Factors Involved in the Vitamin Fortification of Foods

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Abstract

This paper exams the rationale for the fortification of foods with vitamins. Factors that enter in to this equation are vitamin stability, vitamin bioavailability from foods, economics of vitamin supplementation and fortification and the benefits to society from such fortification.

While any vitamin could be used as an example, folic acid (folate) has been chosen as the object for this paper. Folic acid is known to play a role in nucleic acid synthesis and thus the prevention of neural tube defects in embryos. Data is shown on the poor stability of naturally occurring folate in foods, the superiority of synthetic folic acid stability, the economics of folic acid production, the need for folate fortified foods throughout the world and the reduction in neural tube defects in those countries that have mandated folic acid fortification.

Introduction

The factors that negatively affect vitamin stability are: the presence of moisture, the addition of heat, the presence of trace minerals, alteration of pH, any oxidation-reduction reaction or the addition of pressure as experienced in food canning (retorting) or extrusion (McDowell 1989, 423-424). Naturally occurring vitamins are especially susceptible to destruction by factors such as these. While this paper could be focused upon any vitamin, folic acid is of particular interest as its fortification is a controversial subject.

There are several chemicals with folate activity, most of these being intermediates of tetrahydrofolate which is the most active form. The folates act as coenzymes in reactions involved in the metabolism of amino acids or the synthesis of nucleic acids and function to accept and transfer methyl units. This methyl unit transfer function of the vitamin is especially interesting to epigeneticists as methylation of genes tends to inhibit the expression of the gene that is methylated. The folates are absorbed by active transport in the jejunum with some storage of the vitamin occurring in the liver. Being a water soluble vitamin, loss of folate from the body occurs via the urine. Losses of the vitamin also occur in foods before consumption as outlined in this quote from the FAO: “Natural folates rapidly lose activity in foods over periods of days or weeks” (FAO 2002). By contrast, the synthetic form of the vitamin (folic acid) is very stable and its fortification in food may last for several weeks. The experts at DSM[1] (2009) indicate that the loss of activity of naturally occurring folate may be as high as 70%. This estimation seems rather high, so it is imperative that we exam this issue more closely.

[1] DSM is the current name of Roche Vitamins which was a division of Hoffman-LaRoche

Comparison of the Stability of Naturally Occurring Vitamin Form versus the Synthetic Form

A study was conducted by NASA in July 2006 aboard the International Space Station regarding the stability of nutrients in food during long space flight (Zwart et al 2009). Among the nutrients studied was the naturally occurring folate and synthetic folic acid. The loss of folate activity as measured over 596 days by analyzing the folate in flour tortillas was close to 50% while the loss of folic acid in a supplement over the same time period was only 13% (see Table 1). Gujska et al (2009) measured the loss of two forms of folate in baked rye bread over a 16 week period. Losses of 10-formyltetrahydrofolate were less pronounced than the 5-formyl form with losses of 11% and 24%, respectively. Omar et al (2009) reported only a 30% loss of folate activity when measured in bread immediately after baking. Seeking a mechanism for folate destruction, Verlinde et al (2010) measured the kinetics of folate destruction in the presence of either fructose or glucose. The rate of folate degradation was much higher in the presence of fructose, nearly twice the rate of the control.

When considering synthetic folic acid, Galán et al (2010) irradiated hamburger meat fortified with folic acid and noted only losses due to length of irradiation on the order of 25% but not between raw and cooked meat. On the other hand, Riaz et al (2009) measured loss of folic acid during the extrusion of pet food and observed a 45% loss of folic acid. So while not as dramatic as the 70% reported by the vitamin manufacturer, losses of naturally occurring folate in these studies did range from 11% to 50% while it took the extraordinary pressures and heat of the extrusion process to cause activity losses in the synthetic folic acid.

An excellent review of the factors associated with the bioavailability of both the naturally occurring folate and synthetic folic acid was written by Gregory (2001) in which it was stated that little in vivo data is available on the bioavailability of synthetic forms. However, it can still be concluded, as the FAO (2002) did, that the synthetic form (folic acid) is much more stable than the naturally occurring forms.

