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FOLIC ACID – THE OCCURRENCE AND THE ROLE IN HUMAN NUTRITION

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Summary

Folic acid occurs naturally in the salt form of folic acid - the so-called folate. The human body cannot synthesize it, and therefore it must be supplied from outside. Folic acid is involved in the synthesis and proper functioning of RNA and DNA acids. It is essential for growth and division of all body cells, which is particularly important during active growth or in the fetal and newborn life. In children and adults, folate along with vitamin B_{12} are involved in the production of red blood cells. Current research indicate on the existence in Poland and in Central and Northern Europe of significant deficiencies of folic acid in the diet.

Deficiency of folic acid in our diet is due to the fact that we consume more highly processed food. Stored and heat-treated food loses a large part of folates. The most common pathological processes associated with a deficiency of folic acid in the body are neural tube defects, megaloblastic anaemia, disturbances in the functioning of the nervous and cardiovascular system, as well as the development of certain types of cancer. Effective methods to increase folate intake are still being searched for.

key words: folic acid, biological functions, consumption, neural tube defects, cardiovascular disease

INTRODUCTION

Folic acid, *N*-[4-(2-amino-4-hydroxypteridinyl-(6)-methylamino)-benzoyl]-L-aminoglutaric acid, also called pteroylglutamic acid (PGA) is an organic compound belonging to a group of water-soluble B vitamins (Bonechi *et al*. 2004). It is known under the names: folacin, vitamin B_9, vitamin M, vitamin B_{11}. It was first isolated in 1941 as a substance of an acid, which showed a growth-stimulating properties of the bacteria *Streptococcus faecium* and *Lactobacillus casei* (Mitchell *et al*. 1941). It was separated from the spinach leaves, hence its name. Latin word *folium* means leaf.

The commonly used term "folic acid" often includes the proper folic acid and a group of its derivatives with a very complex structure. These compounds are characterized by

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a similar biological activity despite the structural differences of molecules. Formally, this compound has more than 150 forms, in nature there are about 20.

Chemical structure and properties of folic acid

Chemically, folic acid is made up of a bicyclic pterin linked by a methylene bridge (C^9-N^{10}) to *para*-aminobenzoic acid (PABA), which is joined by peptide linkage to a single molecule of L-glutamic acid (Hawkes & Villota 1989). The pteridine moiety of folates can exist in either oxidized or reduced states. There may be a one-carbon substituent group present in N_5 or N_{10} positions of tetrahydrofolic acid, resulting in a number of folate derivatives (Gregory 1989). The structure of folic acid is shown in Fig.1.

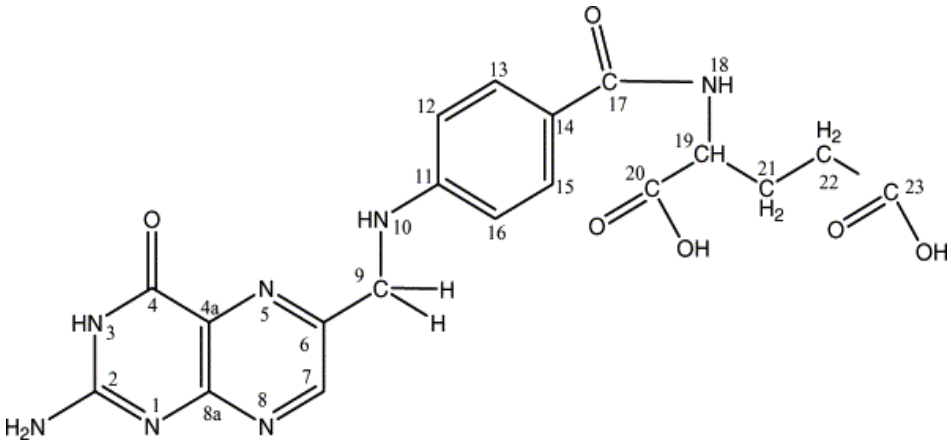


Fig. 1. Structure and numbering of *N*-[4-(2-amino-4-hydroxypteridinyl-(6)-methylamino)-benzoyl]-L-aminoglutaric acid (Bonechi *et al*. 2004)

