British Journal of Nutrition (2007), **98**, 665–666
doi: 10.1017/S0007114507795326

Invited Commentary

Folic acid under scrutiny

A consideration of the absorption and metabolism of folic acid in human subjects is timely, owing to the recent recommendation by the UK Government's Scientific Advisory Committee on Nutrition that a mandatory folic acid fortification programme be implemented in the UK[1]. In this issue of the *British Journal of Nutrition*, Wright *et al.*[2] take us through the processes of absorption and metabolism of folic acid and conclude that there are grounds to propose that the use of this compound as a supplement or a fortificant may increase its concentration in the systemic circulation. They suggest that there may be associated risks.

Folic acid is the most oxidised, monoglutamate, form of folate, and the form in which this vitamin is taken as a supplement or used as a fortificant. Because its lack of glutamate residues obviates the need for deconjugase at the brush-border membrane, and the presence in foodstuffs of dietary inhibitors of folate deconjugation, it has long been considered to have a much higher bioavailability than food folates. In reality, studies show a wide variation in the bioavailability of food folates, depending upon the particular food matrix, and a recent study suggests that the consumption of a mixed diet containing folate-rich foods can be almost as effective as folic acid supplements at improving folate status[3].

With the advent of readily accessible stable isotope-labelled folates it became possible to study folate bioavailability and metabolism in human subjects with a high degree of accuracy. These studies now strongly suggest that a high proportion of folic acid undergoes initial reduction and methylation in the liver[4,5]. On entering a cell folic acid is initially reduced by dihydrofolate reductase (DHFR) to dihydrofolate (DHF), which is subsequently reduced further to tetrahydrofolate (THF). THF is then available for further metabolism to a number of different biologically active forms of folate, with specific metabolic functions. Importantly, in human subjects, some tissues, including liver, have a limited ability to reduce folic acid, because of a low activity of DHFR, and are unable to reduce high concentrations of folic acid[6]. This would be expected to increase the appearance of unmetabolised folic acid in the circulation in the situation of high or repeated doses of folic acid.

How does supplementation/fortification influence the concentration of folic acid in the circulation?

The move to mandatory fortification of flour with folic acid led to an increase in folate intake and in erythrocyte and plasma folate concentrations in the USA population, but the magnitude of the increase in intake was approximately double that anticipated [7]. This occurred against a high background consumption of folic acid supplements [8]. In their studies of postmenopausal women in the USA, in the post-fortification era, Troen and coworkers detected unmetabolised folic acid in the plasma of 78 % of a cohort of women, following an overnight fast[9]. Daily intakes of folate were estimated to be 304 (SD 126) μg from food and 255 (SD 285) μg from supplements.

Other studies have reported the appearance of unmetabolised folic acid in serum following the consumption of folic acid supplements or fortified foods. Kelly *et al.*[10] reported the appearance of unmetabolised folic acid in serum of young and elderly people in response to a period of 5 d consumption of folic acid fortified foods, or foods spiked with folic acid. The serum folic acid was detectable at a folic acid intake of <300 μg per meal. Two subsequent studies from this group further evaluated the effects of folic acid consumption in fortified foods. Intake of 1 mg folic acid in fortified bread, given as a single dose or in two, three, four or five doses spread over a day, to healthy volunteers resulted in the appearance of folic acid in the serum of all volunteers, for all dosing regimens. An accumulative effect was evident for the smallest dose over the test period, so that the highest folic acid concentration was reached following five test doses of 100 μg[11]. A recent publication reports effects of consumption of bread fortified with folic acid at levels comparable to and higher than those used in the USA[12]. Healthy folate-replete men and women received two slices of fortified bread daily at prescribed times, for 7 d. The intervention resulted in the appearance of unmetabolised folic acid in serum following the consumption of 200 μg folic acid in a single slice of bread. The folic acid concentration increased further following the second slice. No effect was seen at lower intakes.

Clearly then, folic acid intake from fortified foods and supplements has the potential to drive the appearance of unmetabolised folic acid in plasma, and the magnitude of the effect shows a dose dependency. Importantly, there also seems to be an accumulative effect of repeated exposure.

What is the evidence that an elevated plasma folic acid concentration might be harmful?

There is a long-standing recognition of the fact that increased intake of folic acid in the elderly population might mask detection of vitamin B_{12} deficiency and enhance a deterioration of central nervous system function[13,14]. Less well understood is the potential for enhancing the progression rate of pre-cancerous lesions to invasive cancer.

Epidemiological studies have suggested that a good folate status may protect against cancers at various sites, and this

is supported by experimental evidence in human subjects and animal models. However, evidence is accumulating from some animal studies to suggest that whereas folate deficiency in normal tissues increases the rate of neoplastic transformation, high doses of folic acid may accelerate the progression of existing neoplastic lesions to cancer[15,16]. The dosage and timing of the folic acid intervention are key determinants of effects. This is of course entirely plausible given the role of folate in DNA synthesis and cell proliferation, which is the basis for using antifolate drugs in chemotherapy. At present, data from human studies are lacking. One case–control study of colorectal cancer in Swedish men and women reported that plasma concentrations of folate reflective of high intakes were strongly associated with increased risk of colorectal cancer[17]. De Vogel *et al.*[18] examined folate intake and colorectal cancer data alongside adenomatous polyposis coli (APC) mutations, in a large Dutch cohort, and found an interaction between folate intake and the APC mutations associated with an increased risk of colon cancer. Recently, the Polyp Prevention Study Group reported results suggestive that a 1 mg folic acid supplement taken for 6–8 years by men and women with a history of colorectal adenomas, increased the risk of colorectal neoplasia[19].

