.- tocotrienol

of the developing embryo (Surai et al., 2016). During egg incubation, vitamin E is shown to be effectively transferred from the egg yolk to the developing embryo (Surai et al., 1996) and there is a clear direct correlation (r = 0.999) between vitamin E in the egg yolk and liver of newly hatched chicks (Surai et al, 1997b). Vitamin E accumulation in the liver of the developing embryo is considered to be an important adaptive mechanism providing optimal antioxidant defense at critical time of hatching and the highest α-tocopherol concentration in embryonic tissues is found at the time of hatching (Surai et al., 1996; Surai and Sparks, 2001; Surai et al., 2016). However, vitamin E is quickly depleted from the chick liver during the first week posthatch (Surai et al., 1998c).

It is interesting to note that chicken embryos can adapt to various stresses during development by upregulating its antioxidant defense mechanisms. For example, the increase in aerobic metabolism induced in the chick embryo by 3 d of hyperoxia was not accompanied by an increase in lipid peroxidation (Stock et al., 1990). The authors suggested that the chick embryo adapts to hyperoxia in such a way as to prevent additional free radical formation and damage, due to increasing the capacity of its antioxidant defenses. Indeed, during the incubation period for chickens, antioxidant defense systems protect the embryo against the lipid peroxidation and protein oxidation due to various undesirable conditions (Yigit et al., 2014).

In chicken tissues, a delicate balance between prooxidative and antioxidant activities plays a vital role in development and chick viability (Surai et al., 1996). Increased resistance of chicken embryonic and postnatal tissues to oxidative stress was observed to be a result of increased dietary vitamin E supplementation of the maternal diet (Surai et al., 1999a; Surai, 2000). It seems likely that the efficiency of vitamin E transfer from egg yolk to the liver of the developing embryo is determined by the initial vitamin E concentration in the egg. For example, in the case of low vitamin E in the diet (4.9 to 10.1 mg feed-derived vitamin E/kg diet), about 30% of total egg yolk vitamin E was found in the liver of newly hatched chicks. In contrast, increased dietary vitamin E supplementation (40 to 200 mg/kg) reduced this efficiency almost by half (13.0 to 15.8%; Surai, 2000). It was suggested that in the developing embryo there are some metabolic mechanisms responsible for an increased vitamin E mobilization from the egg yolk in the case of low vitamin E provision. Interestingly, brain of the newly hatched chick is characterized by extremely low vitamin E concentration (10% of that in the liver) and high susceptibility to lipid peroxidation (Surai et al., 1996). The increased concentration of vitamin E in the brain of the newly hatched chick (23.1 vs. 7.7 μg/g) as a result of high vitamin E supplementation (250 mg/kg) of the maternal diet was shown to significantly reduce the susceptibility of the brain tissue to peroxidation similar to other studied tissues of the chick (Surai et al., 1999a). Similarly, increase in vitamin E concentration in the chicken brain from 4.0 to 27.9 μg/g caused a significant decrease in MDA concentration (from 4.95 down to 1.78 nM/mg; Tsai et al., 2008). When breeder's diet was supplemented with vitamin E at 0, 40, 100, and 200 mg/kg, α-tocopherol concentrations in the egg yolk were 19.6, 153.3, 299.0, and 538.5 μg/g, respectively. This was translated into vitamin E concentrations in the liver of the newly hatched chicks as follows: 119.9, 398.4, 947.3, and 1636.4 μg/g, respectively, while in the brain vitamin E concentrations were 1.5, 5.2, 8.3, and 15.2 μg/g, respectively (Surai, 2000).

It seems likely that dietary vitamin E can also affect antioxidant defenses indirectly by increasing GSH concentration and activating antioxidant enzymes. There are important interactions between various antioxidants within the antioxidant defense network of the newly hatched chick. For example, increased dietary vitamin E supplementation was associated with a significant increase in GSH concentration in the liver of the newly hatched chick indicating improvement in redox status of the tissue (Surai, 2000). In general, molecular mechanisms of interactions between vitamin E and GSH are not well understood, but in liver, α-tocopherol is shown to upregulate γ-glutamate cysteine ligase

(glutathione synthetase) leading to increased GSH concentration (Brigelius-Flohe, 2009). Furthermore, there are also other mechanisms of sparing effects of vitamin E on GSH concentration within the antioxidant system network in various tissues (Surai, 2002).

