Methylation Dysfunction – A Potential Roadblock to Health (with Detours)

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It is clear that one's state of health is a product of gene-environment interactions. We all know people who drink 1 cup of morning coffee and can't sleep at night. And we know people who can drink a whole pot throughout the day and sleep just fine. These genetically different individuals have different amounts of caffeine clearing liver enzymes and therefore differing abilities to clear caffeine from their bodies. A change in lifestyle (less caffeine consumption) can have dramatic effects in some people's health by improving sleep. Others will note that caffeine has no effect on their sleep.

The point here is that our health is a reflection of our genes and our lifestyle. A gene that has been getting a lot of attention because of its far reaching effects in the body is the MTHFR gene. The Methyltetrahydrofolatereductase (MTHFR) gene is a blueprint for making the MTHFR enzyme. This enzyme is involved in set of molecular reactions called methylation. In these chemical reactions enzymes add methyl groups (one carbon and 3 hydrogen atoms) to some molecules (proteins, DNA…) and other enzymes remove methyl groups. Molecules are methylated (the methyl group is placed on it), demethylated (the methyl group is taken off), and re-methylated (the methyl group is put back on). In my head, I imagine the molecules passing them around like hot potatoes as they recycle these little methyl groups around and around. Once a molecule is methylated it will do certain things that it did not do before. There are hundreds of methylation reactions in the body and so dysfunctions in methylation can manifest in many different symptoms and conditions .

People who have inefficient methylation reactions (slow methylators or poor methylators) are at increased risk of cardiovascular disease due to a build up of homocysteine. When the amino acid homocysteine is methylated it is changed into methionine. When methylation is blocked, homocysteine cannot change into methionine and homocysteine accumulates. Homocysteine is a toxin to the blood vessels and weakens artery walls. Individuals with elevated homocysteine are at risk of heart attack, stroke and increased blood clotting. This was first discovered by Dr. Kilmer McCully in 1969. He discovered that children's cardiovascular disease can be related to high homocysteine. His research suggests that optimal blood homocysteine levels are between 4 – 8mmole/l. This is much lower than the "normal" reference ranges used by most conventional labs.

If homocysteine is appropriately methylated to become methionine, then methionine is converted to the infamous SAMe (commonly available as a supplement) which is a methyl donor. By passing along it's methyl group, SAMe can support the proper flow of neurotransmitters like serotonin, dopamine and norepinepherine. Inefficient methylation from SAMe has been linked to conditions such as ADD, bipolar, PMS, chronic fatigue, schizophrenia and depression. Studies of individuals with depression have shown that poor methylation is associated with being 6 times more likely to not respond to antidepressant medications, 13 times more likely to relapse, and an increased risk for more severe and longer episodes of depression.

Methylation turns genes on or off and activates or inactivates enzymes in many other body systems affecting hormonal balance, detoxification, protein synthesis, and immune regulation. Besides cardiovascular disease and mood disorders inefficient methylation has been linked to skin/hair/nail problems, varicose veins, infertility, polycystic ovary syndrome, acne, fibroids, endometriosis, obesity, insulin resistance, anemia, cervical dysplasia, gum disease, tinnitus, poor nerve function, cleft palate, spina bifida, autism, dementia, osteoporosis fractures, and, to bring us full circle – even intolerance of caffeine! There is some controversy about how methylation affects one's risk of cancer though. Methyl groups added to specific regulatory areas of DNA will turn genes on. In the case of cancer, we want the tumor suppressor genes turned on. DNA that is diffusely poorly methylated has been linked to some cancers. However, since methylation can also support more DNA production and growth, it may be risky in the context of an already existing cancer as increasing methylation can increase the tumor DNA production and growth. This research may not be seeing the whole picture though.

Influences on one's ability to methylate include genetic variations, nutrient sufficiencies and lifestyle choices. Necessary nutrients include folate (Vitamin B9), Vitamin B12, Vitamin B2, Vitamin B6, methionine, and trimethyl glycine (also known as betaine). The "lynchpin" in the methylation "cycling" is methylfolate. When folate is not methylated, there is a roadblock that can cause a back up of proper functioning molecules. Several methylation cycles will "get stuck" creating the health conditions listed above. The many neurological, cognitive and mood disorders associated with methylation are related to the fact that folate can only enter the brain in the methylfolate form.

Folic acid in your multivitamin or your B complex is a synthetic vitamin. It will have to be transformed by the body into the natural form of folate found in food, dihydrofolate (DHF). A few more transformations occur before the MTHFR enzyme will convert it into 5-MTHF (also known as methylfolate), the lynchpin. Inability to make adequate methylfolate can occur from using certain medications, having certain health conditions, lifestyle factors, and genetic variations. The genetic variations are called snps (single nucleotide polymorphisms) and 40% of Americans have a snp in their MTHFR gene. There are 40 different variations of the MTHFR gene with the most dysfunctional having 60 - 70% reduced ability to make methylfolate.

Detours for individuals who have roadblocks in their methylation pathways can be designed. Sometimes lifestyle modifications or medication changes/eliminations are possible. Certainly adding folate rich food to the diet is ideal in any case as these foods contain many health benefits. The impact of genetic snps can be reduced by increasing the available methylation nutrients. Individuals having the most ineffective variations of MTHFR will probably need supplementation. High quality multivitamins and B complexes contain the activated forms of folate (5-MTHF or methyl folate) and B12 (methylcobalamin).

Folate rich foods are associated with decreased cancer risk. This makes it hard to understand the research referred to above (that increasing methylation may increase cancer risk in individuals with pre-existing tumors). These studies used synthetic folic acid to affect methylation. Large doses of synthetic folic acid actually inhibit the conversion of folic acid to folate and some individuals are more vulnerable to this effect than others. High levels of "backed-up" folic acid are potentially harmful. In addition, creating this unnecessary roadblock in the pathway to the more beneficial methyl folate will prevent methylation of the regulatory DNA which appears to be protective.

Biological processes are complex and always incompletely understood. For now, it appears that it is safe to eat lots of (organic) green leafy vegetables and take a multivitamin containing methyl folate not folic acid. Be sure the other B vitamins are in your multi (especially methylcobalamin) as these will further support your lynchpin.

Dr. Kate Thomsen's office for holistic health care is located in Pennington, NJ. She is board certified in Family Medicine and in Integrative/Holistic Medicine. She has been practicing Functional Medicine for over 15 years. For more information see www.drkatethomsen.com or call the office at 609-818-9700.

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Medications that affect folate cycling:
- antiseizure, methotrexate, sulfasalazine, birth control pills, metformin, fluoxetine, niacin,warfarin, isotretinoin

Health conditions that affect folate cycling:
- diabetes, atrophic gastritis, Crohn's, colitis, renal failure, hypothyroid

Lifestyle factors that affect folate cycling:
- excess alcohol, smoking, nutrition, pregnancy, aging

Blood tests that may indicate methylation dysfunction:
- Red Blood Cell (RBC) Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH) may be high
- RBC folate (measures activated 5-MTHF) may be low
- Homocysteine may be higher than 8
- Methylmalonic acid (MMA) – (measures activity of B12) may be high
- MTHFR gene (be sure the lab tests for mutations in 2 locations: C677T and A1298C)

Folate Rich Foods:
- Beans, legumes, dark/ leafy vegetables (spinach, asparagus, kale, broccoli, bok choy, turnip/mustard/ collard greens), citrus fruits, beef liver, sunflower seeds, edemame

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