News

How can folic acid prevent anencephaly? The examination of the mechanism behind folic acid and the homocysteine remethylation cycle

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Abstract

Anencephaly is a congenital neural tube defect (NTD) where part of the skull and brain does not develop. Folic acid can reduce NTD development. An NTD occurs when the neural tube fails to close properly during embryogenesis. Women are recommended to take a 0.4mg folic acid supplement daily prior to conception and during the first trimester of pregnancy. Folic acid is a synthetic derivative of vitamin B9. It is important in several mechanisms in the body, including homocysteine remethylation, which is involved in DNA synthesis and repair. Whilst folic acid does play a role in NTD, its effectiveness is likely determined by its correct usage and dependent on other factors. Further research into the effects of too much folic acid is necessary to ensure its safety and continued benefit.

Abbreviations

DHFR - Dihydrofolate reductase
MS - Methionine synthase
5-MTHF - 5-Methyltetrahydrofolate
MTHFR - Methylenetetrahydrofolate reductase
NTD - Neural tube defect
RCOG - Royal College of Obstetricians and Gynaecologists
RCT - Randomised controlled trial
SAH - S-adenosyl-homocysteine
SAHH - S-adenosyl-homocysteine hydrolase
SAMe - S-adenosyl-methionine
THF - Tetrahydrofolate

Anencephaly and prevention

Anencephaly is a neural tube defect (NTD) caused by disturbances of neurulation in early embryogenesis. It results from the failure of neural tube closure between the 23rd and 26th day post-conception.[1] Each case presents with the absence of the calvarium alongside the cerebral cortex, a major component of the human brain composed of tightly packed neural tissue that is responsible for higher brain functions including memory and emotion. Sometimes other elements of the brain are absent, such as the cerebellum **(Figure 1)**. It affects around 1 in 1,000 pregnancies, although most cases lead to miscarriage.[2] It is estimated that 1 in 10,000 infants are born with anencephaly,[3] and the few neonates that survive full-term gestation only live for hours or, at most, a few days. No surgical intervention is currently feasible.[4] Therefore, with such high miscarriage rates and neonatal mortality, it is essential that anencephaly is prevented. To help achieve this, many countries including the UK, Canada and America now advise women planning a pregnancy take a daily dose of 0.4mg of folic acid supplementation before conception and during the first trimester of pregnancy. Folic acid is a synthetic derivative of vitamin B9, whereas folate is the natural water-soluble form of the vitamin.

Figure 1. Hand drawn illustration by author of infant with anencephaly. Noticeable features include absence of calvarium and cerebral hemispheres. Illustration was aided with use of image from Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities.[5]

In this article, the effectiveness of folic acid in preventing anencephaly is considered, whilst research and guidance are examined. Rationale for selection of research material took into account the quality and risk of bias, aided by the Hierarchy of Evidence, which viewed randomised controlled trials (RCTs) and systematic reviews more highly than cohort and case-control studies. Papers were screened using key search terms "Anencephaly", "Folic Acid", "Neural Tube Defect", "Methylation" and "Pregnancy".

Folic acid breakdown and the homocysteine remethylation cycle

The British Dietetic Association states that folic acid is important for the formation of red blood cells, nerve stimulation, DNA and RNA formation and repair.[6] After ingestion, supplemental folic acid is metabolised in the liver by methylenetetrahydrofolate reductase (MTHFR) to 5-methyltetrahydrofolate (5-MTHF).[7] It is then readily absorbed primarily in the small intestine and reduced to tetrahydrofolate (THF) by two reduction reactions that are catalysed by dihydrofolate reductase (DHFR). In contrast, folate, found naturally in fruits and vegetables, is already present in the active form of 5-MTHF.[8] In order to be absorbed in the gut, 5-MTHF must be hydrolysed into monoglutamates.[9] Folic acid and folate become chemically indistinguishable once they have been converted to THF in the enterocytes of the small and large intestine.[10] Therefore, once folic acid is broken down to THF, it is likely to have the same effect as natural folate.

Folic acid plays a role in the formation of the amino acid methionine by homocysteine remethylation **(Figure 2)**. This cycle is important for processes such as nucleotide synthesis. This pathway occurs in several stages: (1) S-adenosyl-homocysteine (SAH) is formed directly from S-adenosyl-methionine (SAMe) through the addition of a methyl group; (2) catalysed by the enzyme SAH hydrolase (SAHH), SAH is further broken down into the amino acid homocysteine;[8] (3) 5-MTHF, the active form of folic acid , as well as methionine synthase (MS), are responsible for converting homocysteine to methionine by the transfer of a methyl group; (4) methionine can then be converted to SAMe, a cofactor for many methylation reactions in the human body, including the methylation of chromatin and proteins;[8,11] (5) the cycle then repeats. Insufficient levels of 5-MTHF can result in a build-up of homocysteine and, therefore, inhibit or reduce the formation of SAMe within the cycle.[8]

