Effects of vitamin K on ruminant animal: A Review

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Abstract: Vitamin K is a group of structurally similar, fat soluble vitamins that are needed for the posttranslational modification of certain proteins, mostly required for blood coagulation but also involved in metabolic pathways in bone and other tissue. They are 2-methyl-1, 4-naphthoquinone derivatives. This group of vitamins includes two natural vitamers: vitamin K1 and vitamin K2. Vitamin K1 is also known as vitamin Kj, phylloquinone or phytomenadione (also called phytonadione). Plants synthesize vitamin K1 while bacteria can produce a range of vitamin K2 forms, including the conversion of K1 to K2 by bacteria in the small intestines. No known toxicity exists for vitamins K1 and K2. Three synthetic types of vitamin K are known: vitamins K3, K4, and K5. Although the natural K1 and K2 forms are nontoxic, the synthetic form K3 (menadione) has shown toxicity. Vitamin K was identified in 1929 by Danish scientist Henrik Dam when he investigated the role of cholesterol by feeding chickens a cholesterol-depleted diet.[2] After several weeks, the animals developed hemorrhages and started bleeding. These defects could not be restored by adding purified cholesterol to the diet. It appeared that—together with the cholesterol—a second compound had been extracted from the food, and this compound was called the coagulation vitamin. The new vitamin received the letter K because the initial discoveries were reported in a German journal, in which it was designated as Koagulationsvitamin.

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1. Introduction

Vitamin K was the last fat-soluble vitamin to be discovered. For many years after its discovery, vitamin K appeared to be limited in its function to only the normal blood-clotting mechanism. However, vita-min K-dependent proteins have been identified that suggest roles for the vitamin in addition to that of blood coagulation. Because of the blood-clotting function, vitamin K was previously referred to as the "coagula-tion vitamin," "antihemorrhagic vitamin," and "prothrombin factor."

Vitamin K is indispensable for maintaining the function of the blood coagulation system in humans and all investigated animals. Even though vitamin K is synthesized by intestinal microorganisms, deficiency signs have been observed under field conditions. Poultry, and to a lesser de-gree pigs, are susceptible to vitamin K deficiency. In ruminants a defi-ciency can be caused by ingestion of spoiled sweet clover hay, which is a natural source of dicumarol (a vitamin K antagonist). In human nutri-tion, vitamin K is most required in infants because of insufficient in-testinal synthesis and in adults in whom fat absorption is impaired.

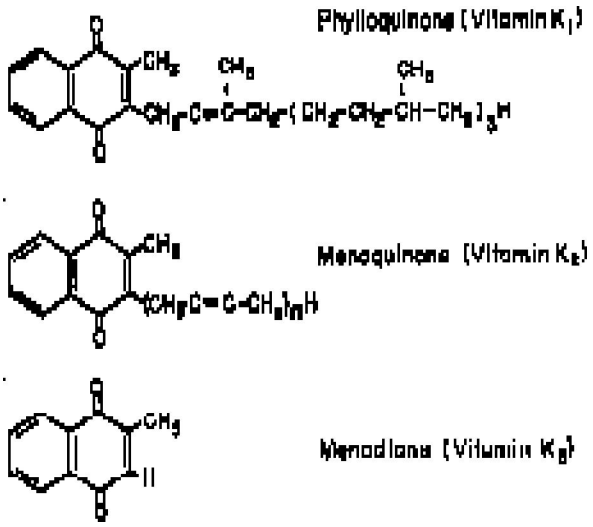
2. CHEMICAL STRUCTURE

The general term vitamin K is now used to describe not a single chemical entity but a group of quinone compounds that have character-istic antihemorrhagic effects Vitamin K is a generic term for a homolo-gous group of fat-soluble vitamins consisting of a 2-methyl-1,4-naph-thoquinone, with the various isomers differing in the nature and length of the side chain (Fig1).

When synthesized in the laboratory, it yields a mixture of cis- and trans-isomers; the cis-form has little, if any, vita-min K activity. Vitamin K extracted from plant material was named phylloquinone or vitamin K1. Phylloquinone has a phytyl side chain composed of four isoprene units, the first of which contains a double bond. Vitamin K-active compounds from material that had undergone bac-terial fermentation were named menaquinones or vitamin K2.

