L22 Natural antioxidants and stresses in poultry production: from vitamins to vitagenes

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Summary

Commercial poultry production is associated with various stresses leading to decrease of productive and reproductive performance of growing chickens, parent birds as well as commercial layers. In general, there are four major types of stress in poultry industry: technological, environmental, nutritional and internal stresses. Growing body of evidence indicates that most of stresses in poultry production at the cellular level are associated with oxidative stress due to excess of free radical production or inadequate antioxidant protection. Therefore, dietary antioxidants are considered to be the main protective means to deal with various stresses in poultry production. Indeed, the development of the effective antioxidant solutions to decrease negative consequences of commercially- relevant stresses is an important task for poultry scientists. One of such approaches is based on possibilities of modulation of vitagenes, a family of genes responsible for animal/poultry adaptation to stress. The new concept of fighting stresses is based on an idea that supplying birds with various antioxidants via the drinking water could help them to effectively deal with stress conditions. In fact, it was proven that inclusion of vitagene-regulating compounds (carnitine, betaine, vitamin E, etc.) in water, as well as some minerals, vitamins, electrolytes and organic acids could be effective in fighting various stresses.

Stresses in poultry production

Commercial poultry production is associated with various stresses leading to decrease of productive and reproductive performance of growing chickens, parent birds as well as commercial layers. In general, there are four major types of stress in poultry industry: technological, environmental, nutritional and internal stresses (Surai and Fisinin, 2016a; 2016b; Table 1).In fact, a list of commercially-relevant stresses in poultry production could be quite long, but the main point is the most of the stresses suppress reproductive performance of parent birds including reduced fertility and hatchability. Furthermore, stresses are associated with impaired feed conversion, reduced average daily weight gain, immunosuppression and increased mortality in growing birds. Growing body of evidence indicates that most of stresses in poultry production at the cellular level are associated with oxidative stress due to excess of free radical production or inadequate antioxidant protection (Surai, 2002; 2006; Surai and Fisinin, 2016a; 2016b). According to the recent literature review, heat and diet are among main means causing oxidative stress in domestic birds that may lead to biological damage, serious health disorders, lower growth rates, and, hence, economic losses (Estevez, 2015). Therefore, dietary antioxidants are considered to be the main protective means to deal with various stresses in poultry production (Surai, 2002; 2006)

Antioxidant systems of the body

During evolution, living organisms have developed specific antioxidant protective mechanisms to deal with ROS and RNS (Surai, 2002). Therefore it is only the presence of natural antioxidants in living organisms which enable them to survive in an oxygen-rich environment. The general term “antioxidant systems” describes these mechanisms, which are diverse and responsible for the protection of cells from the actions of free radicals. These systems include: Natural fat-soluble antioxidants (vitamins A, E, carotenoids, ubiquinones, etc.); water-soluble antioxidants (ascorbic acid, uric acid, carnitine, betaine, taurine, etc.); antioxidant enzymes: glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD); thiol redox system consisting of the glutathione system (glutathione/glutathione reductase/glutaredoxin/glutathione peroxidase and a thioredoxin system(thioredoxin/thioredoxin peroxidase/thioredoxin reductase). The protective antioxidant compounds are located in organelles, subcellular compartments or the extracellular space enabling maximum cellular protection to occur. The antioxidant system of the body is responsible for prevention of damaging effects of free radicals in stress conditions. Therefore, dietary supplementation of antioxidant compounds is a way to improve efficiency of poultry production in commercial conditions associated with various stresses. Dietary-derived antioxidants related to poultry nutrition can be divided into several groups:

• Vitamin E -main chain-breaking antioxidant in the cell, located in biological membranes and proven to be effective in antioxidant protection. The main reason for vitamin E dietary supplementation for poultry and farm animals is to maintain their optimal health and high productive and reproductive performances. It includes positive effects of vitamin E on male and female reproduction, immunocompetence, effective growth and development, high quality of eggs and meat, decreased negative consequences of various stresses (Surai, 2002; 2006, 2014). Extensive research and wide commercial application for a number of years clearly shows essentiality of vitamin E in animal/poultry nutrition. Recently it has been shown that vitamin E recycling in the cell is key for its antioxidant activity. Ascorbic acid, selenium, vitamins B1 and B2 are important elements of vitamin E recycling. Therefore, if recycling is effective, even a low vitamin E concentration, for example in the embryonic brain, can prevent lipid peroxidation *in vivo*. Dietary vitamin E supplementation is an important part of poultry nutrition (Surai, 2002). The main source of vitamin E for poultry is a premix providing the vitamin usually in excess of dietary requirement. There is a range of anti-stress premixes with an increased vitamin E content. After 90 years of extensive research in the field of vitamin E we greatly appreciate its unique role in biological systems, in maintaining growth, development and general health of humans and animals.

