

Depression Biotypes and Advanced Nutrient Therapy

William J. Walsh, Ph.D., F.A.C.N.
Walsh Research Institute



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Walsh Research Institute

- **Public Charity**
- **Behavior disorders, ADHD, anxiety, depression, schizophrenia, bipolar disorder, autism and Alzheimer's**
- **International physician training**
- **Experimental research**

Biochemical Individuality

- **Human share 99.9% of their DNA; it's the 0.1% that makes us different.**
- **Our unique DNA determines our eye color, gender, ethnicity, and many physical and mental characteristics.**
- **DNA differences also cause great variations in our innate biochemistry.**

Epigenetic Gene Regulation

- **DNA constantly nourishes the body's 30 trillion cells. Each gene has only one job – to make a specific protein.**
- **Liver, kidneys, skin and other tissues have identical DNA, but need different proteins.**
- **In-utero methylation at specific DNA sites shuts off unwanted proteins for each organ, tissue, and cell line (epigenetics).**

The Net Result

- **Most humans exhibit major variations in body chemistry and brain chemistry.**
- **Everyone is born with specific physical and mental abilities, personality, and vulnerability to certain medical disorders.**

Nutrient Individuality

- **Most humans have inborn nutrient deficiencies that require many times the RDA to achieve normalization.**
- **Innate nutrient overloads often cause more mischief than deficiencies.**
- **Broad vitamin-mineral supplements can cause more harm than good.**

Biochemical Individuality and Diet

- **Everybody needs high-quality, nutrient-dense foods.**
- **Most undermethylated persons thrive on a protein-based diet.**
- **Overmethylated anxiety & depression patients thrive on a vegetarian diet.**

Advanced Nutrient Therapy for Mental Disorders

Nutrient Therapy Approach

- **Extensive medical history,**
- **Lab testing of blood and urine,**
- **Diagnosis of nutrient imbalances,**
- **Design of individualized nutrient treatment.**

Massive Chemistry Database

- Laboratory testing of **30,000** mental health patients and controls.
- More than **3 million** lab assays for ADHD, BD, autism, depression, anxiety, bipolar, schizophrenia or Alzheimer's.
- **> 2 million** medical history factors.

Database Findings

**Striking blood/urine
chemistry differences
between mental illness populations
and the rest of society**

Walsh WJ (2012). *Nutrient Power*. Skyhorse Publishing, New York, NY.

Crayton JW, Walsh WJ (2007). *J Trace Elements Med Biol*.21:17-21.

Nutrient Imbalances & Mental Disorders

- **More than 300 important nutrients in human biochemistry.**
- **Some nutrients have powerful impacts on serotonin, dopamine, norepinephrine, GABA, and NMDA neurotransmission.**
- **Our nutrient therapies focus on normalizing blood and brain levels of these nutrients.**

The Good News

- **Fewer than a dozen nutrient imbalances dominate mental disorders,**
- **These key nutrients are essential for either NT synthesis or regulation,**
- **Initial lab testing and clinical treatment focus on these factors.**

High-Incidence Imbalances in Clinical Depression

B-6 Deficiency

Zinc Depletion

Copper Overload

Pyrrole Disorder

Toxic-Metal Overload

Methylation Disorder

Folate Deficiency or Overload

Frequently Asked Questions

- 1. How can vitamins, minerals, or amino acids significantly help a person with a serious mental illness?**
- 2. Don't you really need a powerful drug to get the job done?**

The Power of Nutrients

- 1. Neurotransmitter synthesis**
- 2. Epigenetic regulation of gene expression**
- 3. Influence NT reuptake processes**
- 4. Protection against oxidative stress**

B-6 and Neurotransmission

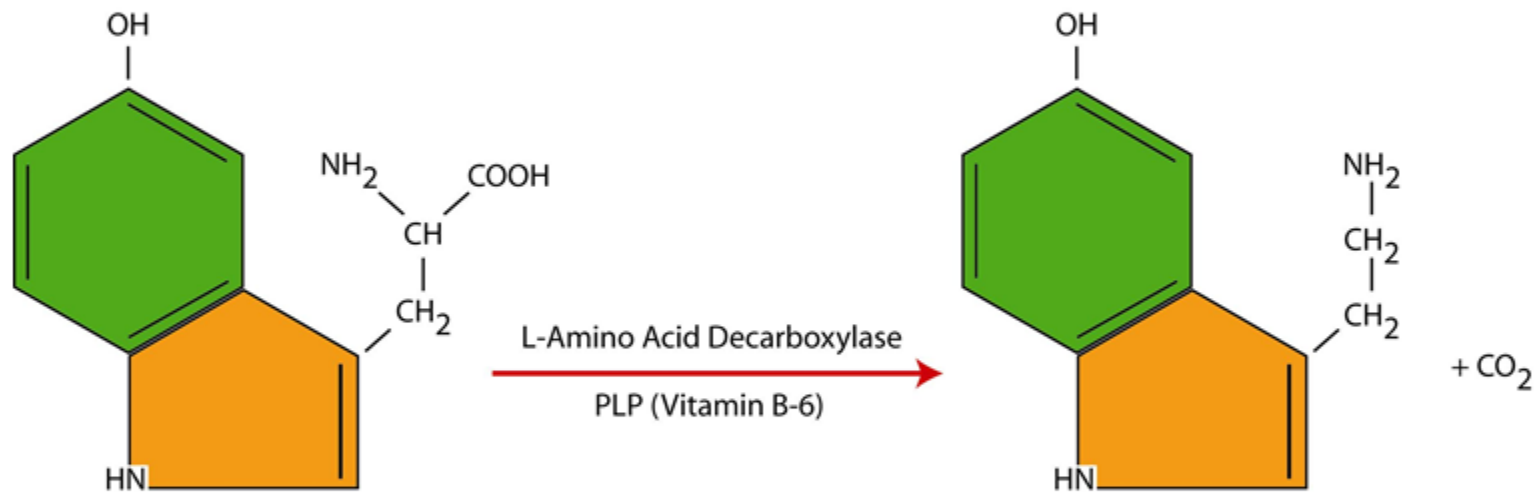
Co-Factor for Neurotransmitter Synthesis

