

BRAIN BIOCHEMISTRY

Dr Inanch Mehmet



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BRAIN BIOCHEMISTRY

- Mental or behavioural condition (Australian bureau of statistics 2014);
 - 17.5% of people
 - Women 19.2% vs Men 15.8%
- Autism; 1 in 70(2018). 40% increase since 2014. (ASPECT)
- ADHD; 5-10% of kids (June 2019 Australian guidelines on ADHD)
- Dementia (Dementia Australia 2019);
 - 1 in 10 over 65.
 - 3 in 10 over 85 .
 - 250 new cases diagnosed daily in Australia expected to increase to 650/day by 2056.

BRAIN BIOCHEMISTRY

- Raw materials for neurotransmitter production comes from nutrients ; amino acids, vitamins, minerals.(Purves et al Neuroscience 2014)
- Good mental health requires proper neurotransmitter (NT) activity at synapses. Transporter reuptake proteins and DNA METHYLATION becomes important here. .(Purves et al Neuroscience 2014)
- Genetic tendencies for a mental health disorder; a lottery left over from all ancestors.
- Genetic tendency for a nutritional overload or deficiency (needs many times the RDI to overcome)

EPIGENETICS

- SNPs; Single Nucleotide Polymorphisms are genetic mutations that developed over thousands of years.
- More than 10 million SNPs identified in the human genome, most of us have about 1000.
- If SNPs expressed then you become vulnerable to certain illnesses including mental health.
- SNPs can be turned on or off with nutrients by correcting dna methylation.
- We now know that during pregnancy, methyl groups can attach to DNA to enhance or inhibit gene expression.
- Environmental insults in utero and throughout our lives can produce deviant bookmarks.
- Insults can be emotional or physical (exposures to toxic metals, radiation, chemicals)

HISTORY

Dr ABRAM HOFFER;

- 1951 found high doses of NIACIN (B₃) reduced auditory hallucinations in schizophrenics.

DR CARL PFEIFFER;

- In the 1950s treated a man who was catatonic for months to full recovery within 7 days with amino acids, vitamins and minerals after working out his biochemistry.
- He was later ordered to stop by the hospital who refused to believe nutrients were the reason and the man returned to catatonia within 2 weeks.
- Studied >20000 schizophrenics and developed 3 distinct biochemical types of schizophrenia.
- Discovered that methyl status has powerful effects on serotonin, dopamine and noradrenalin activity.

HISTORY

DR BILL WALSH

- Studied > 30000 patients with mental illness and >15000 more with ADHD and autism.
- Consistent pattern and high incidence of biochemical abnormalities in blood and urine testing (I will be discussing this today)
- Severe biochemical abnormalities cannot be nurtured away with counselling , diet and good home environments and must be treated nutritionally or biochemically.
- Bill's work has been observational with the largest mental health database of biochemical samples but there are several small studies reinforcing various nutrients we use for mental health .
- It is difficult to do RCT's because it isn't just one intervention and can't be patented. Treatment is individualized which means no funding.
- Funding is given to single interventions that can be patented and used to make money out of and for studies that have 1 intervention.

BILL WALSH



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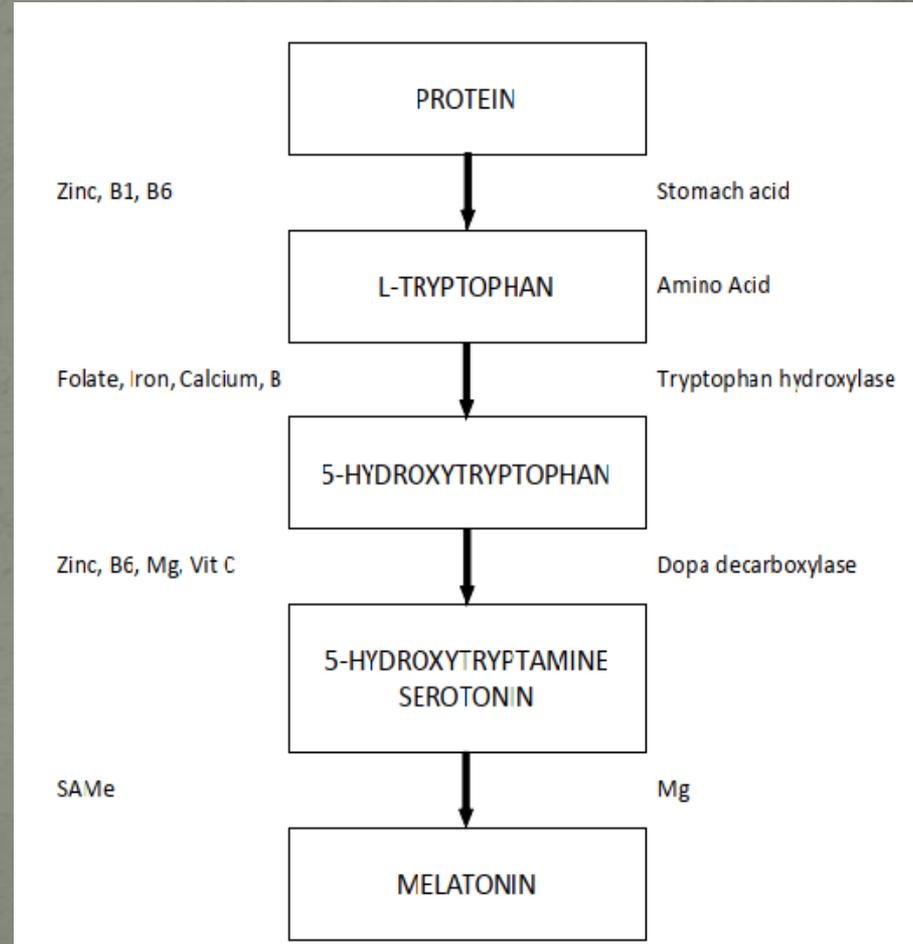
NEUROTRANSMITTERS

- Life Cycle
 1. Synthesis by chemical reaction (needs raw materials)
 2. Packed into vesicles
 3. Release into synapse
 4. Interaction with cell next to it
 5. Reuptake (transport back into original cell for reuse)- Most important. Drugs work here.
 6. Death and deactivation by chemical reaction

NEUROTRANSMITTER SYNTHESIS

Serotonin (happy)

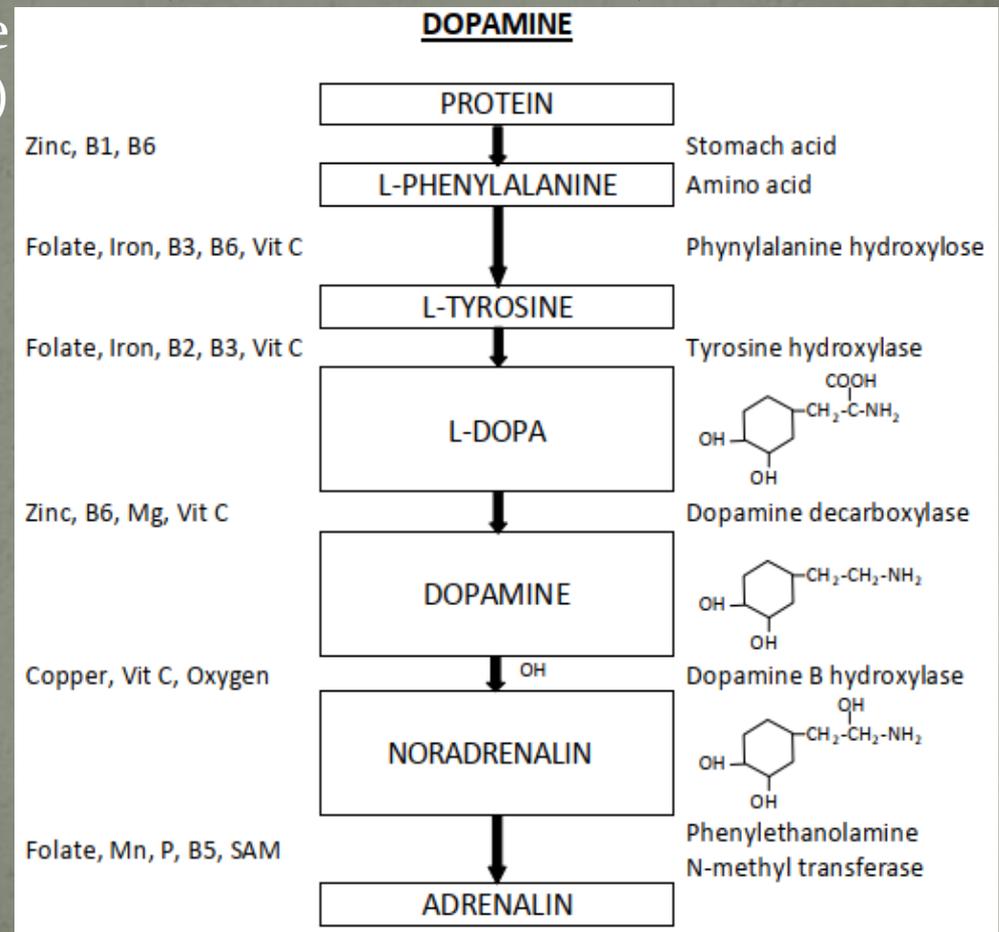
- Requires good protein intake (tryptophan) and ability to digest it.
- Zinc
- Magnesium
- Vit C
- B6, B1
- Iron
- SAMe
- Folate