• Selenium -an integral part of 25 selenoproteins participating in various antioxidant reactions in the body. It is supplied with the diet in various forms and optimal Se status is a key for effective antioxidant protection (Surai, 2006). It has been shown that organic Se in the form of Selenomethionine (SeMet) is the Se form of choice for poultry breeders (Surai and Fisinin, 2014). Generally speaking, there are two major Se sources for poultry, namely inorganic selenium (mainly selenite or selenate) and organic selenium in the form of selenomethionine (SeMet; mainly as Se-Yeast or SeMet preparations). Advantages of organic Se in poultry nutrition have been shown (Surai, 2006; Surai and Fisinin, 2014) and Se-Yeast receive a lot of attention as an effective source of organic selenium in poultry/farm animal nutrition. However, it seems likely that the level of SeMet in the yeast is the major determinant of its value as a Se source. However, that value is still variable (usually in a range 50%~70%) and it is a difficult task to stabilise and guarantee it at the level of production of Se-Yeast. Pure SeMet has some problems related to its stability and therefore an introduction of the new stable supplemental form of Se (Seleno-hydroxy-methionine) could be considered as a next step in improving Se nutrition of poultry.

• Carotenoids -important elements of the antioxidant system, possessing antioxidant activities and participating directly or indirectly (for example, by recycling vitamin E or regulating expression of various genes) in antioxidant defences. There are more than 750 carotenoids in nature and their efficiency varies considerably. Recently, an important role of canthaxanthin in breeder nutrition has been described (Surai, 2012a; 2012b). Indeed, there is a growing evidence indicating that canthaxanthin has a special role in antioxidant defences of the developing embryo and its dietary supplementation of the breeder's diet is a way of improving hatchability.

• Vitamin C (ascorbic acid) - an important antioxidant synthesized in chickens. Its dietary supplementation is shown to be effective only in stress conditions, when its requirement substantially increases. The role of vitamin C in vitamin E recycling is a topic of great interest.

• Polyphenolic compounds -a group of various plant-derived compounds comprising more than 8,000 various compounds possessing antioxidant and pro-oxidant properties in various conditions (Surai, 2014). The main problem with polyphenols, including flavonoids, is their low bio-availability. Their concentration in the diet could be very high, but their levels in blood is low and their concentration in target tissues (liver, muscles, egg yolk) usually is negligible. Therefore, the main site of flavonoid action is the gut where they can have health-promoting properties by participating in maintaining antioxidant-prooxidant balance (Surai, 2006). Emerging findings suggest a large number of potential mechanisms of action of polyphenols in preventing disease, which may be beyond their conventional antioxidant activities. Therefore, it seems likely that antioxidant activity is not a major mechanism for possible beneficial effects of flavonoids in poultry nutrition. Indeed there is a shift in polyphenol-related research from testing their antioxidant activities in vitro to deeper understanding their molecular mechanisms of action including cell-signalling and gene expression. In particular, silymarin (SM), an extract from the *Silybum marianum* (milk thistle) plant containing various flavonolignans (with silybin being the major one), has received a tremendous amount of attention over the last decade as a herbal remedy for liver treatment. In fact, SM has been the gold standard drug to treat liver disorders of different aetiologies and milk thistle extracts have been used as traditional herbal remedies ("liver tonics") for almost 2000 years. Indeed, protective roles of silymarin in poultry production deserves more attention (Surai, 2015d)

• Carnitine is an important element of the antioxidant system of the body (Surai, 2015b) and it has positive effects on chickens when added to the feed or supplemented via water. In fact, carnitine could be considered a new type of antioxidant, regulating the mitochondria, a major site of free radical production. Effects of carnitine on vita-gene expression deserves more attention. Carnitine also has immunomodulating properties in chickens and needs further investigation. Indeed, carnitine is synthesized in animals, including chickens, however, in stress conditions its synthesis is most likely not sufficient and there is a need for its supplementation. In general, carnitine supplementation via drinking water is considered an effective means of improving carnitine status of the birds and their performance.

