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REVIEW ARTICLE

Effect of Vitamin B_9 on Performance of Animal: A Review

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ABSTRACT
Folacin and folate are generic terms used to describe folic acid and relation compounds which exhibit the biological activity of folic acid. The terms folacin, folate, and folic acid will be used interchangeably. For animals, folacin needs are met principally with dietary sources and to some extent with intestinal bacterial synthesis. Different species vary in ability to utilize microbial intestinal synthesis as a source of folacin. Poultry need supplemental folacin under certain conditions. Folacin supplementation is most important when poultry receive diets containing sulfa drugs and grains contaminated by toxin producing molds. To maximize reproductive efficiency, gestating non-ruminant often receive supplemental folacin.
Key Words: *Folacin, Folate, Animals, Non-ruminant.*

INTRODUCTION

Vitamins are defined as group of organic compounds live in few amounts in natural foodstuffs that are essential to normal mal metabolism and lack of which in the diet causes deficiency diseases. Vitamins consist of a blend group of chemical compounds and aren't associated 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, also present in the diet in small quantities, by their organic nature. Vitamins are required in trace amounts in the diet for health, bounce, and reproduction. Classically, vitamins have been divided into two groups based on their solubility's in fat solvents or in water. Fat-soluble vitamins are found in foodstuffs in association with lipids. The fat-soluble vitamins are absorbed along with dietary fats, apparently by mechanisms similar to those include in fat absorption. Conditions favorable to fat absorption, such as adequate bile flow and good micelle formation, also favor absorption of fat-soluble vitamin (Scott *et al* 1982).
Water-soluble vitamins are not associated with fats, and alterations in fat absorption do not affect their absorption. 3 of the 4 fat-soluble vitamins are well stored in appreciable amounts 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, whereas water-soluble vitamins are excreted mainly in the urine. Also, excesses of fat-soluble vitamin A and D can cause serious problems. Fat-soluble vitamins consist only of carbon, hydrogen, and oxygen, whereas some of the water-soluble vitamins also contain nitrogen, sulfur, or cobalt.

CHEMICAL STRUCTURE

Folacin is the group name used distinguishes naturally occurring compounds of this class; the pure substance is designated pteroyl- mono glutamic acid. The chemical structure of folacin is shown in Fig1. It is chemical structure contains three distinct parts. Reading of right to left, this compound consists of glutamic acid, ρ-aminobenzoic acid (PABA), and a pteridine nucleus, the last two making up pteroic acid. Therefore, the name pteroylglutamic acid was suggested. The PABA portion of the vitamin structure was once thought to be a vitamin. If the folacin requirement is met, there is no need to add PABA to the diet.
Many of the folacin in natural feedstuffs is conjugated by a varying numerous of extra glutamic acid molecules. Folacin as pteroyloligo-γ- L-glutamates is generally of one to nine glutamates long, by *n* indicating the number of glutamyl residues. Poly glutamate forms—usually from 3-7 glutamyl residues

linked by peptide bonds—of folacin are the natural coenzymes that are most abundant in every tissue examined (Wagner, 1984).

Synthetic folacin, however, is in the mono glutamate form. It has been concluded which there are more biologically active forms of folacin than any other known vitamin. Naturally occurring pteroyl poly glutamates constitute a large family of closely relation compounds arising of modifications from the three parts of the parent compound pteroylglutamic acid. Changes in the state of reduction from the pteridine moiety, addition of various kinds of one-carbon substituents, and addition of glutamic acid residues lead to a wide array from compounds. Baugh and Krumdieck (Baugh, and Krumdieck, 1971), on the basis of the three known states of reduction of the pyrazine ring, the six different one-carbon substituents which may occur at N-5 and/or N-10, and assuming which the poly glutamyl chain would have no more than seven glutamyl residues, calculated which the theoretical number of folacins approached 150.

