

The Methylation Cycle and Mental Health

by

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Depression, anxiety, and other mental illnesses are very challenging for the individual and their family. Natural mental health approaches can help bring the body, mind and spirit back to the present and closer to balance. Whether someone is already taking medication or are considering natural options, being equipped with current information can help make well informed decisions for improved mental health.

Methylation

Methylation is not one specific reaction that occurs in one location in the body, but many reactions taking place continually in our cells, especially in the liver. A methyl group consists of one carbon atom connected to three hydrogen ones which are passed around a group of molecules in a cycle. So any time this takes place, methylation occurs. This can be written as CH₃.

Methylation is important in gene expression and repair and the process can turn on a gene or activate an enzyme. When the methyl group is removed, the reaction stops, which turns off a gene or deactivates an enzyme. Methylation of DNA plays a role in kidney repair and in dysregulation of inflammatory diseases.

In its influence on mental health, the methylation cycle is critical to the metabolism of catecholamines in the synapse via an enzyme (COMT) as well as the synthesis of melatonin, carnitine, and CoQ10. Methylation is also required to inactivate histamine.

Methylation occurs in the liver when the body takes harmful substances, including phenols, and turns them into a less harmful substances during phase two detoxification. This allows for its safe excretion. Methylation also allows the body to detoxify toxins within the cells, repair damaged DNA, and create new cells.

Methionine, which already contains a methyl group, is an amino acid that occurs naturally in all protein foods, especially meats and dairy. Using magnesium, methionine becomes SAME, which, using ATP (adenosine triphosphate) travels throughout the body delivering a methyl group to any number of reactions. After SAME delivers the methyl group, it becomes homeocysteine. As an aside, ATP, produced by mitochondria within the cells, is stored energy which can be released as fuel for metabolic processes. Vitamins B6, B12, and folic acid are necessary to reduce homocysteine and keep the methylation process occurring.

Homeocysteine is then ready to accept another methyl group which transforms it back into methionine. However, if there are not enough methyl groups to transform the homeocysteine, then levels build in the body. Elevated homeocysteine levels are associated with heart disease,

poor circulation, and other degenerative disorders.

Pathways of Conversion

There are several pathways for the conversion of homocysteine to methionine. One pathway is folate plus B12. A different pathway is supplied by the choline-based TMG (trimethylglycine aka glycine betaine) and DMG (dimethylglycine) which act similar to B12. Either of these pathways can give a methyl group to homocysteine for the conversion to methionine. Some people may make better use of one pathway than another.

TMG converts to S-AdoMet (s-adenosyl methionine), which then converts the amino acid tyrosine to dopamine, noradrenalin and adrenalin. These brain chemicals are important for balanced mood and blood pressure, motivation, concentration, alertness and stress management. S-AdoMet also converts tryptophan amino acid to serotonin and melatonin brain chemicals, which are important for balanced mood and sleep. S-AdoMet helps support healthy joints, and muscle and liver function.

Another pathway for converting homocysteine is with B6 and magnesium. This pathway converts homocysteine to cysteine. Other conversions happen in this pathway including making glutathione and taurine. One step is adding molybdenum and continuing on to convert toxic sulfite molecules to really helpful sulfate molecules.

The methylation process is inhibited by oxidative stress when converting homocysteine to important antioxidants such as glutathione and the sulphur containing amino acids such as taurine and sulphate which are also key in supporting phase II detoxification in the liver.

Other supplements which support the methylation cycle are calcium, zinc, selenium, methionine and folic acid.

Factors Affecting Methylation

According to research by Carl Pfeiffer, MD, PhD, 45% of the population are under-methylators and 15% are over-methylators, (which together totals 60%) and 40% of people are neither. The formation of methyl groups initiates serotonin, and thus melatonin, production. Therefore, if you are a under-methylator, you can increase your methylation and have more appropriate levels of serotonin and melatonin. The dissolution of methyl groups in an over-methylator can decrease methylation which can decrease aggression or hyperactivity.

The process of methylation is influenced by:

Genetic factors

Psychological/emotional/physical stress

Smoking, alcoholism and other environmental toxins

Diet and nutrition (including supplements), especially B-vitamin and methionine intake

Elevated levels of homocysteine suggests a blockage in methylation. Homocysteine has been investigated as a separate risk factor for coronary heart disease. It has been postulated as a

putative factor in endothelial dysfunction and arteriosclerosis.

Undermethylation

According to research by Carl Pfeiffer, undermethylation or high histamine is the dominant chemical imbalance in about 20% of people with psychosis. However, only about 20% of those diagnosed with undermethylation will respond to nutritional therapies designed to remedy the imbalance. Most undermethylated persons in the general population tend to be high-achievers in good mental health. Laboratory indications include whole-blood histamine above 70 mg/ml and folate overload, creating a low methyl to folate ratio. This can result in lower levels of dopamine, norepinephrine, and serotonin. These types can benefit from supplemental methionine, SAMe, and inositol (methyl donor).

