EVALUATION & TREATMENT OF OVER- AND UNDER-METHYLATION IN THE PSYCHIATRIC POPULATION

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Webinar Topics

1. Methylation

2. Epigenetics

3. Treatment of psychiatric patients who exhibit a methylation disorder.

Walsh Research Institute Naperville, Illinois

- 501c3 Public Charity
- Expertise in behavior disorders, ADHD, autism, depression, schizophrenia, bipolar disorder, and Alzheimer's
- International Physician-Training Program
- Research

Massive Chemistry Database

- Laboratory testing of 30,000 mental health patients and controls.
- More than 3 million chemical test results for patients diagnosed with schizophrenia, depression, ADHD, depression, autism, etc.
- More than 2 million medical history factors for these populations.

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.

High-Incidence Imbalances in Mental Disorders

Methylation Disorder

Zinc Deficiency

Copper Overload

Folate Deficiency or Overload

Pyrrole Disorder

Toxic-Metal Overload

EPA, DHA, and/or AA Deficiency

These factors have a powerful impact on synthesis of neurotransmitters and regulation of NT activity.

Methylation and Brain Disorders

- Methylation status has been determined for 30,000 patients over a 30 year period,
- Most persons diagnosed with mental disorders exhibit a serious methylation imbalance,
- Accurate diagnosis of methylation status is essential to effective treatment.

Recent Advances in Understanding of Brain Disorders

Methylation Processes

Epigenetics

New Capability in Nutrient Therapy

- Regulation of enzyme gene expression,
- Control of serotonin & dopamine reuptake,
- Improved antioxidant protection in the brain,
- Promising treatments for addiction disorders.

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

Maya Angelou

Methylation and Mental Health

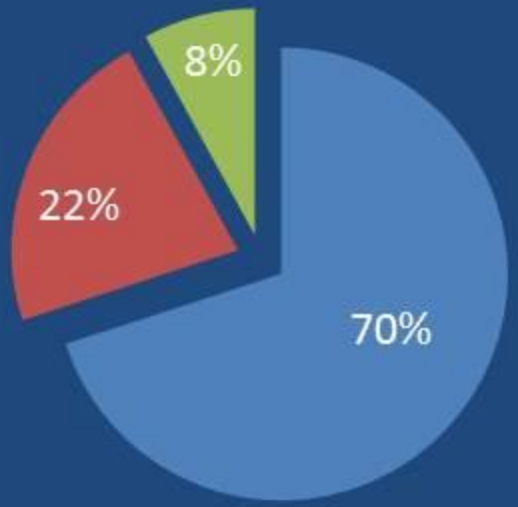
- Methylation is a dominant factor in epigenetic processes that regulate NT activity at serotonin and dopamine receptors,
- The methyl/folate ratio has a powerful impact on gene expression of reuptake transport proteins,
- More than 60% of anxiety, depression and psychosis patients exhibit a serious methylation imbalance.

