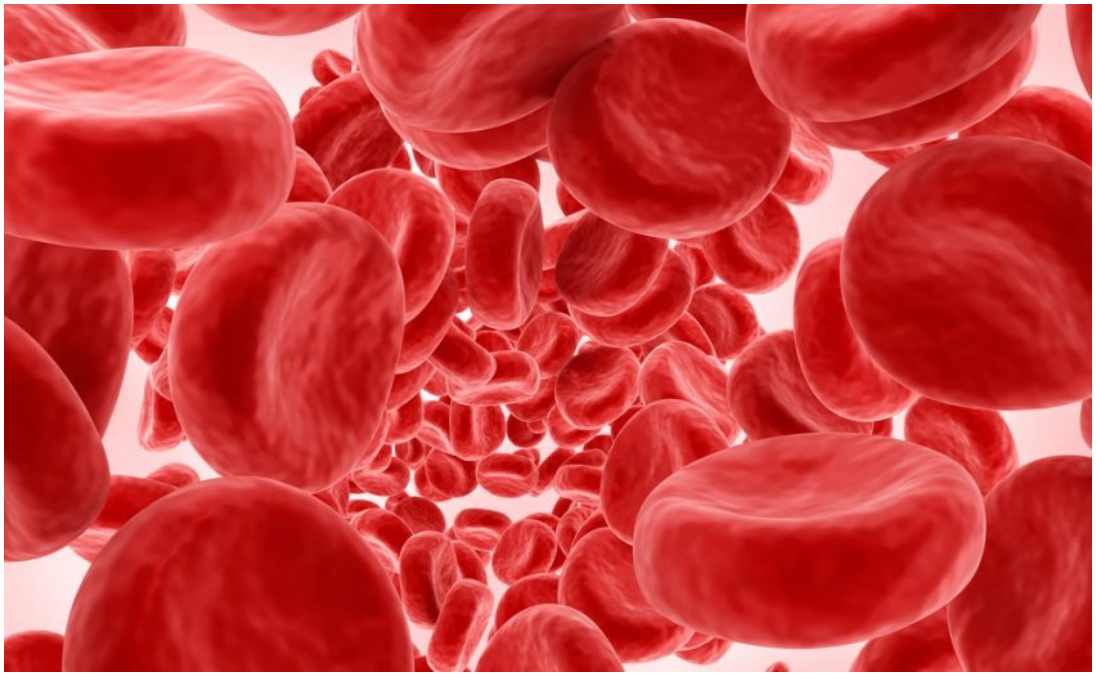


The Mysteries of Kryptopyrroluria

Gilian Crowther MA (Oxon), FBANT, mNNA, mANP, CNHC reg.

AONM Director of Research

Agenda

- The roles of pyrroles, porphyrins and heme in KPU
- The symptoms of KPU
- Testing
- Therapeutic approaches

Agenda

- **The roles of pyrroles, porphyrins and heme in KPU**
- The symptoms of KPU
- Testing
- Therapeutic approaches

What does the word “Kryptopyrroluria” mean?

Krypto = hidden, invisible
Pyrrole = a chemical substance involved in the formation of heme
Uria = excreted in the urine

“undetected, abnormally increased excretion of pyrroles in the urine”

Different terms used over the years: KPU, HPU*, Pyrroluria, Pyroluria, “The Mauve Factor”, Malvaria

* While HPU is characterized by a disorder in the production of heme, KPU is characterized by a disorder in the breakdown of heme. In HPU, the urine is analyzed for the presence of the hemopyrrolactam complex (HPL). In the case of KPU, the total pyrrole compounds found in urine are measured.

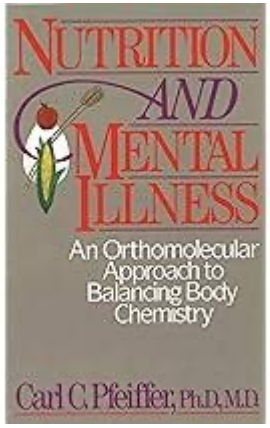
Discovery of the “Mauve Factor” in the early 1960s

Kryptopyrroluria is a condition that was discovered back in the early 1960s, when Drs. Abram Hoffer, Donald Irvine and Carl C. Pfeiffer detected a compound in the urine of psychiatric patients that Hoffer termed the “Mauve factor” due to its appearance on the chromatograms used in its analysis.

Dr. Pfeiffer found that a considerable percentage of patients labelled schizophrenic were suffering from an excess of this mauve factor in their urine, also termed Kryptopyrroles

In Pyrroluria, pyrroles bind with B_6 and then with zinc, thus depleting these nutrients, and often others too, especially manganese

“Approximately 15-30% of "schizophrenics" have pyroluria.” *(Quotation from Nutrition and Mental Illness by Curt C. Pfeiffer)*



Source: Hoffer A. The discovery of kryptopyrrole and its importance in diagnosis of biochemical imbalances in schizophrenia and in criminal behavior . *J Orthomol Med*. 1995;10 (1):3-6; McGinnis WR, Audhya T, Walsh WJ, Jackson JA, McLaren-Howard J, Lewis A, Lauda PH, Bibus DM, Jurnak F, Lietha R, Hoffer A. Discerning the Mauve Factor, Part 1. Altern Ther Health Med. 2008 Mar-Apr;14(2):40-50; https://www.walshinstitute.org/uploads/1/7/9/9/17997321/discerning-mauve-factor-part-1-galley-feb-2008.pdf; https://psychrights.org/Articles/29medicalcausesofsz.htm

Found in families; both a primary and a secondary form exist

Primary: Can be inherited – watch for it in families
Genetic as the primary form
Secondary: Secondary acquired KPU[1]

Therapists report finding it more commonly in women and children than in males[2]

"The physician Carl Pfeiffer, MD, the discoverer of KPU, estimated that more than 10% of the population is affected by KPU."[3] *(Quotation Dr. Curt C. Pfeiffer – many years ago so may be higher now for reasons that will be explained)*

Source: 1. KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann;
2. https://www.drcarrierigoni.com.au/blog/pyrroles-disorder; 3. https://www.galaxus.de/en/s12/product/kpuhpu-common-but-unrecognized-mitochondrial-disorders-kyra-kauffmann-sascha-kauffmann-german-refere-8221719;
https://www.drlamcoaching.com/adrenal-fatigue/complications/pyroluria-afs/

Huge percentage of sufferers found in some cohorts, e.g. Lyme Disease patients

TOWNSEND LETTER

The Examiner of Alternative Medicine

HOME E-LETTER PRINT ISSUES TOWNSEND LETTER BLOG INDEX CALENDAR OF EVENTS

Kryptopyrroluria (aka Hemopyrrollactamuria) 2017 A Major Piece of the Puzzle in Overcoming Chronic Lyme Disease

Subscribe to our FREE e-letter

CLICK HERE to request the e-Letter!

Click here to donate and support the e-Letter

by Scott Forsgren, FDN-P and Dietrich Klinghardt, MD, PhD

Dietrich Klinghardt, MD, PhD, is a practicing physician with a focus on the treatment of chronic neurological conditions such as Lyme disease, autism, and CFIDS. In the years that he has treated patients with chronic

Subscribe to the

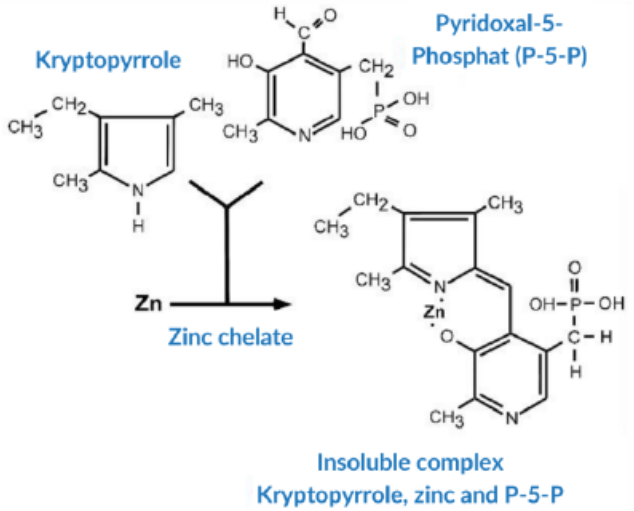
"Dr. Klinghardt has found **the incidence of KPU in Lyme disease to be 80% or higher**; in patients with heavy metal toxicity (lead, mercury, aluminum, cadmium, and others) over 75%; and in children with autism over 80%. These are very significant percentages of the patient population with chronic illness that may benefit from a treatment program that addresses KPU. Healthy controls do not test positive for KPU."

Source: Kryptopyrroluria (aka Hemopyrrollactamuria) 2017: A Major Piece of the Puzzle in Overcoming Chronic Lyme Disease *by Scott Forsgren, FDN-P and Dietrich Klinghardt, MD, PhD, https://www.townsendletter.com/July2017/krypto0717.html; http://cinak.com/editions/articles_eng/hpu%202009.pdf*

The laboratory explanation of what they find

"2,4 dimethyl-3-ethylpyrrole is a byproduct of haemoglobin synthesis. It has been found that circulating kryptopyrrole forms a Schiff base with the aldehyde form of vitamin B6 (pyridoxal 5 phosphate) in the blood. This combination then binds with zinc and builds an insoluble complex. **As large amounts of kryptopyrroles are excreted in the urine, it depletes the blood of vitamin B6 and zinc."**[2]

.



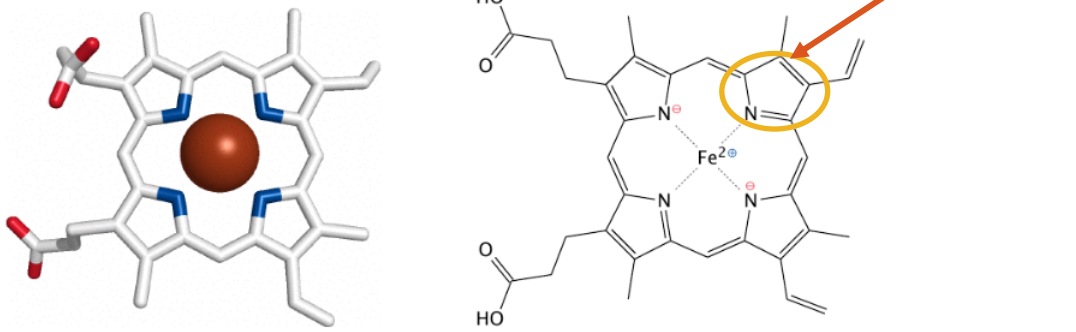
2

Source: KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann;
2. https://www.immundiagnostik.com/en/portfolio/testkits/kr7823/method:others

But what are “pyrroles”? To understand this, we need to first understand what porphyrins are

“Porphyrins are a class of macrocycles **comprised of four pyrrole units** conjugated through methine bridges, with this highly conjugated structure giving intense absorption in both the UV and visible regions of the electromagnetic spectrum. This in turn leads to both the characteristic purple color of these structures and their name; the word porphyrin is derived from the Greek *porphyra*, meaning purple.”[1]

17.1 Structure and function of heme



“Heme consists of a porphyrin ring that holds a central iron ion.”[2]

One example of a porphyrin comprised of pyrrole units: haem/heme

Source: 1. https://www.sciencedirect.com/topics/chemical-engineering/porphyrin#:~:text=Porphyrins%20are%20a%20class%20of, regions%20of%20the%20electromagnetic%20spectrum; 2. http://watcut.uwaterloo.ca/webnotes/Metabolism/Iron.html

So pyrroles are the “scaffolding” holding together these porphyrins

Chapters and Articles

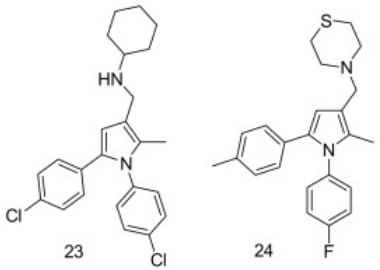
You might find these chapters and articles relevant to this topic.

