Medical Hypotheses 84 (2015) 276–280

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A hypothetical role for vitamin K2 in the endocrine and exocrine aspects of dental caries

Ken Southward *

4920 Thirty Road, Beamsville, Ontario L0R 1B3, Canada

ARTICLE INFO

Article history:
Received 10 September 2014
Accepted 11 January 2015

ABSTRACT

The growing interest in oral/systemic links demand new paradigms to understand disease processes. New opportunities for dental research, particularly in the fields of neuroscience and endocrinology will emerge. The role of the hypothalamus portion of the brain cannot be underestimated. Under the influence of nutrition, it plays a significant role in the systemic model of dental caries. Currently, the traditional theory of dental caries considers only the oral environment and does not recognize any significant role for the brain. The healthy tooth, however, has a centrifugal fluid flow to nourish and cleanse it. This is moderated by the hypothalamus/parotid axis which signals the endocrine portion of the parotid glands. High sugar intake creates an increase in reactive oxygen species and oxidative stress in the hypothalamus. When this signaling mechanism halts or reverses the dentinal fluid flow, it renders the tooth vulnerable to oral bacteria, which can now attach to the tooth's surface. Acid produced by oral bacteria such as Strep Mutans and lactobacillus can now de-mineralize the enamel and irritate the dentin. The acid attack stimulates an inflammatory response which results in dentin breakdown from the body's own matrix metalloproteinases. Vitamin K2 (K2) has been shown to have an antioxidant potential in the brain and may prove to be a potent way to preserve the endocrine controlled centrifugal dentinal fluid flow. Stress, including oxidative stress, magnifies the body's inflammatory response. Sugar can not only increase oral bacterial acid production but it can concurrently reduce the tooth's defenses through endocrine signaling. Saliva production is the exocrine function of the salivary glands. The buffering capacity of saliva is critical to neutralizing the oral environment. This minimizes the de-mineralization of enamel and enhances its re-mineralization. K2, such as that found in fermented cheese, improves salivary buffering through its influence on calcium and inorganic phosphates secreted. Data collected from several selected primitive cultures on the cusp of civilization demonstrated the difference in dental health due to diet. The primitive diet group had few carious lesions compared to the group which consumed a civilized diet high in sugar and refined carbohydrates. The primitives were able to include the fat soluble vitamins, specifically K2, in their diet. More endocrine and neuroscience research is necessary to better understand how nutrition influences the tooth's defenses through the hypothalamus/parotid axis. It will also link dental caries to other inflammation related degenerative diseases such as diabetes.

Introduction

A healthy tooth is well designed to withstand a harsh oral environment because it cleanses itself from the inside out. Dental caries is evidence that the tooth's fluid flow has been halted or reversed and the tooth's defenses have been compromised. The local process of enamel de-mineralization by bacterial acid is significantly influenced by nutrition, specifically refined carbohydrates such as sugar. The caries process to render the tooth vulnerable, however, starts in the hypothalamus part of the brain and changes are initiated in the dentinal fluid flow [1]. Nutrition plays a significant role in both the systemic and local aspects of this process.

Following enamel de-mineralization of a compromised tooth due to acid, dentin breakdown is accomplished by the body's own matrix metalloproteinases (MMP's) [2,3] as a result of an uncontrolled inflammatory response to the acid irritant. This phase of the caries process commences as reversible inflammation or 'dentinitis' and proceeds to irreversible dentin caries. This is similar to reversible or irreversible pulpitis and the terms gingivitis and periodontitis when referring to the periodontium [4].

The systemic concept of dental caries recognizes that the process is multi-factorial. While decreasing the insult side of the

* Tel.: +1 905 563 8387.
E-mail address: drken.southward@gmail.com

http://dx.doi.org/10.1016/j.mehy.2015.01.011
0306-9877/

process by reducing sugar intake and oral bacteria counts is important, increasing the body's defense side with an antioxidant rich diet of fruits, vegetables and K2 may be relatively more important in reducing vulnerability.