Serotonin

Dopamine

GABA

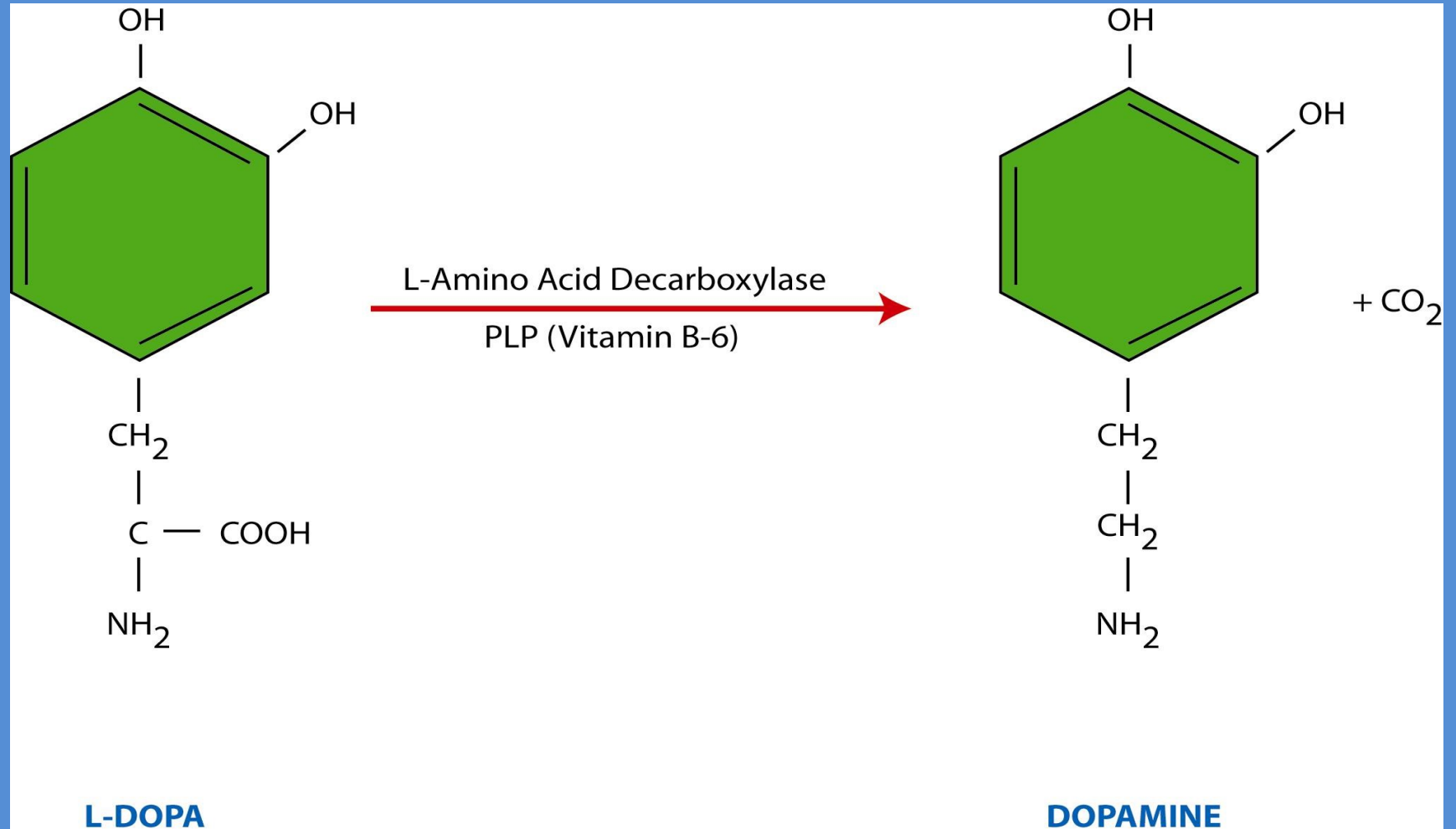
Serotonin Synthesis



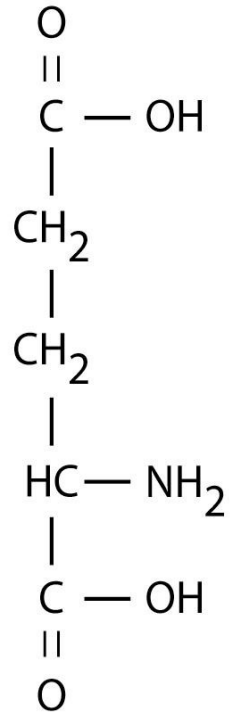
5-HYDROXYTRYPTOPHAN

SEROTONIN

Dopamine Synthesis



GABA Synthesis

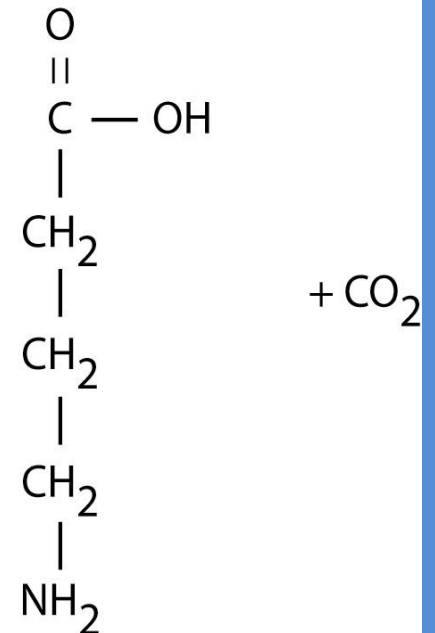


GLUTAMIC ACID

L-Glutamic Acid Decarboxylase



Pyridoxal Phosphate (B-6)



GABA

Metal Metabolism Disorders

- **Zinc Depletion**
- **Copper Overload**
- **Deficiencies of magnesium, calcium, manganese, selenium, iron, etc.**
- **Overload of lead, mercury, cadmium, and other toxic metals.**

Zinc Depletion in Mental Disorders

Median plasma Zn for BD, ADHD, depression, bipolar, SZ, and Alzheimer's, n=15,000

76 mcg/dL

Zn level for optimal brain function:

90-120 mcg/dL

NEARLY ALL DEPRESSION NEED ZINC

Ideal Plasma Zinc Level

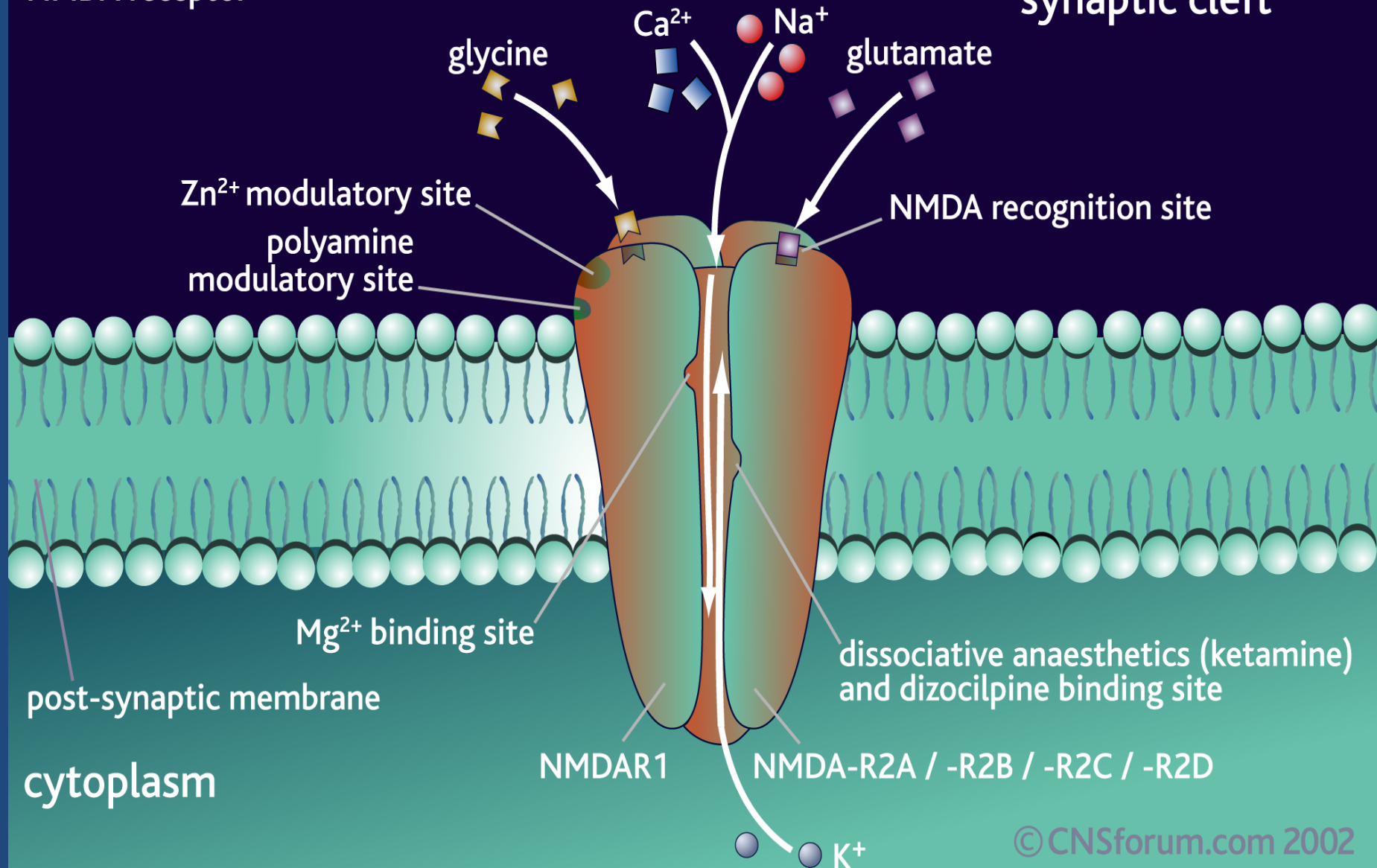
90 - 130 mcg/dL

Symptoms of Zinc Deficiency

- Irritability and anger
- Poor stress control
- Frequent infections
- Delayed puberty and growth
- Sunburn tendency
- Enjoyment of spicy foods
- White spots on fingernails
- Premature graying of hair.

NMDA receptor

synaptic cleft



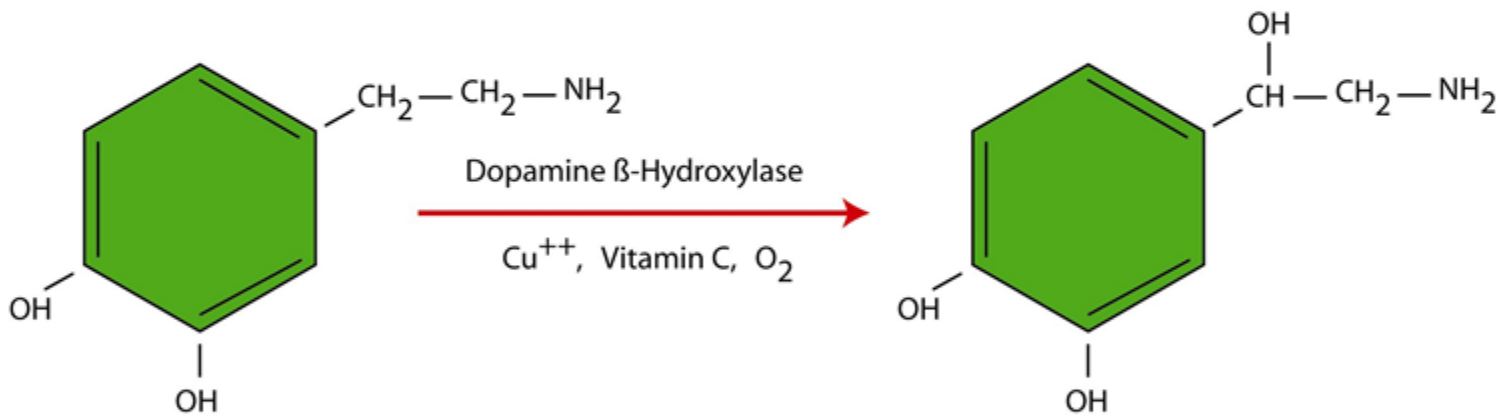
Incidence of Copper Overload

- **Clinical Depression: 35%**
- **Post-Partum Depression: 95%**
- **Hyperactivity: 80%**
- **Anxiety: 40%**
- **Behavior Disorders: 55%**
- **Schizophrenia: 50%**
- **General Population: 22%**

Symptoms of Copper Overload

- **Hyperactivity**
- **Estrogen intolerance**
- **Sensitivity to rough fabrics, tags**
- **Sleep problems**
- **Emotional meltdowns**
- **Tinnitus**
- **Anxiety**
- **Post-Natal depression**

Norepinephrine Synthesis



DOPAMINE

NOREPINEPHRINE

Pyrrole Disorder

- **Deficiency of B-6, Zinc, Biotin**
- **Reduced Serotonin, Dopamine, GABA**
- **Depletion of GSH, MT, Cysteine, Se, SOD, Catalase, etc.**

B-6 and zinc may eliminate symptoms and need for psychiatric medication.