Five-membered Rings with One Heteroatom Together with Their Benzo and Other Carbocyclic-fused Derivatives

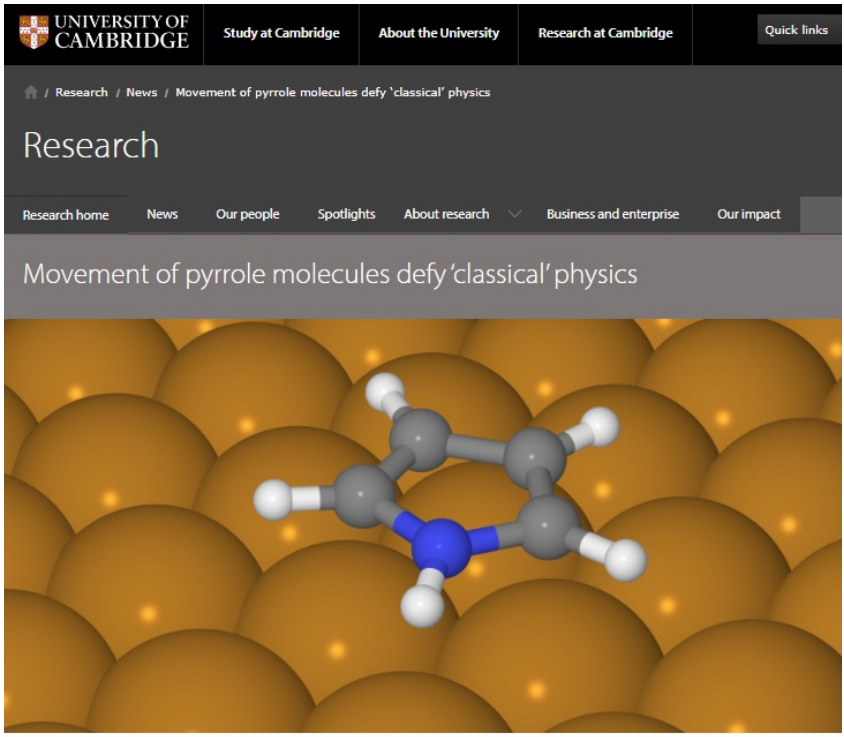
Marco d'Ischia, ... Alessandro Pezzella, in Comprehensive Heterocyclic Chemistry IV, 2022

3.04.3.1 Pyrroles

Pyrroles are widely recognized as biologically active scaffold possessing diverse nature of activities and featuring different pharmacophores in a pyrrole ring system leading to the formation of more active compounds.[75] Notably, anti-bacterial activities exhibited by this class of compounds were extensively investigated in the last decade focusing on drug-resistant Gram-positive and Gram-negative pathogens, like pyrroles of type **23**[76] or mycobacteria as described for pyrrole **24**.[77] Also pyrrole-based scaffolds were employed for the development of anti-tumor agents acting on gene modulation/suppression[78] and conjugate antibody.[79] Pyrrole-based scaffolds were also utilized for the coating of medical implants.[80]



1



Quantum laws loom ever larger in physical world as new research finds quantum phenomena in effect on a molecular level

New research shows that movement of the ring-like molecule pyrrole over a metal surface runs counter to the centuries-old laws of 'classical' physics that govern our everyday world.

“The balance between the activation energy and the energy barrier that sticks the molecules to the surface is critical in determining which networks are able to form under different conditions.”

— Stephen Jenkins

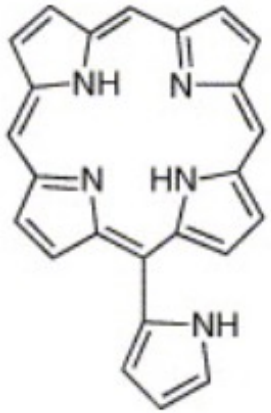
Using uniquely sensitive experimental

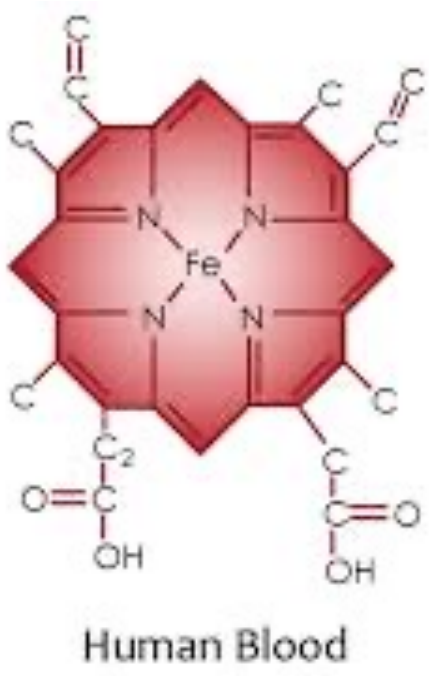
2

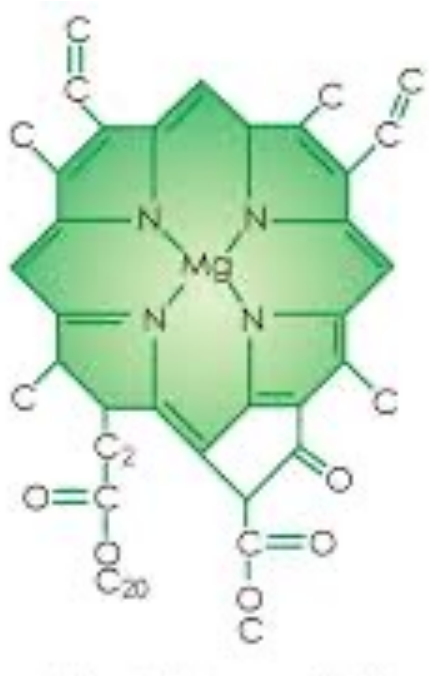
“Pyrrole is defined as an electron-rich heteroaromatic molecule with a five-membered ring containing one nitrogen and four carbon atoms.”

Source: 1. https://www.sciencedirect.com/topics/chemistry/pyrrole; 2. *https://www.cam.ac.uk/research/news/movement-of-pyrrole-molecules-defy-classical-physics, https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201302289; 3. https://www.sciencedirect.com/topics/chemistry/pyrrole#:~:text=Pyrrole%20is%20defined%20as%20an,nitrogen%20and%20four%20carbon%20atoms.*

That's how heme is formed – and Chlorophyll too, interestingly!







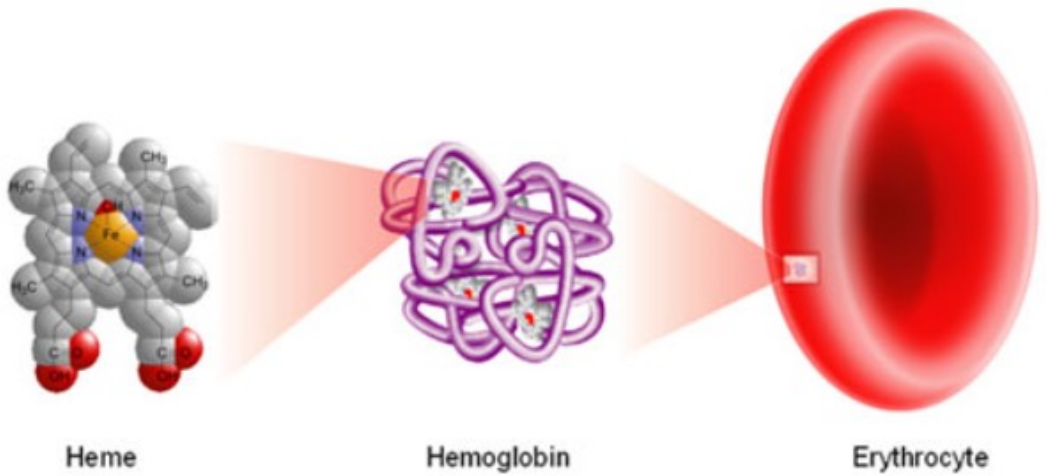
Heme **Chlorophyll**

But there's not just one molecule of heme in one red blood cell …

Source: https://www.sciencedirect.com/topics/chemistry/pyrrole; *https://www.cam.ac.uk/research/news/movement-of-pyrrole-molecules-defy-classical-physics*, *https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201302289;* https://www.sciencedirect.com/science/article/abs/pii/S0040403906022763 https://bhavanajagat.com/2021/10/04/the-designing-of-the-red-blood-cell/

Extraordinary numbers in nature: imagine the pyrroles involved in just one red blood cell

One typical red blood cell contains about 270 million hemoglobin molecules, with each carrying four heme groups, each with four pyrroles.[1]
270 million x 4 = 1,080,000,000 heme groups
1,080,000,000 x 4 = 4,320,000,000 pyrroles

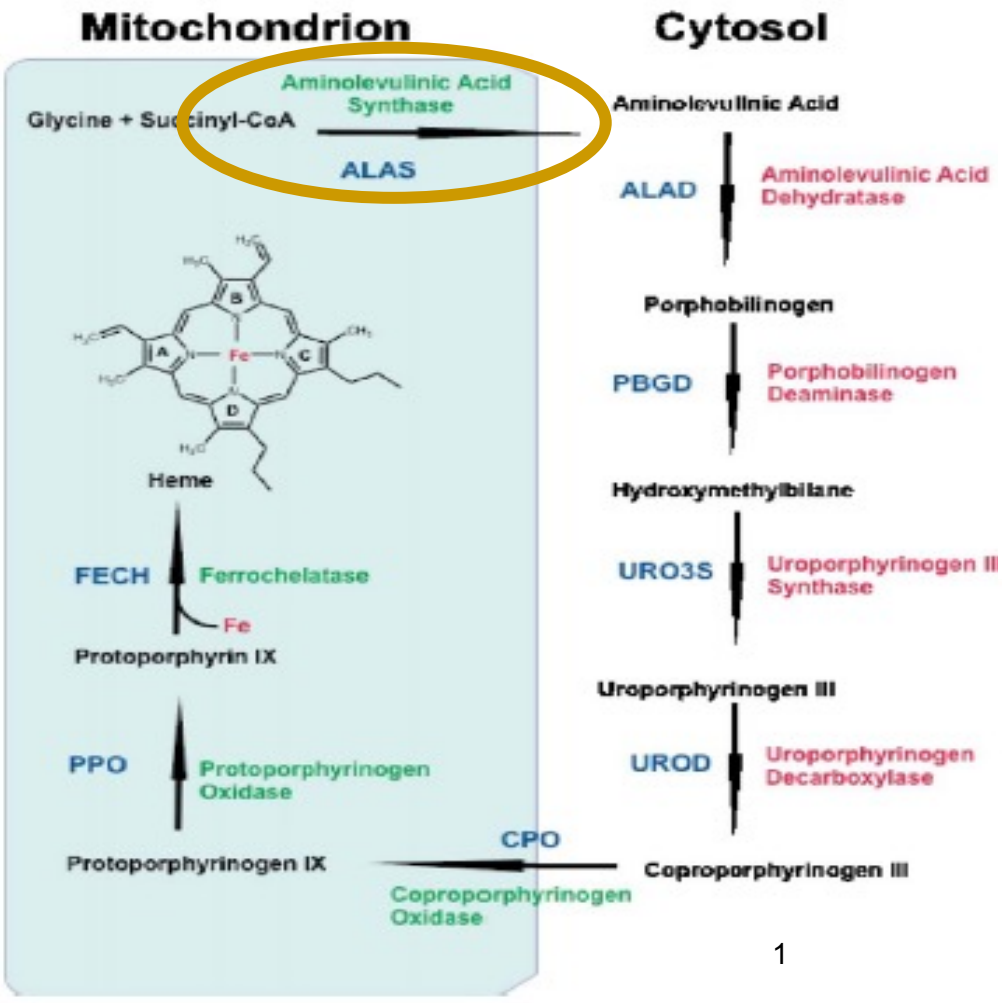


2

… and we make 2 - 3 million red blood cells every second[3]

Source: 1. https://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&v=8&id=102740#:~:text=A%20typical%20erythrocyte%20contains%20about,each%20carrying%20four%20heme%20groups; 2. http://watcut.uwaterloo.ca/webnotes/Metabolism/Iron.html; 3. https://www.ncbi.nlm.nih.gov/books/NBK2263/#:~:text=Every%20second%2C%202%2D3%20million,containing%204%2D6%20million%20cells.

Four key steps in the synthesis of heme take place in the mitochondria: the synthesis *of* Aminolevulinic acid is the first



1

Cellular Level Go to:

Porphyrin synthesis is the process that produces heme. Heme synthesis occurs partly in the mitochondria and partly in the cytosol. The biosynthesis involves an eight-step enzymatic pathway. Heme biosynthesis starts in mitochondria with the condensation of succinyl Co-A from the citric acid cycle and an amino acid glycine. They combine to produce a key heme intermediate, 5'-aminolevulinic acid (ALA) in mitochondria catalyzed by the pyridoxal phosphate-requiring (vitamin B6) enzyme, aminolevulinic acid synthase (ALAS).[3] This reaction is the rate-limiting step in the pathway.[4]

The ALA molecule formed exit the mitochondria into the cytosol where two molecules of ALA condense to produce the pyrrole ring compound porphobilinogen (PBG) catalyzed by a zinc-requiring enzyme, ALA dehydratase enzyme (also called porphobilinogen synthase). The next step of the pathway involves condensation of four molecules of porphobilinogen, aligned to form the linear hydroxymethylbilane (HMB), catalyzed by porphobilinogen deaminase (PBG deaminase) also known as hydroxymethylbilane synthase.