It has been documented that K2 can assist in significantly reducing dental caries [5,6]. Much research, however, is needed to determine why this vitamin can enhance defenses locally through changing saliva composition and systemically through its influence on the hypothalamus and the endocrine aspect of the parotid gland.

This systemic concept is a significant paradigm shift from the traditional 'acid theory' of dental caries. It has many implications for future efforts in dental prevention.

The hypothesis

Oral and other systemic stress responses are similar

The understanding of stress originated in the 1950's [7]. The word 'stressor' was coined to describe the irritant and the body's reaction to the irritation became known as a stress response. If a stressor was local, such as enamel demineralization due to acid, or plaque irritating the periodontal tissues, the body responded with a 'Local Adaptation'. The local adaptations are controlled, inflammatory responses and are similar throughout the body so they are termed a 'Local Adaptation Syndrome' (LAS). In the dentin portion of the tooth, 'dentinitis' represents the local inflammatory response.

A local response can be exaggerated when the whole body becomes involved through the endocrine system. This system wide response is termed a 'General Adaptation Syndrome' (GAS) because the effects on the body are similar despite the location or type of stressor [7]. The hypothalamus/pituitary/adrenal axis controls the body's general response.

Refined carbohydrates like sugar locally stimulate the oral bacteria to produce acid. This causes de-mineralization of enamel and 'dentinitis' in the dentin. This is a local inflammatory adaptation and is part of the LAS. Traditional caries theory is usually limited to this phase.

Beyond this local effect, however, sugar has a significant impact on the body when it is absorbed. Blood sugar spikes need to be managed and centrifugal dentinal fluid flows through the tooth are disrupted by signals coordinated through the hypothalamus of the brain. This general adaptation or GAS is mainly an endocrine driven response, which affects the whole body. The hypothalamus/parotid axis is the endocrine axis most relevant to dental health [8]. The effects of local irritation are magnified in the presence of a GAS response [7,9].

This systemic understanding explains why not all oral acids are equal in their effect. Sucking on lemons, for example, induce enamel demineralization but are not as significantly related to dental caries. The inflammatory stimulus of acid demineralization is handled with local resources through the LAS. Sugar, however, with its significant effect on the whole body, magnifies the local acid attack by triggering the GAS. It does this by causing the hypothalamus/parotid axis to decrease the dentinal fluid flow. This makes the tooth more vulnerable to the acid exposure [1].

The tooth must first become vulnerable to caries

A healthy tooth is nourished by a centrifugal fluid flow through the dentin. This flow can stop or reverse when influenced by a systemic stressor such as a high sugar intake [10]. This step now allows oral bacteria to attach to the surface of the tooth and produce acid which de-mineralizes the enamel surface and irritates the dentin causing inflammation.

The fluid flow through the tooth is stimulated by an endocrine hormone secreted by the parotid gland, hence the term parotid hormone [8]. It is a 30 amino acid protein [11]. The parotid gland is not commonly recognized as a dual function exocrine/endocrine gland. This characteristic makes it similar to the pancreas. Both parotid hormone and insulin [12] are regulated by the hypothalamus part of the brain. This influence is part of the GAS affecting the adrenal glands through the hypothalamus. The stimulus or stressor for parotid signaling can be initiated by sugar intake and it can be manipulated in lab studies with carbamyl phosphate [13], which served as an antioxidant [1].

Once the tooth has become vulnerable, the fibroblasts in the tooth can become irritated or stressed by the low ph or acid attack, which has already demineralized the enamel. This response is a normal inflammatory reaction (LAS). The corresponding increased metabolism increases reactive oxygen species (ROS) production and activates MMP's such as collagenase. Tissue inhibitors of metalloproteinases (TIMP's) neutralize activated MMP's when they are no longer necessary and serve as the body's way of controlling inflammation. Antioxidants help to control inflammation by neutralizing ROS, thus decreasing the need to stimulate the MMP activation. Optimum nutrition can play a role here. Temporary irritations are thus managed by controlled inflammation causing a reversible state but healing occurs. This is 'dentinitis' [14,15]. Excessive irritation causes uncontrolled inflammation which is largely irreversible in the tooth and recognized in dentin as caries.

