Міністерство освіти і науки України
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АКТУАЛЬНІ ЗАДАЧІ ХІМІЇ:
ДОСЛІДЖЕННЯ ТА ПЕРСПЕКТИВИ

МАТЕРІАЛИ КОНФЕРЕНЦІЇ

Житомир
2026

VITAMIN K-DEPENDENT PROCESSES AND POTENTIAL INTERACTIONS WITH ANTICOAGULANTS

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Vitamin K is a family of lipophilic 2-methyl-1,4-naphthoquinones, which includes phylloquinone (K_1) and menaquinones (K_2, MK-n). Its fundamental function in biology is to ensure post-translational modification of proteins – γ-carboxylation of glutamate residues (Glu→Gla) with the formation of calcium-binding Gla clusters. It is these clusters that form a structural module that provides Ca2+-dependent binding to phospholipid membranes and determines the activity of most vitamin K-dependent proteins (VKDP) [2, 9].

The classic "hepatic" group of VKDPs determines hemostasis: prothrombin (factor II), factors VII, IX, X, and natural anticoagulants protein C and protein S. The formation of complete Gla domain(s) is necessary for the assembly of coagulation complexes on platelet/endothelial membranes. At the same time, modern biomedical chemistry considers VKDP as a broader system that includes extrahepatic proteins–matrix Gla protein (MGP), osteocalcin (OC), Gas6, Gla-rich protein (GRP/UCMA), etc., which are involved in the regulation of bone mineralization, inhibition of vascular calcification, cell survival, and inflammation [1, 4].

Biochemically, γ-carboxylation occurs in the endoplasmic reticulum and is catalyzed by γ-glutamyl carboxylase (GGCX). The reaction requires CO_2 and O_2, and the reduced form of vitamin K, hydroquinone (KH2), is used as a redox cofactor, which is converted to vitamin K epoxide (KO) during the process. Thus, carboxylation and epoxidation are tightly coupled stages of a single enzymatic event, which determines the sensitivity of the system to K deficiency and recycling inhibitors [3].

The "vitamin K cycle" maintains the carboxylation flow: KO is reduced back to quinone/hydroquinone mainly with the participation of VKORC1 (vitamin K epoxide reductase complex subunit 1) and related reductases. Vitamin K antagonists (VKAs), primarily warfarin, inhibit VKORC1 and cause functional KH_2 deficiency, resulting in the synthesis of partially carboxylated (biologically deficient) coagulation factors and increased INR [7].

From the perspective of drug chemistry, it is critically important to distinguish between "vitamin K deficiency" and "carboxylation deficiency." Even with normal K intake, situations with impaired VKDP activation are possible due to drug effects (VKA), genetic variants of enzymes (VKORC1, GGCX), impaired absorption of lipophilic vitamins, or changes in the microbiota. For extrahepatic VKDPs, particularly MGP, a clinically relevant marker is the accumulation of uncarboxylated forms (e.g., dp-ucMGP), which is associated with the risk of vascular calcification and cardiometabolic complications in various cohorts [4].

The most significant interactions between vitamin K and anticoagulants concern VKAs and are predominantly pharmacodynamic in nature. Fluctuations in the intake of K_1 from food (greens, cabbage, liver) or K_2 from fermented products/supplements alter the availability of the cofactor for γ-carboxylation and modulate the effectiveness of warfarin [1]. In practice, this manifests as a decrease in the anticoagulant effect (INR ↓) with a sudden increase in vitamin K intake and, conversely, a tendency toward hypocoagulation (INR ↑) with a sharp decrease in its intake [7].

For patients with labile INR, the concept of “stabilizing” the anticoagulant response by low-dose supplementation with vitamin K_1 is being discussed, which reduces daily fluctuations in the cofactor pool and may increase the proportion of time that INR is within the therapeutic range [5]. MK-7 (vitamin K_2) supplements should be considered separately: dose-dependent studies have shown that even low doses of MK-7 can affect the stability/manageability of oral anticoagulant therapy, which must be taken into account when prescribing/self-prescribing nutraceuticals [6].

Antibiotics and changes in the gut microbiota can make a big difference in how well warfarin works. This happens through (I) less microbial input into the pool of menachinones and (II) pharmacokinetic interactions (inhibition/induction of warfarin metabolism, particularly via CYP2C9), which increases the risk of bleeding and requires enhanced INR monitoring during/after antibiotic therapy [8].

Unlike VKAs, direct oral anticoagulants (DOACs) – FXa or thrombin inhibitors – are independent of γ-carboxylation and the vitamin K cycle, so dietary/supplemental fluctuations in vitamin K are not determinative of their anticoagulant activity. For DOACs, interactions via P-gp and/or CYP3A4, as well as clinical factors (renal function, concomitant antiplatelet agents, etc.) are dominant [10].

In addition, vitamin K metabolism involves redox transformations within the vitamin K cycle, specifically quinone ↔ hydroquinone ↔ epoxide, which allows for repeated use of the γ-carboxylation cofactor.

At the cellular level, this cycle is integrated with the work of the endoplasmic reticulum and reductase systems, which restore the active form; disruption of the cycle underlies the effects of vitamin K antagonists.

Conclusion: Vitamin K-dependent processes represent an integrated redox cofactor system, where bioorganic transformations of the quinone nucleus ensure the activation of VKDP. Interactions with anticoagulants have clear class specificity: for VKAs, the key principle is “stable vitamin K” and proactive control of diet/supplements/antibiotics, while for DOACs, transport-enzyme interactions and organ dysfunction are priorities. In the context of biological systems, it is appropriate to consider K_2 as a metabolic “hub” that combines dietary sources, microbial contributions, lipoprotein transport, and cellular redox transformations.

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