Effect of Choline on performance quality of *non-ruminant*

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ABSTRACT

Choline is considered mandatory to the animal organism and is utilized both as a building unit and as essential component in regulation of certain metabolic processes. Choline is tentatively classified as one of the B-complex vitamins even though it doesn't entirely satisfy the strict definition of a vitamin. Choline, unlike B vitamins, can be synthesized in the liver, is required in the body in greater amounts, and apparently functions as a structural constituent rather than as a coenzyme. Although, existence of choline in essential body constituents was recognized long before the first vitamin was discovered. Regardless of classification, choline is an essential nutrient for all livestock and a required dietary supplement for some species (poultry, swine). Choline is likewise an essential nutrient for humans, and studies have investigated the benefits of choline treatment for certain diseases, such as cancer and Alzheimer's disease.

Keywords: Choline. Animal. B-complex Vitamins. Essential Nutrient.

INTRODUCTION

Vitamins are defined as group of complex organic compounds live in slight quantities in natural foods that are mandatory to normal metabolism and lack of which in the ration causes deficiency diseases. Vitamins consist of a blend group of chemical compounds and aren't related to each other as are proteins, carbohydrates, and fats. Their classification together depends not on chemical characteristics but on function. Vitamins are differentiated from the trace elements, although present in the ration in small amounts, whit their organic nature.

Vitamins are required in trace amounts in the ration for health, bounce, and reproduction. Classically, vitamins have been divided into 2 groups based on their solubility's in fat solvents or in water. Thus, fat-soluble vitamins include A, D, E, and K, while vitamins of the B-complex and C are classified water soluble. Fat-soluble vitamins are found in foodstuffs in related by lipids. The fat-soluble vitamins are absorbed along by dietary fats, apparently with mechanisms similar to those include in fat absorption. Conditions favorable to fat absorption, such as adequate bile flow and good micelle formation, favor absorption of the fat-soluble vitamins [24].

Water-soluble vitamins aren't related by fats, and alterations in fat absorption don't affect their absorption. 3 of the 4 fat-soluble vitamins are well stored in appreciable quantities in the animal body. Except for vitamin B_{12}, water-soluble vitamins aren't well stored, and excesses are rapidly excreted. A continual dietary supply of the water-soluble vitamins and vitamin K is needed to shun deficiencies. Fat-soluble vitamins are excreted primarily in the feces via the bile; therefore water-soluble vitamins are excreted mainly in the urine. Water-soluble vitamins are relatively nontoxic, but excesses of fat-soluble vitamin A and D can cause serious problems. Fat-soluble vitamins consist only of carbon, hydrogen, and oxygen, thus some of the water-soluble vitamins contain nitrogen, sulfur, or cobalt.

Metabolism

Choline is present in the ration mainly in the form of lecithin, by less than 10% as either the free base or sphingomyelin. Choline is associated from lecithin and sphingomyelin by digestive enzymes of the gastrointestinal tract, therefore 50% of ingested lecithin enters the thoracic duct intact [5].

Choline is associated from lecithin with hydrolysis in the intestinal lumen. Both pancreatic secretions and intestinal mucosal cells contain enzymes capable of hydrolyzing lecithin in the ration. Phospholipase A_2 is found in pancreatic juice and in the intestinal brush border. Within the gut mucosal cell, phospholipase A_1 cleaves the α-fatty acid, and phospholipase B cleaves both fatty acids. Quantitatively, digestion with pancreatic lipase is the most important process [31]. The net result is that most ingested lecithin is absorbed lysophosphatidylcholine. Within the cells of the gut wall, lysophosphatidylcholine can be deacylated to form glycerophosphocholine, or it can be acylated to reconstitute lecithin. Choline is absorbed from the jejunum and ileum mainly by an energy and sodium dependent carrier mechanism. In the guinea pig, choline was taken up with ileal cells about three times faster than by jejunal cells [13]. Preferential location of the transport system in ileal cells supports earlier findings in the rat and hamster [23]. These results are expected since choline is released from lecithin in the proximal and middle small intestine. Only one-third of ingested choline appears to be absorbed intact. The remaining two-thirds is metabolized with intestinal microorganisms to trimethylamine, that is excreted in the urine between 6 and 12 hours after consumption [9]. In contrast, when an equivalent amount of choline is consumed as lecithin, less urinary tri methylamine is excreted, by most of the metabolite appearing in urine 12-24 hours after consumption. Dietary choline is the principal factor governing excretion, by presence or absence of other sources of protein and of fat having relatively little effect. Absorbed choline is transported into the lymphatic circulation primarily in the form of lecithin bound to chylomicra, it's transported to the tissues predominantly as phospholipids associated by the plasma lipoproteins. Choline is present in all tissues as mandatory component of phospholipids in membranes of all types. All tissues accumulate choline, but uptake by liver, kidney, mammary gland, placenta, and brain are of especial importance. Uptake of choline with mammary cells enables this tissue to concentrate choline almost 70-fold versus maternal blood [6]. Most species can synthesize choline, as lecithin, with the sequential methylation of phosphatidyl ethanolamine by phosphatidyl ethanolamine- *N*-methyltransferase. This activity is actually due to enzymes which use *S*-adenosylmethionine (SAM) as the methyl donor. Choline synthesis activity is low in male rats and absent from chicks until about the thirteenth week of age. The activity is greatest in liver, but is also found in many other tissues.