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%

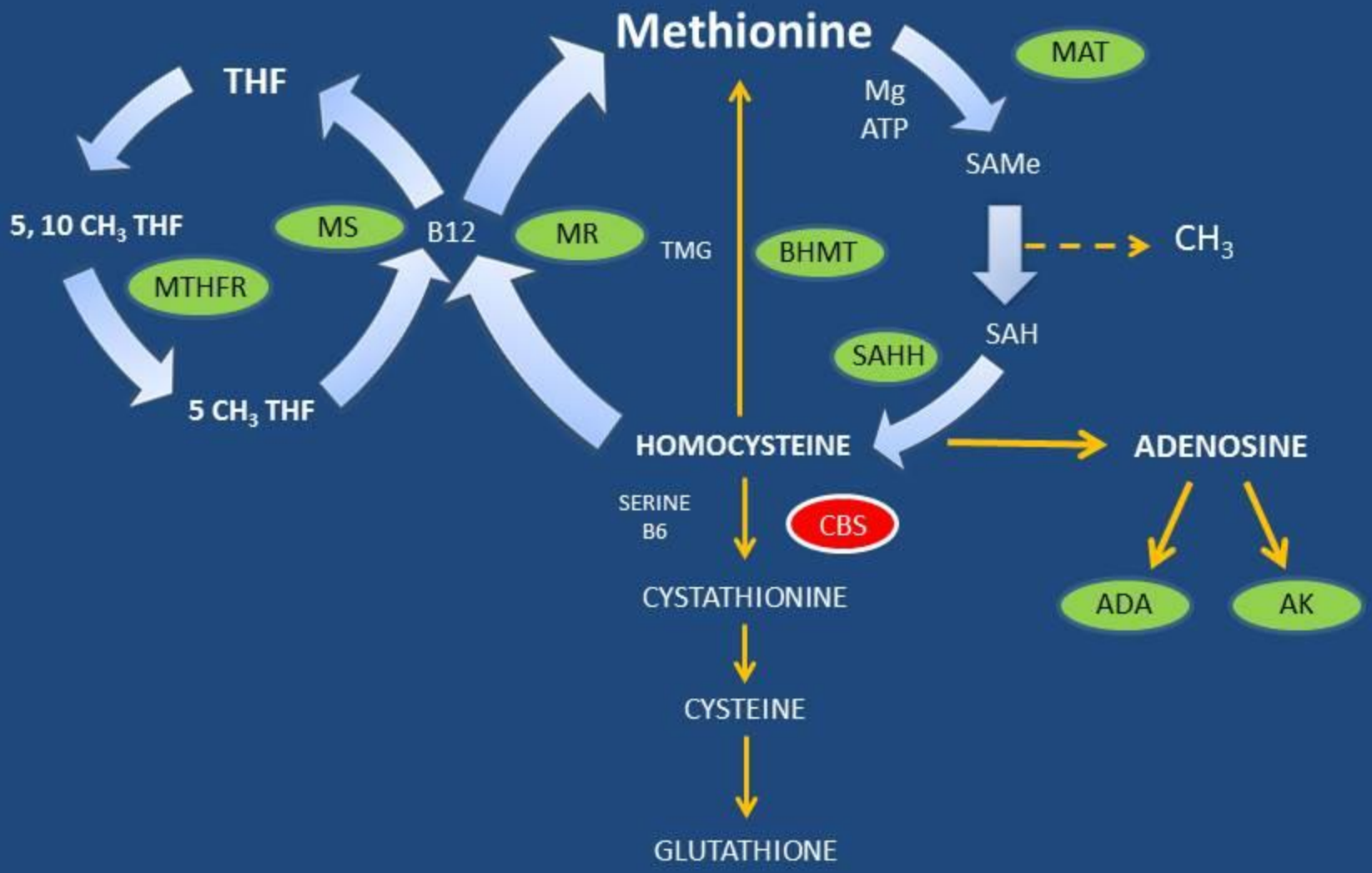
Incidence of OVERmethylation

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

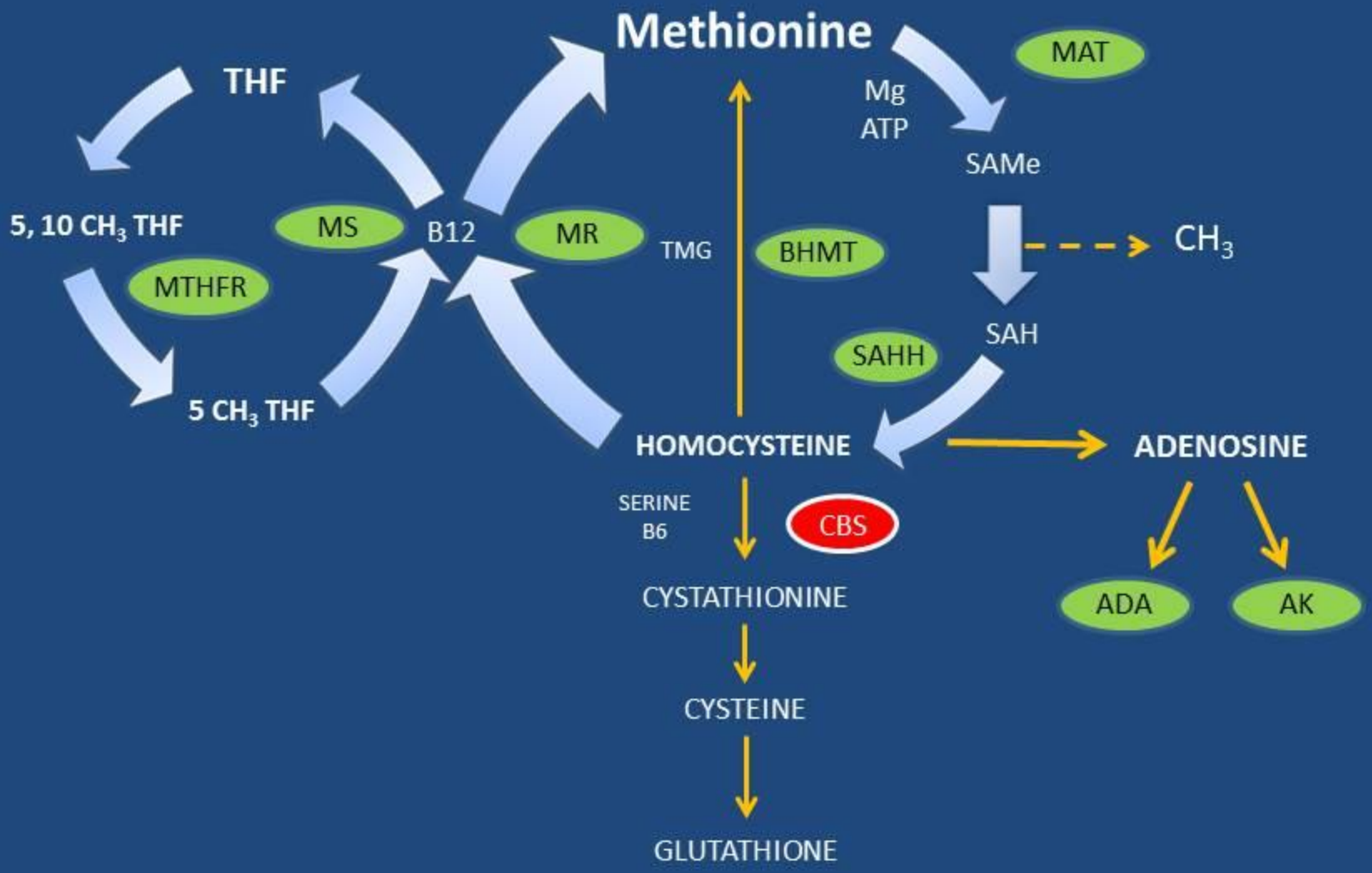
Methylation Cycle Enzymes



SAMe Synthesis

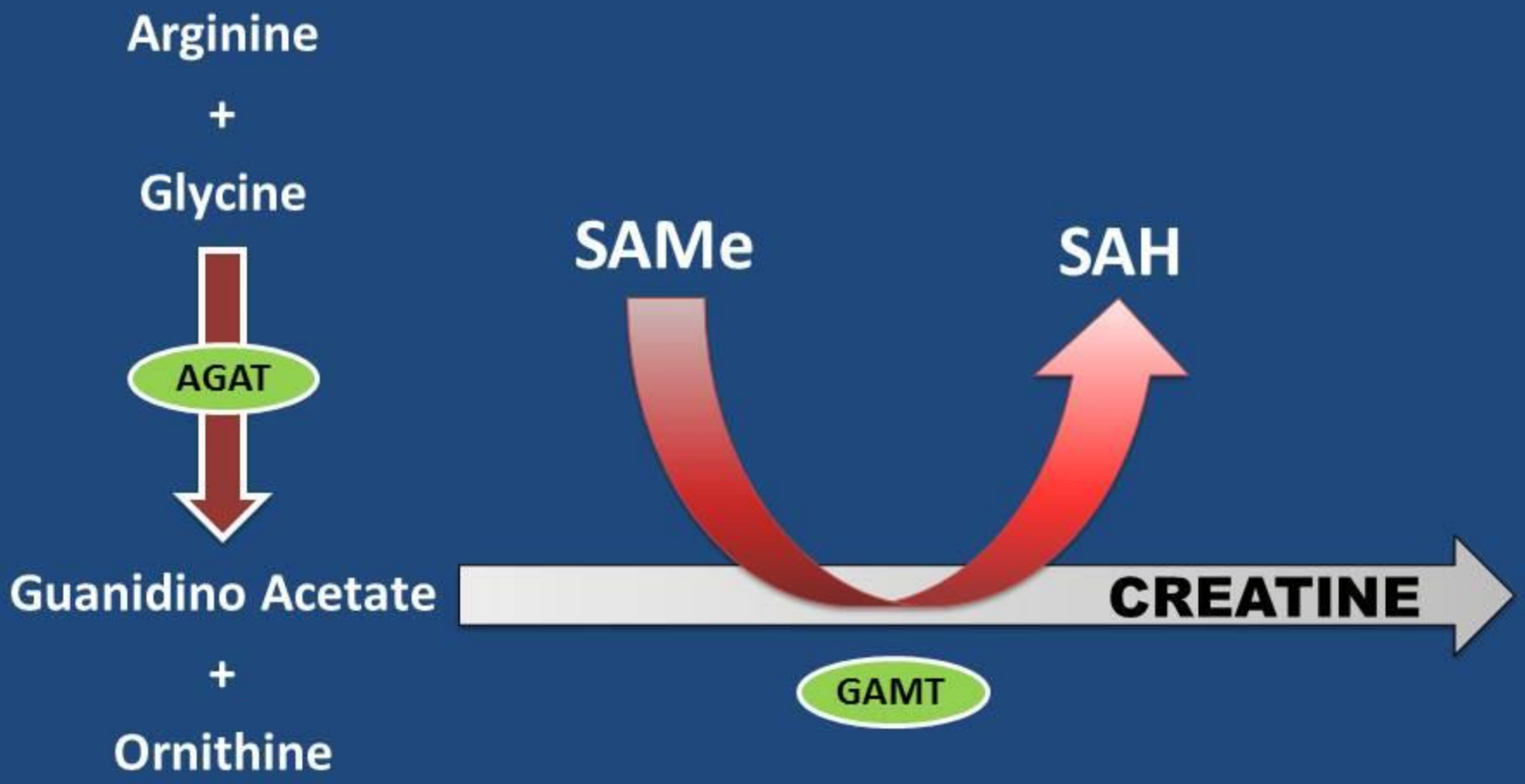
Methyl Donation

Methylation Cycle Enzymes



SAMe Utilization

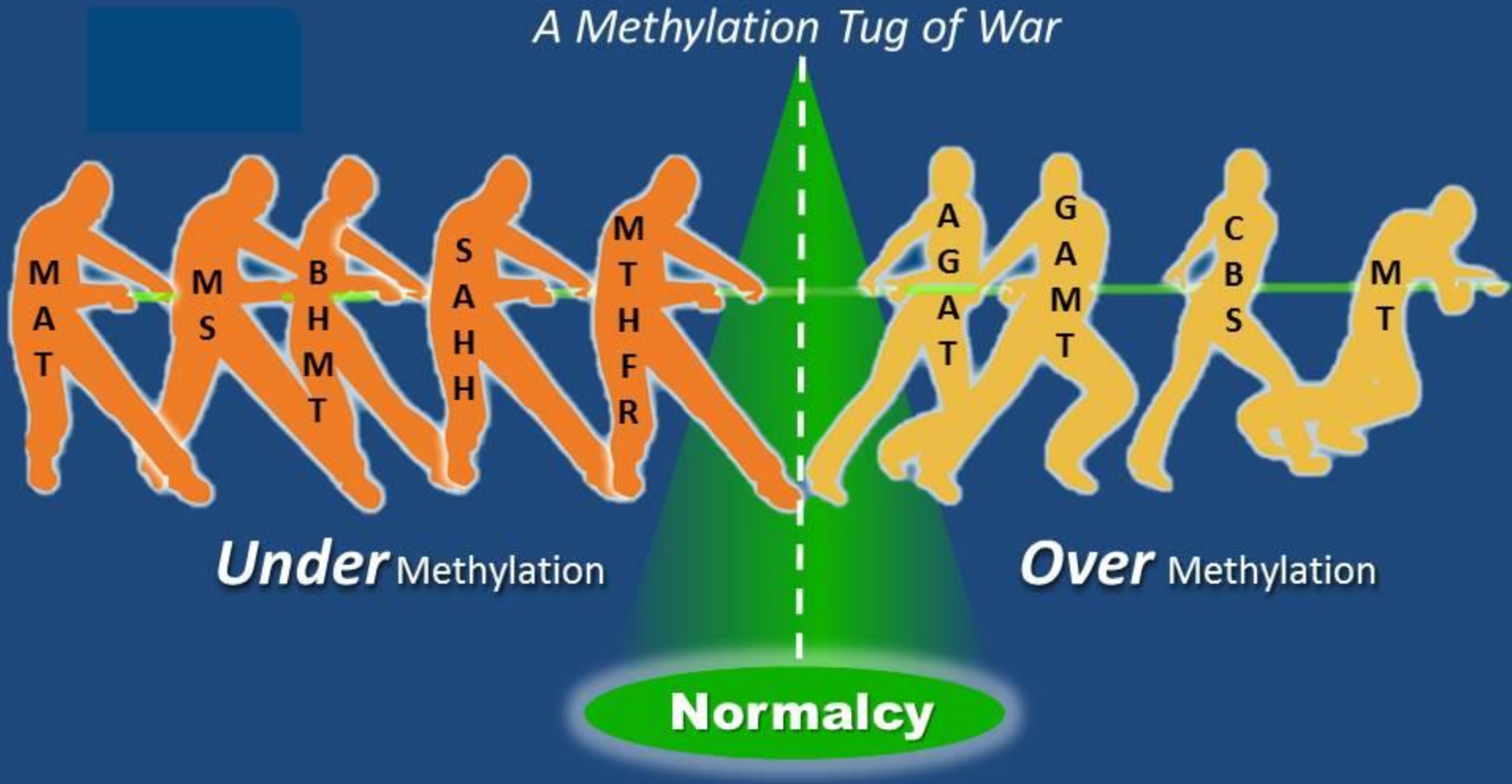
Creatine Synthesis



Primary Causes of OVERmethylation

1. Impaired Creatine Synthesis
    - AGAT or GAMT SNP's
    - Arginine or Glycine Deficiency
2. Impaired Cystathionine Synthesis (CBS SNP)
3. Methyltransferase SNPs

Enzyme Mutations and Methylation



Lab Tests for Methylation Status

1. SAMe/SAH Ratio (limited availability)
2. Whole-blood histamine (methylation marker)

Note: Present genetic tests (MTHFR, etc.) cannot determine ***net effect*** of SNPs that enhance/depress methylation

Under Methylation: Symptoms & Traits

Partial List