Closure of the linear HMB forms an asymmetric pyrrole ring D called uroporphyrinogen III, catalyzed by uroporphyrinogen-III synthase. This step is vital as an incorrect porphyrin ring formation leads to protoporphyria. The correct porphyrin ring III forms, and then the side chains of uroporphyrinogen III are modified, catalyzed by uroporphyrinogen decarboxylase to produce coproporphyrinogen III.

Following its synthesis, coproporphyrinogen III gets transported into mitochondria. The coproporphyrinogen III then gets decarboxylated by coproporphyrinogen oxidase enzyme to form the colorless product protoporphyrinogen IX.

Finally, protoporphyrinogen IX is converted to protoporphyrin IX using protoporphyrinogen oxidase. The final reaction involves the insertion of ferrous iron into protoporphyrin IX catalyzed by the enzyme ferrochelatase leading to the formation of heme.[5]

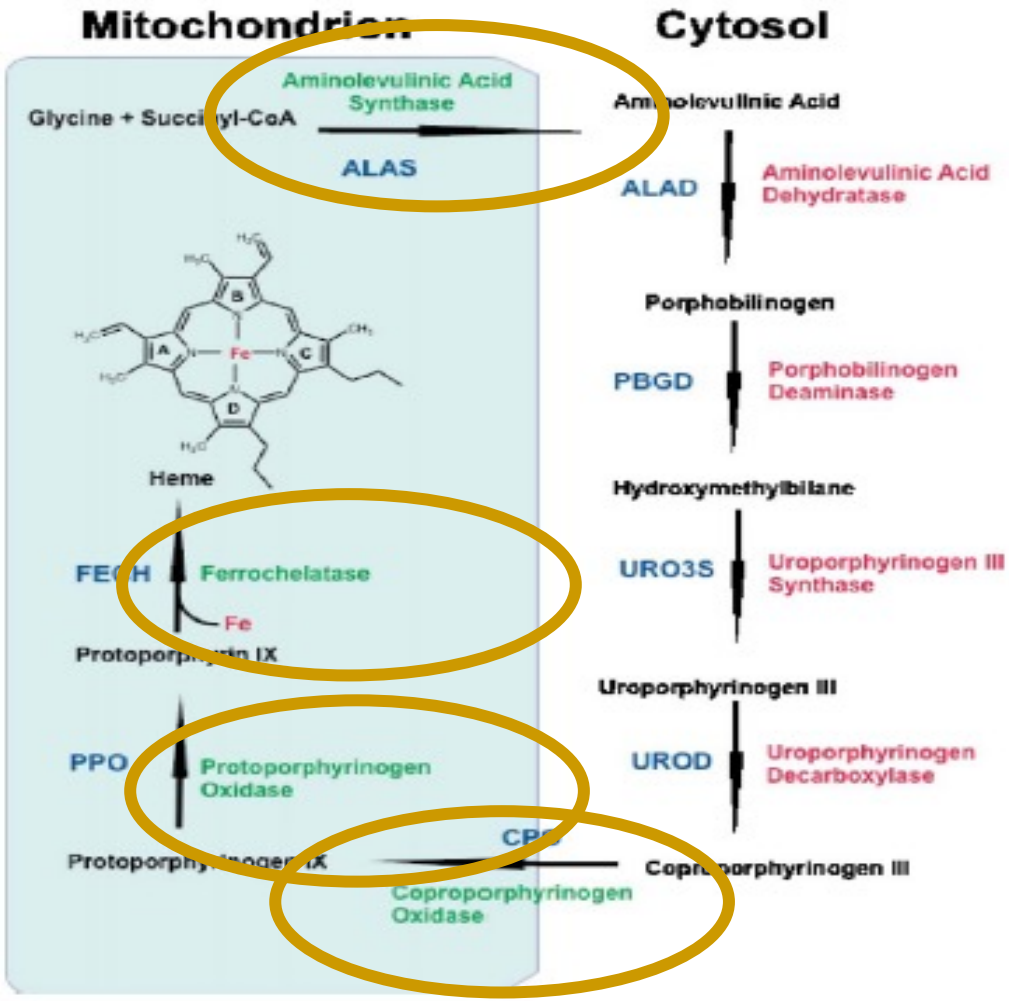
2

"Heme biosynthesis starts in mitochondria with the condensation of succinyl Co-A from the citric acid cycle and an amino acid glycine. They combine to produce a key heme intermediate, 5'-aminolevulinic acid (ALA) in mitochondria **catalyzed by the pyridoxal phosphate-requiring (vitamin B6) enzyme**, aminolevulinic acid synthase (ALAS). This reaction is the rate-limiting step in the pathway."[2]

Source: 1. Ajioka, RS et al, The Biosynthesis of Heme in Mammals. Biochimica et Biophysica Acta 1763 (2006) 723–736; Kuklinski, B. Cryptopyrroluria, nitrosative stress and mitochondrial disease; 2. https://www.ncbi.nlm.nih.gov/books/NBK537329/

The breakdown in heme synthesis can of course be due to a mitochondrial disorder …

… if the mitochondria are dysfunctional, you can't synthesise heme because four steps take place in the mitochondria



However it is caused, important to remember is that **the result is hypoxia** – oxygen deficiency in the blood, tissues and organs

Of note: The spike protein can also bind heme

JBC RESEARCH ARTICLE

Heme binding to the SARS-CoV-2 spike glycoprotein

Received for publication, April 11, 2023, and in revised form, June 12, 2023 Published, Papers in Press, July 4, 2023,
https://doi.org/10.1016/j.jbc.2023.105014

Samuel L. Freeman[1,‡], A. Sofia F. Oliveira[1,‡], Andrea E. Gallio[1], Annachiara Rosa[2], Maria K. Simitakou[2], Christopher J. Arthur[1], Adrian J. Mulholland[1], Peter Cherepanov[2,3,*], and Emma L. Raven[1,*]

From the [1]School of Chemistry, Cantock's Close, University of Bristol, Bristol, United Kingdom; [2]Chromatin Structure and Mobile DNA Laboratory, The Francis Crick Institute, London, United Kingdom; [3]Department of Infectious Disease, St-Mary's Campus, Imperial College London, United Kingdom

Reviewed by members of the JBC Editorial Board. Edited by Clare E. Bryant

The target for humoral immunity, SARS-CoV-2 spike glycoprotein, has become the focus of vaccine research and development. Previous work demonstrated that the N-terminal domain (NTD) of SARS-CoV-2 spike binds biliverdin—a product of heme catabolism—causing a strong allosteric effect on the activity of a subset of neutralizing antibodies. Herein, we show that the spike glycoprotein is also able to bind heme (K_D = 0.5 ± 0.2 μM). Molecular modeling indicated that the heme group fits well within the same pocket on the SARS-CoV-2 spike NTD. Lined by aromatic and hydrophobic residues (W104, V126, I129, F192, F194, I203, and L226), the pocket provides a suitable environment to stabilize the hydrophobic heme. Mutagenesis of N121 has a substantive effect on heme binding (K_D = 3000 ± 220 μM), confirming the pocket as a major heme binding loca-

trimeric spike protein and the S1 protein have been reported to be noticeably green in color (4, 5). Cryo-EM structures of the trimeric SARS-CoV-2 spike protein (at 3.35–3.5 Å) shows biliverdin binding in a deep hydrophobic pocket in each of three NTD domains of the protein (Fig. 1*A*, (4, 5)). An X-ray structure of the isolated NTD domain revealed details of the hydrophobic binding pocket and the binding orientation of the biliverdin metabolite at 1.8 Å resolution (Fig. 1*B*). Unidentified density in the same region in other published structures of SARS-Cov-2 (6–12) indicates that biliverdin was also present (at least at partial occupancy). Biliverdin binding substantially increased thermostability of the isolated NTD and restricted availability of a conformational epitopes on the spike NTD and decreased neutralization activity of a subset of antibodies targeting this

COVID-19 is known to be associated with extensive hemolysis[1]

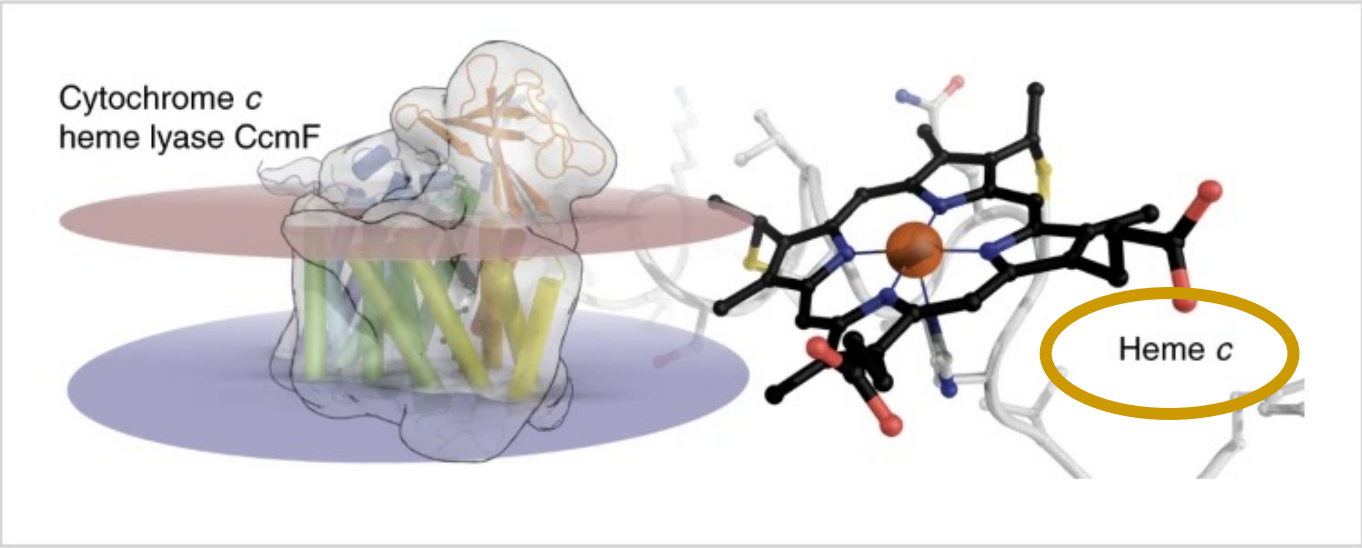
"Herein, we show that the spike glycoprotein is also able to bind heme … The heme trapping and oxidation activities of the spike may allow the virus to reduce levels of free heme during infection to facilitate evasion of the adaptive and innate immunity."[2]

Source: 1. Lazarian, G. et al. (2020) Autoimmune haemolytic anaemia associated with COVID-19 infection. Br. J. Haematol. 190, 29–31 50. Capes, A. et al. (2020) COVID-19 infection associated with autoimmune hemolytic anemia. Ann. Hematol. 99, 1679–1680 51. Sahu, K. et al. (2021) COVID-19 related immune hemolysis and thrombocytopenia. J. Med. Virol. 93, 1164–1170; 2. Freeman SL et al. Heme binding to the SARS-CoV-2 spike glycoprotein. J Biol Chem. 2023 Aug;299(8):105014.

Agenda

- The roles of pyrroles, porphyrins and heme in KPU
- **The symptoms of KPU**
- Testing
- Therapeutic approaches

Heme vital for energy production in the mitochondria



1

"**Cytochrome c transfers one electron at a time via its heme group** from the third complex of the electron transport chain, cytochrome bc_1, to the fourth complex of the electron transport chain, cytochrome c oxidase.[2]

Cytochrome c contains a heme iron metal center that is essential to its function. During the electron transport process, this heme iron interconverts between the Fe^{3+} and Fe^{2+} oxidation states, which allows for electrons to be accepted and donated.[4] When cytochrome c is in its oxidized form, an electron is transferred from the cytochrome bc_1 complex to the heme Fe^{3+}, reducing it to Fe^{2+}. Finally, cytochrome c releases the electron to the final electron carrier of the ETC, cytochrome c oxidase."[2]

Source: Brausemann A, Zhang L, Ilcu L, Einsle O. Architecture of the membrane-bound cytochrome c heme lyase CcmF. Nat Chem Biol. 2021 Jul;17(7):800-805; https://chem.libretexts.org/Courses/Saint_Marys_College_Notre_Dame_IN/CHEM_342%3A_Bio-inorganic_Chemistry/Readings/Metals_in_Biological_Systems_(Saint_Mary%27s_College)/Cytochrome_C

Where do we have heme in the body?

