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AKE
ARBEITSGEMEINSCHAFT KLINISCHE ERNÄHRUNG

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FOLIC

A case for personalized

Fortification of food with folic acid has resulted in significant declines in the occurrence of Neural Tube defect affected pregnancies; however, growing scientific evidence in the field suggests a possible association between high intake levels of folic acid and risks of cancer and other harmful effects. This article discusses the need to translate new epigenetic evidence into a more personalized folic acid supplementation approach.

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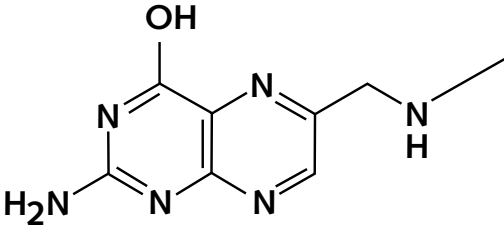
FOLATE DEFICIENCY AND NTDS

The relationship between folate deficiency and Neural Tube Defects (NTDs) occurrence was hypothesized as early as 1965 (Crider, Bailey, & Berry, 2011). Evidence from scientific studies has since then conclusively demonstrated that folic acid supplementation can prevent the occurrence of NTDs (EFSA, 2009); supplementation of >400µg/day is found to prevent as much as 70% of these defects (Van den Veyver, 2002). This has led many countries to recommend women planning to become pregnant to supplement their diet with folic acid (synthetic form of folate). In the EU, the recommended reference intake for folate is set by SCF (Scientific Committee on Foods, EC) : 200µg folate/day for adults, 400µg folate/day for pregnancy (EFSA, 2009). Yet, Public Health campaigns by countries to promote the awareness of this message and promote voluntary supplement intake by pregnant women have been unsuccessful in most countries (EUROCAT, 2005); the fact that the former target group needs to consume folic acid in the 4 weeks before and 8 weeks after conception, makes a voluntary intervention hard to implement effectively. This problem, together with the discovery of another important suspected effect of folic acid in the early 1990s: protection against cardiovascular diseases later in life (Cornel, de Smit, & de Jong-van den Berg, 2005), lead Public Health prevention policies to develop in two ways: some American and developing countries choose to implement mandatory fortification of staple foods (Cornel,de Smit, & de Jong-van den Berg, 2005), like flour, while voluntary fortification of food with folic acid is permitted and obligated in most European countries. Currently no EU country has implemented mandatory fortification (EFSA, 2009). Mandatory folic acid food fortification has since then resulted in significant declines in the occurrence of NTD affected pregnancies (EFSA, 2009). The percent declines range from 28% to 46% in the USA and Canada respectively (EFSA, 2009). Many (European) countries are therefore considering whether to adopt this mandatory fortification policy. American biomarker studies postfortification showed dramatic increases in population blood measurements of folate, this raised concerns that fortification exceeded the original daily intake target by as much as 2-fold (Ulrich & Potter, 2006). At the same time an advertising hyperbole of proactive fortified health foods market seems to have occurred, "where a muddying of waters can occur regarding the ideal between too little or too much of any given nutrient" (Lucock & Yates, 2009). This is of concern, taking into account the growing scientific evidence that has recently emerged suggesting a possible association between high intake levels of folic acid and risks of cancer (EFSA, 2009) and various other harmful effects.

