

NUTRITIONAL METABOLIC DISEASES OF POULTRY AND DISORDERS OF THE BIOLOGICAL ANTIOXIDANT DEFENCE SYSTEM

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Deficiencies or disturbances of nutrition cause a variety of diseases and can arise in different ways. The amount of a particular nutrient in the diet may be insufficient to meet the requirements, the diet may contain substances that inactivate the nutrient or inhibit its absorption/utilisation, or metabolism may be upset by the interaction of dietary and environmental factors. Peroxidation of lipids or oxygen free radical generation in general is a physiological process important for cell metabolism, division and differentiation and also for the biosynthesis of hormones and prostaglandins. Free radicals generated through these processes are effectively scavenged by the antioxidant defence system. Uncontrolled lipid oxidation caused by disturbances of that system may play a crucial role in some important poultry diseases and toxicoses. The first route of lipid peroxide loading of the organism is via the feed, such as through oxidised lipids. Oxidised fatty acids are absorbed from the intestine mainly in the form of unsaturated keto compounds and initiate lipid peroxidation in the tissues. The second problem is the insufficient amount of antioxidants in the feed, e.g. vitamin E deficiency. Nutritional encephalomalacia is a problem in poultry production which depends both on the actual vitamin E supply and the dietary amount of polyunsaturated fatty acids. In young birds the primary target of vitamin E deficiency is the brain because it contains low amounts of vitamin E, and the vitamin E content of the liver acting as store decreases rapidly during the first week of life. Besides vitamin E, other components of the antioxidant system, e.g. the antioxidant enzymes (catalase and glutathione peroxidase) also have low activity in the brain as compared to other major tissues. The brain is highly susceptible to oxidative stress because of the accumulation of polyunsaturated fatty acids. The third source of free radical generation is the toxic level of different feed ingredients, e.g. toxicoses caused by vitamin A, selenium, and ionophore antibiotics. Other important aspects of antioxidants (e.g. vitamin E and selenium) in poultry are stimulation of the immune response (e.g. in the case of vaccination) and reduction of the risks of free radical formation as a result of macrophage function.

Key words: Antioxidants, free radicals, lipid peroxidation, nutritional metabolic diseases, poultry

Feed on one side is essential for normal living functions of animals because it contains macro- and micro-nutrients. On the other side, if the ratio of particular nutrients does not meet the actual requirement of animals or if there is absolute and/or relative nutrient deficiency and potentially toxic materials are present in the feed, nutritional disturbances and disorders can develop. There is a wide range of such disorders. Of them, only those will be discussed in the present review which manifest themselves through disturbances of the biological antioxidant defence. It is beyond the scope of this review to present a detailed discussion of oxygen-derived free radicals and the antioxidant defence mechanism, as these have recently been reviewed in detail (Josephy, 1997). These processes are thought to be involved in the aetiology of some disorders either as a primary factor, or as factors having some involvement in the pathogenesis of the disease at a later stage. It is also important to emphasise that not all reactions that involve oxygen free radicals are damaging in living systems (Rice-Evans, 1994). Several normal *in vivo* biological processes depend on free radicals, such as the oxidative killing of phagocytic cells (Cross and Jones, 1991) and the formation of nitric oxide (Moncada et al., 1990) as well as prostaglandins and prostacyclins via the arachidonic acid cascade (Diplock, 1992). Uncontrolled free radical formation can cause oxidative stress. Oxygen-derived free radicals differ markedly in their reactivity, and their potential to cause damage to living cells depends on their chemical reactivity. There are some targets for attack by oxygen free radicals in biological systems: (i) DNA, (ii) proteins — including enzymes, and (iii) polyunsaturated fatty acids (Diplock, 1994). At tissue or organ level the first target of lipid peroxides of dietary origin would be the gastrointestinal epithelium and the gut-associated immune system and in the second step the liver as the primary detoxifying organ (Dibner et al., 1966). Consumption of oxidised fats and fatty acids impairs the α -tocopherol status of chicks and increases the susceptibility of tissues to lipid oxidation (Sheehy et al., 1994). Further disorders will develop in different tissues partly as an effect of ingested and absorbed lipid peroxides of the feed, partly because of the uncontrolled free radical formation within the organism.