The sim-plest form of vitamin K is the synthetic menadione (K3), which is com- posed of the active nucleus (2-methyl-1,4naphthoquinone) and has no side chain. The menaquinone family of K2 homologs is a large series of vitamins containing unsaturated side chains that differ in number of iso-prene units. Numerous natural analogs have been

isolated, almost all of which are variations of the side chain at position 3. Some of these chains are quite long, with as many as 65 carbon atoms in some bacterial vita-min K forms,but none is specifically required for activity. Menaquinone-4 is synthesized in liver from ingested menadione or changed to a biologically active menaquinone by intestinal microorganisms.



McDowell (2001). Fig. 1: Chemical structures of the vitamin K compounds

Vitamin K is golden yellow viscous oil. Natural sources of vitamin K are fat soluble, stable to heat, and labile to oxidation, alkali, strong acids, light, and irradiation. Vitamin K1 is slowly degraded by atmos pheric oxygen but fairly rapidly destroyed by light. In contrast to nat-ural sources of vitamin K, some of the synthetic products, such as salts of menadione, are water soluble. A number of vitamin K antagonists exist that increase the need for this vitamin. Vitamin K deficiency is brought about by ingestion of dicumarol, an antagonist of vitamin K, or by feeding sulfon-amides (in monogastric species) at levels sufficient to inhibit intestinal synthesis of vitamin K. Mycotoxins, toxic substances produced by molds, are also antagonists causing vitamin K deficiency. A hemorrhagic disease of cattle that was traced to consumption of moldy sweet clover hay was described in the 1920s.The destructive agent was found to be dicumarol, a substance produced from natural coumarins. Dicumarols are produced by molds; particularly those that attack sweet clover, thus giving rise to the term sweet clover disease (see Deficiency).

During the process of spoiling, harmless natural coumarins in sweet clover are con-verted to dicumarol (bis-hydroxycoumarin), and when toxic hay or silage is consumed by animals, hypoprothrombinemia results, presum-ably because dicumarol combines with the proenzyme to prevent for-mation of the active enzyme required for the synthesis of prothrombin. It probably also interferes with synthesis of factor VII and other coagu- lation factors.Dicumarol serves as an anticoagulant in medicine to slow blood co-agulation in people with cardiovascular disease to avoid intravascular blood clots, just as vitamin K under other conditions increases coagula-tion time. Thus additional vitamin K will overcome this action by dicumarol. Goplen and Bell [13] showed that in cattle, vitamin K1 is much more potent than vitamin K3 as an antidote to dicumarol. The most successful dicumarol for long-term lowering of the vitamin K de-pendent clotting factors is warfarin, which is widely used as a rodenticide. Concern has been expressed because of the identification of anticoagulant-resistant rat populations. Spread of this resistance led to synthesis of new and more effective coumarin derivatives [16, 24 and 31].

Because of the use of dicumarol derivatives as clinical anticoagu-lants, investigation of the mechanism of action of dicumarol has been of interest to vitamin K researchers [31 and 24]. Investigations have cen-tered on interconversion of vitamin K and its 2, 3-epoxide as the site of coumarin action. One hypothesis is that metabolic effects of these com-pounds are the consequence of their inhibition of the microsomal epo-ide reductase [2 and 24].

The epoxide apparently acts as a competitive inhibitor of vitamin K at its site of action, and a coumarin such as war-farin is an inhibitor of vitamin K action only to the extent that it in-creases the cellular ratio of oxide to the vitamin.

4. METABOLISM

Absorption and Transfer

Like all fat-soluble vitamins, vitamin K is absorbed in association with dietary fats and requires the presence of bile salts and pancreatic juice for adequate uptake from the alimentary canal. Absorption of vit-amin K depends on its incorporation into mixed micelles, and optimal formation of these micellar structures requires the presence of both bile and pancreatic juice. Thus, any malfunction of the fat-absorption mech- anism, for example, biliary obstruction, will reduce availability of vita-min K. Unlike phylloquinone and the menaquinones, menadione bisul-fites and phosphates are relatively water soluble and therefore are absorbed satisfactorily from low-fat diets. Male animals are more sus-ceptible to dietary vitamin K deprivation than females, apparently as a result of stimulation of phylloquinone absorption by

estrogens. The ad- ministration of estrogens increases absorption in both male and female animals [20 and 24].

