

ISSN 1682-8356
ansinet.org/ijps



INTERNATIONAL JOURNAL OF
POULTRY SCIENCE

ANSI*net*

308 Lasani Town, Sargodha Road, Faisalabad - Pakistan
Mob: +92 300 3008585, Fax: +92 41 8815544
E-mail: editorijps@gmail.com

Vitamin Deficiency-Induced Neurological Diseases of Poultry

Sigfrido Burgos¹, Diego V. Bohorquez¹ and Sergio A. Burgos²

¹Department of Poultry Science, College of Agriculture and Life Sciences,
North Carolina State University, Raleigh, NC, 27695-7608, USA

²Department of Animal and Poultry Science, University of Guelph, Guelph, Ontario, N1G 2W1, Canada

Abstract: Vitamins are organic compounds distinct from fats, carbohydrates and proteins, naturally found in most foods items in minute amounts for normal physiological function. Their essentiality in poultry nutrition is evidenced by diverse deficiency symptoms that manifest when they are lacking. They are intimately involved in a series of roles in organisms as antioxidant molecules, modulators of gene transcription, biosynthesis of neurotransmitters and nucleic acids, drivers of cell division, organ development and embryogenesis, all of which contribute to normal neural function. In poultry, a single or collective vitamin deficiency can induce neurological ailments such as peripheral neuropathies, paralysis, ataxia, areflexia, encephalopathy, opisthotonos, impaired locomotion and convulsions.

Key words: Vitamin, deficiencies, neurological diseases, poultry

Introduction

The health and well being of chickens depends upon the interaction between their genetic potential and exogenous factors like adequate nutrition, proper growth environment, reduced exposure to stressors and appropriate managerial practices. Nutrition has a preeminent role in promoting growth, development, immunity and reproduction. Micronutrients (vitamins and minerals) are required for the integrity and optimal function of living animal systems. There are 13 accepted vitamins, 4 of which are lipid-soluble and 9 are water-soluble. Absolute single vitamin deficiencies are rare, as they are most likely coupled with protein-energy malnutrition. Nevertheless, some cases of specific nutrient deficiencies can be directly related to neurological diseases, as is the case for thiamin, whose discovery came as a result of relating peripheral neuropathies with rice polishing in Javanese birds (Funk, 1911; Burgos and Burgos, 2006). Additionally, it is well known that niacin deficiency leads to reduced cognition and dementia; while a number of other B-vitamins, especially B₁, B₂, B₆, B₁₂ and folic acid are needed for synthesis of various neurotransmitters (Carper, 2000; Guesry, 1998; Kretchmer *et al.*, 1996). Here we examine which vitamin deficiencies induce neurological diseases in birds by congenital malformations, brain underdevelopment, inborn errors of metabolism, reduced catalytic capacity or inhibited product synthesis.

Lipid-Soluble Vitamins

Vitamin A: Both the lack and excess of this vitamin during embryonic development result in congenital malformations. Early development can be successfully examined in the vitamin A-deficient avian embryo, in which bioactive retinoids (Retinoic Acid, RA) can rescue the deficient genotype as well as phenotype. In this

model it has been possible to unequivocally link the physiological function of vitamin A to development of heart, embryonal circulatory and central nervous systems, and the regulation of heart asymmetry (Zile, 1998). An intricate metabolic control system of catabolic and synthetic enzymes, combined with cytoplasmic binding proteins, is used in both embryo and adult to create regions of high and low RA to modulate gene transcription in the hippocampus, a brain region involved in the regulation of neural plasticity and brain regeneration (Mey and McCaffery, 2004) and in other animals, teratogenicity appears to affect tissues derived from the cranial neural crest (Rothman *et al.*, 1995); these effects described above, coupled with a vitamin A deficiency-impaired antioxidant system, most invariably result in neurodiseases (Floyd, 1999). Broad signs of vitamin A deficiency in the nervous system include ataxia, constricted optic nerve and increased cerebrospinal fluid (Combs, 1998).