Free radical related diseases of poultry

Nutritional encephalomalacia

Nutritional encephalomalacia is a well-known disease of young poultry which is obviously caused by a peroxidative dysfunction. It occurs two or three weeks post hatching in absolute or relative deficiency of vitamin E (Sallmann et al., 1991) and the target of that disease is the brain for several reasons:

(i) The developing brain contains a very low amount of vitamin E, while it contains a relatively high amount of ascorbic acid (Table 1) which can also act as antioxidant (Surai et al., 1996). The vitamin E and ascorbic acid content of the brain depends on the supply of the laying hen during egg formation (Surai et al., 1994).

Table 1

Antioxidant content of different regions of the brain of newly hatched chickens (Surai et al., 1996)

Parameter / region	Cerebrum	Cerebellum	Brain stem	Optic lobe
α -tocopherol ($\mu\text{g/g}$)	5.22 \pm 0.32	7.12 \pm 0.29	6.12 \pm 0.38	5.66 \pm 0.40
Ascorbic acid ($\mu\text{g/g}$)	889.40 \pm 41.2	711.30 \pm 51.2	747.70 \pm 61.4	850.53 \pm 66.4

(ii) The tocopherol content of the liver — as a possible store of vitamin E — decreases rapidly during the first week of life (Mézès, 1988a; Surai and Ionov, 1994) because of the extremely rapid lipid transfer from the liver to the peripheral tissues (Surai et al., 1996).

(iii) The activities of antioxidant enzymes — superoxide dismutase and glutathione peroxidase — are very low in the brain (Table 2) in comparison with the liver (Mézès, 1988b; Gaál et al., 1995).

Table 2

Superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity of the liver and brain of the developing chicken embryo (Gaál et al., 1995)

Enzyme	Days of development					
	14		19		22	
	Liver	Brain	Liver	Brain	Liver	Brain
SOD (U/g)	78.1 \pm 1.9	24.4 \pm 1.0	69.1 \pm 2.8	26.2 \pm 1.5	110.3 \pm 5.7	23.6 \pm 2.1
GSH-Px (U/g)	13.9 \pm 1.2	4.0 \pm 0.9	15.0 \pm 0.9	3.0 \pm 0.4	23.8 \pm 1.5	6.0 \pm 1.1

(iv) The increase occurring in the polyunsaturated fatty acid content of the brain (Table 3) during development (Maldjian et al., 1996) will lead to an increased susceptibility of tissues to free radical induced peroxidative damage.

(v) During evolution, an antioxidant defence system has developed against free radical damage within the cells. Among others a special antioxidant compound is present in the brain, the pineal hormone melatonin. Melatonin is synthesised in the pineal gland and has been shown to possess direct free radical

scavenger activity both *in vivo* and *in vitro* (Reiter, 1995). Thus, it potently protects cells from the damage induced by oxidative agents. A recent study has demonstrated that, besides its direct scavenger capacity, melatonin also increases the activity of the antioxidant enzyme glutathione peroxidase in different tissues of chicks (Pablos et al., 1995). The basic problem with melatonin as a potential free radical scavenger in young poultry is the regulation of its release from the pineal gland. Melatonin will be synthesised from its precursor serotonin on the effect of the enzyme hydroxy-indole-o-methyl-transferase (HIOMT), the activity of which is regulated by light (Reiter, 1980). The generally used broiler rearing technologies apply constant light. For that reason, the possibility of *de novo* synthesis and release of melatonin from the pineal gland is low.

Nowadays the incidence of encephalomalacia on poultry farms is very low due to the adequate dietary supply of vitamin E.