RESULTS FROM CLINICAL STUDIES

Effects of folic acid supplementation are reviewed by Lucock & Yates (2009); the main positive effects described are lowering of the risk for birth defects, lower vasculotoxic, embryotoxic and neurotoxic homocysteine with benefit to a range of vascular conditions and Alzheimer's disease. Evidence from in vitro, animal, and human studies has shown that folate supplementation can act to prevent tumour initiation (Smith, Kim, & Refsum, 2008), yet it seems to facilitate progression of precancerous lesions (Lucock & Yates, 2009). A similar effect has also been shown in vascular patients, where supraphysiologic vitamins B6 and B12 along with folic acid did not lower recurrent cardiovascular disease after acute myocardial infarction, with the authors indicating a possible harmful effect of combined vitamin B therapy (Reviewed in: Lucock & Yates, 2009). Furthermore, it now seems that synthetic folate saturates human dihydrofolate reductase (DHFR) leading to unmetabolized folate in the circulation, and possibly masks the irreversible pernicious anaemia of B12 deficiency, the former increasing risk for cognitive impairment, while during pregnancy the same folate-B12 disposition may increase insulin resistance and obesity in offspring (Reviewed in: Lucock & Yates, 2009). Folic acid also reduces natural killer cell cytotoxicity, may increase the prevalence of positional plagiocephaly, and increases multiple births after IVF (Reviewed in: Lucock & Yates, 2009). Since the 1940s antifolate drugs are being used in cancer chemotherapy (Ulrich & Potter, 2006), because removal of folate or a blockade of its metabolism causes inhibition of tumor growth (Smith, Kim, & Refsum, 2008). Recent evidence showed that excess folic acid alters the efficacy of antifolate drugs (Reviewed in: Lucock & Yates, 2009). In general, "intervention studies using folic acid have produced a range of different results including adverse effects; overall they do not support the hypothesis that folic acid supplementation of human populations reduces the chronic disease risk" (EFSA, 2009). It is clear that disruptions in folate metabolism increase risk for a variety of pathologies (Stover & Caudill, 2008), yet while folate supplementation can reduce the risk of some disorders developing (Stover & Cau-



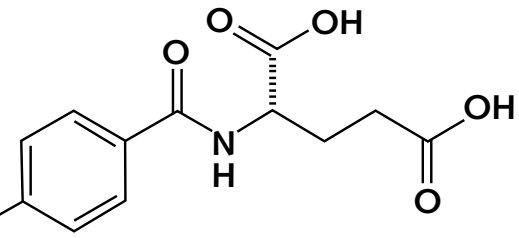
dill, 2008), it can itself likely disrupt the folate metabolism as well. So far, the precise biochemical mechanisms underlying folate-related pathologies have remained elusive despite intensive investigation (Stover & Caudill, 2008), yet new system biological evidence is rapidly emerging.

NUTRIGENETIC AND EPIGENETIC ASPECTS

Adequate folate status is essential for DNA synthesis and cell division and low folate status in humans is associated with an increase in DNA strand breaks, impaired DNA repair and increased mutations (Smith, Kim, & Refsum, 2008). Folate also plays a major role in the folate-mediated one-carbon metabolism; with a main function in the provision of methyl-groups for the conversion of homocysteine to methionine (Smith, Kim, & Refsum, 2008), which in turn can be adenosylated to form S-adenosylmethionine (SAM) (Stover & Caudill, 2008). SAM is a molecule with many functions, including methylation of cytosine residues in DNA and of arginine and lysine residues in histones, both of which are involved in regulating gene expression (Smith, Kim, & Refsum, 2008). By example, methylation of promoter related CpG islands can suppress gene expression by causing chromatin condensation ("silencing"), and could, for instance, silence tumor supressor as well as a tumor oncogenes.

ACID

preventive nutrition?