CONTEMPORARY REVIEW

American Heart Association | American Stroke Association.

Role of Heme in Cardiovascular Physiology and Disease

Konrad Teodor Sawicki, BS;* Hsiang-Chun Chang, PhD;* Hossein Ardehali, MD, PhD

Heme is an essential molecule for living aerobic organisms and is involved in a remarkable array of diverse biological processes. In the cardiovascular system, heme plays a r… production Although most con… also requ… including … and heme … and catala… cular syst… the erythr… important … and patho…

an argon laser, which excites the porphyrins and causes cytotoxic effects.[2]

The function of heme-containing proteins depends strongly …

Heme S…

Heme con… ring syste… the porph… planar net… the chara… and provi…

"In addition to hemoglobin, several hundred other proteins contain heme (Table). Heme is an essential prosthetic group for hemoproteins involved in numerous cardiovascular processes, including oxygen transport (hemoglobin), oxygen storage (myoglobin), oxygen metabolism (oxidases), antioxidation (peroxidases, catalases), and electron transport (cytochromes). Although the heme-containing cytochrome P450 family of enzymes is well known for its role in hepatic detoxification, several cytochrome P450 isoforms are also expressed in the heart and catalyze arachidonic acid oxidation, which attenuates myocardial ischemic injury.7 Heme-containing proteins have also been implicated as signaling molecules (guanylate cyclase), as enzymes (cyclooxygenase, nitric oxide [NO] synthase), and in the synthesis of hormones (hydroxylases). Recently, a heme-containing mitochondrial respiratory complex, succinate dehydrogenase, has been implicated in the generation of reactive oxygen species (ROS) during ischemia–reperfusion injury in different organs, including the heart.8 Consequently, heme is required for the maintenance of cardiovascular health, not only as a catalytic subunit of enzymes but also as a signaling molecule. Although **every cell in the body requires heme**, the 2 major sites of heme synthesis are the bone marrow and the liver. An important function of heme in the liver is the synthesis of cytochrome P450 enzymes, which are required in varying amounts for liver detoxification under different conditions."

Source: Sawicki KT, Chang HC, Ardehali H. Role of heme in cardiovascular physiology and disease. J Am Heart Assoc. 2015 Jan 5;4(1):e001138.

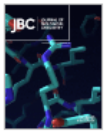
What is heme used for in the body?

- In the **blood stream: haemoglobin** – vital for carrying iron in the blood/for oxygen
- In the **mitochondria**: for Cytochrome C, hence affects our energy levels as well as cellular signalling
- For **apoptosis**, i.e., cell renewal (and for killing cancer cells!), because Cytochrome C is also vital for apoptosis (P57)
- **Cytochrome P450 detoxification** enzymes, crucial for Phase I detoxification: all have haem at their centre, and cannot work without it, so every form of detoxification will be impaired
- Enzymes such as **catalase** and the **peroxidases** rely on heme as essential cofactors
- **Myoglobin** also contains a heme group, so this protein in the cardiac and skeletal muscles will be weakened
- **Nitric oxide synthase** is heme-dependent – there are three NOSs: eNOS, iNOS, and nNOS. NOS a significant enzyme in the urea cycle: catalyses the biosynthesis of nitric oxide: disrupted heme synthesis makes it harder to process/eliminate ammonia, instead creating peroxynitrite, very toxic
- Cystathione ß-synthase – heme-dependent, first step in removing homocysteine

Source: KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann; 2 Kang Z, Zhang J, Zhou J, Qi Q, Du G, Chen J. Recent advances in microbial production of δ-aminolevulinic acid and vitamin B12. Biotechnol Adv. 2012 Nov-Dec;30(6):1533-42. , https://pubmed.ncbi.nlm.nih.gov/22537876/; 3. https://www.sciencedirect.com/topics/materials-science/nitric-oxide-synthase

The cystathionine ß-synthase enzyme is heme- and B6-dependent

JBC | JOURNAL OF BIOLOGICAL CHEMISTRY



Volume 273, Issue 39, 25 September 1998, Pages 25179-25184

ENZYMOLOGY

Evidence for Heme-mediated Redox Regulation of Human Cystathionine β-Synthase Activity *

Shinichi Taoka ‡, Sunil Ohja ‡, Xiaoyin Shan §, Warren D. Kruger §, Ruma Banerjee ‡

Show more

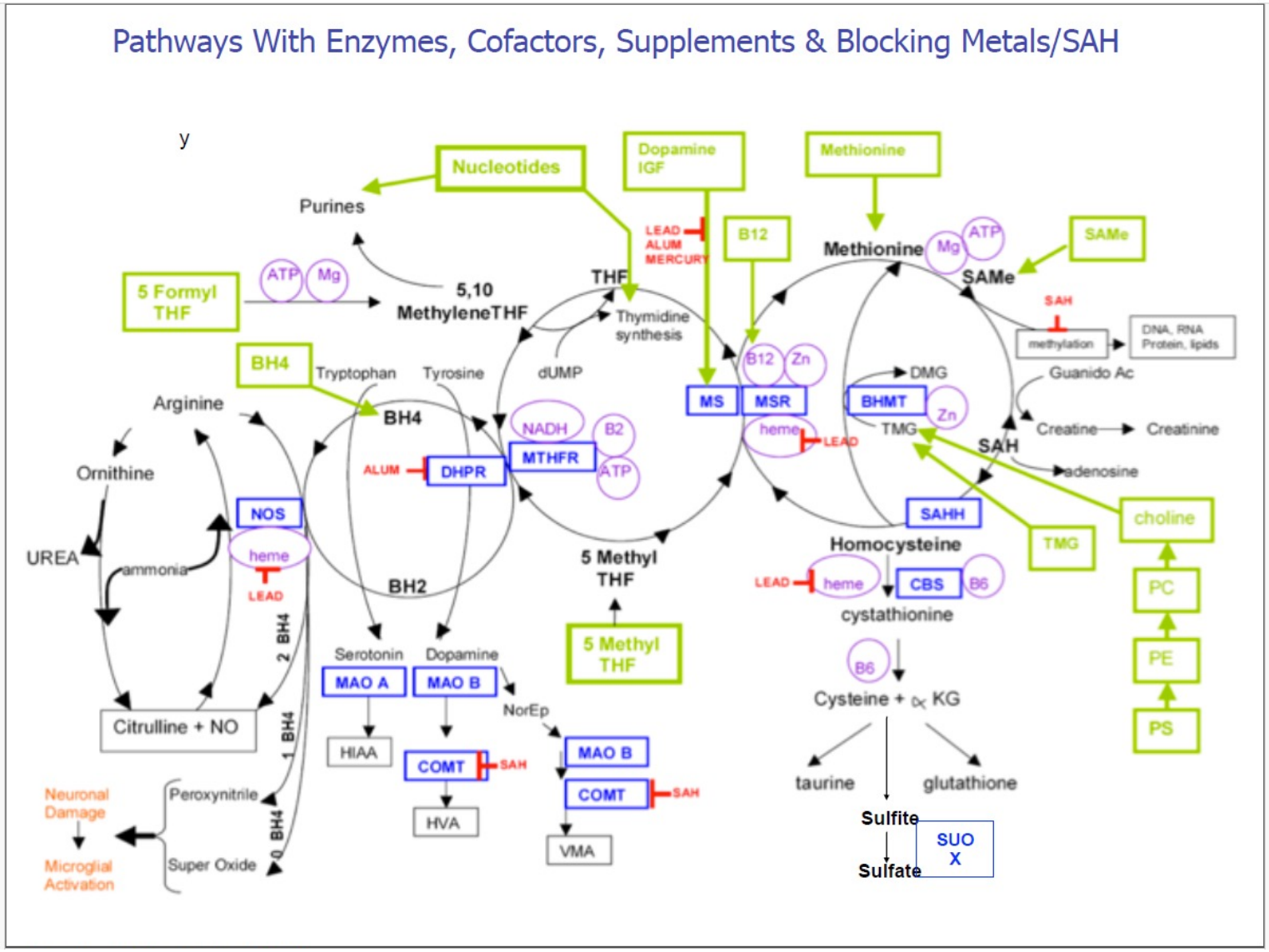
+ Add to Mendeley Share Cite

https://doi.org/10.1074/jbc.273.39.25179 ↗ Get rights and content ↗

Human cystathionine β-synthase catalyzes the first step in the catabolic removal of the toxic metabolite, homocysteine. It is unique in being dependent on both pyridoxal phosphate (PLP) and heme for activity. The reaction involves condensation of serine and homocysteine to give cystathionine. Although the role of PLP can be rationalized in analogy with other PLP-dependent enzymes that catalyze β-replacement reactions, the role of the heme is unknown. In this study, we have purified and characterized the recombinant human enzyme and have examined the effect of heme oxidation state on enzyme activity. We find that under reducing conditions, generated by addition of titanium citrate, the enzyme exhibits a 1.7-fold lower activity than under oxidizing conditions. Reoxidation of the ferrous enzyme with ferricyanide results in alleviation of inhibition. This redox-linked change in enzyme activity correlates with changes in heme

Source: Taoka S, Ohja S, Shan X, Kruger WD, Banerjee R. Evidence for heme-mediated redox regulation of human cystathionine beta-synthase activity. J Biol Chem. 1998 Sep 25;273(39):25179-84.

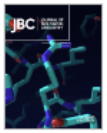
Note the homocysteine/CBS pathway where heme is required



Source: Dr. Amy Yasko; https://naturopathic.doctor/tag/amy-yasko/, Dr. Nicholas Morgan; Dr. Dietrich Klinghardt, https://www.youtube.com/watch?v=THZhANfFnyY

CBS enzyme is heme-dependent

JBC JOURNAL OF BIOLOGICAL CHEMISTRY



Volume 273, Issue 39, 25 September 1998, Pages 25179-25184

ENZYMOLOGY

Evidence for Heme-mediated Redox Regulation of Human Cystathionine β-Synthase Activity *

Shinichi Taoka ‡, Sunil Ohja ‡, Xiaoyin Shan §, Warren D. Kruger §, Ruma Banerjee ‡

Show more

+ Add to Mendeley Share Cite

https://doi.org/10.1074/jbc.273.39.25179 ↗ Get rights and content ↗

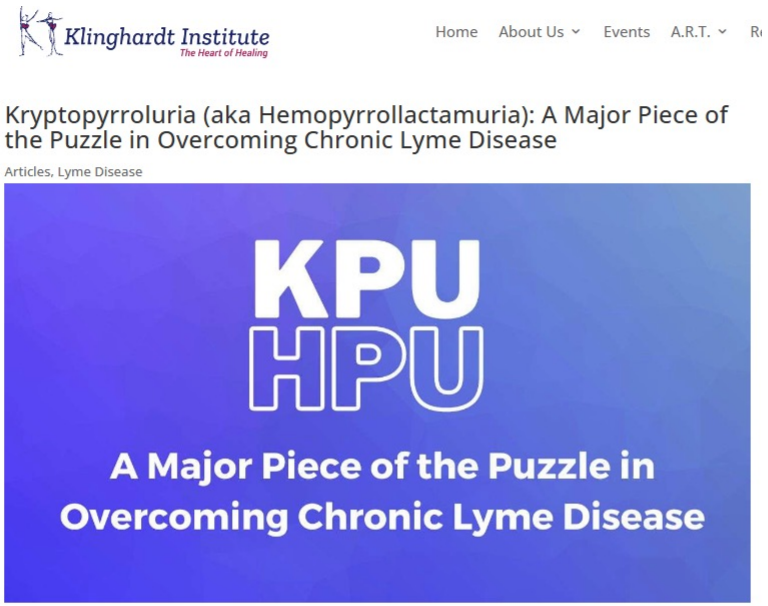
Human cystathionine β-synthase catalyzes the first step in the catabolic removal of the toxic metabolite, homocysteine. It is unique in being dependent on both pyridoxal phosphate (PLP) and heme for activity. The reaction involves condensation of serine and homocysteine to give cystathionine. Although the role of PLP can be rationalized in analogy with other PLP-dependent enzymes that catalyze β-replacement reactions, the role of the heme is unknown. In this study, we have purified and characterized the recombinant human enzyme and have examined the effect of heme oxidation state on enzyme activity. We find that under reducing conditions, generated by addition of titanium citrate, the enzyme exhibits a 1.7-fold lower activity than under oxidizing conditions. Reoxidation of the ferrous enzyme with ferricyanide results in alleviation of inhibition. This redox-linked change in enzyme activity correlates with changes in heme

Source: Taoka S, Ohja S, Shan X, Kruger WD, Banerjee R. Evidence for heme-mediated redox regulation of human cystathionine beta-synthase activity. J Biol Chem. 1998 Sep 25;273(39):25179-84.

