Available online at www.sciencedirect.com
ScienceDirect
Journal of Nutritional Biochemistry 21 (2010) 1083–1088
Journal of Nutritional Biochemistry

Age- and brain region-specific effects of dietary vitamin K on myelin sulfatides ☆,☆☆

Natalia A. Crivello[a,b,*], Sherley L. Casseus[a], James W. Peterson[c], Donald E. Smith[b,d], Sarah L. Booth[b,c]

[a]Nutrition and Neurocognition Laboratory, Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging (JM USDA HNRCA) at Tufts University, Boston, MA 02111, USA
[b]Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy at Tufts University
[c]Vitamin K Laboratory, JM USDA HNRCA at Tufts University, Boston, MA 02111, USA
[d]Comparative Biology Unit, JM USDA HNRCA at Tufts University, Boston, MA 02111, USA

Received 30 March 2009; received in revised form 13 July 2009; accepted 17 September 2009

Abstract

Dysregulation of myelin sulfatides is a risk factor for cognitive decline with age. Vitamin K is present in high concentrations in the brain and has been implicated in the regulation of sulfatide metabolism. Our objective was to investigate the age-related interrelation between dietary vitamin K and sulfatides in myelin fractions isolated from the brain regions of Fischer 344 male rats fed one of two dietary forms of vitamin K: phylloquinone or its hydrogenated form, 2′,3′-dihydrophylloquinone (dK), for 28 days. Both dietary forms of vitamin K were converted to menaquinone-4 (MK-4) in the brain. The efficiency of dietary dK conversion to MK-4 compared to dietary phylloquinone was lower in the striatum and cortex, and was similar to that in the hippocampus. There were significant positive correlations between sulfatides and MK-4 in the hippocampus (phylloquinone-supplemented diet, 12 and 24 months; dK-supplemented diet, 12 months) and cortex (phylloquinone-supplemented diet, 12 and 24 months). No significant correlations were observed in the striatum. Furthermore, sulfatides in the hippocampus were significantly positively correlated with MK-4 in serum. This is the first attempt to establish and characterize a novel animal model that exploits the inability of dietary dK to convert to brain MK-4 to study the dietary effects of vitamin K on brain sulfatide in brain regions controlling motor and cognitive functions. Our findings suggest that this animal model may be useful for investigation of the effect of the dietary vitamin K on sulfatide metabolism, myelin structure and behavior functions.
© 2010 Elsevier Inc. All rights reserved.

Keywords: Myelin; Phylloquinone; Vitamin K; Menaquinone-4; Sulfatides; Diet

1. Introduction

Neurological disorders, and to a lesser extent, normal aging are associated with decline in motor and cognitive behavior [1–3]. Disruption of brain myelin has been implicated as an important contributor to cognitive deficit in humans [2] and animals [4–7]. Myelin, which is an axonal insulator, is formed in the central nervous system (CNS) by oligodendrogliocytes [8–11]. A high concentration of lipids is essential for proper myelin functions. Myelin membranes are particularly enriched with glycolipids, including galactosylceramide and its sulfated form, sulfatide [8,12–15]. Concentrations of sulfatides increase during brain development, parallel to an increase in brain myelination [16–18]. Earlier studies *in vivo* and *in vitro* demonstrated differential rates of myelination among brain regions [19,20]. Decreases in myelin sulfatides content and/or changes in their molecule structure have been implicated as important factors in the disruption of myelin morphological structure, with a subsequent attenuation of myelin efficiency as an axonal insulator [6,21]. Furthermore, dysregulation in brain sulfatide metabolism, and decreases in the content of myelin sulfatides with age, has been implicated as a significant risk factor for behavioral deficits observed in normal aging [7,22], and age-associated neurological disorders [23–25].

Numerous studies suggest that exogenous factors, including nutritional factors, can modulate myelination [11,26,27]. Vitamin K, a fat-soluble vitamin, has been implicated in regulation of brain sphingolipid metabolism, including sulfatide metabolism [28–30]. Furthermore, a recent study reported a positive correlation between sulfatides and vitamin K, which is present almost exclusively in the form of menaquinone-4 (MK-4) in the brain [31,32]. However, there are inconsistencies on the putative role of vitamin K on sulfatides, as reviewed elsewhere [30]. To the best of our knowledge, the dietary effect of vitamin K on brain myelin was not investigated. Under normal dietary conditions, there is a tissue-specific conversion of vitamin K from the dietary form [primarily phylloquinone (K1)] to

☆ Disclaimer Statement: Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the U.S. Dept of Agriculture. No authors report any actual or potential conflicts of interest.

☆☆ This work was supported by USDA agreement no. 58-1950-7-707 and NIH R03AG25781 (to NC).

* Corresponding author. Nutrition and Neurocognition Laboratory, JM USDA HNRCA at Tufts University, Boston, MA 02111, USA. Tel.: +1 617 556 3147; fax: +1 617 556 3243.
E-mail address: natalia.crivello@tufts.edu (N.A. Crivello).