Vitamin D: This vitamin is also known as a quasi hormone, due to the various genes it regulates in living organisms. Evidence of vitamin D receptor presence in brains implies this vitamin may have some function in this organ. Maternal vitamin D deficiency results in profound brain alterations at birth (Eyles *et al.*, 2003). During development and growth, vitamin D receptors interact with transcription factors affecting morphogenesis, gene transcription, and product synthesis (MacDonald *et al.*, 1995). In rats, region-specific enhancement of choline acetyl transferase, -an enzyme joining acetyl CoA to choline resulting in the formation of the pivotal neurotransmitter acetylcholine-, has been reported as a nonclassic function of this vitamin; while in other species, vitamin D deficiency results in tetany and ataxia (Combs, 1998; Singh, 2004).

Vitamin E: This antioxidant vitamin is important for normal neurological function (Muller *et al.*, 1983). Neurons contain large amounts of both PUFAs and iron, but not an extensive antioxidant system, which makes them susceptible to oxidative damage of proteins, fats and nucleic acids. Damage-induced neural death, due to terminal differentiation, does not regenerate; consequently, this vitamin plays an important protective role by quenching endogenous free radicals that are responsible for brain oxidative stress (Combs, 1998; Floyd, 1999). Chronic, severe vitamin E deficiency results in encephalopathy, ataxia, areflexia and other non-specific neurological diseases in most species (Sokol, 1988).

Water-Soluble Vitamins

Vitamin C: This antioxidant vitamin is the generic descriptor for all compounds exhibiting qualitatively the biological activity of ascorbic acid. There are several enzymes that require ascorbic acid as a co-substrate, for example: Dopamine- β -monooxygenase (a copper-dependent enzyme that hydroxylates dopamine to form norepinephrine), peptidylglycine - α - amidating monooxygenase (a copper-dependent enzyme involved in the amidation of the C terminals of biologically active peptides) and 4-hydroxyphenylpyruvate dioxygenase (catalyzes the oxidation and decarboxylation of the intermediate of tyrosine degradation, that is, from 4-hydroxyphenylpyruvic acid to homogentisic acid). In schizophrenic patients with anatomical changes in brain, dopamine- β -monooxygenase has been found to be abnormally low suggesting impaired neurotransmitter synthesis. However, poultry do not exhibit vitamin C deficiency-induced neurological diseases as chickens are renal synthesizers of ascorbic acid and are able to meet the needs for this compound (Combs, 1998; Guesry, 1998). With regards to teratogenicity, vitamin C treatment reduces the rates of congenital malformations and late resorptions in diabetic rats (Siman and Eriksson, 1997).

Thiamin (B₁): This vitamin deficiency -in animals- is characterized by appetite and weight loss, cardiac and neurologic symptoms. The latter, particularly in birds, is seen as a severe hyperextension and spastic tendency in which the individual enters a complete 'bridging' or 'arching' position with the head, neck and spinal column arching backward in extreme extension, most commonly known in the field as stargazing or opisthotonos (Greek: *opistho* for back, behind and *tonos* for tension) and other peripheral neuropathies of various degrees (Combs, 1998). It was with these specific symptoms that Dr. Eijkman, in the 1890's worked out a chicken model to study beriberi in hospital patients. Hass (1988) suggests that these neurologic conditions result as a catalytic dysfunction of glycolysis, tricarboxylic acid cycle,

and branched chain amino acid thiamin-dependent reactions in neurons that provide energy for proper nerve functioning. In humans, there is a syndrome known as Wernicke-Korsakoff resulting from an aberrant transketolase that has very low affinity for thiamin pyrophosphate. It is worth mentioning that Amprolium, a poultry coccidiostat, is a thiamin antagonist whose extended use may result in polyneuritic symptoms of poultry if not corrected by additional thiamin supplementation in diets.

Riboflavin (B₂): This vitamin functions metabolically as the essential component of the coenzymes FMN and FAD, which act as intermediates in transfers of electrons in biological redox reactions. Riboflavin deficiency is potentially fatal in all species (Powers, 2003). In avian species, chicks experience myelin degeneration of the sciatic nerve resulting in an inability to extend the feet digits, a syndrome commonly known in the field as curled-toe paralysis (Jylling, 1971). In layers, it involves reduction in egg production and decreased hatchability of fertile eggs (Romanoff and Bauernfeind, 1942). Turkeys display mild to severe dermatitis, and ducks rapidly die if not supplemented within days. Neurologically speaking, ataxia and paralysis are two common signs of riboflavin deficiency (Combs, 1998).