Key deficiencies are B6 and zinc – but many others are linked, too

The key deficiencies found in KPU are B6 and zinc, due to the pyrroles binding with them and excreting them via the urine. Manganese is also a common deficiency, and others that have been noted are chromium, biotin (B7) and Omega 6

"The KPU condition results in a significant loss of zinc, vitamin B6, biotin, manganese, arachidonic acid, and other nutrients from the body via the kidneys." (Scott Forsgren, Dietrich Klinghardt MD)



Source: Kryptopyrroluria (aka Hemopyrrollactamuria) 2017: A Major Piece of the Puzzle in Overcoming Chronic Lyme Disease *by Scott Forsgren, FDN-P and Dietrich Klinghardt, MD, PhD, https://www.townsendletter.com/July2017/krypto0717.html; http://cinak.com/editions/articles_eng/hpu%202009.pdf; https://epidemicanswers.org/symptoms_and_diagnoses/kryptopyrroluria-pyrrole-disorder-pyroluria/*

KPU can cause so many knock-on effects: appearance/ energy/ detoxification

► **Physical appearance:** Pale, sallow skin, pale lips, pruritis either in certain areas or all over (anal pruritis is particularly prevalent in children); light intolerance, rash in sunlight, yellowish-brown pigmentation after being in the sun, slight puffiness of the face, especially around the cheeks and eyes. Dark rings around the eyes, eyes sunk deep into their sockets; soft gums; striae on the skin similar to stretch marks; white spots on the nails (leukodynia), sometimes hair loss, acne, eczema and dandruff; poor tooth enamel

► **Impaired energy production:** Fatigue, may be severe – M.E./CFS, fibromyalgia, and all the further downstream effects of hypoxia, including **anaemia**

► **Detoxification issues** because Cytochrome P450 mono-oxygenases in Phase 1 also contain heme. Environmental toxins build up as a result, medications cannot be properly metabolised, etc. Common result: multiple chemical sensitivity (MCS) and medication intolerances.

Source: Strienz, Joachim: Leben mit KPU – *Kryptopyrrolurie, Ein Ratgeber für Patienten,* Germe-ring/München 2011 (Living with KPU – Kryptopyrroluria, in German); KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann

Symptoms: Neurological/neuropsychiatric, thyroid, immune

► **Neurological issues**, often labelled psychiatric: Memory and concentration difficulties, problems with short-term memory, “brain fog”, poor dream recall (B 6 dependent!), low mood, fear, panic attacks, withdrawal from social activities, hallucinations, apparent schizophrenia/ psychosis, ADHD, due partly to lack of B6 and zinc metabolism causing low serotonin, adrenalin and dopamine levels. Animal experiments have also shown that injecting rats, cats and guinea pigs with free pyrroles leads to severe neurological disorders.

► **Hyperactivity, behavioural disorders** – typical signs of KPU crossover with PANS/PANDAS

► **Thyroid disorders:** Hypothyroidism, Hashimoto’s thyroiditis (oxygen and zinc deficiency)

► **Immune disorders** as the synthesis of proteins is B6-dependent, which even means you cannot form antibodies properly because they are formed from amino acids

Source: Strienz, Joachim: Leben mit KPU – *Kryptopyrrolurie, Ein Ratgeber für Patienten,* Germe-ring/München 2011 (Living with KPU – Kryptopyrroluria, in German); KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann; Cutler MG, Douglas JM, Graham DJM, Moore MR. The mauve factor of porphyria, 3-ethyl-5-hydroxy-4, 5-dimethyl-delta-3-pyrroline-2-one: Effects on behaviour of rats and mice. *BCPT (Basic & Clinical Pharmacology & Toxicology.* 1990;**66**(1):66–68.

Symptoms: Musculoskeletal, collagen

► **Musculoskeletal symptoms:** Hypermobility (hEDS), pelvic instability, weak muscles. Often muscle and joint pain (due to myoglobin being affected, because it has a haem group)

► **Collagen:** "Yes pyroluria can be a factor in many tendon and joint issues (and ankle/wrist/thumb) pains as it affects all types of collagen. Zinc, B6, EPO and manganese are all needed. " (Dr. Trudi Scott, https://www.everywomanover29.com/blog/pyroluria-questionnaire-from-the-antianxiety-food-solution/)
Cartilage consists of collagenous connective tissue, which requires all 3 – B6, Zn, and Mn. Manganese is especially essential for the synthesis of hyaluronic acid, glucosaminoglycans and chondroitin sulphate

► **Ehlers Danlos Syndrome?:** Hyperextension of the joints – a form of EDS – can be due to manganese deficiency. Bone cells – osteocytes – also require all 3, as well as Mg and Vitamin D

Source: Strienz, Joachim: Leben mit KPU – *Kryptopyrrolurie, Ein Ratgeber für Patienten,* Germe-ring/München 2011 (Living with KPU – Kryptopyrroluria, in German); KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann

Symptoms: Allergy, gastrointestinal issues, histadelia, fructose intolerance

► **Allergies, food intolerances**, lactose intolerance (lactoperoxidase contains haem)

► **Protein maldigestion** (lack of zinc for HCl)

► **Gastrointestinal disorders:** Bloating, pain, nausea, especially in the morning. Alternating diahorrea and constipation, halitosis, aversion to meat (because the conversion of muscle protein to our own protein is B6-dependent)

► **Histamine issues:** Diamine oxidase action disrupted without the cofactors B6 and zinc; DAO needed to break down histamine, so this can cause excess histamine

► **Fructose intolerance:** Zinc is a catalytic cofactor in conversion of fructose into glucose in the liver using the enzyme aldolase B. Lack of it can cause fructose intolerance

Source: Strienz, Joachim: Leben mit KPU – *Kryptopyrrolurie, Ein Ratgeber für Patienten,* Germe-ring/München 2011 (Living with KPU – Kryptopyrroluria, in German); KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann; Wissuwa M, Ismail AM, Yanagihara S. Effects of zinc deficiency on rice growth and genetic factors contributing to tolerance. Plant Physiol. 2006 Oct;142(2):731-41.

Symptoms: Blood sugar disorders, even contribution to MetSyn and diabetes

► **Blood sugar disorders:** Hypoglycaemia because gluconeogenesis is B6-dependent; can contribute to Diabetes type II. The conversion of protein and carbohydrate stores into glucose (gluconeogenesis) requires B6[1, 2]

► **Aspects of metabolic syndrome:** High blood pressure, high triglyceride/LDL level/total cholesterol levels can all be explained by KPU

► **Diabetes:** High pyrrole adducts have been found in diabetes[3] Makes sense as if it is or results in a mitochondrial disorder, the cells can't use oxygen as well as they should, anaerobic glycolysis may result, leading to the overuse of glucose as a fuel

"The effect of the disruption of nitric oxide synthesis in urea cycle disorders is a new research focus and **explains high blood pressure ...**"[4]

Translational Science of Rare Diseases 1 (2016) 23–43
DOI 10.3233/TRD-160002
IOS Press

Defects of the urea cycle

Uta Lichter-Konecki*
Department of Pediatrics, Division of Medical Genetics, Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, USA

Abstract. The elimination of waste nitrogen as urea is a final and central step of amino acid catabolism. It is accomplished by one of the most essential pathways of terrestrial animals, the urea cycle. This article describes the basic function of the 5 catalytic enzymes, the two transporters, and the cofactor synthesizing enzyme that comprise the urea cycle as well as the consequences of their deficiencies and ways to treat them. The article then elaborates on related disorders of metabolism that may either cause hyperammonemia or elevation of an amino acid that is key to urea cycle function.

Keywords: Nitrogen metabolism, hyperammonemia, urea cycle disorders, nitrogen scavenger, ornithine

Subsequently, analyses of the longitudinal study data of the first 8 years showed that hyperammonemic episodes after the neonatal period are most often caused by intercurrent infections, that both plasma ammonia and glutamine elevations may be biomarkers for neuropsychological outcome, that low protein diet causes reduced height in UCD patients, that high dose arginine has a negative impact on liver function in ASA patients, that phenylbutyrate causes low levels of branched chain amino acids, and that patients with OTC deficiency tend to have hepatic dysfunction even liver failure. In addition, at study sites the mortality of neonatal onset disease was 24% and that of post-neonatal onset disease 11% [25]. The effect of the disruption of nitric oxide synthesis in urea cycle disorders is a new research focus and explains high blood pressure and possibly also part of the intellectual disability in patients with ASL [26].

7 General considerations for treatment of urea cycle defects

Prevention of hyperammonemia and treatment of UCDs rely heavily on ammonia-lowering strategies with administration of nitrogen scavengers such as, benzoate, and phenylacetate or phenylbutyrate as well as low protein diet.

Source: 1. Strienz, Joachim: Leben mit KPU – *Kryptopyrrolurie, Ein Ratgeber für Patienten,* Germe-ring/München 2011 (Living with KPU –Kryptopyrroluria, in German); 2. KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann; 3. Chen X et al. Protein pyrrole adducts are associated with elevated glucose indices and clinical features of diabetic diffuse neuropathies. J Diabetes. 2022 Oct;14(10):646-657; 4. Lichter-Konecki, Uta. 'Defects of the Urea Cycle'. 1 Jan. 2016 : 23 – 43.

Symptoms: Fertility, reproduction issues, methylation

► Recurrent miscarriage and **fertility issues** relate to methylation and the MTHFR genes, which can be affected by KPU

► **Reproduction** relies upon zinc and B6. A deficiency can cause infertility. PCOS is one of the leading causes of infertility and is complicated further with a deficiency of zinc and B6. The quality of eggs is reliant upon zinc, and it is also necessary for sperm health. The embryonic development of the fetus is also reliant upon this important mineral[2]

► **Methylation issues**: Problems with the synthesis of B12 because δ-aminolevulinic acid is also necessary as the universal precursor molecule involved in **tetrapyrrole** synthesis - precursor for vitamin **B12[2:]**: this in turn affects the methylation cycle, with multiple knock-on effects

Source: Strienz, Joachim: Leben mit KPU – *Kryptopyrrolurie, Ein Ratgeber für Patienten,* Germe-ring/München 2011 (Living with KPU – Kryptopyrroluria, in German); KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann; 2. https://www.thriveclinic.uk/pyroluria.html#/

Agenda

- The roles of pyrroles and porphyrins in KPU
- The symptoms of KPU
- **Testing**
- Therapeutic approaches

Webpage on the AONM website with all the details

https://aonm.org/kryptopyrroluria-testing/

kiweno

TEST REQUISITION

Kryptopyrroluria (KPU) Testing

AONM ACADEMY of NUTRITIONAL MEDICINE

PATIENT INFORMATION		BARCODE (Lab use only)	Please send results to: ☐ myself ☐ my practitioner
Patient FIRST NAME*:			PRACTITIONER INFORMATION
Patient SURNAME*:			Dr. / Practitioner name:
DATE OF BIRTH (DD/MM/YYYY)*:			Clinic:
Sex* (please circle): male female		Time sample taken*:	Street Address:
Street Address:		Date sample taken (DD/MM)*:	
		Material/Quantity ☐ Urine	Postcode: City:
Postcode:	City:		County: Country:
County:	Country:	AONM HELPLINE: +44 (0) 3331 210 305	Tel no:
Tel no:			Email:
Email*:			

TEST NUMBER	NAME	SAMPLE TYPE	PRICE
☐ KPU1	Kryptopyrrole Test	Urine	£98

Simple urine collection

First morning urine is the test producer's suggestion

The test producer does not specify that one should stop taking the minerals/ vitamins one may be deficient in, but if you can, it would be best to discontinue them for a period of time if you can – Dr. Klinghardt suggests 5 days*

* https://www.youtube.com/watch?v=THZhANfFnyY

Extensive lab report with 7 pages

ACADEMY OF NUTRITIONAL MEDICINE

Kryptopyrroluria

Lab Report

Your lab result

As requested, we have analysed the kryptopyrroles in your urine sample for possible kryptopyrroluria (KPU). Below you will find your result and important information to help you better understand your health and take corrective measures if necessary.