NEUROTRANSMITTER SYNTHESIS

Dopamine (rewarded)

- Requires good protein intake (phenylalanine and tyrosine)
- Zinc
- Magnesium
- Vit C
- B6
- B1, B2, B3
- Iron
- Folate
- Copper (not too much)



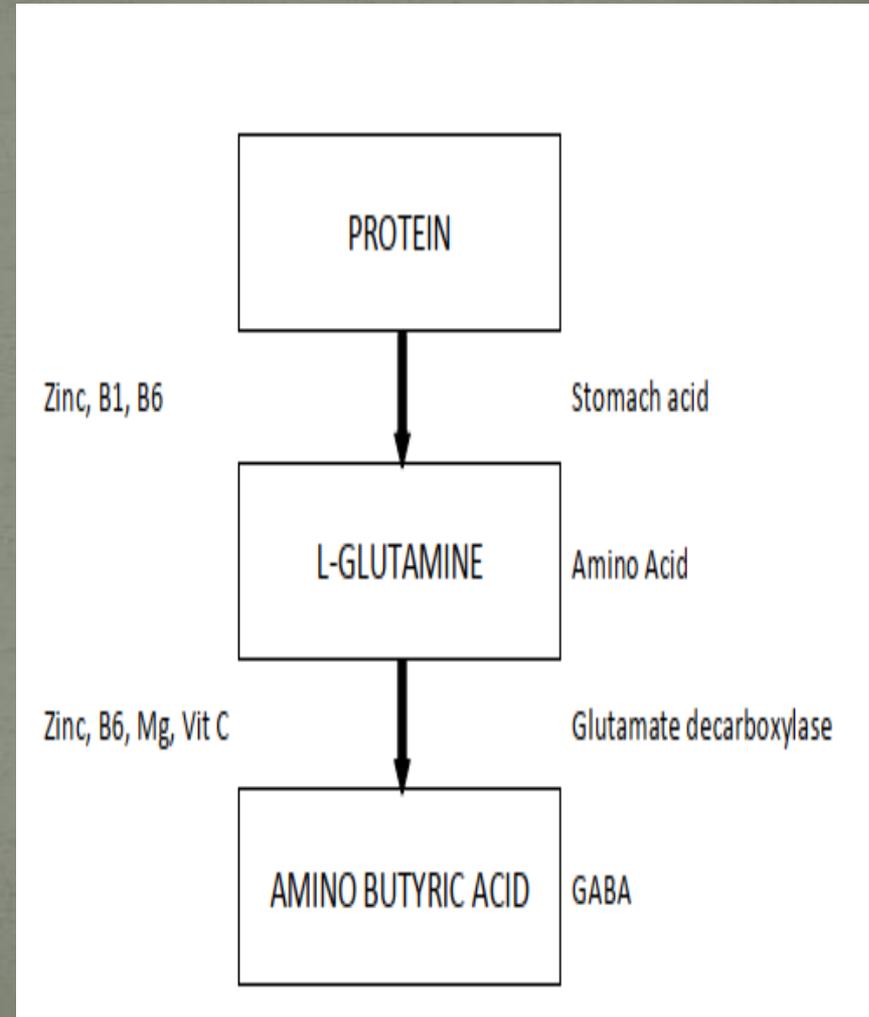
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NEUROTRANSMITTER SYNTHESIS

GABA (calm)

Requires

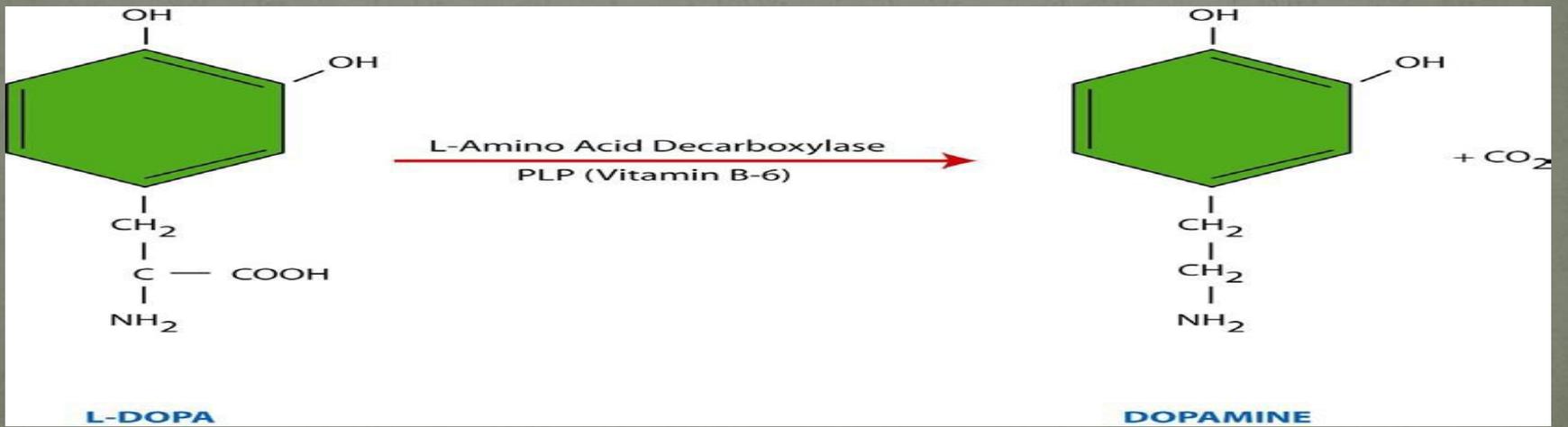
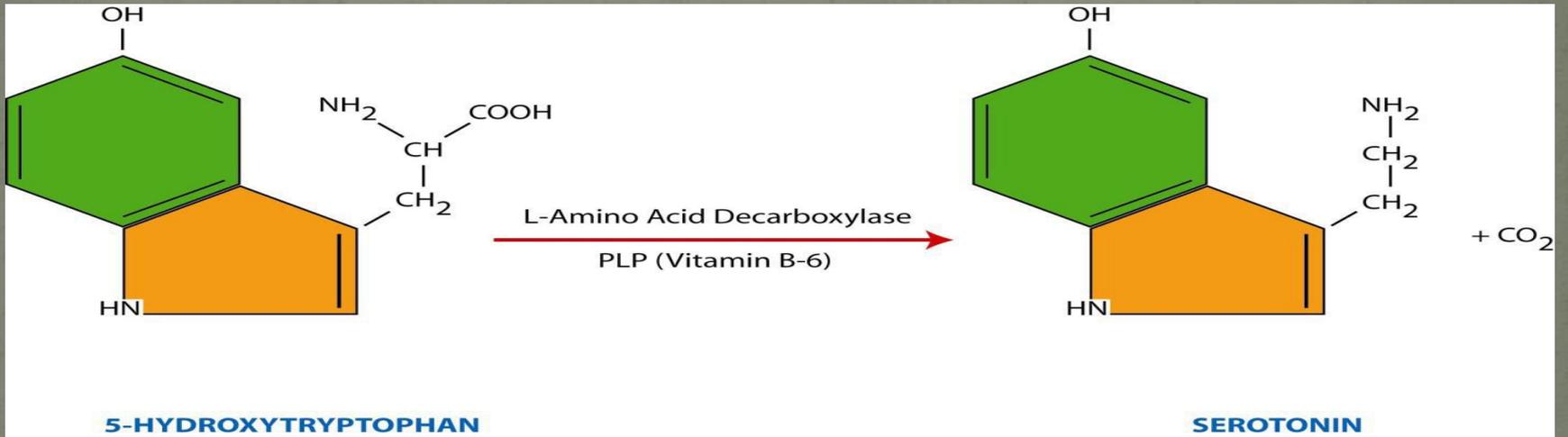
- Glutamine (protein) from diet
- B₁, B₆
- Zinc
- Magnesium
- Vitamin C
- Iron
- Normal copper



