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Review Article

Vitamin B9 and Health

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Received: April 12, 2019; **Published:** May 29, 2019

Abstract

Vitamin B9, commonly known as folate or folic acid, is a micronutrient necessary for key metabolic processes. Because humans cannot synthesize folate, they rely on dietary sources for this essential micronutrient. Low serum levels of folate are associated with an increased risk of several health conditions, including elevated homocysteine, birth defects such as neural tube defects and cleft lip/cleft palate, and an increased cancer risk. This review discusses the metabolic processes involved in the bioconversion of ingested folate to 5-MTHF, the importance of adequate dietary folate/folic acid intake and the role of genetic mutations in malabsorption problems with folates.

Keywords: *Vitamin B9; Health; 5-MTHF*

Introduction

Vitamin B9, commonly known as folate or folic acid, is a micronutrient necessary for key metabolic processes, mental and emotional health and, in conjunction with vitamin B12 and vitamin C, is important in the formation of red and white blood cells. Mammals, including humans, cannot synthesize folate and rely on dietary sources (fruit, vegetables and grains) for this essential micronutrient [1]. Low serum levels of folate are associated with an increased risk of several health conditions, including elevated homocysteine, birth defects and an increased cancer risk.

There is, however, some confusion regarding the use of the terms *folate* and *folic acid.* In fact, folate and folic acid are different forms of vitamin B9 but despite there being a distinct difference between the two, their names are often used interchangeably.

Folic acid vs Folate

Folate is the naturally-occurring form of vitamin B9 although "folate" is actually a generic name for a group of related compounds with similar nutritional properties. The word derives from the Latin word "folium", meaning leaf. This terminology is understandable since leafy vegetables are amongst the best dietary sources of folate.

The bioactive form of vitamin B9 is the folate known variously as levomefolic acid, L-methylfolate or 5-methyltetrahydrofolate (5-MTHF). Most of the intake of dietary folate is converted into 5-MTHF within the digestive system before entering the bloodstream. This metabolic process is briefly discussed below.

Folic acid (FA) is a synthetic form of vitamin B9, also known as pteroylmonoglutamic acid and is the component commonly present in vitamin B supplements and vitamin B-complex supplements. FA also is incorporated as an additive to processed grain food products, typically flour, bread, rice and breakfast cereals to address dietary vitamin B9 deficiencies. Such fortification of cereals apparently helps increase daily average folic acid intake to 100 µg/day.

In contrast to dietary folate [1,2], most ingested folic acid is not converted to 5-MTHF within the digestive system but in the liver or other tissues [2]. This hepatic conversion process is both slow and rather inefficient so that it takes time for the body to convert all ingested FA to 5-MTHF and there may be incomplete metabolization between daily doses of folic acid derived from vitamin B9 or vitamin B-complex supplements. This situation may be exacerbated if folic acid is consumed in both supplements and within fortified foods [3]. This incomplete metabolization of folic acid is commonly detected as excess folic acid in the bloodstream [4], which could be a cause for concern since high levels of un-metabolized folic acid have been associated with various health problems. However, studies indicate that ingesting folic acid along with other B-vitamins, particularly vitamin B6, makes the bioconversion conversion process more efficient [4].

The issue of incomplete conversion of folic acid has been addressed by at least one company, Young Living, which markets a different and very efficacious B-complex. This product, *Super B*, incorporates Orgen-FA®, a natural and organic folate source derived from lemon peels, and methylcobalamin (vitamin B12), to provide a more readily available source of folate for conversion to its bioavailable form 5-MTHF.

Metabolization of folic acid/folate

The current thinking on folate absorption/metabolization is that folic acid/dietary folates are bio-transformed through a methacrylation reaction in the gut. This transformation is a 3-stage process in which the folate or folic acid is converted by means of the enzyme dihydrofolate reductase (DHFR) into dihydrofolate (DHF) and then into tetrahydrofolate (THF). This is followed by transformation to 5,10 methylene tetrahydrofolate (5,10-methylene-THF) followed by the conversion of the latter into 5-MTHF (L-methylfolate) through the action of the enzyme methylene tetrahydrofolate reductase (MTHFR), see Figure 1.