NAME:

ANALYSIS	RESULT
Kryptopyrroles in urine	325,3 ng/ml

Interpretation: The concentration of kryptopyrroles in your urine is ***elevated***

Symptoms

The symptoms associated with KPU can vary among individuals and may be nonspecific, but common symptoms may include:

- **Neurological symptoms**
  - Memory issues and difficulty concentrating
  - Brain fog or mental confusion
  - Mood swings, anxiety, and depression
  - Irritability and emotional instability
  - Sleep disturbances and insomnia
- **Digestive issues**
  - Abdominal pain or discomfort
  - Nausea and vomiting
  - Diarrhea or constipation
  - Poor appetite or food sensitivities
- **Fatigue and weakness**
  - Chronic fatigue and low energy levels
  - Muscle weakness and reduced stamina
- **Skin problems**
  - Sensitivity to sunlight (photosensitivity)
  - Skin rashes or acne
  - Dry or itchy skin
- **Musculoskeletal symptoms**
  - Joint pain and stiffness
  - Muscle pain and cramps
- **Immune system disturbances**
  - Frequent infections or weakened immune response
- **Sensitivity to sensory stimuli**
  - Sensitivity to light, noise, or odours

Note: It's important to note that these symptoms are not specific to KPU and can overlap with various other medical conditions. Additionally, not everyone with KPU will experience all of these symptoms, and the severity can vary significantly among individuals.

Because mitochondrial dysfunction is such a large part of the puzzle, a mitochondrial test alongside may be indicated

RESULTS

Sample type: Blood in CPDA vials

Requisition:
Mitochondrial Health Index / PBMCs

Summary

	Patient´s value	Target value (optimal)
Mitochondrial Health Index (MHI)	1.31	>2.5
Mitochondrial Bioenergetics		
Coupling efficiency, %	100	100
Reserve respiration capacity, %	74	>400
Cellular oxygen consumption profile		
Non-mitochondrial respiration as a share of total respiration, %	42	<10
Proton leak as a share of total respiration, %	0	
Share of respiration used for mitochondrial ATP generation, %	60	>90
ATP turnover rate (mitochondrial oxygen utilisation)		
ATP base turnover, %	59	<20
ATP reserve, %	41	>80
Potential maximum oxygen consumption rate in pmol oxygen/min	45	>300
Cellular energy phenotype		
At rest	Resting/glycolytic	Resting
On energy demand	glycolytic	Energetic/Aerobic
Metabolic potential, mitochondrial percentage	144	>350
Metabolic potential, glycolysis percentage	193	>350
Oxygen consumption/glycolysis on energy demand	Moderate preference for anaerobic glycolysis	

Optimal	Slightly high / low	Moderately high/low	Very high/low	Extremely high/low

Page | 1

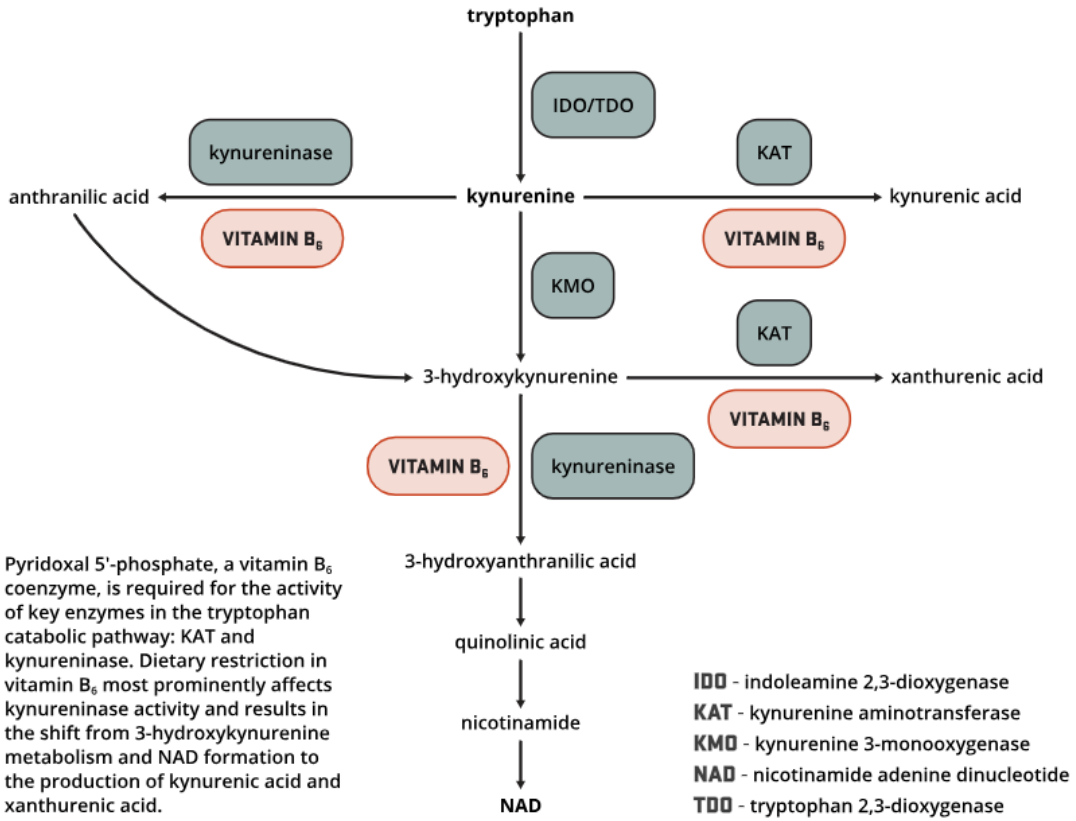
Source: AONM/MMD mitochondrial test results from a patient with K{U, with permission of the patient

Could also be sensible to test micronutrients, as the patient may not be deficient in all the possible vitamins/minerals, but caution*

*** most tests do not show up intracellular/ intramitochondrial levels reliably**

B6 deficiency: example of the possible impact

Figure 2. Overview of the Tryptophan-Kynurenine Metabolic Pathway



"With B6 and Zinc supplementation, my son's has been seizure free now for 3 months and all of the behaviours have disappeared."[2]

EPILEPSY FOUNDATION

Source: https://lpi.oregonstate.edu/mic/vitamins/vitamin-B6; 2. https://www.epilepsy.com/connect/forum-archive/medication-issues/pyroluria

Agenda

- The roles of pyrroles, porphyrins and heme in KPU
- The symptoms of KPU
- Testing
- **Therapeutic approaches**

Therapeutic approaches

Need to compensate the macro- and micronutrient deficiencies

The approach often taken is to give supraphysiological doses of B6, Zinc and Manganese

Need to beware that heavy metal detox will generally be needed (Cd, Pb, Al, Hg)

Plus bioavailable copper may well play a major role

And if it's a mitochondrial dysfunction, need to find out what the issue is and remedy that

Lots of food sources of course, too – but difficult to reach supraphysiological doses with foods

Box 2: Food sources of B6, zinc and manganese

Some good sources of B6:

Chicken	Hazelnuts	Potatoes
Tuna	Pinto beans	Sardines
Walnuts	Halibut	Brussel sprouts
Salmon	Avocados	Cod
Lentils	Chestnuts	Sweet potatoes
Lima beans	Kale	Cauliflower
Blackeyed peas	Whole grain rye	Red cabbage
Brown rice	Spinach	Leeks

Some rich food sources of zinc:

Oysters	Lima beans	Shrimp
Ginger roots	Almonds	Turnips
Pecans	Walnuts	Black pepper
Split peas	Clams	Paprika
Whole grain wheat	Tuna	Chili powder
Whole grain rye	Haddock	Thyme
Whole grain oats	Green peas	Cinnamon

Some food sources of manganese:

Wheat germ	Brussel sprouts	Grapefruit
Green leafy vegetables	Blueberries	Apricots
Spinach	Oranges	Kelp

https://aonm.org/kryptopyrroluria-the-elephant-in-the-room/

Dr. Klinghardt has formulated a KPU remedy that is often recommended

Ingredients	per Daily Dosage (1 capsule)	% NRV *
Vitamin B-6 (Pyridoxal-5-Phosphate, Pyridoxin HCl)	19 mg	1357 %
Biotin	2000 mcg	4000 %
Zinc (zinc monomethionine, zincbisglycinate chelate, zincgluconate, zincpicolinate)	10 mg	100 %
Manganese (aus manganese bisglycinat chelate)	1,8 mg	90 %
Chromium (Chromium-aminoacid-chelate)	125 mcg	312,5 %
Molybdenum (molybdenum-glycinate-chelate)	100 mcg	200 %
Boron (boron citrate / Bororganic glycine)	1 mg	--
Taurin	21 mg	--

** percentage of nutritional reference value*

Source: https://www.kiscience.com/?s=CORE&post_type=product&product_cat=0

Tisso Naturprodukte has also formulated a product specifically for KPU (available from the Natural Dispensary)

FOOD SUPPLEMENT

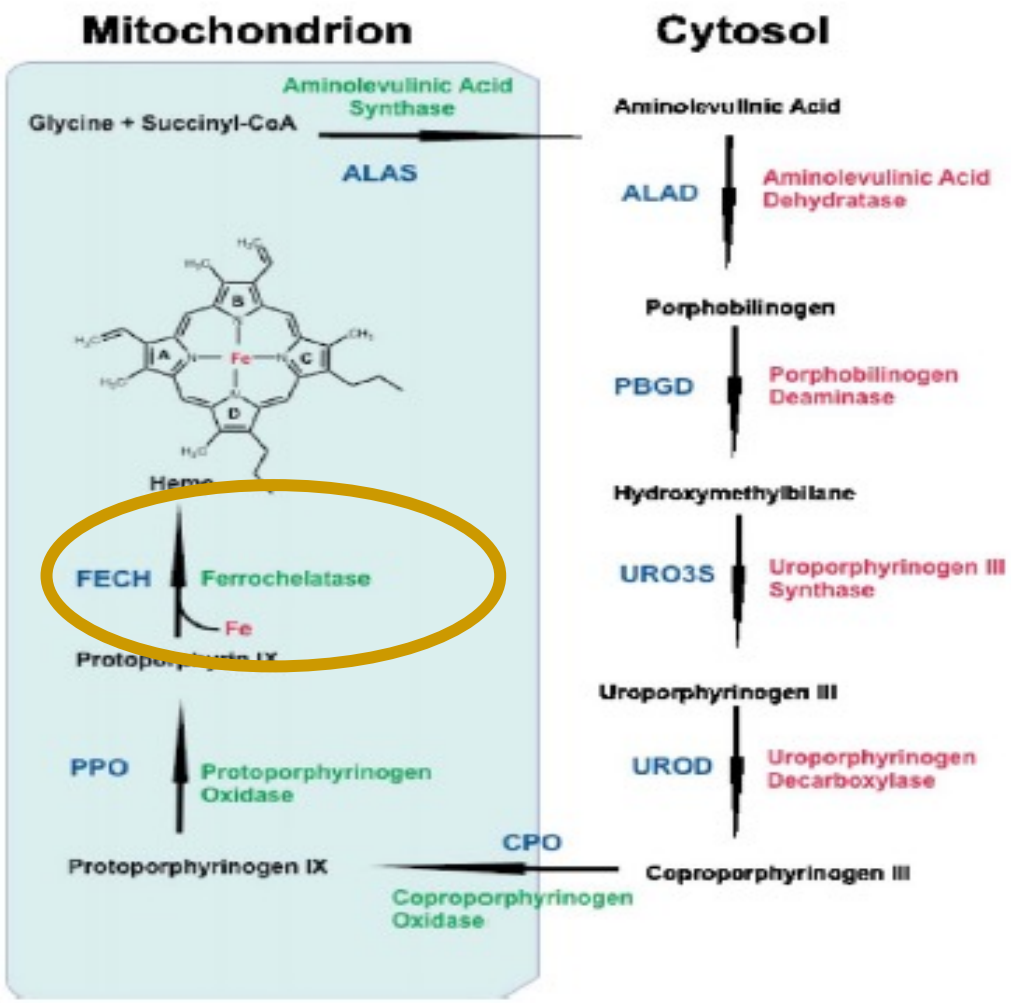
Pro Krypto Balance

For the additional supply of B vitamins, zinc, manganese and chromium: Pro Krypto Balance supplies the body with these nutrients, especially when there is an increased need and in stressful situations. The nutrient complex also provides vitamin C and vitamin E to protect the cells from oxidative stress.

- For increased requirements of B vitamins, zinc, manganese & chromium, e.g. for KPU/HF
- Plus vitamins B6, B12 and folic acid (active form)
- Supports the nervous system & homocysteine metabolism
- With vitamins C and E as cell protection against increased stress

Source: https://naturaldispensary.co.uk/products/Pro_Krypto_Balance_60_s-9999374-0.html

The last step in the synthesis of heme is Ferrochelatase



It has long been considered that the likely cause of pyrroluria in both primary and secondary KPU is a defect in heme metabolism in the inner mitochondrial membrane[2]

Four of the enzymes are copper-dependent (see next page for Ferrochelatase)

Source: 1. Ajioka, RS et al, The Biosynthesis of Heme in Mammals. Biochimica et Biophysica Acta 1763 (2006) 723–736; Kuklinski, B. Cryptopyrroluria, nitrosative stress and mitochondrial disease; 2. KPU/HPU häufige, aber verkannte Mitochondrienstörungen, 3rd edition 2018, Kyra Kauffmann, Sascha Kauffmann

Might copper be a huge missing piece in the puzzle?

