Casual Friday Presents

Fine-Tuning Mitochondrial Function Pt. 2

A BIOGENETIX CLINICAL PRESENTATION

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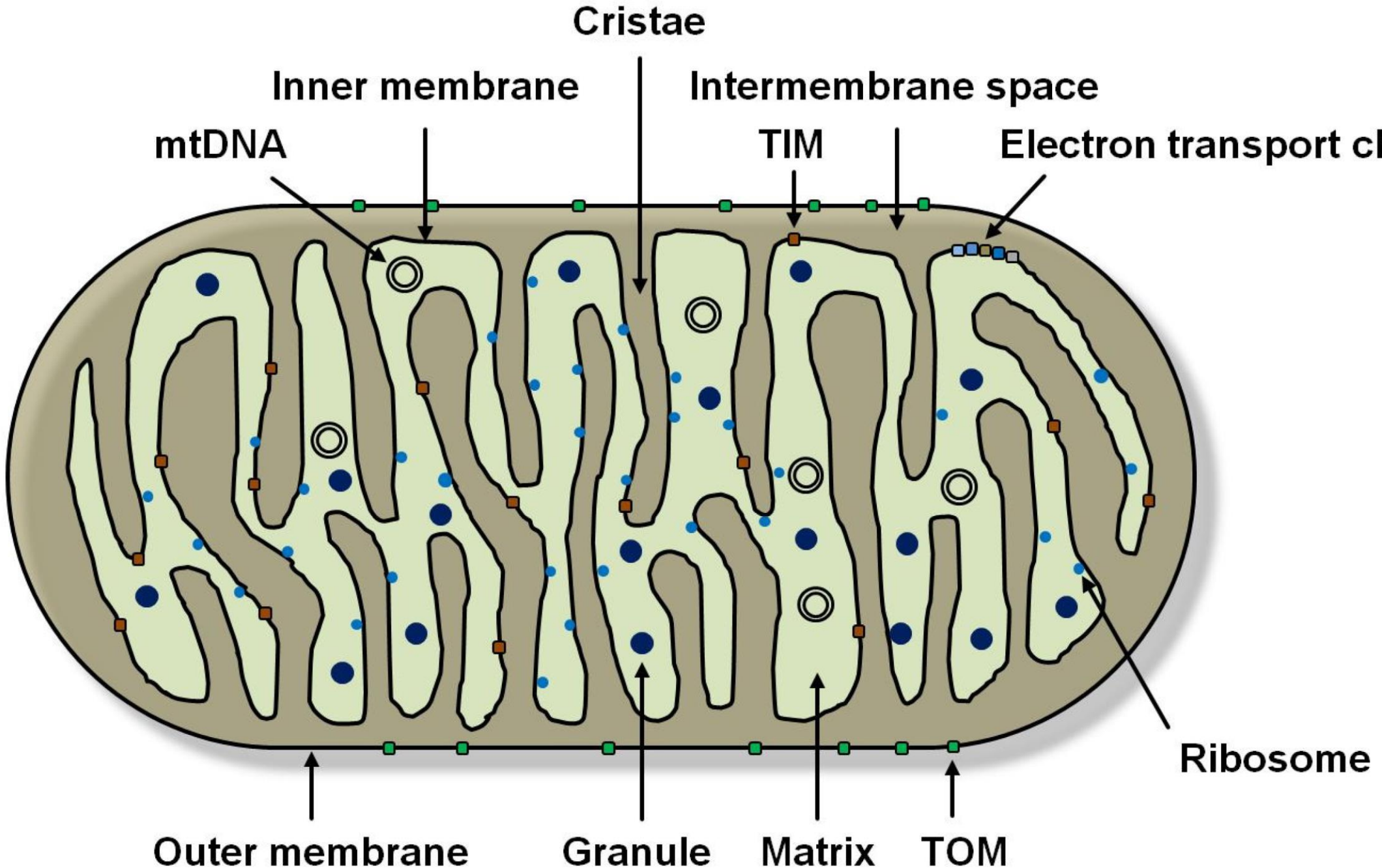