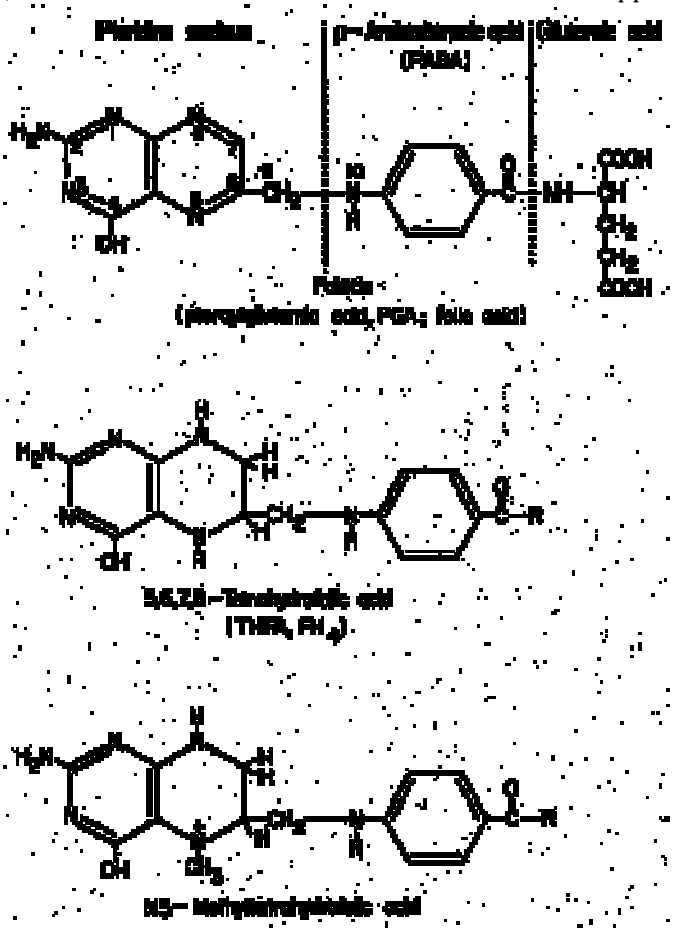

Fig1. Structures of folacin compounds (R is one or more glutamic acid molecules.)

However, this figure includes compounds which have never been identified in natural materials. Since it's clear now which the poly glutamyl chain reaches at 8 or 9 residues in animal tissues, the number of folacin compounds that might be expected to occur in animal tissues still approaches 100 compounds. The active forms of folacin contain a formyl group or a methyl group attached to the 5 or 10 nitrogen of the compound, or a methylene group between nitrogen 5 and 10. Tetra hydrofolic acid is the principal coenzyme form, that the main storage form is 5-methylte- trahydrofolic acid (Fig1).

FUNCTION

Folacin, form 5,6,7,8-tetrahydrofolictat, is indispensable in transfer of single-carbon in different reactions, such as those occurring in the biosynthesis from lipids, proteins, nucleic acid derivatives, hormones, and neurotransmitters—a role analogous to which of pantothenic acid in the transfer of two-carbon units. The one-carbon units can be formyl, formimino, methylene, or methyl groups. The major *In Vivo* pathway providing methyl groups involves transfer of a one-carbon unit of serine to tetrahydrofolate to form 5,10-methylenetetrahydrofolate, that is subsequently reduced to 5-methyltetrahydrofolate. Methylte-trahydrofolate then supplies methyl groups to remethylate homocysteine in the activated methyl cycle, providing methionine for synthesis of the important methyl donor agent *S*-adenosylmethionine (Jacob, *et*

al 1994; Krumdieck, 1990).

These one-carbon are generated primarily during amino acid metabolism and used in the metabolic inter conversions of amino acid and in biosynthesis of purine and pyrimidine components of nucleic which are needed cell division. The important physiological function of tetrahydrofolate (THF) consists of binding the C_1 units to the vitamin molecule and thus transforming those to active formicate or active formaldehyde, that these are inter convertible with reduction or oxidation and transferable to appropriate acceptors. Ability of the vitamin as a coenzyme is governed by three factors: (1) the nature of the carbon-containing substituent attached at either the N-5 or the N-10 position, or bridging them; (2) the state of oxidation or reduction of the pyrazine ring; and (3) the number of glutamat attached in gamma linkage to the glutamate of pteroylglutamic acid. Certain polyglutamates may serve as cofactors for one enzyme while inhibiting another (White, *et al* 1976).