Choline is associated in free form in the tissues with the actions of phospholipase C, that cleaves the circulating form (lecithin) to yield a diglyceride and phosphoryl choline. Free choline can be oxidized with the mitochondrial enzyme choline dehydrogenase to yield betaine aldehyde, that is then converted with the cytosolic enzyme betaine aldehyde dehydrogenase to betaine. Betaine is the actual source of methyl groups. Only a small fraction of choline is acetylated, but which quantity provides the important neurotransmitter acetylcholine. This step involves the reaction of choline by acetyl CoA and is catalyzed with choline acetyltrans-ferase localized in cholinergic nerve terminals, as well as in certain other non-nervous tissues.

Function

Choline functions in four broad categories in the animal body: 1. Choline is a metabolic essential for building and maintaining cell structure. As a phospholipid it's a structural part of lecithin (phosphatidyl-choline), certain plasmalogens, and the sphingomyelins. Choline is incorporated into phospholipid by being converted to phosphoryl choline, then to cytidine diphosphate choline, and finally reacting by phosphatidic acid to lecithin. The phospholipids and total fatty acids present are affected with nutritional state and the type of fatty acids present in the ration. Lecithin is a part of animal cell membranes and lipid transport moieties in cell plasma membranes. Phospholipids exist in the cell membrane bilayers, and it's thought that one of the primary roles of phospholipids is to regulate cell membrane porosity with changing the ionic characteristics of the membrane. Lecithin is an essential component of very-low-density lipoprotein, the blood transport molecule for hepatic triacylglycerol [16]. In the prevention of perosis, choline is required as a constituent of the phospholipids needed for normal maturation of the cartilage matrix of the bone.

2. Choline plays an essential role in fat metabolism in the liver. The first discovered function of dietary choline dealt by prevention of fatty liver in depancreatized dogs, and later in rats, chicks, and other species. Owing to the basic function of choline in membrane structure, the lack of choline is manifested in a variety of phospholipid-related functions, such as fatty liver and lesions of the kidney and impairment of lipoprotein metabolism. Choline prevents abnormal accumulation of fat with promoting its transport as lecithin or with increasing the utilization of fatty acids in the liver itself. Choline is therefore referred to as a lipotropic factor because of its function of acting on fat metabolism with hastening removal or decreasing deposition of fat in liver.

3. Choline is essential for the formation of acetylcholine, the agent released at the termination of the parasympathetic nerves [32]. It makes possible the transmission of nerve impulses from presynaptic to postsynaptic fibers of the sympathetic and parasympathetic nervous systems. For example, acetylcholine released with the stimulated vagus nerve causes a slowing of heartbeat, and oviduct contraction results from action of acetylcholine. Acetylcholine is the most common neurotransmitter in the nervous system. Apparently, brain tissue lacks the ability to synthesize sufficient choline [1] for neural function. However, apparently circulating choline is the major source of choline for acetylcholine synthesis.

4. A fourth function of choline is as a source of labile methyl groups for formation of methionine from homocystine and of creatine from guanidoacetic acid. However, practical significance of the choline-homocystine interrelationship is of no real importance to feeding animals since natural proteins contain very little of the metabolic intermediate homocystine [22]. Methyl groups function in the synthesis of purine and pyrimidine that are used in the production of DNA. Methionine is converted to *S*-adenosylmethionine in a reaction catalyzed with methionine adenosyl transferase. *S*-adenosylmethionine is the active methylating agent for many enzymatic methylations. A disturbance in folacin or methionine metabolism results in changes in choline metabolism and visa versa [31]. The involvement of folacin, vitamin B_{12}, and methionine in methyl group metabolism, and of methionine in de novo choline synthesis, may allow these substances to substitute in part for choline. Severe folacin deficiency has been shown to cause secondary liver choline deficiency in rats [14].