Symptoms of Pyrrole Disorder

- **Poor stress control, frequent anger**
- **Tendency to skip breakfast**
- **Little or no dream recall**
- **Poor short-term memory**
- **Reading disorder**
- **Sensitivity to light and noise**
- **Abnormal menstrual periods**
- **Dark or mauve-colored urine**

Oxidative Stress

What Can Go Wrong?

- **Some persons are born with low levels of natural antioxidants GSH, MT, etc.**
- **Illness, injury, or emotional trauma can produce oxidative stress.**
- **Exposure to toxic metals, pesticides, and industrial pollutants increases oxidative stress.**

Oxidative Stress

- **Excessive oxidative stress observed in 95+ percent of mental patients.**
- **Most behavior, ADHD, anxiety, depression, and psychosis patients need strong antioxidant support.**

The Three Musketeers of Antioxidant Protection in the Brain

Glutathione: First line of defense.

Metallothionein: Nature's back-up system.

Selenium: Speeds up the process.

Recent Advances in Understanding of Brain Disorders

METHYLATION PROCESSES

EPIGENETICS

New Capability in Nutrient Therapy

- Regulation of enzyme gene expression
- Control of serotonin and dopamine reuptake
- Improved antioxidant protection for the brain

***“I did then what I knew how to do.
Now that I know better, I do better.”***

Maya Angelou

Methylation Disorders – Two Types

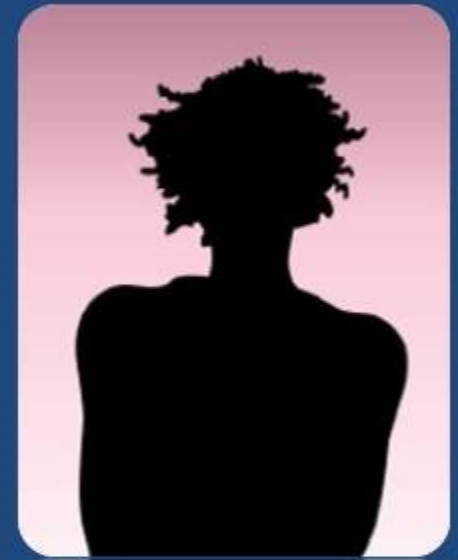
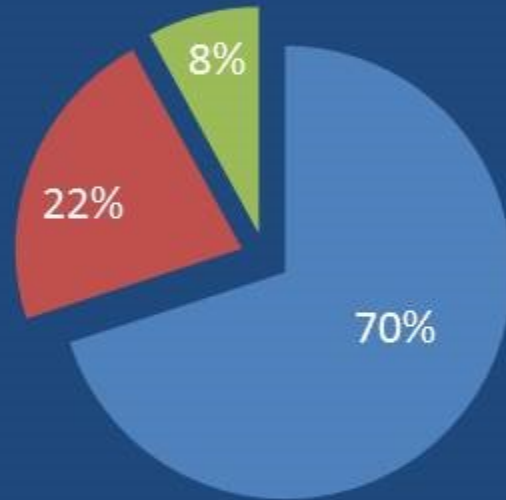
UNDERmethylation



OVERmethylation



Incidence of Methylation Disorders in the General Population



Normal Methylation = 70%

Under Methylation = 22%

Over Methylation = 8%

Incidence of UNDERmethylation

Autism-Spectrum	98%
Antisocial Personality Disorder	95%
Schizoaffective Disorder	90%
Oppositional-Defiance	85%
Anorexia	82%
Depression	38%

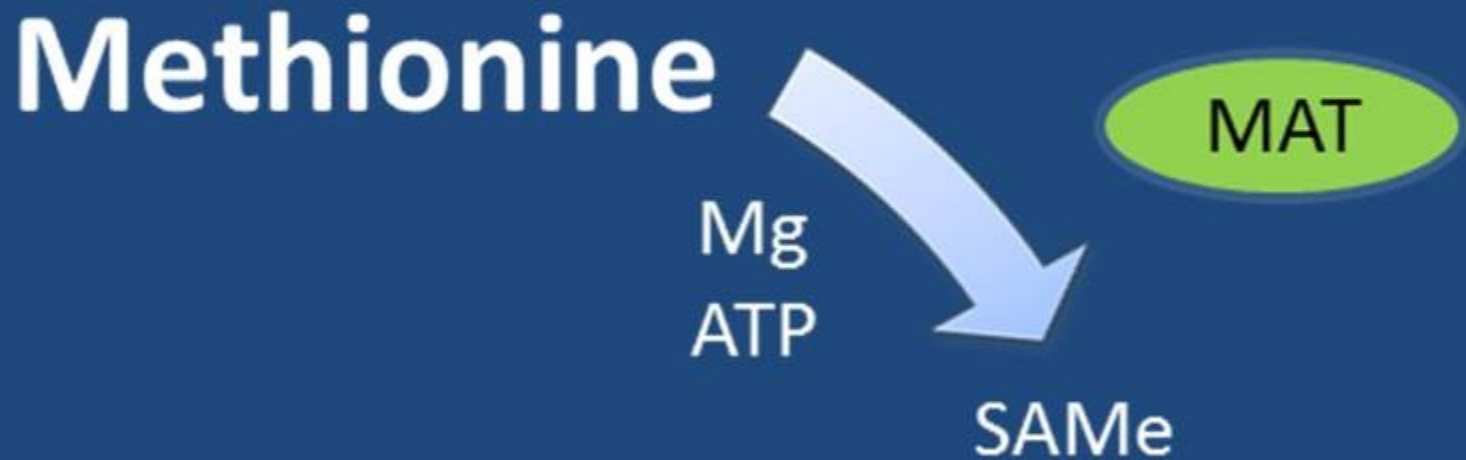
Incidence of OVERmethylation

Panic/Anxiety Attacks	64%
Paranoid Schizophrenia	52%
ADHD	28%
Behavior Disorders	23%
Depression	18%

Primary Causes of UNDERmethylation

1. Enzyme Mutations (SNPs) in Methylation Cycle
MTHFR, MS, BHMT, MAT, SAHH, etc...
2. Histamine Overload
3. Protein Deficiency or Malabsorption