Folic acid has molecular formula $C_{19}H_{19}N_7O_6$, molecular weight 441.4, and pure compound is in the form of yellow crystals. The compound is showing the optical rotation, and is dextrorotary (optical rotation angle of polarized light is equal to $+20^o$). It has limited solubility in water, but is soluble in acidic and alkaline solutions and insoluble in organic solvents (Dick *et al*. 1948, Lund 1994). Acidic conditions, light and high temperatures increase the susceptibility of folic acid to cleavage (Dick *et al.* 1948). There is great variability in the thermal stability of folates (Mnkeni & Beveridge 1982, Day & Gregory 1983). The degree and rate of destruction is largely influenced by the pH of the medium, type of buffer, reducing agents in the buffer and folate derivatives. It has been reported that under identical heating conditions, folic acid and 5-formyltetrahydrofolic acid are quite stable, whereas 5-methyl-tetrahydrofolic acid and tetrahydrofolic acid are very labile (Paine-Wilson & Chen 1979, Hawkes & Villota 1986). Tetrahydrofolic acid is extremely labile to heat compared to 5-methyl-tetrahydrofolic acid with a half-life of 2.25 and 21.4 min. at

100°C, respectively. The stability of both folate derivatives drastically increased with the incorporation of ascorbic acid, thus showing the detrimental effect of molecular oxygen at higher temperatures (Chen & Cooper 1979). Folate compounds are susceptible to light. Hence, folate analysis is most often carried out in subdued light and glass-wares are wrapped with aluminium foil.

Most animals cannot synthesize folic acid because they cannot synthesize PABA or attach the first glutamate to pteroic acid (Stryer 1981). They must derive folic acid from the diet, the best source being green leafy vegetables. There are several forms of folic acid and not all of them are biologically active (Martin 1983). In plants, folic acid exists as a polyglutamate conjugate with a γ-linked polypeptide chain of seven glutamic acids. In the gut, specific enzymes (folyl polyglutamate hydrolases) cleave these molecules. Only the form with one glutamate (monoglutamyl form) is absorbed in humans (Martin 1983).

Folate is as an acceptor and donor of one-carbon units for over 100 biochemical processes. Reduced folate or those without carbon substitution (dihydropteroylglutamates or tetrahydropteroylglutamates) are unstable (O'Broin *et al.* 1975, Cooper & Chen 1978, Gregory 1989, Hawkes & Villota 1989). The presence in foods of antioxidants (ascorbic acid) and reduced thiols protects folate against oxidant instability. Moreover, exposure to the peptic acid of the stomach increases folate instability (Malin 1977, Chen & Cooper 1979). Polyglutamylation of folate is probably necessary to concentrate and store folates in tissues. However, to be in the proximal one-third of the small intestine, polyglutamyl folates must be hydrolyzed to the respective monoglutamyl derivatives. This conversion is catalyzed by intestinal hydrolases (Godwin & Rosenberg 1975, Halsted *et al.* 1986, Keagy *et al.* 1988, Halsted 1989). A large proportion of folate delivered to the liver is secreted into the bile and redistributed to the peripheral tissues. The central folate acceptor molecule in the one-carbon cycle is a polyglutamyl form of tetrahydrofolate (Wagner 1995). The carbon can be carried as a methyl, methylene, formyl, formimino or methenyl group. Folate is particularly required for the methylation of homocysteine to form methionine and the biosynthesis of amino acids and deoxynucleotides needed for DNA replication and repair (Selhub & Rosenberg 1996). Biochemical changes associated with inadequate folate status trigger the onset of abnormalities in one-carbon metabolism.

Importance of folates for the human nutrition

In the early 1990s, several European countries carried out a campaign encouraging young women planning motherhood to increase their daily ration intake of foods rich in folate, as well as dietary supplementation with folic acid. They were informed about the consequences of folic acid deficiency during the first weeks of pregnancy, that is, during the formation of the neural tube, which then develops into the brain and spinal cord of the child. However, the campaign about associated with folate deficiency defects in the formation of the fetal cen-

tral nervous system did not achieve the expected results, as shown by statistics. Poland belongs to countries with the highest death rate due to congenital neural tube defects in Europe (Brzeziński & Mazurczak 1994). The incidence of neural tube defects in Poland is 8.61 per ten thousand live births, whereas the average in Europe is 2.97 per ten thousand live births. The incidence of spina bifida in newborns in Poland is 6.17 per ten thousand live births and is also among the highest in Europe (Brzeziński 1998, Szostak-Węgierek 2004). In most countries, prevention programmes are created, whose purpose is to promote consumption of folic acid by all women of childbearing age, not just those planning to increase their family. There is also the primary prevention of neural-tube defects programme in Poland.