• Betaine is another new entrant into the antioxidant family participating in osmotic balance regulation. It seems likely that as a source of methyl groups in the body betaine plays important roles in many physiological processes related to stress biology.

Vitagene concept development

Since at the molecular level most stresses are associated with overproduction of free radicals and oxidative stress, the development of the effective antioxidant solutions to decrease negative consequences of commercially-relevant stresses is an important task for poultry scientists. One of such approaches is based on possibilities of modulation of vitagenes, a family of genes responsible for animal/poultry adaptation to stress. The term "vitagene" was introduced in 1998 by Rattan who wrote "Our survival and the physical quality of life depends upon an efficient functioning of various maintenance and repair processes. This complex network of the so-called longevity assurance processes is composed of several genes, which may be called *vitagenes"*. Later vitagene concept has been further developed in medical sciences by professor Calabrese and colleagues in 2004-2016. In accordance with Calabrese et al. (2007; 2009; 2014) the term vitagenes refers to a group of genes that are strictly involved in preserving cellular homeostasis during stress conditions and the vitagene family includes heat shock proteins (HSPs), including heme oxygenase-1 (HSP32, HO-1) and HSP70, the thioredoxin system and sirtuins. The list of potential candidates to vitagene family was extended. In particular, SOD, a major inducible enzyme of the first level of antioxidant defence, has been included into the vitagene family (Surai, 2015a; Surai and Fisinin, 2015b). The products of the mentioned genes actively operate in detecting and controlling diverse forms of stress and cell injuries. The cooperative mechanisms of the vitagene network are reviewed in recently published in the aforementioned comprehensive reviews with a major conclusion indicating an essential regulatory role of the vitagene network in cell and whole organism adaptation to various stresses. Indeed, cellular stress response is mediated via the regulation of pro-survival pathways and vitagene activation with the following synthesis of a range of protective antioxidant molecules is the central event in such an adaptation. The vitagene concept helped in developing effective strategies to fight oxidative stress in various human diseases, including neurodegenerative disorders, neuroprotection, aging and longevity, dermatology, osteoporosis and Alzheimer pathology, and other free radical-related diseases (for review and references there see Surai and Fisinin, 2016b). Indeed, HSPs, including heme oxygenase-1 (HO-1) and HSP70, are responsible for protein homeostasis in stress conditions of poultry production (Surai, 2015c), while the thioredoxin system is the major player in maintaining redox status of the cell involved in protein and DNA synthesis and repair as well as in regulation of expression of many important genes (Surai and Fisinin, 2016b). Furthermore, sirtuins regulate the biological functions of various molecules post-translationally by removing acetyl groups from protein substrates ranging from histones to transcription factors and orchestrate cellular stress response by maintenance of genome integrity and protein stability. Finally, SODs belong to the first level of antioxidant defence preventing lipid and protein oxidation at the very early stages (Surai, 2015a). All the aforementioned vitagenes operate in concert building a reliable system of stress detection and adequate response and are considered to be key elements in stress adaptation.