The following issues are associated with undermethylation: depression, compulsions (like OCD), addictions (gambling/shopping/sex/alcohol, etc.), eating disorders (anorexia/bulimia), and phobias. According to Pfeiffer, these folks react badly to folate, even dietary folate in fresh vegetables could worsen their depression. They responded well to methionine and calcium supplements.

The following is a list of characteristics and factors associated with undermethylation. The presence of 30-50% of the factors may be sufficient for diagnosis.

- delusions (thought disorder)
- self-motivated during school years
- very high libido
- higher metabolic rate
- high fluidity (tears, saliva, etc.)
- high accomplishment before onset of serious symptoms
- adverse reaction to B-complex vitamins
- sparse chest/leg/arm hair
- suicidal tendencies
- addictiveness
- phobias
- infrequent and terse speech
- peptic ulcers
- denial of illness
- non-compliance with therapies
- belief that CIA or FBI is after them
- attempt to hide the illness
- 5-10% incidence of hearing voices
- Tourette's Syndrome symptoms
- rumination about past events
- obsessive/compulsive tendencies
- history of perfectionism
- low-normal serum copper
- seasonal inhalant allergies

low tolerance for pain
catatonic behavior during illness onset
very strong willed
slenderness
history of competitiveness in sports
large nose and ears
ritualistic behaviors
calm demeanor, but high inner tension
frequent headaches
family history of high accomplishment
blankminded appearance
poor concentration endurance
social isolation
belief that a friend or relative is an alien
gravitation toward vegetarian diets
high preponderance of male relatives
dietary inflexibility
blood histamine above 70 ng/ml
absolute basophils above 50>M
diagnosis of delusional disorder
good response to antihistamines
good response to SSRI's
diagnosis of schizoaffective disorder
adverse reaction to benzodiazepines
prior diagnosis of OCD or ODD

Overmethylation

Overmethylation or low histamine is the dominant chemical imbalance for about 45% of persons diagnosed with schizophrenia. This imbalance is associated with extreme deficiencies of folate and Vitamin B-12, and usually coincides with elevated serum copper. Laboratory indications include whole-blood levels below 40 mg/ml, and depressed absolute basophils.

These folks tend to suffer from paranoid schizophrenia, bipolar disorder, psychosis, anxiety/panic attacks, hallucinations, hyperactivity, and depression. Pfeiffer found that these people often benefitted from large doses of folic acid, B12, B3, B6, zinc, and manganese.

The following is a list of characteristics and factors associated with overmethylation. The presence of 30-50% of the factors may be sufficient for diagnosis.

auditory hallucinations
high anxiety or panic tendency
hyperactivity
low libido
religiosity
tendency to be overweight

nervous legs, pacing
dry eyes and mouth
belief that everyone thinks ill of them
low motivation during school years
high pain threshold
paranoia
depression
sleep disorder
history of eczema
absence of seasonal allergies
frenetic activity during illness onset
tinnitus
upper body/neck/head pain
hirsutism
food/chemical sensitivities
artistic or musical ability
copper overload
adverse reaction to estrogen therapy
adverse reaction to anti-histamines
adverse reaction to SAME
improvement after lithium
self mutilation
obsessions without compulsions
post-partum onset of psychosis
adverse reaction to SSRI's
adverse reaction to methionine
improvement after benzodiazepines
diagnosis of paranoid schizophrenia
low blood histamine
low absolute basophils

Pyroluria

Pyroluria could overlap with either under-or-over-methylation or exist on its own. It is associated with anxiety, depression, food sensitivities/celiac disease, social withdrawal, learning disabilities/ADHD, schizophrenia and autism. Very severe cases result in mental retardation and delayed growth and puberty. In some cases psychological symptoms could be alleviated within just a few days with supplemental B6 and zinc.

During the synthesis of hemoglobin in the body, kryptopyrroles are generated as waste products. Kryptopyrroles, however, don't serve any useful biological purpose and are normally excreted. If someone with pyroluria is low in either zinc, B6 or both, they won't secrete kryptopyrroles which then tend to build up in the blood, more so under stress. Heavy metal toxicity can also cause elevated kryptopyrroles.

Kryptopyrroles have a tendency to bind with zinc and vitamin B6, when then reduces their availability to the rest of the body. Zinc and B6, of course, are nutrients critical for the functioning of your entire body and mind—including your digestion, immune system, cognitive functioning and emotions. Over time, zinc and B6 deficiencies have serious effects on the function of the body. Often supplementation with manganese, vitamins C and E may be necessary.