B6

- Needed for production of;
 - Serotonin
 - Dopamine
 - Gaba
 - P5P is active form
- Deficiency leads to;
 - Depression
 - OCD
 - ADHD
 - Anxiety
 - Sleep disorders
 - Irritability
 - Poor memory
 - Psychosis
 - (food and nutrition board institute of medicine 2001)

B6



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ZINC

- Essential cofactor for >200 body biochemical processes. (prasad 1993)
- Over 90% of people with Depression, ADHD, Autism, and Schizophrenia exhibit low normal to deficient zinc levels. (Walsh research institute)
- Oxidative stress and toxic metal overload depletes zinc. (Walsh)

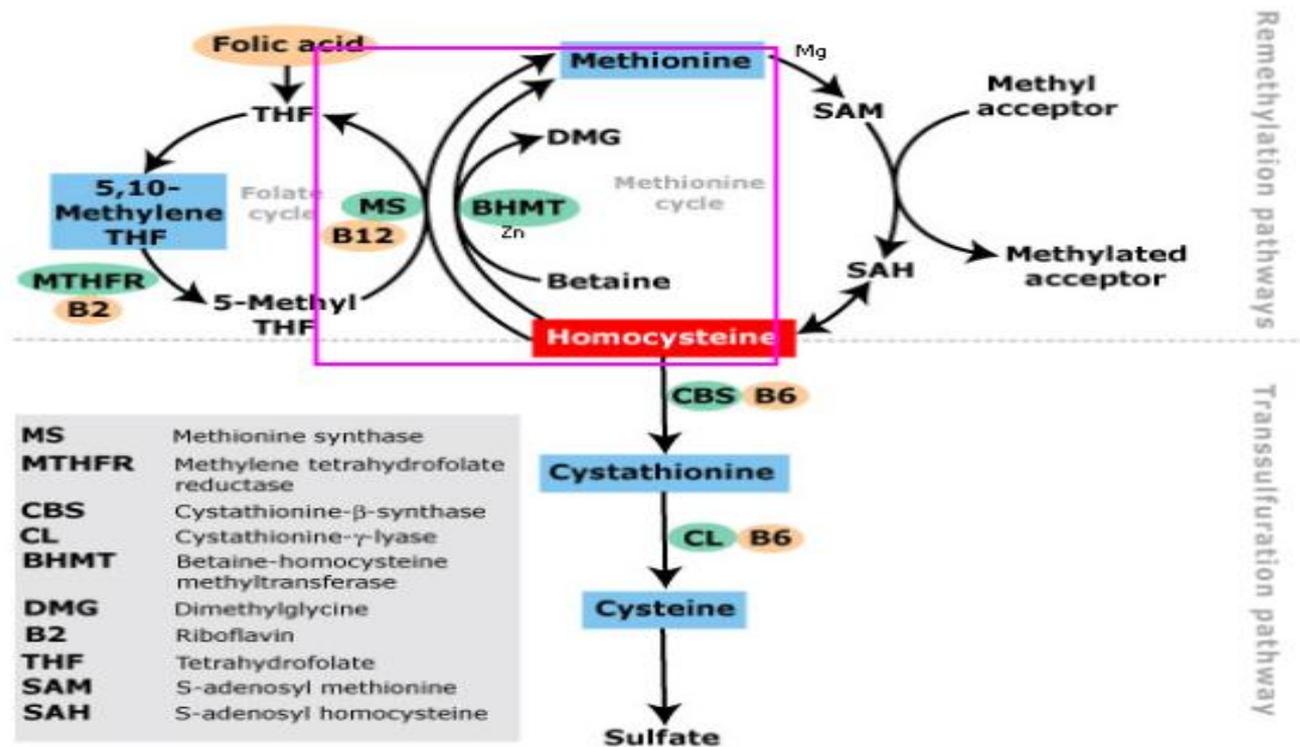
ZINC

Deficiency associated with (Walsh research institute);

- Delayed growth
- Poor temper control/irritability
- Poor immune function
- Depression
- Poor wound healing
- Epilepsy
- Anxiety
- Neurodegenerative disorders
- Hormone imbalances
- Learning problems

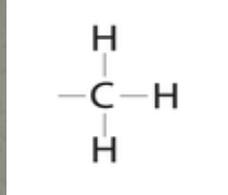
DNA METHYLATION

Homocysteine → Methionine (via TMG, with Zn) OR Homocysteine → Methionine (via methylB12)



DNA METHYLATION

- Meet methyl
- It's complicated!
- Methyl groups are added to an atom or molecule to silence gene expression.
- Occurs a billion times/second via methylation cycle .
- Homocysteine must be converted to methionine then S-AdoMet
- S-AdoMet donates methyl.
- Regulated by enzymes which require cofactors (derived from vitamins/minerals) to activate
- Needs active folate- 5-MTHF
- Needs active B12-methylcobalamin
- Makes Glutathione as well; a powerful antioxidant.



