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## ■ Effects of concomitant selenium and vitamin E administration on thyroid hormone metabolism in broilers

### Se, vitamin E and thyroid function in broilers

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**ABSTRACT.** A total of 400, as hatched, broilers were used to investigate the effect of selenium (Se) and vitamin E supplementation on thyroid hormones metabolism. There were 5 replicates of 4 dietary treatments namely: control (C), a soybean meal maize basal diet with adequate Se and vitamin E (0.3 mg Se per kg diet and 80 mg vitamin E per kg diet), control diet with Se added (Se<sup>+</sup>, with an additional 1 mg of Se per kg of diet), control diet with vitamin E added (E<sup>+</sup>, with an additional 350 mg of vitamin E per kg of diet) and Se<sup>+</sup>E<sup>+</sup> (with additional 1 mg of Se and 350 mg of vitamin E per kg of diet). Diets were isonitrogenous and isocaloric. Zinc L-selenomethionine complex was used to increase Se content and dl- $\alpha$ -tocopheryl acetate to increase vitamin E content. The experiment lasted 42 days. Plasma Se concentration increased in Se<sup>+</sup> groups, while whole blood glutathione peroxidase (GPx) activity increased in Se<sup>+</sup>, E<sup>+</sup> and Se<sup>+</sup>E<sup>+</sup> groups compared to control. Hepatic type I iodothyronine deiodinase (ID-I) and thyroid hormone concentrations were unaffected by any dietary treatment. It is concluded that supplementation with Se or vitamin E alone or in combination above animal's requirements does not affect thyroid hormone metabolism and liver ID-I activity under the conditions examined.

**Key words:** Broiler, glutathione peroxidase, selenium, type I iodothyronine deiodinase, vitamin E

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**ΠΕΡΙΛΗΨΗ.** Τετρακόσιοι νεοσσοί κρεοπαραγωγής, ηλικίας μιας ημέρας, χρησιμοποιήθηκαν για να μελετηθεί η επίδραση του σεληνίου και της βιταμίνης E σε επεξεργασμένα σεληνιοένζυμα που σχετίζονται με τη λειτουργία του θυροειδούς αδένος. Υπήρχαν τέσσερις διατροφικές επεμβάσεις με πέντε επαναλήψεις η κάθε μία. Οι πειραματικές ομάδες περιελάμβαναν την ομάδα του μάρτυρα στην οποία χορηγήθηκε ένα βασικό σιτηρέσιο επαρκές σε σελήνιο και βιταμίνη E (0,3 και 80 mg/kg αντίστοιχα), την ομάδα Se<sup>+</sup> στην οποία χορηγήθηκε επιπρόσθετα 1 mg/kg σεληνίου, την ομάδα E<sup>+</sup> στην οποία χορηγήθηκε επιπρόσθετα 350 mg/kg βιταμίνη E και τέλος την ομάδα Se<sup>+</sup>E<sup>+</sup> στην οποία χορηγήθηκε συνδυασμός σεληνίου και βιταμίνης E σε συγκεντρώσεις 1 και 350 mg/kg αντίστοιχα. Τα σιτηρέσια ήταν ισοαζωτούχα και ισοενεργειακά. Για την επιπλέον προσθήκη σεληνίου χρησιμοποιήθηκε σύμπλοκο της L-σεληνομεθειονίνης με ψευδάργυρο, ενώ για την προσθήκη βιταμίνης η DL-α-τοκοφερόλη. Το πείραμα διήρκεσε 42 ημέρες. Η συγκέντρωση σεληνίου στο πλάσμα αυξήθηκε στις επεμβάσεις με σελήνιο, ενώ η ενεργότητα της υπεροξειδάσης της γλουταθειόνης στο αίμα αυξήθηκε σε όλες τις επεμβάσεις σε σχέση με τον μάρτυρα. Η αποϊωδίαση της ιωδιοθυρονίνης (τύπου I) στο ήπαρ και οι συγκεντρώσεις των θυροειδικών ορμονών στο αίμα δεν επηρεάστηκαν από οποιαδήποτε επέμβαση. Συμπερασματικά, η συμπλήρωση με σελήνιο ή βιταμίνη E μεμονωμένα ή σε συνδυασμό πέραν των αναγκών του ζώου δεν επηρέασαν τα επίπεδα των θυροειδικών ορμονών, ούτε την ενεργότητα της ηπατικής αποϊωδίασης υπό τις συνθήκες που εξετάστηκαν.

