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REVIEW

The epigenetic potential of vitamin K2 in brain health

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ABSTRACT

Vitamin K2 refers to a subfamily of vitamin K isoforms known as Menaquinones and, therefore, indicated as MK-n, the "n" indicating the number of isoprene units present in the side chain. Like the other members of the Vitamin K family, K2 is an enzymatic cofactor for the γ-glutamyl carboxylase (GGCX). This enzyme's substrates, which carboxylate glutamic acid residues, are known as Vitamin K-dependent proteins (VKDPs). Besides being involved in bone homeostasis, vitamin K exerts its primary function in the coagulation process. More recently, a function of Vitamin K also in brain homeostasis has been claimed. In addition to these so-called "canonical" effects, recent research highlights the possibility that Vitamin K, particularly Vitamin K2 May 2001have or induce epigenetic effects through the modulation of DNA methylation, histone modifications, and microRNAs expression. This evidence seems particularly relevant in brain diseases, where epigenetics is gaining a central role as a modulator of multiple diseases-associated molecular metabolisms. The present review examines the recent literature (PubMed) to collect evidence for the role of Vitamin K2 in neurodegenerative diseases with the goal of fostering interest in its epigenetic potential.

PLAIN LANGUAGE SUMMARY

The term Vitamin K includes a family of molecules, with partially conserved structure, known to exert their primary function in the coagulation process (contributing to the activation of the coagulation factors) and to maintain the bone structure. It was recently suggested that Vitamin K could also exert other roles, mainly in contributing to brain health and to prevention of neurodegenerative diseases. Exploring this possibility, some research work suggests the possibility that this neuroprotective effect is mediated by epigenetic mechanisms. Epigenetics describes how modification of the DNA, not involving a change in the sequence (i.e. not causing DNA mutations) can modulate the expression of the genes, therefore modulating the production of the coded proteins and the cellular phenotype. These modifications include DNA methylation (the presence of a methyl-group, -CH3, in the cytosine residues of the DNA), histone modifications (i.e. the presence of methyl-, acethyl-, and other chemical residues in the histone proteins that bind DNA), and the expression of non-coding RNAs (mainly microRNAs, which reduce the translation of the messenger RNAs). The present review is based on the new evidence describing how Vitamin K effects, and specifically the K2 isoform, may be mediated by these epigenetic modifications in neurodegenerative disease, opening a new field of research.

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1. Introduction

Vitamin K was first identified nearly a century ago, along with its critical role in coagulation [1]. Since then, there has been a growing body of evidence supporting the role of vitamin K as a protective nutrient in aging and neurodegenerative diseases [2].

There are different isoforms of vitamin K, including phylloquinone, commonly known as vitamin K1, and menaquinones, collectively referred to as vitamin K2. Vitamin K2 represents a group of menaquinones (MK-n), differentiated by a common naphthoquinone ring structure and side chains of varying lengths made up of unsaturated isoprenoid units. The letter "n" indicates the number of isoprene units in the side chain [3]. Phylloquinone is found in green leafy vegetables, such as spinach, and in some plant oils. The short-chain menaquinone MK-4 is present in animal-origin foods like eggs and chicken meat, while long-chain menaquinones, such as MK-7, MK-8, and MK-9, are predominantly found in fermented foods, notably cheese and natto [4] (Figure 1).

Vitamin K serves as an essential cofactor for the enzyme γ-glutamyl carboxylase (GGCX), which facilitates the post-translational γ-carboxylation of specific glutamic acid residues in various vitamin K-dependent proteins (VKDPs). Beyond the

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Article highlights

- Vitamin K2 (Menaquinone) is a member of the Vitamin K family.
- Vitamin K2 shows non-canonical effects on brain homeostasis.
- Low Vitamin K2 levels are associated to different neurodegenerative diseases.
- Vitamin K2 effects may be mediated through epigenetic mechanisms.
- The epigenetic molecular mechanisms associated with Vitamin K2 are still not clear.

well-known VKDPs involved in coagulation, key extrahepatic VKDPs include osteocalcin (OCN), which plays a critical role in bone mineralization, and matrix Gla-protein (MGP), a powerful inhibitor of vascular calcification. Recently, osteocalcin [5] and other extrahepatic VKDPs have also been implicated in brain function, highlighting their broader biological importance.