It should be noted that pregnancy is not the only period when folate plays an important role for health. Folic acid is involved in the synthesis of purines, pyrimidines, nucleic acid formation and the metabolism of certain amino acids (for example: glycine, histidine, methionine). It plays an important role in tissues where cell division occurs, especially in fetal tissues, the hematopoietic system and gut epithelium. The presence of folic acid in appropriate amounts in the diet ensures the proper functioning of tissues and organs of our body. In many clinical and epidemiological studies, folate deficiency in the diet has been shown to favour the development of atherosclerosis (Ballal *et al.* 1997, Gerhard & Duell 1999) and some cancers (Rohan *et al*. 2000, Cole *et al*. 2007) and also to lead to the formation of many neuropsychiatric disorders (Morris *et al*. 2005, Ryglewicz & Graban 2005).

Dietary folate deficiency promotes the development of atherosclerosis. Homocysteine plays an important role in the pathogenesis of this disease. An excess of homocysteine with the deficiency folate and vitamin B_{12} causes vascular endothelial damage and a prooxidant effect, leading to an increased risk of atherosclerosis (Quinlivan *et al*. 2002). Several studies have shown an inverse correlation between the concentration of folate and homocysteine in the blood (Verhoef *et al*. 1997, Van Oort *et al*. 2003).

Epidemiological and nutritional observations show that the consumption of fresh vegetables rich in folic acid protects against the formation of certain types of cancer (Choi & Mason 2000, Jones & Baylin 2002). Published results of cohort and case-control studies show that the deficit of folic acid in the body increases the risk of the emergence and development of certain cancers: colorectal, breast, ovary, uterus, lung, pancreas, etc. (Zhang *et al.* 1999, Su & Arab 2001, Terry *et al.* 2002). Recently, several papers have shown that high doses of folic acid may accelerate the development of cancers including colon, larynx and prostate (Kim 2004, Kim 2006, Rampersaud *et al.* 2002). Results obtained in the studies show that folate deficiency may induce neoplastic transformation. Moderate amounts may inhibit the cancer development but high doses of folic acid may accelerate it (Kim 2004). It is believed that excess folic acid leads to DNA hypermethylation, which may be a consequence of the inactivation

of tumour suppressor genes responsible for the proper control of cell division (Jones & Baylin 2002).

In recent years, there is increasing evidence indicating the important role of folic acid in the functioning of the nervous system. Its beneficial effects on the function of this system is associated with its participation in the formation of neuro-stimulating substances in the body such as dopamine, norepinephrine and epinephrine (Paul *et al*. 2004, Coppen & Bolander-Gouaille 2005, Reynolds 2006). Many clinical and epidemiological studies have shown that folate deficiency in the diet leads to a number of neuropsychiatric disorders such as depression, psychosis, dementia and seizures (Quadri *et al.* 2004, Luchsinger *et al.* 2007).

A deficiency of folic acid and its derivatives in the human body may be due to an inadequate supply of products containing it. Increased folic acid demand during pregnancy and lactation, intestinal malabsorption, biochemical folic acid metabolism disorders due to its interaction with certain medications such as anti-epileptics, analgesics and neutralizing gastric acid, folic acid antagonists (eg. methotrexate, trimethoprim) or hormonal oral contraceptives may also be the reason for its deficiency (Kishi *et al.* 1997, Lewis *et al.* 1998, Olatunji & Soladoye 2008). Folic acid and its derivatives practically exhibit no toxic effects on the human body. Consumption of excessive quantities (eg. 15 mg daily) can only sometimes cause allergic skin reactions and disorders of the digestive and nervous systems. Some reservations about the safety of folic acid in humans may be raised by a few reports about the influence of large doses on the progression of adenomas and their transformation into colorectal cancers (especially colon).

Sources and intakes of folates

Folate are present in almost all food products – both vegetable and animal products. They are mostly in the form of polyglutamine compounds representing approximately 75% of total folate content (mainly from vegetables), while approximately 30% are monoglutamine, the main source of which is bread and meat. Folates are absorbed in the human gastrointestinal tract at the rate of 50-90%, averaging 80% (Melse-Boonstra *et al.* 2002, Winkels *et al.* 2007).