**Λέξεις Κλειδιά:** Ορνίθια, υπεροξειδάσης της γλουταθειόνης, σελήνιο, αποϊωδίαση της ιωδιοθυρονίνης (τύπου I), βιταμίνη E

## INTRODUCTION

Thyroid hormones control metabolic and respiratory rates in virtually all cell types. They are related to oxidative stress not only by their stimulation of metabolism, but also by controlling several antioxidant enzymes (Venditti et al., 2011; 2013; Villanueva et al., 2013). The principal pathway of thyroid hormone metabolism is deiodination, which is mediated by specific selenoproteins, the deiodinases (Kohrle et al., 1999; Darras et al., 2000). Selenium is required for the expression of the selenoenzymes type I (ID-I) and type II (ID-II) iodothyronine deiodinase, which are crucial for the generation of the active hormone 3,3',5-tri-iodothyronine (T<sub>3</sub>). Type I iodothyronine deiodinase (ID-I) catalyzes the deiodination of thyroxine (T<sub>4</sub>) to 3, 3'5-tri-iodothyronine (T<sub>3</sub>). It is mainly expressed in the liver, kidney, thyroid, pituitary, and heart. The tissue-specific expression of ID-I is distinct from that of type II iodothyronine deiodinase (ID-II) and only a few tissues express both enzymes (Kohrle 1999; Bianco et al., 2002; Schmutzler et al., 2007; Drutel et al., 2013). Apart from being an essential component of deiodinases, Se is also an integral part of other selenoproteins involved in the antioxidant defense system. Among them glutathione peroxidases have a prominent role in preventing lipid-free radical chain re-

actions that cause peroxidative damage (Kohrle, 2013).

Vitamin E is well known for preventing peroxidative damage of biological membranes and lipoproteins (Burton and Traber 1990; Packer, 1991). A complementary role in the protection of cells against the detrimental effects of lipid peroxides and free radicals produced during normal metabolism has been postulated for both vitamin E and Se (Rooke et al., 2004). Type I iodothyronine deiodinase, as a membrane bound enzyme (Toyoda et al 1995), is susceptible to lipid peroxidation process (Maiti et al., 1995; Chaurasia et al., 1996; 1997) and previous data showed that administration of vitamin E prevents toxic induced thyroid dysfunction, probably through protecting the stability of microsomal membrane in which ID-I exists (Chaurasia and Kar, 1997).

Previous studies in a number of different species have examined the synergistic role of vitamin E and Se under oxidative stress conditions on thyroid hormone metabolism (Sarandöl et al., 2005; Mancini et al., 2013; Kocer-Gumusel et al., 2015; Soliman, 2015). Studies in broilers have mainly focused on their synergistic effects on the antioxidant defense status (Traş et al., 2000; Ozkan et al., 2007; Basmacioğlu Malayoğlu

et al., 2009), while data on their synergism on ID-I activity and thyroid hormone metabolism are sparse.

The present study was designed as part of a project on the effects of antioxidants on thyroid hormone metabolism in broilers. Previously, data showed that excess Se supplementation did not alter thyroid hormone levels, while it increased liver antioxidant enzymes activity (Chadio et al., 2015). Given the role of vitamin E in protecting the stability of microsomal membrane in which ID-I exists (Chaurasia and Kar, 1997; Yue et al., 1998) the aim of the present study was to investigate if concomitant supplementation of additional vitamin E and Se could influence thyroid hormone metabolism and antioxidant enzyme activity in broilers.