Structural differences affect vitamin K bioavailability and activity. While both K1 and MK-7 are well absorbed, MK-7 has a significantly longer half-life, accumulating 7- to 8-fold with extended use [6]. MK-7 is also more bioactive than K1 in fully carboxylated osteocalcin.

Beyond being a cofactor for GGCX, vitamin K2 also exerts non-canonical (GGCX-independent) functions, such as reduction of oxidative stress and inflammation, regulation of sphingolipid synthesis and mitochondrial function [7]. Recently, a novel aspect of vitamin K2 has gained attention: its potential impact on epigenetic regulation (Figure 2).

2. The role of vitamin K2 in brain health

Vitamin K2 is broadly distributed throughout human tissues, including the central nervous system (CNS). Recent research has linked low vitamin K intake and poor extrahepatic vitamin

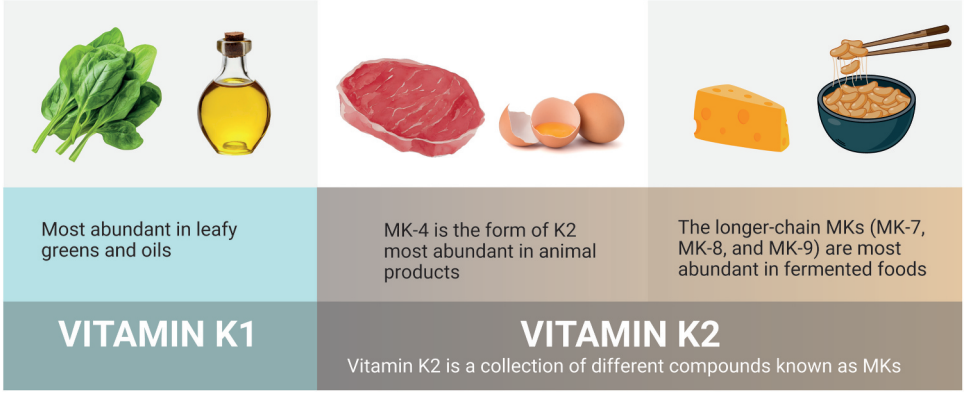

Figure 1. Nutritional sources of Vitamin K.

On the left, natural sources of Vitamin K1: green plants, oils. On the right, natural sources of Vitamin K2: meat, eggs (MK4), natto, cheese (MK7).

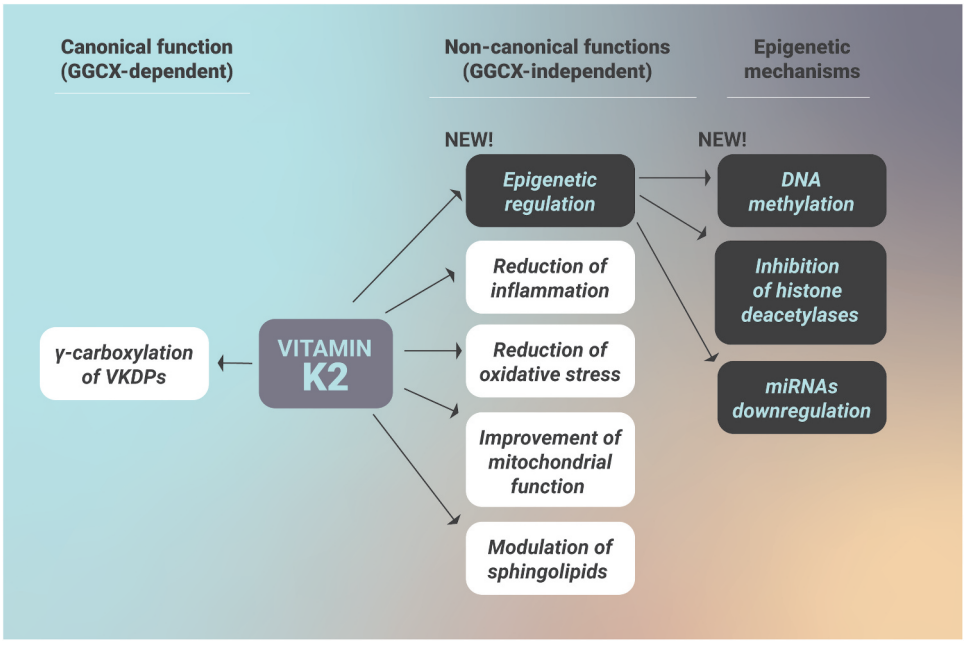

Figure 2. Canonical and non-canonical functions of vitamin K.