Deficiency
The most common signs of choline deficiency include poor growth, fatty liver, hemorrhagic tissue, and hypertension. In general, severity of clinical signs in animal species is influenced by other dietary factors, including methionine, vitamin B_{12}, folacin, and dietary fat. When feed intake—and consequently growth—are depressed with choline deficiency, severity of choline deficiency is then reduced.

Poultry
Growth retardation and perosis result from choline deficiency in young poultry. Perosis is the primary clinical sign of choline deficiency in chicks and turkey poults, whereas bob white quail develop enlarged hocks and bowed legs [20]. Perosis is characterized first by pinpoint hemorrhages about the hock joint, followed with an apparent flattening of the tibiometatarsal joint [24]. Progressively, the Achilles tendon slips from its condyles, therefore rendering the bird relatively immobile. Some studies indicated which in prevention of perosis, choline is required for the phospholipids needed for normal maturation of the cartilage matrix of bone. Adult chickens probably synthesize sufficient choline to meet requirements for egg production. Minimal dietary choline doesn't affect hatchability by either chickens or turkeys, but Japanese quail and their developing embryos readily express general signs of deficiency [17; 20]. Supplementary choline may be necessary for maintenance of egg size in quail [20]. Contrary to some reports, 500ppm supplemental choline to Leghorn hens increased egg weight while reducing specific gravity [28]. Although, the choline growth requirement for quail is apparently higher than which for chicks or poults. Choline requirement of growing chicks decreases by age, and it's generally not possible to produce a deficiency at an age over 8 weeks. It was observed which methylation of amino ethanol to methyl amino ethanol seems to be the rate limiting step in choline biosynthesis for young birds. High levels of dietary methionine or other methyl donors, thus, cannot completely spare the chick's requirement for dietary choline that is in contrast to the situation by growing mammals such as the rat. Apparently, choline requirement of laying hens can be influenced by choline level in the diet of the growing pullet [24]. Hens that received choline-free diets after 8 weeks of age were able to synthesize all the choline required for good egg production. Those that received choline supplements in the growing ration required supplemental choline in the laying diet for maximum egg production. The deficiency signs noted in these hens were a reduction in egg production and an increase in fat content of liver. Even by choline deficiency, however, choline content of the egg was not affected by low dietary choline. Despite lack of evidence which laying chickens require a dietary source of choline for maximum egg production, addition of choline to practical ration markedly reduces the amount of fat in the liver [20]. However, a number of reports by chicks and turkey poults didn't find fatty livers in chicks deficient in choline [22]. A choline response in laying chickens is likely to occur only if inadequate daily sulfur amino acid is provided. Addition of 0.1% of supplemental methionine resulted in no response in laying hens to supplemental choline [8]. It appears which benefits from supplemental choline in layer diets occur mainly when supplemental methionine is just adequate to meet methionine requirements. Miles and Harms [18] demonstrated which the addition of 0.11% choline plus 0.1% sulfate could essentially spare all supplemental methionine in broiler ration. However, in turkey poult ration [12], responses to sulfate and choline addition weren't equivalent to the addition of supplemental methionine. Pesti et al. [21], using young chicks, found which supplementation by methyl donors from either 0.23% choline or 0.23% betaine was equivalent to supplementation by 0.23% methionine in 21day chick experiments, using basal rations containing 0.31% methionine and 0.43% cystine. Spires et al. [27] found that supplemental choline could replace up to two-thirds of

the supplemental methionine required in broiler rations from0-47 days in rations containing 0.30% methionine and 0.43% cysteine in the starter phase, and 0.25 and 0.42% methionine and cystine, respectively, in the finisher phase.

Horses
No studies of choline requirements or deficiencies have been under-taken in the horse.