Niacin (B₃): This vitamin functions metabolically as an essential component of the enzyme cosubstrates NAD(H) and NADP(H), each acting as an intermediate in most of the hydrogen transfers in more than 200 reactions in living cells. Because a substantial amount of niacin can be synthesized from tryptophan, nutritional status with respect to niacin involves not only the level of intake of the preformed vitamin, but also of its potential amino acid precursor. Ducks are particularly sensitive to niacin deficiency. In most birds dementia cannot be assessed, although it can be rapidly caused by severe niacin deficiency. In fact, dietary niacin may protect against Alzheimer's disease and age related cognitive decline in humans (Morris *et al.*, 2004). Other symptoms in chickens are inflammation of the upper gastrointestinal tract, dermatitis of the legs, reduced feather growth and an inflammatory misalignment of the tibiotarsal joint known as perosis. Broadly speaking, dementia and ataxia are two common signs of niacin deficiency in animals (Singh, 2004; Combs, 1998).

Pyridoxine (B₆): The metabolically active form of this vitamin is pyridoxal phosphate (PP), which serves as a cofactor of numerous enzymes, most of which are involved in amino acid metabolism as transaminases, decarboxylases and racemases. PP-dependent enzymes function in the biosynthesis of the neurotransmitters serotonin, epinephrine and norepinephrine, and an important source of energy for

the brain, γ -aminobutyric acid (GABA), thus lack of any of these results in neurologic impairment (Haenggeli *et al.*, 1991). B₆ deficiency affects various enzymes in folate metabolism such as thymidylate synthetase, glycinamide ribonucleotide transferase and N¹⁰ formyl tetrahydrofolate transformylase that invariably results in reduced purine and pyrimidine synthesis, and impaired cell division affecting embryogenesis and brain development. Chickens and turkeys exhibit reduced appetite and poor growth, dermatitis, marked anemia, convulsions, reduced egg production and low fertility. Overall, most species develop paralysis, convulsions and peripheral neuropathies related to reduced neurotransmitter synthesis (Combs, 1998).

Biotin: Domestic fowl fed biotin-deficient diets develop congenital malformations (Dakshinamurti, 2005). Maternal biotin deficiency is teratogenic in mice even if the dams are asymptomatic (Watanabe, 1990). High levels of biotin have been reported in hippocampal tissues, a brain region important for learning and memory (Wang and Prevsner, 1999) and in specific telencephalic nuclei of juvenile songbird males related to vocalizations (Johnson *et al.*, 2000), evidencing the pivotal role that biotin-related mechanisms might play in neuronal plasticity. In general, biotin deficiency results in impaired growth, reduced efficiency of feed utilization and bucal dermatitis (Combs, 1998).

Pantothenic Acid: This vitamin is metabolically active as the prosthetic group of coenzyme A (CoA) and the acyl-carrier protein. Pantothenic acid deficiency, although rare, in most species results in reduced growth, decreased efficiency of feed utilization, anorexia, changes in hair, feather, or skin, locomotor abnormalities, gastrointestinal problems, impaired adrenal functions, altered lipid and carbohydrate metabolism, and adverse breeding outcomes (Smith and Song, 1996). In chickens, deficiency symptoms include myelin degeneration of the spinal column with paralysis, ataxia and lethargy; coupled with high rates of embryonic and posthatch mortality (Watanabe, 1990; Combs, 1998).

Folate: This vitamin functions as an enzyme cosubstrate serving as an acceptor or donor in many single-carbon reactions of amino acids and nucleic acids. It is generally established that folate has an important role in embryogenesis due to its pivotal role in DNA synthesis to support normal cell division (Rosenquist and Finnell, 2001). A deficiency of this vitamin in birds initially results in severe anemia, followed by leukopenia (abnormally low numbers of leukocytes), poor growth, poor feathering, perosis (as in niacin), lethargy and reduced feed intake (Singh, 2004). Other highly pigmented feathered birds show achromotrichia, and in turkey poults a spastic type of cervical paralysis in which the

neck is held rigid is seen (Combs, 1998). In humans, folate deficient status has been linked to malformation of the embryonic brain and/or spinal cord (spina bifida), collectively referred as neural tube defects (Rosenquist *et al.*, 1996).

