

# Biopterin:

## New Findings (awesome ones)

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Relationship with commercial interests - None

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A decorative graphic of a DNA double helix is positioned at the top right of the slide. It consists of two parallel strands made of small circles, with one strand colored blue and the other green.

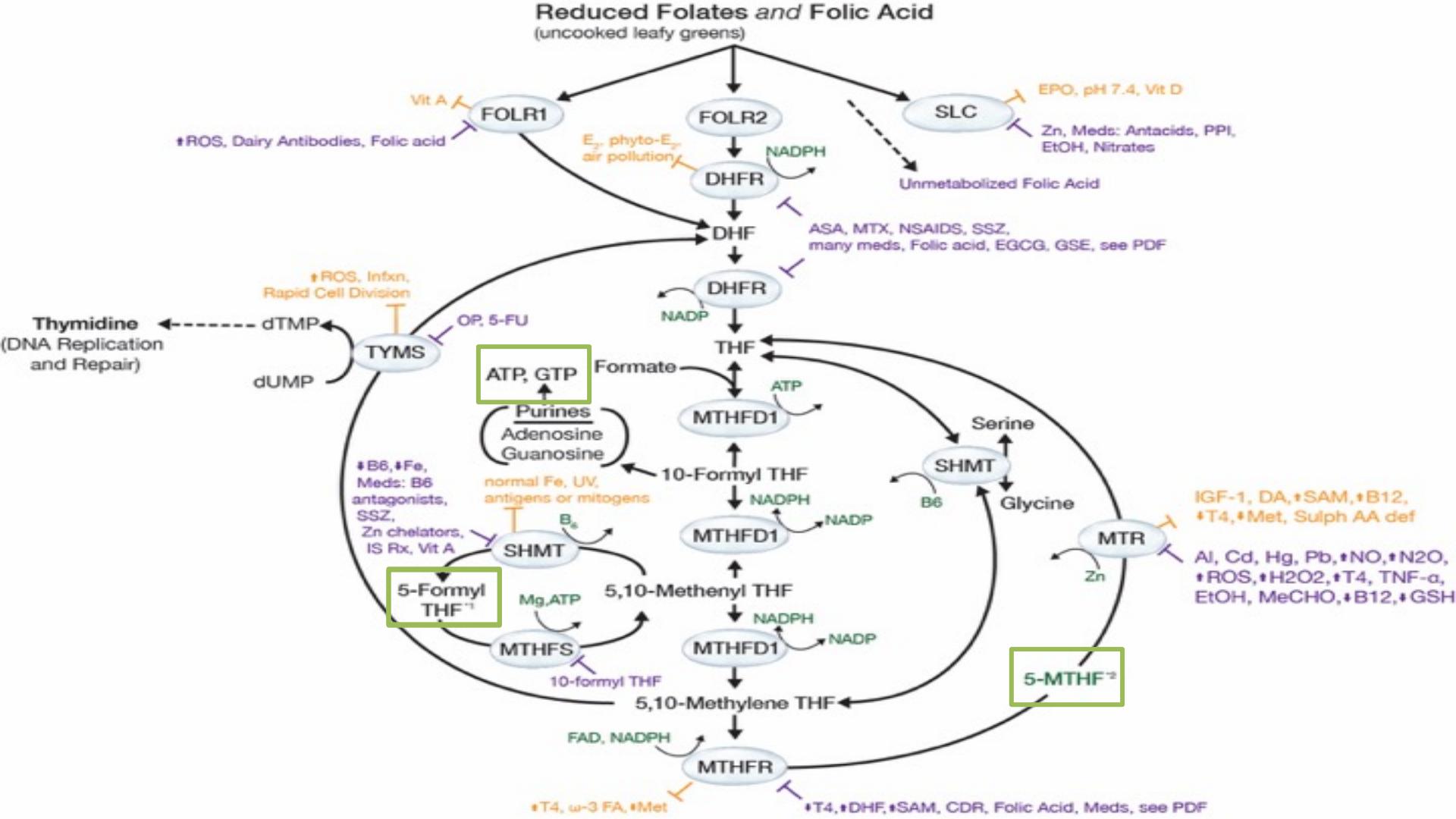
## **What is GTP?**

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## How is GTP equivalent to ATP?

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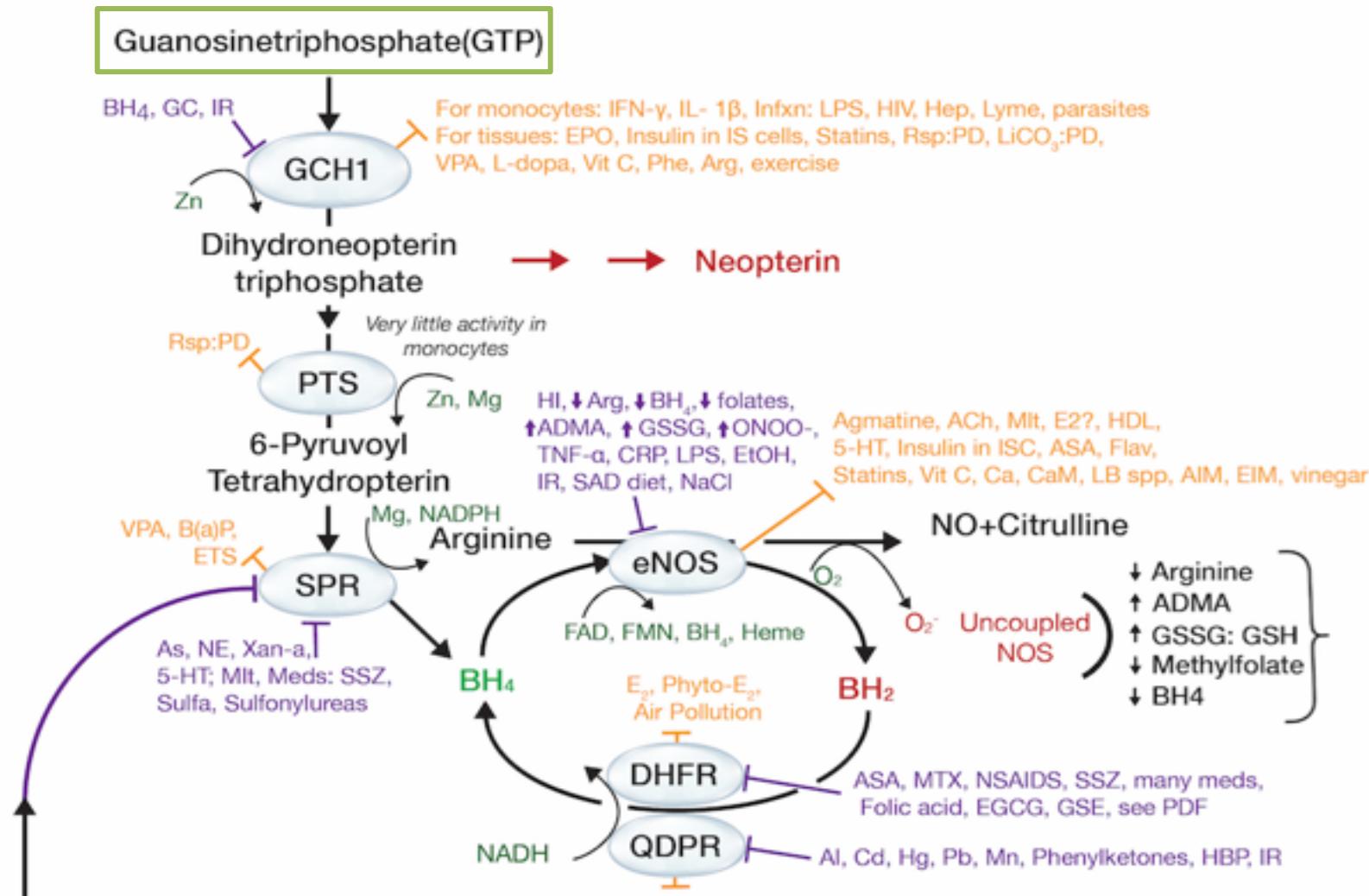
A molecule of GTP has an amount of energy built into its triphosphate group which is equivalent to the amount of energy built into the triphosphate group of a molecule of ATP. Those molecules have an equivalent amount of energy, but they are not equivalent molecules.

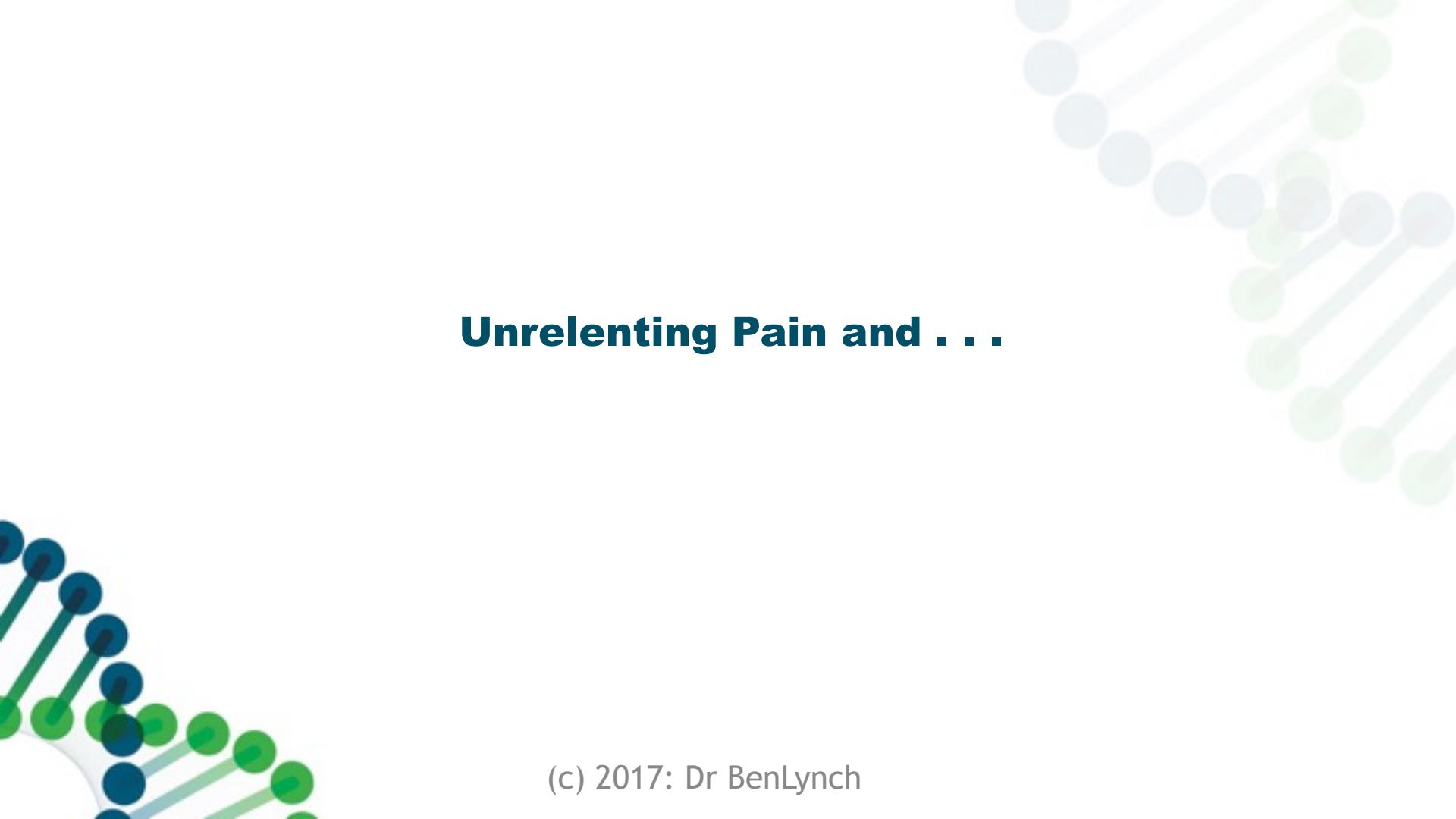


A decorative graphic of a DNA double helix is positioned at the top right of the slide. It consists of two parallel strands made of small circles, with one strand colored blue and the other green, representing the A-T and G-C base pairs respectively.

## Why does GTP matter?

# BH<sub>4</sub> Synthesis





## **Unrelenting Pain and . . .**

# Analgesia by inhibiting tetrahydrobiopterin synthesis.

Costigan M<sup>1</sup>, Latremoliere A, Woolf CJ.

## Author information

## Folate Side Effects?

### Abstract

Physiological control of the co-factor tetrahydrobiopterin (BH4) is tight in normal circumstances but levels increase pathologically in the injured somatosensory system. BH4 is an essential co-factor in the production of serotonin, dopamine, epinephrine, norepinephrine and nitric oxide. Excess BH4 levels cause pain, likely through excess production of one or more of these neurotransmitters or signaling molecules. The rate limiting step for BH4 production is GTP Cyclohydrolase 1 (GCH1). A human GCH1 gene haplotype exists that leads to less GCH1 transcription, translation, and therefore enzyme activity, following cellular stress. Carriers of this haplotype produce less BH4 and therefore feel less pain, especially following nerve injury where BH4 production is pathologically augmented. Sulfasalazine (SSZ) an FDA approved anti-inflammatory agent of unknown mechanism of action, has recently been shown to be a sepiapterin reductase (SPR) inhibitor. SPR is part of the BH4 synthesis cascade and is also upregulated by nerve injury. Inhibiting SPR will reduce BH4 levels and therefore should act as an analgesic. We propose SSZ as a novel anti-neuropathic pain medicine.



# GCH1, BH4 and pain.

Latretnoliere A<sup>1</sup>, Costigan M.

## Author information

### Abstract

Understanding and consequently treating neuropathic pain effectively is a challenge for modern medicine, as unlike inflammation, which can be controlled relatively well, chronic pain due to nerve injury is refractory to most current therapeutics. Here we define a target pathway for a new class of analgesics, tetrahydrobiopterin (BH4) synthesis and metabolism. BH4 is an essential co-factor in the synthesis of serotonin, dopamine, epinephrine, norepinephrine and nitric oxide and as a result, its availability influences many systems, including neurons. Following peripheral nerve damage, levels of BH4 are dramatically increased in sensory neurons, consequently this has a profound effect on the physiology of these cells, causing increased activity and pain hypersensitivity. These changes are principally due to the upregulation of the rate limiting enzyme for BH4 synthesis GTP Cyclohydrolase 1 (GCH1). A GCH1 pain-protective haplotype which decreases pain levels in a variety of settings, by reducing the levels of endogenous activation of this enzyme, has been characterized in humans. Here we define the control of BH4 homeostasis and discuss the consequences of large perturbations within this system, both negatively via genetic mutations and after pathological increases in the production of this cofactor that result in chronic pain. We explain the nature of the GCH1 reduced-function haplotype and set out the potential for a 'BH4 blocking' drug as a novel analgesic.