SAMe Synthesis



Methyl Donation

SAMe

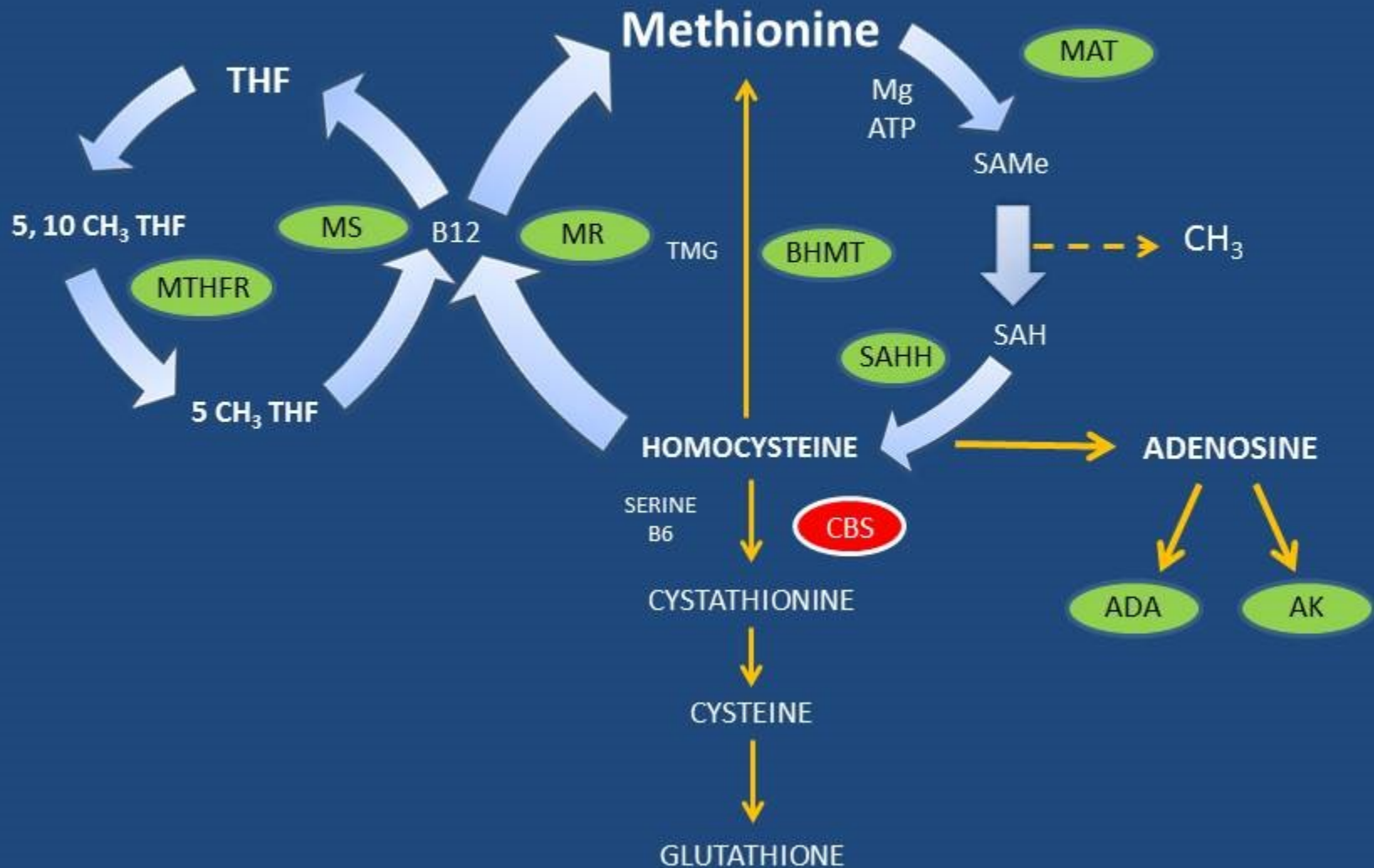


SAH



CH₃

Methylation Cycle Enzymes



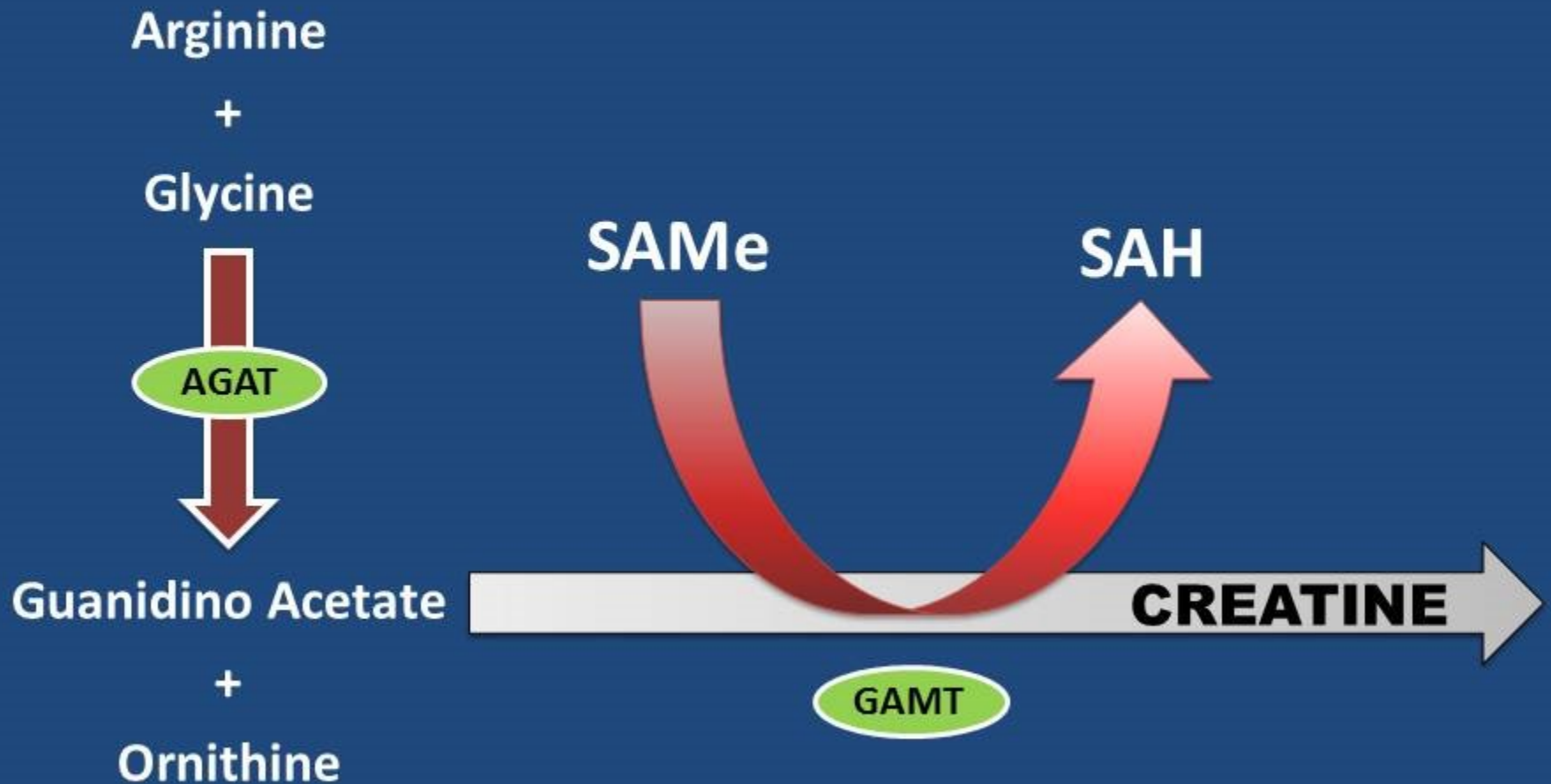
Primary Cause of Overmethylation

Impaired SAMe Utilization

SAMe Utilization

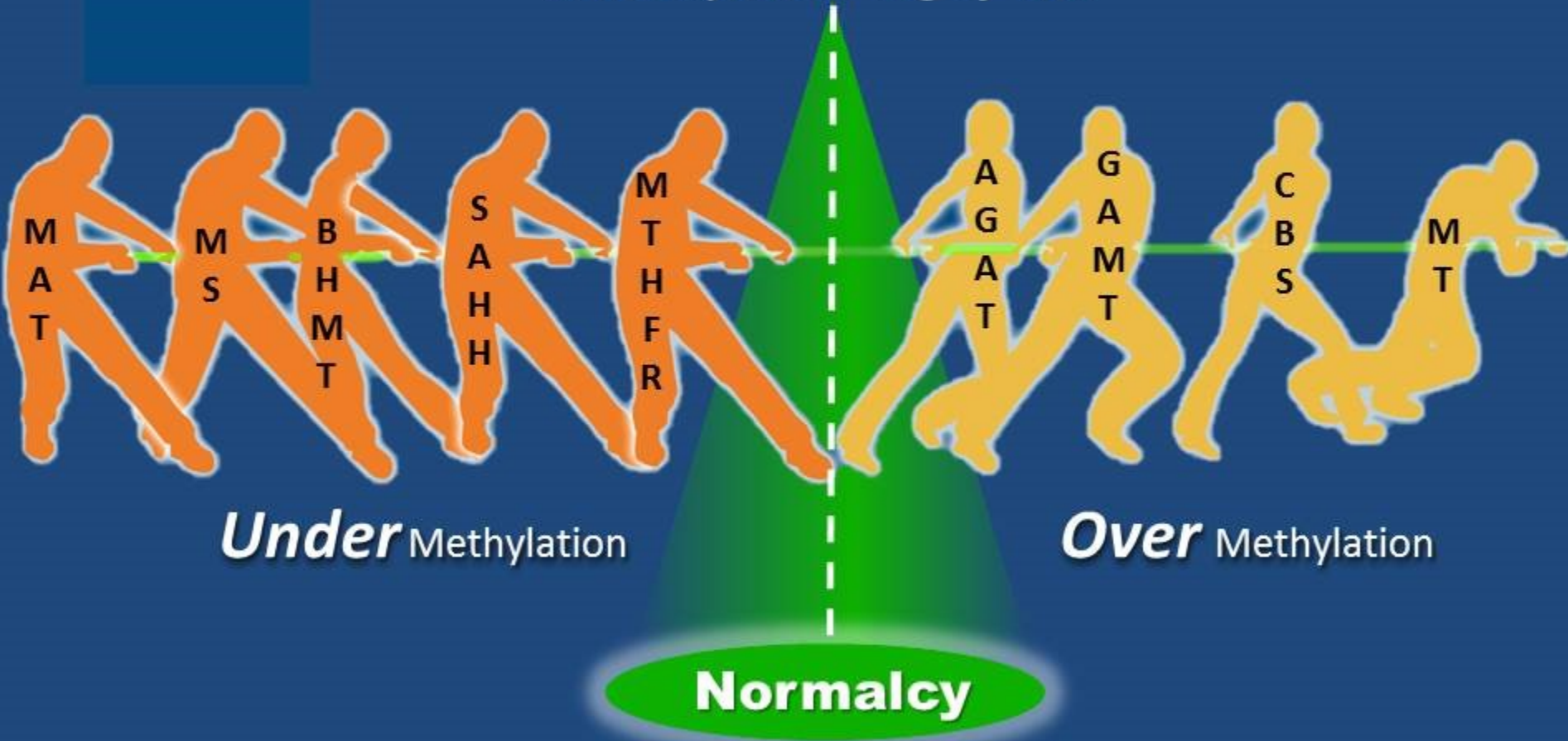


Creatine Synthesis



Enzyme Mutations and Methylation

A Methylation Tug of War



Methylation Diagnosis

- **Whole-blood histamine**
- **SAM/SAH methylation panel**
- **Genetic testing for SNPs**
- **Characteristic symptoms and traits**