Pyrolurics also have a greater than normal need for omega-6 fatty acids, particularly dietary arachidonic acid (AA), which is found in eggs, butter, red meat and liver) and the essential fatty acid GLA (gamma linolenic acid), found in black currant seed oil and evening primrose oil. Once determined, supplementation, along with stress management, can improve symptoms but should be continued over time. Omega 3s can worsen symptoms of pyrolurics since both omega 3 and 6 compete for certain receptors.

Additional considerations for the pyroluric include the need for improving digestion and hydrochloric acid status and the avoidance of phytate-containing foods such as grains, legumes and soy. If positive for pyroluria one must also avoid excess fish oil, copper, and red and yellow food dyes.

The characteristics and factors associated with pyroluria are:

- severe inner tension
- ongoing anxiety or anxiousness
- episodes of irritability or anger
- poor stress tolerance (with added stress of any kind making the symptoms worse)
- digestive issues and difficulty digesting protein
- frequent colds and infections
- joint pain or stiffness
- acne
- eczema or psoriasis
- mood swings and reactivity
- poor short term memory
- tendency towards being a loner
- little or no dream recall
- white spots on finger nails
- poor morning appetite with tendency to skip breakfast
- morning nausea
- pale skin which burns easily in sun with poor tanning
- sensitivity to bright light
- hypersensitive to loud noises
- reading difficulties (e.g. dyslexia)
- poor ability to cope with stress
- mood swings or temper outbursts
- easily upset by criticism
- histrionic (dramatic) tendency
- augmentative/enjoy argument

new situations or changes in routine (i.e., traveling) particularly stressful
 higher capability and alertness in the evening, compared to mornings
 poor short term memory
 abnormal body fat distribution
 belong to an all-girl family with look-alike sisters
 dry skin
 reaching puberty later than normal
 difficulty digesting, a dislike of protein or a history of vegetarianism
 tendency toward being a loner and/or avoiding larger groups of people
 stretch marks on skin
 poor sense of smell or taste
 feel very uncomfortable with strangers
 frequently experience fatigue
 tendency to overreact to tranquilizers, barbiturates, alcohol or other drugs (in other words, a little produces a powerful response)
 tendency toward anemia
 family history of mental illness or alcoholism in family
 sweet smell (fruity odor) to breath or sweat when ill or stressed
 prone to acne, eczema or psoriasis
 tendency toward feeling anxious, fearful and carrying lifelong inner tension
 difficulty recalling past events or people
 bouts of depression or nervous exhaustion
 prone to frequent colds or infections

Summary Table

	High Histamine (under- methylated)	Low Histamine (over- methylated)	Pyroluria
Common nutritional imbalances	Depressed calcium, methionine, B6 and excess folic acid	Depressed folate, B3, B12 and excess copper and methionine	Depressed zinc, B6, manganese and arachidonic acid (an omega-6 fat)
Common neurotransmitter imbalances	High histamine and low serotonin, dopamine and norepinephrine	Low histamine and elevated serotonin, dopamine and norepinephrine	Low serotonin
Laboratory tests*	Whole blood histamine over 70 ng/ml, elevated	Whole blood histamine under 40 ng/ml,	Elevated urine kryptopyrroles

	direct absolute basophils and low ceruloplasmin	depressed direct absolute basophils and high serum copper	
Cause of imbalances	Genetic tendency for under-methylation	Genetic tendency for over-methylation	Abnormal hemoglobin synthesis
Beneficial supplements	Calcium, methionine, magnesium, zinc, TMG, omega-3 oils, B6, SAmE, inositol, A, C and E	B3, B12, DMAE, folate, choline, manganese, zinc, omega-3 oils, C and E	B-6, zinc, and Primrose Oil
Potentially Harmful supplements	Folate, choline, DMAE, copper and histidine	Methionine, SAmE, inositol, tryptophan, phenylalanine, St. John's wort, tyrosine, copper, TMG and DMG.	Histidine, copper and omega-3 fatty acids.

ADD/ADHD

Avoid boredom and correct authority issues.

Work on balancing any chemical imbalances using Pfeiffer's method.

Autism

Possible lack of mercury detox ability due to depletion of metallothionein, a protein needed by the body and brain to detox metals. It is synthesized in the liver and kidneys and its production is dependent on the availability of the dietary minerals, as zinc, copper and selenium, and the amino acids histidine and cysteine.

Pfeiffer believed that autism is caused by an inability to cope with environmental oxidative stress, involving weak functioning of the neuroprotective metallothionein/glutathione system. The causes for this can include genetics, infection or trauma during pregnancy, and exposure to environmental toxins. This condition results in inability to regulate copper and zinc, hypersensitivity to metal toxins, extremely poor immune function & hypersensitivity to vaccines, yeast overgrowth, inability to break down casein & gluten, and worst of all..... incomplete

maturation of brain cells and synaptic connections.... especially in hippocampus, amygdala, and pineal gland.