N.B. Ferrochelatase for example requires copper as a cofactor – is this perhaps a huge missing piece in the Pyrrolia mystery?

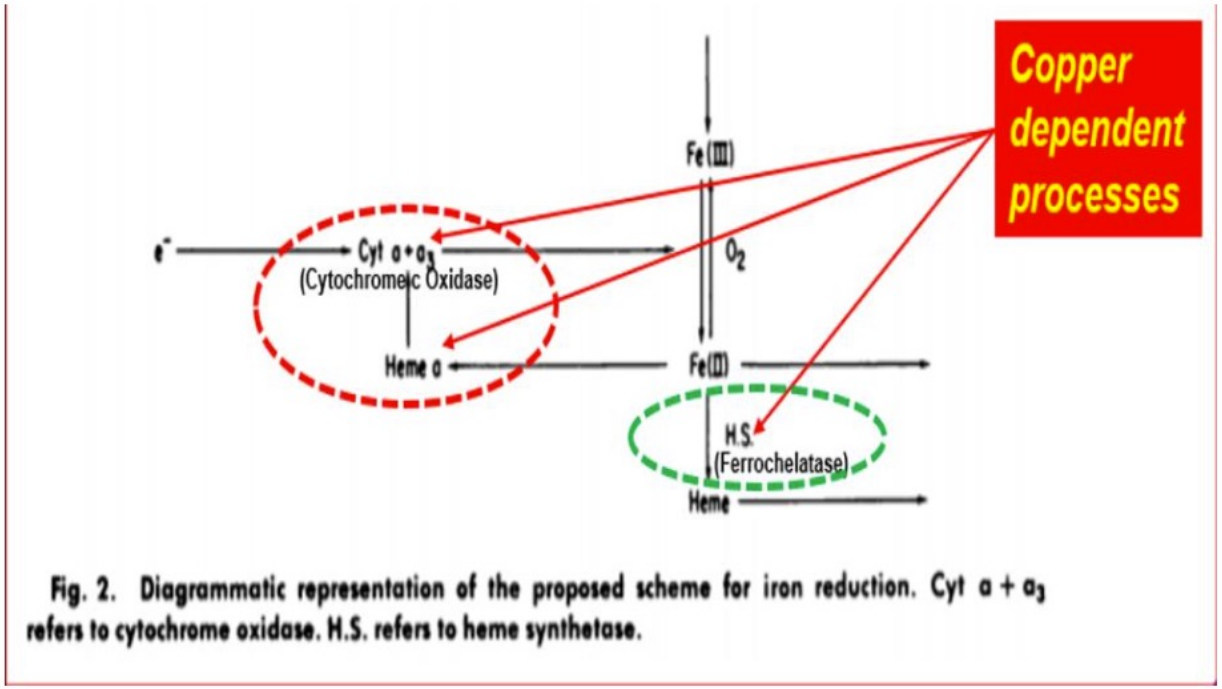


Fig. 2. Diagrammatic representation of the proposed scheme for iron reduction. Cyt $a + a_3$ refers to cytochrome oxidase. H.S. refers to heme synthetase.

1

Source: https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/heme-synthesis#:~:text=ferrochelatase%2C%20the%20final%20enzyme%20in,of%20iron%20with%20cysteine%20residues; Kyra/Wagner GS, Tephly TR. A possible role of copper in the regulation of heme biosynthesis through ferrochelatase. Adv Exp Med Biol. 1975;58(00):343-54; Root Cause Protocol, https://therootcauseprotocol.com/; https://therootcauseprotocol.com/iron-toxicity-post-75-formerly-itp76/, 1. https://ashpublications.org/blood/article/48/1/77/160532/Role-of-copper-in-mitochondrial-iron-metabolism

Copper is also vital for the production of erythrocytes: erythropoiesis and hematopoesis

THE ROLE OF COPPER IN ERYTHROPOIESIS*

GEORGE E.CARTWRIGHT, CLARK J.GUBLER AND MAXWELL M.WINTROBE†

Introduction. For the past eight years studies on the role of copper in erythropoiesis have been conducted in our laboratory in collaboration with Drs. Gubler and Wintrobe. We have been assisted in this work by M.E.Lahey, M.S.Chase, J.A.Bush, W.N.Jensen, J.W.Athens, Helen Ashenbrucker and H.Markowitz and the results of our work have been published in detail in a series of articles.[1–8] The purpose of the present paper is to summarize these studies. Our research confirms in great part and extends the much earlier observations of the Wisconsin group.[9,10] Pertinent literature on this subject has been reviewed in previous publications.[1–8]

A deficiency of copper has been produced in swine by feeding a diet of homogenized evaporated milk to which a liberal amount of "copper-free" iron was added (30 mg./kg. body weight daily). Control animals were given 0.5 mg. of copper/kg. of body weight daily in addition to iron. The animals were two to ten days of age at the start of the experiment.

Description of the Anemia. During the first month of the copper-deficient dietary regime, there is generally little or no decline in the hemoglobin or volume of packed red cells (V.P.R.C.) (fig. 1). Thereafter, a precipitous fall in these values occurs. If the animals are not treated, the hemoglobin decreases from 15 to 2 gm./100 ml. and the V.P.R.C. from 40 to 8 ml/100 ml in about 40 to 50 days. The animals become extremely pale and weak, the respiratory rate increases, and death supervenes, apparently as a result of tissue anoxia.

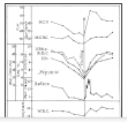


FIG. 1.

Showing the development of microcytic, hypochromic anemia, leukopenia and neutropenia in a pig deficient in copper and the response of the blood to an oral administration of 0.5 mg. of copper/kg. of body weight/day. M.C.V., mean

On the other hand, if the decreased life span were due to an intracorpuscular cause, one would expect that the copper-deficient cells would not survive for a normal period when transfused into a normal recipient. Such is not the case. When cells from a copper-deficient pig are transfused into a normal pig, the survival time approaches normal. An explanation for this observation is that copper may enter the "copper-deficient" red cells from normal plasma and correct the intracorpuscular defect. In support of this explanation, it has been demonstrated that radiocopper, when added to plasma either *in vitro* or *in vivo,* is taken up by erythrocytes within several hours.[7]

Role of Copper in Erythropoiesis. The vital role of copper in erythropoiesis is confirmed by these studies. However, the manner whereby copper so profoundly influences erythropoiesis is obscure.

Since the daily hemoglobin (or red cell) production of normal pigs may be increased fourfold under the stimulus of anemia, and since the rate of hemoglobin (or red cell) production in copper-deficient pigs is only 1.1 to 1.3 times greater than in normal animals, it is apparent that the ability to produce hemoglobin is greatly impaired in copper-deficient swine. Furthermore, both ferrokinetic studies and chromium erythrocyte survival studies indicate that the life-span of the erythrocyte in copper deficiency is shortened. It seems, therefore, that anemia develops in the absence of copper because of a limitation of the capacity of the marrow to produce cells and because of a shortened erythrocyte survival time.

A possible explanation for the decreased survival time of the erythrocytes is that the copper is an essential component of adult red cells and when the copper concentration of the erythrocyte is below a certain minimal, critical level, the survival time of the cells is shortened. There are several observations which are compatible with this hypothesis. Copper is a normal constituent of the adult red cell (table II). In copper-deficient pigs, the concentration of copper in the erythrocytes decreases from the normal value of 100 µg/100 ml. of packed cells to 67. Furthermore, when the anemia is severe there is a tendency for the concentration of copper within the red cells to increase slightly (fig. 3). One possible explanation of the latter observation is that the cells with the least amount of copper have been selectively destroyed.

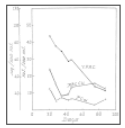


FIG. 3.

Showing the development of anemia (V.P.R.C., volume of packed red cells), and decrease in plasma copper (PCu) and red cell copper (RBC Cu) in copper-deficient swine (mean of 7 pigs).

The role of copper within the erythrocytes is unknown. Dr. Harold Markowitz in our laboratory has recently isolated a copper protein from human erythrocytes.[12] A few of the physical characteristics of this protein are given in table X. We have chosen to call this compound erythrocuprein, rather than hemocuprein, the name originally used by Mann and Keilin.[13] Its physical characteristics seem to be slightly different than those of the protein isolated by them and the name, erythrocuprein, clearly distinguishes this red cell protein from another "hemocuprein" ceruloplasmin, the

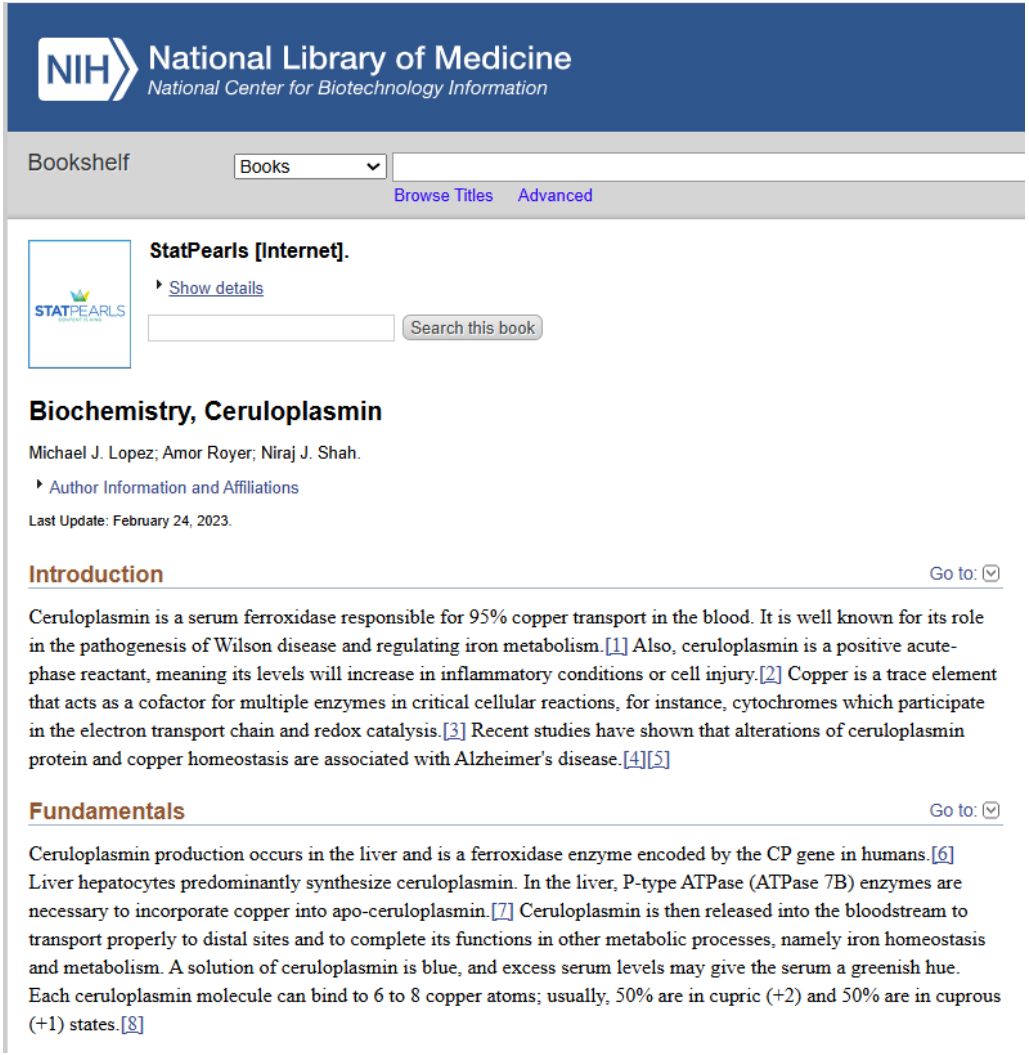
Source: https://www.ncbi.nlm.nih.gov/books/NBK224294/

Giving the organism access to bioavailable copper is not a straight replacement

Need to ensure sufficient caeruloplasmin, since it is what carries bioavailable copper into the cells/ mitochondria

"Ceruloplasmin is a serum ferroxidase responsible for 95% copper transport in the blood."

To do that requires vitamin A – not beta carotene, which is just a precursor, and many people lack the ability to convert it fully



NIH National Library of Medicine
National Center for Biotechnology Information

Bookshelf Books Browse Titles Advanced

StatPearls [Internet].