Undermethylation Symptoms/Traits

- **Strong willed; oppositional to authority**
- **Seasonal inhalant allergies**
- **Competitive in sports or games,**
- **Calm demeanor but high inner tension**
- **High fluidity (tears, saliva, etc.)**
- **OCD tendencies; controlling behavior**
- **High libido**
- **Good response to SSRIs**

Overmethylation Symptoms/Traits

- **High anxiety, panic tendency**
- **Hyperactivity, nervous legs, pacing**
- **Sleep disorder**
- **Low libido**
- **Absence of seasonal allergies**
- **Food, chemical sensitivities**
- **Excellent socialization, empathy**
- **Non-competitive in sports or academics**

EPIGENETICS

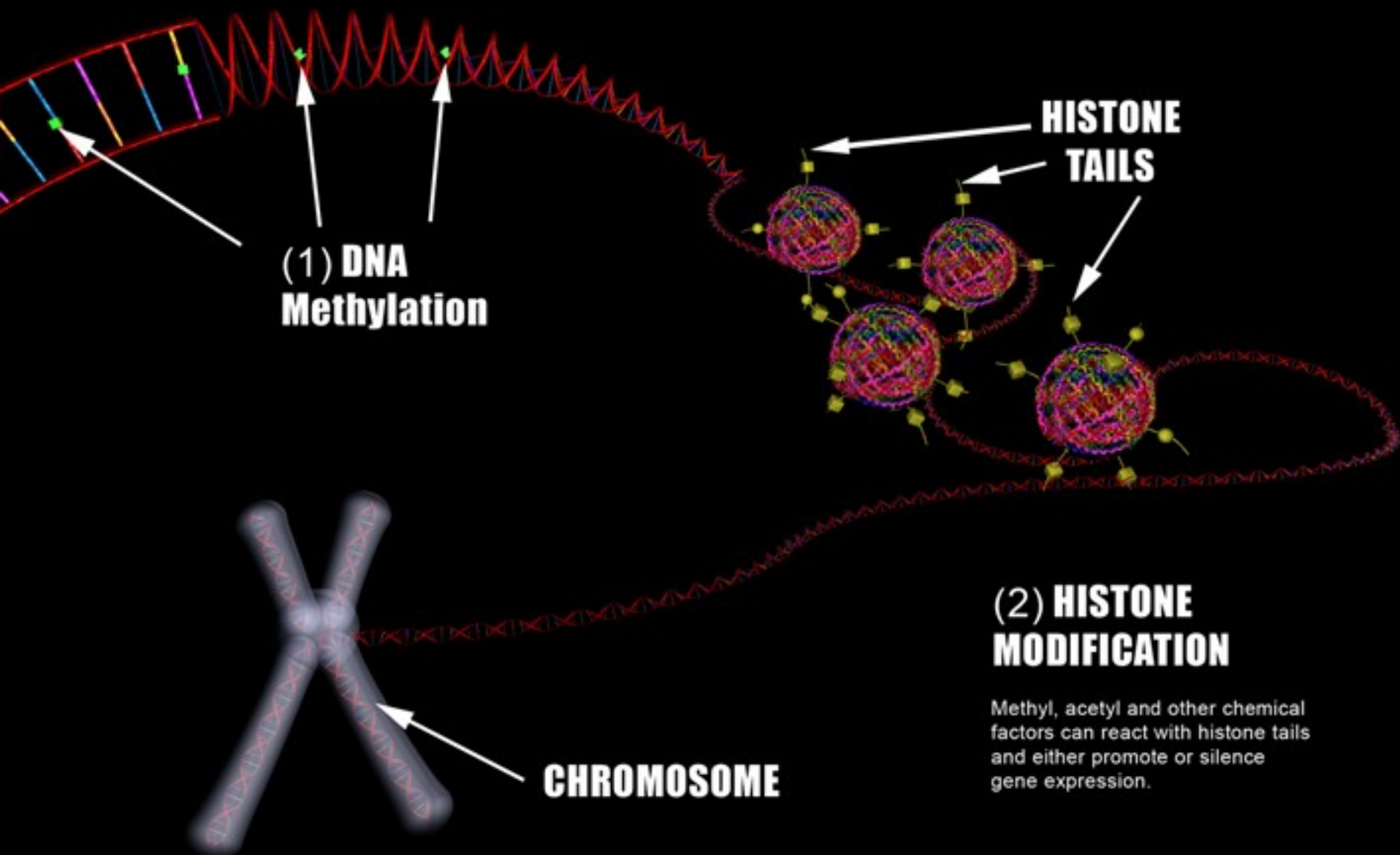
- **DNA constantly nourishes our body and brain by producing special proteins.**
- **Each of our 20,000 genes has only one job -- to make a specific protein.**
- **Epigenetics: In-utero DNA programming that determines which proteins are expressed in liver, kidney, brain and other tissues.**

Primary Epigenetic Processes

DNA Methylation

Histone Modification

The Two Main Components of the Epigenetic Code



**(1) DNA
Methylation**

**HISTONE
TAILS**

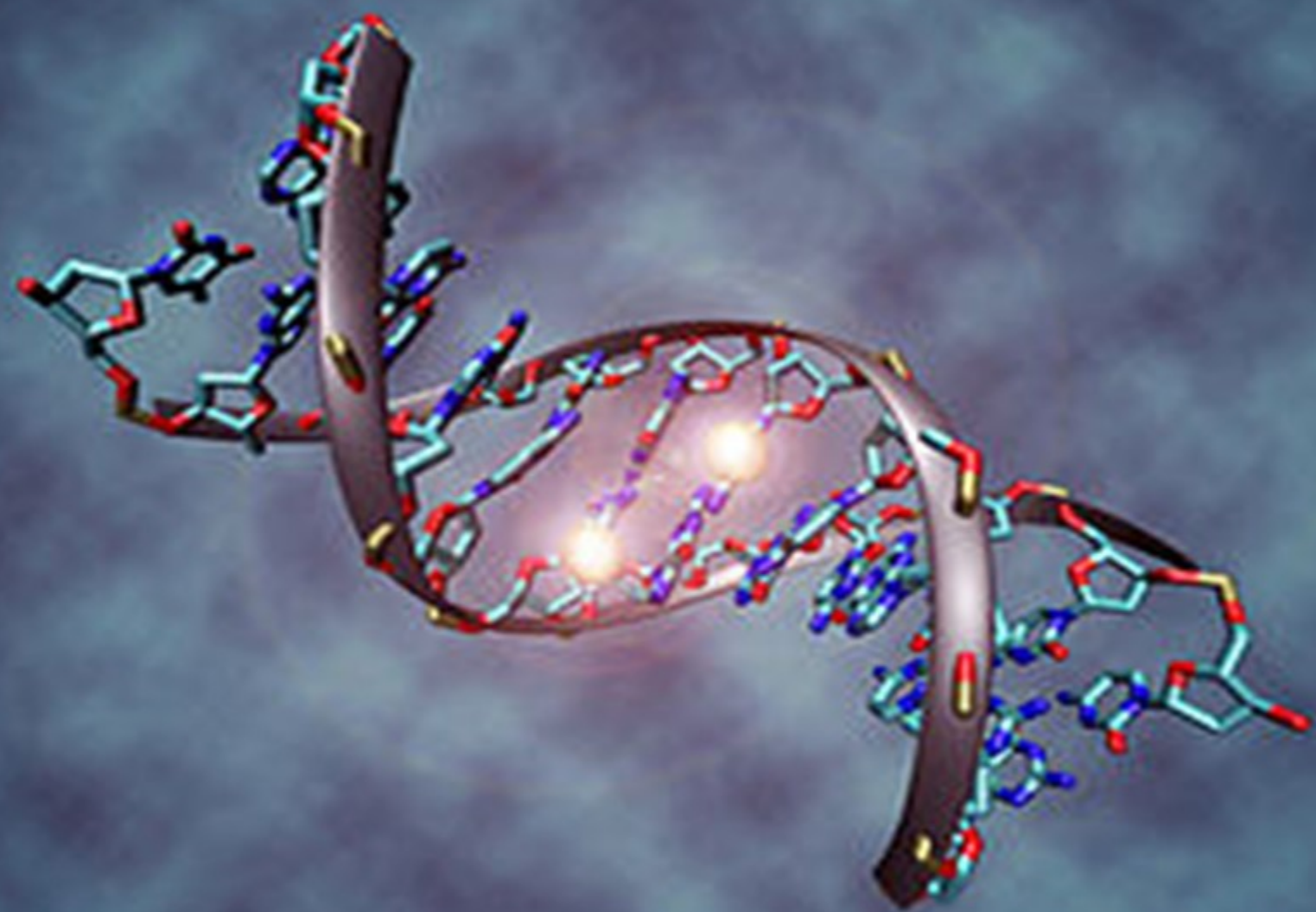
**(2) HISTONE
MODIFICATION**

Methyl, acetyl and other chemical factors can react with histone tails and either promote or silence gene expression.