## MATERIALS AND METHODS

Four hundred (400), as hatched, day-old, Cobb broilers were used in total. The broilers were obtained from a commercial hatchery. Housing and care of animals conformed to Ethical Committee guidelines of Faculty of Animal Science and Aquaculture. There were five replicate pens of four dietary treatments namely, control (C), Se<sup>+</sup>, E<sup>+</sup> and Se<sup>+</sup>E<sup>+</sup> randomly allocated in the house. Pen was the experimental unit. Each replicate was assigned to a clean concrete floor pen (2 m<sup>2</sup>) and birds were raised on a wheat straw shavings litter. There were 20 broilers per pen, 100 per treatment. Broilers of treatment C were fed a commercial diet with adequate Se and vitamin E (0.3 mg Se per kg diet and 80 mg vitamin E per kg diet). In

**Table 1.** Composition (%) of the experimental broiler diets

| Ingredients (%)     | Starter (0-14 d) | Grower (15-28 d) | Finisher (29-42 d) |
|---------------------|------------------|------------------|--------------------|
| Maize               | 60.0             | 63.2             | 66.8               |
| Soybean meal        | 26.8             | 24.8             | 23.8               |
| Fishmeal            | 7.1              | 5.0              | 2.2                |
| Soybean oil         | 3.0              | 4.0              | 4.0                |
| Limestone           | 1.6              | 1.3              | 1.2                |
| Dicalcium phosphate | 0.7              | 0.9              | 1.2                |
| Methionine          | 0.1              | 0.1              | 0.1                |
| NaCl                | 0.3              | 0.3              | 0.3                |
| Premix <sup>1</sup> | 0.4              | 0.4              | 0.4                |

<sup>1</sup>Premix supplied per kg of diet: 12,000 IU vitamin A, 4000 IU vitamin D<sub>3</sub>, 80 mg vitamin E, 9 mg vitamin K<sub>3</sub>, 3 mg thiamin, 7 mg riboflavin, 6 mg vitamin B<sub>6</sub>, 0.025 mg vitamin B<sub>12</sub>, 50 mg nicotinic acid, 15 mg pantothenic acid, 1.5 mg folic acid, 0.15 mg biotin, 400 mg choline, 0.25 mg cobalt, 1.5 mg iodine, 0.3 mg selenium, 50 mg iron, 130 mg manganese, 20 mg copper, 100 mg zinc. In supplemented diets, an additional 1 mg of Se and 350 mg of vitamin E per kg of diet was provided.

Se<sup>+</sup> treatment, broilers were fed the C diet with 1 mg of added Se per kg of diet, in E<sup>+</sup> treatment, they were fed the C diet with 350 mg of added vitamin E per kg of diet and finally in Se<sup>+</sup>E<sup>+</sup>, treatment broilers were fed the C diet with 1 mg of Se and 350 mg of vitamin E added per kg of diet (Table 1). Diets were isonitrogenous and isocaloric. Zinc L-selenomethionine complex (ZnSeMet) was used to increase Se content (Availa-Se 1000, Zinpro Corporation, Eden Prairie, Minnesota, USA) and dl- $\alpha$ -tocopheryl acetate (Rovimix E50 Ads, DSM Nutritional Products Hellas) was

used to increase the vitamin E content.

The duration of the experiment was 42 days. The broilers were raised in a house where light and ventilation were controlled. The lighting program was 23 hours of light and 1 hour of darkness. Heat was provided with a heating lamp per pen. The broilers were fed a starter diet to the 14<sup>th</sup> day of their life, a grower diet to the 21<sup>st</sup> day and a finisher diet until the 42<sup>nd</sup> day (Table 1). Feed and water were provided *ad libitum*. At the end of the 42<sup>nd</sup> day of the study, one broiler per replicate pen was sacrificed with electrical stunning

so that liver and blood samples were collected. Blood samples were collected in EDTA treated tubes (Ap-taca, Canelli, Italy), centrifuged at 1700 g at 4 °C for 10 min and the obtained plasma samples were kept at -20 °C until analysis.