Folacin poly glutamates work at least as well as or better than the corresponding mono glutamate forms in every enzyme system examined (Wagner, 1995).

It's now accepted that the pteroylpolyglutamates are the acceptors and donors of one-carbon units in amino acid and nucleotide metabolism, therefore the mono glutamate is merely a transport form. Glutamate chain length of folacin poly glutamate may affect metabolism of one-carbon units (Foo and Shane, 1982].

In hamster ovary cells by normal extracellular methionine, poly glutamate chain lengths were longer, by high levels of octa glutamates, nona glutamates, and even decaglutamates occurring, while by suboptimal levels of methionine, shorter chain lengths were found. This observed phenomenon of a profound effect of extracellular methionine concentration on glutamate chain elongation may be interpreted to mean which there is a regulatory action of poly glutamate chain length on one-carbon metabolism.

Specific reactions involving single-carbon shift with folacin compounds are (1) purine and pyrimidine synthesis, (2) inter conversion of serine and glycine, (3) glycine-α-carbon as a source of C_1 for many syntheses, (4) histidine degradation, and (5) synthesis of methyl groups for such as compounds as methionine, choline, and thymine.

Purine bases as well as thymine are constituents of nucleic acids, and by folacin deficiency, there is a reduction in the biosynthesis of nucleic essential for cell formation and function. Hence, deficiency of the vitamin leads to impaired cell division and alterations of protein synthesis; these effects are most noticeable in rapidly growing tissues. In absence of adequate nucleoproteins, normal maturation of primordial red blood cells doesn't take place, and hematopoiesis is inhibited at the megaloblast stage. As a result of this megaloblastic arrest of normal red blood cell maturation in bone marrow, a typical peripheral blood pictures a result which is characterized with macrocytic anemia. White blood cell formation is also affected, resulting in thrombopenia, leukopenia, and old, multilobed neutrophils.

In folacin deficiency, formimino glutamat, formed as an intermediate in degradation of histidine, can no longer be transformed completely into glutamate and formimino tetrahydrofolic acid, and is therefore excreted in urine. This excretion is suitable as biochemical criterion for diagnosis of folacin deficiency, appearing at an early stage of deficiency.

Vitamin B_{12} is also closely associated with the progress of the folacin-dependent reactions of intermediary metabolism (Savage, and Lindenbaum, 1995).

Vitamin B_{12} has two main effects in facilitating folacin: (1) Vitamin B_{12} regulates the proportion of methyl to nonmethyl tetrahydrofolates according to the methyl trap theory, and (2) vitamin B_{12} is mandatory for shift of methyl-THF across cell membrane and promotes folacin retention with tissues. According to the methyl trap concept (Herbert, and Zalusky, 1962), vitamin B_{12} deficiency decreases the formation of methionine of homocysteine and methyl-THF with the B_{12}-dependent methionine synthetase. This results in enhance in methyl-THF and a decrease in THF that is the active coenzyme of which functions in the degradation of FIGLU and formate.

Vitamin B_{12} is mandatory in the reduction of one-carbon compounds of the oxidation stage of formate and formaldehyde, and in this way, it participates, by folacin, in biosynthesis of labile methyl groups. Folacin is also essentially involved in all these reactions labile methyl groups. The metabolism from labile methyl groups plays an important role for the body in the biosynthesis of methionine from homo cysteine and of choline of ethanolamine. Folacin has a sparing effect on requirements of choline. Folacin is needed to maintain the immune system; the blasto genic response of T lymphocytes to certain mitogens is decreased in folacin-deficient humans and animals, and the thymus is preferentially altered (Dhur, *et al* 1991). The effects folacin deficiency upon humoral immunity have been more thoroughly investigated in animals than in humans, and the antibody responses to several antigens have been shown to reduce. As de novo synthesis of methyl groups requires the participation from folacin coenzymes, the effect of folacin deficiency on pancreatic exocrine function was examined in rats (Balaghi, and Wagner, 1992 and Balaghi, *et al* 1993).