Humans
In humans, as in experimental animals, dietary choline can arrest cirrhosis of the liver and reverse the fatty infiltration. However, these conclusions aren't useful and some reports show no benefit of choline in the treatment of cirrhosis [15]. It remains uncertain whether alcoholic cirrhosis in humans and animals is caused by one or more nutritional deficiencies, but accepted dietary regimens for treatment involve a high-calorie, high-protein, low-fat ration supplemented by choline and perhaps other lipotropic factors, such as methionine and inositol. Choline is an essential nutrient for humans when excess methionine and folacin aren't available in the ration. Healthy male subjects fed a choline-deficient ration for 3 weeks had depleted stores of choline in tissues and developed signs of incipient liver dysfunction [29]. People receiving total parenteral nutrition have developed fatty infiltration of the liver and hepatocellular damage. One study in humans fed parenterally showed which supplemental choline could reverse fatty livers [3]. The relationship of choline to atherosclerosis has been under study for a number of years. Choline-deficient rations can result in arterial damage, by a high percentage of young rats maintained on low-choline rations developing pathological changes in the most arterial trunks and in the coronary arteries. These changes are similar to those observed in early stages of atherosclerosis of the aorta and large arteries in humans. In a 3-year study of coronary thrombosis patients, there was a significant reduction in death rates and lowered blood cholesterol in athero- matous patients administered choline [11]. During acute myocardial is chemia, plasmalogen (a choline phospholipid found in the cell membranes of heart muscle) was broken down [4]. Further observations have included increases in high-density lipoprotein and decreases in low-density lipoprotein following lecithin treatment in hypercholesterolemic humans [7]. Deficiency of choline enhances the initiating potency of several carcinogens [19] and exerts a strong promoting effect by liver carcinogens. Choline deficiency alone can lead directly to liver tumor formation [19]. A number of possible mechanisms have been proposed to account for the development of cancer as a result of choline deficiency, including increased cell death followed with increased proliferation and regeneration, deceased DNA methylation and repair, increased lipid peroxidation and free radical damage, and decreased methylation and detoxification of carcinogens [4]. Reports indicate which lecithin or choline supplements may be benefit in preventing age-related memory deficits and certain neurological diseases [15]. Evidence suggests which dietary choline and lecithin produce clinical improvement with supplying precursors for formation of the neurotransmitter acetylcholine. Notable but sometimes limited success has been achieved by choline or lecithin therapy for tardive dyskinesia syndrome, Huntington's disease, and Friedreich's ataxia disease. Studies of both Alzheimer's disease and senile dementia patients given choline or lecithin have shown mixed results [30].

Smith et al. [25], in a controlled experiment, noted some improvement in 40% of the cases by advanced Alzheimer's syndrome. In general, studies have found which patients by less severe symptoms show greater response to choline supplementation. Therefore, the use of choline in severe cases of Alzheimer's disease does not appear to be very helpful, but may be of value in early stages of memory-loss disorders [11].

Toxicity
Experimental animal toxicity data on clinical symptoms of choline over-dosage include salivation, trembling, jerking, cyanosis, convulsions, and respiratory paralysis. Estimates of the oral LD50 of choline chloride in rats varied from 3.4-6.7g/kg [5]. Bell [2] reported that when rats were exposed perinatally to 22mg of soy lecithin preparation daily, sensorimotor development and brain cell maturation were altered. Choline levels somewhat above the requirement (868-2,000ppm) were shown to reduce rate and efficiency of gain in swine [26]. Derilo and Balnave [10] reported reduced gain and efficiency in young broiler chicks fed a level of choline only slightly in excess of the requirement. Studies by chickens suggest which dietary choline double the requirement is safe, with swine having a higher tolerance for choline [20]. Work with Southern et al. [26] showed which excess choline, up to 2,000mg/kg above the recommended level, had no adverse effect on swine performance. In humans, high intakes of lecithin or choline produced acute gastrointestinal distress, sweating, salivation, and anorexia [30]. However, therapeutic doses of choline chloride and of choline dihydrogen citrate administered in amounts ranging from 3-12 g/day have been used in the treatment of alcoholic cirrhosis for up to 4months by no toxic effects reported. In treatment of tardive, up to 16g/day of choline has been used; in other cases, lecithin at doses greater than 100g/day for more than 4months has been used by no evidence of ill effects [15].

<div align="center">REFERENCES</div>

[1] Ansell, G.B., and Spanner, S. **1971**. *Biochem J.* 122, 741.

[2] Bell, J.M. **1985**. *Devel. Psychobiol.* 18, 383.

[3] Buchman, A.L., Dubin, M., Jenden, D., and Moukarzel, A. **1992**. *Gastroenterology* 102, 1363.