The systemic approach reveals the overlooked importance of antioxidants

The systemic view of dental caries links dental caries to diabetes. When high blood glucose in the hypothalamus increases metabolic activity, more positively charged free radicals, specifically reactive oxygen species (ROS), are produced. They are the warning signs for the hypothalamus to down regulate parotid hormone while up regulating the pancreas to produce insulin. Antioxidants help manage the free radical storm in the hypothalamus [16] caused by the blood glucose spike.

Methamphetamine produces a hurricane of free radicals [17] which could shut down all parotid hormone and dentinal fluid flow. The dental caries devastation known as "meth mouth" demonstrates the exaggerated response [18].

Antioxidants are a powerful defense to free radical damage, as evidenced by the "Asian Paradox", which refers to high rates of cigarette smoking but less heart disease and cancer amongst green tea drinkers [19]. Green tea is well known for its antioxidant properties, especially epigallocatechin gallate (EGCG). The same paradox applies to periodontal disease [20]. Green tea and its antioxidants have also proven effective in reducing caries rates [21]. This study also demonstrated that the tea was just as effective when all fluoride was removed, thus eliminating fluoride as a confounding factor. While the systemic antioxidant effects of green tea on dental caries and tooth vulnerability are significant, vitamin K2 may prove a more potent antioxidant [22–24].

The critical importance of antioxidants, such as resveratrol and curcumin, is now emerging relative to oxidative stress caused by fluoride. The fluoridation of drinking water has long been touted by the dental profession as beneficial for dental health. Now it appears that fluoride causes significant oxidative stress and antioxidants are the antidote. [25,26]

A brief description of K2

K2 is in the quinone group and is known as menaquinone. K1 is phylloquinone and Co-enzyme Q10 is ubiquinone. Quinones have oxygen containing ring structures, which can make them very

active in electron transport reactions [27]. K2 was placed in the K vitamin category because it is produced in the body from K1 [28].

K1 is essential to blood clotting. Accordingly, the body has found ways to re-cycle K1 for repeated use and, thus, depend less on dietary intake of K1. The anti-coagulant, warfarin, interferes with the re-cycling process to decrease K1 and reduce the body's ability to clot. High dietary intakes of K1 defeat warfarin's effect because the K1 is available without re-cycling.

K2 has several forms, which are numbered according to side chains. (eg. MK4 and MK7) While MK4 is the form the body produces from K1, supplemental MK4 is synthetic. MK7 is a biologically active form that has a longer half-life in the body so it is often preferred in supplementation [29].

K2 acts in the body as a co-factor of 'vitamin K dependant carboxylase'. This enzyme, when enabled by its cofactor K2, can alter the structure of proteins by the process of gamma-carboxylation. Two examples of proteins are osteocalcin, found in bones and teeth, and matrix GLA protein found in cardiovascular tissues. Both of these proteins require the fat soluble vitamins A and D in their production [30]. Carboxylation of osteocalcin by K2 permits it to attract and retain calcium, which is good in bones [31,32]. The reverse of this process happens in cardiovascular tissues because matrix GLA proteins allow calcium to settle in arteries when they are uncarboxylated but shed calcium when they are carboxylated with sufficient K2 [33–35]. Calcification or 'hardening of the arteries' is not good. Essentially, K2 helps direct calcium to where it is supposed to be and away from where it is not supposed to be. With an understanding of the importance of calcium signaling relative to mitochondrial associated membranes (MAMs) [36], it may be that K2 will be found to be involved but this has not been reported as yet. There is growing recognition of its importance in the nervous system, specifically in the Gas6 protein and shingolipids, plus the actions of K2 with respect to oxidative injury and inflammation [37].

Dietary K2, after absorption, is processed in the liver and released into the circulation via high and low density lipoproteins. This makes them available for extrahepatic tissue uptake [38]. Fermented foods such as cheese have significantly higher levels of K2 than milk. The higher levels are provided by the bacteria. Natto (fermented soy), while not common in the American diet, is by far the post potent source of K2 [30]. Most K2 supplements are cultured from natto.

