家禽营养与饲料科技进展

ADVANCES IN POULTRY NUTRITION AND FEED SCIENCE

——第二届全国家禽营养与饲料科技研讨会论文集

Proceedings of the Second National Symposium on Poultry Nutrition and Feed Science

吴于明 齐广海 主编

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《家禽营养与饲料科技进展》

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前 言

由中国畜牧兽医学会动物营养学分会和动物营养学国家重点实验室联合主办的第二届全国家禽营养与饲料科技研讨会成功召开了！要特别感谢20个协办单位在财力和人力方面的慷慨支持！感谢同行们的积极响应！

中国的现代家禽业经过了近三十年的快速发展，家禽生产能力得到了很大提高，但在生产效率、产品质量与安全、健康与福利以及环境保护方面仍然面临严峻的挑战。本届大会的主题定为“高效、优质、安全”。大会收到科技论文100余篇，其中有12篇来自国外专家。按照研究内容将论文大致分为“营养素代谢与营养需要”、“营养免疫与肠道健康”、“饲料营养与产品品质”、“酶制剂与饲料利用”和“饲料安全与生物学效价评定”等五大领域。

特邀参加本届大会的英国Rowett研究所的J. Arthur教授、美国California大学Davis分校的K. Klasing教授、美国North Carolina州立大学的P. Ferket教授和J. Shih教授、加拿大Alberta大学F. Robinson教授和J. Sim教授、澳大利亚Queensland大学的W. Bryden教授、德国Goetingen大学F. Liebert教授、西班牙IRTA的Mas Bove中心主任J. Brufau博士、Aviangen集团全球营养总监M. Kenny博士、Novus公司研发中心主任C. Knight博士和Adisseo公司P. Dalibard博士等12位外国专家在相关研究领域都是世界顶级的，他们的论文反映了本学科研究的动态和前沿热点，定会使读者受益匪浅；国内的论文也涵盖了学科基础理论和产业实用技术，在研究思路和研究方法方面均反映了家禽营养与饲料科技的发展趋势，有些内容具有明显的创新性。希望通过本届大会，进行充分研讨和交流，能够更新和丰富理论知识，能够了解和掌握实用新科技。

15年前首届大会时的许多听者成为了本届大会的讲者，他们的成长和成功无疑得益于老师的培养。本届大会适逢教师节召开，借此祝教师们节日快乐！

吴于明

2007年9月

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营养素代谢与营养需要

Nutrient Metabolism and Requirement

Selenium in Animal Nutrition: Opportunities for Improved Health and Production

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Abstract: Understanding of the wide range of functions of selenium in animals has been improved greatly by the use of bioinformatic, genomic, proteomic and metabolomic techniques. Such research has revealed roles for selenium that reveal a much wider potential for diseases to be caused by deficiency than had been recognised previously. There are likely to be up to 25 selenoprotein genes in most economically-important farm animals. Thus it is very important to recognise the biochemical functions of the proteins derived from these genes and how their under, or over-expression may have adverse effects on health and production. It is also essential to consider the mechanisms whereby selenium is incorporated into selenoproteins derived from these genes. This should help to predict other stages where problems due to selenium deficiency or any inadequate selenium supply may occur. Since most of the discoveries of the role of selenium in a range of metabolic systems have occurred recently, much research from the past decades needs to be reappraised. We may not recognise fully the extent to which marginal selenium supply in the diet has had adverse effects on both animals and man. Recognition of and amelioration of such problems is still a major challenge facing agriculture and by implication animal and human health.