Folate does this to me:  
(select multiple options as needed.  
Add new ones if needed)

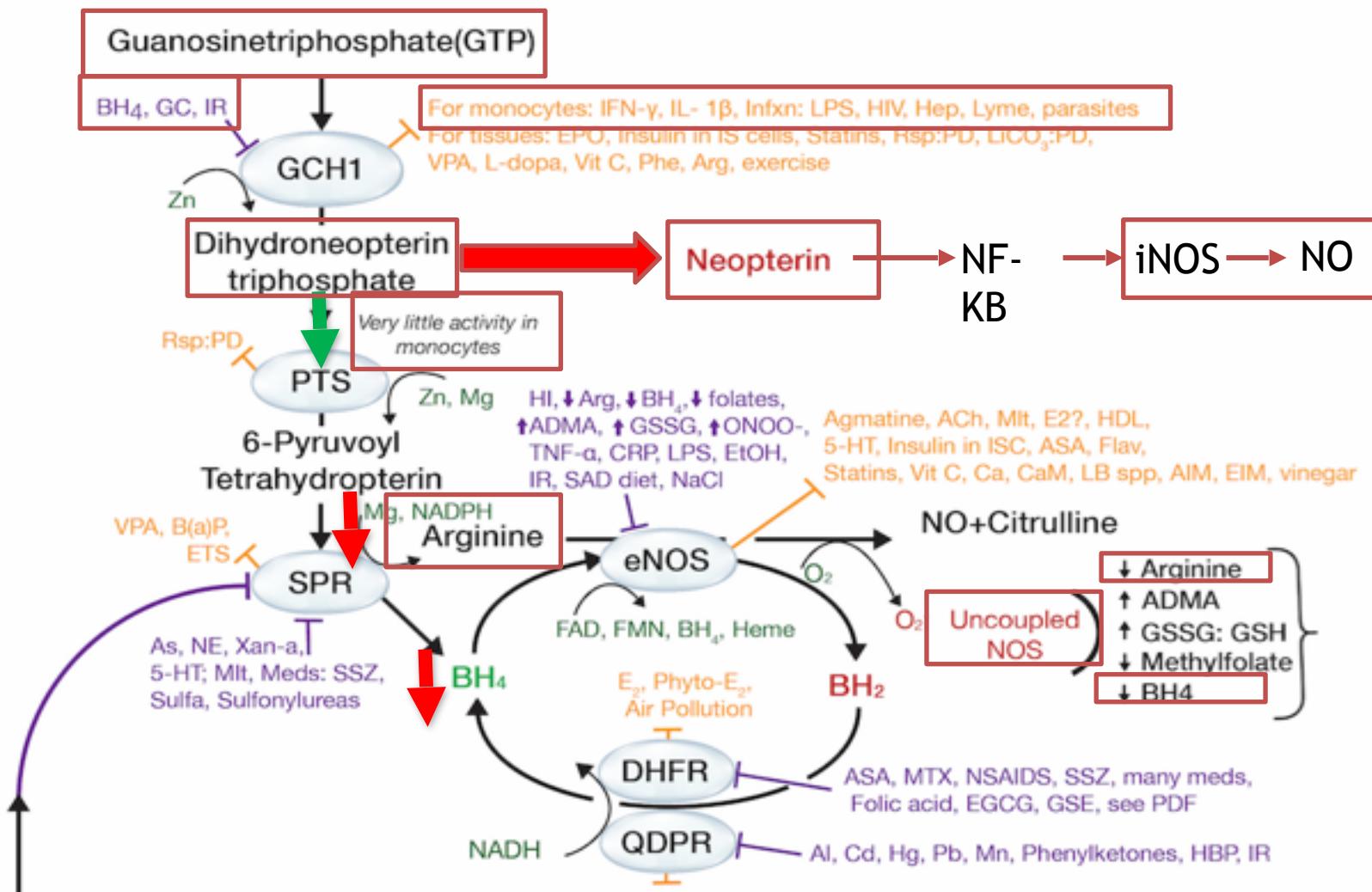
- Anxious
- Irritable
- Insomnia
- Depressed
- Pain
- Angry
- Nothing
- Headache
- Increased ability to think
- Unsure
- Heart palpitations/ tachycardia
- Happy



## **Are Infections Important to Spot and Treat?**

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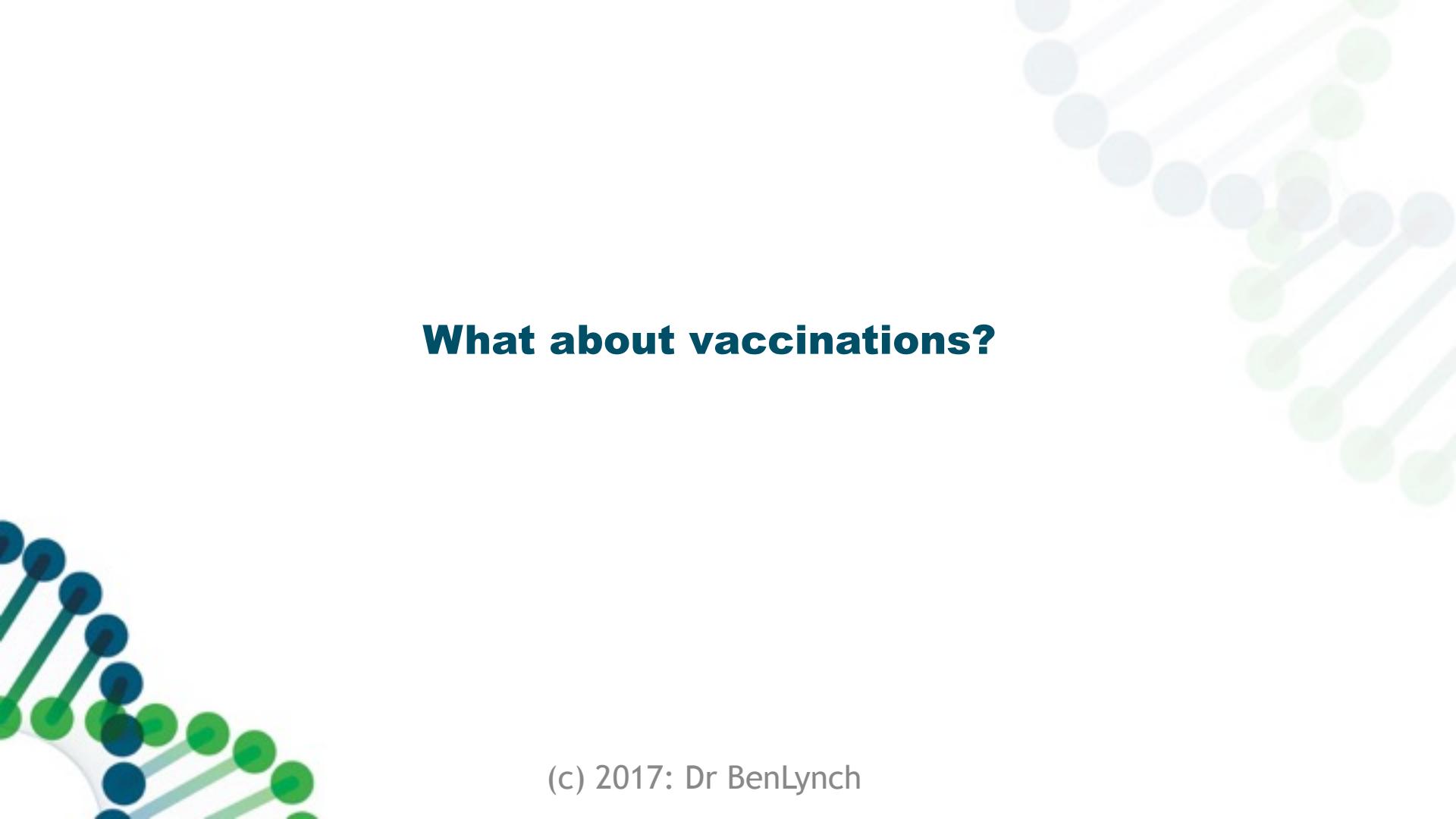
# BH<sub>4</sub> Synthesis



# **Measuring Neopterin Useful Clinically?**

Neopterin is produced by activated monocytes, macrophages, and dendritic cells upon stimulation by interferon gamma produced by T-lymphocytes. Quantification of neopterin in body fluids has been achieved by standard high-performance liquid chromatography, radioimmunoassays, and enzyme-linked immunosorbent assays. Neopterin levels predict HIV-related mortality more efficiently than clinical manifestations. Successful highly active antiretroviral therapy is associated with a decrease in neopterin levels. Elevated neopterin levels were associated with hepatitis by hepatitis A, B, and C viruses. Serum neopterin levels were found to be a predictor of response to treatment of chronic HCV infection with pegylated interferon combined with ribavirin. Neopterin levels of patients with pulmonary tuberculosis were found to be higher in patients with more extensive radiological changes. Elimination of blood donors with elevated neopterin levels to reduce risk of transmission of infections with known and unknown viral pathogens has been undertaken. Neopterin measurement is hereby more cost effective but less sensitive than screening using polymerase chain reaction based assays. In conclusion neopterin is a nonspecific marker of activated T-helper cell 1 dominated immune response. It may be a useful marker for monitoring of infectious disease activity during treatment and for more accurate estimation of extent of disease and prognosis.