0955-2863/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jnutbio.2009.09.005

MK-4. The hydrogenated form of vitamin K [2′,3′-dihydrophylloquinone (dK)] does not convert to MK-4 to the same extent that K1 is converted to MK-4 [33,34]. The objective of this study was to investigate the age- and brain region-specific effects of different dietary forms of vitamin K on myelin sulfatides. This is the first attempt to establish and characterize a novel animal model that exploits the inability of dietary dK to convert to brain MK-4 to study the dietary effects of vitamin K on brain sulfatide in brain regions controlling motor and cognitive functions.

2. Material and methods

2.1. Reagents

Reagents were obtained from Sigma (St. Louis, MO, USA) and Fisher Scientific (Houston, TX, USA). AIN-93G diet (cat. no. TD.94045), AIN-93-VX vitamin mix (cat. no. TD.94047), AIN-93G-MX mineral mix, vitamin K-deficient powdered diet (cat. no. TD. 97053) and AIN-76 mineral mix (cat. no. CA.170915) were purchased from Harlan Teklad (Madison, WI, USA). A purified source of vitamin K [phylloquinone (K1)] was purchased from Sigma (cat. no. V-3501). The dK was a gift from Dr. J. Pyrek (University of Kentucky, Mass Spectrometry Facility, Lexington, KY, USA). Protein assay kits were obtained from Bio-Rad Laboratories (Hercules, CA, USA; cat. no. 500-0116). Sulfatide standards were purchased from Sigma (cat. no. S1006).

2.2. Diets

In the current study, we used a standard rat diet, AIN-93G; and two experimental diets: (a) vitamin K-deficient diet supplemented with phylloquinone (K1 diet) and (b) vitamin K-deficient diet supplemented with dK (dK diet). The concentrations of the two dietary forms of vitamin K (i.e., K1 and its hydrogenated form, dK) were experimentally determined (K1 diet: 198±9.0 μg/kg diet; dK diet: 172±13.0 μg/kg diet). We selected amounts of dK or K1 that were adequate to sustain coagulation based on our preliminary studies (data not shown). Diets were stored at 4°C until used. Aliquots of the diets were analyzed by HPLC for both forms of vitamin K (i.e., K1 and dK) to confirm their stability and concentrations [35].

2.3. Animals

Sixty male Fischer 344 rats 2- (young), 12- (adult) and 24 months old (old) (n=10 per age group) were obtained from the National Institute of Aging (Harlan Sprague Dawley, Indianapolis, IN). All experimental animals were provided with *ad libitum* water and AIN-93G diet for 14 days of the acclimatization period, followed by the experimental dietary intervention for 28 days (Fig. 1). Animals were group pair fed (by age and diet). The amount of diets provided to each animal was adjusted daily to accommodate consumption patterns (in accordance with the amounts of food remaining from any animal or, in the case of consumption of all of the previous day's diet, incrementally increased). This procedure ensures that all age-matched animals have comparable caloric and nutrient daily food consumptions. Body weights were recorded weekly. All health- or other related observations were also recorded. Animals were used in compliance with all applicable laws and regulations and principles expressed in the National Institutes of Health, USPHS, Guide for the Care and Use of Laboratory Animals. The study was approved by the Animal Care and Use Committee of the Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University (Boston, MA, USA).

2.4. Sample preparation

Upon completion of the 28-day dietary intervention, animals were sacrificed and brain regions (i.e., striatum, hippocampus and cortex) were dissected on ice, immediately frozen in liquid nitrogen and stored at −80°C until further analyses. Myelin fractions were isolated from individual brain regions.

2.5. Isolation of myelin fractions

Myelin fractions were isolated from the brain regions by differential centrifugation using a modified procedure as described previously [36]. Briefly, individual brain regions (cortex, striatum and hippocampus) were homogenized in 0.32 M sucrose buffer containing protease inhibitors to prevent protease activation and protein cleavage. Crude membrane fractions (P-2) were separated from the crude nuclear fractions in each of the brain regions by low-speed centrifugation, followed by ultracentrifugation on a Ficoll gradient (7% and 14%) for separation of myelin fractions. The purity of the isolated myelin fractions was confirmed previously by electron microscopic and biochemical analyses [37,38]. Collected myelin fractions were assessed for protein, sulfatide and vitamin K concentrations.

2.6. Analysis of protein

The concentration of protein in myelin homogenates was determined by using a Bio-Rad Protein Assay (cat no. 500-0116) for 96-well plate, as described previously [39].