Introduction

The micronutrient selenium when first investigated in diets was studied for its toxic effects in farm and other animals. However, in 1957 selenium was shown to be an essential component of factor 3 that prevented liver necrosis in rats consuming vitamin E-deficient diets. Very rapidly thereafter, very small amounts of selenium were demonstrated to prevent a number of conditions in farm animals including myopathies in sheep and cattle and exudative diathesis and muscle problems in poultry (van Metre & Callan, 2001; Rayman, 2000; Wichtel, 1998a, b). The mechanisms whereby selenium prevented liver necrosis were first postulated after selenium was shown to be a component of cytosolic glutathione peroxidase. Metabolism of hydrogen and lipid peroxides by this enzyme was thought to be an antioxidant function complimentary to that of vitamin E; stabilising cell membranes damaged during necrotic processes (Burk & Gregory, 1982; Hafeman & Hoekstra, 1977). The exploration of such mechanisms and their replications in many diseases formed the basis of much of the initial research on selenium function in farm animals, experimental animals and humans. Nevertheless, it became clear that many functions of selenium could be dissociated from changes in glutathione peroxidase activity Hill & Burk 1987; Arthur *et al.*, 1987). Indeed, distinct plasma and membrane-associated forms of glutathione peroxidase were also identified attesting to the complexity of selenium function in animals (Takahshi & Cohen, 1986; Ursini *et al.*, 1985). These functions also pointed towards the existence of other selenoproteins a fact that was confirmed through initial experiments with in vivo and in vitro labelling with ^{75}Se; this labelling specific proteins in many organs and cell types (Behne *et al.*, 1988; Miller *et al.*, 2002). Using conventional protein purification techniques many of these selenoproteins were isolated then characterised. Many of these selenoproteins had functions unrelated

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to glutathione peroxidase activity and the range of processes these affected provided a mechanistic basis for the very wide range of diseases and other functions that were associated with changes in dietary selenium intake in animals.

Bioinformatic recognition of selenoproteins

Use of molecular techniques and complete sequencing of genomes has gone a long way towards identifying the complete range of cell functions that may be regulated by selenium containing proteins. Thus in humans, rats and mice there are 24 or 25 genes that code for selenoproteins (Kryukov *et al.*, 2003). With alternative splicing this can account for the more than 25 selenoproteins identified by ^{75}Se labelling of cells and experimental animals. The basis of the bioinformatic identification of selenoprotein genes is the encoding of selenocysteine by a UGA codon in mRNA that would normally act as a stop codon during translation. The mechanism for the recognition of UGA as selenocysteine requires a selenocysteine insertion sequence (SECIS element) in the 3' untranslated region of the mRNA. Such sequences are conserved and their occurrence in relation to the UGA codons was used to predict the number of genes encoding selenocysteine-containing proteins in different organisms (Table 1) (Hatfield & Gladyshev, 2002; Hoffmann & Berry, 2005; Small-Howard & Berry, 2005). This work also provided some insight into the evolution of selenocysteine-containing proteins, many of which have cysteine-containing analogues in lower organisms. Although there is a wide range of both procaryotic and eucaryotic genomes have been completed, those of agricultural importance are less available. Chicken, fish and bovine are completed and pig, sheep, rabbit and goat are only partially completed. Search of these genomes for SECIS elements and UGA codons will no doubt confirm the presence of similar selenoprotein genes that are already recognised in humans, mice and rats. Certainly, conventional protein purification and biochemical techniques show that the selenoproteins expressed in farm animals are similar in structure and function to those in rodents and humans. For example, the selenoproteins involved in thyroid hormone metabolism are very similar not only in function but expression in rats and humans and the activities also occur in sheep and cattle (Zagrodzki *et al.*, 1998; Arthur *et al.*, 1999; Beckett & Arthur, 2005).

Table 1 Selenoproteins in different genomes

(predicted genes, Kryukov *et al.*, 2003)

Organism	number	Organism	number
Sacchromyces cerevisiae	0	Zebrafish	18
Arabidopis	0	Mouse	24
Chlamydomonas	≥10	Human	25
C elagans	1	Fugu (puffer fish)	≥28
Drosophila M	<3		