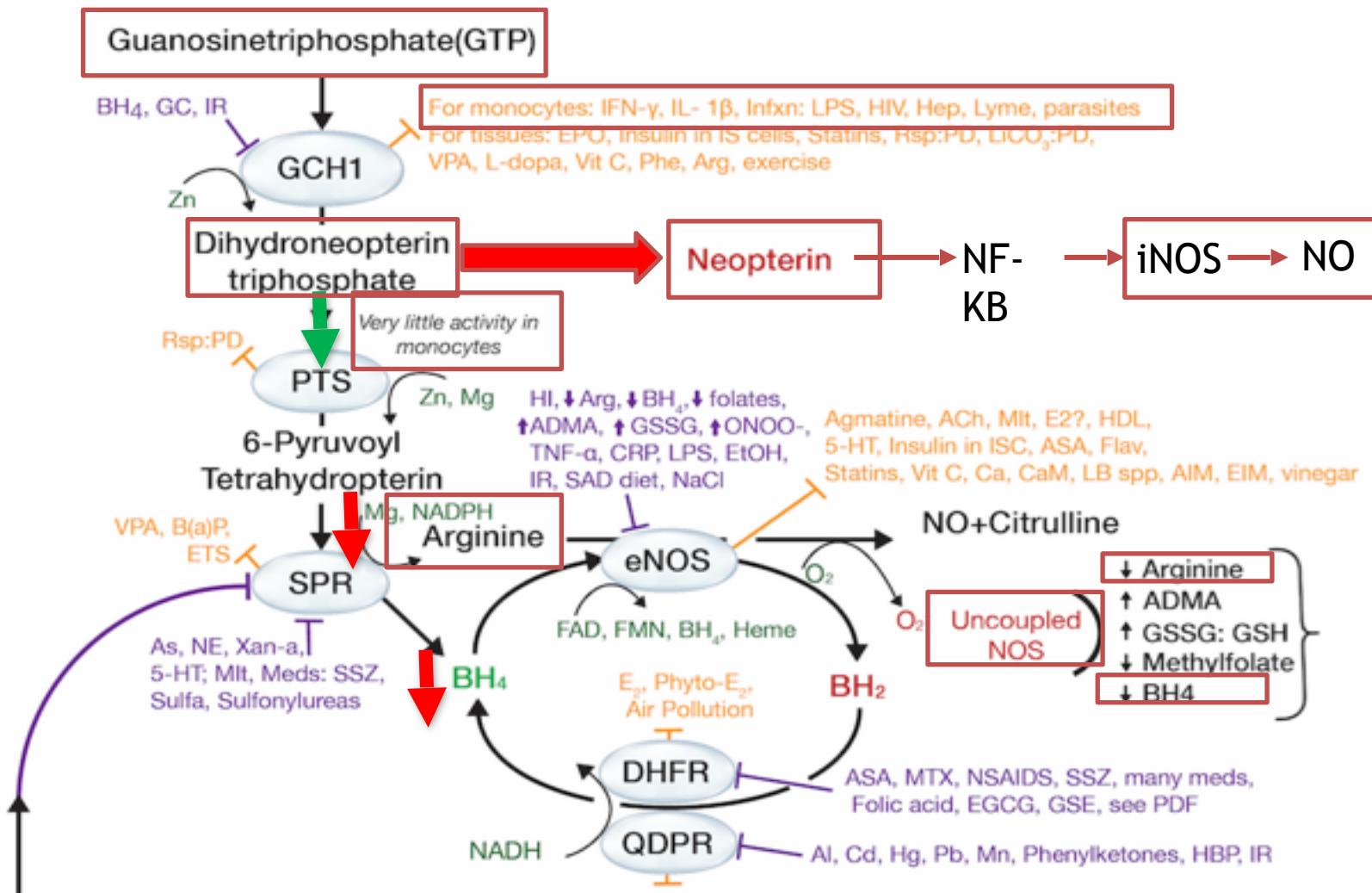


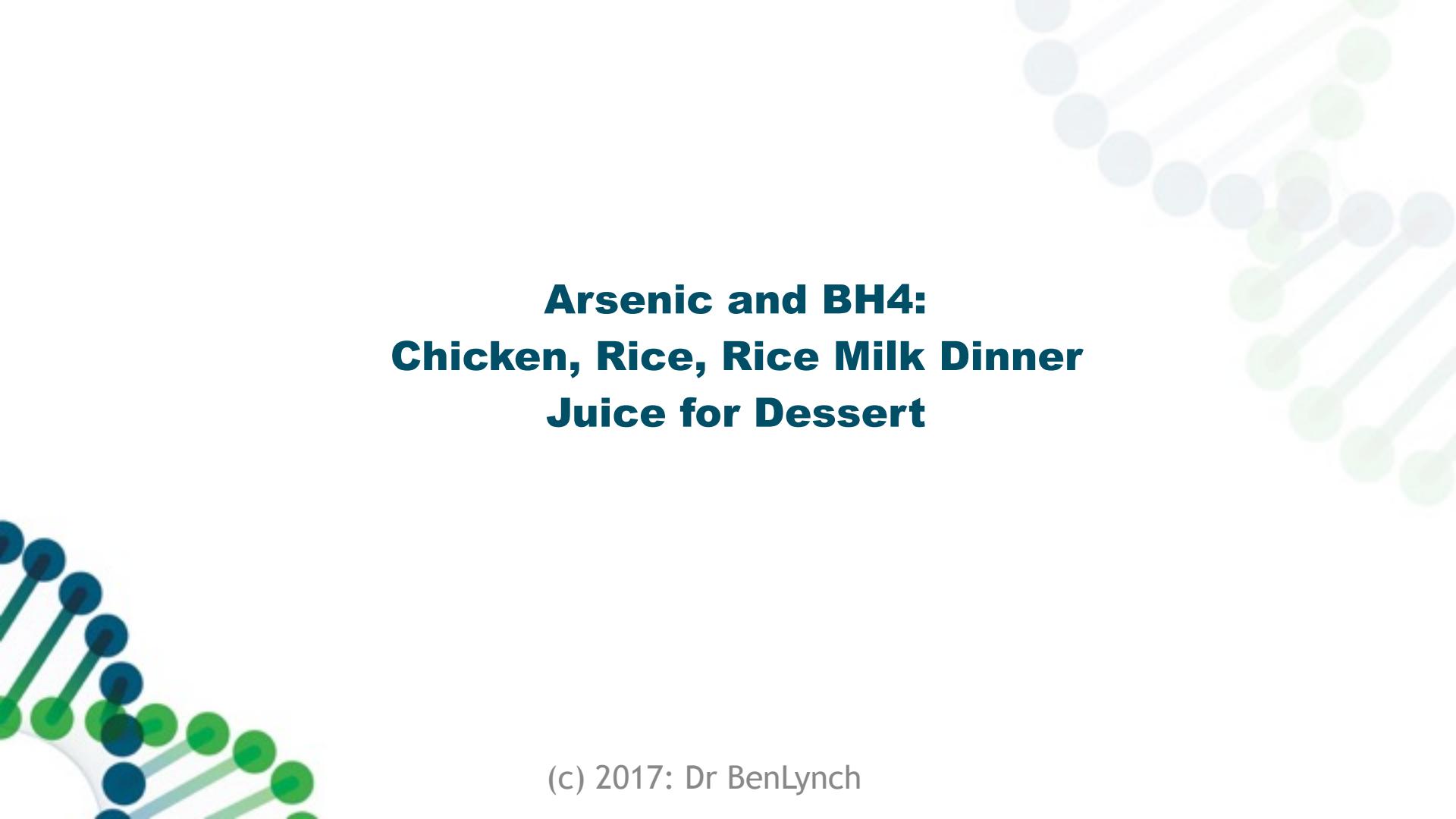
## **What about vaccinations?**



Immunisation with live viruses, for example, measles, mumps and rubella and virus vaccine, resulted in a significant increase of neopterin independent of presence of any symptoms. In measles vaccination neopterin levels were observed to rise at a median of 5 days after vaccination about 7 days before the appearance of antibodies [13]. These investigations point to a future application of measurements neopterin as a correlate of a successful vaccination. Neopterin should be investigated as a marker to evaluate protective efficacy of vaccines stimulating cell mediated immunity against mycobacterial, parasitic, or viral diseases. The magnitude of the elicited neopterin levels could be put into relationship to incidence of the disease immunised against the population of immunised children.

## BH<sub>4</sub> Synthesis



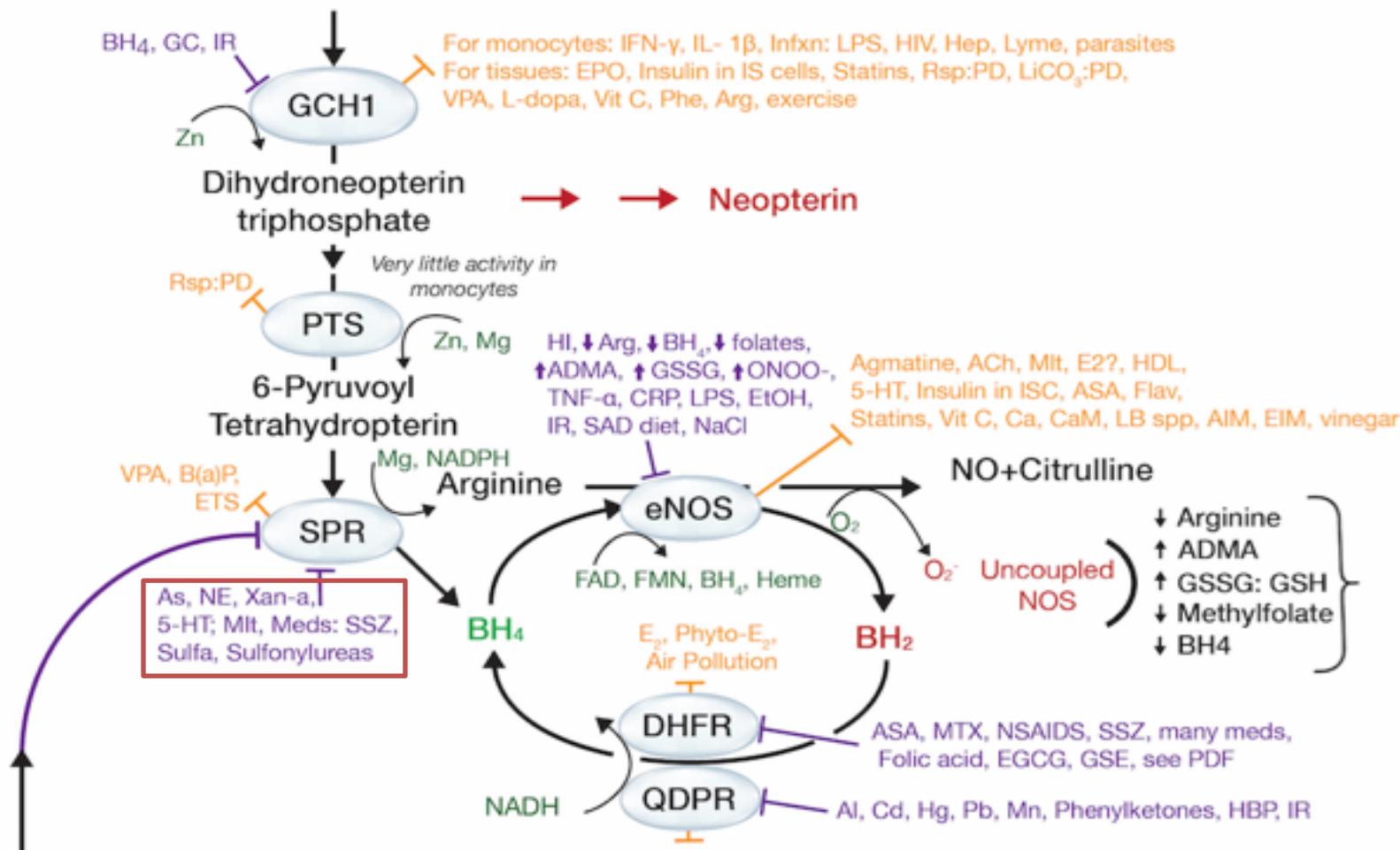


# **Arsenic and BH4: Chicken, Rice, Rice Milk Dinner Juice for Dessert**

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# $\text{BH}_4$ Synthesis

## Guanosinetriphosphate(GTP)





## **Folic acid and NSAIDs are Fine, right?**

## Critical role for tetrahydrobiopterin recycling by dihydrofolate reductase in regulation of endothelial nitric-oxide synthase coupling: relative importance of the de novo biopterin synthesis versus salvage pathways.

Crabtree MJ<sup>1</sup>, Tatham AL, Hale AB, Alp NJ, Channon KM.

### Author information

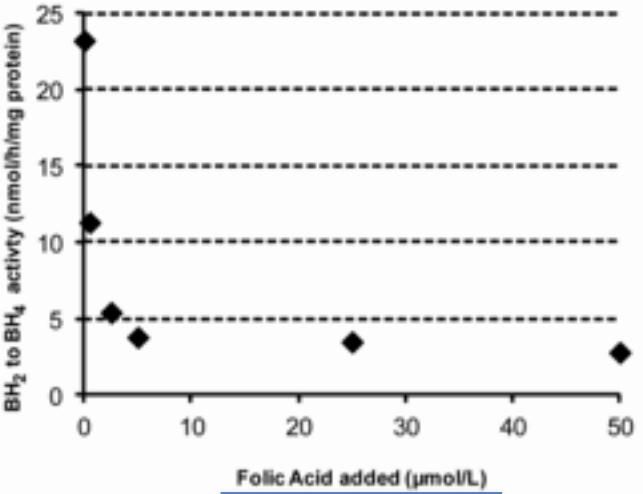
#### Abstract

Tetrahydrobiopterin (BH4) is a required cofactor for the synthesis of nitric oxide by endothelial nitric-oxide synthase (eNOS), and BH4 bioavailability within the endothelium is a critical factor in regulating the balance between NO and superoxide production by eNOS (eNOS coupling). BH4 levels are determined by the activity of GTP cyclohydrolase I (GTPCH), the rate-limiting enzyme in de novo BH4 biosynthesis. However, BH4 levels may also be influenced by oxidation, forming 7,8-dihydrobiopterin (BH2), which promotes eNOS uncoupling. Conversely, dihydrofolate reductase (DHFR) can regenerate BH4 from BH2, but the functional importance of DHFR in maintaining eNOS coupling remains unclear. We investigated the role of DHFR in regulating BH4 versus BH2 levels in endothelial cells and in cell lines expressing eNOS combined with tet-regulated GTPCH expression in order to compare the effects of low or high levels of de novo BH4 biosynthesis. Pharmacological inhibition of DHFR activity by methotrexate or genetic knockdown of DHFR protein by RNA interference reduced intracellular BH4 and increased BH2 levels resulting in enzymatic uncoupling of eNOS, as indicated by increased eNOS-dependent superoxide but reduced NO production. In contrast to the decreased BH4:BH2 ratio induced by DHFR knockdown, GTPCH knockdown greatly reduced total biopterin levels but with no change in BH4:BH2 ratio. In cells expressing eNOS with low biopterin levels, DHFR inhibition or knockdown further diminished the BH4:BH2 ratio and exacerbated eNOS uncoupling. Taken together, these data reveal a key role for DHFR in eNOS coupling by maintaining the BH4:BH2 ratio, particularly in conditions of low total biopterin availability.



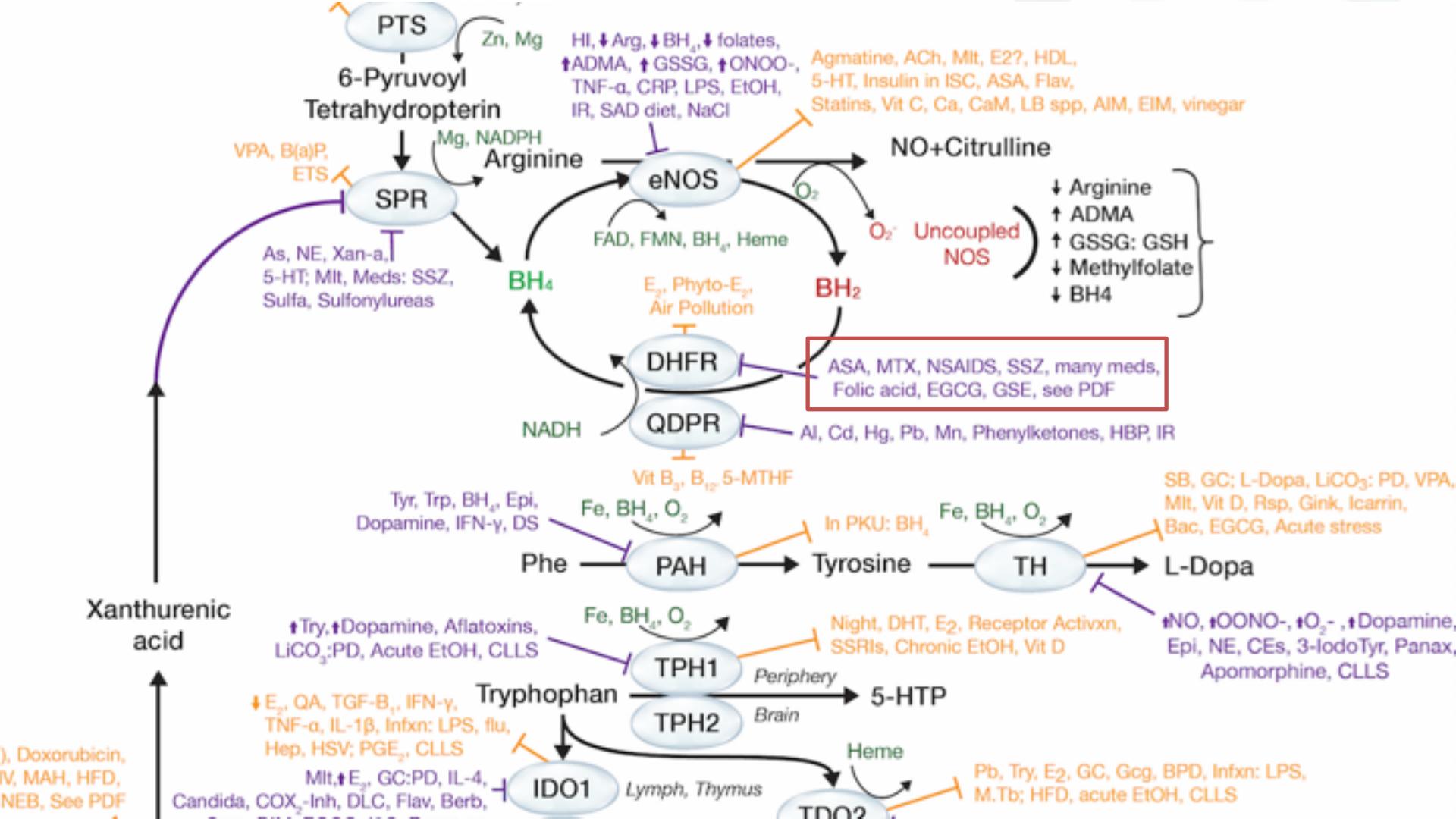
#### Alterations in BH<sub>2</sub> conversion to BH<sub>4</sub> due to FA

The addition of FA to lymphoblast extracts inhibited the conversion of BH<sub>2</sub> to BH<sub>4</sub> considerably. As is shown in Figure 4, addition of a 100 fold lower amount of FA to the assay mixture in comparison to BH<sub>2</sub> (concentration in the assay mixture is 250  $\mu$ mol/L) already halves the amount of BH<sub>2</sub> that is converted to BH<sub>4</sub>.