2.7. Analysis of sulfatides

Sulfatide concentration in myelin membranes was assessed using a spectrophotometric method [31,40]. Briefly, sulfatides were purified from the myelin lipids prior

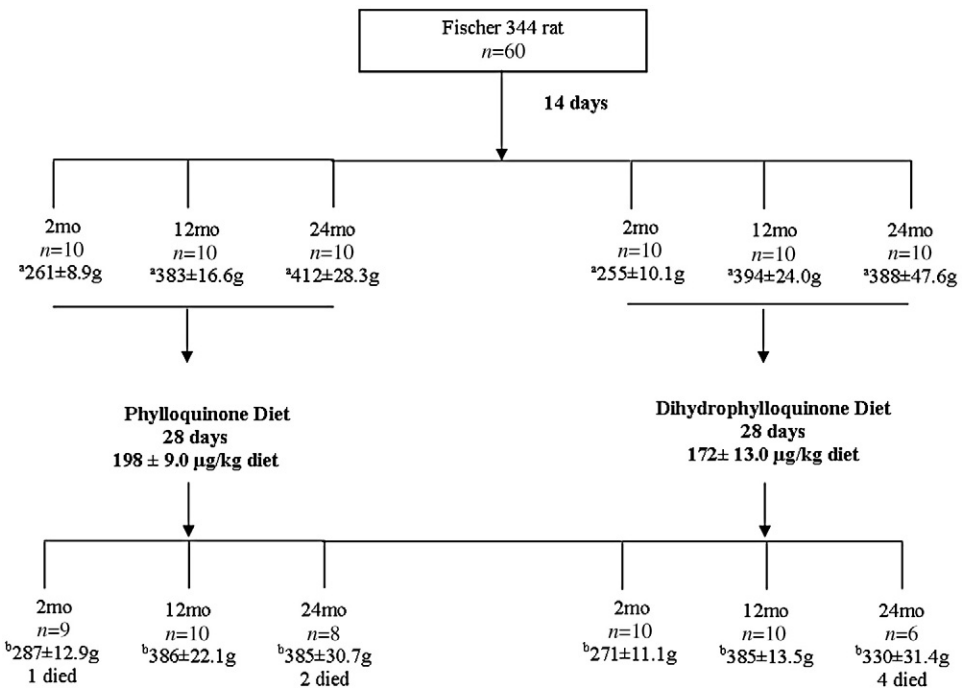

Fig. 1. Twenty 2-month-old (young), twenty 12-month-old (adult) and twenty 24-month-old (old) male Fischer rats were obtained from the National Institutes of Aging (Harlan Sprague Dawley). Rats were maintained on experimental diets for 28 days. Vitamin K and sulfatide content was determined in myelin fraction isolated from brain regions as described in Material and Methods.

to their quantitative assessment. Specifically, glycolipids, including gangliosides and other water-soluble myelin constituents, were removed by the chloroform–methanol (2:1 vol/vol) Folch procedure as described previously [36]. The potentially remaining traces of water-soluble constituents were further removed by washing the lower phase with "pure solvents upper phase" prepared with 0.1 M KCl. Sulfatides were then purified from the other classes of myelin lipids (e.g., phospholipids, cholesterol, etc.) by two-dimensional high-performance thin layer chromatography [36]. Sulfatides were identified using sulfatide standards (Sigma; cat. no. S1006). The absorbance of the colored sulfatide-Azure A complex was measured at 645 nm by using a Perkin-Elmer Lambda 7 spectrophotometer. The concentration of sulfatide was calculated based on calibration curve by using sulfatide standard (0–30 nmol). The results for sulfatide concentration in myelin fractions were adjusted per gram of myelin protein and expressed as micromole sulfatide per gram of protein (μmol/g protein).

2.8. Analysis of vitamin K

Aliquots of myelin were assessed for concentration of vitamin K (i.e., K1, MK-4 and dK) by reversed-phase HPLC [34]. Results were adjusted per myelin protein and expressed as picomole of MK-4 per gram of protein (pmol/g protein).

2.9. Statistical analysis

The results of biochemical measurements were analyzed by Analysis of Variance and *post hoc* Fisher's LSD tests. All statistical analyses, including correlations, were performed using SYSTAT version 10.2.01 (SPSS, Chicago, IL, USA). Data points collected from two rats (12 months, K1 diet; 24 months, dK diet) were excluded from the analyses as outliers. Three cortical samples from the dK dietary group (two, 12 months; one, 24 months) did not contain a sufficient amount of sample for the assessment of MK-4 (i.e., values were below the minimum detectable concentrations of 0.05 nmol/kg tissue). Results were considered statistically significant if the observed significance value was less than .05.

3. Results

A total of 53 rats completed the dietary intervention (Fig. 1). One young (2 months old) rat died shortly after arrival and prior to the start of the dietary trial; six old rats (24 months; two rats from the vitamin K1-supplemented group and four rats from the dK-supplemented group) died of apparent age-related pathologies, including neoplasia, which did not appear to result from experimental treatments. There were no significant differences in the weights between two dietary groups of rats within the same age groups (Fig. 1).

