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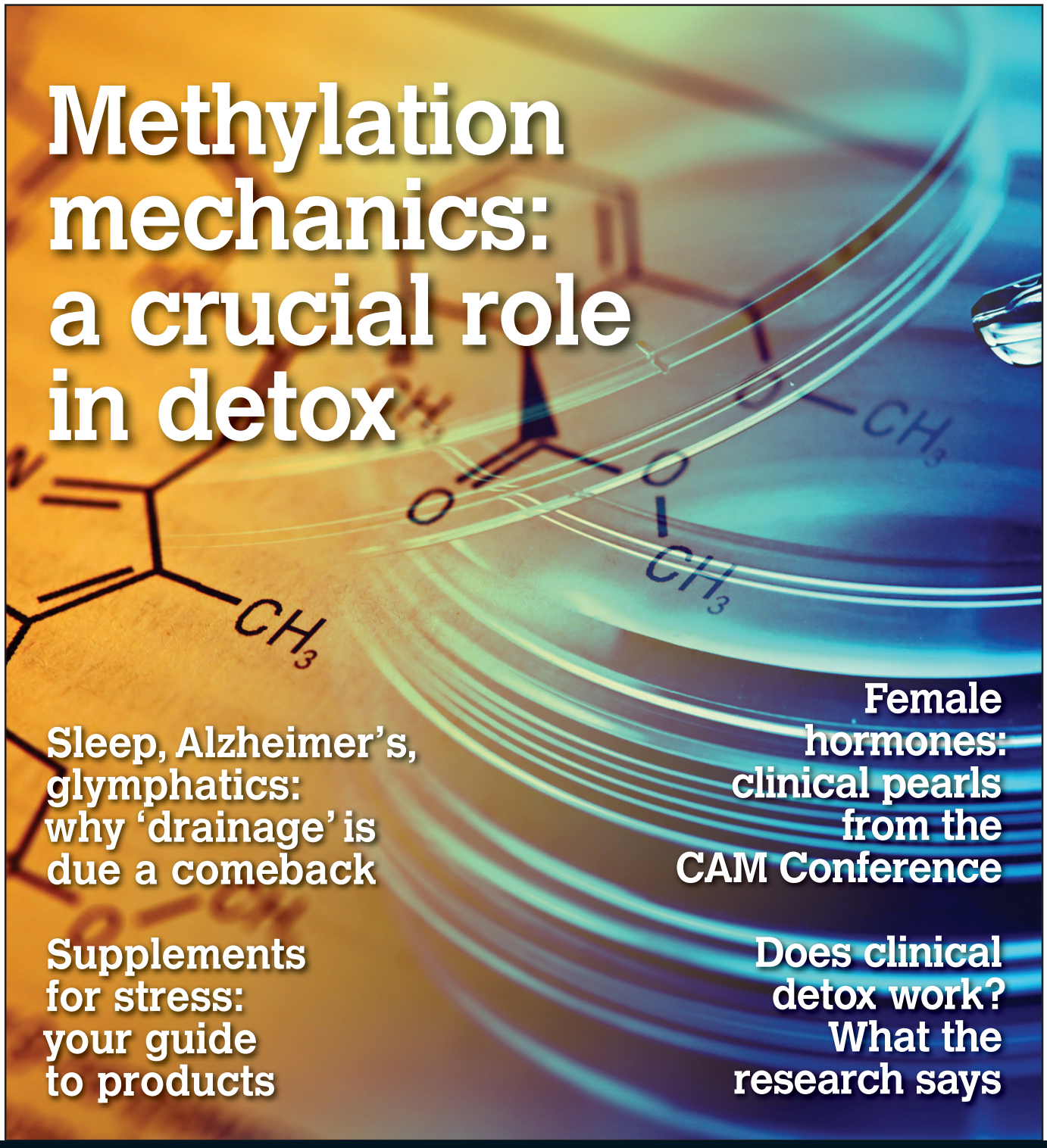

Methylation mechanics: a crucial role in detox

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The mechanics of methylation and its crucial role in detoxification

In human biology, the methylation cycle is an indispensable life support system. Practitioners concerned with chronic, complex illness can't afford to ignore this "heavyweight" of biochemical pathways. Here, *CAM* contributing editor **Niki Gratrix**, BA (Hons), Dip ION, gives an overview of this crucial system, and introduces some of the latest teachings of leading experts on methylation, including **Dr Amy Yasko**, PhD, and **Dr Ben Lynch**, ND, as part of our ongoing series on dealing with toxicity.