**Figure 4.** The inhibition of the conversion of BH<sub>2</sub> to BH<sub>4</sub> by folic acid in lymphoblast extracts.

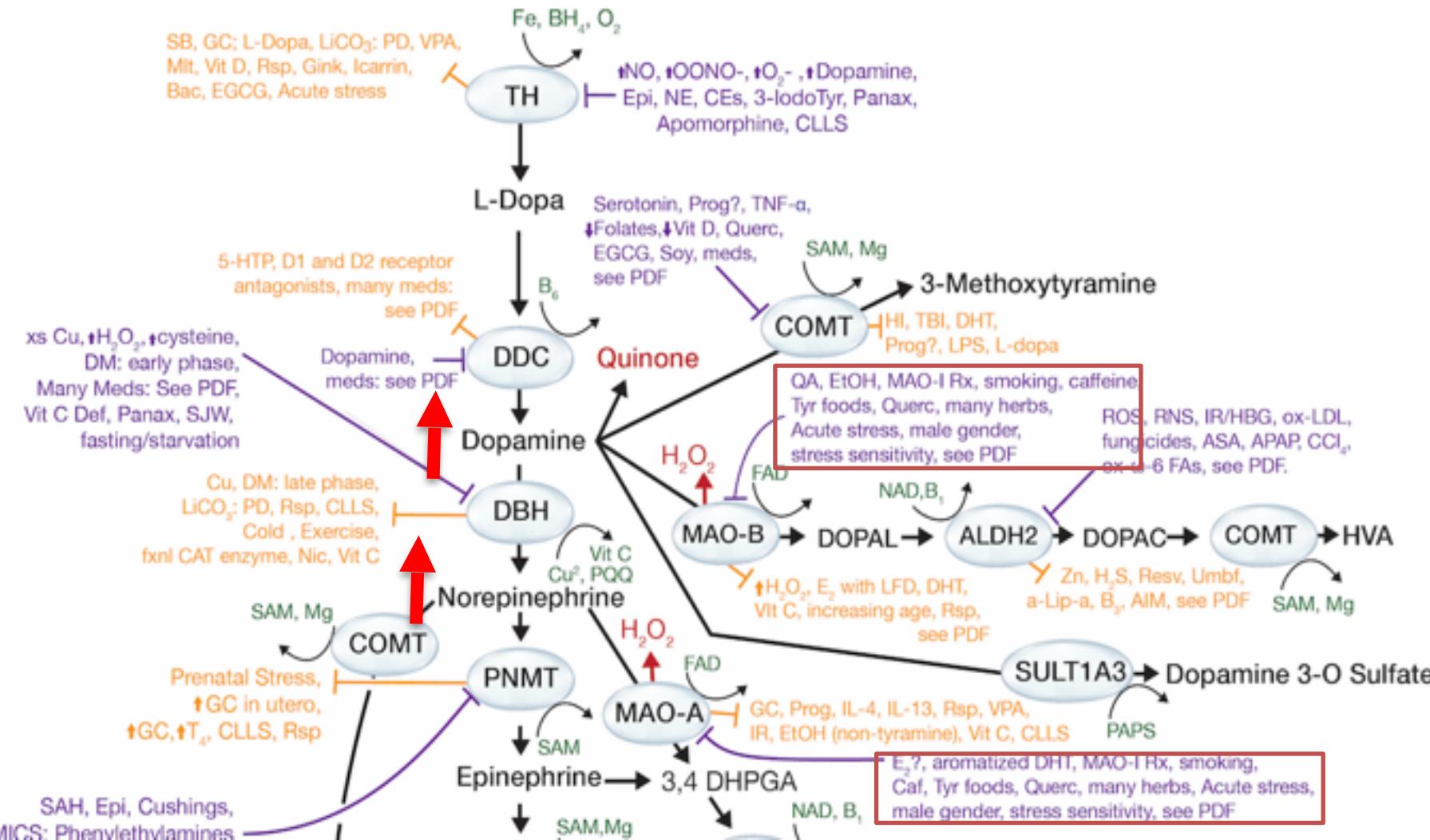
Lymphoblast lysates were pre-incubated for 5 min with different amounts of FA prior to performing the enzyme assay. BH<sub>2</sub> concentration used was



A decorative graphic of a DNA double helix is positioned at the top right of the slide. It consists of two parallel strands made of vertical bars of varying shades of blue and green, with circular nodes at the junctions where the bars cross.

## **Mad Dad Annoyed Boy**

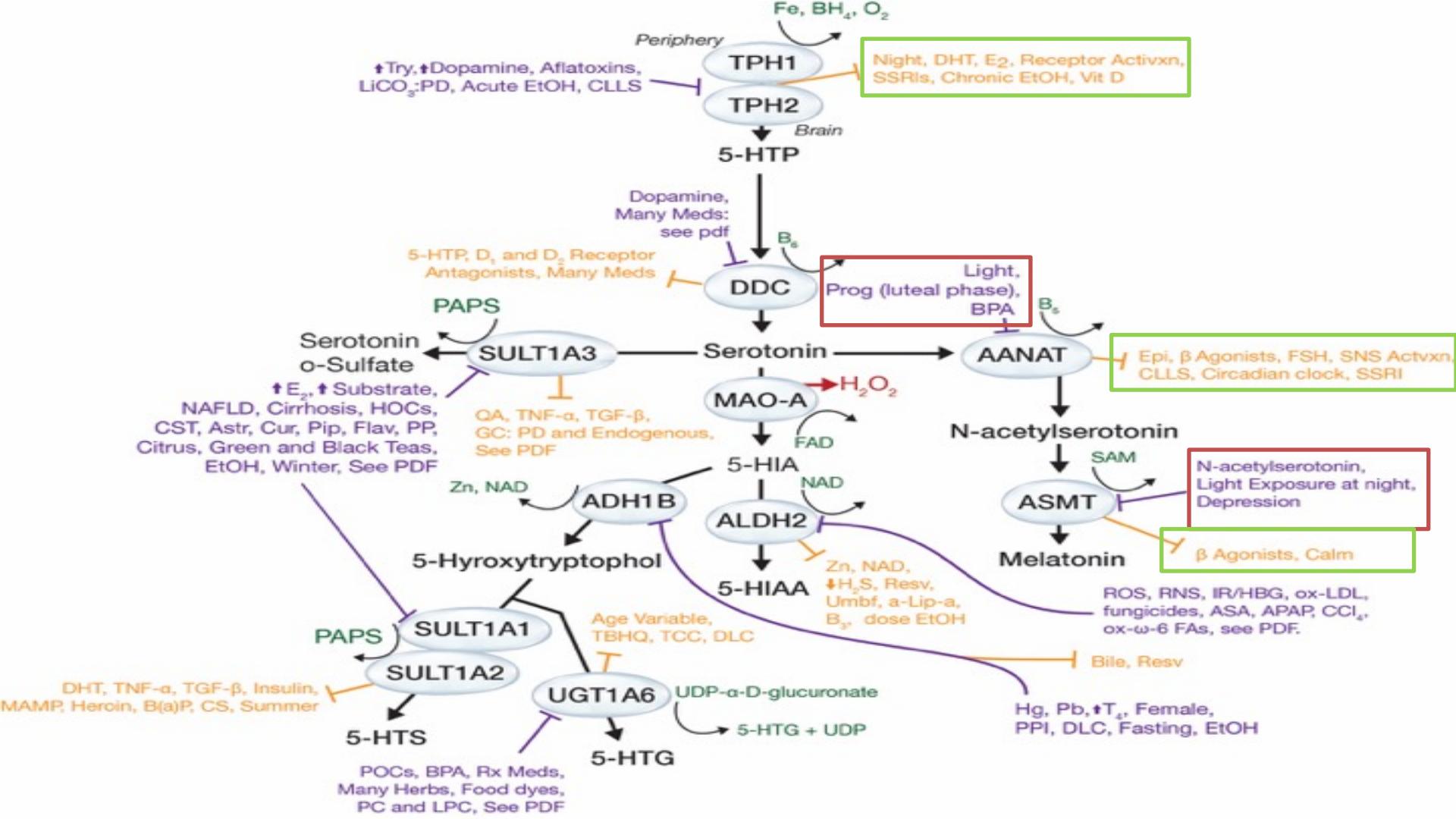
(c) 2017: Dr BenLynch





**It's Nighttime:  
Turn Off Your Lights and Screens**

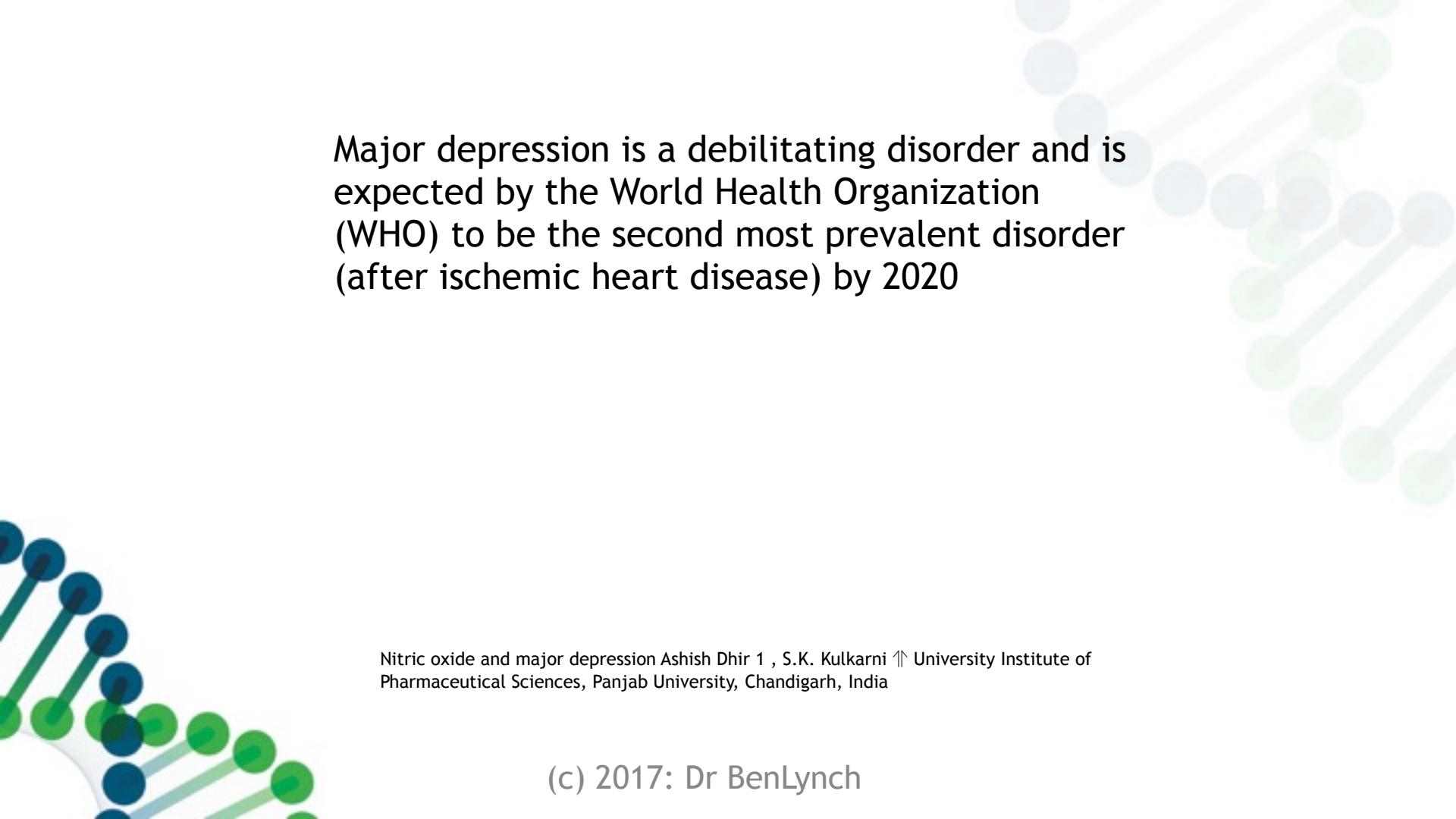
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## **Depression: The SSRI Myth**

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Major depression is a debilitating disorder and is expected by the World Health Organization (WHO) to be the second most prevalent disorder (after ischemic heart disease) by 2020

Nitric oxide and major depression Ashish Dhir 1 , S.K. Kulkarni 1 University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