Menaquinones are stored in several tissues of the body. Some of the highest concentrations are in the pancreas and the salivary glands [39]. There is a close relationship between both of these exocrine/endocrine glands through the hypothalamus. High concentrations of K2 are also found in the brain, heart and bone. Recent research begins to shed light on some of the antioxidant potential of K2 in the brain [40,41]. The significance of this potential cannot be underestimated with relation to all degenerative diseases, including dental caries, that have been related to oxidative stress. K2 is also starting to receive much more of the public's attention that it deserves in the literature [6,24].

Teeth are also nourished from the outside

Saliva is the medium for nourishment from the outside of the tooth [42]. Human saliva is made up of water, minerals, enzymes and buffering agents. Cytosolic free calcium plays the most critical role in signaling the salivary gland secretions [43–45]. Given calcium's dependency on K2 assisted carboxylation with respect to osteocalcin and matrix GLA proteins, further study may show that K2 is similarly involved in activation of salivary signaling and composition. It has already been demonstrated with insulin [46] and the exocrine secretions of the pancreas [47]. Saliva is a significant factor in the mineralization and demineralization of the erupted tooth's enamel as pH changes. It buffers against acid demineralization and provides minerals for re-mineralization when necessary. The critical pH of the tooth, or the pH at which it will de-mineralize, is variable rather than fixed at 5.5 [48]. This variability is based on saliva composition and flow. In common circumstances, this is why it is best to store an evulsed tooth in milk, which has calcium and phosphorus in it, rather than water. It is not presently known how saliva is connected to K2, but it has been associated with increased inorganic phosphate, the buffering agent, which leads to decreasing counts of lactobacillus acidophilus [5]. This would be indicative of an increasing pH or less acid saliva since lactobacillus thrive at lower pH levels.

Cheese has been classified as having anti-cariogenic properties while milk has been classified as non-cariogenic [49]. Milk may have a local effect on the caries process due to its mineral composition. Cheeses, on the other hand, are fermented in bacteria, which contributes to a significantly higher amount of K2 [30,50]. The beneficial effect of cheese then could be systemic as a source of K2 rather than local as a non-acid producing food or mineral provider. Alternately or additionally, there is a possibility that K2 may be absorbed across the oral mucous membranes. Recent studies have effectively applied ubiquinone as a topical to suppress periodontal inflammatory reactions due to oxidative stress [51].

Briefly, K2's effect on the outside of the tooth is accomplished through its influence on saliva composition. Primary prevention or maintaining mineralization is best focused on dietary nutrients. Secondary prevention or re-mineralization success will be largely determined by whether the composition of saliva can be altered to create a pro re-mineralization environment.

Designing a randomized controlled trial

To research the potential of K2 to prevent dental caries requires a properly designed randomized controlled trial (RCT). The ideal first step would be to identify an appropriate 'control group' who have never exhibited any dental caries. Secondly, a 'comparative group' would have to be identified with minimal confounding factors. Latitude, altitude, age, water fluoridation, income and education levels, professional care availability, smoking, diabetes, pharmaceuticals, food quality, supplementation and even behavioral differences due to monitoring could all be considered confounding factors. In an ideal RCT, the only difference would, in general, be diet and specifically the key nutrients involved.

Dentistry is very fortunate. The data has already been collected and documented. It needs to be re-analyzed with fresh eyes and a broader understanding of the dental caries process.

Collecting the data

Scientific research has always been a priority of the American Dental Association (ADA). Its' research department was chaired by Dr. Weston A. Price from 1914 to 1928 [52].

Price was an experienced researcher who knew how to collect and record data. In the 1930's, he focused on nutrition, particularly its effect on dental caries. Price collected data, photographs and reported on 14 groups of primitive cultures from different parts of the world. This was not a random selection of cultures. Each group was specifically selected because they were on the cusp of civilization. Some members of the group were still primitive in nutrition and customs while others had shifted to a modern, civilized diet and routine. Only this primitive/civilized blend could provide both the control and the study group. Importantly, studying a variety of racial groups from around the world would eliminate virtually all of the confounding factors listed previously. It would be safe to say that this quantity and quality of data could never be collected again due to the spread of modern culture and diet. The significant differences in the caries rates are summarized in Table 1.