Populations at Risk of Folate Deficiency

It is generally accepted among biochemists and those in the medical professions that, because of its function in the transferring of methyl groups (along with vitamin B-12), folic acid is involved in nucleic acid synthesis and thus aids in the prevention of neural tube defects in growing fetuses. As the FAO (2002) rightly stated, "folate deficiency is common in people consuming a limited diet." However, those most at risk tend to be pregnant women and their unborn children. The need for folate increases sharply in the second and third trimesters of pregnancy. The need is also urgent early on (between 21 and 27 days post conception) while the neural tube closes and formation of the spinal cord and brain begins (FAO 2002). Lack of folate at this critical time will result in the neural tube defects of Spina bifida, anencephaly and some early childhood cancers. In areas of the world where fortification of foods with synthetic folic acid is either not yet possible or not permissible, many children are born with neural tube defects. De Steur et al (2010) stated that up to a third of still births and infant mortality in China are due to neural tube defects. Becquey and Martin-Prevel (2010) noted that only 12% of women of reproductive age in Burkina Faso had adequate folate levels. In a study of iron deficiency anemia in infants of India, Pasricha et al (2010) observed a collateral deficiency of folate in the infants. This is somewhat disturbing as folic acid is involved in proper erythrocyte formation. Thus the infants faced a downward cycle of lack of folic acid to form erythrocytes and lack of iron to place in the hemoglobin of the few erythrocytes produced.

As I attempt to build a prima fascia case, we now have two evidences to consider: 1) the synthetic form of folic acid is much more stable than the naturally occurring forms and 2) around the world, the folate status of women of child bearing age and their offspring is poor to inadequate. A logical and cost effective way of alleviating this problem is through vitamin supplements or food fortification. The next question to be answered, then, is what economic and political forces are at work to prevent the fortification of food with folic acid?

Economics of Folic Acid Production

Most of the folic acid produced in the world goes into the animal feed industry, specifically into the feed of non-ruminant animals (DSM 2009). As of March 4, 2011, the price of feed grade folic acid was $50/kg while the price of human food grade[2] was $197/kg. Production of folic acid is based upon petroleum derivatives (DSM 2009), so as the price of crude oil increases so does the cost of folic acid production. Margins are so low on the buying and selling of this vitamin that BASF ceased to handle the vitamin in 2009 (Hopkins 2010, personal communication). As with all the water soluble vitamins, every kilo of folic sold is sold at a loss. With Chinese production of the vitamin coming online quickly, margins are only expected to become less lucrative. Alternatives to the chemical synthesis of folic acid are known, but have proved to have such a poor yield as to be economically impractical. For example, fermentation would lower the cost of production but this has been tried for many years without success. Sirotnak et al (1963) and Zhu et al (2005) demonstrate 50 years of frustration trying to engineer via biotechnology a microbe that would yield enough folic acid to make the process economically viable. Therefore, we may conclude that in some third world countries, women of childbearing age may not be able to afford supplements because of the lack of availability and cost. Fortification of food with the vitamin would be a cost effective alternative to supplements.

Mandated Folic Acid Fortification

Mandated fortification of grain based food started in Canada, Chile and the United States in 1998. Thus, breads, pasta, and other grain based food products have been fortified in these countries for nearly 14 years. Has this fortification been successful in the reduction of neural tube defects and/or other childhood disorders?

French et al (2003) obtained data from the Canadian province of Ontario on the incidence of neuroblastoma, acute lymphoblastic leukemia and hepatoblastoma in young children both pre- and post- fortification. The data was further divided into two periods she defined as "near

[2] USP grade

complete" to "complete" fortification due to communication with a local flour miller that fortification in Ontario had begun as early as January of 1997. Thus, her analysis contains a time period from January 1985 to December 1997 versus January 1998 to October 2000 that she labels as "complete", and a time period from January 1985 to December 1996 versus January 1997 to October 2000 that she labels as "nearly complete." In either case, the number of new neuroblastoma cases declined from the pre-fortification period (1.57/10,000 births) to the post-fortification period (0.62/10,000 births) by 40%. Reductions in hepatoblastoma or acute lymphoblastic leukemia were not statistically significant.