Raw and frozen vegetables, mainly: lettuce, spinach, cabbage, broccoli, asparagus, cauliflower, Brussels sprouts, beans, peas, tomatoes and beets are a rich source of folates in the human diet (Table 1). Valuable folate sources are also liver, yeast, eggs, cheese and wheat bran. Low levels of folates are meat, milk and dairy products (Table 2). Grain products are a major folate source in the diet of the citizen of Poland. They provide nearly 40% of the vitamin in relation to the total daily intake. Approximately 25% of folates is supplied by vegetables, 13% by potatoes and 6-7% by fruits, milk, dairy products and eggs (Wartanowicz 1997). Spinach is a vegetable, which besides having a high folic acid content, also contains an active enzyme which catalyzes the breakdown of polyglutamine folate derivatives.

Table 1. Content of folate in fruit and vegetables (Kunachowicz *et al*. 2005)

Product	Folate content µg·100g^{-1}	Product	Folate content µg·100g^{-1}
Fruit		Vegetables	
Apple	6	Cabbage, Savoy	72
Avocado	62	Cabbage, Chinese	77
Banana	22	Cabbage, white	57
Grapes	6	Cauliflower	55
Orange	30	Chicory	52
Orange juice	24	Chives	64
Raspberries	30	Kale	120
Sour cherries	8	Leek	56
Strawberries	17	Lentil sprouts	84
Water-melon	3	Lettuce	75
Vegetables		Parsley, leaves	170
Asparagus	150	Parsley, root	180
Beetroot	87	Peas, green	62
Broad beans	145	Pepper, red	52
Broccoli	119	Pepper, green	36
Brussels sprouts	130	Potato	20
		Soya bean sprouts	160
		Spinach	193
		String-beans	70
		Tomato	39

Table 2. Content of folate in meat, cereals, dairy products and others (Kunachowicz *et al*. 2005)

Product	Folate content µg·100 g^{-1}	Product	Folate content µg·100 g-1
Meat		Milk and dairy products	
Beef	6-10	Brie cheese, whole fat	60
Pork	3	Cheddar cheese, whole fat	18
Veal	5	Milk	1-5
Chicken liver	590	Quark	27
Ox's liver	330		
Pig's liver	110		
Cereals and cereal products		Other	
Rye grain	113	Baker's yeast	1407
Rye brown bread	28.5	Chicken eggs, whole	65
Wheat bran	260	Chicken eggs, yolk	152
Wheat bread	30.7	Ice-cream	6-8
Wheat grain	145	Mackerel	10

Table 3. Folate retention in spinach and broccoli following typical cooking procedures (McKillop *et al*. 2002)

Food	Cooking metod	Cooking duration (min)	Folate ($\mu g \cdot 100g^{-1}$)	
			Raw foods	Cooked foods
Spinach	Boiled	3.5	191.8	94.4
Spinach	Steamed	3.0	218.5	189.5
Broccoli	Boiled	10.0	177.1	77.0
Broccoli	Steamed	10.0	172.0	156.2

Thermal processing of vegetables is the cause of large folic acid losses, which can reach 40-70% of their initial content. Cooking vegetables leads to partial decomposition and reduces the content of folic acid. Because of the high solubility in water, folic acid is washed out into the water used in cooking like other vitamins B and vitamin C (McKillop *et al*. 2002, McNulty & Pentieva 2004). The study conducted by McKillop *et al*. (2002) indicated significant reductions of 51% and 56% in the folate content of spinach and broccoli compared with raw values respectively, as a result of boiling for typical time periods. In contrast, the steaming of spinach or broccoli did not result in a significant loss of folate content, even after the maximum steaming periods of 4.5 min and 15.0 min respectively, which produced overcooked consistencies (Table 3). Steam blanching resulted in greater retention of folate compared with water blanching. Likewise, other forms of cooking that minimize the direct contact of food with the cooking water such as pressure cooking and microwave cooking have been found to be preferable to boiling in terms of folate retention. According to Polish standards, the recommended folate intake for adults is from 280 to 340 μg per day, depending on gender, age and physical activity (Table 4). The recommendations also included low bioavailability of natural polyglutamate and large losses that occur during storage and food processing. The negative folate balance during pregnancy is a physiological phenomenon. It is assumed that the demand for folic acid increases 2 to 4-times during pregnancy (Gawędzki & Hryniewiecki 2003). Statistical data show that the intake of natural folate is still insufficient in Poland. Nutritional education for people has been introduced and prevention programmes have been implemented to prevent the most common pathological processes associated with folate deficiency in the body such as fetal developmental disorders, megaloblastic anaemia, neurological disorders and cardiovascular disease. This action aims to increase the folate amounts from natural sources or from pharmaceutical supplementation.