3.1. Sulfatides

To test the hypothesis that lack of conversion of dietary dK to MK-4 in the brain will affect sulfatides in brain myelin, we compared sulfatide content in myelin fractions isolated from the cortex, striatum and hippocampus of young (2 months), adult (12 months) and old (24 months) rats maintained on dK or K1 diets. Results showed a significant diet *vs.* age effect on sulfatides in the hippocampus [$F(2,47)=6.47$; $P=.003$] and cortex [$F(2,47)=5.48$; $P=.007$], whereas in the striatum this effect was not significant ($P=.408$) (Table 1). Young rats fed with dK diet had lower sulfatide content compared to those fed K1 diet in the hippocampus (K1 *vs* dK diet: $P=.014$) and cortex (K1 *vs* dK diet: $P=.012$), whereas in the striatum there were no significant differences between the two diets ($P=.242$) (Table 1). Adult and old rats fed with dK diet showed lower sulfatide content than K1 dietary groups in the striatum (12 months; K1 *vs* dK: $P=.003$) and cortex (24 months; K1 *vs* dK: $P=.001$) (Table 1). Age-related changes in the sulfatide content were observed in the hippocampus (young *vs* adult, $P=.004$; young *vs* old, $P=.001$), striatum (young *vs* adult, $P=.001$) and cortex (young *vs* old, $P=.037$; adult *vs* old, $P=.006$) in rats fed with dK diet (Table 1). There were no age-related differences in the content of myelin sulfatides in rats fed with K1-supplemented diet.

Table 1
Age- and region-specific effects of dietary phylloquinone (K1) and dihydrophylloquinone (dK) on sulfatides and MK-4 content in brain myelin[1]

Brain regions	Age (mos)	Sulfatides (μmol/g protein)		Menaquinone-4 (pmol/g protein)	
		K1 diet	dK diet	K1 diet	dK diet
Hippocampus	2	31.98 ± 6.14^{a}	$14.05\pm2.82^{a,j,k}$	1049 ± 244	782 ± 52
	12	20.81 ± 2.57	35.35 ± 4.61^{j}	1089 ± 115	1065 ± 180
	24	33.63 ± 6.06	44.03 ± 10.63^{k}	1230 ± 273	859 ± 226
Striatum	2	23.71 ± 6.65	15.91 ± 1.33^{l}	449 ± 46^{e}	221 ± 20^{e}
	12	16.91 ± 1.91^{c}	$10.12\pm0.70^{c,l}$	527 ± 67^{f}	286 ± 48^{f}
	24	11.95 ± 0.67	12.79 ± 1.96	418 ± 54^{g}	241 ± 41^{g}
Cortex	2	3.76 ± 0.37^{b}	$2.66\pm0.16^{b,m}$	182 ± 15^{h}	114 ± 14^{h}
	12	2.80 ± 0.20	2.96 ± 0.27^{n}	229 ± 41^{i}	99 ± 25^{i}
	24	3.01 ± 0.11^{d}	$1.85\pm0.19^{d,m,n}$	314 ± 53	266 ± 13

[1] Values are mean±S.E.M. Values in column with superscripts with a common letter differ by diet (a–i) and by age (j–o). Dietary effect: $^{a}P=.014$; $^{b}P=.005$; $^{c}P=.012$; $^{d}P=.001$, $^{e}P=.001$; $^{f}P=.01$; $^{g}P=.032$; $^{h}P=.005$; $^{i}P=.021$. Age effect: $^{j}P=.004$; $^{k}P=.001$; $^{l}P=.001$; $^{m}P=.025$; $^{n}P=.003$; $^{o}P=.001$.

3.2. Vitamin K

In this study, we investigated whether the differences in the conversion efficiency of the vitamin K dietary forms (i.e., K1 and dK) to MK-4 would differentially affect MK-4 content in myelin fractions isolated from the hippocampus, striatum and cortex with age. Results showed that both dietary forms of vitamin K were converted to MK-4 in the brain. However, dietary dK had lower than K1 conversion efficiency as reflected through a lower content of MK-4 in the striatum (2 months, $P=.001$; 12 months, $P=.01$; 24 months, $P=.04$) and cortex (2 months, $P=.005$; 12 months, $P=.019$) (Table 1; K1 *vs* dK). There were no significant differences in MK-4 content between the two dietary groups in the hippocampus (Table 1). These findings suggest that the efficiency of the dietary dK conversion to MK-4 in the hippocampus was similar to the dietary K1. There were no significant diet *vs* age effects on MK-4 content in myelin fractions isolated from the hippocampus ($P=.61$), striatum ($P=.81$) or cortex ($P=.49$).

3.3. Association between sulfatides and MK-4

No significant correlations were observed between sulfatides and MK-4 in evaluated brain regions in young (2 months) rats fed with either K1 or dK diets ($P>.05$; data not shown). However, there were significant positive correlations between sulfatides and MK-4 in the adult (12 months) rats fed with K1 diet (K1: hippocampus, $r=.71$, $P=.02$; cortex, $r=.90$; $P=.001$) or dK diet (dK: hippocampus, $r=.83$; $P=.003$) (Fig. 2). These correlations were also significant in old (24 months) rats fed with K1 diet (K1: hippocampus, $r=.87$; $P=.005$; cortex, $r=.82$, $P=.014$) (Fig. 2A and C). There were no significant correlations between sulfatides and MK-4 in old rats fed with dK diet. Furthermore, no significant correlations were observed in the striatum within the same age groups (Fig. 2B).

Serum MK-4 concentrations [34] were significantly positively correlated with sulfatide concentrations in myelin fractions isolated from the hippocampus in the individual animals ($r=.601$, $P=.001$).