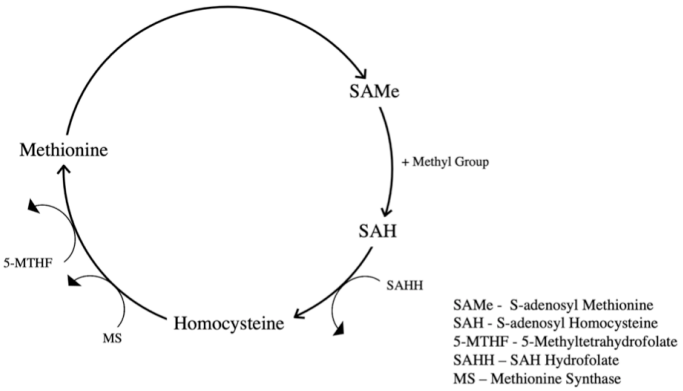

Figure 2. Homocysteine remethylation cycle. Pathway of the homocysteine remethylation cycle, drawn by author. Illustration was aided with use of previous publications.[7,10]

Significance in relation to anencephaly

Importantly, raised plasma concentrations of homocysteine and SAH have been identified in women with pregnancies affected by NTDs.[12] This suggests a possible link between anencephaly and metabolic disruption. Adequate concentrations of folic acid broken down to 5-MTHF may, therefore, be necessary to reduce interference within the homocysteine remethylation cycle and the prevention of homocysteine build-up within the body. An enzyme abnormality within the metabolic pathway could also be a factor in determining anencephaly development. This could include enzymes such as SAHH or MS.[13] Enzyme malfunction could also lead to pathway inhibition and, therefore, cause build-up of substances, such as homocysteine, which could lead to increased anencephaly risk.

One animal study, in chick embryos, analysed the effects of administered homocysteine in the chicks' development and methylation metabolism. Results showed a delayed closure of the anterior neural pore.[14] The failure of the anterior neuropore to close causes anencephaly.[15]

> *Therefore, a lack of folic acid and the subsequent effects of increased levels of homocysteine could well be linked to increased anencephaly risk.*

On the other hand, women who have had pregnancies resulting in NTDs are most often not deficient in folate.[16] This could further support the fact that anencephaly may develop as a result of an abnormality of one of the enzymes involved in homocysteine remethylation, such as MS, rather than folic acid deficiency.

Discussion and conclusion

There is strong evidence to suggest that folic acid is effective in preventing NTDs.[8,17] However, anencephaly will not necessarily develop if the vitamin is not taken during the recommended timeframe. Furthermore, even when folic acid is administered correctly, anencephaly could still develop. Genetics could also play a role; particular ethnic groups are more likely to develop NTDs.[18] There is also research to support that after having a pregnancy with an NTD, the risk of having another increases.[19] One study identified the presence of unmetabolised folic acid in the bloodstream in those who consumed the daily recommendation of 0.4mg, questioning the effect of having too much folic acid.[20] Additionally, papers have suggested that supplementation of folic acid could stimulate cancer progression.[21,22] However, there is conflicting evidence, with some RCTs reporting that folic acid has no effect on specific cancer biomarkers.[23,24,25] The participants of these studies were not pregnant women, which is a limitation.

A further point of study would be to see whether a diet very rich in folate, as well as folic acid supplementation, would exceed the recommended dosage of the vitamin and therefore cause adverse effects. Despite this, a diet rich in folate should not be discouraged since the health benefits of fruit and vegetables are well-documented. There are also instances where mothers are advised to take higher doses of folic acid to prevent NTDs. This includes pregnancies where there have been previous children with NTDs, or where the mother either smokes, is obese, has diabetes mellitus or poor adherence to folic acid is predicted.[26]

In 2018, the Royal College of Obstetricians and Gynaecologists (RCOG) acknowledged that fortification of folic acid in foods, such as flour, would see a "significant reduction in the incidence of NTDs".[27] This evidence is supported by early RCTs which concluded supplementation with folic acid is an effective preventative measure against most NTDs.[28,29] Despite this, fortification is not implemented in all countries for the following reasons: financial cost; challenge in accessing resources to roll out large-scale projects; fortified foodstuffs, such as flour, may not support a country's classic diet.[30] Also, in countries where there are high unplanned pregnancy rates, women may be unaware of the need for folic acid supplementation at pre-conception, conception and first-trimester periods.[31]

In conclusion, folic acid can be an excellent primary strategy in preventing anencephaly. To move forward, more research into the

consequences of higher folic acid levels and possible cancer risks is required.