Table 4. The recommended daily intake of folic acid in μg per person (Szostak-Węgierek 2004)

Population group Gender, years	Safe level	Recommended level
Infants		
0-0.5	25	35
0.5-1.0	50	70
Children		
1-3	55	70
4-6	75	90
7-9	85	105
Girls		
10-12	160	190
13-15	170	200
16-18	185	220
Boys		
10-12	170	200
13-15	180	220
16-18	200	240
Men over 18 years old of moderate physical activity	280	300
Women over 18 years old of moderate physical activity	240	290
Pregnancy	400	450
Lactation	480	530
Over 60 years old		
Women	300	320
Men	320	340

In many countries, enriching some food products in folic acid for mass consumption, such as flour and bread is being considered. This programm implementation would effectively prevent the occurrence of neural tube defects in a high proportion of the population and overcome the limitations associated with individual prevention. The preparation of a program for folic acid enrichment of certain mass consumption foods would require a significant increase in research on nutritional habits in order to balance the supply of folate fortification technology and the social acceptance of this kind of massive preemptive intervention. In the United States the fortification of flour, rice, pasta and other cereal products has been applied since early 1998 and after its introduction the number of newborns with congenital neural tube defects has decreased by almost 47% and the number of older people with ischemic stroke has also decreased (Honein *et al*. 2001, Williams *et al.* 2002, Bazzano *et al.* 2006). In the UK, since 2000, 0.24mg folic acid per 100g flour has been added. Quite a small dose of folic acid added to flour products is subject to concerns about exceeding the maximum daily level of this vitamin in certain population groups. High folic acid doses in the diet of older people may mask the symptoms of anaemia associated with B_{12} deficiency and consequently damage the nervous system, whereas in people with cancer, it can affect the course of treatment. In recent years, food enrichment is the most frequently chosen solution to dietary deficiencies. However, food fortification with folic acid is not accepted in most European countries.

New solutions to increase folate intake from natural sources are being sought. Among other things, the Folate FuncHealth foundation has proposed the following ways to increase levels of natural folate in foods (Jägerstad *et al* 2005):

- Increasing the folate concentration in fermented products like bread,

beer and wine by using yeast strains rich in folate;
- Increasing the folate content in fermented dairy products (cheese, yogurt, etc.) by the appropriate selection of lactic acid bacteria strains;
- Elaboration and application of production technology methods to minimize the loss of folate;
- Increasing folate content in processed foods such as soup concentrations, vegetable and fruit juices, through using varieties of fruit and vegetables rich in folate;
- Increasing the folate content in flour by grinding the whole grain and bran.

In Poland folic acid food fortification is voluntary and applies to most cereal products and confectionery. The consumer can make an informed choice between the products enriched with folic acid or unenriched ones.

In the near future can be expected that new food products fortified with folic acid will appear on the market and that food producers meeting the expectations of consumers will use methods of increasing levels of natural folate in foods promoted by the Folic FuncHealth.

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KWAS FOLIOWY - WYSTĘPOWANIE I ROLA W ŻYWIENIU CZŁOWIEKA

Streszczenie

Kwas foliowy występuje naturalnie w postaci soli kwasu foliowego – tzw. folianów. Organizm ludzki nie potrafi go syntetyzować i dlatego musi on być dostarczany z zewnątrz.

Kwas foliowy bierze udział w syntezie i prawidłowym funkcjonowaniu kwasów RNA i DNA. Jest niezbędny do wzrostu i podziału wszystkich komórek organizmu, co jest szczególnie istotne w okresie intensywnego wzrostu, czyli w życiu płodowym i niemowlęcym. U dzieci i dorosłych foliany razem z witaminą B_{12} biorą udział w produkcji czerwonych krwinek. Aktualne badania wskazują na występowanie znacznych niedoborów folianów w diecie mieszkańców Europy Środkowej i Północnej. Niedobór kwasu foliowego w naszej diecie wynika z tego, że spożywamy coraz więcej żywności wysoko przetworzonej. Żywność przechowywana i poddawana obróbce cieplnej traci w dużej części foliany. Najczęstsze procesy patologiczne związane z niedoborem kwasu foliowego w organizmie to: wady cewy nerwowej, niedokrwistość megaloblastyczna, zaburzenia w działaniu układu nerwowego i sercowo-naczyniowego, jak również rozwój niektórych typów nowotworów. Poszukiwane są wciąż skuteczne metody, służące zwiększeniu spożycia folianów.