Vitamin K2 has diverse non-canonical mechanisms of action including serving as a mitochondrial electron carrier and protecting neurons and oligodendrocytes from oxidative damage and inflammation.

K status not only to an increased risk of cardiovascular diseases but also to neurodegeneration [2,7].

Vitamin K is primarily present in the brain as MK-4 [8] and dietary intake of any form, whether K1 or K2, can effectively increase the concentration of this isoform [9]. Additionally, several extrahepatic VKDPs play critical roles in the central nervous system [7,10]. For example, growth arrest-specific protein 6 (Gas6) promotes cell survival and myelination, protein S supports blood–brain barrier integrity, and MGP, an inhibitor of vascular calcification, is linked to vascular elasticity and cognitive performance.

Recent evidence highlights vitamin K2's key role in brain health and neurodegeneration, through both GGCX-dependent and independent mechanisms [2,3,11–13].

Apart canonical actions, based on the GGCX of VKDPs, vitamin K exerts also non-canonical functions GGCX independent (Figure 2). It is now well established the role of Vitamin K in biosynthesis of sphingolipids, widely present in brain cell membranes and key factors in maintaining the neurophysiological functions [14,15]. Moreover, increasing evidence underline both anti-inflammatory and antioxidant properties of Vitamin K2 [2,3,16], together with the ability to counteract the mitochondrial dysfunction [3]. In addition, recent findings showed that vitamin K2 (mainly MK-4) after the reduction to hydroquinone by Ferroptosis suppressor protein 1 (FSP1), has a potent anti-ferroptotic effect, by trapping free radicals so reducing lipid peroxidation [12,17].

Recently, the epigenetic effect of vitamin K has been suggested as a new non-canonical function, even if in depth studies on the mechanisms and vitamin-mediated epigenetic alterations are still to be investigated [18–22].

The neuroprotective properties of vitamin K2 have recently been confirmed through both in vitro and in vivo research [23,24]. Specifically, a very recent study provides compelling evidence that long-term low vitamin K (LVK) intake adversely affects hippocampal-dependent cognitive functions in C57BL/6 mice. These findings suggest that LVK impairs neurogenesis and promotes neuroinflammation [25]. Additionally, the observed sex differences – with male mice showing lower survival rates, reduced body weight gain, and lower MK-4 concentrations – indicate that males may be more vulnerable to Vitamin K deficiency. Overall, these results not only align with previous human observational data but also highlight the need for more research into the biological mechanisms by which vitamin K supports brain health. Its potential role in the pathophysiology of neurodegenerative diseases, including Alzheimer's, Parkinson's, and multiple sclerosis (Figure 3), is explored further below.

2.1. Vitamin K2 in multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disorder affecting individuals aged 20–40 years, with higher prevalence in women [26]. MS is considered an autoimmune disease and is characterized by demyelination, inflammation, and neuroaxonal damage, driven by inflammatory cytokines and reactive oxygen species [27]. Emerging evidence highlights a potential role of vitamin K2 in MS [28–32].

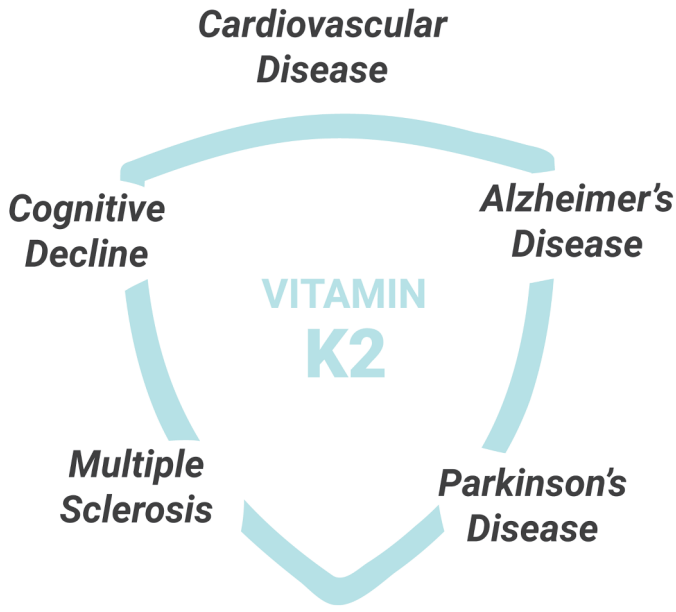

Figure 3. Vitamin K2 and neurodegenerative disease.
Examples of neurodegenerative diseases, which can benefit from K2, as discussed below.