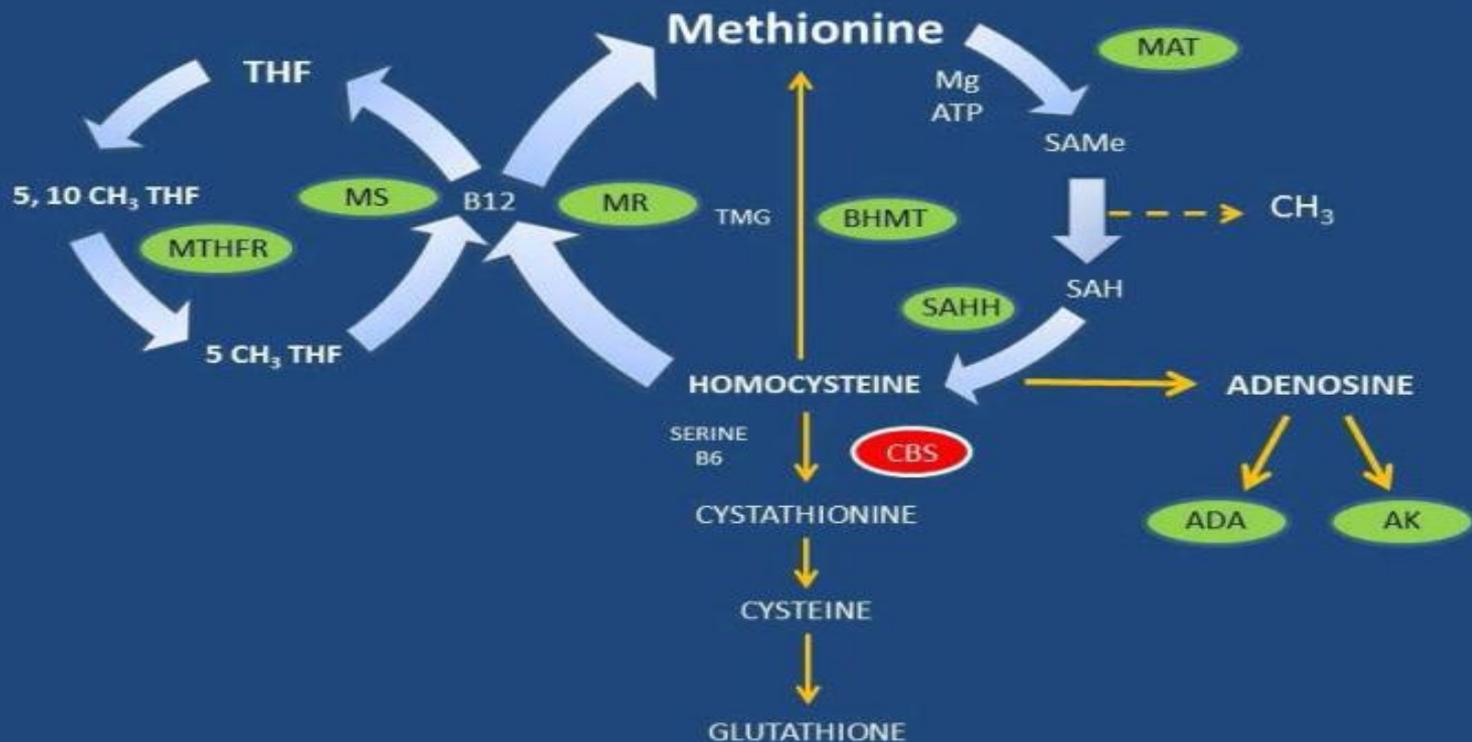
DNA METHYLATION

DNA Methylation is disturbed by:

- Diet - excess animal proteins, saturated fats, sugars, coffee, alcohol
- Medications e.g. Antacids (lowers B12), oral contraceptive pill, diuretics
- Poor digestion, leaky gut
- Smoking (depletes folate, S_AMe)
- Niacin B₃(depletes methyl groups)
- Environmental toxins e.g. acetaldehyde (alcohol, yeasts), heavy metals - As, Hg
- SNPs /Genetic mutations to enzymes (MTHFR, CBS, COMT, MS/MTR)

DNA METHYLATION

Methylation Cycle Enzymes



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DNA METHYLATION

Important for;

- Drug metabolism and excretion;
- Neurotransmitters
- Hormones, excretion;
- The synthesis and repair of myelin in nerves (neurodegenerative conditions)
- Produce energy (CoQ10, carnitine, ATP)
- Reduces atherosclerosis
- Regulates weight
- Genetic expression

(NUTIPATH HANDBOOK)

MTHFR

- Most important enzyme in methylation cycle but NOT the only one
- Needed to produce methyl folate which is then needed to convert homocysteine to methionine.
- **MTHFR C677T HETEROZYGOUS SNP = 40% loss of function**
MTHFR C677T HOMOZYGOUS SNP = 70% loss of function
- Increased risk of CVD, Dementia, Mental health disorders, Autism, ADHD, Neural tube defects, Colon cancer, Leukaemia, fertility issues.
- May lead to high homocysteine and dna methylation imbalance but there are other SNPs.
- Can be overcome with B2 and folic acid/Methyl folate supplementation.

NEUROTRANSMITTERS

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HISTAMINE IMBALANCE

HISTAMINE;

- Indirect methylation measure.
- Methylation destroys histamine so inverse relationship
- Histamine imbalance refers to higher histamine and lower DNA methylation.
- LOWER LEVELS OF DOPAMINE SEROTONIN AND NORADRENALINE

HISTAMINE IMBALANCE

- **Calm outside but high inner tension**
- **High self motivation**
- **High achiever**
- **Stubborn**
- **Bossy**
- Doesn't care what people think or how they feel
- **Perfectionism**
- **Fear of failure**
- **Addictions**
- **Obsessions (OCD)**
- **Collects things**
- **Anorexia/bulimia**
- **Self conscious**
- **High energy when well**
- **Oppositional (poor compliance)**
- **Denies illness**
- **Ruminates about the past**
- **Social isolation**
- **Difficult transitions**
- **Sudden breakdown**
- **Easy tearfulness**
- **Delusions (not hallucinations)**
- **Phobias**
- **Catatonia**
- **Low pain t/hold**
- **Headaches/migraine**
- **Insomnia**
- **Sparse hair growth**
- **Prominent veins**
- **Elongated fingers and 2nd toe**
- **Hears pulse in ears**
- **Slender and fast metabolism**
- **Feel better on animal protein**
- **Seasonal allergies**
- **High libido**
- **Often Athletes and professionals**

HISTAMINE IMBALANCE

NUTRIENTS;

- Zinc /b6/p5p/Vit C –always used
- Methyl donors;
 - SAME (silences the reuptake transport protein)
 - Methionine + Magnesium
 - Methylcobalamin (B12)
- Eat Animal protein
- NOT folate/folinic acid or methylfolate if mental health disorder (overexpresses serotonin reuptake transport)
- Antidepressants often work but have side effects.
- May take 8-12 months to see improvement.

FOLATE DEFICIENCY

- Elevated/ Normal Folate and B12 in blood does not necessarily mean good cellular or tissue levels.
- We are talking cerebral folate deficiency.
- **Formiminoglutamate (FIGLU)** is a functional marker of folate need (ORGANIC ACIDS TEST)
- **Folate deficiency will mean lower histamine hence more methylation (reuptake receptor silenced)**
- **HIGHER SEROTONIN, DOPAMINE AND NORADRENALINE**

FOLATE DEFICIENCY

- **High anxiety/nervousness**
- **panic attacks**
- Easily frustrated
- **Depression**
- **Self mutilation/harm**
- Self isolation
- Paranoia
- Psychosis; hyperactive
- Mania
- Sleep disorder
- **Poor motivation**
- **Poor achiever**
- **Often late**
- **Not keen on sport**
- **Fatigue**
- **ADHD**
- Expects perfection in others
- Concerned by what others think
- **Caring/empathetic/good neighbours**
- Generous/kind/loving
- Religiosity
- Grandiosity
- **Artistic/musical/creative**
- May stutter
- **Overweight/slow metabolism**
- **Better on vegetables**
- **Hairy body**
- Young looking body
- Dental caries
- Food/chemical sensitivities
- Eczema
- **High pain t/hold**
- Never gets sick
- Upper body pain
- Prone to OA
- **Restless legs**
- Stubby fingers
- **Tinnitus**
- **Reacts badly to antihistamines and antidepressants**

FOLATE DEFICIENCY

NUTRIENTS

- Zinc/b6/p5p increases GABA (calming).
- Folate ; reduces neurotransmitter activity by increasing reuptake .
- Niacin (b3); lowers dopamine activity
- No SAMe, methionine or antidepressants. Can make people worse even suicidal because they increase serotonin.
- Eat vegetables and fruit .
- Xanax, valium and other benzodiazepines work but have addictive potential and side effects.
- Takes 3-6 months to feel better on nutrients .May have more anxiety initially.

OXIDATIVE STRESS

- **URINARY
HYDROXYHEMOPYRROLINE-2-1
(KRYPTOPYRROLES) MEASURED
IN URINE IF HIGH IS ONE
MARKER OF OXIDATIVE STRESS!**

OXIDATIVE STRESS

- Kryptopyrroles are a metabolite of hemoglobin (a protein in red blood cells that carries oxygen throughout the body).
- Pyrroluria is not a problem and does not cause disease. We all have them.
- They do however, bind Vitamin B6 and Zinc. When kryptopyrroles leave the body (through urine), they take some B6 and zinc with them. This is not a problem either.
- The problem comes when kryptopyrroles are being overproduced for genetic reasons (Celtic and Scandinavians) or because of physical or emotional stress. This can lead to severe B6 and zinc deficiencies hence neurotransmitter abnormalities (low Serotonin and GABA).
- Oxidative stress causes kryptopyrroles (marker)
- High Kryptopyrroles make mental health disorders worse.