The lymphatic system is the major route of transport of absorbed phylloquinone from the intestine in mammals but by portal circulation in birds, fishes, and reptiles. Shearer et al. [29 and 24] demonstrated the association of phylloquinone with serum lipoproteins, but little is known of the existence of specific carrier proteins. The ab-sorption of various forms of vitamin K has been studied and found to differ significantly. Ingested phylloquinone is absorbed by an energy-de-pendent process from the proximal portion of the small intestine (13 and 24). In contrast to the active transport of phylloquinone, menaquinone is absorbed from the small intestine by a passive non–car- rier-mediated process. Menadione can be absorbed from both the small intestine and the colon by a passive process and can be alkylated to a bi-ologically active form (14 and 24).

Efficiency of vitamin K absorption has been measured at 10 to 70%, depending on the form in which the vitamin is administered. Some re-ports have indicated that menadione is completely absorbed, but phyl-loquinone only at a rate of 50%. Rats were found to excrete about 60% of ingested phylloquinone in the feces within 24 hours of ingestion but only 11% of ingested menadione [14, 15 and 24]. However, 38% of ingested menadione but only a small amount of phylloquinone was excreted via the kidneys in the same period. The conclusion was that although menadione is well ab-sorbed, it is poorly retained, while just the opposite is true for phyllo-quinone. Poor retention of menadione can be explained by the need to add, in theliver, a difarnesyl chain and thus transform it into menaquinone (vitamin K2) with a 20-carbon chain (MK-4). Apparently there are quantitative limitations in this biosynthetic step. The mena-dione not converted is rapidly detoxified and excreted. The turnover of liver phylloquinone was found to be 2 to 4 times more rapid than menaquinone initially, but no difference was found between the sources at 48hours [38 and 24]. However, phylloquinone was much more effective than menaquinone in maintaining normal vitamin K sta-tus in rats at low dietary concentrations(0.2 μmol/kg diet),whereas at high dietary concentrations(5.6 μmol/kg diet) they were equally effec-tive.

Konishi et al. [21 and 24] administered radioactive menadione, phyllo-quinone, or menaquinone-4, to rats and found that radioactive mena-dione was spread over the whole body much faster than the other two compounds, but the amount retained in the tissues was low. Martius and Alvino [23 and 24] utilized radioactive menadione to establish that it could be converted to a more lipophilic compound that, on the basis of their limited characterization, appeared to be menaquinone-4. Therefore, they concluded that the vitamin K form of animal tissues was menaquinone-4.They found that when either a menaquinone or a phyl-loquinone was given to animals, the side chain was removed, probably by the microorganisms in the gut.

On the contrary, Griminger and Brubacher [15 and 24] showed that a major portion of the phylloquinone they fed to chicks was absorbed and deposited in the liver intact, and that as such it had as good biological activity upon prothrombin synthesis as the menaquinone-4, which they found in the chick's liver following feeding of menadione. Therefore, menaquinone-4 is most likely produced only if menadione is fed, or if the intestinal microorganisms degrade the dietary K1 or K2 to mena-dione. The formation of menaquinone-4 is not obligatory for metabolic activity, since phylloquinone is equally active in bringing about synthe- sis of the K-dependent blood-clotting proteins [28 and 24].

Newborn infants have low vitamin K body stores, indicating poor placental transfer. Correlation of vitamin K between mothers and babies has suggested that the vitamin passes the placenta only in small quan-tities [34 and 24]. The vitamin is frequently not detectable in the cord blood from mothers with normal plasma levels, and sometimes, levels from neonates are only half those of their mothers.

Storage and Excretion:

About half of the total body pool of vitamin K is in the liver. A num-ber of studies has shown that phylloquinone and menaquinones are specifically concentrated and retained in the liver. Menaquinone con-centrations exceed those of phylloquinone in organs other than liver [38 and 24]. Menadione is found to be widely distributed in all tissues and very rapidly excreted. Although phylloquinone is rapidly concentrated in liver, it does not have a long retention time (17 hours half-life) in this organ [24, 29 and 38]. Therefore, the inability to rapidly develop vitamin K deficiency in most species results from the difficulty in preventing absorption of the vitamin from the diet or from intestinal synthesis rather than from a significant storage of the vitamin. Some breakdown products of vitamin K are excreted in the urine. One of the principal excretory products is a chain-shortened and oxi-dized derivative of vitamin K, which forms a γ-lactone and is probably excreted as a glucuronide. Vitamin K oxide has also been identified as a metabolite of vitamin K in rats [23 and

24]. The principal metabolites of menadione are the sulfate and glucuronide of dihydrom-enadione [22 and 24]. Some vitamin K is re-excreted into the intestine with bile, part of which is excreted in the feces. In humans, 20% of injected phylloquinone was excreted in the urine, and 40 to 50% was excreted in the feces via the bile [4 and 24].