De Wals et al (2007) looked at the effect of folic acid fortification on the rate of neural tube defects from data reported from seven Canadian provinces (British Columbia, Alberta, Manitoba, Quebec, Prince Edward Island, Nova Scotia and Newfoundland). The incidence of neural tube defects declined from 1.55/1000 live births in 1993 to 0.86/1000 live births in 2002, a reduction of 46% (see Figure 1). The observed reduction in rate was greater for spina bifida than for anencephaly. Decreases in spina bifida went from 0.83/1000 live births in 1993 to 0.41/1000 in 2002. Anencephaly decreased from 0.51/1000 to 0.34/1000.

When looking at data from the United States, Mersereau et al (2004) reported for the CDC that, when comparing a pre-fortification period of 1995 to 1996 with a post-fortification period of 1999 to 2000, the incidences of spina bifida and anencephaly dropped 26.4%. In a later CDC report, Alvelo-Maldonado et al (2008) noted that in Puerto Rico, the incidence of neural tube defects declined from 14.7 per 10,000 births in 1996 to 5.3 per 10,000 births in 2003, a statistically significant reduction of 64%. The rate remained fairly constant at approximately 8/10,000 births for the years 2004 and 2005. It was estimated in the early 1990's that folic acid fortification of grain based foods would have a cost benefit in excess of $200 million (Stevenson, 1995). Grosse et al (2005) observed that the incidence of neural tube defects was actually lower than predicted and that this resulted in an increased economic benefit of approximately $422 million annually in the United States.

In Chile, López-Camelo et al (2005) noted a 51% reduction in spina bifida cases and a 42% reduction in anencephaly cases when comparing pre-fortification periods to post-fortification.

In Australia and New Zealand, Dalziel et al (2009) admitted that fortification of grain based food had resulted in neural tube defects decreasing from a rate of 1.43/10,000 births in the pre-fortification era to 1.18/10,000 in the post-fortification era, but she insisted that oral supplements were a more cost effective approach to the issue.

In countries where wheat is not the main staple, fortification is a more difficult option. In a study conducted in Thailand, Porasuphatana et al (2008) fortified a quick-cooking rice product with iron, calcium, zinc, thiamin and folate. The data indicated that such a rice product could be produced economically and with palatable attributes. De Steur et al (2010) reported a slightly different approach taken in the Shanxi province of China. There, a genetically modified rice cultivar with higher levels of folate received a 62% acceptance rate among the surveyed population. These workers reported that modified rice was a more viable way to improve the folate status of the population than was fortification.

Voices of Caution

In their commentary, Smith et al (2008) voiced concerns that fortification of grain based foods might cause, in some individual cases, folate intake to exceed the upper safe limit. They point out that other effects of folic acid fortification could include anemia and low cognitive abilities in senior adults due to compromised vitamin B-12 status, decreased activity of natural killer cells of the immune system, reduced response to anti-folate drugs (methotrexate for example), an increased risk of insulin resistance in pregnant mothers and babies and higher rates of colorectal and breast cancers. In a study conducted with lab rats, Omar et al (2009) observed an increase in premalignant lesions in the rats fed folic acid. Smith et al (2008) pointed out that there could also be other epigenetic effects caused by this increase in folate intake that might not be foreseen at this time. While a call to step back and look at all the facts is welcomed, is the dark picture painted by Smith really all that bleak? For example, when one looks at the incidence rates in the United States of colorectal cancer since the fortification of grain based foods began, we see rates have decreased from 56.4/100,00 in 1999 to 49/100,000 in 2005 (CDC 2011). While not a dramatic decrease, the incidence have gone down for some reason and have not increased as Smith et al (2008) predicted. A similar picture is seen for the incidence of breast cancer. The rate falls from 134.4/100,000 cases in 1999 to 119.6/100,000 in 2005 (CDC 2011). Peter (2007) noted that the incidence of Type I Diabetes or Insulin-Dependent Diabetes Mellitus has been increasing for over 50 years. While this increase in the incidence of the malady has obvious epigenetic overtones, it is assuming too much to conclude that increased folate intake due to fortification of food would exacerbate the problem. Finally, when the drug methotrexate is used to treat patients with rheumatoid arthritis, it is now generally felt that folic acid should be given along with the drug to ameliorate the effects of the drug (Morgan et al, 1994). So while Smith et al (2008) brings up several points to ponder, a broader look at the data suggest some of them are overstated.