The role of methylation in the production of excess homocysteine and the link to heart disease has dominated practitioner awareness about this crucial system. Most are also aware of the profound role DNA methylation plays in epigenetics, cancer and theories of ageing. Yet the essential role of methylation in phase II detoxification and the production of glutathione, the body's master detoxifier and primary cellular antioxidant through the transsulfuration pathway, seems to have been forgotten.

Methylation and detoxification

Nutrition balancing consultant Dr Lawrence Wilson, MD, a former CDC (Centres for Disease Control) researcher, says: "Methylation is a primary method of removing toxins in the phase II liver detoxification system of the body. More precisely, methylation converts toxins of all kinds from insoluble, less-soluble or fat-soluble compounds into water-soluble compounds. This, in turn, allows the body to eliminate them much more easily.

"Methylation, in this sense, is somewhat like first tagging toxic substances and then altering them in a way that allows the body to identify them as toxins, and then to eliminate them rapidly and simply. Larger molecules are then able to be eliminated through the bile, while smaller ones pass into the bloodstream and are removed by the kidneys in the urine."(1)

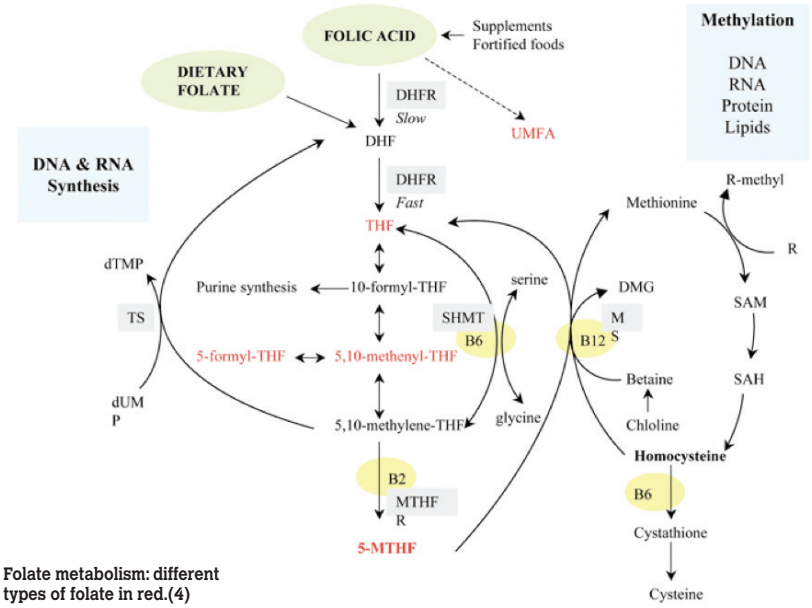
Similarly, most of us know about the dangers of HIGH homocysteine, but little has been understood with regards to the dangers of LOW homocysteine, often found for example in autism. We live in a world of biological dualism, and as Dr Guy Schenker, DC, aptly points out: "All physiological systems are maintained through a negative feedback mechanism that operates in a dualistic manner. Dualistic means that for every normal condition, there are two abnormals – abnormally high and abnormally low."(2)

Easy access to comprehensive genetic testing has not been available in the UK, but Regenerus Labs has just launched the Doctor's Data Methylation Panel test here (www.regeneruslabs.com). In addition, a world-class training on methylation became available through a two-day, sold-out training given at Bastyr University this October by naturopathic physician Dr Ben Lynch, now available online.(3) So this is a good time to revisit the methylation cycle with detoxification in mind.

Overview of the methylation cycle

The methylation cycle is a central pathway in the body that is responsible for producing "methyl" groups. Methyl groups are small groups of molecules similar in size to a water molecule, containing hydrogen and carbon: CH3. When methyl groups attach to other molecules in the body it is called "methylation."

The cycle is primarily made of up two tightly-linked cycles; the methionine and folate cycle. The methionine cycle converts homocysteine to L-methionine. This can be done through two routes. The first involves vitamins B12 and folic acid, which participate in converting homocysteine into L-methionine. Dr Amy Yasko, the pioneering clinician working with



Folate metabolism: different types of folate in red.(4)

polymorphisms in the methylation cycle in autistic children, calls this the "long route".

The second route uses the molecule trimethylglycine, also known as TMG or betaine. TMG transfers a methyl group from itself to homocysteine, converting it into L-methionine through a specific enzyme present in the liver and the kidneys. Dr Yasko calls this the "short-cut route".