Selenocysteine synthesis

In mammalian systems, the translation of selenoprotein mRNAs is dependent on both *cis*-acting sequences within the RNA and at least 3 *trans*-acting factors unique to selenocysteine synthesis and incorporation. The SECIS elements for mammalian selenoproteins have very similar physical structures although they may not be very highly conserved at the sequence level. However, within the helical SECIS structures, certain bases do occur in the same positions and deletion or alteration of these bases results in decreases or loss of SECIS activity (Tamura *et al.*, 2004; Hoffmann & Berry, 2005). Different SECIS elements within the 3' untranslated regions of selenoproteins can be linked to the coding regions of different selenoproteins. In such systems the SECIS elements can be more or less efficient that the original element and this may underlie some of the mechanisms whereby the expression of certain selenoproteins is maintained when selenium supplies are limiting. It is important to realise that many other factors can also influence the synthesis and incorporation of selenocysteine into proteins. These factors occur at several or different levels ranging from the availability of selenium in food right through to the complex mechanisms already described. As well as the different SECIS elements, recognition of the UGA stop codon requires specific tRNAs (tRNAsec) with trans acting factors, selenium binding protein 2 and EFsec

(Figure 1). These trans-acting factors are a minimum requirement and other proteins have been implicated in the translation of mRNA UGA as selenocysteine (Small-Howard & Berry, 2005). The actual incorporation of selenocysteine into mammalian selenoproteins requires reaction of a serine with selenophosphate in a co-translational mechanism. The synthesis of selenophosphate is carried out by two different mechanisms controlled by selenophosphate synthetases 1 and 2 (Figure 2) (Tamura *et al.*, 2004).

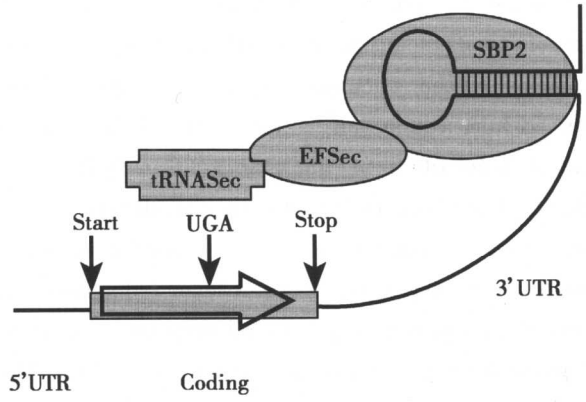

Figure 1 Trans-acting factors essential for selenocysteine synthesis in animal cell

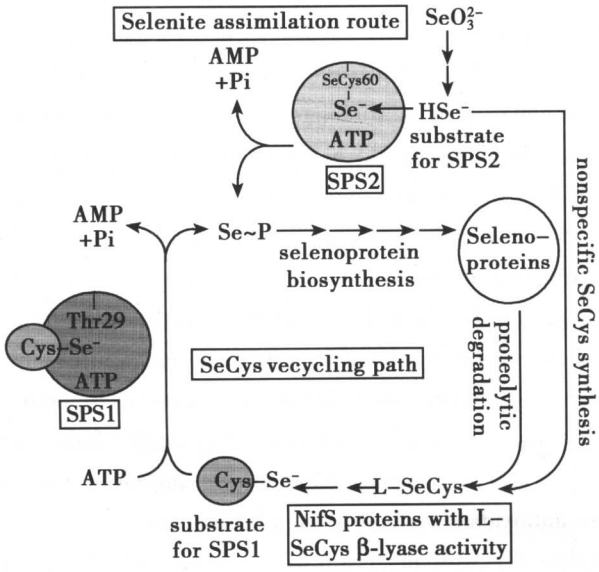

Figure 2 Hypothetical selenium assimilation routes

Modified from Tamura *et al.*, (2004) Proc. Natl. Acad. Sci. USA 101, 16162 ~ 16167; Bold arrow represents processes shown in Figure 1

