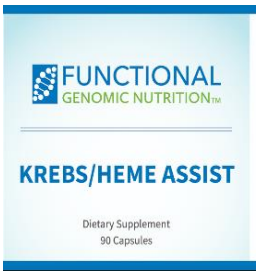
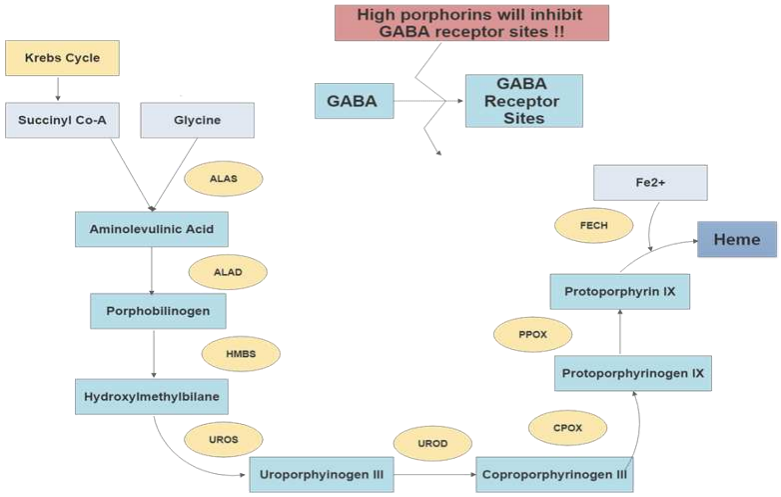
KREBS / HEME ASSIST (FGN – 011)

SUPPORT FOR HEALTHY HEME CYCLE AND KREBS CYCLE FUNCTION



The Heme pathway in humans is involved in the production of a wide range of proteins involved in detoxification, antioxidant processes, gas delivery, electron transport, and signaling molecules. This makes the Heme pathway one of the *most essential biochemical pathways* among most living organisms.

The human Heme pathway is an intracellular, enzymatic process of eight sequential enzymatic reactions to produce heme. The intermediates of these enzymatic reactions are collectively called porphyrins and porphyrinogens, which are quickly converted from one intermediate to the next to the final product of heme. Heme itself acts as a regulatory molecule, tightly controlling the heme production process. The Heme pathway moves from the cytosol to the mitochondrion, back to the cytosol.[5]



The first step of the heme pathway is ALA synthase conversion, which occurs in the mitochondrion combining glycine from the mitochondrion amino acid pool and succinyl Co-A from the TCA cycle to produce δ-Aminolevulinic acid.[5(p875)] In the second step of the heme pathway, the enzyme ALA dehydratase converts δ-Aminolevulinic acid to Porphobilinogen in the cytosol. The process continues in the cytosol in the next few steps as Porphobilinogen deaminase converts Porphobilinogen to Hydroxymethyl bilane in step three. In the fourth step, Uroporphyrinogen synthase converts Hydroxymethyl bilane to Uroporphyrinogen III. The fifth step involves the conversion of Uroporphyrinogen III to Coproporphyrinogen III by Uroporphyrinogen III decarboxylase. The pathway transitions back to the mitochondrion, with the conversion of Coproporphyrinogen III to Protoporphyrinogen IX by Coproporphyrinogen III oxidase in step six. Step seven converts Protoporphyrinogen IX to Protoporphyrin IX via the Protoporphyrinogen oxidase enzyme. The final step occurs in the mitochondrion as the Ferrochelatase enzyme inserts Fe2+ into Protoporphyrin IX to produce heme.[5]

The following are all Heme-based proteins that occur in humans:

- Hemoglobin, Myoglobin, Neuroglobin, Cytoglobin – involved in the delivery of oxygen to red blood cells, muscles, nerve cells, and brain, respectively
- Cytochrome p450 – involved in Phase I detoxification
- Cytochrome B5 and Cytochrome c – involved in the electron transport chain
- Peroxidase and Catalase - involved in hydrogen peroxide break down
- Tryptophan pyrrolase – involved in the conversion of tryptophan to NAD and NADPH via the Kynurenine pathway
- Nitric oxide synthase – involved in production of nitric oxide from L-arginine and BH4
- Sulfite Oxidase – involved in conversion of sulfites to sulfates[1-4]

Heme Pathway Support formula provides necessary cofactors to optimize theheme pathway and the functioning of heme dependent processes:

Oxygen delivery to the tissues
Phase I detoxification
Electron Transport
Hydrogen Peroxide degradation
NADPH production
Nitric Oxide production
Sulfite to Sulfate conversion

Without heme, these enzymes will not be produced. If these enzymes cannot be produced in adequate quantity due to lack of heme production, then downstream enzymatic supports will be fruitless.

Without Heme, these processes cannot occur properly and downstream upregulation support will fail. Heme Pathway Support Formula forms the foundation of supporting these mechanisms.

Heme/Krebs Assist contains the following nutrients to support function and is made with a vegetable capsule. 90 caps per bottle.

Vitamin E (as d-Alpha Tocopheryl Succinate) may help reduce certain heme pathway dysregulation issues involved in skin symptoms[6, 7] and oxidative stress.[8]

The heme pathway is initiated when succinyl-CoA is combined with glycine to form δ--aminolevulinic acid (ALA), a precursor to heme.[9] The

succinate can be converted to succinyl-CoA in a reversible reaction by the enzyme Succinyl coenzyme A synthetase[10] to support the initiation of the heme pathway.