Methionine is combined with the energy molecule adenosine triphosphate (ATP) to produce the vitally important molecule S-adenosyl-methionine, or SAMe. SAMe is the body's exclusive methyl donor group.

The folate cycle is hugely important, as it drives the methionine cycle. Dietary folates and folic acid are converted through a series of steps to tetrahydrofolate (THF) through to 5,10-methylenetetrahydrofolate, then an important enzyme, Methylenetetrahydrofolate reductase (MTHFR), converts this to 5-methyltetrahydrofolate (5-MTHF). 5-MTHF is very important, as it is used as the co-substrate for homocysteine remethylation to methionine and is also recycled back to THF.

The cofactors which support methylation are zinc, magnesium and vitamins B12, B2 and B6.

Methyl groups – your body's personal mechanic

Dr Yasko calls methyl groups the body's "personal mechanic". Methyl groups are involved in a very wide array of methylation reactions which synthesise, rebuild and repair the body. Methyl groups are involved in methylation (and thus silencing) of DNA and the synthesis of DNA, RNA, creatine, choline, carnitine, coenzyme Q-10, melatonin and myelin basic protein. Methyl groups are used to repair protein and metabolise niacin, oestrogen, xenobiotics, and the catecholamines dopamine, norepinephrine and epinephrine. Methyl groups are also used to inactivate histamine, and to methylate phospholipids, the all-important fatty acids in cellular membranes. Finally, methylation also plays a key role in immunity as it helps with the production of natural killer cells and T cells.

As Braly and Holford put it: "Methylation takes place over a billion times a second in the body. It is like one big dance with biochemical passing of methyl groups from one partner to another".(5)

Methylation and heart disease

The methylation cycle first rose to fame when the correlation of high homocysteine with cardiovascular disease was finally accepted in the 1990s – some 20 years after Dr Kilmer McCully discovered the link. High levels are associated with atherosclerosis, an increased risk of heart attacks, strokes, blood clot formation and possibly Alzheimer's disease.(6,7) In men, hyperhomocysteinaemia is also associated with the prevalence of frailty and is predictive of mortality from all causes, independent of frailty. (8) But homocysteine testing is still not standard conventional screening.

Elevated homocysteine levels suggest that some part of the methylation system is impaired. Dr Paul Frankel, PhD, author of *The Methylation Miracle*, estimated that supplemental support of the methylation cycle with nutrients including folic acid, betaine, vitamin B12 and choline, could save thousands of lives per year.(9)

"Agouti mice": yellow-coated, obese and unhealthy without methylation support; brown-coated, lean and longer-lived with support.

DNA methylation and epigenetics

Methyl groups attach to cytosine, one of the four bases of DNA, and their presence blocks the expression of the gene involved. One of the founders of epigenetics, Duke University's Dr Randy Jirtle, PhD, and postdoc Robert Waterland showed how supplementing the methylation cycle of pregnant mice with folic acid, B12, choline and betaine permanently affected the expression of a gene called Agouti in their offspring, although the gene itself remained unchanged.

Mice with an unmethylated Agouti gene tended to have yellow coats, suffer obesity and die early from diseases like diabetes and cancer. By supporting methylation during pregnancy, the additional methyl groups silenced the gene in the offspring leading to the healthier, less obese, brown-coated mice. (10) Jirtle commented that manipulating DNA methylation could potentially affect dozens of other genes that make humans and animals susceptible to cancer, obesity, diabetes and autism.(11) →

DNA methylation and cancer

Methylation has become an important topic for cancer research. As Song and He report, there is a balance of methylation and demethylation involved, and "a highly distorted epigenome (including aberrant DNA methylation and histone modification patterns) is now accepted to be a general feature of many cancers".(12)