The epidemiological data showed that serum vitamin K2 levels were more than three times higher in healthy controls compared to MS patients [33]. Recent research has also identified a link between MS progression and reduced microbial production of vitamin K2 [34]. The role of vitamin K2 in MS development and progress deserves further research.

2.1.1. Limitations and future directions

Currently, the data regarding the implications of vitamin K2 in MS are extremely limited and obtained by observational and/or experimental studies. Large prospective epidemiological studies and RCTs are warranted to fully elucidate the exact role of vitamin K2 in MS.

2.2. Vitamin K2 in Parkinson's disease

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, yet its pathogenesis remains poorly understood. PD pathogenesis is primarily associated with oxidative stress, mitochondrial dysfunction, and inflammation. Among these factors, neuroinflammation plays a particularly critical role in PD progression as evidenced by studies showing a lower incidence of PD in long-term non-steroidal anti-inflammatory drug users [35].

Vitamins are well known for their anti-inflammatory and antioxidant properties and have been suggested as a potential neuroprotective therapeutic approach, including PD.

Observational studies revealed that vitamin K levels in human plasma were inversely associated with various biomarkers of inflammatory factors [36]. Additionally, unpublished research suggests that vitamin K2 significantly improves behavioral disorders in a rotenone-induced rat model of PD [37].

Epidemiological research on vitamin K2 in PD is limited. A case–control study revealed an association between vitamin

K2 deficiency and PD progression, suggesting its potential as a diagnostic biomarker. Serum vitamin K2 levels were significantly lower in PD patients than in healthy controls and declined further with disease severity [37].

Mitochondrial dysfunction, linked to PD for nearly 40 years, is supported by the growing evidence [38]. Genetic defects like PINK1 and Parkin mutations further impair mitochondrial function in PD patients. Vitamin K2 has shown the ability to restore mitochondrial function in PINK1 mutant models. It improved electron transport and increased ATP production. Consequently, vitamin K2 improved locomotor function in adult PINK1 and parkin mutant flies [39] and has been suggested as a potential therapeutic option for PD patients with PINK1 or parkin deficiencies. Currently, recruitment is planned for the clinical study (DRKS00019932), to investigate the effects of vitamin K2 in genetically determined PD associated with mitochondrial dysfunction [40].

Emerging research also highlights the role of VKD protein OCN as a promising neuroprotective factor in PD. OCN administration improved motor function and reduced neuronal loss in PD rat model [41].

These findings collectively highlight the promising role of vitamin K2 in developing novel therapeutic strategies for PD.

2.2.1. Limitations and future directions

The data regarding vitamin K2 in PD are derived by experimental studies and/or observational studies and therefore preclude any causality. Moreover, the associations examined are mainly with surrogate endpoints and not clinically hard endpoints. Since vitamin K2 is a safe supplement, future, large RCTs examining the possible beneficial role of vitamin K2 in cognitive function, quality of life and longevity in PD patients might shed some light in this area.

2.3. Vitamin K2 in Alzheimer's disease

Accumulating evidence suggests that vitamin K has a protective effect against the progression of Alzheimer's disease (AD) by modulating several cellular mechanisms, including neuroinflammation, sphingolipid metabolism, oxidative stress, and mitochondrial dysfunction [2].

Dietary intake of vitamin K1 (assessed by food questionnaires or measuring circulating phylloquinone levels) has been directly correlated with memory function, suggesting a causal relationship between vitamin K and cognitive function [42,43]. Since the main dietary source of vitamin K1 is green leafy vegetables, this correlation might also be an epiphenomenon reflecting healthy lifestyle and these studies did not assess the forms and levels of vitamin K in the brain. To address these issues, the Rush Memory and Aging Project [8] showed that increased brain MK-4 concentrations were associated with a 17%–20% reduction in the likelihood of dementia or mild cognitive impairment (MCI), and lower AD global pathology scores [8].