Clearly a distinction needs to be made between the beneficial effects of dietary folates and the potential deleterious effects of high intakes of folic acid, and if the UK moves towards implementation of a strategy of fortification of some flour with folic acid it will be important to monitor biochemical, clinical and health effects in the population.

Hilary J Powers

Human Nutrition Unit
School of Medicine and Biomedical Sciences
University of Sheffield
S10 2RX
UK
h.j.powers@sheffield.ac.uk

References

1. Scientific Advisory Committee on Nutrition (2006) *Folate and Disease Prevention*. London: The Stationery Office.
2. Wright AJ, Dainty JR & Finglas PM (2007) Folic acid metabolism in humans revisited: potential implications for proposed mandatory folic acid fortification in the UK. *Brit J Nutr*, **98**, 667–675.
3. Winkels EM, Brouwer IA, Siebelink E, Katan MB & Verhoef P (2007) Bioavailability of food folates is 80 % of that of folic acid. *Am J ClinNutr* **85**, 465–473.
4. Rogers LM, Pfeiffer CM, Bailey LB & Gregory JF (1997) A dual stable-isotope protocol for determination of plasma folate bioavailability in humans: evaluation of urinary excretion and plasma folate kinetics of intravenous and oral doses of (^{13}C5) and (^{2}H2) folic acid. *J Nutr* **127**, 2321–2327.
5. Wright AJ, Finglas PM, Dainty JR, Wolfe CA, Hart DJ, Wright DM & Gregory JF (2005) Differential kinetic behaviour and distribution for pteroylglutamic acid and reduced folates: a revised hypothesis of primary site of PteGlu metabolism in humans. *J Nutr* **135**, 619–623.
6. Whitehead VM, Kamen BA & Beaulieu D (1987) Levels of dihydrofolate reductase in livers of birds, animals, primates and man. *Cancer Drug Delivery* **4**, 185–189.
7. Choumenkovitch SF, Selhub J, Wilson PW, Rader JI, Rosenberg IH & Jacques PF (2002) Folic acid intake from fortification in United States exceeds predictions. *J Nutr* **132**, 2792–2798.
8. Radimer K, Bindwald B, Hughes J, Ervin B, Swanson C & Picciano MF (2004) Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol* **160**, 339–349.
9. Troen AM, Mitchell B, Sorensen B, Wener MH, Johnston A, *et al.* (2006) Unmetabolised folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. *J Nutr* **136**, 189–194.
10. Kelly P, McPartlin J, Goggins M, Weir DG & Scott JM (1997) Unmetabolised folic acid in serum: acute studies in subjects consuming fortified food and supplements. *Am J Clin Nutr* **65**, 1790–1795.
11. Sweeney MR, McPartlin J, Weir J, Daly S & Scott J (2006) Post-prandial serum folic acid response to multiple doses of folic acid in fortified bread. *Brit J Nutr* **94**, 1–8.
12. Sweeney MR, McPartlin J & Scott J (2007) Folic acid fortification and public health: Report on threshold doses above which unmetabolised folic acid appears in serum. *BMC Public Health* **7**, 41–47.
13. Reynolds EH (2002) Benefits and risks of folic acid to the nervous system. *J Neurol Neurosurg Psychiat* **72**, 567–571.
14. Morris MS, Jacques PF, Rosenberg I & Selhub J (2007) Folate and vitamin B12 status in relation to anaemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr* **85**, 193–200.
15. Song J, Medline A, Mason JB, Gallinger S & Kim YI (2000) Effects of dietary folate on intestinal tumorigenesis in the Apc^{Min} mouse. *Cancer Res* **60**, 5434–5440.
16. Song J, Sohn KJ, Medline A, Ash C, Gallinger S & Kim YI (2000) Chemopreventive effects of dietary folate on intestinal polyps in Apc-/-Msh2-/- mice. *Cancer Res* **60**, 3191–3199.
17. Van Guelpen B, Hultdin J, Johansson I, Hallmans G, Stenling R, Riboli E, Winkvist A & Palmqvist R (2006) Low folate levels may protect against colorectal cancer. *Gut* **55**, 1461–1466.
18. De Vogel S, van Engeland M, Luchtenborg M, *et al.* (2006) Dietary folate and APC mutations in sporadic colorectal cancer. *J Nutr* **136**, 3015–3021.
19. Cole BF, Baron JA, Sandler RS, *et al.* (2007) Folic acid for the prevention of colorectal adenomas: a randomised clinical trial. *JAMA* **297**, 2351–2359.

British Journal of Nutrition