4. Discussion

In this study, the insufficiency of dietary 2′,3′-dihydropilloquinone conversion to MK-4, when compared with the equal intake of phylloquinone, differentially affected sulfatides in myelin fractions isolated from the brain regions of Fischer 344 male rats. Our finding of lower sulfatide content in the cortex (2 and 24 months), striatum (12 months) and hippocampus (2 months) in the dK dietary group, compared to K1, suggests a potential dietary dK-associated

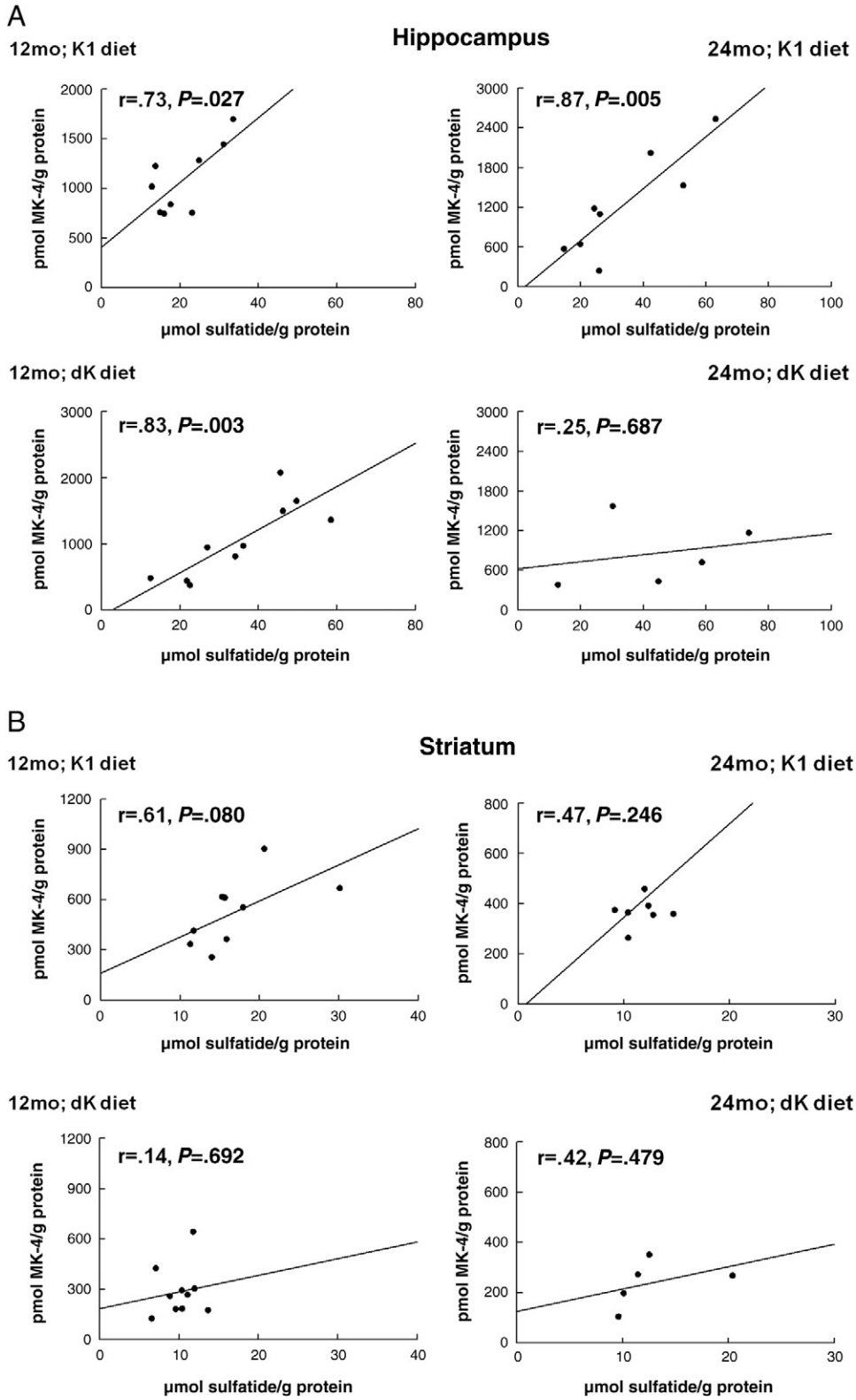

Fig. 2. (A–C) The association between MK-4 and sulfatides in myelin fractions isolated from the hippocampus (A), striatum (B) and cortex (C) of adult (12 months) and old (24 months) rats exposed to dietary phylloquinone (K1 diet) and dihydrophylloquinone (dK diet). Data points are concentrations of MK-4 and sulfatides from the hippocampus (*n* per K1 group: 12 months — 9; 24 months — 8; *n* per dK group: 12 months — 10; 24 months — 5), striatum (*n* per K1 group: 12 months — 9; 24 months — 8; *n* per dK group: 12 months — 10; 24 months — 5) and cortex (*n* per K1 group: 12 months — 9; 24 months — 8; *n* per dK group: 12 months — 10; 24 months — 4) of rats fed with K1 or dK diets. Data points collected from two rats (12 months, K1 diet; 24 months, dK diet) were excluded from the analyses as outliers. Three cortical samples from the dK dietary group (two, 12 months; one, 24 months) did not contain a sufficient amount of sample for the assessment of MK-4 (i.e., values were below the minimum detectable concentrations of 0.05 nmol/kg tissue).