The question also arises as to why, if folic acid fortification is so needed, does the rate of neural tube defects not fall to zero in those countries where fortification is already mandated? The answer is twofold: First is the discussion of the bioavailability of synthetic folic acid that was given by Gregory (2001) in which he outlines the antagonistic interaction between the naturally occurring folate and the synthetic form of the vitamin. Second is the fact that some women may not have all the enzymes necessary to convert the synthetic form into tetrahydrofolate.

Conclusion

Women in developing countries tend to have poor folic acid status and this water soluble vitamin is necessary for the synthesis of nucleic acids and the prevention of neural tube defects in the growing fetus. Since the greatest need for the vitamin occurs before most women realize they are pregnant, the fortification of food consumed daily by a majority of women is a cost effective way to prevent these birth defects. Data from the United States suggest that even a small decrease in neural tube defects more than repays the cost of the fortification. It is therefore incumbent upon governments around the world to mandate folic acid fortification of their food supply to improve the health of their populations.

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Table 1. Loss of Folic Acid Activity over Time

Folic Acid Level	Time 0	13 d	353 d	596 d
Tortillas				
Mg/100 g	0.129±0.006 a	0.11±0.005 b	0.085±0.004 b	0.076±0.004 b
Supplement				
Mg/Tablet	0.61±0.5 a	0.55±0.2 b	0.53±0.14 b	0.53±0.23 b
Zwart et al (2009), Journal of Food Science 74:H209-H217				

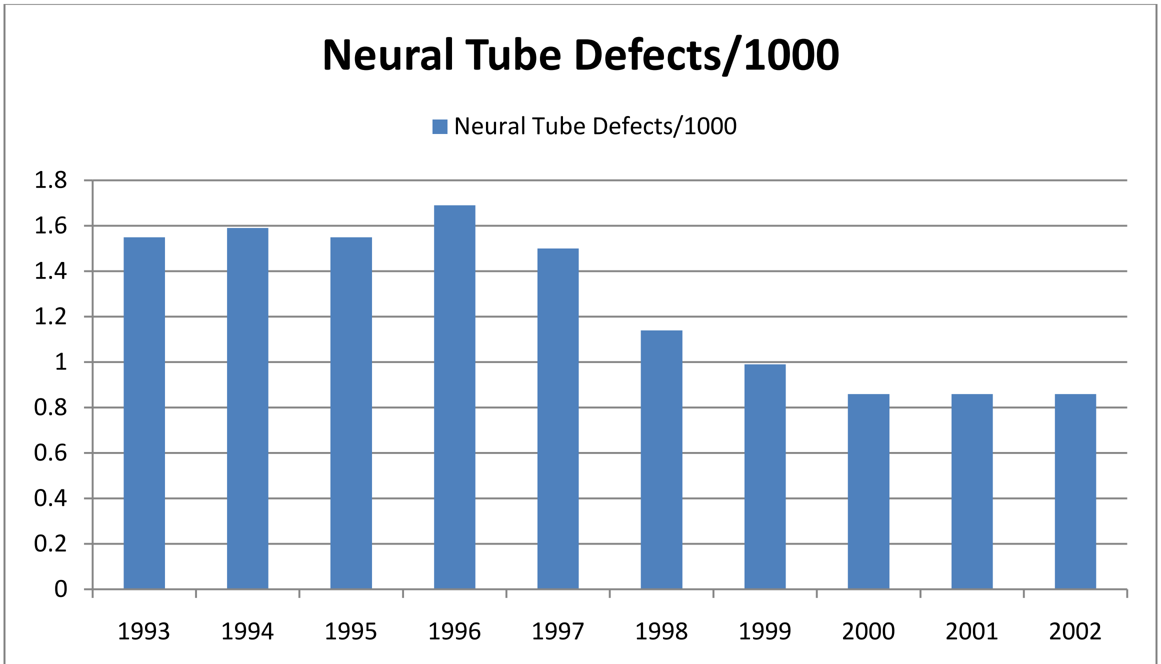

Figure 1. All Neural Tube Defects in Pre-Fortification and Post-Fortification Years in Canada.

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