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References

1. O'Rahilly M, Muller F. Human Embryology & Teratology. New York: Wiley-Liss; 1992.
2. Cook RJ, et al. Prenatal management of anencephaly. International Journal of Gynecology and Obstetrics. 2008;102304–308.
3. Anon. Genetics Home Reference. Anencephaly. Available from: www.ghr.nlm.nih.gov/condition/anencephaly#statistics. Accessed: 17 November 2019.
4. Fetal Health Foundation. Anencephaly. Available from: www.fetalhealthfoundation.org/fetal-syndromes/anencephaly/. Accessed 17 April 2021.
5. Centers for Disease Control and Prevention. Facts about Anencephaly. Available from: www.cdc.gov/ncbddd/birthdefects/anencephaly.html. Accessed 18 April.
6. Rees G. British Dietetic Association. Folic Acid. Available from: www.bda.uk.com/foodfacts/folic_acid. Accessed: 14 November 2019.
7. Wright A, Dainty J, Finglas P. Folic acid metabolism in human subjects revisited: potential implications for proposed mandatory folic acid fortification in the UK. Br J Nutr. 2007;98:667-75.
8. Imbard A, Benoist J, Blom H. Neural Tube Defects, Folic Acid and Methylation. Int J Environ Res Public Health. 2013;10:4352-4389.
9. Stover P. Physiology of Folate and Vitamin B12 in Health and Disease. Nutri. Rev. 2004;62:S3-12.
10. Gregory J. Case Study: Folate Bioavailability. J Nutr. 2001;131:1376S-82.
11. Finkelstein J. Metabolic regulatory properties of S-adenosylmethionine and S-adenosylhomocysteine. Clin Chem Lab Med. 2007;45:1694-9.
12. Zhao W, et al. Neural tube defects and maternal biomarkers of folate, homocysteine, and glutathione metabolism. Birth Defects Res A Clin Mol Teratol. 2006;76:230-236.
13. Mills J, et al. Homocysteine and Neural Tube Defects. J Nutr. 1996;126:756S-60.
14. Afman L, et al. Homocysteine interference in neurulation: A chick embryo model. Birth Defects Res A Clin Mol Teratol. 2003;67:421-428.
15. Gest T. University of Michigan Medical School. Nervous System. Available from: www.med.umich.edu/lrc/coursepages/m1/embryology/embryo/08nervoussytem.htm. Accessed 14 November 2019.
16. Molloy A, et al. Maternal serum folate and vitamin B12 concentrations in pregnancies associated with neural tube defects. Arch Dis Child. 1985;60:660-65.
17. Viswanathan, M et al. Folic Acid Supplementation for the Prevention of Neural Tube Defects. JAMA. 2017;317:190.
18. Peake, J et al. Maternal ethnicity and the prevalence of British pregnancies affected by neural tube defects. Birth Defects Research. 2021.
19. Limb M. Flour to be fortified with folic acid within weeks. BMJ. 2018;363:4348.
20. Sweeney M, McPartlin J, Scott J. Folic acid fortification and public health: Report on threshold doses above which unmetabolised folic acid appear in serum. BMC Public Health. 2007;7(1).
21. Kim Y. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? Gut, 2006;55:1387-1389.
22. Kim, Y. Folic Acid Supplementation and Cancer Risk: Point. Cancer Epidemiology Biomarkers & Prevention, 2008;17:2220-2225.
23. Figueiredo J, et al. 2011. Folic acid and prevention of colorectal adenomas: A combined analysis of randomized clinical trials. International Journal of Cancer. 2011:129;192-203.
24. Butterworth C, et al. Oral folic acid supplementation for cervical dysplasia: A clinical intervention trial. American Journal of Obstetrics and Gynecology, 1992:166;803-809.
25. Childers JM, et al. Chemoprevention of cervical cancer with folic acid: a phase III Southwest Oncology Group Intergroup study. Cancer Epidemiol Biomarkers Prev. 1995;4:155-159.
26. Kennedy D, Koren, G. Identifying women who might benefit from higher doses of folic acid in pregnancy. Canadian family physician Medecin de famille canadien. 2012;58:394–397.
27. Figueiredo J, et al. 2011. Folic acid and prevention of colorectal adenomas: A combined analysis of randomized clinical trials. International Journal of Cancer. 2011:129;192-203.
28. Wald N, et al. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Medical Research Council Vitamin Study Research Group. Lancet. 1991;338(8760):131–7.
29. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832–5.
30. Tsang B, et al. Public and Private Sector Dynamics in Scaling Up Rice Fortification. Food and Nutrition Bulletin, 2016;37(3):317-328.
31. Botto L, et al. Neural-Tube Defects. New England Journal of Medicine, 1999;341(20):1509-1519.