Selenophosphate synthetase 1 can use free selenocysteine in the presence of ATP and a threonine at the active site to produce seleno-phosphate, AMP and free phosphate. The alternative mechanism requiring selenophosphate synthetase 2 uses a compound similar to hydrogen selenide and ATP to produce the same selenophosphate, AMP and inorganic phosphate as does selenophosphate synthetase 1. In contrast to selenophosphate synthetase 1, selenophosphate synthetase 2 has a selenocysteine at its active site (Tamura *et al.*, 2004). Thus when selenium supplies are limiting, decreases in selenophosphate synthetase 2 activity would provide a sensitive auto-regulatory mechanism for synthesis of certain selenoproteins. Research remains to be carried out to identify which selenoproteins are dependent on the alternative pathways for selenophosphate synthetase. Particularly in farm animals such knowledge will be critical in determining which are the body systems that are "at risk" from limiting supplies of dietary selenium. This may differ from species to species given the range of diseases that can be associated with low selenium status in different species of agricultural importance. Examination of the selenoproteins in humans and rats that are likely to be common to most farm animals reveals that they have similar functions that are prominent in antioxidant systems, redox control and thyroid hormone metabolism (Table 2). In addition, the selenoproteins have many unique and critical functions in reproductive systems and methionine metabolism (Ursini *et al.*, 1999; Kryukov *et al.*, 2002). As well as the mechanisms that are specific to incorporation of selenocysteine into selenoproteins, several more general influences exist that can affect the process of selenoprotein synthesis. The most important of these is the overall supply of selenium in the diet (Table 3) A low intake can be severe enough to cause clinical symptoms or when more marginal will modulate the activity of metabolic systems which are dependent on selenium. Such effects may lead to impaired immune or other functions that will have adverse effects on animal production and welfare.

Table 2 Mammalian selenoproteins

(Updated from Beckett and Arthur 2005)

	Selenoprotein	Proposed Function
Glutathione Peroxidases (GPX)	GPX-1	Antioxidant in cell cytosol. Se Store?
	GPX-2	Antioxidant in GI tract
	GPX-3	Antioxidant in extracelluar space and plasma
	GPX-4	Membrane antioxidant. Structural protein in sperm. Apoptosis?
	GPX-5	Unknown
	GPX-6	Specific antioxidant in nasal cavity?
Thioredoxin Reductases (TR)		Multiple roles including:-Dithiol-disulphide oxoreductase. Detoxifies peroxides, reduces thioredoxin-control of cell growth. Maintains redox state of transcription factors.
	TR 1	Mainly cytosolic-ubiquitous
	TR 2	Mitochondrial - ubiquitous
	TR 3	Expressed by testes
Iodothyronine deiodinases	Type ID1&ID2	Converts thyroxine (T4) to bioactive 3,5,3′ triiodothyronine (T3)
	Type ID1&ID3	Converts thyroxine (T4) to bioinactive 3′,3′,5′ reverse T3
Selenoprotein P		Selenium transport protein may protect endothelium.
Selenoprotein W		Mainly expressed in cardiac and skeletal muscle
Selenophosphate Synthetase (SPS2)		Synthesis of selenophosphate for selenoprotein synthesis.
15Kda selenoprotein (Sep 15)		Protects against cancer?
H,I,KM,N,O,R,S,T,V		Role largely unknown-mutations of N in some myopathies

Table 3 Stages at which synthesis of selenoproteins may be regulated both mechanistically and by selenium supply

1.	2.	3.	4.	5.
UGA stop codon recognised by tRNAsec with trans-acting factors SBP2 and EFsec	Protein(s) involved in selenophosphate synthesis	Overall supply of selenium from the diet	Interfering metals eg Hg, Cu, Ag	Regulation by PUFAs, isothiocyanates etc

Influences on selenoprotein synthesis

In addition, many dietary components can decrease the availability of selenium even when its absolute levels are adequate within the diet. Such toxic effects are rare in agricultural practice but can happen for example, when errors occur during the formulation of dietary mineral supplements. Excess levels of copper can interfere with selenium absorption by animals (Abdel-Rahim *et al.*, 1986). Other components of the diet can also be involved in the regulation of the expression of specific selenoproteins perhaps through response elements in the selenoprotein genes. Sulphorophane derived from isothiocyanates will induce thioredoxin reductase 1 activity in *in vitro* systems (Campbell *et al.*, 2007). If this occurs *in vivo* such high dietary components would contribute to redox regulation of cells, which can be regulated by thioredoxin reductases. Of particular relevance to agricultural practice is induction of glutathione peroxidases by iodine deficiency. The most sensitive site for this interaction is the thyroid gland where even a mild iodine deficiency will cause a substantial induction in glutathione peroxidase 1 activity (Vanderpas *et al.*, 1993; Arthur *et al.*, 1999; Moreno-Reyes *et al.*, 2005). This presumably reflects the increased hydrogen peroxide production in the thyroid gland as it is stimulated through lack of iodine. The interactions between iodine deficiency and selenium deficiency in the human population are well recognised. In areas where such interactions take place it is likely that similar effects occur in farm animals although this is less widely studied. A further area of nutrition, which may be of importance to monogastric animals and poultry, is the induction of glutathione peroxidase activity by polyunsaturated fatty acids. Induction of peroxidase activities may provide improvements in the antioxidant systems of the animals that will act synergistically with other nutrients such as vitamin E to decrease risk of disease. A further, potentially beneficial, consequence of the effects of polyunsaturated fatty acids on selenoprotein expression may be the modulation of eicosanoid metabolism. Many of the intermediates in the synthesis of bioactive derivatives of polyun-

