B12 Deficiency and Folate

Folate is the term used for many similar molecules, all of which are essential for the production and control of DNA. They are important for the production of the bases that make up the 'code' of DNA and RNA and for the production of S-adenosyl methionine (SAMe) which is important for switching genes on and off via methylation.

B12, folate and the conversion of homocysteine to methionine

Vitamin B12 and one particular form of folate – tetrahydromethylfolate (THMF) work together in the production of methionine (which is then converted to SAMe).

The conversion of homocysteine (hCys) to methionine (met) is carried out by the enzyme methionine synthase. The first step in the process is the removal of the top ligand of the various types of B12 to form cob(I)alamin. This binds to methionine synthase enzyme. Then a molecule of MTHF also binds to the enzyme. The methyl group of MTHF passes to the cob(I)alamin, producing enzyme-bound methylcobalamin and releasing a molecule of tetrahydrofolate (THF). This binding activates the enzyme, allowing a molecule of hCys to bind to a zinc atom in the enzyme. The methyl group is passed from the methylcobalamin to the sulfur atom of the hCys to produce met, which is then released.

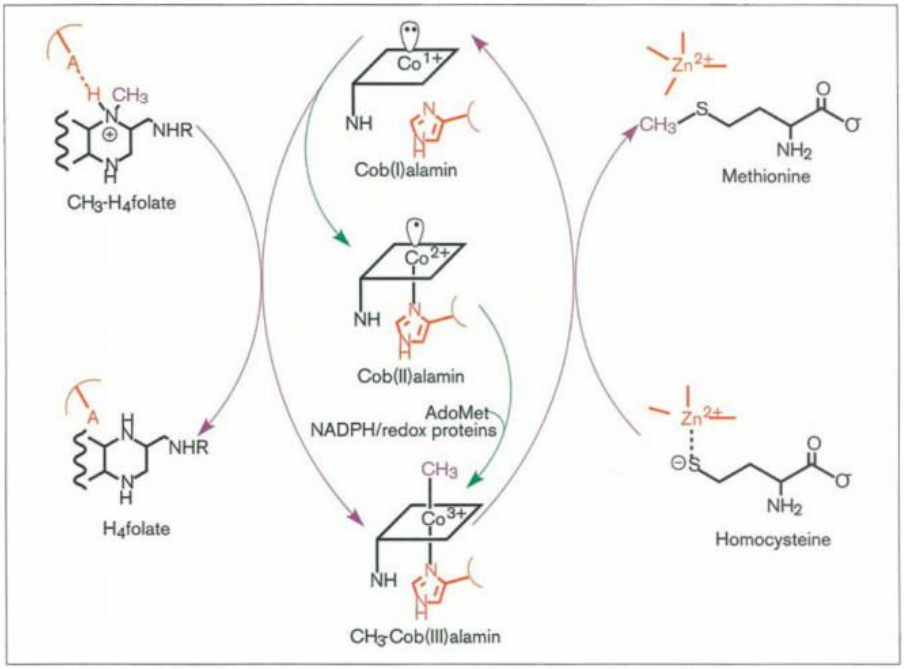


Image source: Cobalamin Biochemistry

The body only makes as much cob(I)alamin and met as it needs. To make more would be extremely wasteful. As long as there is enough B12 and MTHF then the reaction will proceed at the normal rate. If you add extra B12 then it will not use it to make more met. This means that the body doesn't need more folate when levels of B12 are high. Some sources suggest that doses of 5000 mcg a day are required when injecting B12. This is not only wrong, but potentially harmful.

Potential dangers of folate supplementation

The most common warning about supplementing with folic acid is that it should not be done if there is a possibility of a B12 deficiency. If you do have a B12 deficiency then taking folate supplements can prevent macrocytic anaemia. This is only a problem if your B12 deficiency is undiagnosed and you have a doctor who believes that the lack of macrocytic anaemia is sufficient to rule out a B12 deficiency. If this happens then the B12 deficiency will not be rectified and the damage, especially neurological damage, would become more serious.

However, there is some evidence that high dose folate in the presence of a B12 deficiency can exacerbate the neurological damage.