One of the most prominent pathophysiologic pathways underlying the onset and progression of AD is arterial stiffness. The ARIC (Atherosclerosis Risk in Communities – Neurocognitive Study) study showed that among subjects >67 years old, those in the highest quartile of carotid-femoral pulse wave velocity (cfPWV) experienced a higher rate of white matter hyperintensities, decreased total brain volumes, and poorer performance scores in executive function, processing speed, and global cognition [44], which were independent of age, sex, hypertension, and blood pressure [45,46]. In agreement with these results, a meta-analysis of 38 studies and 43,115 patients [47] showed that PWV was negatively associated with general cognition, executive function, and memory status, and it has been calculated that each 1 m/s increase in PWV increased the risk of cognitive impairment by 3.9 [48].

Vitamin K antagonists (VKAs), an "old-fashioned" class of anticoagulant drugs, which reduce blood clotting by antagonizing vitamin K recycling and metabolism, might increase the risk of cognitive impairment up to 15% [49]. Long-term use of these agents in patients with normal cognitive function at baseline is associated with worsening of visual memory and verbal fluency [50]. The deleterious effects of VKAs on the duration of focal cerebral atrophy are dose- and time dependent [51]. Based on these data, several studies have highlighted the beneficial role of vitamin K2 supplementation in vascular health and arterial stiffness prevention, mainly via downregulation of circulating dephosphorylated, uncarboxylated Matrix Gla protein (dp-ucMGP) [52,53]. Given that stiffening of cerebral arteries is strongly associated with the progression of cognitive decline, vitamin K2 presents a promising, safe, and well-tolerated treatment option for AD prevention.

2.3.1. Limitations and future directions

There are various limitations regarding the data on the association of vitamin K2 and AD that should be acknowledged. These data are derived from observational studies, which preclude any causality; moreover, as has been mentioned before, the association between dietary intake of vitamin K1 and cognitive function might be an epiphenomenon of a healthy, plant-based diet. Finally, the data are mainly preclinical and human data are sparse and indirect. Future, large randomized controlled trials examining the potential effect of vitamin K2 supplementation on cognitive function in AD patients are needed in order to draw definite conclusions.

3. Vitamin K2 in cardiovascular diseases

It is now largely recognized that maintaining cardiovascular health may be beneficial in mitigating the progression of neurodegenerative diseases, since these pathologies share many common risk factors. The first epidemiologic study to indicate the pivotal role of vitamin K consumption in cardiovascular prevention was the Rotterdam study [54], showing that among 4807 subjects with no preexisting CVD, only vitamin K2 intake was significantly and inversely associated with all-cause mortality and severe aortic calcification. In a randomized control trial (RCT) Knapen et al. [55] showed that among postmenopausal women, 3-year supplementation with 180 μg/day of MK-7 significantly improved arterial stiffness, which was even more pronounced in those who had higher baseline arterial stiffness [55].

Data from the Danish Diet, Cancer, and Health Study [56] in 53,372 participants free of CVD, which were followed up for two decades, showed that high daily vitamins K1 and K2 were associated with a 21% and 14% lower risk of hospitalization due to atherosclerotic CVD, respectively. Similarly, supplementation with vitamin K2 (720 µg daily) and vitamin D (25 µg daily) versus placebo for 2 years patients with established coronary artery calcification (CAC), significantly delayed the valve calcification process [57].

CKD patients carry a heavy CV burden which is partially attributed to the accelerated vascular calcification, which occurs even at early stages. The KING trial (Vitamin K2 in Renal Graft) showed that 8-week daily MK-7 supplementation (360 µg/day) in 60 kidney transplant recipients reduced cfPWV by 14.2%, through a 40% improvement in subclinical vitamin K deficiency [58]. Another RCT involving 40 kidney transplant recipients found that a 12-week MK-7 supplementation significantly decreased dp-ucMGP levels and arterial stiffness [59]. Similarly, a study by Naiyarakseree et al. [60] evaluated MK-7's effects in 96 hemodialysis patients with established arterial stiffness at baseline and found that 24 weeks of MK-7 supplementation (375 µg/day) reduced cfPWV in participants with diabetes mellitus by 10.0%. It has been calculated by meta-analyses that vitamin K supplementation reduces vascular calcification by 9.1% through a 44.7% reduction of dp-ucMGP levels, which still is modest [61]. In addition, VKDPs were associated with a 0.45-fold lower risk of cardiovascular disease and mortality [61].

3.1. Limitations and future directions

Although these results seem promising, these RCTs presented drawbacks and limitations, including the small sample size, the short follow-up period, the large heterogeneity of design, and the lack of clinical hard endpoints. Currently, well-designed trials in various populations, including CKD, are conducted. The results of these trials are expected to improve our understanding of the area of vitamin K2 in CVD.