Vitamin B₁₂: This bacterially derived vitamin functions in metabolism in two coenzyme forms: adenosylcobalamin and methyl cobalamin, both of which are related to methionine synthetase, leucine mutase and methyl malonyl-CoA mutase, whose roles in nutrition are widely accepted worldwide to stave off pernicious anemia (Stabler and Allen, 2004). A frank deficiency of this vitamin affects B₁₂-dependent methionine synthetase in folate metabolism, thus directly affecting synthesis of sulfur amino acid methionine from N⁵ methyl tetrahydrofolate. Additionally, due to impaired production of transferable methyl groups (from methionine) it reduces synthesis of melatonin, epinephrine and phosphatidylcholine, with a concomitant effect on DNA-histone methylation that selectively modulates gene expression throughout embryogenesis (Bolinder and Reichard, 1959). Deficiency signs in chicks and turkey poults include locomotor impairment, non-specific neurodiseases and peripheral neuropathies. It also causes embryonic death in chickens, with embryos exhibiting myopathies of leg muscles, hemorrhages, myocardial hypertrophy and perosis (Healton *et al.*, 1991; Combs, 1998).

Choline: This conditional vitamin (otherwise known as trimethyl-ethanol amine) is an important methyl donor for the biosynthesis of structural compounds phosphatidylcholine, ceramide and sphingomyelin, and neurotransmitter acetylcholine (Zeisel, 1993; 2000). It is supplemented to young birds because they do not have fully functional S-methyl transferase enzymes at an early age. A choline deficiency expresses as depressed growth, hepatic steatosis, impaired nerve function and defective neurotransmission resulting in limited body movement and consequently infrequent access to food and water (Combs, 1998).

Conclusions: Micronutrients perform specific biochemical functions in living organisms, some of which are pivotal to sustain life. Amongst varied functions performed; it is important to mention that 3 out of 13 vitamins have major antioxidant roles (Vitamin A, C and E), whose main task is to provide reducing equivalent to molecules that would otherwise be oxidized and consequently lose function. If sustained oxidative damage proceeds unchecked it can lead to cellular death and tissue dysfunctions. Apoptosis, or better known as cell death, has been implicated as a contributor in multi-factorial neurological diseases (Savitz and Rosenbaum, 1998). Vitamin D, B₆, biotin, pantothenic acid and folate are intimately involved with gene transcription and nucleic acid synthesis that are

absolutely necessary for proper functioning of cell division and embryogenesis. Finally, choline, B₁, B₂ and B₁₂ are in many ways involved in neurotransmitter synthesis, histone- methylation, brain development and morphogenesis. Cautious oversight of vitamins in poultry nutrition is warranted due to the role that these trace nutrients have on various metabolic processes with focal roles in growth, reproduction, development and maintenance of homeostasis in birds and other species.