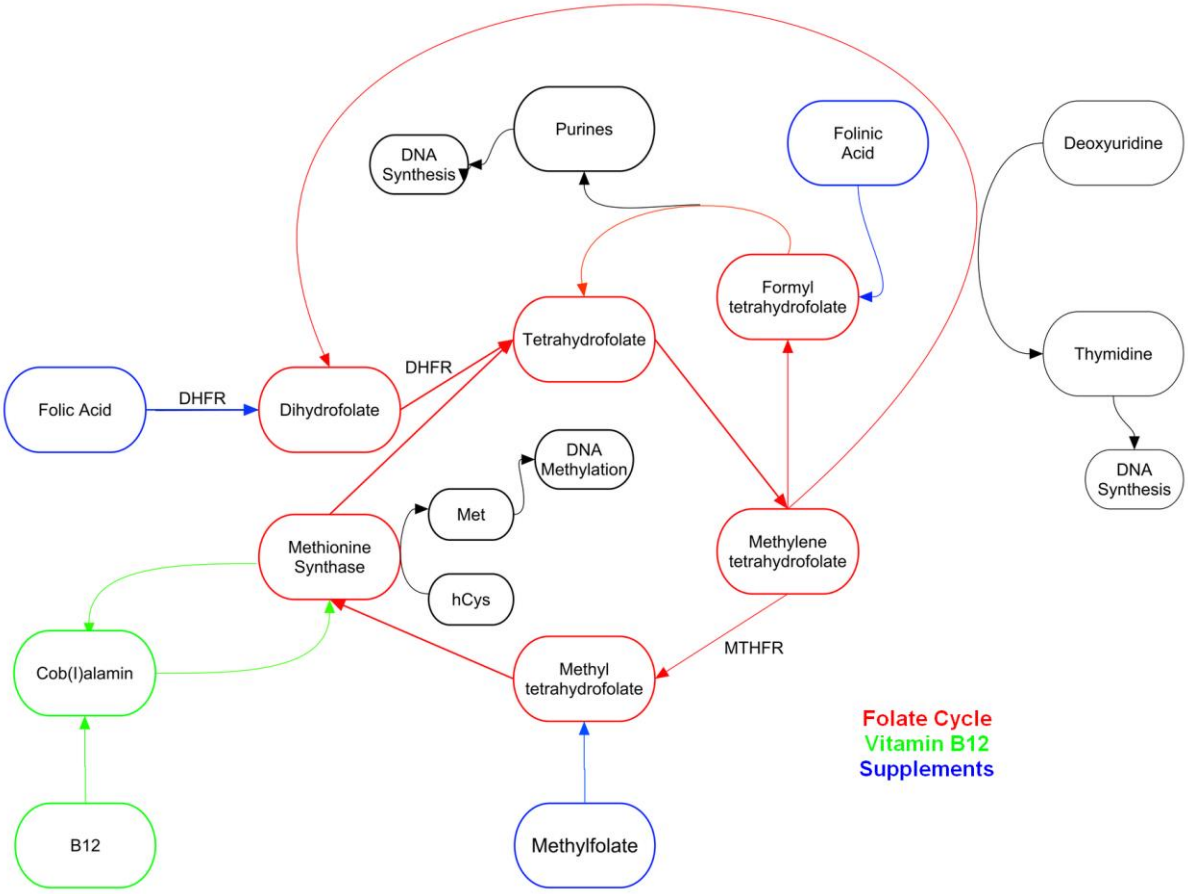
Even in the absence of a B12 deficiency, there is evidence that excess folate can contribute to cancer and cardiovascular disease.

Some suggest that the safe upper limit of folate should be reduced to 1000 mcg a day.

In the UK people with a very low serum folate will be prescribed 5000 mcg tablets of folic acid. These should only be taken for a short time, until the deficiency has been rectified, and should not be taken until a B12 deficiency has been ruled out, or adequate treatment started.

Folate supplements

As I said at the beginning, there are many different chemicals that are called folates. Which ones are available as supplements and which ones should people take?



The diagram shows the folate cycle (in red), the contribution by Vitamin B12 (green) and the supplements commonly taken. As you can see, all three supplements need to enter the folate cycle to enable the different functions of the different folates.

Folic Acid is the most common folate supplement. It is cheap and easily obtainable. For the vast majority of people it is perfectly acceptable. It easily enters the folate cycle by conversion into dihydrofolate. It is recommended that women of childbearing potential take 400 mcg of folic acid a day, to prevent neural tube defects such as spina bifida. There is no reason for those worried about their folate status not to do the same.

Methyl Folate is also known as methyltetrahydrofolate. It enters the folate cycle at a point that bypasses the MTHFR conversion. As such, some people with one particular mutation (homozygous C677T) in the gene for MTHFR may find it worth paying ten times the price to take methylfolate instead of folic acid.

Folinic Acid is the new, trendy, supplement. It offers no advantages over the other two supplements unless you are taking methotrexate.

The folate trap

Serum levels of folate cannot affect the levels of Vitamin B12, but B12 can adversely affect folate levels in an unusual way.

We saw above that methyltetrahydrofolate (MTHF) is converted to tetrahydrofolate (THF) during the conversion of hCys to met – a reaction that requires B12. This is the only way that MTHF can be converted to THF. If there is insufficient B12 in the cell then this reaction cannot be carried out at full capacity. This results in a build-up of both hCys and MTHF and a shortage of THF and met.

High levels of hCys are associated with an increased risk of cardiovascular disease. Low levels of met cause many of the symptoms of a B12 deficiency. But there is an unexpected problem that arises because MTHF is not being converted to THF.

As you can see from the diagram of the folate cycle, THF is an important part. If the levels of THF drop then so do the levels of all the other forms of folate, including those forms required for the synthesis of DNA bases. This causes the symptoms of a folate deficiency.

But when a patient is tested for folate levels, all forms of folate are measured together. Because the patient has lots of MTHF building up in their body the test result will be normal, possibly high. The patient can have the symptoms of a folate deficiency, whilst blood tests show normal levels. If the patient is tested with folate supplements then the deficiency can be rectified, but that additional folate will soon get trapped as MTHF. Blood levels will increase with unknown effects.

This paradox of high folate levels with all the symptoms of low folate is called the Folate Trap. It is fixed by ensuring the underlying cause – a B12 deficiency – is adequately treated.