L-Glycine is a cofactor along with Succinyl-Co-A at the top of the heme pathway to produce δ-aminolevulinic acid (ALA), a precursor to heme[9]

B3 (as Niacinamide) is essential for NAD+ production, which is a cofactor for the TCA cycle enzymes Pyruvate dehydrogenase complex, α-Ketoglutarate dehydrogenase complex, Isocitrate dehydrogenase, and Malate dehydrogenase.[11] B3 deficiency may contribute to increased heme dysregulation and porphyrin excretion.[12] Lack of B3 may affect NAD+ production and also impact glycine synthesis from serine.[13]

B2 (as Riboflavin 5 Phosphate) is a precursor of the coenzymes flavin mononucleotide and FAD needed in the TCA cycle for the enzymes pyruvate dehydrogenase, α-Ketoglutarate dehydrogenase complex, succinyl-CoA synthetase, and succinate dehydrogenase.[11] B2 is also a cofactor for protoporphyrinogen oxidase (PPOX) enzyme of the heme biosynthetic pathway.[14] Lack of B2 can contribute to heme dysregulation and increased urinary coproporphyrins.[15] B2 deficiency can also reduce B6 levels, another necessary cofactor in the TCA cycle and Heme pathway.[16]

Supplement Facts

Serving Size 3 Capsules
Servings Per Container 30

	Amount Per Serving	%DV
Vitamin E (as d-Alpha Tocopheryl Succinate)	50 IU	167%
Riboflavin (as Riboflavin 5 Phosphate)	15 mg	882%
Niacin (as Niacinamide)	50 mg	250%
Vitamin B-6 (as Pyridoxal 5 Phosphate)	25 mg	1250%
Folate (as Quatrefolic L-5-Methyltetrahydrofolate, glucosamine salt)	200 mcg	50%
Vitamin B12 (as Methylcobalamin)	25 mcg	417%
Biotin	1000 mcg	333%
Zinc (as TRAACS® Zinc Bisglycinate Chelate)	10 mg	67%
Thiamine (as Thiamine Mononitrate)	50 mg	3333%
L-Glycine	100 mg	*
L-Threonine	25 mg	*
L-Isoleucine	25 mg	*
L-Valine	25 mg	*
Alpha Lipoic Acid	200 mg	*
Vitamin C (as Ascorbyl Palmitate)	300 mg	*
DiMagnesium Malate	200 mg	*

* Daily Value not established.

Other ingredients: Micro Crystalline Cellulose (USP), Vegetable Capsule (cellulose, purified water). No artificial colors, artificial flavors, milk or milk derivatives or sodium added.

Vitamin B6 (as Pyridoxal 5 Phosphate) is a necessary cofactor for the ALAS enzyme, a rate limiting step of heme synthesis.[17] , an important cofactor in the Kynurenine pathway conversion of tryptophan to NAD+, which is a necessary cofactor for the TCA cycle.[18] B6 is a necessary cofactor of the δ-Aminolevulinate synthase (ALAS) enzyme at the top of the heme pathway.[19] B6 also serves as a possible activator of the Ferrochelatase (FECH) enzyme in the last step of the heme pathway.[20, 21]

Vitamin C (as Ascorbyl Palmitate) – is a potent antioxidant that may reduce oxidative damage and restore expression of the heme enzyme Protoporphyrinogen oxidase PPOX.[8] Vitamin C also supports the absorption and proper regulation of bioavailable iron,[22] a necessary cofactor of the Ferrochelatase (FECH) enzyme at the last step of the Heme pathway.[5]

Magnesium (as Magnesium Malate) plays an important role in regulating iron,[23, 24] which is a necessary cofactor in the last step of the heme pathway, the Ferrochelatase (FECH) enzyme.[25] Malate is an important intermediate of the TCA cycle.[5]

Folate (as Quatrefolic® - L-5-Methyltetrahydrofolate, glucosamine salt) is a non-essential activator of the Heme pathway enzyme Porphobilinogen-Deaminase (PBGD)[26] and may be involved in Uroporphyrinogen III Synthase (UROS) activity.[27] The active form of folate is also involved in glycine synthesis,[28] a required cofactor for the imitation of the Heme pathway.

Vitamin B12 (as Hydroxocobalamin) is a cofactor in the conversion of methylmalonyl-CoA to succinyl-CoA, the step in the TCA cycle immediately preceding the Heme Pathway.[11]

Biotin is an essential cofactor for the metabolism of lipids, carbohydrates, and proteins needed to initiate the TCA cycle.[29] , a cofactor for the TCA cycle enzymes pyruvate carboxylase, propionyl-CoA carboxylase, β-methylcrotonyl-CoA carboxylase and acetyl-CoA carboxylase,[11] which precedes the Heme pathway. Lack of biotin directly affects heme synthesis.[30]

Zinc (as TRAACS® Zinc Bisglycinate Chelate) is required in the conversion of δ-Aminolevulinate (ALA) by the enzyme ALA dehydratase to Porphobilinogen[31]. Zinc deficiency may be a factor in Heme pathway dysregulation.[32]

Thiamine (as Thiamine Mononitrate) is a cofactor for the pyruvate dehydrogenase enzyme responsible for pyruvate synthesis and for the α-ketoglutarate dehydrogenase enzyme required for succinyl-CoA synthesis, the step in the TCA cycle immediately preceding the Heme Pathway.[11]

Lipoic Acid as Alpha Lipoic Acid is a required cofactor in the pyruvate dehydrogenase and α-Ketoglutarate dehydrogenase enzymes of the TCA cycle.[11] Alpha lipoic Acid may be a non-essential cofactor of the Uroporphyrinogen Decarboxylase (UROD) enzyme in the heme pathway.[33]

L-Isoleucine, L-Threonine, and L-Valine are amino acids that are converted to Succinyl Co-A,[11] which is involved at the initiation of the heme pathway. Valine and isoleucine may be incorporated directly into δ-Aminolevulinic Acid via the enzyme ALA synthase (ALAS) more efficiently even than Succinyl Co-A.[34]

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