- Very 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
- Good response to SSRI's
- High libido

Over Methylation: Symptoms & Traits

Partial List

- High anxiety; panic tendency
- Hyperactivity; nervous legs; pacing
- Sleep disorder
- Low libido
- Absence of seasonal allergies
- Food, chemical sensitivities
- Dry eyes and mouth
- Excellent socialization, empathy
- Non-competitiveness in sports, academics
- Adverse reaction to SSRIs, anti-histamines

Single Nucleotide Polymorphisms

- We share 99.9% of our DNA with everyone of the same gender -- It's the 0.1% that makes us different.
- SNPs are gene mutations that developed over thousands of years.
- More than 10 million SNPs have been identified in the human genome. Most humans have more than 1,000 SNPs.

ENZYME SNPs

- More likely in very-large enzymes,
- Most SNPs have little or no effect on enzyme function,
- Some strategically-placed SNPs significantly weaken enzyme function (MTHFR 677T, etc.),
- Impact of a SNP varies from person to person.

Size Matters

- MTHFR – more than 500 amino acids, MW 77,000; 677T SNP present in >20% of all humans; 52% of all Italians.

- Metallothionein – 61 amino acids – SNPs far less common but generally more harmful with respect to function.

Methylation and Epigenetics

- Methylation is a dominant factor in epigenetic processes,
- SAMe, folates, niacin, and other nutrients have a powerful epigenetic impact on neurotransmitter activity at synapses,
- More than 60% of ADHD, anxiety, depression and psychosis patients exhibit a serious methylation imbalance.

Epigenetics

- >20,000 genes in every cell's DNA, each capable of producing a specific protein,
- Liver, skin, brain, and other tissues require a unique combination of proteins,
- During pregnancy, chemical "bookmarks" attach to DNA to enhance or inhibit gene expression in each tissue,
- Environmental insults at any age can alter gene bookmarks and produce mental disorders and other disease conditions.