(WALSH)

OXIDATIVE STRESS

- **Poor stress control**
- **Severe anxiety**
- **Severe depression**
- Severe inner tension
- **High irritability and temper.**
- **Violence potential**
- Acting out and losing control
- **Mood swings extreme**
- **Long recovery from angry outbursts**
- Histrionic behaviour
- **Impulsive**
- **Hyperactive**
- Denies any problems
- **Fear of airplane travel, tornadoes, etc.**
- **Obsessions with negative thoughts eg disasters**
- Paranoia
- **History of underachievement**
- **History of a reading disorder or learning problem**
- Poor short-term memory
- **Intolerance of annoyances**
- **Sensitivity to bright lights/glare**
- **Sensitivity to loud noises**
- **Sensitivity to smells/ obsesses about smells**
- **Sensitivity to being touched/tag cutter**
- Tendency to stay up very late
- **Morning nausea/hates mornings**
- **Tendency to delay or skip breakfast**
- **little or no dream recall**
- Very dry skin
- Pale skin, inability to tan
- White spots on fingernails
- **Poor Growth**
- Acne
- Coarse eyebrow hair
- **Stretch marks (striae) on skin**
- Delayed puberty
- **Affinity for spicy and salty foods**
- Abnormal fat distribution
- Delicate facial features (china doll)
- Frequent infections/poor immune function
- **Premature graying of hair**
- Poor muscle development
- “Fruity” breath and/or body odour
- **Spleen-area pain**
- Joint pains
- Poor wound healing
- Psoriasis
- Abnormal or absent menstrual periods
- Autoimmune disorders

OXIDATIVE STRESS

NUTRIENTS

- Higher doses of Zinc and B6/P5P
- Evening primrose oil (B6 deficiency results in arachidonic acid deficiency)
- Antioxidants ; Vit A, C, E
- Fish oil can make severe kryptopyrroles worse
- Respond quickly 1 -3 months.

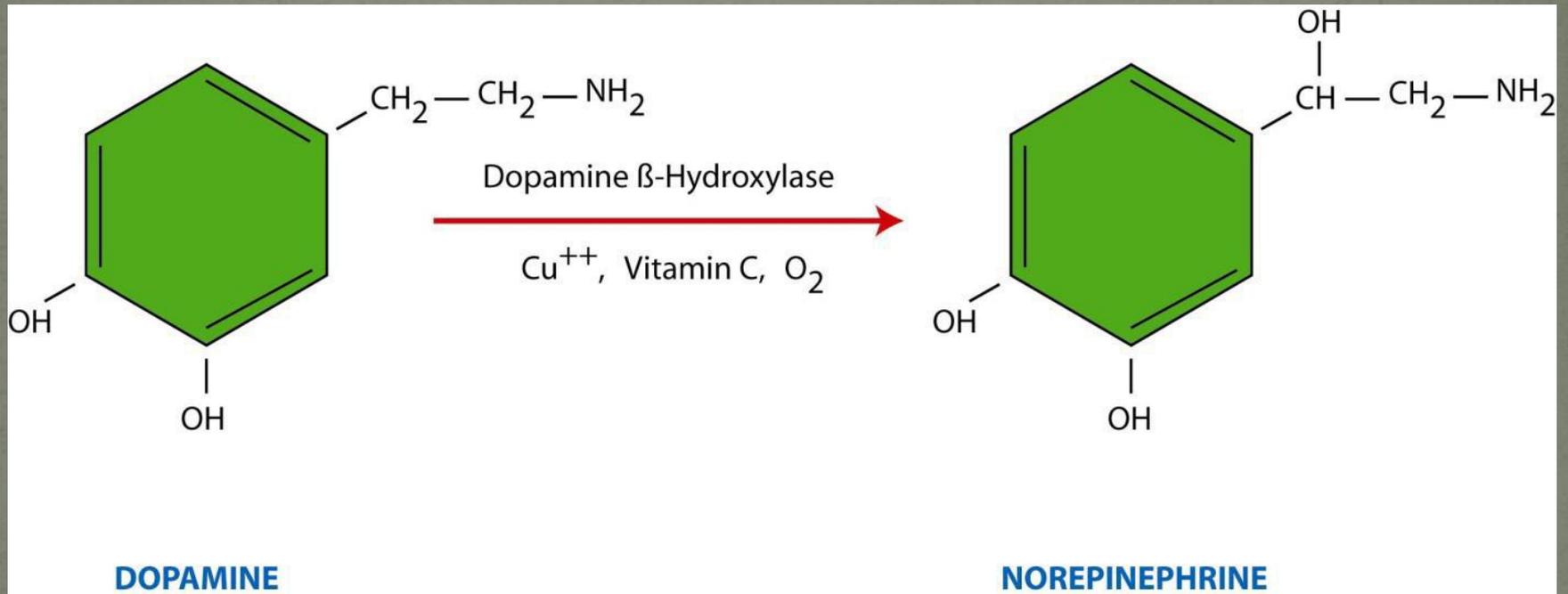
Address the stress;

- Underlying illness
- Diet
- Gut flora imbalances
- Intestinal yeast overgrowth
- Emotional stress
- Psychotherapy
- Lifestyle changes
- Exercise
- Mindfulness
- Learning to prioritize
- Develop coping skills

FREE COPPER OVERLOAD

- Essential trace element important in the synthesis of neurotransmitters, respiration, immune function, energy metabolism and growth.
- Pregnant women must produce more copper for angiogenesis (blood supply) of the fetus.
- Normally eliminate excess copper within 24 hrs after delivery.
- If there is a genetic inability to regulate FREE copper levels a serious copper overload can result.
- High FREE copper results in lower Dopamine (less calm) and higher Noradrenalin levels (fight or flight) implicated in paranoid schizophrenia, bipolar disorder, post- partum depression, ADHD, autism, and violent behaviour. (Walsh)
- SSRIs improve mood but worsen anxiety
- Xanax reduces anxiety but makes depression worse
- 85% came off psychiatric medications eventually with nutrient therapies (Walsh)

FREE COPPER OVERLOAD



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DEPRESSION



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CLINICAL STUDIES

Elevated serum copper levels in women with a history of post-partum depression

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Received 1 March 2006; accepted 16 October 2006

Abstract

Previous observations suggested that there may be an association between elevated serum copper (Cu) levels and post-partum depression (PPD). In this study, we examined Zn and Cu levels in women with completed pregnancies who had a history of PPD and compared them to women who did not have depression, and to women who reported having been depressed, but without a history of PPD. Cu levels were significantly higher in women having a history of PPD compared both to non-depressed women and to depressed women without a history of PPD. The mean serum Cu level of 78 women with a history of PPD was 131 ± 39 $\mu\text{g/dL}$ compared with 111 ± 25 $\mu\text{g/dL}$ in 148 women without such a history, and 106 ± 20 $\mu\text{g/dL}$ in non-depressed controls ($p < 0.001$). Zn levels did not differ across the three groups. Cu/Zn ratios were significantly higher in the PPD-history-positive group, due to the significant differences in Cu levels. Cu and Zn levels were not significantly different in depressed and non-depressed men, nor between non-depressed women and non-depressed men. Depressed women had higher Cu, but not Zn, levels compared with men. The nature of the association between elevated Cu values and PPD is, as yet, unknown; however Cu has roles in a variety of physiological systems that may be implicated in the development of PPD.