4. Vitamin K epigenetic potential

Epigenetic changes play a pivotal role in many diseases, especially in aging and neurological disorders, given their complex and multifactorial nature. As a matter of fact, the delicate interplay between genetic and epigenetic mechanisms in processes involved neurodegeneration, i.e., neuroinflammation, accumulation of toxic proteins, and related to the pathophysiological control of brain functions, make the brain the most responsive tissue to epigenetic modification [62–65]. Moreover, the increase in the lifespan makes the organism more prone to different environmental injuries that accumulate over the years, even if the manifestation of the pathology is evident later in life.

Diet and nutrition are retained the main environmental factors inducing epigenetic modifications, especially in aging related diseases, since every individual experiences the strong interconnection between dietary environment and health all lifelong. Nutritional deficiencies can over time become risk factors or causes of many diseases, being related to epigenetic dysregulations that hamper not only normal brain functions but are also associated to neurodegenerative diseases like AD and PD [64,66,67]. Neuroepigenetics, connecting neuroscience and epigenetics, and nutrigenomics, studying how specific nutrients interact with the epigenome, cooperate to highlight the significant and intricate interplay between nutrients and epigenetic regulation mechanism providing novel potential strategies to personalized therapy [63,68]. In recent years, there has been growing evidence that vitamins are micronutrients that might modulate the epigenetic mechanism, affecting both directly or indirectly DNA methylation, histone modifications, and miRNA expression [18,19,66]. These epigenetic modifications take part in the regulation of the expression of essential genes related to cell functions and development. Since vitamins are also involved in many biochemical pathways, their role in maintaining physiological homeostasis conditions is well recognized. Moreover, several studies underlined the association between vitamin deficiency and neurodegeneration, highlighting the protecting role of these nutraceutical supplements as potential co-treatments in neurodegenerative diseases [69,70]. For instance, in the last few years, the key role of B vitamins in brain health and the epigenetic mechanisms involved was evidenced, being these vitamins also co-factors in the one-carbon metabolism, involving methyl-donors [64,71,72]. Indeed, we have already demonstrated the role of B vitamins as micronutrient involved in the epigenetic modulation in brain diseases, showing that B vitamin deficiency leads to methylation impairment with hypo-methylation of PSEN1 gene promoter and consequent overexpression of PSEN1, enhancing Aβ accumulation and exacerbation of AD-like features in TgCRND8 mice [73,74]. Conversely, in the same mouse AD-model, S-adenosylmethionine supplementation was able to epigenetically counteract these effects, preventing PSEN1 overexpression, reducing amyloidogenesis and amyloid plaque burden to control-like values, resulting in a reduction of the AD-like phenotype induced by B vitamin deficiency [75].

Despite the broadly recognized role of Vitamin K in brain functions [76], an in-depth study aiming to understand vitamin K mediated epigenetic regulation is still needed, also given that recent findings pointed out that Vitamin K exerts epigenetic effects in different cellular models, mainly in tumor cell lines. These studies evidenced that vitamin K is able to exert epigenetic modifications in terms of DNA methylation, miRNA expression, and histone acetylation, but further in-depth investigations are needed to elucidate the molecular mechanisms involved.

Moreover, it is noteworthy the role of DNA methylation levels in the variable response to vitamin K supplementation, as evidenced by a microarray-based epigenome – wide association study performed on blood samples from 48 healthy older adults under phylloquinone treatment for 3 years [77]. This study evidenced differential methylation at both known and novel loci, with previously unknown relationships to phylloquinone metabolism, like the TMEM263 locus, and a strong correlation between the epigenomic signatures of steady-state plasma phylloquinone and its response to supplementation. This research also pointed out the role of the NPC1L1 gene in

phylloquinone absorption, and even further investigations are needed. Although the statistical power of this research is limited due the low sample size and the reduced heterogeneity, these results could be useful to discriminate responders and non-responders to vitamin K supplementation, providing valuable information for possible personalized nutritional approaches.