Glutathione peroxidase enzyme activity was determined in whole blood and liver samples according to Paglia and Valentine (1967). Units of enzyme activity were expressed as per mg haemoglobin (Hb) or per mg of liver protein (prot). Briefly, livers were minced in 0.9 % NaCl, washed twice with 0.125 M phosphate buffer, pH 7.4, containing 1.0 mM EDTA (PBS-EDTA) and homogenized with a Polytron homogenizer (Brinkmann Instruments, Westbury, NY,

USA) for 1 min in PBS-EDTA (3 ml/g of liver tissue) at 4 °C. Haemoglobin concentration was determined spectrophotometrically using Drabkin's reagent (Sigma-Aldrich, MI, USA). Liver protein concentration was determined according to Bradford (1976) using commercially available kit. (BioRad, CA, USA). ID-I activity was determined in tissue homogenates with substrate of 3  $\mu$ M  $^{125}$  I rT<sub>3</sub> as previously described (Sawada et al., 1986).

Plasma T<sub>3</sub> and T<sub>4</sub> concentrations were determined by radioimmunoassay, using commercially available kits (Biocode, Liege, Belgium). The sensitivity for the T<sub>3</sub> assay was 0.1 ng/ml, whereas that for T<sub>4</sub> 1.8 ng/ml. Intra- and inter assay coefficients of variation were 2.9

**Table 2.** Dietary treatment effects on Se concentration in blood plasma and the activity of antioxidant enzymes

| Parameter                              | Treatment           |                     |                     |                                | S.E.M. |
|--|---------------------|---------------------|---------------------|--------------------------------|--------|
|  | C                   | Se <sup>+</sup>     | E <sup>+</sup>      | Se <sup>+</sup> E <sup>+</sup> |        |
| Plasma Se concentration<br>(ng Se/ g)  | 211.05 <sup>a</sup> | 364.80 <sup>b</sup> | 191.49 <sup>a</sup> | 314.70 <sup>b</sup>            | 21.751 |
| Whole blood GPx activity<br>(U/ mg Hb) | 497.0 <sup>a</sup>  | 1680.5 <sup>b</sup> | 1173.0 <sup>b</sup> | 1860.3 <sup>b</sup>            | 2.55   |
| GPx activity in Liver<br>(U/ mg prot.) | 0.91                | 1.05                | 0.97                | 0.81                           | 0.06   |

a, b: different superscripts indicate significant ( $P < 0.05$ ) difference between treatments

and 8.4 for T<sub>3</sub> and 3.27 and 4.94 for T<sub>4</sub>, respectively.

Finally, Se concentration was determined in plasma using inductively coupled plasma mass spectrometry, ICP-MS (Perkin Elmer, Elan 9000, Perkin Elmer Life and Analytical Sciences Inc, Waltham, MA, USA) as described previously (Pappas et al., 2011).

#### Statistical analysis

The statistical analysis was performed using SAS software (SAS Institute Inc., Cary NC, USA). All

variates were analyzed by ANOVA. Descriptive statistics, including mean and standard error of the mean (SEM), are presented. The statements of significance presented in this study were based on  $P \leq 0.05$  unless otherwise stated.

#### RESULTS

Selenium supplementation to broiler diets (treatments Se<sup>+</sup> and Se<sup>+</sup>E<sup>+</sup>) resulted in significantly higher plasma Se concentration ( $P < 0.05$ ) compared to that

of broilers fed diets with no additional Se (treatments C, and E<sup>+</sup>). Most notably, an approximately 1.7 times higher Se levels were found in Se<sup>+</sup> and Se<sup>+</sup>E<sup>+</sup> groups (Table 2).

The activity of GPx differed between the four dietary treatments. In particular, a significant ( $P < 0.05$ ) 3-fold increase in blood GPx activity was detected in the two Se supplemented groups compared to control. Interestingly, a significant ( $P < 0.05$ ) 2-fold increase of GPx activity was also detected in group supplemented only with vitamin E. Liver GPx activity was not affected by any of the dietary treatments (Table 2).

Dietary treatments did not significantly affect liver ID-I activity, although a numerical higher activity was detected in all treated groups. Supplementation with Se, vitamin E or their combination did not affect thyroid hormones concentrations or the rate of deiodination of T<sub>4</sub> to T<sub>3</sub> (Table 3).