Under or over methylation and malabsorption also influence the incidence of autism.

Depression

The major causes of depression include nutritional imbalances, metabolic disorders, abuse, chronic stress, chronic pain, life circumstance such as the death of a loved one, moving, or personal problems, genetics, chronic or serious illness and substance abuse. Nutritional imbalances include zinc deficiency, copper overload, folate imbalances, and omega 3 and 6 imbalances. Other nutrients that may affect depression include methionine, folate, vitamins B 6 and 12, niacin, vitamins C, A and E, and the minerals selenium, chromium, manganese and iodine. Metabolic imbalances include methylation disorders, severe oxidative stress, toxic metal overload, adrenal deficiency and low thyroid.

Herbs Aids for Natural Mental Health

Nervines

Mugwort (*Artemissa vulgaris*)
California Poppy (*Eschscholtzia californica*)
St. Johns Wort (*Hypericum perforatum*)
Lemon Balm (*Melissa officinalis*)
Passion Flower (*Passiflora incarnata*)
Valerian Root (*Valeriana officinalis*)
Skullcap (*Scutellaria lateriflora*)
Wild lettuce (*Lactuca virosa*)
Hops (*Humulus lupulus*)
Sage (*Salvia officinalis*)
Mints (*Mentha sp.*) catnip, spearmint, peppermint
Blue vervain (*Verbena hastata or brasiliensis*)
Chamomile (*Anthemis nobilis*)
Wood betony (*Betonica officinalis*)
Peach (*Prunus persica*)
Lemon verbena (*Aloysia triphylla*)
Kudzu (*Pueraria montana*)
Mimosa (*Albizia julibrissin*)

Stimulating Herbs

Cayenne (*Capsicum frutescens*)
Lobelia (*Lobelia inflata*)
Rosemary (*Rosmarinus officinalis*)
Thyme (*Thymus vulgaris*)
Basil (*Ocimum basilicum*)

Bay (*Myrica cerifera*)
Peppermint (*Mentha piperita*)
Ginger (*Zingiber officinale*)
Horseradish (*Cochlearia armoracia*)
Cinnamon (*Cinnamomum cassia*)
Prickly Ash (*Xanthoxylum fraxineum*)
Black pepper (*Piper nigrum*)

Adaptogens

Ashwagandha (*Withania somnifera*)
American ginseng (*Panax quinquefolium*)
Maca (*Lepidium meyenii*)
Siberian ginseng (*Eleutherococcus*)
Black cohosh (*Cimicifuga racemosa*)
Fo-Ti (*Polygonum multiflorum*)
Gotu kola (*Hydrocotyle asiatica*)
Kelp (*Fucus vesiculosus*)

Blood Cleansers

Blessed thistle (*Cnicus benedictus*)
Milk thistle (*Silybum marianum*)
Red clover (*Trifolium pratense*)
Yellow dock (*Rumex crispus*)
Burdock (*Arctium lappa*)
Black walnut (*Juglans nigra*)

Non-Herbal Aids

Exercise
Counseling
Diet and nutrition
Bach Flower Remedies
Aromatherapy
Meditation/Prayer
Animal-assisted therapies
Music therapy
Dance therapy
Marital arts
Energy Medicine
Massage
Social interaction
Sweat lodge
Support groups
Talking Circle
Guided imagery
Biofeedback

Acupuncture

Nutritional Supplements

Zinc

Folate

Magnesium

Manganese

L-tyrosine

L-methionine

SAMe

GABA

Vitamins B6 and B12

Addictions

Addictions must be addressed on the physical, mental/emotional, and spiritual levels to effect recovery.

Alcoholism: Based on the research of Abram Hoffer, M.D., Ph. D. Supply the nutrients vitamin C to saturation, B-50 complex, L-glutamine, lecithin, chromium, magnesium, vitamin E and a good multivitamin. In addition, other research indicates additional supplementation with thiamine, milk thistle, GABA, kudzu, and mimosa. Well-balanced diet. No sugar or simple carbohydrates. Mucous membrane support.

Meth: Detox. Adrenal and thyroid support. Increase protein intake. Sleep. L-tyrosine (precursor to dopamine). Well-balanced diet. Digestive aid support. B-50. Vitamin C.

Nicotine: Detox. Liver and kidney support. Good nervine formula with lobelia. Sweating. Lymphatic support.

Opioids: Detox. Liver, kidney, and pancreas support. Nervine formula. Herbal support for chronic pain if needed.

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