Two Epigenetic Processes

DNA Methylation

Histone Modification

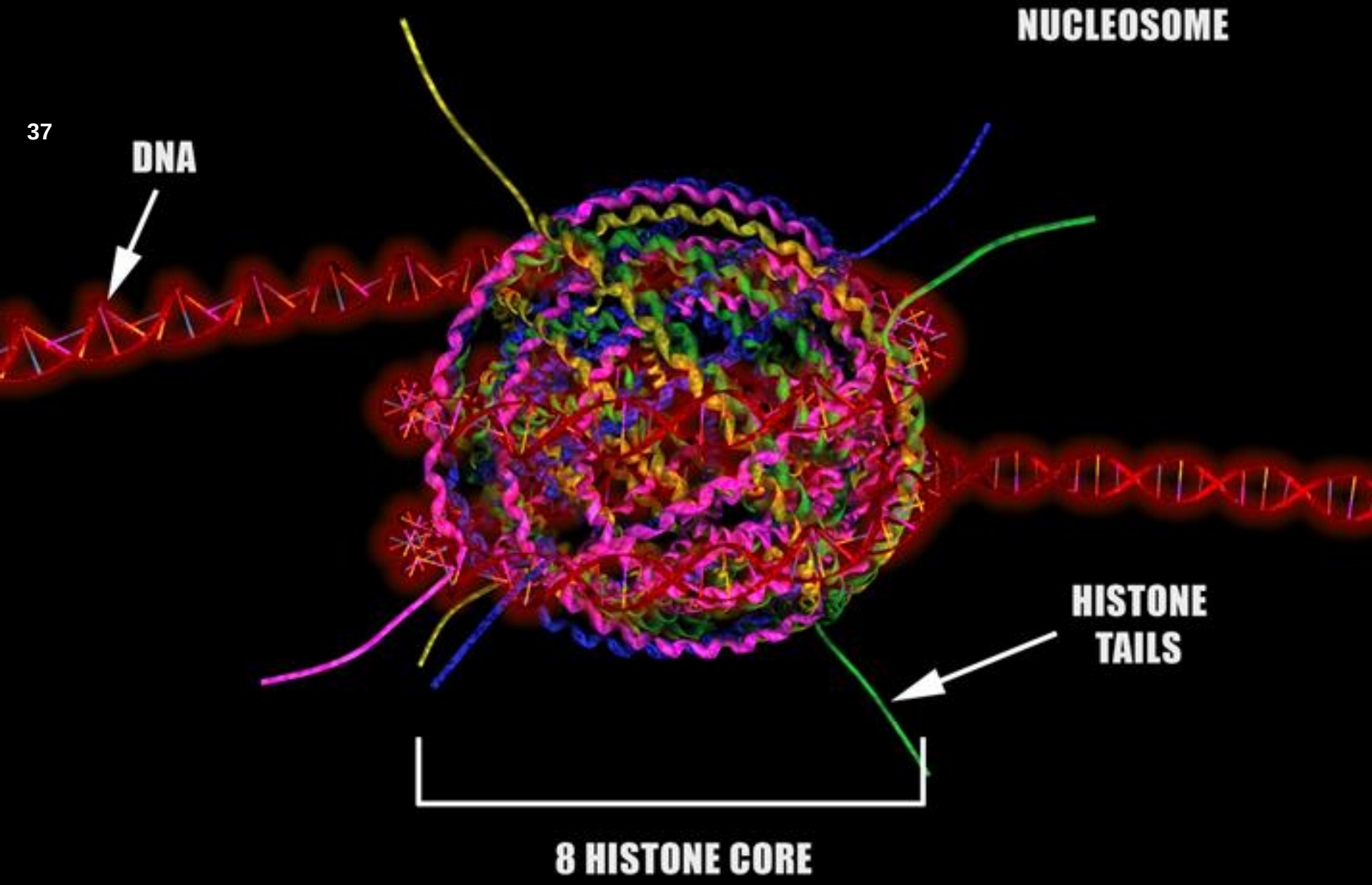
DNA Methylation

- Established in the womb,
- Methylation of cytosine at promoter CpG island clusters can reduce expression (protein production) for the corresponding gene. These methyl “bookmarks” usually remain in place throughout a lifetime,
- In-utero environmental insults can produce deviant bookmarks & serious disorders or birth defects,
- Throughout life, a severe environmental insult may alter one or more gene-regulation marks and produce an epigenetic disorder such as cancer or a mental illness.