Table 3

Fatty acid composition of total phospholipid from chicken embryo brain
(Maldjian et al., 1996)

Fatty acid (wt %)	Day of development	
	12	19
16:0	37.0 ± 0.2	34.4 ± 0.2
16:1 n-7	3.3 ± 0.1	2.4 ± 0.1
18:0	12.6 ± 0.1	15.9 ± 0.1
18:1 n-9	16.4 ± 0.2	16.2 ± 0.3
18:2 n-6	2.3 ± 0.1	2.0 ± 0.1
18:3 n-3	0.2 ± 0.1	0.4 ± 0.0
20:4 n-6	7.8 ± 0.1	8.1 ± 0.3
22:5 n-6	0.6 ± 0.0	0.4 ± 0.1
22:6 n-3	16.7 ± 0.4	17.8 ± 0.2

Vitamin A toxicosis

Vitamin E deficiency can be provoked by low doses of that vitamin in the diet. The other possible problem is the overdose of vitamin A or, in other words, vitamin A toxicity. In the presence of excess vitamin A marked depletion of vitamin E was found in the egg yolk (Table 4) and the vitamin E and carotenoid content of the liver also markedly decreased (Surai et al., 1993, 1994; Kuklenko et al., 1996). Carotenoids also occur as antioxidants both *in vitro* and *in vivo* (Tsuchihashi et al., 1995). Low vitamin E content will reduce the antioxidant capacity of the tissues and at the same level of free radical formation the conse-

quence will be a higher rate of lipid peroxidation which will impair some cellular functions and can cause cell damage. In most cases the antioxidant enzymes effectively decompose the resulting free radicals but some negative changes in production traits could be detected (Mézès and Sályi, 1992).

Table 4

Effect of vitamin A overdose on mean vitamin A, vitamin E and carotenoid content of egg yolk and liver of day-old chickens (Surai et al., 1994)

Parameter / vitamin A dose	10,000 IU / kg diet	100,000 IU/ kg diet	400,000 IU / kg diet	0 IU / kg diet
Egg yolk vitamin A content (µg/g)	7.0	20.5	85.1	4.0
Egg yolk carotenoid content (µg/g)	12.57	8.58	7.74	10.82
Egg yolk vitamin E content (µg/g)	90.7	50.5	24.3	92.0
Chicken liver vitamin E content (µg/g)	253.1	155.7	94.6	245.3

Selenium toxicosis

The biological essentiality of selenium was first discovered when selenium was found to be an important factor against liver necrosis, exudative diathesis and nutritional muscular dystrophy in chicks (Schwartz and Foltz, 1957). Its physiological importance was recognised when it was found to be an essential structural component of the glutathione peroxidase enzyme (Rotruck et al., 1973). The toxic effects of excess amounts of selenium in the diet have been suggested to be related to the glutathione redox system. It was found that selenium, in oxidised state as selenite, was metabolised through a reductive pathway using reduced glutathione as substrate (Ganther, 1986). Other studies have suggested that excess selenite administration stimulates the rate of lipid peroxidation (Hoffman et al., 1989). According to our results, acute oral selenium toxicosis, induced by selenium administered in the form of selenite, increases the rate of lipid peroxidation without exerting a significant effect on the glutathione system (Mézès and Sályi, 1994).

Monensin toxicosis

Ionophore antibiotic poisoning causes gross lesions and microscopic changes in striated muscles and myocardium, and similar pathomorphological changes were found in the case of vitamin E and selenium deficiency (Sályi et al., 1988). This resemblance and the finding that pretreatment with vitamin E and selenium reduces the severity of monensin toxicosis (Van Vleet et al., 1983) suggests that uncontrolled oxidation of lipids and/or impairment of the biological antioxidant defence may have a key role in monensin toxicosis. There is experimental evidence that acute monensin poisoning induced substantial enhancement of lipid peroxidation in the liver but not in the skeletal muscles (Sályi et al., 1990). There is also a good evidence that monensin affects the antioxidant defence system, namely erythrocyte glutathione-peroxidase activity without exerting a measurable effect on selenium (Khan et al., 1995).