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## Depressive Disorder

## Postpartum Depression

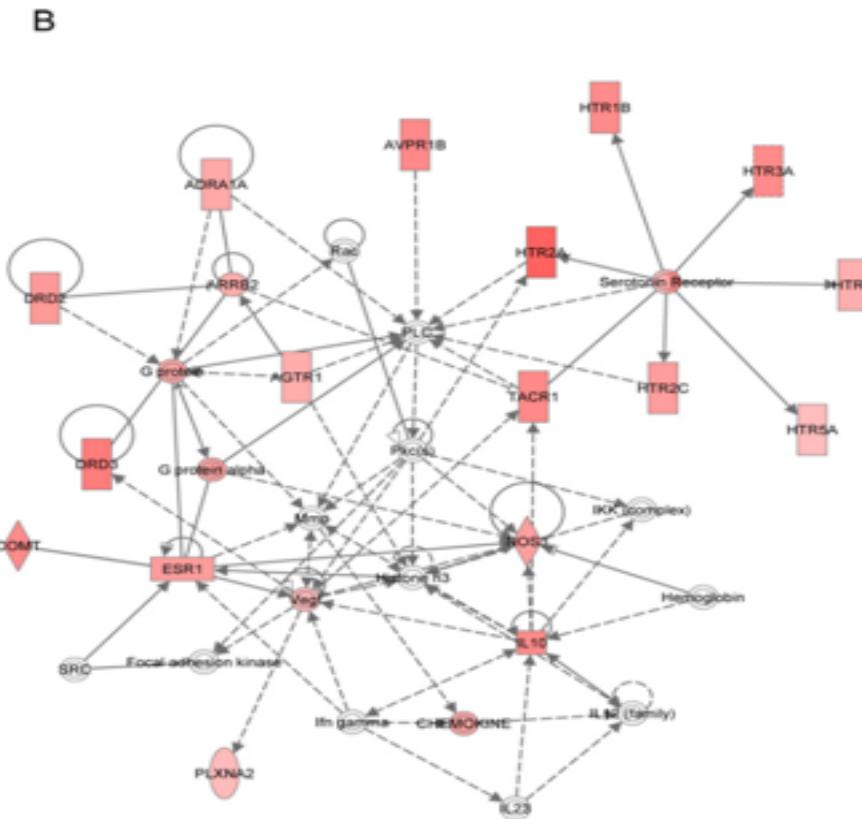
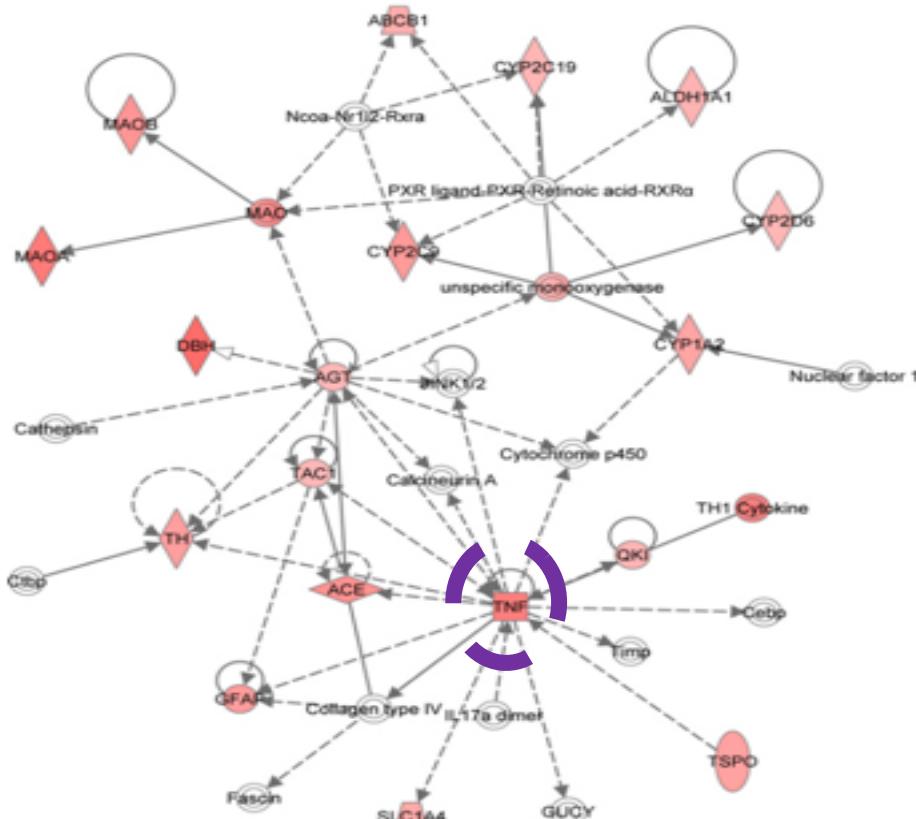
Depressive Disorder,  
Major

|          |            |          |           |          |            |
|----------|------------|----------|-----------|----------|------------|
| SLC6A4 ↗ | <u>369</u> | SLC6A4 ↗ | <u>10</u> | SLC6A4 ↗ | <u>191</u> |
| BDNF ↗   | <u>158</u> | OXTR ↗   | <u>3</u>  | BDNF ↗   | <u>82</u>  |
| HTR2A ↗  | <u>94</u>  | COMT ↗   | <u>3</u>  | COMT ↗   | <u>54</u>  |
| COMT ↗   | <u>81</u>  | ESR1 ↗   | <u>2</u>  | HTR2A ↗  | <u>52</u>  |
| HTR1A ↗  | <u>64</u>  | MAOA ↗   | <u>2</u>  | HTR1A ↗  | <u>41</u>  |
| TPH1 ↗   | <u>51</u>  | TPH2 ↗   | <u>2</u>  | TPH1 ↗   | <u>30</u>  |
| MAOA ↗   | <u>47</u>  | OXT ↗    | <u>2</u>  | SLC6A2 ↗ | <u>28</u>  |
| TPH2 ↗   | <u>43</u>  | BDNF ↗   | <u>2</u>  | MAOA ↗   | <u>26</u>  |
| APOE ↗   | <u>42</u>  | TPH1 ↗   | <u>1</u>  | TPH2 ↗   | <u>25</u>  |
| CYP2D6 ↗ | <u>39</u>  | PER3 ↗   | <u>1</u>  | CYP2D6 ↗ | <u>20</u>  |
| SLC6A2 ↗ | <u>38</u>  | PER2 ↗   | <u>1</u>  | ABCB1 ↗  | <u>20</u>  |
| MTHFR ↗  | <u>37</u>  | FADS2 ↗  | <u>1</u>  | GNB3 ↗   | <u>17</u>  |
| FKBP5 ↗  | <u>30</u>  | MTHFR ↗  | <u>1</u>  | CRHR1 ↗  | <u>16</u>  |
| GNB3 ↗   | <u>25</u>  | NR3C1 ↗  | <u>1</u>  | APOE ↗   | <u>16</u>  |
| NR3C1 ↗  | <u>25</u>  | FADS1 ↗  | <u>1</u>  | NR3C1 ↗  | <u>16</u>  |
| DRD2 ↗   | <u>25</u>  | CRHR1 ↗  | <u>1</u>  | FKBP5 ↗  | <u>16</u>  |
| CRHR1 ↗  | <u>25</u>  | CYP2D6 ↗ | <u>1</u>  | DRD2 ↗   | <u>14</u>  |
| ABCB1 ↗  | <u>25</u>  |          |           |          |            |
| ACE ↗    | <u>24</u>  |          |           |          |            |



Barking up the wrong tree. Who funds these studies?

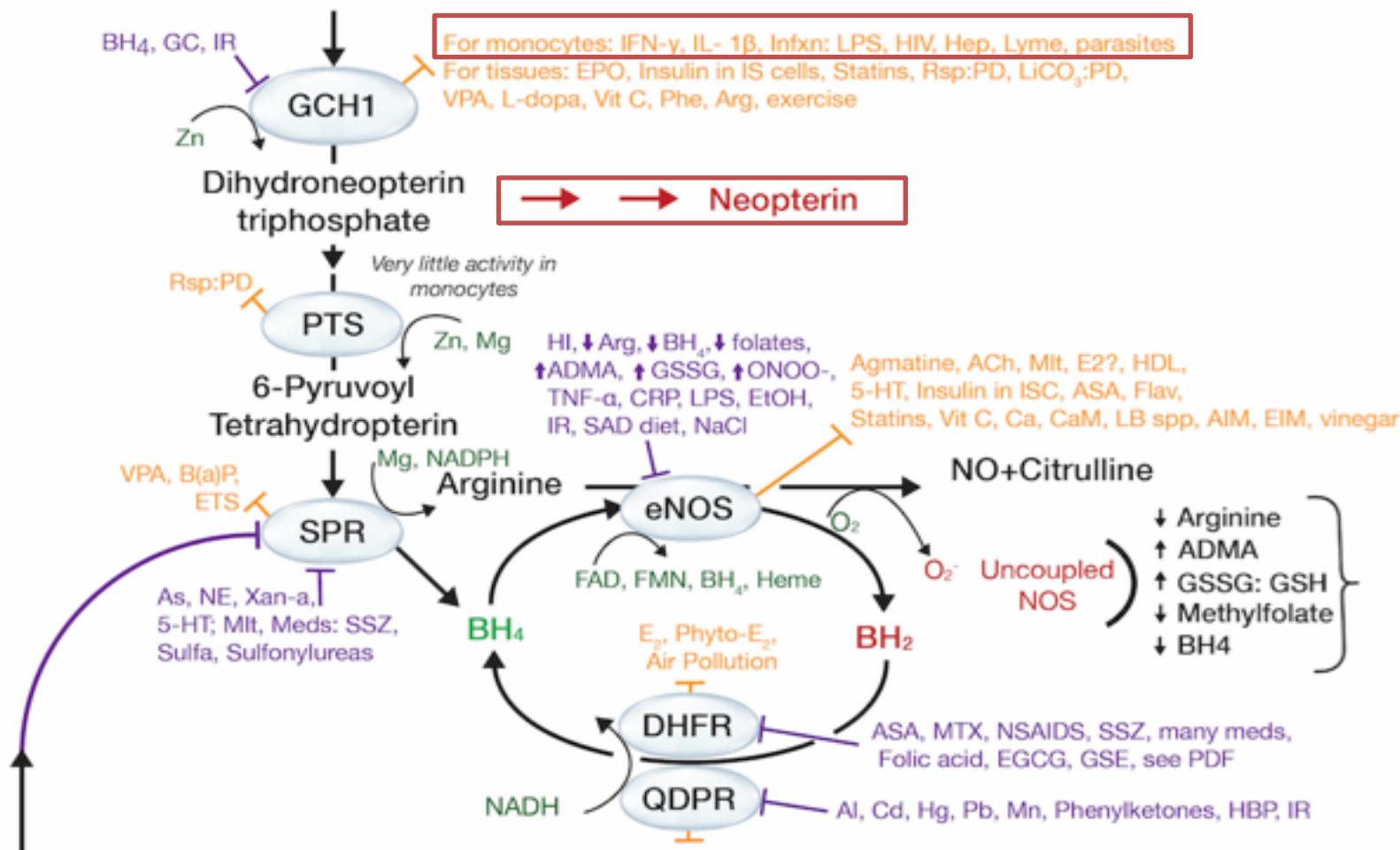
# A comprehensive network and pathway analysis of candidate genes in major depressive disorder

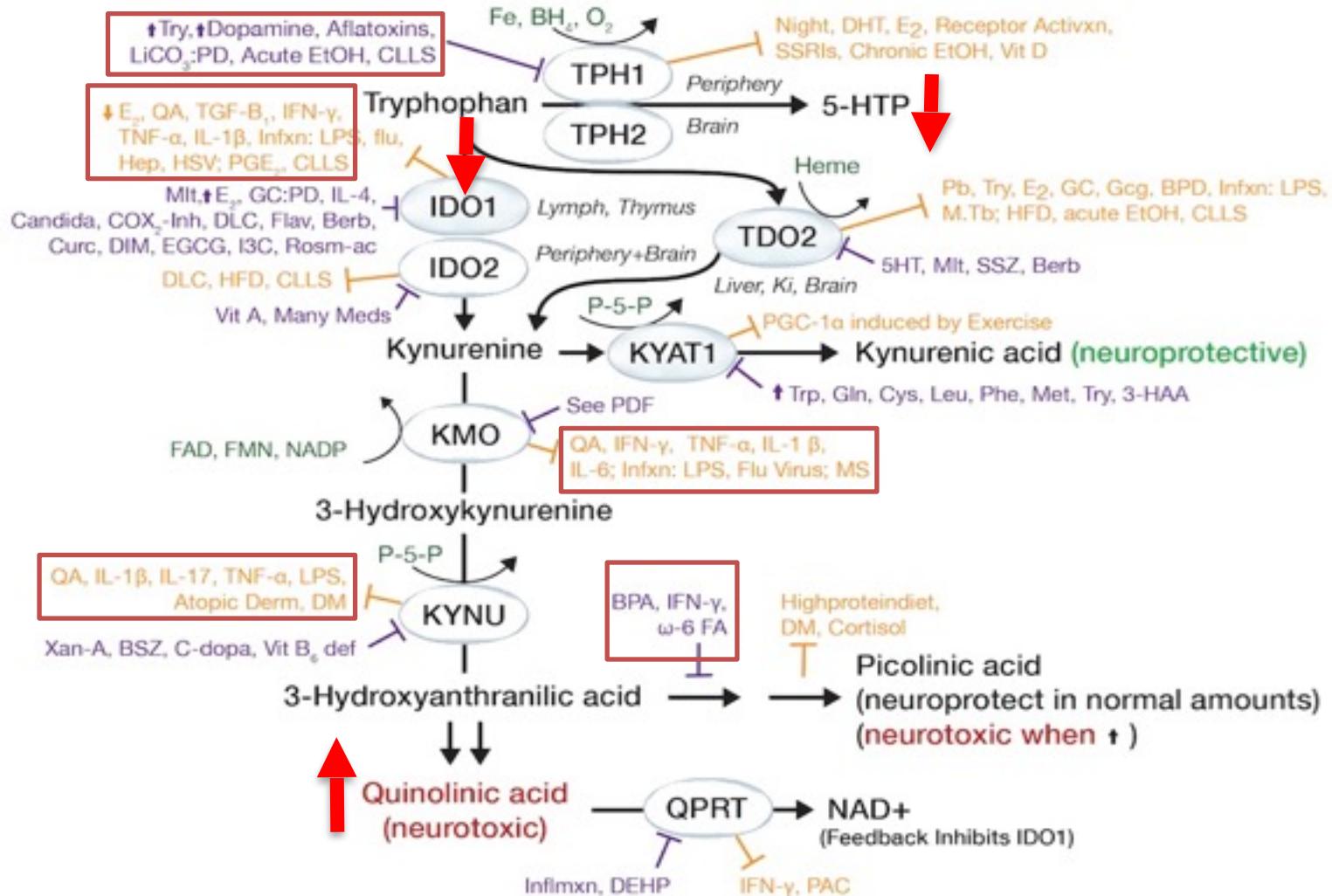


**Figure 3 The top two molecular networks identified by Ingenuity Pathway Analysis (IPA).** (A) The most significant molecular network by IPA pathway enrichment analysis. (B) The second most significant molecular network. Color of each node indicates the score of each DEPgene calculated by multiple lines of genetic evidence, as described in Kao et al [19].