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Keywords: Copper; Depression; Post-partum depression; Zinc

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Reasons;

- Genetic inability to regulate copper; metallothionein and ceruloplasmin defects.
- High estrogen; ocp, pregnancy, puberty.
- Xeno-oestrogens; pesticides
- Multivitamins with copper
- Drinking tap water, from copper pipes
- Algae treatments for swimming pools
- High in certain foods such as chocolate, seafood, avocado, beans, nuts, lamb and organ meat.
- Zinc deficiency (competes with copper)
- Protein deficiency (makes ceruloplasmin to bind copper)

FREE COPPER OVERLOAD

- Mostly women
- Hormonal issues common
- Hot sweats
- Tinnitus
- Climacteric issues ; perimenopausal symptoms.
- React to OCP
- Oestrogen dominance; endometriosis, fibroids, excessive menstrual bleeding
- Post natal depression
- High anxiety and depression
- Moodiness
- Annoyed by tight clothing
- Prone to OA.
- Muscle and joint pain
- Headaches
- Brain fog
- Fibromyalgia
- Fatigue
- Cancer
- Men and boys ;
 - hyperactivity,
 - inattention,
 - impulsiveness,
 - anger or violence.

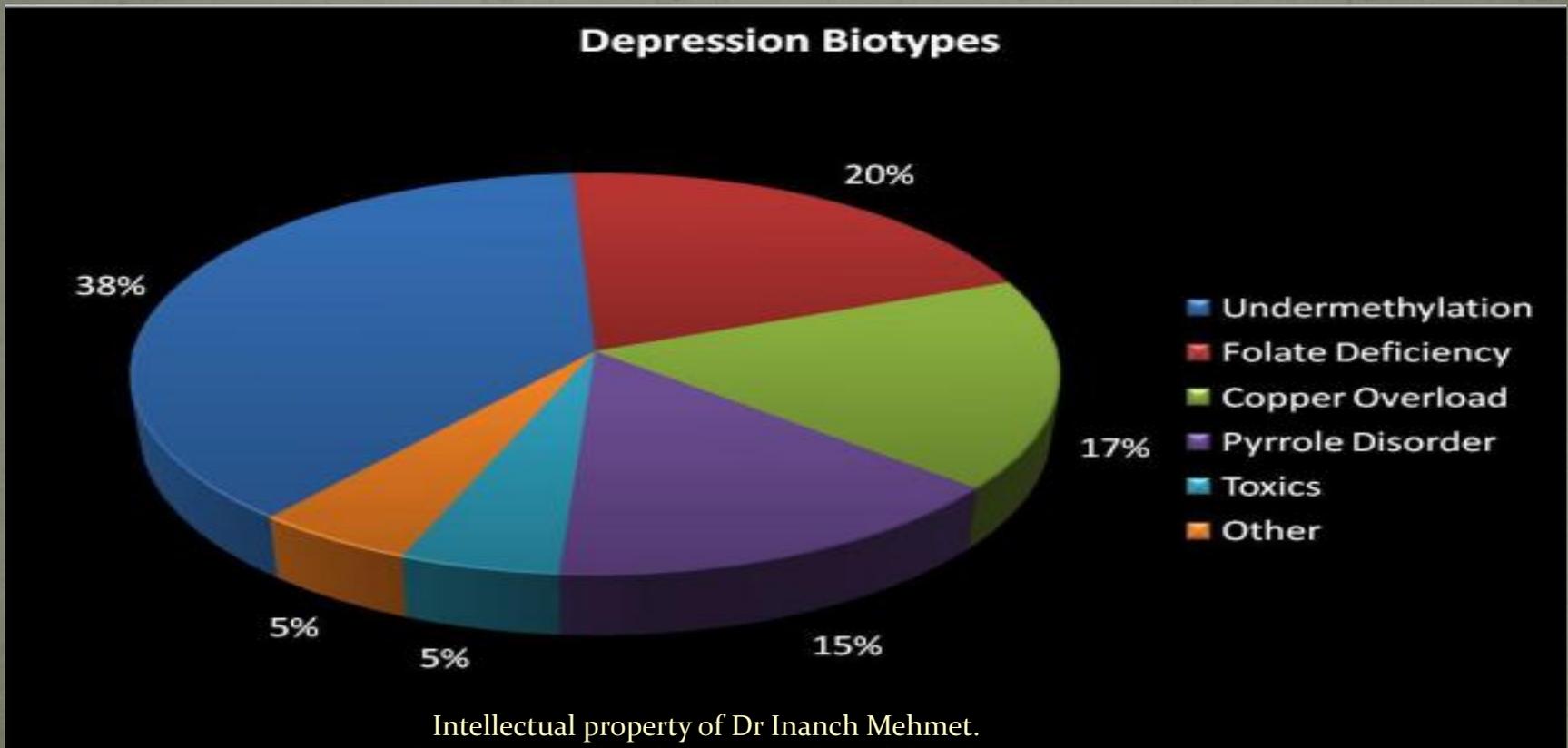
FREE COPPER OVERLOAD

NUTRIENTS

- Zinc; replace slowly can get copper dumping
- Manganese
- Selenium
- Molybdenum
- Omega 3
- MT promotor
- Avoid oestrogens
- Avoid copper sources
- Takes 1-2 months

DEPRESSION (Walsh)

- Walsh research institute; 300000 blood and urine tests for 2800 depressed patients;
- 70% of the general population exhibit normal dna methylation, 22% have histamine imbalance, and 8% are cerebral folate deficient.



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DEPRESSION

Toxic Metals;

- lead, mercury, cadmium, arsenic.
- Weaken BBB
- Alter neurotransmitters
- Destroy myelin
- Oxidative stress
- Reduce glutathione.

Other;

- Thyroid
- Fe deficiency

- **Separate Nutrient protocols for each biotype**
- **Biotypes can overlap leading to more severe conditions.**

DEPRESSION



Am J Psychiatry. 2012 Dec;169(12):1267-74. doi: 10.1176/appi.ajp.2012.11071114.

L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials.

Papakostas GI¹, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M.

Author information

Abstract

OBJECTIVE: The authors conducted two multicenter sequential parallel comparison design trials to investigate the effect of L-methylfolate augmentation in the treatment of major depressive disorder in patients who had a partial response or no response to selective serotonin reuptake inhibitors (SSRIs).

METHOD: In the first trial, 148 outpatients with SSRI-resistant major depressive disorder were enrolled in a 60-day study divided into two 30-day periods. Patients were randomly assigned, in a 2:3:3 ratio, to receive L-methylfolate for 60 days (7.5 mg/day for 30 days followed by 15 mg/day for 30 days), placebo for 30 days followed by L-methylfolate (7.5 mg/day) for 30 days, or placebo for 60 days. SSRI dosages were kept constant throughout the study. In the second trial, with 75 patients, the design was identical to the first, except that the L-methylfolate dosage was 15 mg/day during both 30-day periods.

RESULTS: In the first trial, no significant difference was observed in outcomes between the treatment groups. In the second trial, adjunctive L-methylfolate at 15 mg/day showed significantly greater efficacy compared with continued SSRI therapy plus placebo on both primary outcome measures (response rate and degree of change in depression symptom score) and two secondary outcome measures of symptom severity. The number needed to treat for response was approximately six in favor of adjunctive L-methylfolate at 15 mg/day. L-Methylfolate was well tolerated, with rates of adverse events no different from those reported with placebo.

CONCLUSIONS: Adjunctive L-methylfolate at 15 mg/day may constitute an effective, safe, and relatively well tolerated treatment strategy for patients with major depressive disorder who have a partial response or no response to SSRIs.

TRIAL REGISTRATION: ClinicalTrials.gov [NCT00321152](#) [NCT00955955](#).