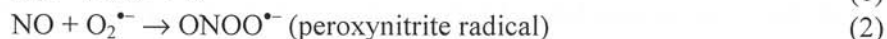
Salinomycin-tiamulin toxicosis

One of the most important drug incompatibilities known in the poultry veterinary practice is the interaction between some ionophore antibiotics and tiamulin. The mechanism of this toxic interaction is not yet known but there are some explanations incriminating changes of free radical generation and impairment of the antioxidant system as a possible cause of the damages. There have been some contradictory results in different experiments, e.g. in respect of the activation (Laczay et al., 1990) or moderate inhibition (Mézés et al., 1992) of the cytochrome P-450 content of liver microsomal fraction in salinomycin toxicosis. Otherwise a rapid and marked decrease in reduced glutathione content of the liver was found both in salinomycin and tiamulin toxicosis with a concomitant decrease of glutathione peroxidase activity (Mézés et al., 1992).

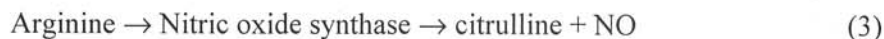
Pulmonary hypertension (ascites) syndrome

Pulmonary hypertension (PHS) or ascites syndrome is a metabolic disease caused by many different factors. The accumulation of ascites fluid in the abdominal cavity represents the terminal consequence of excessively high blood pressure in the pulmonary circulation. The excessively high pressure in the right ventricle will cause pulmonary oedema, and ascites fluid will be produced from the liver as well because of the high pressure in the hepatic vein, resulting in the release of fluid from the sinusoids. Mortality is caused by congestive heart failure (Huchzermeyer and De Duyck, 1986). Free radicals possibly have an indirect effect on the pathogenesis of PHS because antioxidant treatment decreases the severity and incidence of that disorder (Bottje et al., 1995). There are some possible routes of free radical formation during that process. First is hydrogen per-

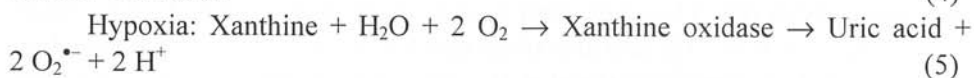
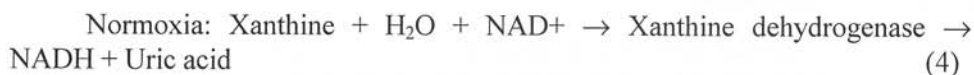
oxide or hypochlorous acid formation during the inflammatory response reaction of phagocytic cells (Bottje and Wideman, 1995) because those processes are a highly likely event in PHS. The second possible source would be, as another effect of the inflammatory response or phagocytic function, the formation of nitric oxide and, from that, peroxy nitrite radicals in the presence of oxygen free radicals (Hibbs et al., 1988). Otherwise it can be stated that nitric oxide also possesses antioxidant capabilities, e.g. scavenges peroxy radicals in the presence of glutathione to form S-nitroso-glutathione.



The formation of nitric oxide depends on the presence of arginine but it has to be mentioned that the growth requirement of arginine is lower than the requirement for normal cytotoxic function (Taylor et al., 1992); for that reason, NO formation is sometimes impaired. It was also found that L-arginine supplementation of the diet attenuated PHS due to the pulmonary vasodilator effect of nitrogen oxide (Wideman et al., 1995).



The third possible source is the change of mitochondrial processes due to hypoxia — which is an important process in this syndrome — when xanthine dehydrogenase is converted to xanthine oxidase to produce oxygen free radical instead of NADH.