CHROMOSOME

DNA Methylation

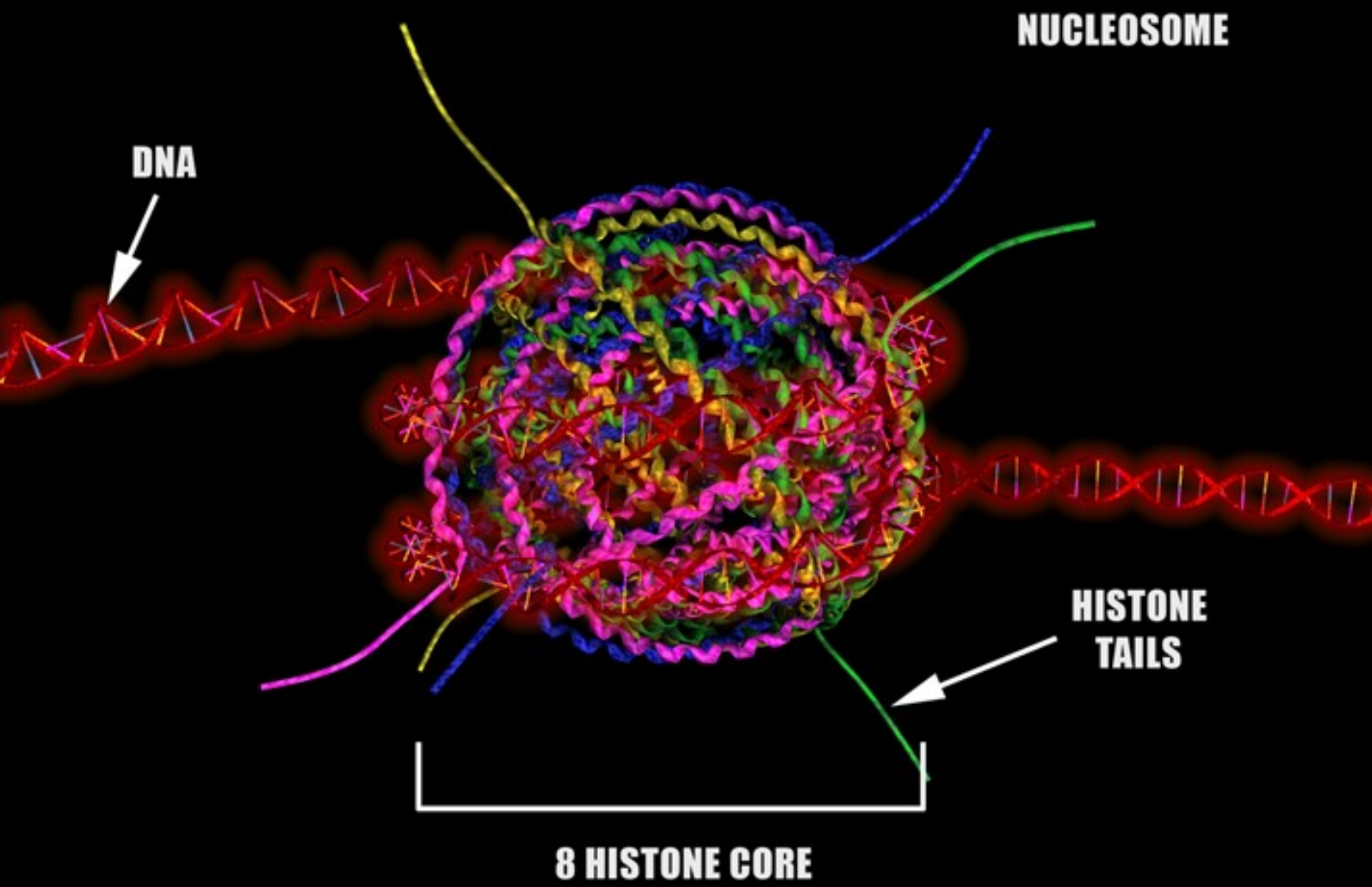
- **Established in the womb.**
- **Methyl “bookmarks” regulate gene expression.**
- **In-utero insults can alter methylation bookmarking and cause birth defects.**



DNA Methylation

Histones

- **Eight linear proteins twisted together like a ball of yarn; Structural support for DNA.**
- **Chemical reactions at histone “tails” promote or inhibit gene expression.**
- **Nutrient therapy can modify histones that control reuptake at serotonin, dopamine, and other receptors.**



Depression and NT Reuptake

- **1985 Research: Serotonin reuptake identified as the dominant factor in most cases of clinical depression.**
- **The amount of serotonin in the brain is relatively unimportant.**

Reuptake Dominated by Transport Proteins (SERT, DAT, NET)

- **Neuron membrane proteins that remove neurotransmitters from the synapse like a vacuum cleaner inhaling dust particles (reuptake).**
- **Nutrient therapy can alter expression of reuptake proteins that dominate serotonin, dopamine and norepinephrine activity.**

Methyl-Acetyl Competition

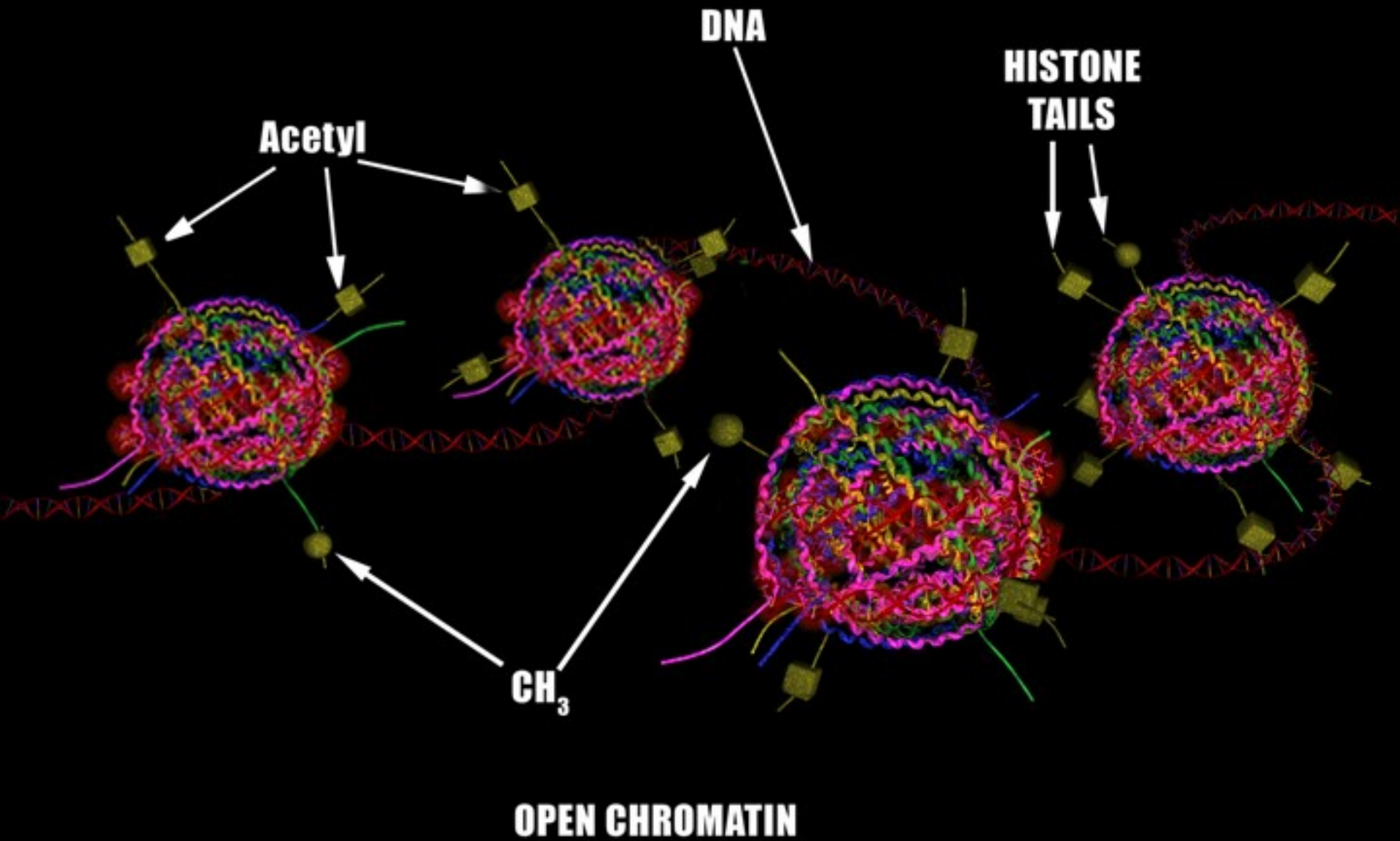
- **Acetylation at histone tails promotes gene expression,**
- **Methylation at histone tails usually inhibits gene expression,**
- **Nutrient therapy can alter production of SERT, DAT, and NE transport proteins that dominate neurotransmission.**