Glutathione concentration in the liver decreased almost 2-fold between day 10 of embryonic development and hatching time (Surai, 1999b). Therefore, increased GSH concentration in the liver of newly hatched chick due to increased vitamin E dietary supplementation (Surai, 2000) could be considered as an important element in maintaining signaling pathways sensitive to perturbations of the endogenous redox state (Hansen and Harris, 2015; Timme-Laragy et al., 2018). Furthermore, progeny chicks from pullets given a high level (160 vs. 0 or 40 mg/kg) of supplemental vitamin E were characterized by increased brain SOD (Lin et al., 2005b; Tsai et al., 2008) and increased catalase activity in the liver of progeny chicks obtained from breeders fed on the diet supplemented with increased (120 vs. 40 mg/kg) vitamin E level (Lin et al., 2005b). This was associated with decreased MDA and ROS concentrations in the brain and ROS level in the liver of newly hatched chicks (Lin et al., 2005b). Importantly, antioxidant enzymes, including SOD and GSH-Px, belonging to the first level of the antioxidant defense network, are considered to be key players in the embryonic antioxidant defense network (Surai et al., 1999b, 2018c,d; Surai, 1999b, 2016). Recently, it has been shown that an increase in yolk vitamin E concentration in gulls was associated with improved total antioxidant capacity and reduced concentration of pro-oxidants in the plasma of gull hatchlings (Parolini et al., 2017). The evidence is quickly accumulating to prove that detrimental consequences of oxidative stress during embryonic development potentially can impact growth, survival, and reproductive success in the chick and the adult (Monaghan et al., 2009). Indeed, antioxidant defenses in the developing embryos are the key for a successful postnatal development of poultry. Therefore, nutritional modulation of the antioxidant capacities represents an important tool for poultry nutritionist to deal with commercially-relevant stresses. Indeed, recently, evidence has been presented indicating that yolk-derived antioxidants effectively protect the avian embryo from oxidative stress imposed by environment. Therefore, maternally derived yolk antioxidants, where vitamin E has a major role, can buffer the developing avian embryo against oxidative stress induced by various factors, including hyperoxia (Watson et al., 2018).

In general, in all 3 models described above, antioxidant system enhancement due to dietary vitamin E supplementation was mainly manifested via increased concentration of α-tocopherol in different tissues (Figure 1). This direct antioxidant effect of vitamin E is well researched and explained. However, there is also indirect effect of vitamin E on the efficiency of antioxidant defense networks in different tissues. This includes modulation of:

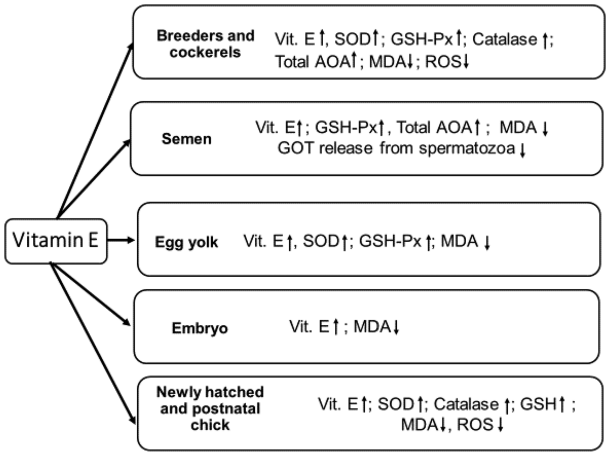

Figure 1. Antioxidant system modulation by dietary vitamin E.

1. SOD—main adaptive enzyme of the first level of antioxidant defense, responsible for detoxification of the main biological radical, namely superoxide radical;
2. GSH-Px and catalase—2 other important enzymes of the first level of antioxidant defense essential for completion of superoxide radical detoxification with a conversion of toxic H_2O_2 into water;
3. GSH—one of the most important cellular antioxidant participating in maintaining redox balance in the cell being co-substrate of GSH-Px;
4. total antioxidant activity—an important index of the antioxidant defense system reflecting a redox (antioxidant-prooxidant) balance in the cell.

Commercial Applications of Dietary Vitamin E

The protective effect of natural antioxidants supplied with poultry diet depends on experimental conditions used in various experiments (Surai, 2002). Generally speaking, in most of well controlled studies conducted in "ideal" conditions with small number of birds and with low stress, commercial doses of vitamin E supplementation of breeders (100 mg/kg diet) are adequate to maintain antioxidant defenses, productive, and reproductive performance of poultry. Indeed, it was shown that experimental results obtained with the feeding of different dietary levels of vitamin E are affected by genetic stock, duration, and level of feeding dietary vitamin E, age, and measurement criteria (Siegel et al., 2001).