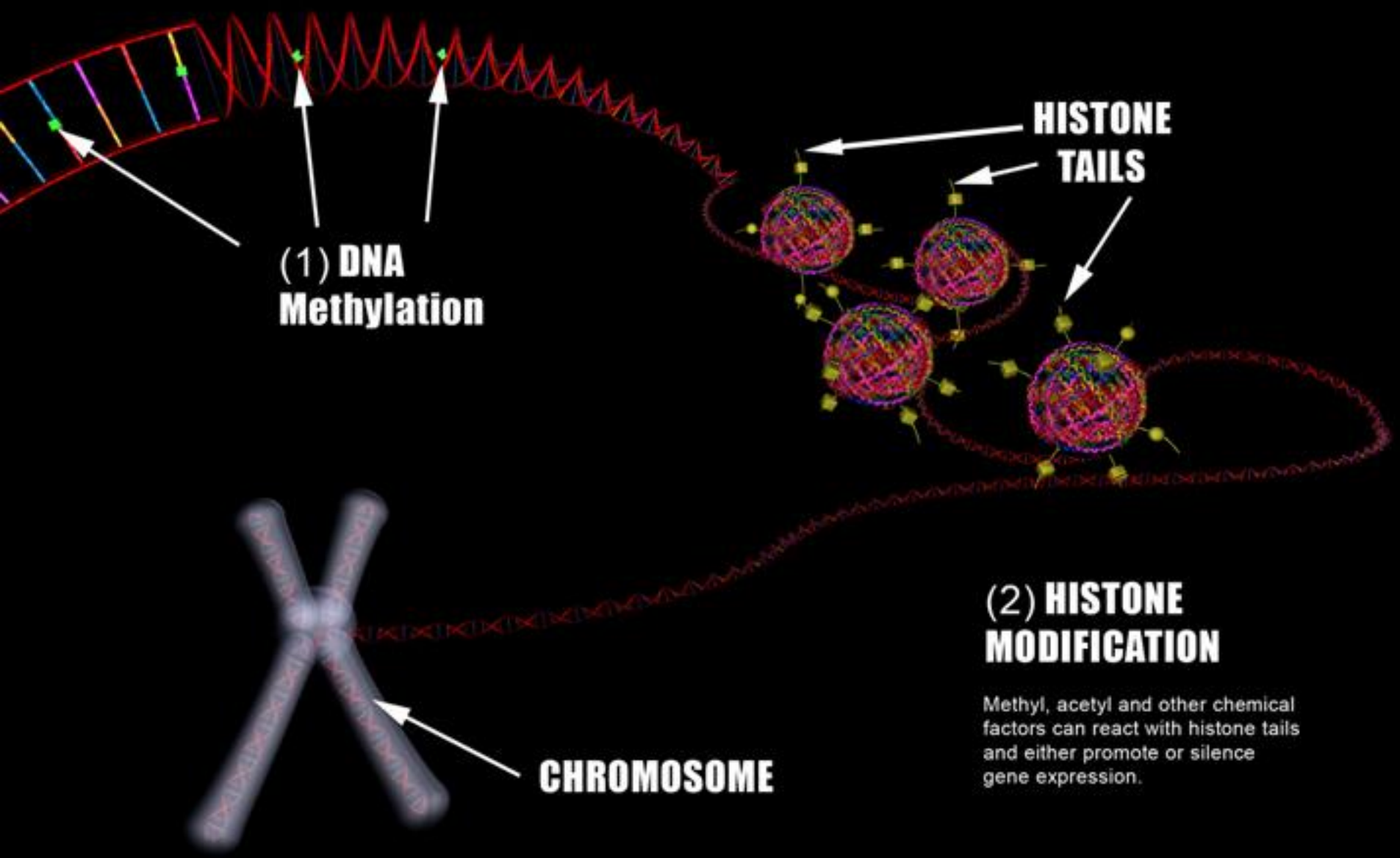
DNA Methylation

Histones – Support Structures for the Fragile DNA

- Composed of 8 linear proteins twisted together like a ball of yarn,
- Originally believed to serve only as structural support for DNA packaging,
- Later found to inhibit or promote gene expression depending on chemical reactions at histone tails.
- Nutrient therapies can modify histones that control reuptake of serotonin, dopamine, and other NTs.


NUCLEOSOME
DNA
HISTONE
TAILS
8 HISTONE CORE

The Two Main Components of the Epigenetic Code



Methyl-Acetyl Competition

- Competition between acetyl and methyl groups often determines whether genes are expressed or silenced,
- Acetyl bookmarks promote gene expression,
- Methyl bookmarks inhibit expression,
- Nutrient therapy can change methyl/acetyl ratios and adjust production of enzymes that control serotonin and dopamine neurotransmission rates.