Price subsequently had food samples from these groups sent to his lab for analysis. Repeatedly, he found the primitive diets to be high in nutrients including the fat soluble vitamins A and D and, in particular, a critical factor which he called Activator X. Price knew Activator X could be found in butter from grass fed animals, especially in the early growing season when the grass was growing quickly [5]. He understood it was a fat soluble nutrient. It was not till the year 2007, almost 60 years after his death, that Activator X was linked to menaquinone or K2 [6]. Since that time, it has received growing attention in the fields of cardiovascular disease, osteoporosis and diabetes.

Dentistry is in the fortunate position of having the evidence of what works based on Price's research and documentation. Activator X can positively affect the outside of the tooth through saliva and the inside by helping regulate dentinal fluid flow. While this can be determined in lab research, we cannot duplicate the primitive control group in society. New research will have to focus on the ability of a K2 rich diet to arrest an existing caries process. This would provide the greatest benefits to children.

Evaluation of the hypothesis

The traditional theory of dental health, known as the 'acid theory', has been limited to the oral environment as though it is a unique process. Oral bacteria collect on the tooth's surface as plaque. Refined carbohydrates like sugar feed these bacteria which produce acid. This de-mineralizes the enamel of the tooth. The incorrect assumption is that bacterial MMP's then break down the dentin collagen in the caries process. There is no evidence to support this theory when it comes to dentin caries. Preventive efforts have focused on tooth brushing and flossing to reduce the bacteria, limiting sugar or substituting zylitol to reduce acid production and applying fluoride to re-mineralize enamel. After decades of the same approach, dental caries remains a significant problem despite valiant efforts to prevent it. Clearly a new approach is warranted.

The systemic theory of dental caries recognizes the impact of refined carbohydrates on the body through the influence of the hypothalamus and endocrine system. This is beyond traditional dentistry. Meticulous research done in the 1980's and 90's has been pushed aside because it did not suit the 'acid theory' model. This lab research can be duplicated and enhanced with better measuring tools. Free radicals, specifically reactive oxygen species, (ROS) have typically been considered the exhaust of energy production in mitochondria and a critical weapon for our immune system. Now we are seeing them as critical signals to trigger the hypothalamus to up or down regulate hormones such as parotid hormone and insulin. This is the realm of endocrinology or neuroscience. Now we need to determine what nutrients would optimally affect the hypothalamus and maintain centrifugal fluid flow through the tooth. Antioxidants such as EGCG of green tea have proven effective. K2, however, may prove to be a more potent nutrient. This is the realm of nutrition that goes well beyond sugar's effect on acid producing bacteria. While it would be virtually impossible today to collect data such as Dr. Weston Price did in the 1930's, there is great opportunity in re-analyzing his data within this new systemic paradigm.

Table 1
Percentage of teeth attacked by caries in primitive and modernized groups. Source: Nutrition and Physical Degeneration, 8th edition, page 402.

	Primitive	Modernized
Swiss	4.60	29.8
Gaelics	1.20	30.0
Eskimos	0.09	13.0
Northern Indians	0.16	21.5
Seminole Indians	4.00	40.0
Melanesians	0.38	29.0
Polynesians	0.32	21.9
Africans	0.20	6.8
Australian Aborigines	0.00	70.9
New Zealand Maori	0.01	55.3
Malays	0.09	20.6
Coastal Peruvians	0.04	40.0+
High Andes Indians	0.00	40.0+
Amazon Jungle Indians	0.00	40.0+

Some of the most revolutionary concepts in dentistry, such as dental implants and nickel-titanium metals in orthodontics and endodontics have their roots outside dental research. Data exists to support the systemic theory of dental caries and K2 as a critical component. Bringing dentinal fluid flow research up to date in the lab by substituting K2 and other antioxidants for carbamyl phosphate is the first step in proving this hypothesis. Re-evaluation of Price's data is important as Activator X is now associated with K2. Determining a community evaluation group to test this hypothesis would be necessary. The objective would be seeking to halt the dental caries process in a study group since it would be virtually impossible to assemble a group of "never decayed" without many confounding factors. To minimize compliance issues, a controllable group such as the armed forces might be an appropriate place to start. Nutritional supplements, placebos and no supplements would differentiate the three test groups. Staff dentists could determine base line measurements and ongoing changes. Another option might be school age children who could volunteer to take their supplements at school. Changes will happen faster in younger children with more rapid metabolisms than adults. It would be monitored by dental public health teams.