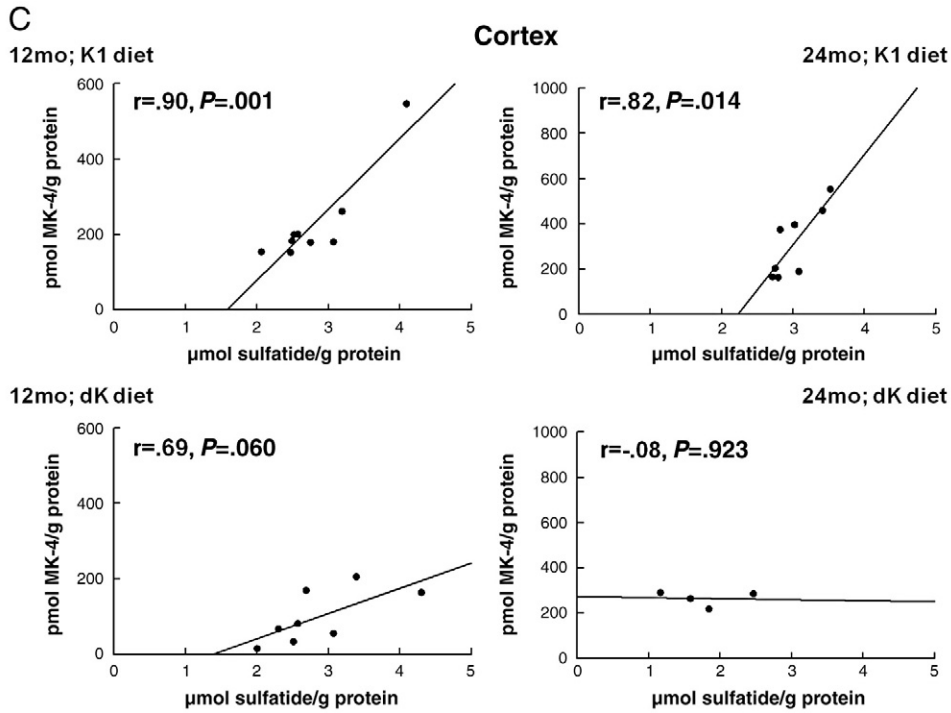

Fig. 2 (*continued*).

dysregulation in the sulfatide metabolism in oligodendrocytes, brain cells which are responsible for the biosynthesis of myelin constituents in CNS [8–10] in these brain regions. Recent studies demonstrated the ability of vitamin K to modify the activity of galactocerebroside sulfotransferase, the key enzyme of sulfatide synthesis [41].

The differential activity of oligodendrocytes and the differential rates of myelin formation among brain regions [17–20,42] may also be accountable for the region-specific dietary effects observed in the present study. The myelination of rat brain regions occurs at a different age and continues up to 20 months of age with a higher rate during earlier period of life (i.e., 20 days is the peak of myelin formation) and a lower rate during later period of life (18–20 months) [17–20,42]. Therefore, our findings of a relatively higher responsiveness to the dietary intervention among young (2 months) rats as compared to those among older rats can be attributed to the age-related differences in the compensatory reactions in these animals. However, it is also plausible that experimental conditions, including low dietary intake doses of vitamin K and relatively short-term of the dietary intervention (i.e., 28 days), chosen for the present study, limited our ability to detect dietary effects on myelin sulfatides across all age groups in the evaluated brain regions.

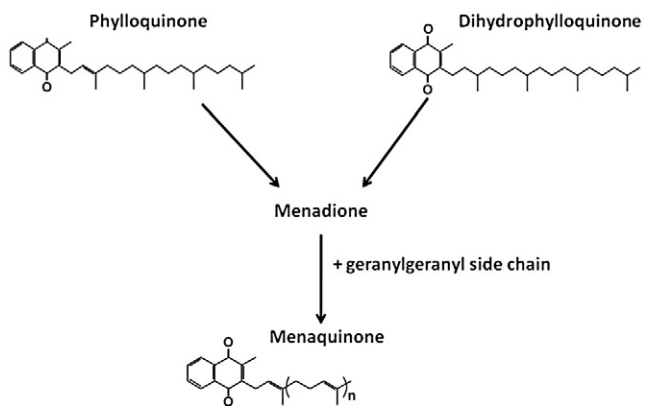

Fig. 3. Potential mechanism of conversion of the dietary forms of vitamin K to MK-4.

Low sulfatide content in brain myelin has been recently linked with the disruption of myelin integrity [14,21]. The disruption of myelin integrity was recently implicated as an essential contributor to cognitive deficit [6,7,43,44]. Therefore, our findings of dietary-associated decreases in myelin sulfatides suggest a potential disruption in myelin integrity in evaluated brain regions. However, it is currently unknown whether such disruption would be sufficient to modify motor and cognitive functions controlled by these brain regions.