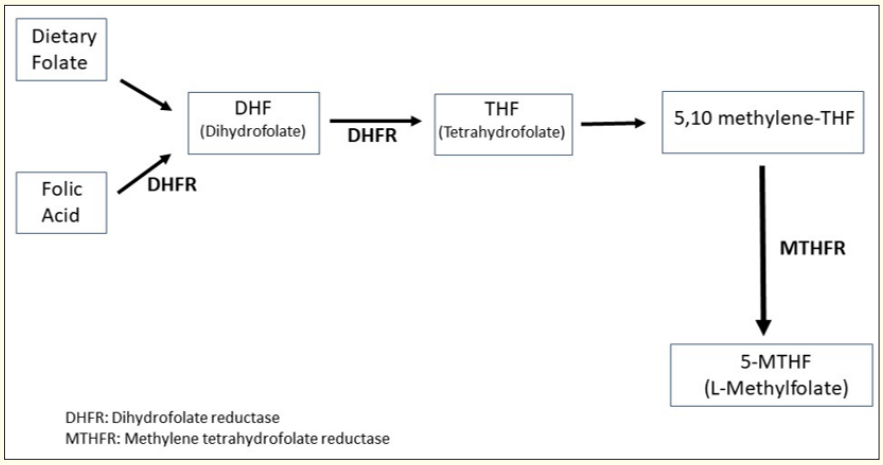

Figure 1: *Biotransformation of folate/folic acid to 5-MTHF.*

Once the biotransformation is complete, the methylated product can be transported as the natural circulating plasma folate, 5-methyltetrahydrofolate (5-MTHF), to the liver and then to the systemic blood supply [5].

The intestinal folate uptake process, however, is quite complex but has received increased scientific study in recent years [6-8]. It has been shown that what is known as the reduced folate carrier (RFC) is the only folate uptake system functioning in the gut. Although the gut is very efficient in converting dietary folates to 5-MTHF, its ability to reduce folic acid is limited and humans rely on the liver for folic acid reduction (biotransformation) and absorption [5].

Dietary requirements of vitamin B9

Although it is more correct to refer to the bioavailable form of vitamin B9, namely 5-MTHF, 5-methyltetrahydrofolate or simply L-methylfolate, for convenience the term folate will be used here. It was indicated above that folate is an essential micronutrient for the body, but a diminished folate status may be caused by low dietary intake, poor absorption of ingested folate and impairment of folate metabolism due to genetic defects or drug interactions. Such deficiency has been linked with an increased risk of neural tube defects, elevated homocysteine levels, cardiovascular disease, cancer and cognitive dysfunction [1]. It has also been reported that obesity and consumption of caffeinated beverages can cause depressed serum folate levels [9-12].

It is questionable whether the modern diet with its almost wholesale ingestion of fast and convenience foods satisfies the body's natural folate requirements, especially during pregnancy and fetal development. One consequence of this ongoing debate is the advocation of vitamin B9 supplements during pregnancy and fortification of bread, cereal and rice with folic acid [13]. It has also been suggested that folic acid supplementation may protect against obesity and insulin resistance [14]. Contributing to this issue is that the bioavailability of natural food folates is lower than that of synthetic folic acid, and for many years, folic acid was thought to be much better absorbed by the body than naturally-occurring folate. A recent study, however, has shown that a diet containing a variety of folate-rich, whole foods to be almost as effective as folic acid supplementation [15]. On the other hand, whereas folate dietary insufficiency can impair hematopoiesis, there are indications that excessive folic acid supplementation can lead to a similar functional impairment [16].

The daily dietary requirement of folic acid is 400 µg/d [17]. In Europe, the average daily natural folate intake is reported to be 230 - 290 µg [18,19] and comparable intakes are likely the same or possibly even lower in the U.S.A. It follows from this that a relatively high percentage of the population has insufficient folate intake [20].

As previously indicated, this folate deficiency can result in congenital neural tube defects (NTDs), notably spina bifida (See figure 2 [21]) and anencephaly, as well as megaloblastic anemia [1,22-25], an impaired metabolism, compromised hematopoiesis and elevated homocysteine levels [16,26]. Consequently, folic acid supplementation is highly recommended for pregnant women. Further, statistics from the CDC [21] indicate that the previously mentioned fortification of grain products with folic acid has resulted in a reduction of 35% in the prevalence of NTDs such as spina bifida. In other words, the U.S. folic acid fortification program appears to have resulted in the birth of about 1300 babies each year that might otherwise have had an NTD. Reductions in rates of NTDs such as spina bifida (53%) and anencephaly (38%) have been reported in Canada after folic acid fortification of cereal products [27].