Pancreatic secretion was significantly decreased in the deficient group compared by the pair-fed control after 5 weeks. The results reported which severe folacin deficiency impairs pancreatic exocrine function. The ratio of *S*-adenosylmethionine to *S*-adeno-sylhomocysteine was rapidly reduced in the deficient pancreas. The pancreas of deficient rats had more immature secretory granules, and the ducts were devoid of secreted material.

DEFICIENCY

Folacin deficiency has been produced experimentally in many animal species, with macrocytic anemia and leukopenia being consistent findings. Tissues which have a rapid rate of cell growth or tissue regeneration, such as epithelial lining from the gastrointestinal tract, the epidermis, and bone marrow, are principally affected (Hoff ,1978).

For some animals, such the chick, guinea pig, the presence of adequate amounts of folacin in the diet is essential, and deficiency signs can readily be induced with feeding diets deficient in the vitamin. In other animals, such as the rat, folacin produced with the intestinal micro flora is usually adequate to meet requirements. Consequently, deficiency signs don't develop unless an intestinal antiseptic is included in the diets to depress bacterial growth.

Ruminants

Folacin synthesis occurs in the rumen. Therefore, young animals that don't have a fully developed rumen would be expected to be folacin deficient. Draper and Johnson (1952) suggested folacin deficiency in lambs fed synthetic diets. The disease was characterized with leukopenia followed diarrhea, pneumonia, and death. Folacin therapy promoted regeneration of by blood cells, and 0.39mg/L of milk in control animal diets prevented the deficiency. There was no indication of folacin deficiency in calves fed synthetic milk containing 52mg of folacin per kilogram of liquid feed fed at 10% of live weight (Lévesque, *et al* 1993; Wiese, *et al* 1947).

Supplemental folacin increased serum and red blood cell folacin concentrations and decreased the rearing period to reach 180kg without increasing feed intake.

Girard et al. (1994) studied whether ruminal folacin is affected with dietary folacin and if this response is modified by the diets. Concentrations of folacin in rumen contents were enhanced with supplemental folacin and by ingestion of concentrate compared with hay-based diets.

The efficiency of folacin and synthesis with rumen micro flora and whether this is adequate at weaning and later isn't yet established. For example, in an experiment in which supplemental folacin was administered to dairy heifers intramuscularly weekly during the first4 months of life, average daily gain increased by 8% during the 5weeks following weaning (Dumoulin, *et al*, 1991).

This supplementation also increased serum and hepatic folates, as well as blood hemoglobin and packed cell volume. Girard et al (1989b) observed concentration from serum folacin of calves at 2weeks of age is half that of 4-month-old heifers.

Girard et al (1989) fed supplemental folacin to both pre-ruminant and ruminant calves in an attempt to maintain high serum folacin concentrations. Serum folacin was increased in both groups receiving dietary folacin, but the amount needed to reach similar concentrations was higher in ruminant than in pre ruminant calves. These observations seem to confirm which during the weeks before and after weaning, the supply of folates with the diet and the rumen microorganisms might not be optimum for dairy heifers and possibly other pre ruminants and ruminant livestock.

Girard et al (1989b) evaluated serum folates in gestating and lactating dairy cows and found that serum folacin decreased by 40% of 2 months postpartum to parturition. The synthesis of folacin with rumen microorganisms wasn't sufficient to prevent fluctuations of serum folacin during gestation and lactation in dairy cows. Serum folacin can be increased by an intramuscular injection of folacin at the end of gestation, but in cows during early lactation, this didn't markedly affect serum and milk folacin concentrations.

Girard et al (1992) injected folacin (160mg) weekly to dairy cows 45days after mating to 6weeks after parturition. The supply of folates by the diet and the synthesis by ruminal micro flora were found to be sufficient to prevent folacin deficiency in dairy cows and to maintain normal gestation and lactation, but not to achieve maximal production from milk and protein in multiparous, but not primiparous, dairy cows during gestation and lactation.

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