Earlier studies indicated a beneficial effect of increased vitamin E supplementation for turkey males (up to 60 to 80 mg/kg; Surai, 1983a, 1991) and ganders (up to 40 mg/kg, Surai, 1991; Surai and Ionov, 1992b). However, current commercial level of vitamin E supplementation of toms and ganders exceeds those "beneficial" levels. It seems likely that increased

vitamin E supplementation would be beneficial in various stress conditions, including omega-3 enrichment of the diet (Cherian et al., 1996; Cerolini et al., 2005, 2006; Fernandes et al., 2018), usage of young breeders (Siegel et al., 2006), end of reproductive period (Siegel et al., 2001), usage of corn dried distillers grains containing high levels of n-6 PUFA (Jiang et al., 2013), a corticosteroid drug dexamethasone (Eid et al., 2006, Min et al., 2016, 2018), mycotoxin contamination (Khan et al., 2014), heat stress (Khan et al., 2011; El-Hack et al., 2017), etc. There is also an opportunity to use in ovo vitamin E supplementation to improve antioxidant defences of the developing embryo with potential improvements in incubation results, chick quality and performance results (Araujo et al., 2018).

CONCLUSIONS

Antioxidant defense mechanisms are responsible for prevention of the harmful effects of free radical overproduction and oxidative stress in commercially-relevant stress conditions of industrial poultry production (Surai and Fisinin, 2016a,b,c, 2018d). Vitamin E was discovered as "vitamin of reproduction" in 1922 and today this vitamin is considered to be the main chain-breaking antioxidant in the cell, located in biological membranes, and is proven to be a leading player in antioxidant protection (Surai, 1999a). After 95 yr of extensive research in the field of vitamin E, its unique role in biological systems has been greatly appreciated. In fact, vitamin E is shown to be essential for male and female reproduction, immunocompetence, effective growth and development, high quality of eggs and meat, and high resistance to various stresses (Surai, 1999a, 2002; Panda and Cherian, 2014; Surai and Fisinin, 2014; Rengaraj and Hong, 2015; Surai et al., 2016; Surai and Kochish, 2018b).

It is clear from the analysis of the aforementioned data that increased vitamin E supplementation in the breeder's or cockerel's diet increased their resistance to various stresses, including high PUFA, mycotoxin, or heat stress. Increased vitamin E supplementation of poultry males was shown to be associated with significant increases in α-tocopherol level in semen associated with an increased resistance to oxidative stress imposed by various external stressors. Similarly, increased vitamin E concentration in the egg yolk due to dietary supplementation was shown to be associated with increased α-tocopherol concentration in the tissues of the developing embryos and newly hatched chicks resulting in increased antioxidant defenses and decreased lipid peroxidation. Furthermore, increased vitamin E transfer from the feed to egg yolk and further to the developing embryo was shown to be associated with upregulation of antioxidant enzymes reflecting antioxidant system regulation and adaptation. Clearly, using 3 model systems including poultry breeders/males, semen, and chicken embryo/postnatal chickens, the possibility of modulation of the antioxidant defense mechanisms has been clearly demonstrated. For the last 3 decades, vitamin E recycling in the cells as an effective mechanism of the antioxidant defenses has received substantial attention. Indeed, ascorbic acid, selenium, and vitamins B_1 and B_2 are shown to be important elements of vitamin E recycling. Therefore, if recycling is effective, even a low vitamin E concentration, for example in the chicken embryonic brain (Surai et al., 1996), can prevent lipid peroxidation in vivo. Furthermore, adaptation to stressful conditions is mediated via a range of vitagenes responsible for additional synthesis of protective molecules, e.g., SOD, heat shock proteins, thioredoxin, sirtuins, etc. (Surai and Fisinin, 2016 c,d). By nutritional manipulation, it is possible to upregulate vitagene network (Surai and Kochish, 2017; Surai et al., 2017a) and improve adaptive ability of poultry to various stresses. Vitamin E can affect expression of a range of various genes (Rimbach et al., 2010), including selenoproteins (Sun et al., 2018). Therefore, protective effects of vitamin E in biological systems go beyond direct free radical scavenging activities and additional regulatory effects should be considered. In particular, data obtained with cell culture and animal experiments clearly indicate vitamin E participation in modulation of transcriptional regulation and cell signaling (for review see Galli et al., 2017; Azzi, 2018) and they deserve more attention. On the one hand, vitamin E can affect activities of free radical producing enzymes, for example, xanthine oxidase (Catignani et al., 1974). On the other hand, vitamin E can also inhibit activity of another free-radical producing enzyme namely monocyte NADPH oxidase (Cachia et al., 1998) mediated via inhibition of protein kinase C (Tasinato et al., 1995). Finally, many important transcription factors including Nrf2, NF-κB, PPARγ, Hif1α, etc. can be regulated by vitamin E directly or indirectly (Zingg, 2018). It remains to be elucidated to what degree these regulatory effects of vitamin E represent physiological events that also occur in poultry in commercially-relevant doses of vitamin E supplementation. Molecular mechanisms of antioxidant system regulation in poultry by vitamin E by various mechanisms including gene expression, vitagene activation, transcription factor activation and signal transduction, and vitamin E interaction with microbiota (Surai et al., 2017b) and maintaining gut health in poultry (Surai and Fisinin, 2015) awaits further investigation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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