# BH<sub>4</sub> Synthesis

## Guanosinetriphosphate(GTP)





# Neopterin production, tryptophan degradation, and mental depression--what is the link?

Widner B<sup>1</sup>, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D.

## Author information

### Abstract

The cytokine interferon-gamma stimulates human monocytes/macrophages to release large amounts of neopterin. Increased neopterin concentrations in body fluids of patients are observed during diseases with activated cellular (=TH1-type) immune response such as allograft rejection, virus infections, autoimmune disorders, or malignant tumors but also in neurodegenerative diseases or during pregnancy. In various cells interferon-gamma induces indoleamine 2,3-dioxygenase (IDO) which degrades tryptophan via the kynurenine pathway. Therefore like increased neopterin formation, enhanced tryptophan degradation is observed in diseases concomitant with cellular immune activation. Disturbed metabolism of tryptophan affects biosynthesis of neurotransmitter 5-hydroxytryptamine (serotonin), and it appears to be associated with an increased susceptibility for depression. In fact, enhanced neopterin concentrations together with increased degradation of tryptophan and low serum levels of tryptophan correlate with neuropsychiatric abnormalities like cognitive decline and depressive symptoms especially in long-lasting and chronic diseases. Activation of IDO could represent an important link between the immunological network and the pathogenesis of depression.



## Elevated Serum Levels of Neopterin at Admission Predicts Depression After Acute Ischemic Stroke: a 6-Month Follow-Up Study.

Tang CZ<sup>1</sup>, Zhang YL<sup>1</sup>, Wang WS<sup>2</sup>, Li WG<sup>1</sup>, Shi JP<sup>3</sup>.

 Author information

### Abstract

Inflammation and cell-mediated immune activation are attributed to the pathogenesis and pathophysiology in depression. Our aim was to test the possible association between serum levels of neopterin and the development of post-stroke depression (PSD) in Chinese patients. The subjects were first-ever acute ischemic stroke patients who were hospitalized at the First Affiliated Hospital of Xinxiang Medical University during the period from December 2012 to December 2013. Clinical information and stroke severity were collected at admission. Neurological and neuropsychological evaluations were conducted at the 6-month follow-up. Serum neopterin levels were measured using fluorometry and a high performance liquid chromatography (HPLC) method. Multivariate analyses were performed using logistic regression models. During the study period, 226 patients were included and finished the 6-month follow-up. Sixty-nine patients (30.5 %) were diagnosed as having major depression at 6 months. Patients with major depression showed higher levels of serum neopterin (21.6[IQR, 18.9-25.7]nmol/L vs. 14.6[IQR, 12.2-18.4]nmol/L,  $P < 0.0001$ ) at admission. In multivariate analyses, serum neopterin was an independent predictor of PSD at 6 months [odds ratio (OR): 1.952 (95 % CI, 1.358-2.805),  $P < 0.0001$ ]. With an AUC of 0.850 (95 % CI, 0.797-0.902), neopterin showed a significantly greater discriminatory ability as compared with high-sensitivity C-reactive protein, age, body mass index, and National Institutes of Health and Stroke Scale score. Neopterin is a novel, independent predictor of the development of depression 6 months after stroke. This indicated that the elevated neopterin levels may play a significant role in the pathology of depression and that the pathways leading to inflammation and cell-mediated immune activation warrant further exploration.



# A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise



Adrian L. Lopresti <sup>a,\*</sup>, Sean D. Hood <sup>b</sup>, Peter D. Drummond <sup>a</sup>

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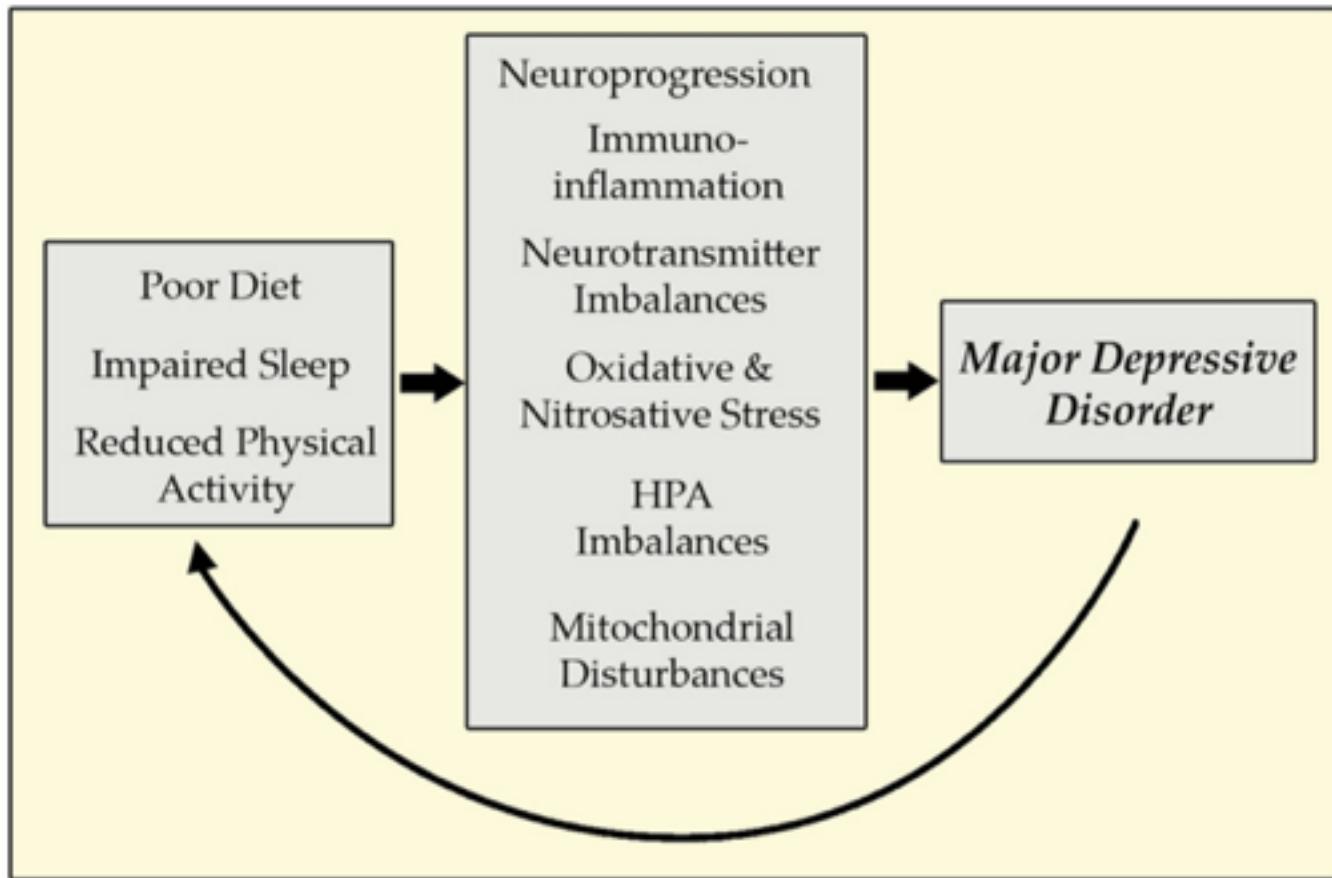
Exercise

Sleep

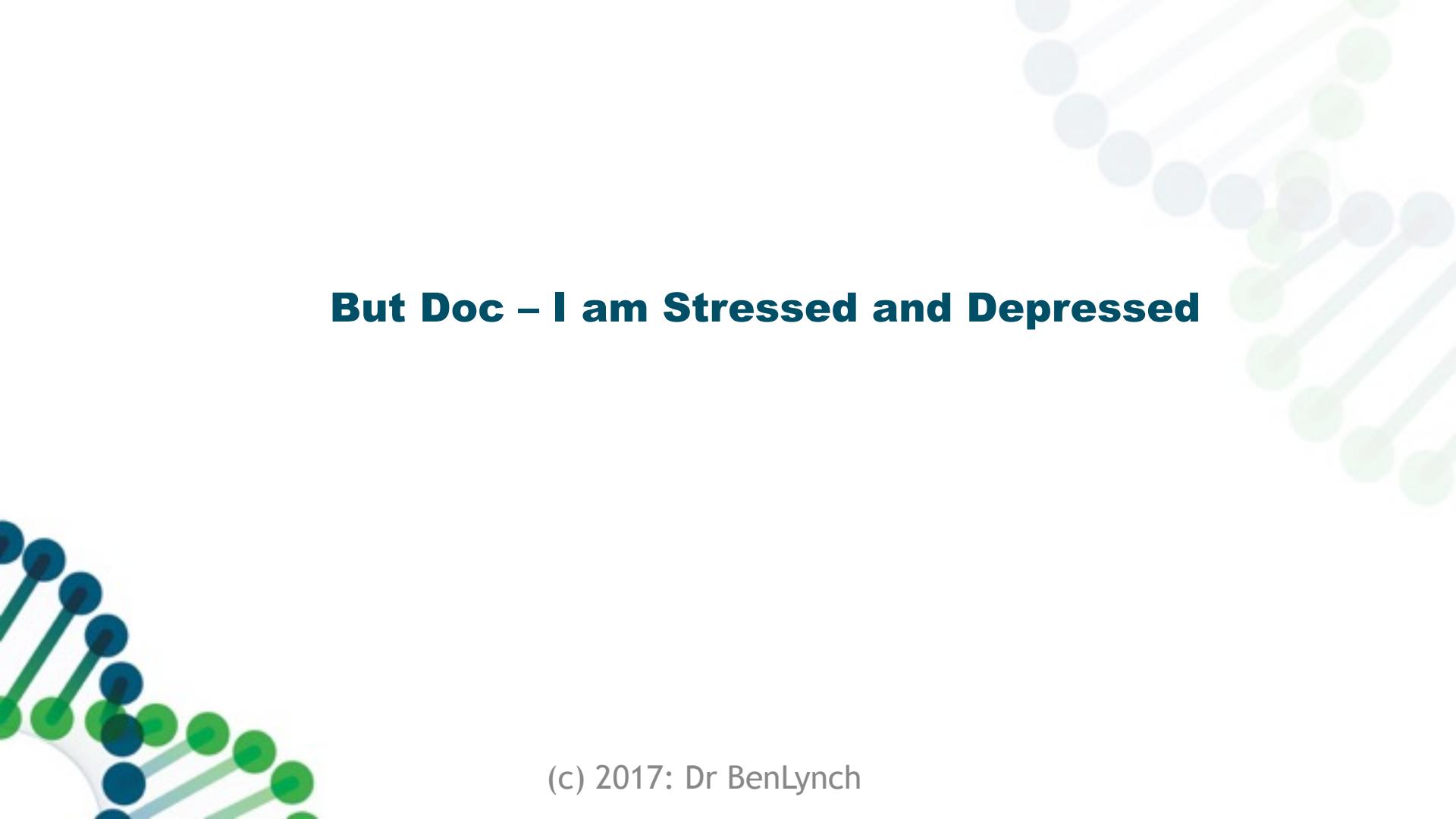
Physical activity

## ABSTRACT

Research on major depression has confirmed that it is caused by an array of biopsychosocial and lifestyle factors. Diet, exercise and sleep are three such influences that play a significant mediating role in the development, progression and treatment of this condition. This review summarises animal- and human-based studies on the relationship between these three lifestyle factors and major depressive disorder, and their influence on dysregulated pathways associated with depression: namely neurotransmitter processes, immuno-inflammatory pathways, hypothalamic-pituitary-adrenal (HPA) axis disturbances, oxidative stress and antioxidant defence systems, neuroprogression, and mitochondrial disturbances. Increased attention in future clinical studies on the influence of diet, sleep and exercise on major depressive disorder and investigations of their effect on physiological processes will help to expand our understanding and treatment of major depressive disorder. Mental health interventions, taking into account the bidirectional relationship between these lifestyle factors and major depression are also likely to enhance the efficacy of interventions associated with this disorder.



A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise



**But Doc – I am Stressed and Depressed**

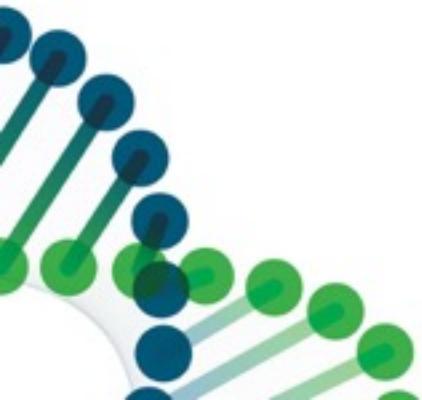
HPA axis hyperactivity is the hallmark of major depression and accounts for the alterations in the immune system. A study, involving 16 females suffering major depression and 16 control subjects, found that the basal concentration of cortisol was significantly higher in depressed subjects than control subjects (35).

WHY?