In the present study, both dietary forms of vitamin K were converted to MK-4 in the brain. However, the efficiency of dietary dK conversion to MK-4 compared to K1 was lower in the striatum and cortex, and was similar to K1 in the hippocampus. The location and the mechanism for the conversion of the dietary forms of vitamin K to MK-4 are largely unknown. However, the potential mechanism was proposed recently suggesting that in mice the side chain of phylloquinone can be removed by a currently unknown enzyme to form menadione followed by the geranylgeranylation of menadione to form MK-4 [45] (Fig. 3).

The presence of MK-4 in myelin fractions, and the positive correlations between MK-4 and sulfatides in brain myelin, supports recent findings in female rats [31], which suggests that the physiological role of MK-4 may be independent from its well-known role as a cofactor for the γ-carboxylation reactions [30,34,46]. It is currently unknown whether long-term dietary dK consumption will modulate these functions through further reduction in dK conversion to MK-4, and whether MK-4 may have a role in myelin formation and maintenance. Our finding of positive correlation between sulfatides in the hippocampus and MK-4 in serum may be potentially important for human studies.

In summary, this is the first study to demonstrate the effect of dietary vitamin K on sulfatides and MK-4 in the purified brain myelin. It remains to be determined whether long-term and/or higher dietary

dK consumption would be sufficient to affect brain region-specific changes in the (a) number and/or metabolic activity of oligodendrocytes; (b) rate of myelin formation and loss; and (c) activity of genes responsible for the synthesis of myelin constituents. Furthermore, the behavioral consequences of altered sulfatide concentrations through manipulation of dietary vitamin K remain to be assessed.

Acknowledgments

We thank Beverly Dobson for her assistance in the manuscript preparation.

