FUNCTIONAL MEDICINE SERIES:

A Crash Course in Methylation

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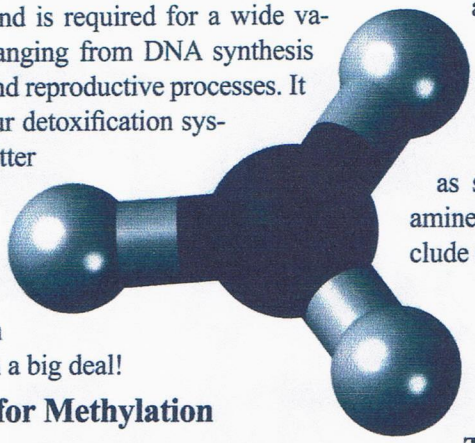
Introduction

Methylation has been a very hot topic in medical literature lately, but what exactly is it? Methylation is actually a simple but imperative biochemical process involving the transfer of four atoms—one carbon and three hydrogens—to an organic compound.

The structure is known as a methyl group (-CH3). Chemically, this transfer can happen via an addition or substitution reaction. In either case, the methyl group takes the place of a hydrogen atom on the compound.

Methylation is vital for life and is required for a wide variety of biochemical processes ranging from DNA synthesis to cardiovascular, neurological, and reproductive processes. It also plays an important role in our detoxification systems. It is vital for neurotransmitter production, immunity, histamine metabolism/inflammation, eye health, fat metabolism, and cellular energy at the cellular level of mitochondria. It is required in every cell, so no wonder it is such a big deal!



Nutritional Requirements for Methylation

The methionine cycle is responsible for DNA, RNA, protein, and lipid synthesis, as well as shunting homocysteine down the path of the transsulfuration cycle. Before we get to that point in the scheme of our metabolism, though, we need the products of the urea cycle, neurotransmitter (BH4) cycle, folate cycle, methionine cycle, and transsulfuration cycle to come into play and work in concert.

The big takeaway is that methylation is interconnected with nearly every bodily function and interconnected with the function of other cycles to work properly. In school, there was a focus on the Krebs (citric acid) cycle, but all of the interconnecting cycles are also important. Methylation is also the lynchpin in our bodily functions, which is why current research has focused on it. To put this in perspective, here is a quick "bird's eye" view of our chemical metabolism before we move forward. The arrow shows our Krebs cycle, so just know that our methylation process is working in the same vicinity.

So methylation is interconnected with nearly every bodily function and interconnected with the function of other cycles within our scheme of metabolism. As we support methylation, we need an adequate supply of folate to convert to bioactive folate. We also need B2 in the folate cycles to help the MTHFR enzyme to create bioactive folate, B12 to convert homocysteine to methionine in the methionone cycle, and B6 to push homocysteine through the process of glutathione production (glutathione being the mother of all antioxidants) in our transsulfuration pathway. In the neurotransmitter cycle, we require bioactive folate (which requires B6) so we can convert cofactor BH4 to BH2 and synthesize important NTs, such as serotonin (from tryptophan) and catecholamines (from phenylalanine/tyrosine), which include dopamine, epinephrine, and norepinephrine.

The interconnection is profound, and the nutritional cofactors are vital. We will come back to nutritional concepts in just a moment.

The Role of the Gene SNP

First a note about methylation and our genes. Genes can be turned on and off like a light switch. We all have a gene for breast cancer, for example, but for many of us it remains "off." For others, it gets turned "on" and the disease develops. Why and how? The role of methylation is being looked at closely here. A number of mechanisms exist to control gene expression (in cancer and many other gene functions), but DNA methylation is a commonly used epigenetic signaling tool that can fix genes in the "off" position. In the case of cancer, this is a good thing. When a CpG island in the promoter region of a gene is methylated, expression of the gene is repressed, or "off."

The addition of methyl groups is controlled by a variety of different levels within cells, and is carried out by a family of enzymes called DNA methyltransferases. What is exciting about these

studies is that they show us that just because we have a gene, it does not mean that it will be expressed, and nutrition plays a powerful role.

A single nucleotide genetic polymorphism, or SNP, is an alteration in a gene that is inherited. (Note that the ugly word for this is "mutation," but we don't like to say it—there is no need and it scares patients.) Certain SNPs can affect our methylation function. Methyl groups (-CH3) are provided to the body through a universal methyl donor called SAMe (S-adenosylmethionine). You can see how it is produced within our methionine cycle. SAMe gives away its methyl group to other substances, which enables our body's systems to perform their functions. The "catch" is that the creation of SAMe is reliant on one switch that is turned on in the folate cycle so that we create 5MTHF (bioactive folate). Folic acid must be converted from the diet to its bioactive form to be adequately utilized in the methylation cycle and create those needed end-products that our bodies require.

An SNP to Look For

Many people easily convert ingested folic acid to bioactive folate (5MTHF) with the assistance of a functioning MTHF reductase enzyme. However, approximately 60% of the population in the U.S. has a genetic mutation (SNP) that affects the conversion enzyme that facilitates the creation of the all-important bioactive folate (5-MTHF). What can this do? This turns off our vital methylation switch, and we can't produce enough SAMe. When this happens, a large number of required molecules can't be efficiently produced, and thus our end-functions suffer, such as DNA/RNA and hormone production. Such molecules include glutathione (mother of all antioxidants), coenzyme Q10, melatonin, serotonin, nitric oxide, epinephrine, norepinephrine, L-carnitine, cysteine, and taurine.

Can you think of symptoms that might manifest with this SNP alone? Immunity? Mood disorders? You may also find that patients with the MTHFR SNP exhibit things such as high homocysteine (a blood marker for CVD risk) as the effects of a lack of bioactive folate trickle over from the folate cycle to the methylation cycle, and without enough bioactive folate, we pump out homocysteine en masse.

How to Intervene

The good news is that we can intervene if we know about this SNP in patients. They can be supplemented with 5MTHF since we know they can't make it themselves. (If they have the SNP, then it doesn't matter how much folic acid they consume, it won't be converted.) A supplement helps to bypass that enzyme.

For others, food sources help support the methylation cycle, such as asparagus, avocado, broccoli, Brussels sprouts, green/leafy vegetables, beets, and legumes.

In summary, our top seven essential nutrients include 5MTHF, active vitamin B12 (methylcobalamin), active vitamin B6 (pyridoxal 5-phosphate), active vitamin B2 (riboflavin 5-phosphate), magnesium, betaine (trimethylglycine), and vitamin D3.

This was a bare concept crash course in methylation. There is a lot more to it; some patients may be overmethylators, some undermethylators, and some may have a gene SNP or other comorbidity, so every individual warrants a different treatment strategy. The information in this article was meant to provide a broad foundation to begin to understand this growing area in health care.

Laurie Mueller, BA, DC, CFMP served in private practice in San Diego, California. She was the post-graduate director at Palmer College from 2000-2010; served as the ACC Post Graduate subcommittee chair for 6 years; and peer reviewed for the Research Agenda Conference. Dr. Mueller currently works as a private eLearning consultant with a focus on healthcare topics and functional medicine through her company, Impact Writing Solutions, LLC. She is a consultant, clinician, an educator and an expert in online educational pedagogy and is the founder of www.FxMedOnline.com.