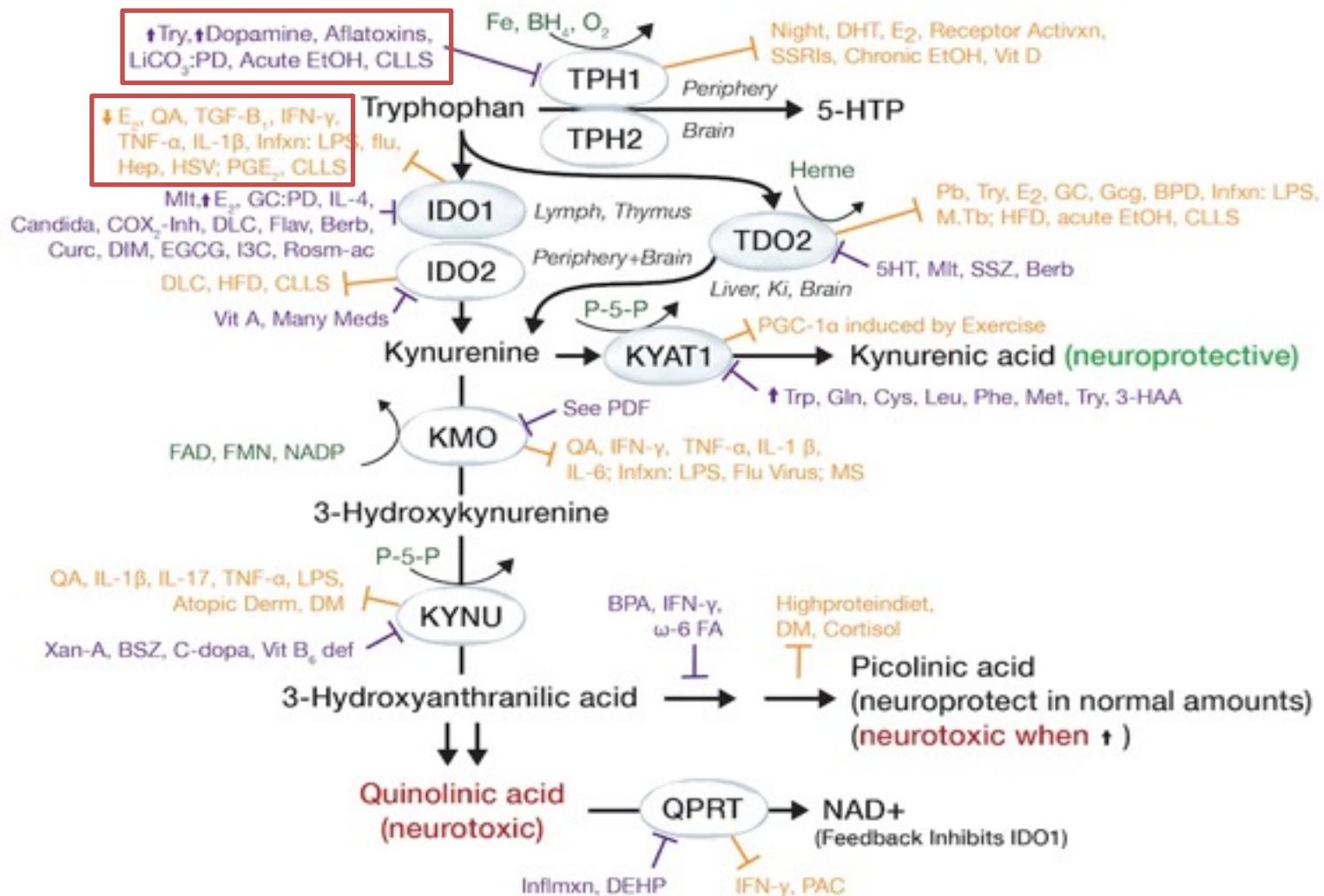


Role of inflammatory cytokines in depression: Focus on interleukin-1 $\beta$

Interestingly, Clark and colleagues<sup>114</sup> suggested that a glucocorticoid-mediated reduction of *TPH2* mRNA may be relevant to the etiology of major depression in cases where glucocorticoids are elevated, since *TPH2* mRNA is regulated by glucocorticoids but not estradiol.



Pharmacogenetics of antidepressant response



# **Kynurenine**

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kynurenone, a compound identified originally in studies of the chemical composition of canine urine, from which it takes its name. **The breakthrough into cognitive neuroscience**

The kynurenone pathway as a therapeutic target in cognitive and neurodegenerative disorders

(c) 2017: Dr Ben Lynch





## **Tryptophan: Serotonin or Kynurenone?**

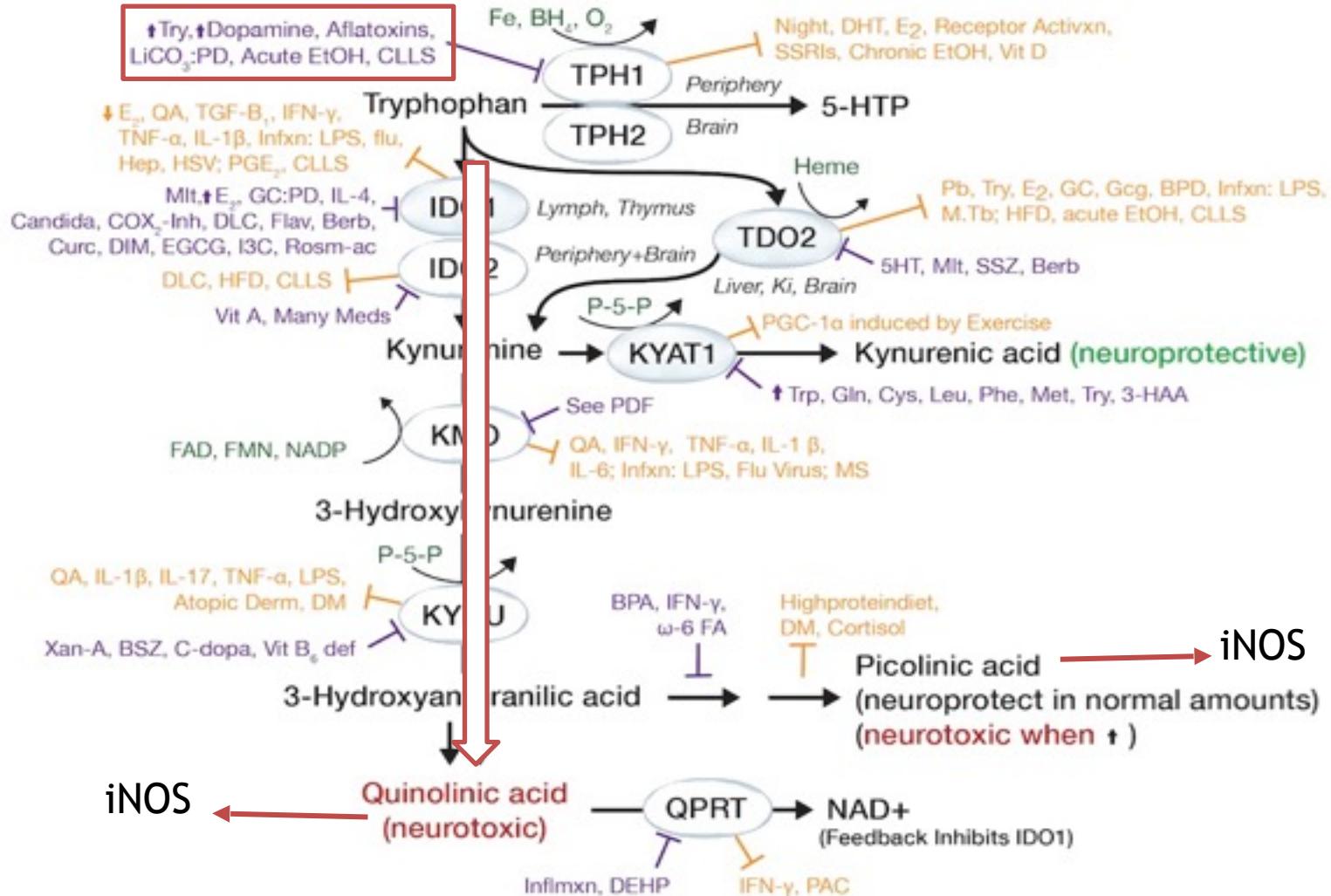
(c) 2017: Dr BenLynch

## **THE KYNURENINE PATHWAY**

About 95% of TRY is metabolized via the KYN pathway

**Carb Intake??**

Tryptophan-Kynurenine Metabolism as a Common Mediator of Genetic and Environmental Impacts in Major Depressive Disorder





## **Tryptophan: 95% to Kynurenone – Why?**

# Kynurenine Pathway

Kynurenine → Immunosuppressant

Tryptophan → Microbial growth

Pregnancy

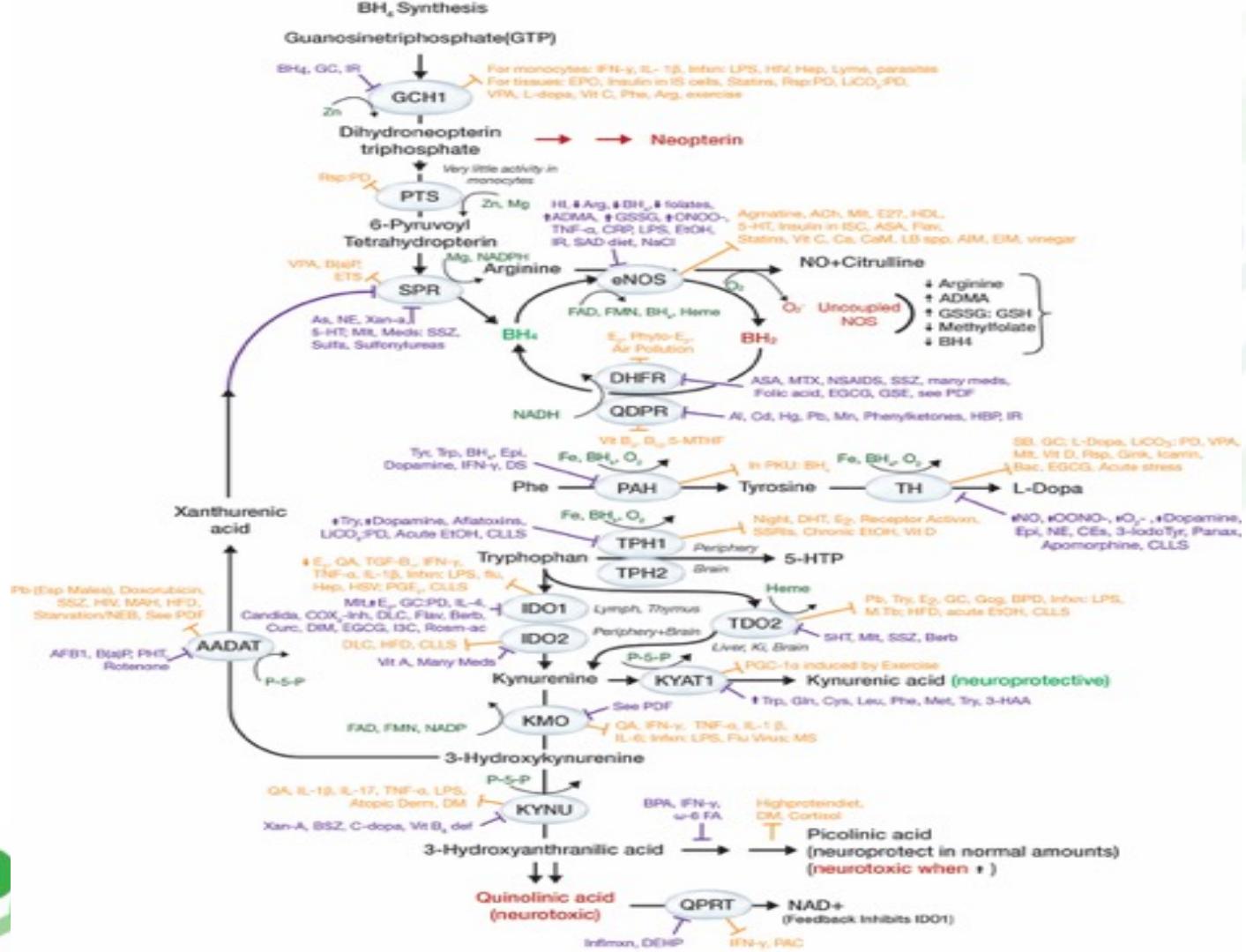
Organ protection: brain, testes, eyes, placenta, hair

Cancer's Immune Escape - *hmmmmmmmm*

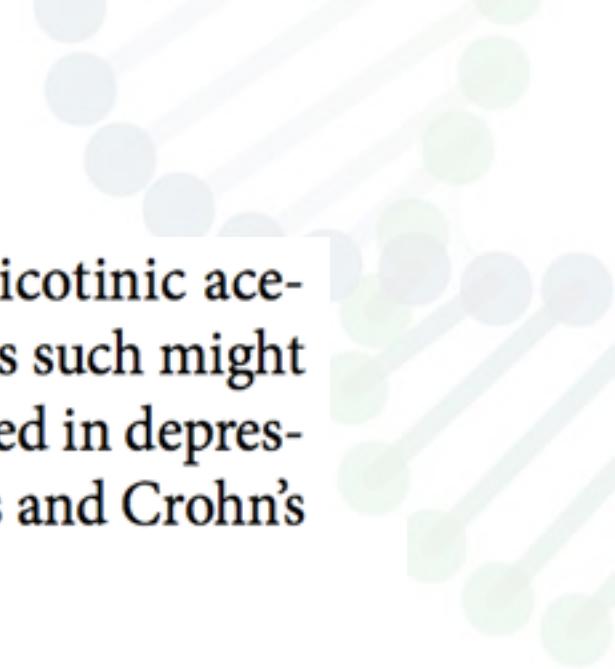
NMDA Antagonist (in low amounts -> agonist in high amounts)