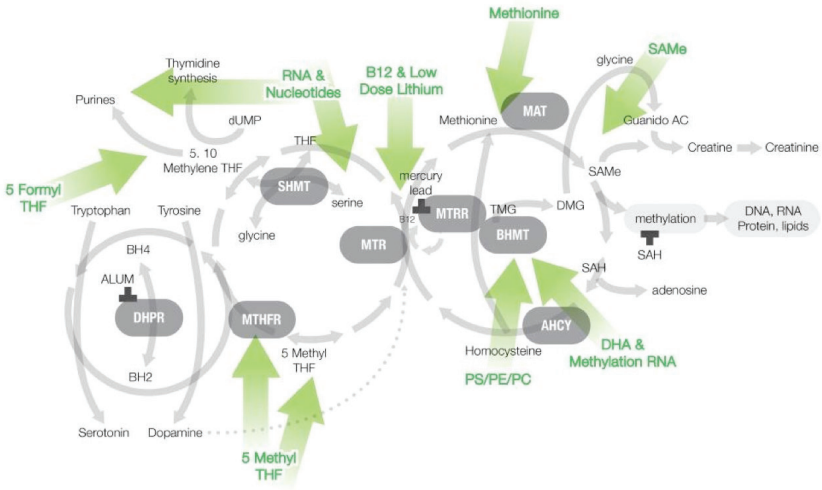
DNA methylation and ageing

An interesting and novel theory of ageing is the idea that as we age, fewer methyl groups attach to DNA, thus affecting the expression and integrity of the genome. Miguel Toribio-Mateas discusses this in more depth elsewhere in this issue.

Methylation and autism

As was pointed out above, homocysteine can be recycled into L-methionine via the long route or short route of the methionine cycle. A third pathway converts homocysteine into the beneficial sulphur-containing amino acid L-cysteine using the cofactors vitamin B6 and zinc. Generating L-cysteine provides the key amino acid to produce L-glutathione in the transsulfuration pathway.

Given this, it should be understood that LOW homocysteine is also not good for us, given the impact on glutathione levels and L-methionine levels (which is required for the all-important SAMe). It is notable that many autistic children have been found to have low homocysteine. James et al (13) found that in autism the methylation cycle was blocked at methionine synthase, which is the step involving methylation of homocysteine to form methionine. The effect of this block is a significant decrease in the level of plasma methionine and reduced capacity to methylate.



From Dr Amy Yasko's concept of "nutritional bypass": diagram shows the supplement required (in green) for each polymorphism (grey boxes). For example, a person with a MAT polymorphism could be taking all the right cofactors and follow a good diet, but still not feel good because L-methionine is not being converted to SAMe; in this case SAMe supplementation will make the difference.

These researchers also found that the flow through the transsulfuration pathway was decreased, resulting in lower plasma levels of cysteine and glutathione and a lowered ratio of reduced to oxidised glutathione. The block in the methylation cycle and the glutathione ratio problem were linked, since supplements used to restore the methylation cycle to normal operation (methylcobalamin, folinic acid and trimethylglycine – TMG) also restored the levels of reduced and oxidised glutathione.

In later research they found measurable differences between children with autism and healthy controls in genes that encode enzymes and other proteins impacting the methylation cycle, the folate metabolism and the glutathione system.(14)

This research led Dr Amy Yasko to focus on genetically testing the methylation pathways in autistic children as the core of her clinical protocol. Dr Yasko writes about personalised medicine and the ability to create a "nutritional bypass" to limit the effects of genetic polymorphisms in the cycle.(15)

These examples highlight the importance of genetic testing as part of our work with patients and developing personalised programmes. Protocol-driven supplement programmes are no longer desirable or appropriate.

Methylation, Chronic Fatigue Syndrome and related illnesses

The late Dr Rich Van Konynenberg, PhD (a

6 tips from Dr Ben Lynch on detox reactions

Starting methylation support is renowned for creating detox reactions in patients. It switches on glutathione and phase II liver detox, causing enhanced toxin excretion. One way Dr Yasko tackles this is by focusing on the short-cut route in recycling homocysteine before focusing on the long route. (13) Many of us working with sick patients often find they cannot tolerate folic acid or folinic acid, others can't take vitamin B12 at all, and still others feel very bad on glutathione. Here's why and what to do:

Tip 1: go slowly, learn more
We need to make our patients better every step of the way, so we must go slowly and adjust the protocol as needed. A comprehensive history-taking is even more important than lab tests, and a commitment to ongoing education and learning is critical.

Tip 2: first things first
Do NOT jump straight in to giving 5-Methyltetrahydrofolate and other methylation nutrients once a methylation defect or under-function has been diagnosed in very sick patients. FIRST you must reduce oxidative stress in the cells, heal the mitochondria and cell membranes with nutrients like CoQ10, niacin, carnitine and phosphatidylcholine.

Tip 3: careful with glutathione
Increasing methylation and therefore glutathione can just increase levels of oxidised glutathione in the mitochondria, which further damages and kills cells. The enzyme glutathione reductase is needed to quench oxidised glutathione; it is dependent on niacin, so providing niacin at the same time can help.