Once the hypothesis is proven, the issue of initiating a program and compliance may pose a challenge. If armed forces and dental public health teams are involved in the study, it may only require ramping up the proven program.

Consequences of the hypothesis

Nature has provided the evidence to prevent dental caries. Nutrition is the dominant factor in this process. It affects the endocrine aspects of enhancing the tooth's defenses by maintaining a nourishing dentinal fluid flow. The exocrine aspects of salivary glands or saliva secretion and composition are also nutritionally related. In terms of prevention of dental caries, optimum nutrition with fat soluble vitamins like K2 plays a far more significant role than the traditional dental recommendation to simply eat less sugar to minimize oral bacterial acids. Dental disease will be recognized as another inflammation related degenerative lifestyle disease like cardiovascular disease, osteoporosis and diabetes.

Who will lead this new nutrition paradigm? Will a field of 'neurodontics' emerge as dentists expand their research to include the brain? The dental profession has an advantage in application because optimal nutrition can be added to the beneficial 'cradle to grave' services presently being provided. The impact, however, may be felt well beyond dental disease. It could affect all degenerative diseases that are inflammation based. Expanding beyond the silo of the oral cavity may meet some resistance. Alternately, other disciplines such as nutritionists may offer dental nutrition programs that may prove more effective than present dental prevention programs. In the end, public health teams may play the key role.

Author's information

Dr. K. Southward received his dental degree from the University of Toronto in 1971. He maintained a private dental practice for

43 years with a focus on preventive dentistry and nutrition. He has published articles in dental journals relative to dental caries theory and periodontal health. He has recently retired.

Conflict of interest

The author declares that he has no conflicts of interest.

Acknowledgement

Dr. Weston A. Price's research data, which is presented in Table 1, is used with the kind permission of the Price-Pottenger Nutrition Foundation.