4.1. Vitamin K and DNA methylation

The involvement of vitamin K in epigenetic regulation could be hypothesized based on the study of Sueoka et al. [78] on hepatocellular carcinoma (HCC) cell lines. They studied the expression levels of SAM domain, SH3 domain, and nuclear localization signal 1 (SAMSN1), belonging to the SH3-protein family SAMSN1, indicating its downregulation as a poor prognosis marker for HCC patients. The expression of *SAMSN1* is regulated by the methylation of its promoter, the hypermethylation correlating with decreased expression and *vice versa*. Interestingly, an association between lower *SAMSN1* expression and vitamin K deficiency was evidenced, finding also an inverse correlation between preoperative levels of protein induced by vitamin K antagonists and the tumor size. The same research group evidenced, in the same cellular model, another cancer-related gene, protein tyrosine kinase 7 (PTK7), which expression is regulated in a similar way [79]. Further research is needed to study the correlation between vitamin K deficiency and hypermethylation in HCC cell lines, since the above-mentioned study did not report any direct assessment of the relationship between vitamin K status and DNA methylation.

The epigenetic potential of vitamin K is also suggested by the research of Łuczkowska et al. [80,81] investigating the effect of vitamin D (VD) and vitamin K2 (MK-7) (hypothesizing that they reciprocally potentiate) on epigenetic modulations related to the proliferative potential of human multiple myeloma (MM) U266 cells and the bortezomib (BTZ) resistance occurrence. The results indicated that the development of BTZ resistance is associated with a global DNA hypomethylation, whereas both control and BTZ-resistant MM cells showed an increase in methylation when treated with VD alone and with the combination of VD and vitamin K. Given the correlation between hypermethylation and the decreased proliferative potential of malignant plasma cells, it can be hypothesized that VD and vitamin K are able to induce epigenetic modifications, reducing the proliferative potential of plasma cells, leading also to a better response to the therapy by partially overcoming the development of resistance to BTZ. Further research is needed, both to confirm these results in patients and to deeply understand the link between vitamin K and methylation.

Further evidence of the potential role of vitamin K2 in epigenetic regulation of gene expression in brain diseases was provided by Saputra [82], showing that MK-4 was able to reduce inflammation signaling in mouse-microglia-derived MG6 cells by downregulating the expression of inflammatory cytokines IL-1β and IL-6. These research findings together with the growing evidence underlining the role of vitamins as powerful epigenetic regulators, based also on our experience in epigenetic alterations induced by B-vitamin deficiency in cellular and animal AD models prompted us to investigate the role of vitamin K2 vitamers (MK-4 and the reduced form of MK-7) in the epigenetic regulation of key genes involved in neurodegeneration and neuroinflammation in SK-N-BE cell line. We found that vitamin K2 vitamers were able to hinder the amyloidogenic process downregulating PSEN1 and BACE1 while promoting non-amyloidogenic pathway by the upregulation of ADAM17 and ADAM10, leading to a decrease of Aβ production together with an increase of the soluble and neuroprotective sAPPα peptide [20]. Moreover, also the neuroinflammatory process also appears to be modulated by NF-kB signaling pathway inactivation, with a significant decrease of the expression of IL-1β and IL-6 genes, confirmed also at protein levels. Given that it was previously reported that PSEN1, IL-1β and IL-6 genes expression are modulated by the methylation of the promoter in SK-N-BE as well as in AD brains [83–86], we analyzed the DNA methylation profiles of these genes, to investigate potential epigenetic regulation exerted by vitamin K2 vitamers. Interestingly, we observed that the observed gene downregulation is correlated with hypermethylation of the promoters, involving both CpG and non-CpG DNA methylation, with no significant modulation of DNA methyltrasnferases [20].

Although SK-N-BE cell line is a preliminary model, useful to assess the molecular pathways and targets modulated by vitamin K, the obtained results encourage further preclinical experiments in animal models and primary neurons to confirm the important role of vitamin K2 as a neuroprotective coadjuvant in brain disease treatment. Further studies are needed to explain the mechanism involved in the DNA methylation induced by vitamin K, possibly by an indirect effect exerted by an intermediate vitamin K dependent and hypothetically involved one-carbon metabolism modulation.

4.2. Vitamin K and histone acetylation

Due to the well-known vitamin K3 anti-cancer effect, Lin et al. [87] conducted a study in leukemia HL-60 cells aiming to understand the involved molecular mechanism. The study demonstrated that vitamin K3 treatment-induced tumor cell death through hydrogen peroxide generation and histone hyperacetylation, in both dose and time-dependent manner.