Vitagene−based concept of fighting stresses in poultry production

Recently, he vitagene concept has been successfully transferred from medical sciences to poultry science (Fisinin and Surai, 2011; Surai and Fisinin, 2012a; 2012b; Surai, 2015a; 2015b; 2015c; 2015d; Surai and Fisinin, 2015b). The new concept of fighting stresses is based on an idea that supplying birds with various antioxidants via the drinking water could help them to effectively deal with stress conditions. Indeed, a decreased feed consumption at time of stress is observed and existing feeding systems do not allow to include anything into the feed loaded into the feed storage bins. Therefore, water-soluble additive supplementation via drinking system is shown to be a valuable option. In fact, modern commercial poultry houses are equipped with water medication systems, which can be effectively used for the aforementioned supplementations. It was proven that inclusion of vitagene-regulating compounds (carnitine, betaine, vitamin E, etc.) as well as some minerals, vitamins, electrolytes and organic acids in water, could be effective in fighting various stresses (Fisinin and Surai, 2011; Surai and Fisinin, 2012a; 2012b). This helps at chick placement, when the antioxidant system is crucial for the digestive and immune system development (Fisinin and Surai, 2012a; Surai and Fisinin, 2015a). In particular it was proven that inclusion of an anti- stress composition (PerforMax) into the drinking water at the University trial improved chicken growth and feed conversion ratio (FCR; Fotina et al., 2011; Fotina et al., 2014). Using the same anti- stress composition in commercial conditions improved FCR during a 39 day broiler growth trial. At the end of the trial, the improvement in FCR due to the anti-stress composition during the first three days post-hatch as well as before and after vaccination was highly significant (Velichko et al., 2013; Velichko and Surai, 2014). The importance and efficacy of the anti-stress composition for rearing birds and adult egg type parent stock (Hy-Line) at one of the biggest egg producing farms in Russia (Borovskaya poultry farm, Tumen region) have been recently reviewed (Shatskich et al., 2015).In particular it was shown that usage of the anti-stress composition with drinking water at specific periods of the increased stress can improve breeder's performance. In particular there was an increase by 2% of the egg peak production and peak plateau lasted about 50 days longer than that in the control birds. It is interesting to note that hen housed egg production in the control group (260.8 eggs) was higher than the target for the line (253.4 eggs) and in the experimental group it was increased by 6 eggs. Furthermore, improved egg production was associated with increased weight of the oviduct in the experimental layers. It is also important to mention that FCR (feed per 10 eggs) was also improved by usage of the anti-stress composition and was better than the target for the line. Notably, shell strength at age 26, 36 and 56 weeks was improved in the experimental group by 2.8, 5.6 and 5.6%, respectively. The most interesting finding was related to a significant increase of the carotenoid level in the egg yolk of experimental birds. Since carotenoids were not supplied with the anti-stress composition, this increase could be due to improved absorption of nutrients resulting from anti-stress composition usage. This can also explain improved FCR in the experimental birds. Vitamin A level in the egg yolk from the experimental layers was also increased probably reflecting its transfer from the anti-stress composition. In particular, anti-stress composition usage was associated with improved fertility at 16, 40, 48 and 56 weeks by 2.5; 2.7; 2.8 and 3.7%, respectively. In the same experimental group the hatch of condition chicks improved at 26, 32, 40, 48 and 56 weeks by 3.6; 2.1; 3.4; 4.9 and 4.3%, respectively (Shatskih et al., 2015). In addition, it was shown that the anti-stress composition had an immune-modulating effect in broilers (Fotina et al., 2011) and growing ducklings (Surai et al., 2012). Improvement of the antioxidant system via supplying an antioxidant composition via the drinking water could also help dealing with various mycotoxins in feed, including DON (Fisinin and Surai, 2012b; 2012c), ochratoxin (Fisinin and Surai, 2012d; 2012e) and T-2 toxin (Fisinin and Surai, 2021f; 2012g). Furthermore, such a technology could help fight heat stress (Surai and Fotina, 2013) and immunosuppression (Fisinin and Surai, 2013a; 2013b). However, further work is required to understand molecular mechanisms of the interactions of vitagenes with various signaling systems and transcription factors in the cell to build an adequate adaptive response to minimize detrimental consequences of commercially-relevant stresses in poultry production.

Table 1. Stresses in poultry production (Adapted from Surai and Fisinin, 2016a)

Technological stresses
Chick placement
Increased stocking density
Weighing, grading, group formation, catching, transferring to breeder houses
Prolonged egg storage, egg transportation, inadequate egg storage conditions, incorrect incubation regimes
Environmental stresses
Inadequate temperature
Inadequate ventilation and increased dust
Inadequate lightning
Nutritional stresses
Mycotoxins
Oxidised fat
Toxic metals (lead, cadmium, mercury, etc.)
Imbalance of minerals (Se, Zn, Cu, etc.) and other nutrients
Low water quality
Usage of coccidiostats and other drugs via feed or water
Internal stresses
Vaccinations
Microbial or virus challenges
Gut dis-bacteriosis
Pipping and hatching

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