References

[1] Southward K. The systemic theory of dental caries. Gen Dent 2011;59(5):367–73.
[2] Sorsa T, Tjäderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis 2004;10(6):311–8.
[3] Tjäderhane L, Larjava H, Sorsa T, et al. The activation and function of host matrix metalloproteinases in dentin matrix breakdown in caries lesions. J Dent Res 1998;77(8):1622–9.
[4] Listgarten MA. Pathogenesis of periodontitis. J Clin Periodontol 1986;13(5):418–30.
[5] Weston Price DDS. Nutrition and Physical Degeneration, 8th ed. Price-Pottenger Nutrition Foundation Inc., Pages 364–369, 362–368, 398.
[6] <http://www.westonaprice.org/fat-soluble-activators/x-factor-is-vitamin-k2> accessed: 2013-09-14 (archived by WebCite at <http://www.webcitation.org/6JdK30Qf1>).
[7] Hans Selye MD. The Stress of Life. New York: McGraw-Hill Book Co.; 1978. 3–54, 57–168, 259–264.
[8] Leonora J, Tieche JM, Steinman RR. Further evidence for a hypothalamus–parotid gland endocrine axis in the rat. Arch Oral Biol 1993;38(10):911–6.
[9] Kesim S, Unalan D, Esen C, Ozturk A. The relationship between periodontal disease severity and state-trait anxiety level. J Pak Med Assoc 2012;62(12):1304–8.
[10] Leonora J, Tieche JM, Steinman RR. Stimulation of intradentinal dye penetration by feeding in the rat. Arch Oral Biol 1993;38(9):763–7.
[11] Zhang Q, Szalay AA, Tieche JM, et al. Cloning and functional study of porcine parotid hormone, a novel proline-rich protein. J Biol Chem 2005;280(23):22233–44.
[12] Leloup C, Tourrel-Cuzin C, Magnan C, et al. Mitochondrial reactive oxygen species are obligatory signals for glucose-induced insulin secretion. Diabetes 2009;58(3):673–81. http://dx.doi.org/10.2337/db07-1056.
[13] Steinman RR, Leonora J. Effect of selected dietary additives on the incidence of dental caries in the rat. J Dent Res 1975;54(3):570–7.
[14] Liu Y, Chen M, Yao X, et al. Enhancement in dentin collagen's biological stability after proanthocyanidins treatment in clinically relevant time periods. Dent Mater 2013;29(4):485–92. http://dx.doi.org/10.1016/j.dental.2013.01.013.
[15] Liu Y, Dusevich V, Wang Y. Proanthocyanidins rapidly stabilize the demineralized dentin layer. J Dent Res 2013;92(8):746–52. http://dx.doi.org/10.1177/0022034513492769.
[16] Leloup C, Casteilla L, Carrière A, et al. Balancing mitochondrial redox signaling: a key point in metabolic regulation. Antioxid Redox Signal 2011;14(3):519–30. http://dx.doi.org/10.1089/ars.2010.3.
[17] Barayuga SM, Pang X, et al. Methamphetamine decreases levels of glutathione peroxidases 1 and 4 in SH-SY5Y neuronal cells: protective effects of selenium. Neurotoxicology 2013;37:240–6. http://dx.doi.org/10.1016/j.neuro.2013.05.009.
[18] Ravenel MC, Salinas CF, et al. Methamphetamine abuse and oral health: a pilot study of "meth mouth". Quintessence Int 2012;43(3):229–37.
[19] Sumpio BE, Cordova AC, et al. Green tea, the "Asian paradox", and cardiovascular disease. J Am Coll Surg 2006;202(5):813–25.
[20] Nugala B, Namasi A, et al. Role of green tea as an antioxidant in periodontal disease: the Asian paradox. J Indian Soc Periodontol 2012;16(3):313–6.
[21] Yu H, Oho T, Tagomori S, Morioka T. Anticariogenic effects of green tea. Fukuoka Igaku Zasshi 1992;83(4):174–80.
[22] Ferland G. Vitamin K, an emerging nutrient in brain function. BioFactors 2012;38(2):151–7. http://dx.doi.org/10.1002/biof.1004. Epub 2012 Mar 15.
[23] Vervoort LM, Ronden JE, Thijssen HH. The potent antioxidant activity of the vitamin K cycle in microsomal lipid peroxidation. Biochem Pharmacol 1997;54(8):871–6.
[24] Oldenburg J, Marinova M, Müller-Reible C, Watzka M. The vitamin K cycle. Vitam Horm 2008;78:35–62. http://dx.doi.org/10.1016/S0083-6729(07)00003-9.
[25] Sharma C, Suhalka P, Sukhwal P, et al. Curcumin attenuates neurotoxicity induced by fluoride: an in vivo evidence. Pharmacogn Mag 2014;10(37):61–5. http://dx.doi.org/10.4103/0973-1296.126663.