The suggestion of the use of vitamin K as a potential epigenetic supplement in anti-cancer therapy also comes from the role of vitamin K3 derivatives in liver tumor cells on the inhibition of histone deacetylase HDAC6, involved also in the deacetylation of cytoplasmic proteins like α-tubulin, HSP90, p53. One of the vitamin K3 derivatives (VKT-2) tested by Dawood et al. [21,22,88] showed strong binding to HDAC6 protein in silico and in vitro, leading to inhibition its activity, hyperacetylation of α-tubulin, decrease of cell mobility and stabilization of microtubules.

Alterations in histone acetylation in neurodegeneration were first evidenced by Rouaux [89], demonstrating the correlation between histone hypoacetylation and neurodegenerative diseases, which is now well established for several neurological pathologies associated with cognitive and movement disorders [90]. Histone acetylation plays a pivotal role in

the epigenetic regulation of processes associated with long-term memory, learning, and cognitive functions [91]. As a matter of fact, HDACs inhibitors, mostly studied for their anticancer potential, are now suggested as neuroprotective agents in several neurodegenerative disorders like AD, PD, and Huntington's disease (HD) [92,93], enhancing histone acetylation together with increasing BDNF levels, attenuating motor deficits and neuroinflammatory markers. Butyrates are the most studied HDACs as neuroprotective agent, also for their ability to easily reach the brain [90]. Interestingly, vitamin K2 can increase intestine butyrate levels in animal models [94]. Moreover, recent findings showed that PD patients have alterations in gut microbiome leading to reduced bacterial production of the epigenetic regulator butyrate, which correlates with epigenetic modifications in leucocytes and neurons and to the severity of the symptoms of the disease [95]. Therefore, it could be hypothesized that the enhanced secretion of gut butyrate is one of the mechanisms underlying the vitamin K epigenetic potential of histone acetylation, contributing to its neuroprotective effect in neurodegenerative diseases, although the relationship among vitamin K, butyrate-producing bacteria, and butyrate secretion still needs to be well elucidated [96].

We then hypothesize that Vitamin K could affect histone acetylation by several mechanisms, both direct, like the binding to the HDAC6 protein, and secondary, by the stimulation of butyrate production. However, further studies are necessary to understand the detailed mechanism underlying these epigenetic modulations.

4.3. Vitamin K and miRNAs expression

A study conducted by Zhang et al. [18,97] in human bone marrow stromal cells overexpressing microRNA (miR)-133a (hBMSCs) by analyzing the expression levels of osteogenesis-associated proteins, demonstrated that vitamin K2 can stimulate osteogenesis by inhibiting microRNA miR-133a, a negative regulator of osteogenic differentiation. Moreover, the authors showed also that vitamin K epoxide reductase (VKOR) complex subunit 1 expression is downregulated by miR-133a and upregulated by vitamin K2, so potentiating the γ-carboxylation processes. Therefore, miR-133a has been suggested as the target of vitamin K2 in the epigenetic regulation of osteogenesis and bone metabolism, but the detailed underlying mechanism remains to be ascertained.

5. Future perspective

All these studies suggest that vitamin K, especially the most studied vitamin K2, retains neuroprotective effects not only based on the canonical mechanism, so involving VKDPs, but also on non-canonical. Among these, an epigenetic role is now evident, by harnessing the modulation of DNA methylation, histone modifications, and microRNAs that intricately interplay to regulate the expression of genes involved in molecular pathways whose alterations contribute to the development or the progression of the disease. The epigenetic effects observed could be direct (i.e., HDAC6 binding), or indirect, i.e., stimulation of butyrate production, and further investigations are needed to identify the potential vitamin K-dependent intermediates responsible for the observed effects. The epigenetic approach appears to be particularly intriguing, since it has the potential to regulate multiple pathways involved in neurodegeneration, thus responding to the need for a multi-target treatment deserved by multi-factorial diseases. Studies on the epigenetic potential of vitamin K are still limited in number, therefore more mechanistic studies, in specific neurodegenerative models are needed.

Author contributions

All the authors contributed to the writing of the manuscript. Andrea Fuso, Rosaria A. Cavallaro, and Katarzyna Maresz prepared the manuscript for submission. All the authors read and approved the final manuscript.

Disclosure statement

Andrea Fuso and Katarzyna Maresz are consultant at "Gnosis by Lesaffre." Niccolò Miraglia and Jean-Francois Jeanne are employee at "Gnosis by Lesaffre. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
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