saturated fatty acid involve peroxide intermediates. Metabolism of these intermediates by the different glutathione peroxidases may have both specific metabolic effects and also prevent non-specific oxidative damage (Cao *et al.*, 2000, 2002; Lemaitre *et al.*, 1997). Thus selenocysteine incorporation into proteins can be regulated when influenced at the level of the diet, absorption and distribution of selenium within the body and through specific molecular mechanisms such as those triggered by iodine deficiency (Table 3). In all animals such mechanisms contribute to a cycle of selenoprotein synthesis from selenium in the diet that is being fed by different forms of selenium that are converted to hydrogen selenide-like compounds, selenophosphate and finally selenocysteine at the active site of the enzyme (Figure 2). However, low dietary selenium intake will contribute to low selenium status in farm animals (Arthur, 1988; Wichtel, 1998a,b). Low available levels of selenium in the soil contribute to plant products with low selenium that directly affect animal production and eventually, the human population which consume products based on these soils. Dietary intake of humans can vary throughout the world from as low as 7 micrograms per day up to approximately 250 micrograms per day indicating the potential for regulation of selenoprotein expression. Similar ranges of intake occur in farm animals when supplementation regimes are not instituted. There are also some areas where selenium intake is higher and which may result in symptoms of toxicity. This is a very rare occurrence and more important is the understanding of how different selenium intakes within the non-toxic range may influence health in the context of complex and highly regulated mechanisms for selenoprotein synthesis.

Conclusions

The use of genomic and proteomic techniques have allowed major advances in our understanding of the role of nutrients in controlling processes in cell lines and experimental animals. For example, the range of "new" selenoproteins that have been recognised using bioinformatics have pointed to areas such as methionine metabolism and aspects of the immune system that need to be investigated in the context of selenium deficiency. Unfortunately, a large body of work, which examines the role of selenium in maintaining production and health in farm animals, was carried out before the potential of such "-omic" and bioinformatics techniques were available or recognised. For example, a modest increase in selenium status of human volunteers recruited in the United Kingdom has had beneficial effects on their response to vaccination with attenuated polio virus. The beneficial effects of the selenium included stimulation of the innate immune system and a speedier clearance of the virus from the body. Furthermore, fewer mutated viruses were recovered from the faeces of the volunteers and overall the effects of the increased selenium status were considered to be beneficial (Broome *et al.*, 2004). Such information is as yet, not available for the response of both mammals and birds of agricultural importance to vaccinations in the presence of improved selenium status. Such an area of research is extremely important and there is potential for large gains in animal production and welfare should similar effects become apparent.

Work with human volunteers has also indicated that polymorphisms in selenoprotein P, the major selenium transport protein in the plasma, can affect the response to selenium supplementation in a gender specific manner also influenced by body mass index (Meplan *et al.*, 2007). Much greater knowledge of polymorphisms in selenoprotein genes in farm animals would be of great benefit. Again such polymorphisms may influence the response of animals to selenium depletion or selenium supplementation. Knowledge of such different responses would allow agricultural practice to better meet the challenges presented by low selenium diets. Thus overall recent advances in understanding of selenium metabolism are being applied in animal studies and in human health. It is very important that work on selenium in agriculturally important animals does not lag behind as a great opportunity would be missed to both improve animal production and ensure better animal welfare.