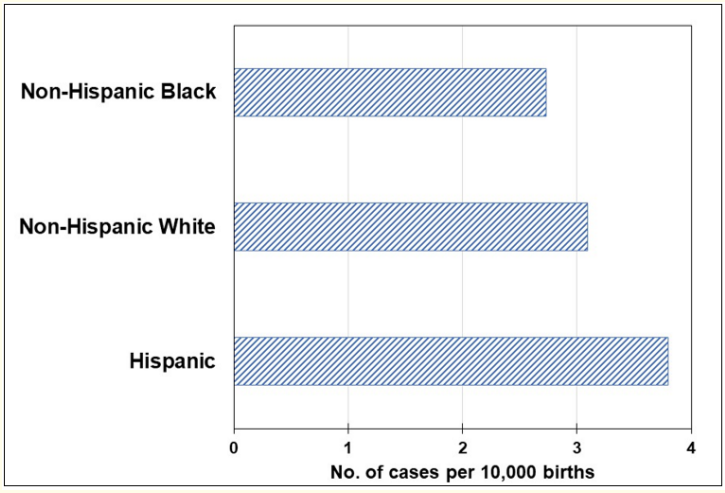

Figure 2: *Prevalence of spina bifida in the U.S.A. per 10,000 live births [21].*

It is, of course, possible that daily B9 or vitamin B-complex supplementation might reduce the prevalence of NTDs (spina bifida and anencephaly) even more. In support of this contention are studies that indicate that folic acid supplementation may reduce the incidence of cleft lip/cleft palate by up to one-third [28,29].

Vitamin B9 malabsorption

Neural tube defects still occur with a small percentage of live births despite the folic fortification of grain products and vitamin B9 supplementation. These NTDs may be ascribable to genetic susceptibility but also to mutational defects in the genes involved in the biotransformation of folate and folic acid.

During pregnancy, the reduced folate carrier (RFC) transports folate via certain genes to folate receptors for the developing embryo, these genes are known as the proton-coupled folate transporters, designated as SLC19A1, SLC46A1, SLC25A32, and FOLH1. Any loss of function due to variants in these genes may affect folate availability and contribute to the risk of NTDs [8]. Variations (i.e. mutations) in any of these genes or the folate receptors also may be the cause of unexplained recurrent pregnancy loss [30].

Mutations in these genes are uncommon and, in fact, the very uncommon hereditary folate malabsorption disorder [31,32] is linked to systemic and neurological disorders. The systemic disorders associated with hereditary folate malabsorption include macrolytic anemia, leukopenia, recurrent pneumonia, diarrhea, mouth ulcers and recurrent infections. Likewise, a variety of neurological effects such as psychomotor retardation, behavioral disorders and early-onset seizures. has been ascribed to mutations in folate transporter SLC46A1 [30,31].

Interestingly, there is a paucity of scientifically-validated data available in the literature on the role of genetic mutations in folate malabsorption. The consensus opinion, however, appears to be that even when such mutations are present, the absorption of folate does not shut down but is just reduced to a greater or lesser degree than in their absence. Unfortunately, the Internet is rife with dire warnings regarding folate malabsorption for the relatively few women who have such genetic mutations. In other words, there is no evidence suggesting that folate absorption is prevented by mutations of the genes involved in vitamin B9/folate absorption and bioconversion.

Conclusions

Vitamin B9 (folate) occurs naturally in food, whereas folic acid is the synthetic form of this vitamin and is present in dietary supplements and fortified foods. Folate is necessary for the development of red blood cells and is essential during pregnancy to prevent neural tubular defects in the developing fetus. It also is essential for DNA and RNA synthesis. Folate functions in concert with vitamin B12 and vitamin C in the utilization of proteins to ensure the proper growth and reproduction of all body cells. Folate, vitamin B6, and vitamin B12 likewise collaborate to prevent excess accumulation of serum homocysteine and low levels of these nutrients are associated with high levels of homocysteine and an increased risk of atherosclerosis. Folate deficiency can lead to anemia and GI disorders as well as to vitamin B12 deficiency. Premature grey hair may also be an indication of folate deficiency.

Most people have an inadequate dietary intake of vitamin B9 and require daily supplementation, particularly women of child-bearing age and those who wish to become pregnant. The data indicate that expectant mothers should be encouraged to take vitamin B9/vitamin B-complex supplements and refrain from consumption of caffeine and tannin-containing beverages (e.g. tea) during their pregnancies.

Although certain gene mutations can cause folate malabsorption, such enzymatic/gene variations are uncommon. Further, while folate malabsorption can result from genetic mutations, absorption is not prevented, just rendered somewhat less efficient.

There have been some studies of the role of synthetic 5-MTHF in preventing folate deficiency. The evidence is that naturally-occurring 5-MTHF is absorbed better than the synthetic product even when the gastrointestinal pH is altered through diet or other influences and, further, its bioavailability is unaffected by metabolic defects.

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Volume 18 Issue 6 June 2019