Gene Expression

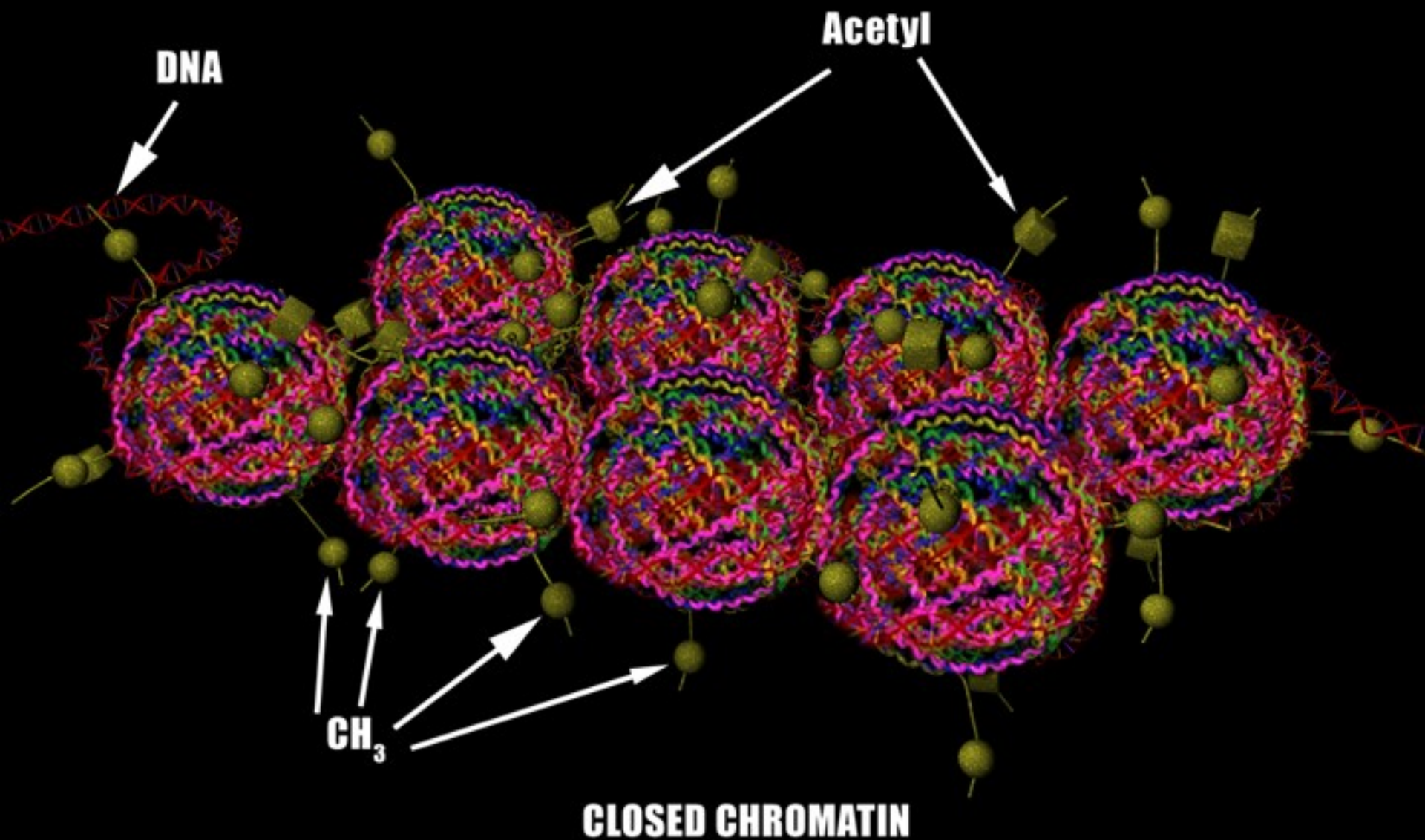
Requires Uncoiling of DNA

- RNA polymerase and a transcription factor must access DNA to make a protein.
- Attachment of DNA to histones results from electrostatic attraction – DNA is an acid and histones are weak bases (pH above 7.0).
- Acetylation decreases histone pH causing uncoiling of DNA; methylation increases histone pH, with the opposite effect.

LOW METHYLATION PROMOTES GENE EXPRESSION



HIGH METHYLATION INHIBITS GENE EXPRESSION



A Methylation Mystery for More Than 30 years.

- A. Folates are effective methylating agents.**
- B. Most undermethylated depression patients are intolerant to folic acid, folinic acid, and methylfolate.**
- C. Overmethylated depression patients thrive on folate supplements.**

WHY?

**Methylation Mystery
Solved In Year 2000
by the Science of**

EPIGENETICS

Epigenetics and Serotonin Reuptake

- **SAMe and methionine act as serotonin reuptake inhibitors.**
- **Methylfolate, folinic acid, and folic acid act as serotonin reuptake promoters.**
- **Folate supplements must be avoided for disorders dominated by low serotonin neurotransmission.**

Folates and Undermethylation

- **Folates and B-12 represent the “gold standard” undermethylation treatment,**
- **Folates enhance serotonin synthesis,**
- **Folates sharply reduce serotonin activity by an epigenetic mechanism.**

Undermethylated Depression - Impact of Folate Therapy -

- Methylation improves.
- Depression worsens

Methylation and Autism

- **Most ASD patients are undermethylated and thrive on folates,**
- **Methylfolate more effective than folic acid or folinic acid,**
- **Occasional methylfolate intolerance: ASD patients with unusually-low serotonin or dopamine activity.**

Insights From Epigenetics

- **Methionine and SAMe are serotonin reuptake inhibitors,**
- **Niacin & folates are dopamine reuptake promoters,**
- **Biotin represses expression of certain genes,**
- **Zinc increases metallothionein expression,**
- **Resveratrol suppresses histone acetylation,**
- **Curcumin can inhibit gene acetylation,**
- **Genistein enhances expression of certain cancer prevention genes.**

CLINICAL DEPRESSION

Large Depression Database

- Evaluation of 2,800 patients diagnosed with clinical depression,
- More than 230,000 blood/urine chemical assays,
- Approximately 320,000 medical history factors .

Database Findings

Striking blood and urine chemistry differences between our depression population and the rest of society.

Walsh WJ (2012). *Nutrient Power*. Skyhorse Publishing, New York, NY.

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Mainstream Psychiatry Misconception

Depression - regarded as a single entity with variations along a central theme.

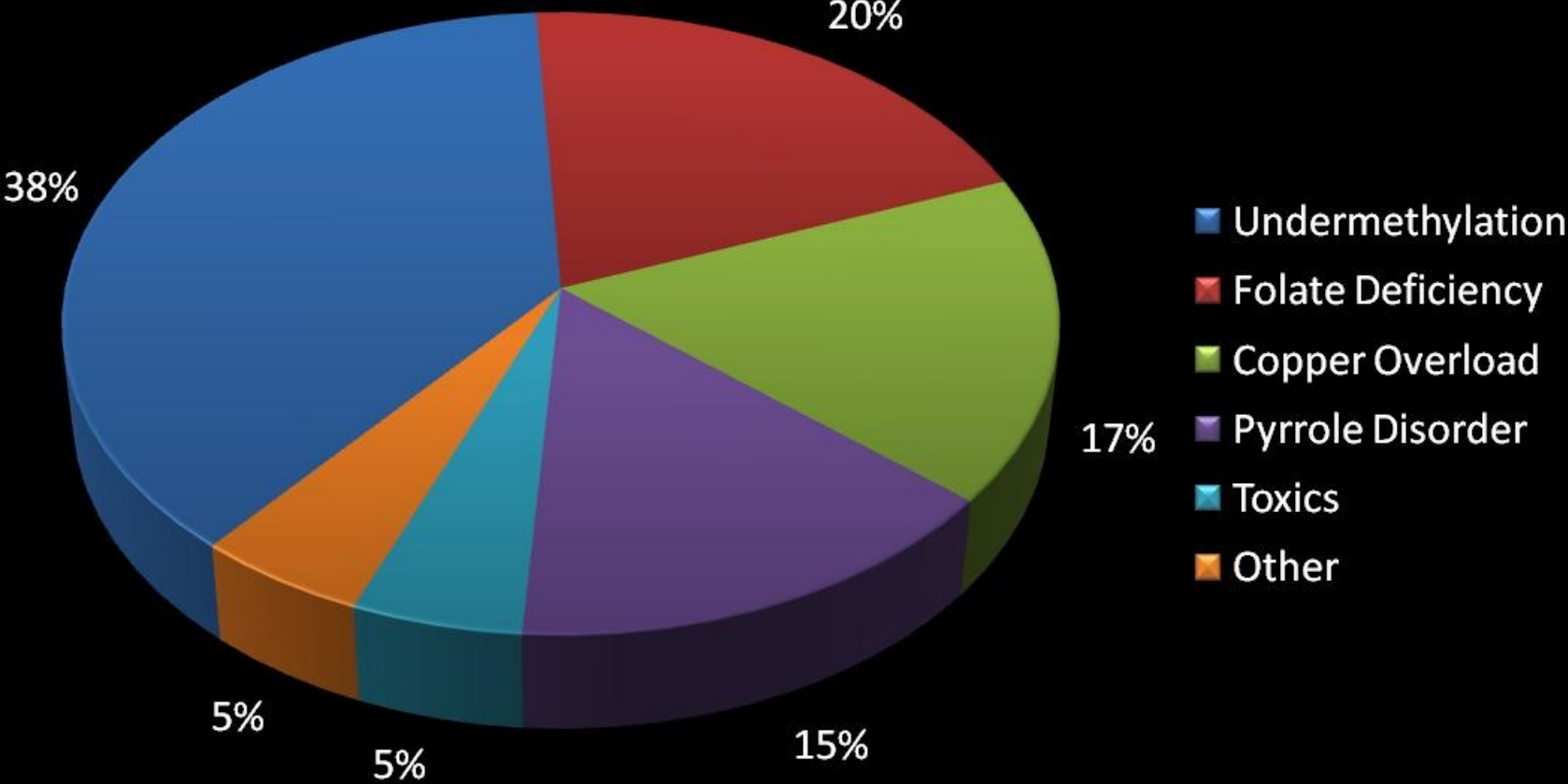
Central Belief - Low activity at serotonin receptors.