Comment in

The evolving story of folate in depression and the therapeutic potential of L-methylfolate. [*Am J Psychiatry*. 2012]

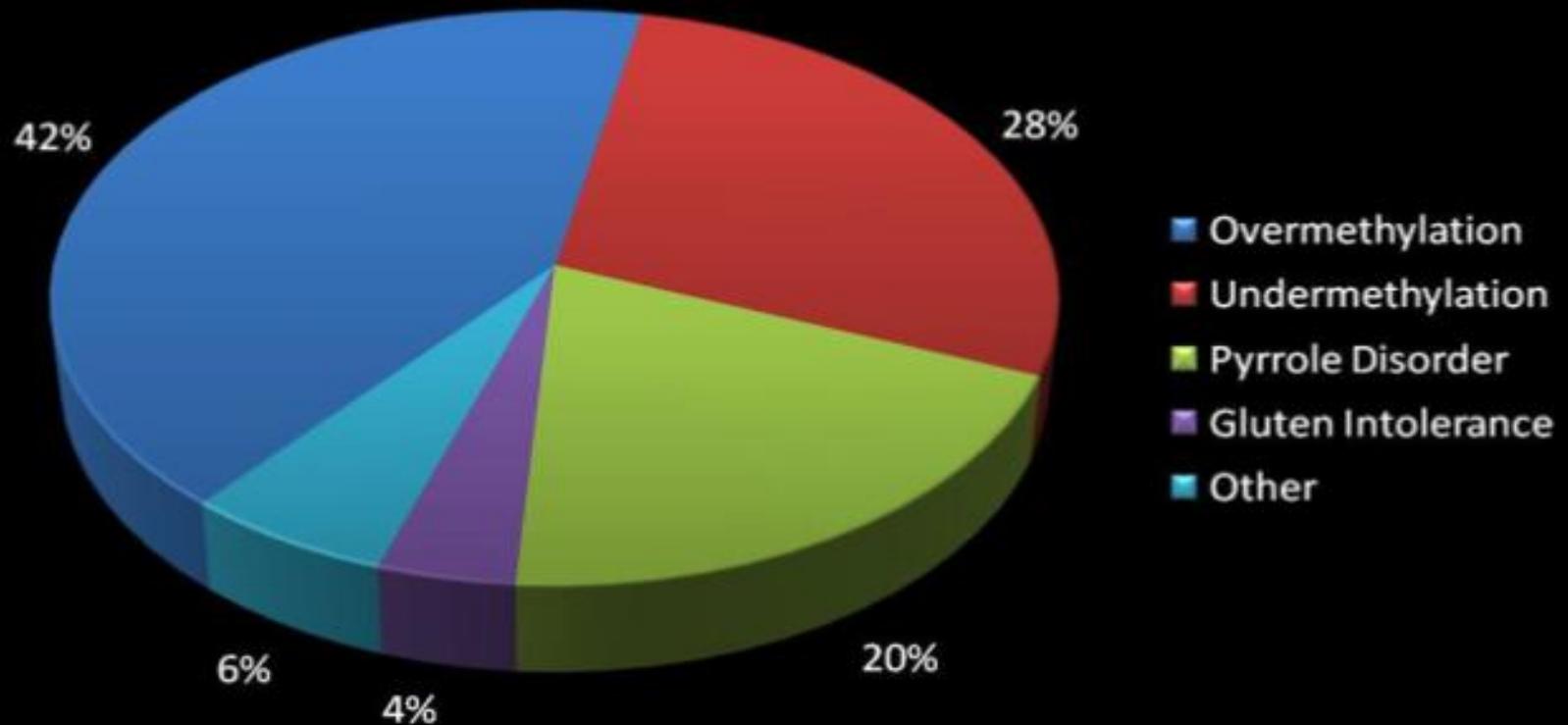
Methylfolate as adjunctive treatment in major depression. [*Am J Psychiatry*. 2013]

Higher-dose L-methylfolate may be an effective adjunctive therapy for adults with major depression who have had a partial response to SSRIs.

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SCHIZOPHRENIA (Walsh)

Schizophrenia Biotypes



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SCHIZOPHRENIA

Histamine imbalance

- Sudden breakdown
- Catatonic (shut down)
- Severe delusions (irrational beliefs or ideas)
- Get worse on benzodiazepines

Folate deficiency

- Warning signs <10 yrs old
- More physically active
- Hear voices
- Get worse on SSRIs

Oxidative stress

- Warning signs <10 yrs old
- Wild mood swings
- Great fears; delusions and auditory hallucinations
- Deteriorate under stress

CAN LIVE NORMAL LIVES AND GRADUALLY MINIMISE MEDICATIONS WITH THE AID OF APPROPRIATE NUTRITIONAL SUPPLEMENTATION.

Behavioural Disorders

Social and emotional environments

+

Bad brain biochemistry

- Walsh research institute collected 1.5 million samples off 10000 patients with behavioural disorders and 5600 with ADHD
- 94% of behavioural disorders had chemical imbalances
- 6% other; head injuries, epilepsy, O₂ deprivation at birth.
- 86% of ADHD had chemical imbalances

Behavioural Disorders

2004 open label study of behavioural disorders and ADHD (Walsh research institute)

- Copper overload 75.4% (high cu/zn)
- Folate deficiency 29.5%
- Histamine imbalance 37.7%
- Oxidative stress 32.9%
- Heavy Metal overload ; lead, cadmium 17.9%

Behavioural Disorders (Walsh)

Type of behaviour;

- **Intermittent explosive;** Copper overload+ oxidative stress (90%)
- **ODD;** Histamine imbalance
- **Antisocial personality disorder;** histamine imbalance/ oxidative stress/toxic metals/zinc deficient/low normal copper.
- **Conduct disorder;** histamine imbalance /oxidative stress
- **ADD;** primarily inattentive but intelligent; Folate deficiency/ zinc deficient/B12 deficient
- **Primarily impulsive and hyperactive;** Copper overload
- **ADHD;** Copper overload (68%), DNA Methylation disorders, Heavy metals, oxidative stress (need to test).

Behavioural Disorders

Micronutrient Therapy for Violent and Aggressive Male Youth: An Open-Label Trial

Jessica L. Hambly, MPharm (Hons),¹ Kelly Francis, MBBS, FRACGP,² Sohil Khan, PhD,^{1,3} Kristen S. Gibbons, PhD, AStat,³ William J. Walsh, PhD,⁴ Brett Lambert, MAppSc,⁵ Chris Testa, BPharm, BBus,⁶ and Alison Haywood, PhD^{1,3}

Abstract

Objectives: Pharmacotherapy for problematic aggressive and violent behavior disorders in male children and adolescents is associated with significant adverse events. Treatments with more acceptable risk–benefit ratios are critically needed. Micronutrient intervention will be investigated as an alternative to bridge the therapeutic gap in the management of these behaviors.

Methods: Males aged 4–14 who displayed ongoing violent and aggressive behaviors received micronutrient intervention containing alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), biotin, chromium, pyridoxal-5-phosphate (P5P), pyridoxine (vitamins B6), selenium, and zinc, in a 16-week open-label trial. Plasma zinc, plasma copper, copper/zinc ratio, and urinary hydroxyhemopyrroline-2-one (HPL) tests were conducted at baseline and endpoint. Participants were examined for changes in aggressive and violent behaviors measured using the Children’s Aggression Scale (CAS) and the Modified Overt Aggression Scale (MOAS), improvements in family functioning measured using the Family Functioning Style Scale, improvements in health-related quality of life (HRQoL) measured using the Pediatric Quality of Life Inventory (PedsQL) at baseline, 8 weeks, endpoint, and at 4–6-month follow-up.

Results: Thirty-two male children and adolescents met inclusion criteria. Thirty-one (mean 8.35 ± standard deviation 2.93 years) completed the study, with one participant lost to follow-up. Micronutrient therapy significantly improved parent-reported aggressive and violent behaviors measured using the CAS for all domains except the use of weapons ($p < 0.001$ to $p = 0.02$) with medium to large effect size (Cohen’s $d = 0.72$ – 1.43) and the MOAS ($p < 0.001$) with large effect size (Cohen’s $d = 1.26$). Parent-reported HRQoL ($p < 0.001$; Cohen’s $d = -1.69$) and family functioning ($p = 0.03$; Cohen’s $d = -0.41$) also significantly improved.

Conclusion: Micronutrient therapy appeared well tolerated, with a favorable side effect profile. It appeared effective in the reduction of parent-reported aggressive and violent behaviors, and showed improvement in family functioning and HRQoL in male youth after 16 weeks. Further research in the form of a double-blinded, randomized controlled trial is required to verify these initial positive observations.