Show details

Search this book

Biochemistry, Ceruloplasmin

Michael J. Lopez; Amor Royer; Niraj J. Shah.

Author Information and Affiliations

Last Update: February 24, 2023.

Introduction Go to:

Ceruloplasmin is a serum ferroxidase responsible for 95% copper transport in the blood. It is well known for its role in the pathogenesis of Wilson disease and regulating iron metabolism.[1] Also, ceruloplasmin is a positive acute-phase reactant, meaning its levels will increase in inflammatory conditions or cell injury.[2] Copper is a trace element that acts as a cofactor for multiple enzymes in critical cellular reactions, for instance, cytochromes which participate in the electron transport chain and redox catalysis.[3] Recent studies have shown that alterations of ceruloplasmin protein and copper homeostasis are associated with Alzheimer's disease.[4][5]

Fundamentals Go to:

Ceruloplasmin production occurs in the liver and is a ferroxidase enzyme encoded by the CP gene in humans.[6] Liver hepatocytes predominantly synthesize ceruloplasmin. In the liver, P-type ATPase (ATPase 7B) enzymes are necessary to incorporate copper into apo-ceruloplasmin.[7] Ceruloplasmin is then released into the bloodstream to transport properly to distal sites and to complete its functions in other metabolic processes, namely iron homeostasis and metabolism. A solution of ceruloplasmin is blue, and excess serum levels may give the serum a greenish hue. Each ceruloplasmin molecule can bind to 6 to 8 copper atoms; usually, 50% are in cupric (+2) and 50% are in cuprous (+1) states.[8]

Source: https://therootcauseprotocol.com/handbook-download/; https://therootcauseprotocol.com/book/;

When the influx of zinc begins to displace the heavy metals …

When zinc is lacking, the body will substitute it with another bivalent metal, such as cadmium, lead, aluminium, or mercury

You need to be prepared for these metals to begin leaching out if you supply zinc again, so this will require a powerful binder – Chlorella (vulgaris or pyrenoidosa) or Zeolite, for example

Plus exercise, infrared sauna

Good overall electrolyte solution useful to supply all the missing trace minerals

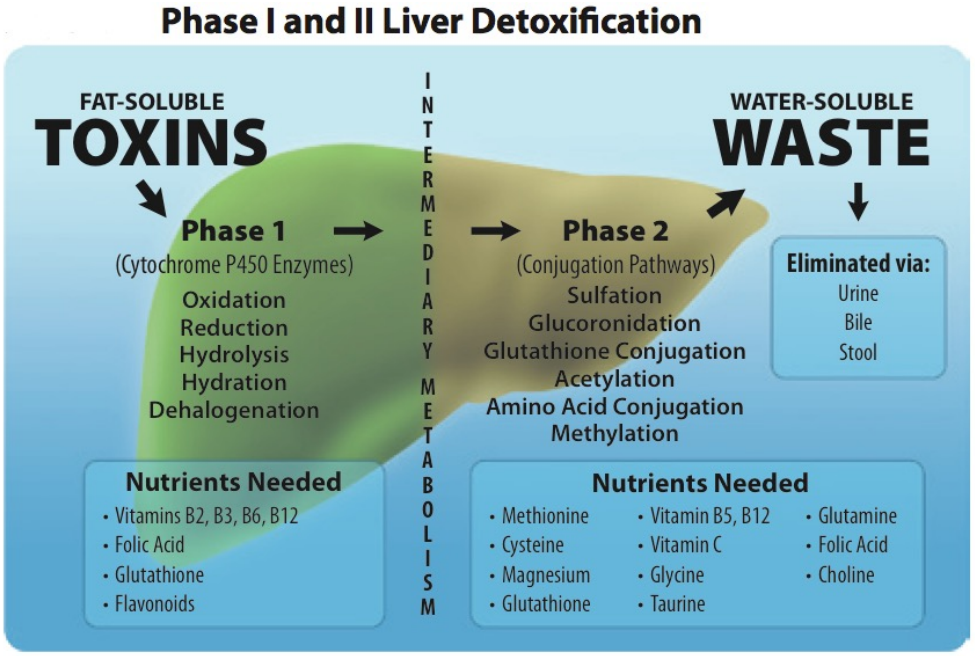
N-acetyl cysteine, glutathione, milk thistle to support the liver,

Not to forget a good digestive enzyme, as the HCl has been deficient for a long time

GI restoration may be needed as zinc deficiency also causes gut permeability and lowers SIgA. This in turn can leads to food sensitivities, especially IgG intolerances

Source: https://www.youtube.com/watch?v=-z3kRDYcvhA&t=679s: ***Dietrich Klinghardt M.D.'s presentation on HPU / KPU / Pyroluria, Lyme disease and Autism***

Detoxification – support for every cell, especially the liver (1/2)



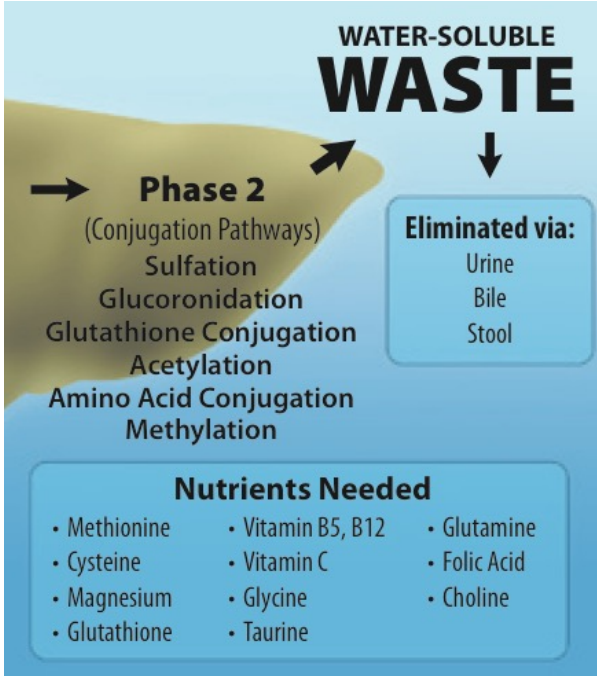
- **Phase 1 detoxification:**
  Beets, carrots – beta-carotene other carotenoids that protect the liver;
  Papaya, plantains, guava – beta-carotene and vit. C
  Broccoli – B & C vits., folate
  Eggs – B vitamins
  Glutathione: sulphur-rich Amino acids to synthesise it, incl. asparagus, broccoli, avocado, spinach, raw eggs, garlic
  Spinach – Also folate and other B vitamins
  Tomatoes – vitamins C & E, the antioxidant lycopene
  Melons/peppers – sources of vitamin C

https://naturalmeddoc.com/blog/detox-cleanse/ (previously Great Plains Laboratory, now Mosaic Diagnostics); https://mosaicdx.com/resource/priming-detoxification-pathways-for-optimal-health/

Detoxification – support for every cell, especially the liver (2/2)

Phase 2 detoxification:

Broccoli and other cruciferous vegetables – natural sulphur compounds
Eggs – contain methionine, a sulphur-containing compound needed for detoxification
Brazil nuts contain selenium, an antioxidant needed for detoxification
Garlic has methionine, and also glutathione
Onions – sulphur compounds as well as glutathione
Asparagus and watermelon – rich natural sources of glutathione
Papaya, avocado – help the body to produce glutathione
Mushrooms – have a lot of glutamic acid, needed to produce glutatione
And sufficient amino acids (protein) for methionine, cysteine, glycine, taurine, glutamine, choline



https://naturalmeddoc.com/blog/detox-cleanse/ (previously Great Plains Laboratory, now Mosaic Diagnostics); https://mosaicdx.com/resource/priming-detoxification-pathways-for-optimal-health/

Article on AONM's "Health Hub" about the links with mitochondrial disorders

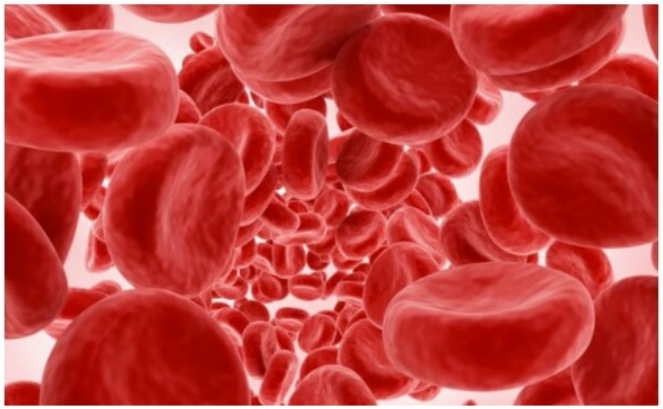
AONM
ACADEMY of NUTRITIONAL MEDICINE

AONM Health Hub

LYME DISEASE TESTING | CANCER MONITORING | MITOCHONDRIAL TESTING | WEBINARS | PANS/PANDAS TESTING | COVID-19

WORLD ENCEPHALITIS DAY 2023 | ONLINE SHOP | CONTACT US

Home » The Hidden Link Between Kryptopyrroluria (KPU) and Mitochondrial Disorders



ACADEMY OF NUTRITIONAL MEDICINE

The Hidden Link Between Kryptopyrroluria (KPU) and Mitochondrial Disorders

- BY AONM HEALTH HUB

Published on 28 May, 2024

Visit our Main AONM Website

Maintrac®: A New Paradigm in Personalised Cancer Support

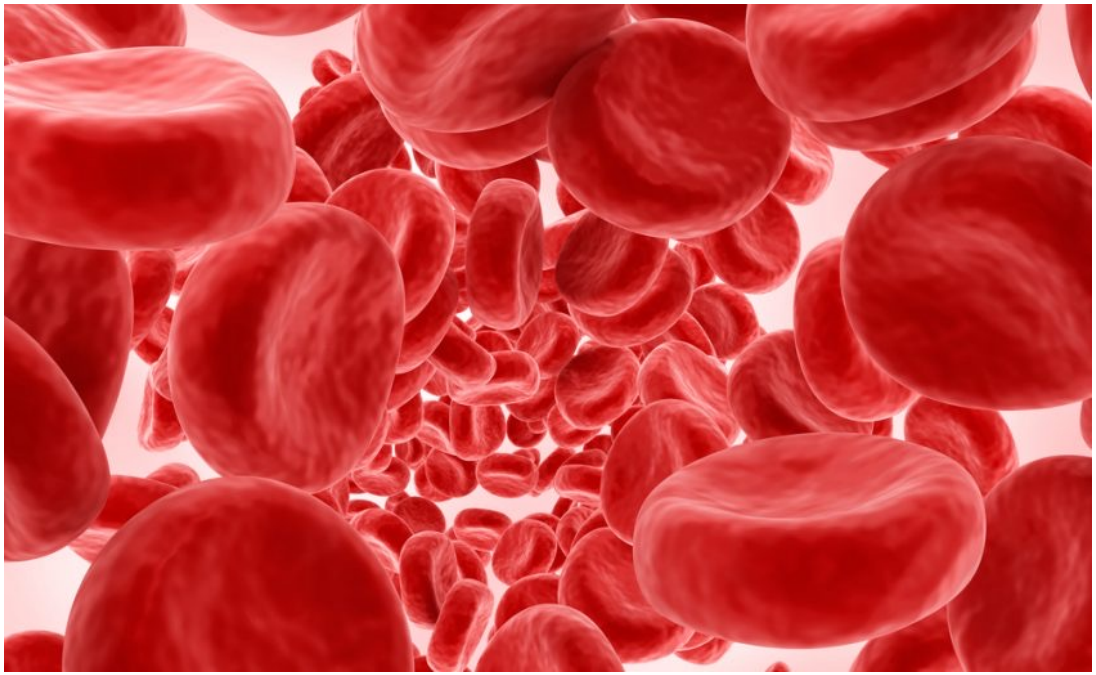
The Hidden Link Between Kryptopyrroluria (KPU) and Mitochondrial Disorders

Unveiling the Mysteries of Post-COVID Fatigue: A Paradigm Shift in Long COVID Understanding

Indulge in Wellness: Exploring the Formula Food Complex – Chocolate and Vanilla

Understanding the Escalation of Neuroinflammation Post-COVID: A Growing Concern

https://aonmhealthhub.org/the-hidden-link-between-kryptopyrroluria-kpu-and-mitochondrial-disorders/academy-of-nutritional-medicine/;
https://aonm.org/kryptopyrroluria-the-elephant-in-the-room/



Thanks very much for your attention!

info@aonm.org

0333 121 0305

gilian@aonm.org/0786 772 6387