Treatment of choice - SSRI antidepressants to elevate serotonin activity at synapses.

Chemical Classification of Depression

- 1. Our 2,800 patient database identified five high-incidence depression biotypes.**
- 2. The biotypes represent very different disorders with distinctive symptoms & neurotransmission imbalances.**
- 3. Separate treatment approach needed for each biotype.**

Depression Biotypes



Biotype #1

Undermethylated Depression

- **38% of the depression population,**
- **Elevated histamine and low SAMe/SAH ratio in blood; High incidence of MTHFR SNPs,**
- **Excessive gene expression of SERT reuptake proteins (transporters),**
- **Low activity at serotonin receptors.**

Classic Symptoms

Undermethylated Depression

- Strong will
- OCD tendencies
- Calm exterior, but inner tension
- Competitive & perfectionistic
- Seasonal allergies (75%)
- High libido
- Seasonal affective disorder
- **SSRI medications usually effective**

Treatment Approach

Undermethylated Depression

- Enhance methylation and suppress acetylation of DNA and histones,
- SAMe and methionine to inhibit serotonin reuptake – reduced gene expression of SERT,
- Avoidance of folate supplements,
- Augmenting nutrients – zinc, serine, inositol, TMG, Cal/Mag, Vitamins A, B-6, C, D, E.

Biotype #2

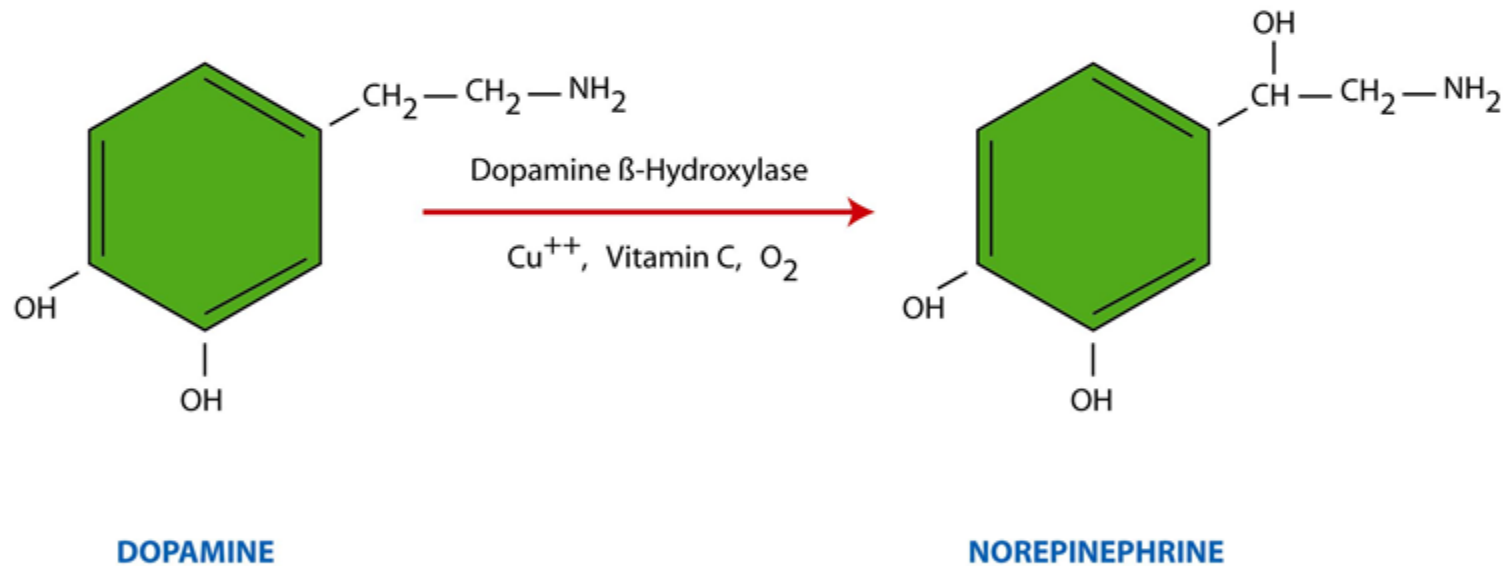
High-Copper Depression

- **Elevated norepinephrine, low dopamine**
- **More than 95% are female**
- **Inability to eliminate excess copper**
- **High anxiety, tendency for panic**
- **Onset during hormonal event**
- **High incidence of post-natal depression**
- **Estrogen intolerance**
- **Sensitive skin, sensitive to cheap metals**
- **SSRI antidepressants ineffective**

Postpartum Depression

- **Serum Cu more than doubles during gestation to promote angiogenesis for fetus.**
- **Cu levels > 220 mcg/dL at term (from 100).**
- **Some women unable to eliminate excess Cu.**
- **Depression/anxiety can persist for years.**

Norepinephrine Synthesis



Treatment Approach High-Copper Depression

- **Zn therapy to stimulate MT expression and remove excess Cu,**
- **Gradual increase in dosage to minimize side effects,**
- **Antioxidants and nutrients needed for other imbalances that may be present.**

Biotype #3

Pyrrole Depression

- **Low GABA, NMDA, 5-HT activity**
- **Severe mood swings**
- **Explosive anger**
- **Extreme anxiety, fears**
- **Poor short-term memory**
- **Little or no dream recall**
- **Sensitivity to light, noise**
- **Very poor morning appetite**
- **Fair response to SSRIs**

Pyrrole Depression and Neurotransmission

- **B-6 deficiency = Low 5-HT, DA, GABA synthesis**
- **Zn deficiency = Impaired NMDA, GABA function**

Treatment Approach Pyrrole Depression

- **Emphasis: Normalize B-6 and zinc,**
- **Zinc: Goal = 90-130 mcg/dL (plasma)**
- **Antioxidants to enhance NMDA function,**
- **Augmenting nutrients – Biotin, Primrose Oil.**

Biotype #4

Toxic Metal Depression

- Unrelenting depression
- Absence of emotional triggers
- Abdominal distress
- Cognitive deficits in children
- Metallic taste in mouth, bad breath
- Irritability, anger
- High oxidative stress
- **SSRI antidepressants ineffective**

Treatment of Toxic-Metal Overload

- **Avoid toxic-metal exposure**
- **Zinc, Manganese**
- **Glutathione**
- **Selenium, NAC**
- **MT-Promotion Nutrients**
- **Calcium (lead poisoning)**
- **Vitamins C and E**
- **Chelation for severe poisoning**

Biotype #5

Low-Folate Depression

- **High dopamine, norepinephrine activity**
- **Anxiety, sleep problems**
- **Low libido**
- **Non-competitive in sports or games**
- **Absence of inhalant allergies**
- **Food/chemical sensitivities**
- **Dry eyes and mouth**
- **Adverse reaction to SSRI medications**

Low-Folate Depression Nutrient Therapy Approach

- Support histone acetylation with folates and B-3 (powerful deacetylase inhibitors).
- Augmenting nutrients Zn, DMAE, Cr, Vitamins B-6, B-12, C, D, E, antioxidants.
- **Benzodiazapines usually effective (but addictive).**

Individualized Nutrient Therapy

- **Medical history and review of symptoms**
- **Special blood/urine lab tests**
- **Diagnosis of chemical imbalances**
- **Prescribed nutrient program to normalize brain chemistry and NT activity.**

The Bottom Line

80% of depression patients report improvement and ability to reduce or eliminate medication.

References

- Nutrient Power (Revised 2014). W.J. Walsh. Skyhorse Publishing, New York, NY.
- “Micronutrient Therapy for Violent and Aggressive Male Youth: An Open-Label Trial”, Hambly, Walsh, Haywood, et. al. *J Child and Adolesc Psychopharmacol.* (May 28, 2017).
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To Learn More

Over his impressive career, Dr. Walsh has worked with 30,000 patients with conditions ranging from autism to schizophrenia to Alzheimer's. His book is an essential tool for anyone who would prefer to heal the brain with nutrients rather than drugs.

—Teri Arranga, editor-in-chief, *Autism Science Digest*

NUTRIENT POWER

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AND HEAL YOUR BRAIN



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