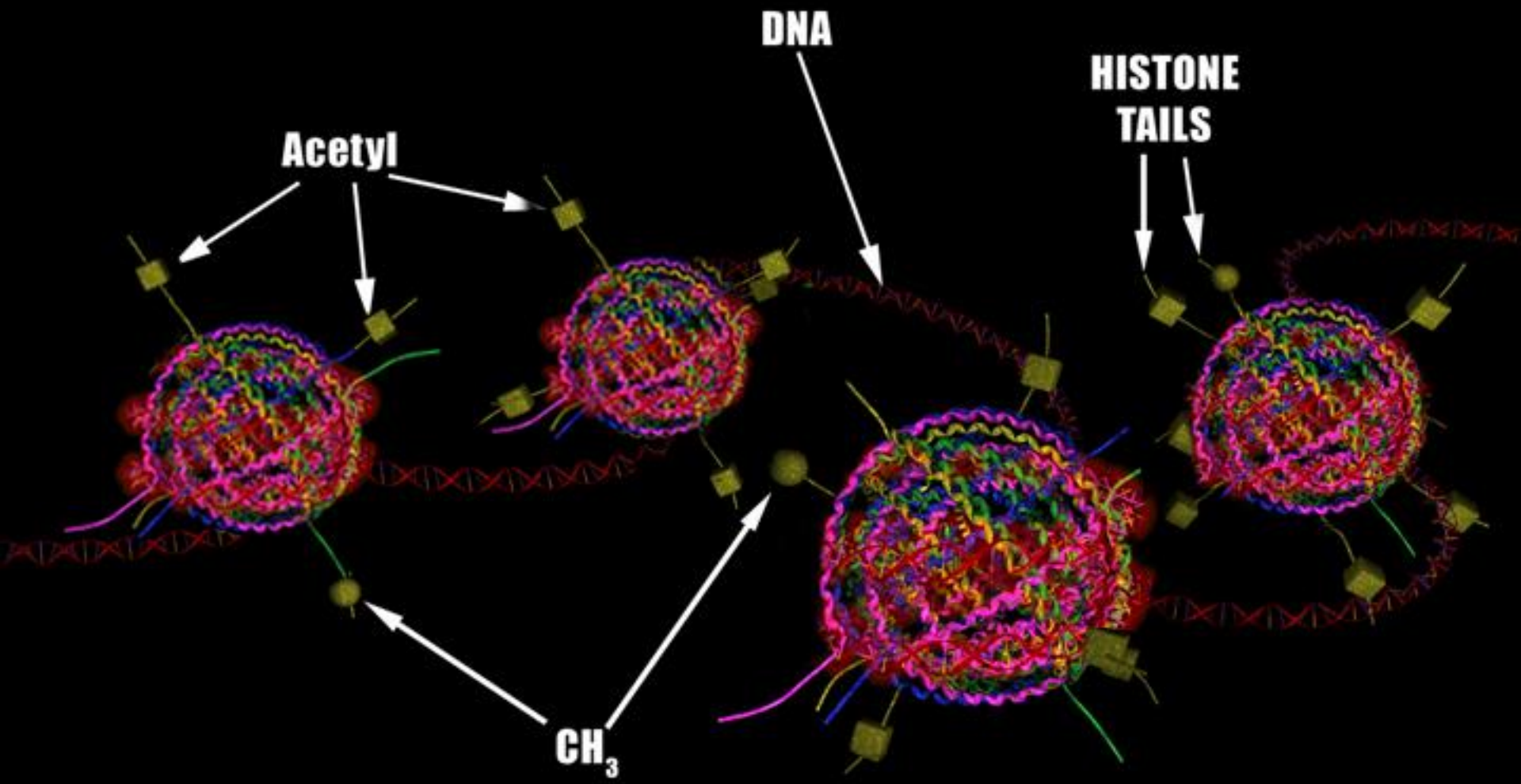
Gene Expression Requires Uncoiling of DNA

- Gene expression involves direct interaction of RNA polymerase and transcription factors with DNA. These large molecules cannot gain access to DNA/histone regions that are densely compacted,

- The gentle attachment of DNA to histones involves electrostatic attraction – DNA is a weak acid and histones are mild bases (pH above 7.0),

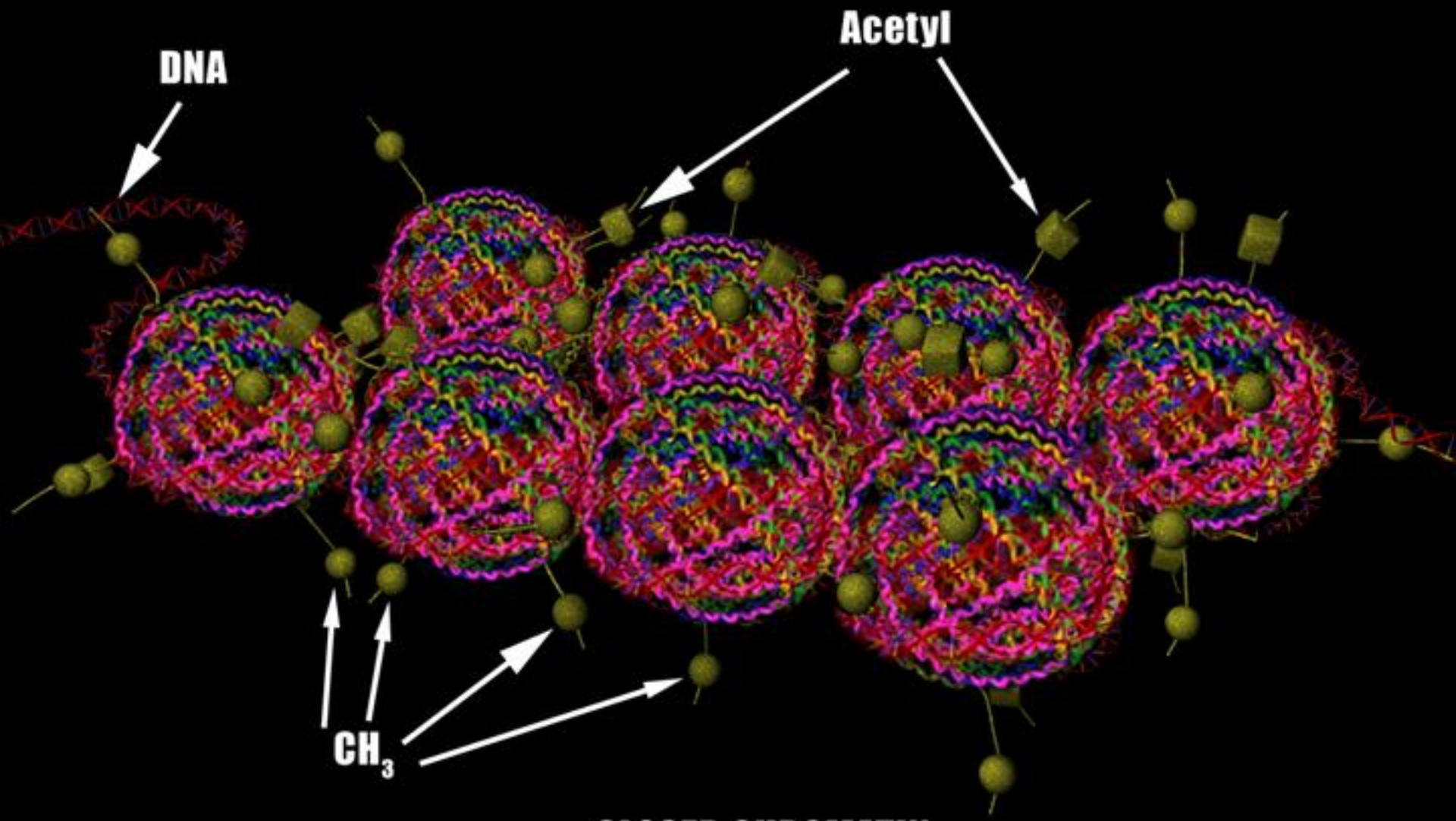
- Acetylation decreases histone pH, causing uncoiling of DNA; methylation increases histone pH, increasing DNA/Histone compaction.