Therefore, folate plays a major role in epigenetic mechanisms; "any processs that alters gene activity without changes of the DNA sequence" (Haslberger, Varga, & Karlic, 2006). Gene variants that encode folate-dependent enzymes and alter the efficiency of nucleotide and SAM biosynthesis can confer both, protection and risk for specific pathologies; examples are the common SNPs in the methylenetetrahydrofolate dehydrogenase gene (MTHFD1), 1958G>A and methylenetetrahydrofolate reductase gene (MTHFR), 677C>T, which increases the risk for NTDs (Stover & Caudill, 2008). It is described that periconceptual exposure to folic acid might genetically select the latter gene, and lead to an increase in prevalence of individuals with MTHFR, 677C>T. This SNP is also associated with degenerative disorders (Lucock & Yates, 2009), however, seems protective against colon cancer in folate-replete individuals (Stover & Caudill, 2008). So far, "The functional role of these polymorphisms in the etiology of NTDs and cancer is unknown but is likely related to DNA synthesis, repair, and/or methylation mechanisms (Stover & Caudill, 2008)". "Low folate status is often associated with impairment of DNA methylation, but sometimes it leads to hypermethylation and thus could affect gene expression in complex ways. It is not known whether an excess of folate might have any adverse effects on these functions (Smith, Kim, & Refsum, 2008)". Changing the folate status in humans has been shown to influence DNA methylation, but, it is not yet established whether alterations in DNA methylation after changes in folate status are harmful in humans, for example, by regulating the expression of oncogenes or tumor suppressorgenes (Smith, Kim, & Refsum, 2008) and studies published have shown many contradicting results. However, animal studies on colorectal cancer have shown that the timing and dose of folate intervention are critical: If folate supplementation is started before the establishment of neoplastic foci, the development and progression of the tumor is suppressed, if started after, it enhances their growth and progression (Smith, Kim, & Refsum, 2008). This dichotomy has been consistently shown for colorectal adenomas, colorectal cancer rates, breast and prostate cancers (Lucock & Yates, 2009). Furthermore, a recent study by Berner, et al. (2010) found that exposure to a high concentration of folic acid enhanced cancer cell growth, and concomitant increased methylation of estrogen receptor and tumor suppressor promotors was observed, while a lower concentration of folic acid decreased cell growth. Aberrant promotor hypermethylation that is associated with inappropriate gene silencing of tumor suppressor genes is hypothesised to affect virtually every step in tumor progression (Haslberger, Varga, & Karlic, 2006).

It is important to note that Smith, Kim, & Refsum (2008) stated that additional biological explanations for contradictions in study outcomes are also likely: "For example, it is biologically plausible that any effect of folate on carcinogenesis will interact with a large number of other risk factors and that the patterns of these risk factors will differ between individuals. Observational studies have identified many factors, apart from age and sex, that might interact with folate in cancer risk, including vitamin B-12, alcohol, smoking, and polymorphisms in genes coding for enzymes related to one-carbon metabolism (Smith, Kim, & Refsum, 2008)". Furthermore, the influence of folate status on DNA methylation in both animals and humans is hypothesised to be tissue-, site-, and gene-specific (Smith, Kim, & Refsum, 2008). Overall, studies reviewed by Smith, Kim, & Refsum (2008) show that it is not justified to assume that the finding of a protective effect of high folate in a whole population necessarily applies to all people within that population, moreover, evidence provides cause for concern that increasing folate levels in an entire population may, in some people, increase the risk of cancer.

A NEED FOR AN INDIVIDUALIZED APPROACH?

Because the interactions between the epigenome and folic acid methylation-diets are complex and the fact that underlying biochemical mechanisms remain elusive, a population-based prevention method like folic acid food fortification is hazardous. "The highly complex and critical biological importance of folic acid-related molecular nutrition makes it a difficult micronutrient to deploy as a simple intervention at a population level – it has far too many biochemical spheres of

influence to predict effects in a generalized way" (Lucock & Yates, 2009). It remains unclear whether the possible harm of high folic acid levels outweighs the known and potential benefits. Furthermore, this harm-benefit balance may differ across individuals and populations, by genetic characteristics and by life stage (Ulrich & Potter, 2006). Therefore, recommended folic acid supplementation may need to be adapted to individual genotypes (Van den Veyver, 2002), and epigenetic DNA methylation profiles. Yet, to individualize folic acid dietary recommendations it seems necessary to have a detailed understanding of all genetic and physiological variables that influence the interaction of folate with the genome and their relationship to the disease process (Stover & Garza, 2002). Moreover, a thorough understanding of the role of epigenetic variables in this interaction seems crucial.

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