FUNCTIONS

Coagulation time of blood is the major function ascribed to vitamin K. Four vitamin K-dependent proteins involved in blood coagulation were discovered early in the investigations of the vitamin as a result of hemorrhagic disease caused by deficiency. The vitamin is required for the synthesis of the active form of prothrombin (factor II) and other plasma clotting factors (VII, IX, and X). These four blood-clotting pro- teins are synthesized in the liver in inactive precursor forms (zymogens) and then converted to biologically active proteins by the action of vita-min K [32 and 24]. In deficiency, administration of vita-min K brings about a prompt response and return toward normal of de-pressed coagulation factors in 4 to 5 hours. In the absence of the liver, this response does not occur. The blood-clotting mechanism can apparently be stimulated by ei-ther an intrinsic system, in which all the factors are in the plasma, or an extrinsic system. In the extrinsic system of coagulation, injury to the skin or other tissue frees tissue thromboplastin that, in the presence of vari-ous factors and calcium, changes prothrombin in the blood to thrombin. The enzyme thrombin facilitates the conversion of the soluble fibrinogen into an insoluble fibrin clot. Fibrin polymerizes into strands and enmeshes the formed elements of the blood, especially the red blood cells, to form the blood clot [14 and 24]. The final active com-ponent in both the intrinsic and extrinsic systems appears to activate the Stuart-Prower factor, which in turn leads to activation of prothrombin. It is recognized that vitamin K-deficient animals synthesize vitamin K-dependent proteins but in an inactive form, and vitamin K is needed to convert these inactive protein precursors to biologically active pro-teins [30 and 24].

Investigations related to vitamin K mechanisms re-vealed that prothrombin contained 10 residues of a previously unrecog-nized amino acid, γ-carboxyglutamic acid (Gla). Likewise, the Gla residues were found in the three other vitamin K-dependent proteins. The aminoterminal regions of these proteins are homologous, and the Gla residues are in essentially the same position in all of these clotting factors [33 and 24]. The metabolic function of vitamin K is as the coenzyme in the car-boxylation of protein-incorporated glutamate residues to yield γ-car boxyglutamate, thus converting inactive precursor proteins to biological activity. Carboxylation allows prothrombin and the other procoagulant proteins to participate in a specific protein-calcium-phospholipid interaction that is necessary for their biological role [34 and 24]. To participate in this reaction, vitamin K is converted to hydroquinone and is then reconstituted to the quinone form via vitamin K-epoxide. Liver microsomes contain enzymes that oxidize the vitamin to its 2,3-epoxide and reduce the epoxide back to the reduced vitamin. The carboxylase activity and epoxidase activity appear to share a common oxygenated intermediate, and available data suggest that this may be a hydroperoxide of the vitamin. Evidence indicates that the role of vitamin K is to labilize the γ-hydrogen of the substrate for CO2 attack rather than to activate or transfer the CO2 [30 and 24]. Warfarin and other anticoagulants of the coumarin type interfere with 2,3-epoxide reduc- tase and therefore with the reconstitution of the active form of vitamin K (see Chemical Structure, Properties, and Antagonists).

Four other vitamin K-dependent proteins have been identified in plasma (C, S, Z, and M). Proteins C and S play an anticoagulant rather than a procoagulant role in normal hemostasis [31, 20 and 24]. Protein C inhibits coagulation, and stimulated by protein S, it promotes fibrinolysis. Also, a protein C-S complex can partially hy-drolyze the activated factors V and VIII and thus inactivate them. Individuals with inherited deficiency of factor C are at high risk for thromboses. Protein S also has the potential to be involved in the regulation of bone turnover [30 and 24]. Functions for pro-teins M and Z are unknown.