[26] Atmaca N, Atmaca HT, Kanici A, Antepliogluu T. Protective effect of resveratrol on sodium fluoride-induced oxidative stress, hepatotoxicity and neurotoxicity in rats. Food Chem Toxicol 2014;70(5):191–7. http://dx.doi.org/10.1016/j.fct.2014.05.011. Epub 2014 May 22.
[27] Davidson VL. Electron transfer in quinoproteins. Arch Biochem Biophys 2004;428(1):32–40.
[28] Thijssen HH, Drittij MJ, Vermeer C, et al. Menaquinone-4 in breast milk is derived from dietary phylloquinone. Br J Nutr 2002;87(3):219–26.
[29] Sato T, Schurgers LJ, Uenishi K. Comparison of menaquinone-4 and menaquinone-7 bioavailability in healthy women. Nutr J 2012;12(11):93. http://dx.doi.org/10.1186/1475-2891-11-93.
[30] Kate Rheaume-Bleue, Vitamin K2 and the Calcium Paradox: How a Little-Known Vitamin Could Save Your Life. Mississauga, Canada: Wiley Pages 182–185.
[31] Knapen MHJ, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. Osteoporos Int 2007;18(7):963–72.
[32] Hosoi T. Clinical implications of under carboxylated osteocalcin. Clin Calcium 2009;19(12):1815–21.
[33] Kyla Shea M, Holden Rachel M. Vitamin K status and vascular calcification: evidence from observational and clinical studies. Adv Nutr 2012;3(2):158–65.
[34] Kyla Shea M, O'Donnell Christopher J, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. Am J Clin Nutr 2009;89(6):1799–807.
[35] Dalmeijer GW, van der Schouw YT, et al. The effect of menaquinone-7 supplementation on circulating species of matrix Gla protein. Atherosclerosis 2012;225(2):397–402.
[36] Patergnani S, Suski JM, Agnoletto C, et al. Calcium signaling around mitochondria associated membranes (MAMs). Cell Commun Signal 2011;22(9):19. http://dx.doi.org/10.1186/1478-811X-9-19.
[37] Ferland G. Vitamin K and the nervous system: an overview of its actions. Adv Nutr 2012;3(2):204–12. http://dx.doi.org/10.3945/an.111.001784.
[38] Leon J. Schurgers, Cees Vermeer, Determination of Phylloquinone and Menaquinones in Food, Effect of Food Matrix on Circulating Vitamin K Concentrations, Department of Biochemistry and Cardiovascular Research Institute. Maastricht, The Netherlands: Maastricht University.
[39] Komai M, Shirakawa H. Vitamin K metabolism. Menaquinone-4 (MK-4) formation from ingested VK analogues and its potent relation to bone function. Clin Calcium 2007;17(11):1663–72.
[40] Li J, Lin JC, Wang H, et al. Novel role of vitamin K in preventing oxidative injury to developing oligodendrocytes and neurons. J Neurosci 2003;23(13):5816–26.
[41] Ferland G. Vitamin K and brain function. Semin Thromb Hemost 2013;39(8):849–55. http://dx.doi.org/10.1055/s-0033-1357481. Epub 2013 Oct 9.
[42] Dowd FJ. Saliva and dental caries. Dent Clin North Am 1999;43(4):579–97.
[43] Ambudkar IS. Regulation of calcium in salivary gland secretion. Crit Rev Oral Biol Med 2000;11(1):4–25.
[44] Ambudkar IS. Dissection of calcium signaling events in exocrine secretion. Neurochem Res 2011;36(7):1212–21.
[45] Ambudkar IS. Polarization of calcium signaling and fluid secretion in salivary gland cells. Curr Med Chem 2012;19(34):5774–81.
[46] Choi HJ, Yu J, et al. Vitamin K2 supplementation improves insulin sensitivity via osteocalcin metabolism: a placebo-controlled trial. Diabetes Care 2011;34(9):e147.
[47] Thomas DD, Krzykowski KJ, Engelke JA, et al. Exocrine pancreatic secretion of phospholipid, menaquinone-4, and caveolin-1 in vivo. Biochem Biophys Res Commun 2004;319(3):974–9.
[48] Dawes C. What is the critical pH and why does a tooth dissolve in acid? J Can Dent Assoc 2003;69(11):722–4.
[49] Telgi RL, Yadav V, et al. In vivo dental plaque pH after consumption of dairy products. Gen Dent 2013;61(3):56–9.
[50] Elder SJ, Haytowitz DB, et al. Vitamin K contents of meat, dairy, and fast food in the U.S. Diet. J Agric Food Chem 2006;54(2):463–7.
[51] Yoneda T, Tomofuji T, et al. Anti-aging effects of Co-enzyme Q10 on periodontal tissues. J Dent Res 2013;92(8):735–9. http://dx.doi.org/10.1177/0022034513490959.
[52] <http://en.wikipedia.org/wiki/Weston_Price> accessed: 2013-09-14 (archived by WebCite at <http://www.webcitation.org/6JdJqgOao>).