LOW METHYLATION PROMOTES GENE EXPRESSION



OPEN CHROMATIN

HIGH METHYLATION INHIBITS GENE EXPRESSION



CLOSED CHROMATIN

Reuptake Transport Proteins

- Primary determinant of neurotransmitter activity at serotonin & dopamine receptors – brain concentrations of serotonin and dopamine are less important,
- Transmembrane proteins that remove neurotransmitters from the synapse (reuptake) like a vacuum cleaner inhaling dust particles,
- Formed by gene expression: amount present depends on methyl/acetyl competition at specific DNA regions.

Enzymes Dominate the Methyl-Acetyl Competition

- Acetyl-Coenzyme A and SAMe are the donors of acetyl and methyl, respectively – but their concentrations in brain cells are relatively unimportant.
- Acetylases, deacetylases, methylases and demethylases dominate attachment or removal of acetyl or methyl groups.
- Epigenetic nutrient therapy for adjustment of serotonin or dopamine activity concentrates on the enzymes.
- Example: B-3 inactivates a major deacetylase inhibitor, increasing expression of SERT, DAT transporters and reducing serotonin and dopamine neurotransmission.

Epigenetic Insights Into Nutrient Therapy

- Niacin & niacinamide act as dopamine reuptake promoters,
- Methionine and SAMe are serotonin reuptake inhibitors,
- Folates reduce synaptic activity at serotonin, dopamine, and norepinephrine receptors,
- Zinc and glutathione increase glutamate activity at NMDA receptors,
- Many nutrients influence neurotransmitter activity and brain function.

Folates Reduce NT Activity

- Folic Acid, folinic acid, and L-methylfolate are effective methylating agents.
- However, folates also increase gene expression of SERT transport proteins, resulting in reduced serotonin neurotransmission.
- Most undermethylated depressives with low-serotonin activity are intolerant to folates.

Low Serotonin Activity
Nutrient Therapy Approach

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

Treatment Example (160 lb adult)
Undermethylated Depression

- **SAMe, 400 mg/day (reduce SERT expression and inhibit serotonin reuptake)**
- **B-6, 200 mg/day and P5P, 50 mg/day (enhance synthesis of serotonin and glutathione)**

Antioxidant Support

Vitamin C, 2000 mg/day

Vitamin E, 400 mg/day

Zinc (chelated form), 50 mg/day

Selenium, 100 mcg/day

Augmenting Nutrients as indicated

Biotin, Ca, Mg, Cr, TMG, Inositol, Serine, Vitamins A, D

Excessive Dopamine Activity
Nutrient Therapy Approach

- **Support acetylation of histones with folic acid and niacinamide (powerful deacetylase inhibitors).**
- **Augmenting nutrients DMAE, zinc, selenium, chromium, Vitamins B-6, B-12, C, D, E.**
- **Especially promising for paranoid schizophrenics with excessive dopamine activity.**

Treatment Example (160 lb adult)
Excessive Dopamine Activity

- **Folic Acid, 2400 mcg/day, and Niacinamide, 1000 mg/day to support acetylation of histones and promote reuptake of dopamine.**
- **Augmenting nutrients DMAE, zinc, manganese, selenium, chromium, Vitamins B-6, B-12, C, D, E.**
- **Especially promising for paranoid schizophrenics and anxiety/depression patients with excessive dopamine activity.**

The Power of Nutrients

1. Neurotransmitter synthesis

2. Epigenetic regulation of gene expression

3. Reuptake processes at synapses

4. Antioxidant protection

Summary

- Methylation imbalances play a critical role in most mental disorders,
- Recent research in methylation and epigenetics is providing a roadmap for advanced nutrient therapies.
- Nutrient therapy represents an effective weapon in the arsenal of a mental health practitioner.

THANK YOU!

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Walsh Research Institute

www.walshinstitute.org

Additional Information Sources

Nutrient Power, Chapters 3-8

www.walshinstitute.org

Physician Education Workshop
Chicago Area ● May 27-30, 2015
Contact: sue@walshinstitute.org