References

[1] Colombo PJ, Gallagher M. Individual differences in spatial memory among aged rats are related to hippocampal PKC gamma immunoreactivity. Hippocampus 2002;12:285–9.
[2] Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. Neuron 2007;56: 924–35.
[3] Hinman JD, Abraham CR. What's behind the decline? The role of white matter in brain aging. Neurochem Res 2007;32:2023–31.
[4] Ando S, Tanaka Y, Toyoda Y, Kon K. Turnover of myelin lipids in aging brain. Neurochem Res 2003;28:5–13.
[5] Peters A, Rosene DL, Moss MB, Kemper TL, Abraham CR, Tigges J, et al. Neurobiological bases of age-related cognitive decline in the rhesus monkey. J Neuropathol Exp Neurol 1996;55:861–74.
[6] Peters A, Rosene DL. In aging, is it gray or white? J Comp Neurol 2003;462:139–43.
[7] Duce JA, Podvin S, Hollander W, Kipling D, Rosene DL, Abraham CR. Gene profile analysis implicates Klotho as an important contributor to aging changes in brain white matter of the rhesus monkey. Glia 2008;56:106–17.
[8] Norton WT. Recent advances in myelin biochemistry. Ann N Y Acad Sci 1984;436: 5–10.
[9] Baumann N, Pham-Dinh D. Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiol Rev 2001;81:871–927.
[10] Larocca JN, Rodriguez-Gabin AG. Myelin biogenesis: vesicle transport in oligodendrocytes. Neurochem Res 2002;27:1313–29.
[11] Maier O, Hoekstra D, Baron W. Polarity development in oligodendrocytes: sorting and trafficking of myelin components. J Mol Neurosci 2008;35:35–53.
[12] Kirschning E, Rutter G, Hohenberg H. High-pressure freezing and freeze-substitution of native rat brain: suitability for preservation and immunoelectron microscopic localization of myelin glycolipids. J Neurosci Res 1998;53:465–74.
[13] Ishibashi T, Dupree JL, Ikenaka KA. Myelin galactolipid, sulfatide, is essential for maintenance of ion channels on myelinated axon but not essential for initial cluster formation. J Neurosci 2002;22:6507–14.
[14] Marcus J, Honigbaum S, Shroff S, Honke K, Rosenbluth J, Dupree JL. Sulfatide is essential for the maintenance of CNS myelin and axon structure. Glia 2006;53: 372–81.
[15] Oshida K, Shimizu T, Takase M, Tamura Y, Yamashiro Y. Effects of dietary sphingomyelin on central nervous system myelination in developing rats. Pediatr Res 2003;53:589–93.
[16] Jungalwala FB. Synthesis and turnover of cerebroside sulfate of myelin in adult and developing rat brain. J Lipid Res 1974;15:114–23.
[17] Jurevics H, Hostettler J, Muse ED, Sammond DW, Matsushima GK, Toews AD, et al. Cerebroside synthesis as a measure of the rate of remyelination following cuprizone-induced demyelination in brain. J Neurochem 2001;77:1067–76.
[18] Muse ED, Jurevics H, Toews AD, Matsushima GK, Morell P. Parameters related to lipid metabolism as markers of myelination in mouse brain. J Neurochem 2001;76:77–86.
[19] Jacobson S. Sequence of myelinization in the brain of albino rat: A. Cerebral cortex, thalamus and related structures. J Comp Neurol 1963;121:5–29.
[20] Smith ME. A regional survey of myelin development: some compositional and metabolic aspects. J Lipid Res 1973;14:541–51.
[21] Han X, Cheng H, Fryer JD, Fagan AM, Holtzman DM. Novel role for apolipoprotein E in the central nervous system. Modulation of sulfatide content. J Biol Chem 2003;278:8043–51.
[22] Bartzokis G, Cummings JL, Sultzer D, Henderson VW, Nuechterlein KH, Mintz J. White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. Arch Neurol 2003;60: 393–8.
[23] Gisslen M, Fredman P, Norkrans G, Hagberg L. Elevated cerebrospinal fluid sulfatide concentrations as a sign of increased metabolic turnover of myelin in HIV type I infection. AIDS Res Hum Retroviruses 1996;12:149–55.
[24] Svennerholm L, Bostrom K, Helander CG, Jungbjer B. Membrane lipids in the aging human brain. J Neurochem 1991;56:2051–9.
[25] Svennerholm L, Gottfries CG. Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset form (type I) and demyelination in late-onset form (type II). J Neurochem 1994;62:1039–47.
[26] Wiggins RC. Myelin development and nutritional insufficiency. Brain Res 1982;257:151–75.
[27] Di Biase A, Salvati S. Exogenous lipids in myelination and myelination. Kaohsiung J Med Sci 1997;13:19–29.
[28] Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. Thromb Haemost 2008;100:530–47.
[29] Lev M, Milford AF. The 3-ketodihydrosphingosine synthetase of bacteroides melaninogenicus: induction by vitamin K. Arch Biochem Biophys 1973;157:500–8.
[30] Denisova NA, Booth SL. Vitamin K and sphingolipid metabolism: evidence to date. Nutr Rev 2005;63:111–21.
[31] Carrie I, Portoukalian J, Vicaretti R, Rochford J, Potvin S, Ferland G. Menaquinone-4 concentration is correlated with sphingolipid concentrations in rat brain. J Nutr 2004;134:167–72.
[32] Huber AM, Davidson KW, O'Brien-Morse ME, Sadowski JA. Tissue phylloquinone and menaquinones in rats are affected by age and gender. J Nutr 1999;129: 1039–44.
[33] Sato T, Ozaki R, Kamo S. The biological activity and tissue distribution of 2′,3′ dihydrophylloquinone in rats. Biochim Biophys Acta 2003;1622:145–50.
[34] Booth SL, Peterson JP, Smith DE, Chamberland J, Salisbury N, Crivello NA. Age and dietary form of vitamin K affect menaquinone-4 concentrations in male Fischer 344 rats. J Nutr 2008;138:492–6.
[35] Booth SL, Sadowski JA. Determination of phylloquinone in foods by high performance liquid chromatography. Methods Enzymol 1997;282:446–56.
[36] Denisova NA, Gorbunov NV, Avrova NF. Fatty acid composition of phospholipids of myelin and synaptosomal proteolipid complexes from vertebrate brain. Int J Biochem 1991;23:811–8.
[37] Denisova NA. Phospholipid composition of myelin and synaptosomal proteolipids from vertebrate brain. Int J Biochem 1990;22:439–43.
[38] Zabelinsky SA, Denisova NA. Proteolipid proteins and lipids in subcellular fractions and whole brain of vertebrates. Neurochemia 1986;5:397–403.
[39] Crivello NA, Rosenberg IH, Dallal GE, Joseph JA. Age-related changes in neutral sphingomyelin-specific phospholipase C activity in striatum, hippocampus, and frontal cortex: implication for sensitivity to oxidative stress and inflammation. Neurochem Int 2005;47:573–9.
[40] Kean EL. Rapid, sensitive spectrophotometric method for quantitative determination of sulfatides. J Lip Res 1968;9:319–27.
[41] Sundaram KS, Fan JH, Engelke JA, Foley AL, Suttie JW, Lev M. Vitamin K status influences brain sulfatide metabolism in young mice and rats. J Nutr 1996;126: 2746–51.
[42] LoPresti P. Regulation and differential expression of tau mRNA isoforms as oligodendrocytes mature in vivo: implications for myelination. Glia 2002;37:250–7.
[43] Haroutunian V, Davis KL. Introduction to the special section: myelin and oligodendrocyte abnormalities in schizophrenia. Int J Neuropsychopharm 2007;10:499–502.
[44] Bartzokis G, Lu PH, Tingus K, Mendez MF, Richard A, Peters DG, et al. Lifespan trajectory of myelin integrity and maximum motor speed. Neurobiol Aging 2009 PMID: 18926601 [in press].
[45] Okano T, Shimomura Y, Yamane M, Suhara Y, Kamao M, Sugiura M, et al. Conversion of phylloquinone (vitamin K1) into menaquinone-4 (vitamin K2) in mice: two possible routes for menaquinone-4 accumulation in cerebra of mice. J Biol Chem 2008;283:11270–9.
[46] Li J, Lin JC, Wang H, Peterson JW, Furie BC, Furie B, et al. Novel role of vitamin k in preventing oxidative injury to developing oligodendrocytes and neurons. J Neurosci 2003;23:5816–26.