Tip 5: check B12
Many people are deficient in B12 due to difficulty of absorption and the need for transcobalamin. Serum B12 should be no less than 4-500 and a more accurate test for B12 is urinary methylmalonic acid (MMA).

Tip 6: deal with B12 sensitivity
Patients can react to B12 because they cannot process the cobalamin left-over once the methyl or hydroxyl groups have been cleaved. Quoting a paper by Deth et al (23), Dr Lynch says type 1 cobalamin can be oxidised and needs to be converted to the reduced type 3, which interestingly requires methylfolate. So provide methylfolate FIRST with your B12 reactive patients and bring in the vitamin B12 later.

→ nuclear physicist by training and profession), inspired by Dr Yasko, worked tirelessly to prove that impaired methylation and low glutathione are a significant contributing factor in chronic fatigue syndrome (CFS).(16)

Dr Konynenberg made a compelling case, summarising all the scientific literature which supports proof of impaired methylation in CFS and documented the similarities to autism. He believed the only difference was the timing – in effect CFS is "adult onset autism".

One correlation of particular interest is that methylation is profoundly important in killing viruses, and papers have been published both on the link between methylation and hepatitis C (with SAMe and betaine supplementation improving response) and also Epstein Barr virus, which has been strongly associated with onset of many cases of CFS.(17,18)

MTHFR gene mutation and other illnesses

Mutation in the MTHFR gene can cause up to a 70% inhibition of the production of 5MTHF – the major co-substrate in both the methionine and folate cycles – significantly impacting methylation. According to naturopathic physician Dr Ben Lynch, ND, (19) a mutation in this gene is associated with at least 64 conditions, including occlusive vascular disease, neural tube defects, dementia, colon cancer, acute leukaemia, autism, CFS, fibromyalgia, chemical sensitivity, Alzheimer's, Parkinson's, epilepsy, MS, psychiatric disorders, infertility, miscarriages, congenital heart defects, pulmonary embolisms, strokes, blood clots, type 1 diabetes and more.

MTHFR mutation is highly prevalent, with almost one out of two people in the US having some level of mutation. Nearly 40% of Mexicans have a mutation, 30% of Hispanics, and 35% of Italians.(20)

Interestingly, Dr Lynch says the levels of neural tube defects in countries almost exactly matches the level of MRHFR prevalence (except in Italy) – confirming that diet and environmental factors are also key, not just gene mutations in disturbed methylation.

Correcting disturbed methylation, improving detox capability

Diet, gut health, medications, environmental toxicity, gene mutations and stress can all profoundly impact methylation. Dr Lynch's presentation at Bastyr University included four startling suggestions:

1. "Stop using folic acid"

Folic acid does not occur naturally; it was first introduced synthetically in 1943. With mandatory food fortification since 1998, there is now concern about chronic high exposures and a possible link with cancer. Folic acid is very slowly processed and now a new chemical marker called "Unmetabolised folic acid" (UMFA) has been shown to lead to decreased natural killer cells. Dr Lynch says to stop using folic acid; instead use methylfolates, folinic acid etc, and rely on natural food sources.

2. Some 40-70% of your available methyl groups are used to produce creatine – vegetarians beware!

Half of our need for creatine is met from food – meat. The rest of it is made by the body, but production is very demanding on methyl groups. This may explain why many of our patients do better on meat. Vegetarians are putting a great demand on methyl groups at the expense of other major functions, such as DNA repair. Vegetarians/vegans should probably also B12 and choline.(21)

3. DNA methylation is significantly DOWN-regulated by dietary catechols

Foods highest in chlorogenic acid include green tea and coffee, potatoes and sweet potatoes. These foods should probably be avoided by pregnant women.(22)

4. Patients with the MTHFR mutation will not do well on chemotherapy or nitrous oxide

Nitrous oxide can cause a 80-90% inhibition of methylation for up to two days. Studies exist showing a SINGLE dose of nitrous oxide can produce irreversible neurological damage. If a patient must take it pre and post, load with methionine, B12 and the folates.

About the author

Niki Gratrix, BA (Hons), Dip ION, mBANT, is one of the UK's leading nutritional therapists specialising in Chronic Fatigue Syndrome/ME and related illnesses. She is one of *CAM's* contributing editors and a former CAM Award winner. See her website for practitioners at www.ExpertPractitioner.com

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