AUTISM

- Poor connectivity between different brain areas (Dziobek et al 2010)
- Immature undeveloped brain cells and synapse connections (Kemper et al 2005)
- Oxidative damage to the brain fats (McGinnis et al 2008)
- Rapid acceleration of brain size in year 1 (Couchesne et al 2003)
- Brain immaturity occurs in areas with little protection from the blood brain barrier
- NET result brain can't connect which is important for speech, learning and socialisation.
- Cerebellum affected; odd movements
- Amygdala affected; Poor social skills
- Hippocampus affected; Poor speech
- Brain cells and synapses develop rapidly until age 4 then slow down however continue to develop throughout life.
- Inflamed brain ; can regress after an insult. (Vargas et al 2005)
- Early intervention is CRUCIAL.

AUTISM

- Genetic component ; 60-90% identical twins (however heritable DNA mutations take centuries to develop)
- However incidence 3/10000 when first described in 1943. Now 1/100. Epidemic
- Epigenetic reasons; severe environmental insults before the age of 3 and possibly in utero affects dna methylation (gene expression).
- What's changed?
 - Food supply (processed, pesticides)
 - Water supply
 - Toxin exposures (including heavy metals)
 - In utero family stress .
 - Hotly debated.

AUTISM

TYPICAL FINDINGS (Walsh 50000 assays)

- Histamine imbalance 90% (however folate important here)
- Copper overload
- Toxic metals (mercury and lead)
- Oxidative stress (99%)
- Zinc deficiency
- B6 deficiency
- Vit A deficiency
- Magnesium deficiency
- Selenium deficiency
- Glutathione deficiency
- Food sensitivities ; Gluten and Dairy can't break it down and crosses the gut and BBB causing inflammation (85% reported major benefits on GFDF)
- Gut abnormalities including dysbiosis, yeast and leaky gut.

ALHEIMER'S DISEASE

RISK FACTORS

- Genetic APOE4 protein carrier 10-30x incr risk (Saunders et al 1993)
- Age > 70 (katzman et al 2000)
- Head injury (plassman et al 2000)
- Education level ; higher education means less risk (Roe et al 2008)
- Mental activity; stimulating brain activity reduces risk, watching TV increases risk (Wilson et al 2002)
- Physical activity/ reduced obesity; improves risk (Larson 2008)
- Alcohol use; red wine protects 1-2 /day. Any more increases risk.(Copenhagen heart study)
- Type 2 diabetics
- Autoimmune diseases

ALHEIMER'S DISEASE

- TOXIC METALS; Aluminium and mercury (amalgams) cause oxidative stress and cross BBB.(Cornett et al 1998)
- OXIDATIVE STRESS;
 - Vit A, C, E deficiencies (not eating) (Sofrizzi et al 2003)
 - Studies on vit e, coq10, selenium, glutathione and alpha lipoic acid show increased life span not reversal.(Lee HP et al 2010)
- HOMOCYSTEINE elevated; Folic acid and B12 deficiencies (Shesadri et al 2002)
- Chronic Inflammation; being studied
- Free Copper overload= free radicals(Bush et al 2010)

ALHEIMER'S DISEASE

Metallothionein protocol (Walsh)

- MT protein can bind and regulate metals
- AD patients have severe MT deficiency (YU W H et al 2001 autopsy study)
- MT protects the BBB from metals
- Regulates copper
- Powerful antioxidant
- 100 patients did a MT protocol; 70% reported partial return of memory and stable cognitive function (Walsh research).
- No RCT .

TESTING

HISTAMINE;

- Range 0.35-0.6 (>0.6 histamine imbalance, <0.35 cerebral folate def WALSH research)

SAM/SAH

- Functional labs; methylation index. GOOD FOLLOW UP TOOL

MTHFR SNPS;

- May have low DNA methylation if you have a MTHFR SNP however there are other SNPs that reduce methylation and others that tend to increase methylation, a patient's overall methyl status depends on the overall combined impact of these counterbalancing SNPs.
- May cause high homocysteine.
- MTHFR more important in AUTISM and ALZHEIMER'S
- Can also measure other SNPs (functional labs)

TESTING

HOMOCYSTEINE:

- Must be methylated to methionine
- Elevated when b12, folate and b6 needed
- Marker of oxidative stress; less glutathione
- More relevant in Alzheimer's and cardiovascular disease
- High risk > 9

PLASMA B12/FOLATE

- Elevated/ Normal Folate and B12 in blood does not necessarily mean good cellular or tissue levels.
- Elevated B12 may mean low MTHF
- MTHFR mutations may show as low plasma folate levels
- **Formiminoglutamate (FIGLU)** is a functional marker of folate need

ORGANIC ACIDS

- **Methylmalonate (MMA)** is a functional marker of vitamin B12 need
- ## ORGANIC ACIDS

TESTING

URINARY HYDROXYHEMOPYRROLINE-2-1 (KRYPTOPYRROLES)

- Urine sample collected at specific labs in a specific way (NOT NATA ACCREDITED YET)
- Normal <10 mcgm/dl
- Borderline 10-15 mcgm/dl
- High > 15 mcgm/dl
- Walsh data

PLASMA ZINC

- Low <11.5 mcmol/L
- Low normal 11.5-14 mcmol/L
- Optimal 14- 20 mcmol/L
- High normal 20-23 mcmol/L
- High >23 mcmol/L

TESTING

SERUM COPPER

- Low <10 $\mu\text{mol/L}$
- Low normal 10- 12.5 $\mu\text{mol/L}$
- Optimal; 12.5- 17.5 $\mu\text{mol/L}$
- High Normal; 17.5-20 $\mu\text{mol/L}$
- High; >20 $\mu\text{mol/L}$

CERULOPLASMIN

- measured to calculate free copper (5-25%)
- Note ceruloplasmin and copper may rise to fight infections

Cu/ Zn ; 1-1.2

CASE HISTORY

- 36 WOMAN
- Anxiety
- Depression
- Panic attacks
- Fatigue
- Moods swings
- Foggy brain
- Heart palpitations
- 2 kids anxiety worse after 2nd child
- Sensitive to light and noise

CASE HISTORY

- Sees psychiatrist ; lovan(ssri) and anafranil(TCA)

Lovan making her worse ,

- More anxiety,
- More fatigue,
- Suicidal thoughts
- Thoughts of harming children (intrusive)
- Low libido

Anafranil causing side effects;

- Constipation
- Dry mouth
- Lethargy

CASE HISTORY

Lab results;

- Histamine 0.2 (cerebral folate deficiency)
- MTHFR C677T
HETEROZYGOUS
- Homocysteine 7.8
- Copper 13 Free copper 17%
- Zinc 10.5 (low normal)
- KRYPTOPYRROLES; 40
- Ferritin 14 (low iron stores)
- B12 656 pmol/L
- Methylmalonic acid (b12 marker) high
- Vit D 62
- TSH 1.02

Management;

- Compounded vitamin;
Vit C/ B6/ P5P/ Zinc/ Mg
Folic acid
B3
B12 (cyanocobalamin)
Biotin
Evening Primrose Oil
- Continue counselling
- Wean lovan

CASE HISTORY

6 week follow up

- Off lovan still on anafranil
- Focus much improved
- Fatigue better
- Intrusive thoughts better
- Best she has felt in a long time
- Husband commented she is a new person
- GP said it was a placebo (same GP that said her Iron was normal)
- Psychiatrist laughed at her .(Found her a new integrative psychiatrist to see if she can wean anafranil)
- Decided to give her an Iron infusion at this point.

IN SUMMARY

- Good diet ; protein, folate
- Good gut function and digestion
- Correct nutritional deficiencies; iron, B12
- Improve sleep
- Reduce stress (cortisol)
- Exercise
- Counselling
- Correct methylation/ copper imbalance/ oxidative stress.
Will antidepressants help?
- Correct hormonal imbalances
- Improve thyroid and adrenal function
- Eliminate heavy metals

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