The fourth possible source of free radical formation is thyroid hormone overproduction and its consequences. It is well known that PHS is more common in lines of fast growth rate than in others. By improving the growth rate, the animals have been selected over many generations for hyperthyroid state, and it is also known that experimentally induced hyperthyroidism increases the incidence of PHS (Buys et al., 1994). During hyperthyroid state, the formation of thyroxine will enhance cellular respiration and, for that reason, the mitochondrial GSH will decrease and will cause a marked increase in mitochondrial lipid peroxidation. The other effect of thyroxine overproduction is increasing the rate of unsaturation of the inner mitochondrial membrane phospholipids which become more susceptible to oxidation (Maddaiah, 1990).

The exact mechanism of free radical effects during PHS is not known yet but there are several possible explanations. For instance, it is well known that

vasoactive eicosanoids (mainly thromboxanes and leukotrienes) will be produced when the enzyme prostacycline synthase is inhibited by reactive oxygen species. Such vasoactive metabolites have importance in the pathogenesis of PHS. There is also some experimental evidence suggesting that antioxidant status is lower (Table 5) in PHS (Enkvetchakul et al., 1993) and vitamin E supply can improve the health status of birds affected by PHS (Bottje et al., 1995).

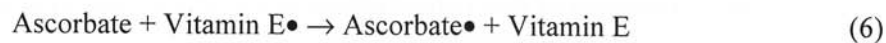
Table 5

Tissue concentrations of α -tocopherol (α -T), reduced glutathione (GSH) and ascorbic acid (AA) in the liver and lungs of 3-, 5- and 7-week-old broilers affected with PHS (Enkvetchakul et al., 1993)

Age/ compartment	3 weeks	5 weeks	7 weeks
	per cent of control		
α -T liver	46	48	48
α -T lungs	52	72	72
GSH liver	65	68	55
GSH lungs	67	67	67
AA liver	98	65	75
AA lungs	67	45	51

Tibial dyschondroplasia

Modern broiler fattening technologies require birds characterised by a very high growth rate. However, high growth intensity has several undesirable consequences such as PHS and also tibial dyschondroplasia which was found to be a nutritional disorder (Whitehead et al., 1994). The nutritional factor involved is ascorbic acid which participates in the biosynthesis of stable cross-linked collagen and also stimulates the hydroxylation of vitamin 25(OH)D to its active metabolite 1,25(OH)₂D. For that reason, ascorbic acid would be a potential preventive factor against tibial dyschondroplasia in broilers (Farquharson et al., 1997). This and other metabolic functions of ascorbic acid are derived from its reducing potential. The same reducing property makes vitamin C an excellent antioxidant. Ascorbate is considered to be the most important antioxidant in extracellular fluids and many cellular activities of antioxidants are associated with the actions of this important vitamin (Uddin and Ahmad, 1995). Its functions also include reducing the tocopheroxyl radical and restoring the radical scavenging activity of vitamin E (Niki, 1987).



The *Fusarium* toxin fusarochromanone is a useful compound for the experimental reproduction of tibial dyschondroplasia (Haynes and Walser, 1986) and selenium was found to be an effective treatment for lowering the mortality in the above-mentioned model (Walser et al., 1988).

Antioxidants and immunity

The nutritional and, within it, the antioxidant status of an animal exerts a significant influence on the host defence mechanisms (Finch and Turner, 1996). Selenium and vitamin E have been shown to play a major role in the development and maintenance of the defence systems (Tengerdy et al., 1973). Deficiencies of vitamin E and selenium in chicks depressed bursa weight, reduced the number of lymphocytes and resulted in destructive histological changes within the primary lymphoid organs and the spleen (Marsh et al., 1982). Dietary supplementation of vitamin E enhanced immunisation against coccidiosis (Colnago et al., 1984), increased protection against *E. coli* infection (Heinzerling et al., 1974) and against infectious bursal disease (McIlroy et al., 1993).

Conclusion

Research into metabolic disorders of poultry holds out the promise of continuing its tradition of leading the way, and the author shares the view that lipid peroxidation and antioxidants have a central role in that problem.

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