References

- Bolinder, A. and P. Reichard, 1959. The biosynthesis of deoxyribonucleic acid by the chick embryo. III. Influence of vitamin B₁₂ deficiency. *J. Biol. Chem.*, 234: 2723-2728.
- Burgos, S. and S.A. Burgos, 2006. The role of chickens in vitamin discoveries. *Int. J. Poult. Sci.*, 5: 704-707.
- Carper, J., 2000. *Your Miracle Brain*. Harper Collins Publishers, Manhattan, NY.
- Combs, G.F. Jr., 1998. *The Vitamins - Fundamental aspects in nutrition and health*. 2nd Edition. Academic Press, San Diego, CA.
- Dakshinamurti, K., 2005. Biotin - a regulator of gene expression. *J. Nutr. Biochem.*, 16: 419-423.
- Eyles, D., J. Brown, A. Mackay-Sim, J. McGrath and F. Feron, 2003. Vitamin D3 and brain development. *Neurosci.*, 118: 641-653.
- Floyd, R.A., 1999. Antioxidants, Oxidative Stress, and Degenerative Neurological Disorders. *Proc. Soc. Exp. Biol. Med.*, 222: 236-245.
- Funk, C., 1911. On the chemical nature of the substance that cures polyneuritis in birds induced by a diet of unpolished rice. *J. Physiol.*, 43: 395-400.
- Guesry, P., 1998. The role of nutrition in brain development. *Prev. Med.*, 27: 189-194.
- Hass, R.H., 1988. Thiamin and the brain. *Ann. Rev. Nutr.* 8: 483-515.
- Haenggeli, C.A., E. Girardin and L. Paunier, 1991. Pyridoxine-dependent seizures, clinical and therapeutic aspects. *Eu. J. Pediatr.*, 150: 452-455.
- Healton, E.B., D.G. Savage, J.C. Brust, T.J. Garrett and J. Lindenbaum, 1991. Neurologic aspects of cobalamin deficiency. *Med. (Baltimore)*, 70: 229-245.
- Jylling, B., 1971. B₂ avitaminosis (curled-toe paralysis) in chickens. *Nord. Vet. Med.*, 23: 253-259.
- Johnson, R., E. Norstrom and K. Soderstrom, 2000. Increased expression of endogenous biotin, but not BDNF, in telencephalic song regions during zebra finch vocal learning. *Dev. Brain Res.*, 120: 113-123.
- Kretchmer, N., J.L. Beard and S. Carlson, 1996. The role of nutrition in development of normal cognition. *Am. J. Clin. Nutr.*, 63: 997S-1001S.
- MacDonald, P.N., D.R. Sherman, D.R. Dowd, S.C. Jefcoat, Jr. and R.K. DeLisle, 1995. The vitamin D receptor interacts with general transcription factor IIB. *J. Biol. Chem.*, 270: 4748-4752.
- Mey, J. and P. McCaffery, 2004. Retinoic acid signaling in the nervous system of adult vertebrates. *The Neuroscientist*, 10: 409-421.
- Morris, M.C., D.A. Evans, J.L. Bienias, P.A. Scherr, C.C. Tangney, L.E. Hebert, D.A. Bennett, R.S. Wilson and N. Aggarwal, 2004. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. *J. Neuro. Neurosur. Psych.*, 75: 1093-1099.
- Muller, D.P., J.K. Lloyd and O.H. Wolff, 1983. Vitamin E and neurological function. *Lancet*, 1: 225-228.
- Powers, H.J., 2003. Riboflavin (vitamin B₂) and health. *Am. J. Clin. Nutr.*, 77: 1352-1360.
- Romanoff, A.L. and J.C. Bauernfeind, 1942. Influence of riboflavin-deficiency in eggs on embryonic development (*Gallus domesticus*). *Anatom. Rec.*, 82: 11-23.
- Rosenquist, T.H., S.A. Ratashak and J. Selhub, 1996. Homocysteine induces congenital defects of the heart and neural tube: Effect of folic acid. *Proc. Natl. Acad. Sci. USA*, 93: 15227-15232.
- Rosenquist, T.H. and R.H. Finnell, 2001. Genes, folate and homocysteine in embryonic development. *Proc. Nutr. Soc.*, 60: 53-61.
- Rothman, K.J., L.L. Moore, M.R. Singer, T.S. Nguyen, S. Mannino and A. Milunsky, 1995. Teratogenicity of high vitamin A intake, 333: 1369-1373.
- Savitz, S. and D.M. Rosenbaum, 1998. Apoptosis in neurological diseases. *Neurosurgery*, 42: 555-574.
- Siman, C.M. and U.J. Eriksson, 1997. Vitamin C supplementation of the maternal diet reduces the rate of malformation in the offspring of diabetic rats. *Diabetologia*, 40: 1416-1424.
- Singh, M., 2004. Role of micronutrients for physical growth and mental development. *Ind. J. Pediatr.*, 71: 59-62.
- Smith, C.M. and W.O. Song, 1996. Comparative nutrition of pantothenic acid. *J. Nutr. Biochem.*, 7: 312-321.
- Sokol, R.J., 1988. Vitamin E deficiency and neurologic disease. *Ann. Rev. Nutr.*, 8: 351-373.
- Stabler, S.P. and R.H. Allen, 2004. Vitamin B₁₂ deficiency as a worldwide problem. *Ann. Rev. Nutr.*, 24: 299-326.
- Wang, H. and J. Prevsner, 1999. Detection of endogenous biotin in various tissues: novel function in hippocampus and implications for its use in avidin-biotin technology. *Cell Tissue Res.*, 296: 11-16.
- Watanabe, T., 1990. Micronutrients and congenital anomalies. *Congenit. Anom.*, 30: 79-92.
- Zeisel, S.H., 1993. Choline phospholipids: signal transduction and carcinogenesis. *FASEB J.*, 7: 551-557.
- Zeisel, S.H., 2000. Choline: an essential nutrient for humans. *Nutr.*, 16: 669S-671S.
- Zile, M.H., 1998. Vitamin A and Embryonic Development: An Overview. *J. Nutr.*, 128: 455S-458S.