[4] Canty, D.J., and Zeisel, S.H. **1994**. *Nutr. Rev.* 52, 327.

[5] Chan, M.M. **1991**. In Handbook of Vitamins (L.J. Machlin, ed.), 2nd Ed., p. 537. Marcel Dekker, New York.

[6] Chao, C.K., Pomfret, E.A., and Zeisel, S.H. **1988**. *Biochem. J.* 254, 33.

[7] Childs, M.T., Bowlin, J.A., Ogilvie, J.T., Hazzard, W.R., and Albers, J.J. **1981**. *Atherosclerosis* 38, 217.

[8] Crawford, J.S., Griffith, M., Teekell, R.A., and Watts, A.B. **1969**. *Poult. Sci.* 38, 620.

[9] De La Huerga, J., and Popper, H. **1952**. *J. Clin. Invest.* 31, 598.

[10] Derilo, Y.L., and Balnave, D. **1980**. *Poult. Sci.* 21, 479.

[11] DuCoa L.P. **1994**. In Choline Functions and Requirements, p. 91. DuPont/ConAgra Co., Higland, Illinois.

[12] Harms, R.H., and Miles, R.D. **1984**. *Poult. Sci.* 63, 1464.

[13] Hegazy, E., and Schwenk, M. **1984**. *J. Nutr.* 114, 2217.

[14] Kim, Y., Miller, J.W., Da Costa, K., Nadeau, M. Smith, D. Selhub, J., Zeisel, S.H., and Mason, J.B. **1994**. *J. Nutr.* 124, 2197.

[15] Kuksis, A., and Mookerjea, S. **1984**. In Present Knowledge in Nutrition (R.E. Olson, H.P. Broquist, C.O. Chichester, W.J. Darby, A.C. Kolbye, and R.M. Stalvey, eds.), p. 383. Nutrition Foundation, Washington, D.C.

[16] Lombardi, B., Ugazio, G., and Raick, A. **1966**. *Am. J. Physiol.* 210, 31.

[17] Latshaw, J.D., and Jensen, L.S. **1972**. *J. Nutr* 102, 749.

[18] Miles, R.D., and Harms, R.H. **1983**. In Proc. 1983 Florida Nutrition Conference, p.75. Gainesville, Florida.

[19] Mikol, Y.G., Hoover, K.L., Creasia, D., and Poirier, L.A. **1983**. *Carcinogenesis*. 4, 1619. Nutrient Requirements of Poultry. 1994. 9th Ed.

[20] NRC. **1987**. Vitamin Tolerance of Animals. National Academy of Sciences-National Research Council, Washington, D.C.

[21] Pesti, G.M., Harper, A.E., and Sunde, M.L. **1980**. *Poult. Sci.* 59, 1073.

[22] Ruiz, N., Miles, R.D., and Harms, R.H. **1983**. *WPSA J.* 39, 185.

[23] Sanford, P.A., and Smyth, D.H. **1971**. *J. Physiol.* (Lond.) 215, 769.

[24] Scott, M.L., Nesheim, M.C., and Young, R.J. **1982**. Nutrition of the Chicken, p. 119. Scott, Ithaca, New York.

[25] Smith, C.M., Swase, M., Exton-Smith, A.N., Phillips, M.J., Overstall, P.W., Piper, M.E., and Bailey, M.R. **1978**. Lancet. 2, 318.

[26] Southern, L.L., Brown, D.R., Werner, D.D., and Fox, M.C. **1986**. *J. Anim. Sci.* 62, 992.

[27] Spires, H.R., Botts, R.L., and King, B.D. **1982**. Syntex Research Report, Series A, No. 1.

[28] Tapia Romero, E., Rojas, R.E., Arias, L.E., and Avila, G.E. **1985**. In Resumenes ALPA 85 (C.F.Chicco, ed.), p. 49 (Abstr.). Acapulco, Mexico.

[29] Zeisel, S.H., Costa, K.A., Franklin, P.D., Alexander, E.A., Lamont, J.T., Sheard, N.F., Beiser, A., and Costa, K.A. **1991**. *FASEB J*. 5, 2093.

[30] Wood, J.L., and Allison, R.G. **1982**. *Fed. Proc*. 41, 3015.

[31] Zeisel, S.H. **1990**. *J. Nutr. Biochem*. 1, 332.

[32] Wauben, P.M., and Wainwright, P.E. **1999**. *Nutr. Rev*. 57, 35.