BH4 Feedback Control

The kynurenine pathway is a double-edged sword



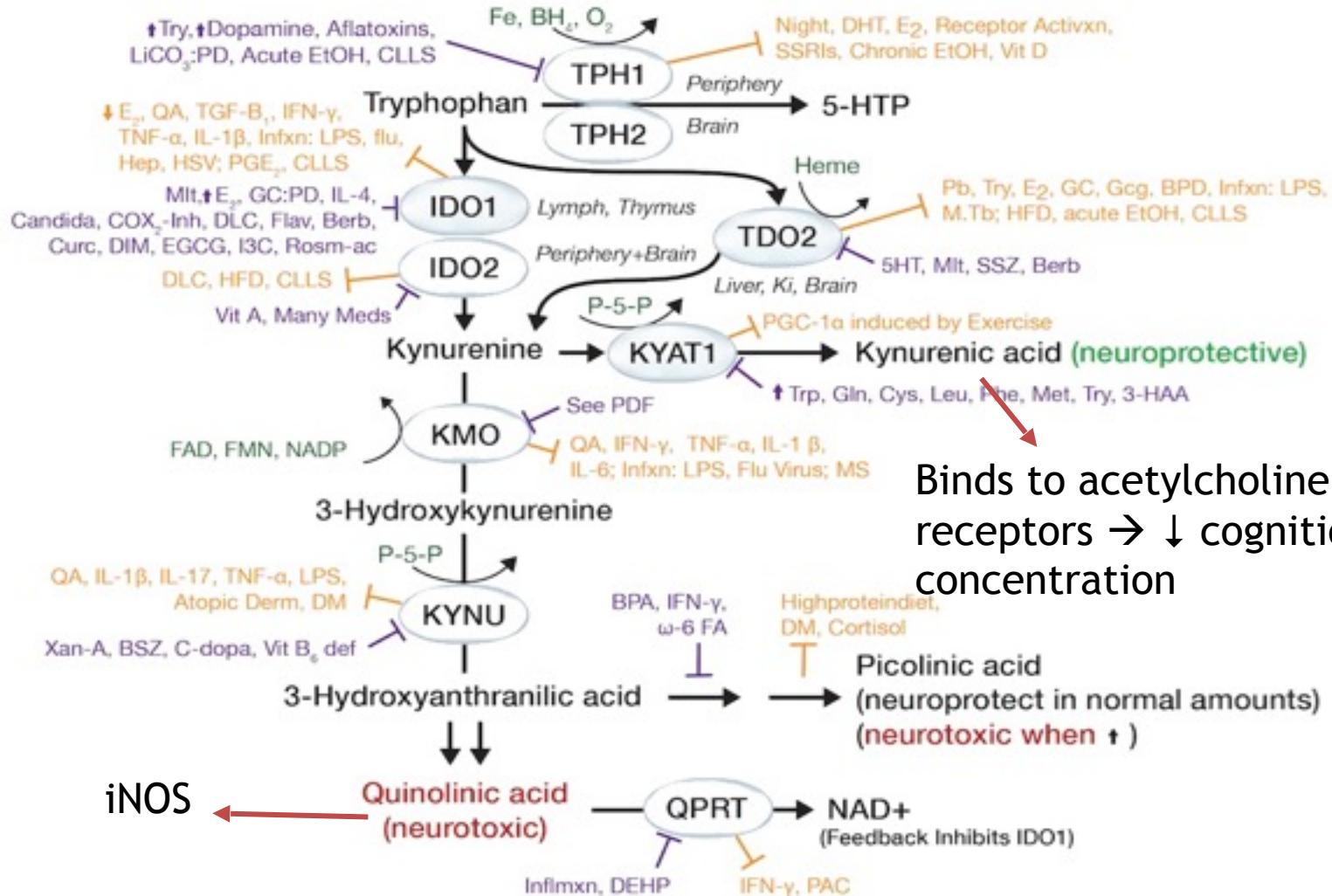
## **Concentration and Memory Impairments**



KYNA has higher affinity to alpha-7-nicotinic acetylcholine than to NMDA receptors, and as such might contribute to cognitive impairment observed in depression, schizophrenia, dementia, and Down's and Crohn's syndromes (21, 22).

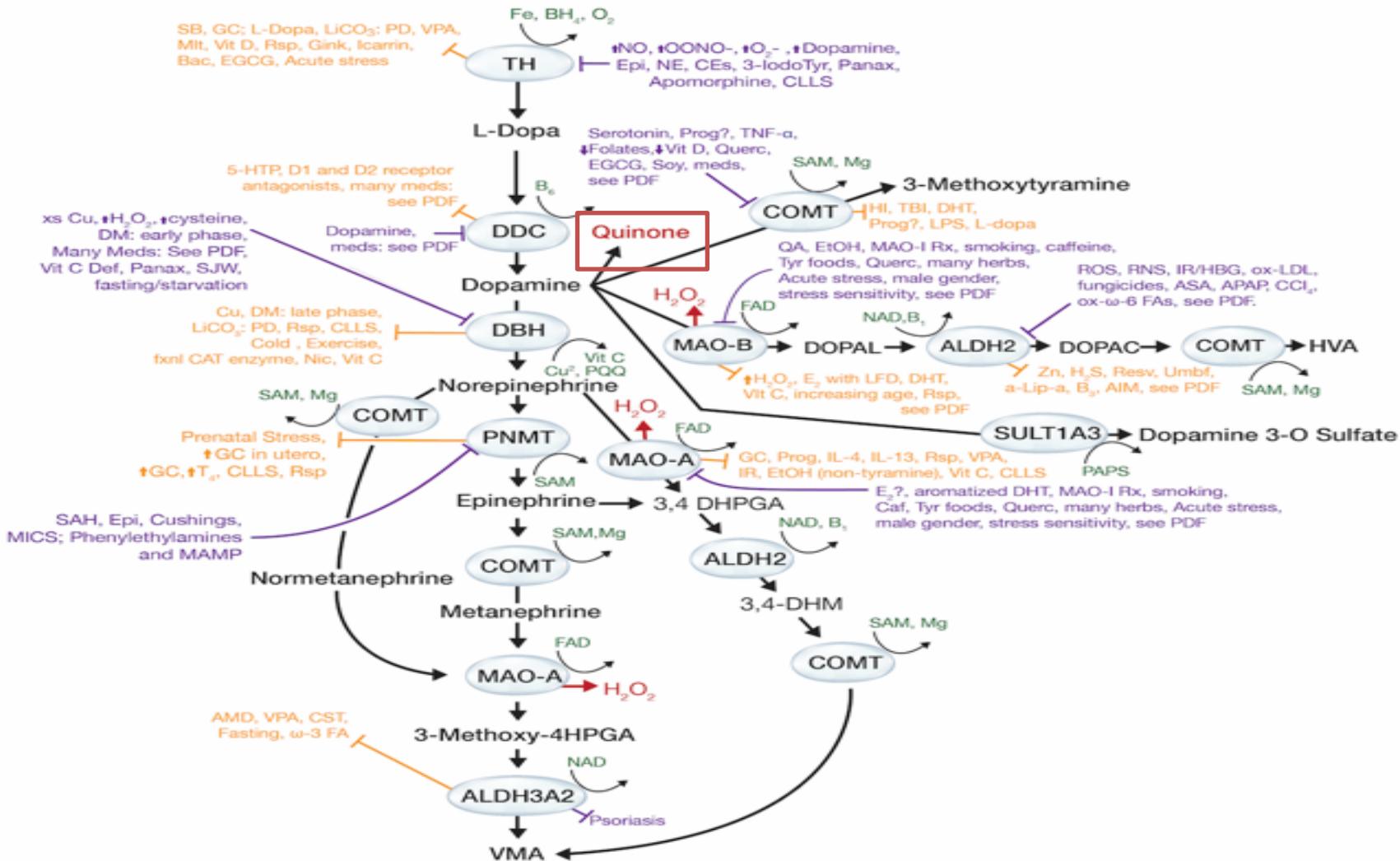


Tryptophan-Kynurenone Metabolism as a Common Mediator of Genetic and Environmental Impacts in Major Depressive Disorder





# **A Slow COMT: Concentration, Focus, Irritability and . . . What else?**



# **Most Common Poisoning Associated with Biopterin?**

# Affective outcome following carbon monoxide poisoning: a prospective longitudinal study.

Jasper BW<sup>1</sup>, Hopkins RO, Duker HV, Weaver LK.

## Author information

### Abstract

**OBJECTIVE:** To longitudinally assess the prevalence of depression and anxiety following carbon monoxide (CO) poisoning and to assess the contributions of mode of poisoning (accidental versus suicide attempt), cognitive sequelae, and oxygen dose (hyperbaric oxygen versus normobaric oxygen) to depression and anxiety.

**BACKGROUND:** CO is the most common cause of poisoning in the United States and may result in neuropathologic changes and cognitive and neurologic sequelae, yet little is known regarding affective outcomes.

**METHOD:** We prospectively assessed affect in 127 CO-poisoned patients. Self-report inventories of depression and anxiety were administered at 6 weeks and at 6 and 12 months post CO poisoning. The primary outcome was prevalence of depression and anxiety at 6 weeks. To determine the effect of mode of poisoning, cognitive sequelae, and oxygen dose, odds ratio estimates were calculated at all three times using logistic regression.

**RESULTS:** Depression and anxiety were present in 45% of patients at 6 weeks, 44% at 6 months, and 43% at 12 months. Patients with suicide attempt and cognitive sequelae had higher prevalence of depression and anxiety at 6 weeks. At 12 months, there were no differences in depression or anxiety regardless of mode of poisoning, presence of cognitive sequelae, or oxygen dose.

**CONCLUSIONS:** CO poisoning results in significant depression and anxiety that persist to at least 12 months. Patients with cognitive sequelae and suicide attempt had a higher rate of depression and anxiety at 6 weeks but not at 12 months. Clinicians need to be aware of affective morbidity following CO poisoning and remain vigilant about CO prevention.

## Seven questions to ask patients when you suspect chronic CO poisoning

1. Is your home heating system or water heater 10 or more years old or malfunctioning?
2. Do you use a gas range or stove for supplemental heat?
3. Do symptoms improve or worsen in certain environments or at a certain time of day?
4. Have fireplace flues and/or chimney vents been checked within the past year?
5. Has another household member—including a pet—also been ill?
6. Is a family member who remains at home persistently ill, whereas others who leave periodically improve?
7. Do symptoms improve or worsen during certain months or seasons?

Mrs. A, age 64, lives alone in an old farmhouse. For approximately 8 months, she had complained of depressed mood, decreased interest, difficulty sleeping, low energy, decreased concentration, and feelings of hopelessness. She met DSM-IV-TR criteria for major depressive disorder with underlying anxiety.

Checking COHb blood levels is the simplest way to confirm CO poisoning.<sup>6,14</sup>

# CO binding studies of nitric oxide synthase: effects of the substrate, inhibitors and tetrahydrobiopterin.

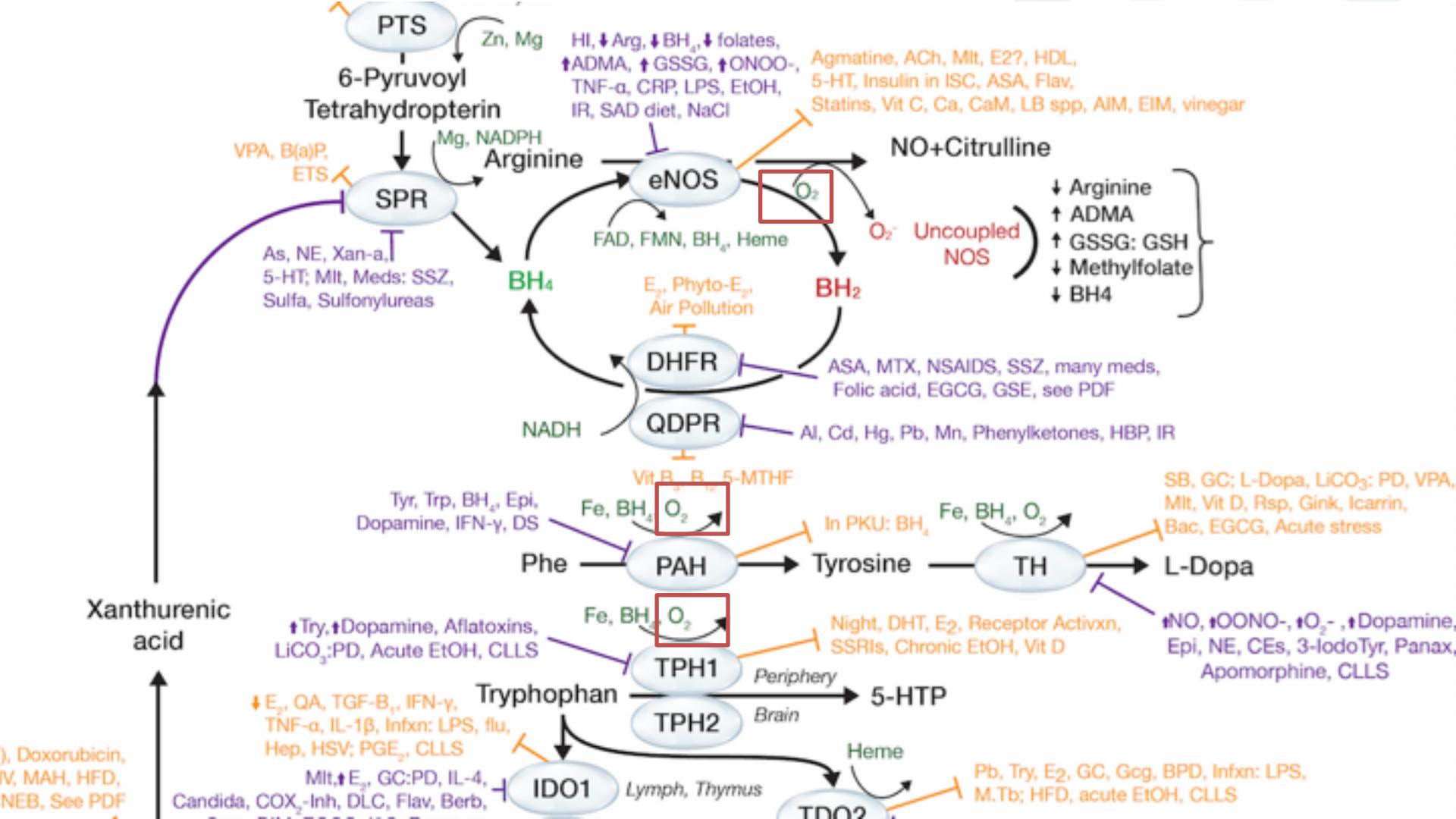
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## Author information

### Abstract

The dissociation constant ( $K_d$ ) for CO from neuronal nitric oxide synthase heme in the absence of the substrate and cofactor was less than 10(-3) microM. In the presence of L-Arg, it dramatically increased up to 1 microM. In the presence of inhibitors such as N(G)-nitro-L-arginine methyl ester and 7-nitroindazole (NI), the  $K_d$  value further increased up to more than 100 microM. Addition of the cofactor, 5,6,7,8-tetrahydrobiopterin (H4B), increased the  $K_d$  value by 10-fold in the presence of L-Arg, whereas it decreased the value to less than one 250th in the presence of NI. Addition of H4B increased the recombination rate constant ( $k_{(on)}$ ) for CO by more than two-fold in the presence of L-Arg or N6-(1-iminoethyl)-L-lysine, whereas it decreased the  $k_{(on)}$  value by three-fold in the presence of L-thiocitrulline. Thus, the binding fashion of some of inhibitors, such as NI, may be different from that of L-Arg with respect to the H4B effect.





## **Carbon Monoxide Sources**

Vehicles, Boats, Gas Powered Equipment

Furnaces and Water Heaters

Generators and Portable Heaters

Kitchen Ranges and Dryers

Wood Stoves and Propane Fryers

Tobacco products

Power washers

## Put Strategic Medicine to Use



## References

All papers shown in presentation are published in PubMed and cited

All diagrams shown have references organized by pathway and gene.

References may be found here:

<https://seekinghealth.org/bibliography/>