## DISCUSSION

The results of the present study showed that excess Se supplementation resulted in a significant increase in plasma Se levels and blood GPx activity, in good agreement with our previous findings in broilers supplemented with 0.5 ppm Se as zinc L-selenomethionine complex (Chadio et al., 2015). More interestingly elevated GPx activity was also detected in broilers

supplemented with vitamin E alone or in combination with Se. An augmented blood GPx activity has also been reported for humans following vitamin E administration (Giray et al., 2003) while in growing lambs a synergistic action between Se and vitamin E in terms of GPx activity has also been detected (Ramos et al., 1998; Soliman, 2015). These findings support the well-defined antioxidant activity of vitamin E and further emphasize the synergistic action between the two antioxidants. On the other hand hepatic GPx activity was not affected by either Se, vitamin E or their combination, indicating that excess supplementation elicits no further increase in enzyme activity, in accordance with previous results (Whanger and Butler, 1988; Ip and Hayes, 1989).

Although a considerable number of studies have examined the effects of Se and vitamin E deficiency on plasma thyroid hormone concentrations both in mammals (Beckett et al., 1987; Mitchell et al., 1996; Yue et al., 1998) and birds (Jianhua et al., 2000; Chang et al., 2005), very little is known about the effects of Se and more particularly vitamin E administration on thyroid hormone metabolism and IDs activity. In the present study supplementation with Se, vitamin E or their combination did not influence thyroid hormones levels or the rate of deiodination of T<sub>4</sub> to T<sub>3</sub>. The absence of any influence on thyroid hormone metabolism is consistent with the lack of an effect of these

**Table 3.** Dietary treatment effects on the concentration of iodothyronine deiodinase and thyroid hormones

| Parameter                                       | Treatment |                 |                |                                | S.E.M |
|---|-----------|-----------------|----------------|--------------------------------|-------|
|   | C         | Se <sup>+</sup> | E <sup>+</sup> | Se <sup>+</sup> E <sup>+</sup> |       |
| ID-I activity in Liver<br>(pmol /min/ mg prot.) | 49.42     | 57.53           | 53.98          | 64.91                          | 5.756 |
| T <sub>4</sub> (ng/ml)                          | 32.67     | 31.83           | 29.17          | 27.83                          | 1.444 |
| T <sub>3</sub> (ng/ml)                          | 2.78      | 2.95            | 2.72           | 2.82                           | 0.137 |
| T <sub>4</sub> /T <sub>3</sub> (ng/ml)          | 12.53     | 12.00           | 11.06          | 10.31                          | 0.835 |



antioxidants on hepatic ID-I activity. However, it is of interest to note that a numerically higher, although no significant increase in ID-I activity was detected in groups of broilers received both vitamin E and Se. Therefore, it seems that supplementation with Se or vitamin E above animal's requirements has no effect on thyroid hormone metabolism, providing strong evidence that the upper limit of the tissue concentrations of selenoenzymes are homeostatically controlled and that additional Se does not further increase the selenoenzyme activities, as has already been reported (Behne et al 1992; Chadio et al., 2006).

Previous studies in different animal species revealed a protective role of vitamin E under various stress conditions (Brzezińska-Slebodzińska 2001; Sahin et al., 2001; Sarandöl et al., 2005). Most notably, in lead induced thyroid dysfunction in mice administration of vitamin E has been shown to maintain ID-I activity (Chaurasia and Kar ,1997) and in Se and

vitamin E deficient rats vitamin E administration increased hepatic ID-I activity (Yue et al 1998). Given previous reported data that oxygen radicals may inactivate ID-I through at least reduction of thiol cofactors (Brzezińska-Slebodzińska and Pietras, 2001), it seems that vitamin E protects the stability of microsomal membrane in which ID-I exists, avoiding from free radical damage, as has already been suggested (Chaurasia and Kar, 1997; Yue et al., 1998).

The results of the present study clearly show that supplementation with Se or vitamin E alone or combined above animal's requirements has no effect on thyroid hormone metabolism under physiological conditions. However, given the positive reported effects of vitamin E supplementation under stress conditions it is of particular interest to further elucidate the role of vitamin E and its synergism with Se on ID-I activity and thyroid hormone metabolism. ■

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