Continuing research has revealed that vitamin K-dependent reac-tions are present in most tissues and not just blood, and that a reason- ably large number of proteins are subjected to this posttranslational car- boxylation of specific glutamate residues to γ-carboxyglutamate residues [24, 36 and 38]. Gla-containing proteins have been pu-rified from kidney, liver mitochondria, spermatozoa, urine, chick chorioallantoic membrane, and snake venoms. Atherocalcin is a vitamin K-dependent protein in atherosclerotic tissue. A vitamin K-dependent carboxylase system has been identified in skin, which may be related to calcium metabolism in skin [9 and 24]. Two of the best characterized vitamin K-dependent proteins not involved in he- mostasis are osteocalcin or bone Gla protein (BGP) and matrix Gla pro-tein, which were initially discovered in bone. Osteocalcin is a protein containing three Gla residues that give the protein its mineral-binding properties. Osteocalcin appears in

embryonic chick bone and rat bone matrix at the beginning of mineralization of the bone [12 and 24]. It accounts for 15 to 20% of the non-collagen protein in the bone of most vertebrates and is one of the most abundant proteins in the body. Osteocalcin is produced by osteoblasts, with synthesis controlled by 1, 25-dihydroxy vitamin D. Matrix Gla protein-deficient mice have abnormal calcification leading to osteopenia, fractures, and premature death due to arterial calcification [4 and 24].

As is true for other non-blood vitamin K-dependent proteins, the physiological role of osteocalcinremains largely unknown [27 and 24]. However, reduced osteocalcin content of cortical bone [35 and 24] and alteration of osteocalcin distribution within osteons [19 and 24] are associated with aging. It remains unknown whether any of these findings are related to the age-related increased risk of fracture. Osteocalcin may play a role in the control of bone remodel-ing because it has been reported to be a chemoattractant for monocytes, the precursors of osteoclasts [25 and 24]. Serum osteocal-cin has been shown to be a good predictor of bone turnover in pigs [6 and 24]. This suggests a possible role for osteocalcin in bone resorption [3 and 24].

Effects of Deficiency

Ruminants

Intestinal microorganisms provide vitamin K to preruminant ani-mals. Nestor and Conrad [24 and 26] studied vitamin K in preruminant veal calves and concluded that intestinal microorganisms synthesized suffi-cient menaquinone-4 to meet needs of the vitamin prior to rumen de-velopment. Microorganisms in the rumen synthesize large amounts of vitamin K, and a deficiency is seen only in the presence of a metabolic antago- nist, such as dicumarol from moldy sweet clover. Dicumarol is a fungus metabolite produced from substrates in sweet clover hay. The coumarin derivatives are not active in the fresh plant because they are bound to glycosides, but are active when sweet clover is improperlycured [24 and 36].

This condition, referred to as sweet clover poisoning or hemorrhagic sweet clover disease, has been responsible for a large num-ber of animal losses. Ruminants may die from hemorrhage following a minor injury, or even from apparently spontaneous bleeding. Dicumarol passes through the placenta in pregnant animals, and newborn animals may become affected immediately after birth. All clinical signs of dicumarol poisoning relate to the hemorrhages caused by failure of blood oagulation. The first appearance of clinical disease after consumption of spoiled sweet clover varies greatly and de-pends to a large extent on dicumarol content of the particular sweet clover fed and animal age. If dietary dicumarol is low or variable, ani-mals may consume it for months before signs of disease appear. In an ex-periment with calves, dicumarol poisoning was produced by feeding nat- urally spoiled, sweet clover hay that contained a minimum of 90mg dicumarol per kilogram of hay [1 and 24]. The minimum time required to develop clinical signs of vitamin K deficiency in these calves was 3 weeks. In veterinary practice, another common cause of induced vitamin K deficiency is the accidental poisoning of animals with war-farin (a synthetic coumarin used as a rodent poison). Initial clinical signs may be stiffness and lameness from bleeding into muscles and articula-tions. Hematomas, epistaxis (nose bleed), or gastrointestinal bleeding may be observed. Death may occur suddenly, with little preliminary ev-idence of disease, and is caused by spontaneous massive hemorrhage or bleeding after injury, surgery, or parturition. [10 and 24] reported that two possible early embryonic deaths occurred and one cow aborted from sweet clover poisoning. Measurement of clotting time or prothrombin is considered a fairly good measure of vitamin K deficiency.

In experimentally induced dicumarol poisoning (hemorrhagic sweet clover disease), Alstad et al. (1985) reported that ormal prothrombin time is equal to or less than 20 seconds. Deficiency of vitamin K was characterized by prothrombin times longer than 40 to 60 seconds; with severe deficiency, prothrombin time can be as long as 5 to 6 minutes.

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