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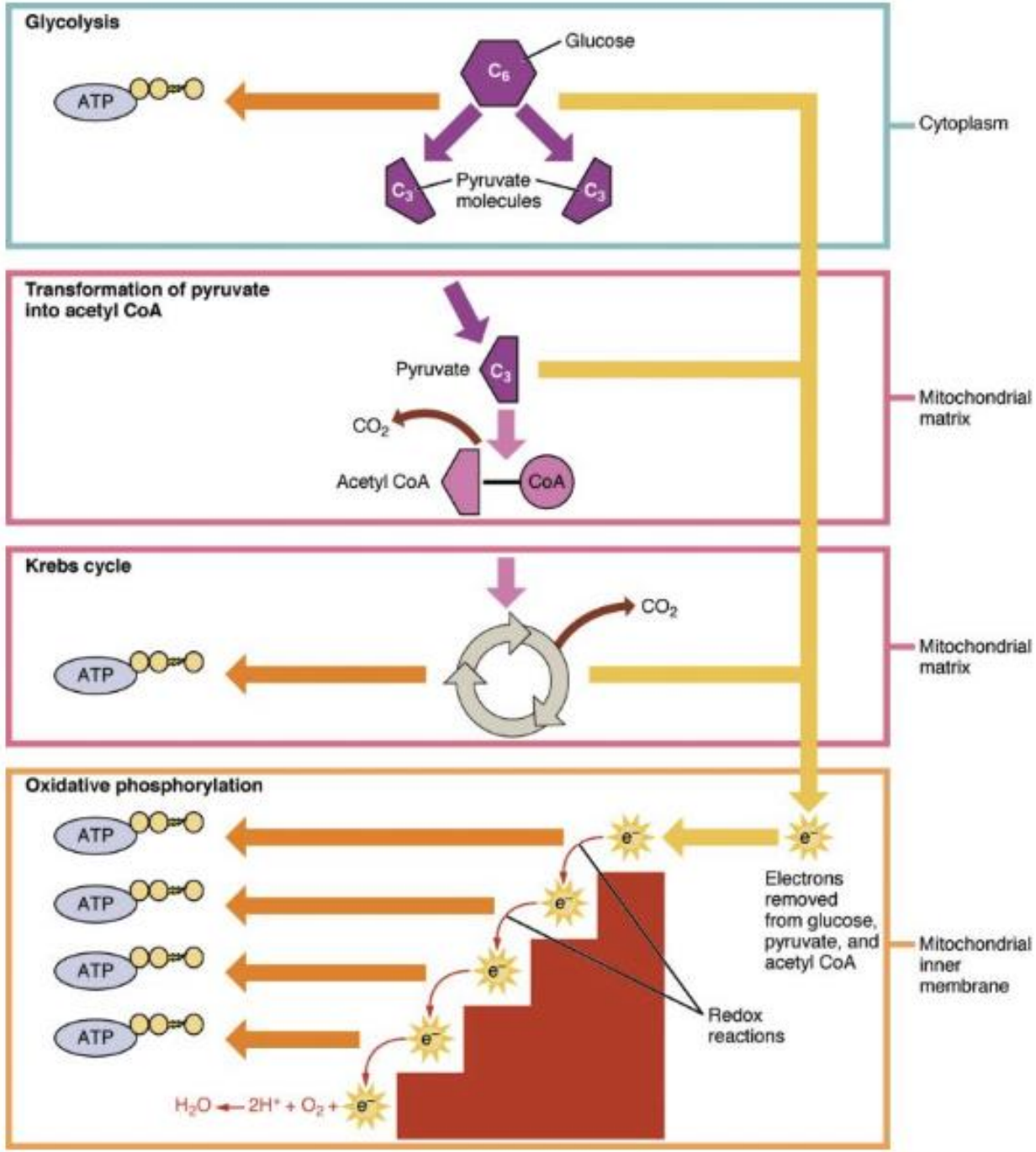
Glycolysis
Glucose
C_6
ATP
Cytoplasm
C_3
Pyruvate molecules
C_3
Transformation of pyruvate into acetyl CoA
Pyruvate
C_3
Mitochondrial matrix
CO_2
Acetyl CoA
CoA
Krebs cycle
CO_2
ATP
Mitochondrial matrix
Oxidative phosphorylation
ATP
ATP
ATP
ATP
e^-
e^-
e^-
e^-
e^-
Electrons removed from glucose, pyruvate, and acetyl CoA
Mitochondrial inner membrane
Redox reactions
$H_2O \leftarrow 2H^+ + O_2 + e^-$

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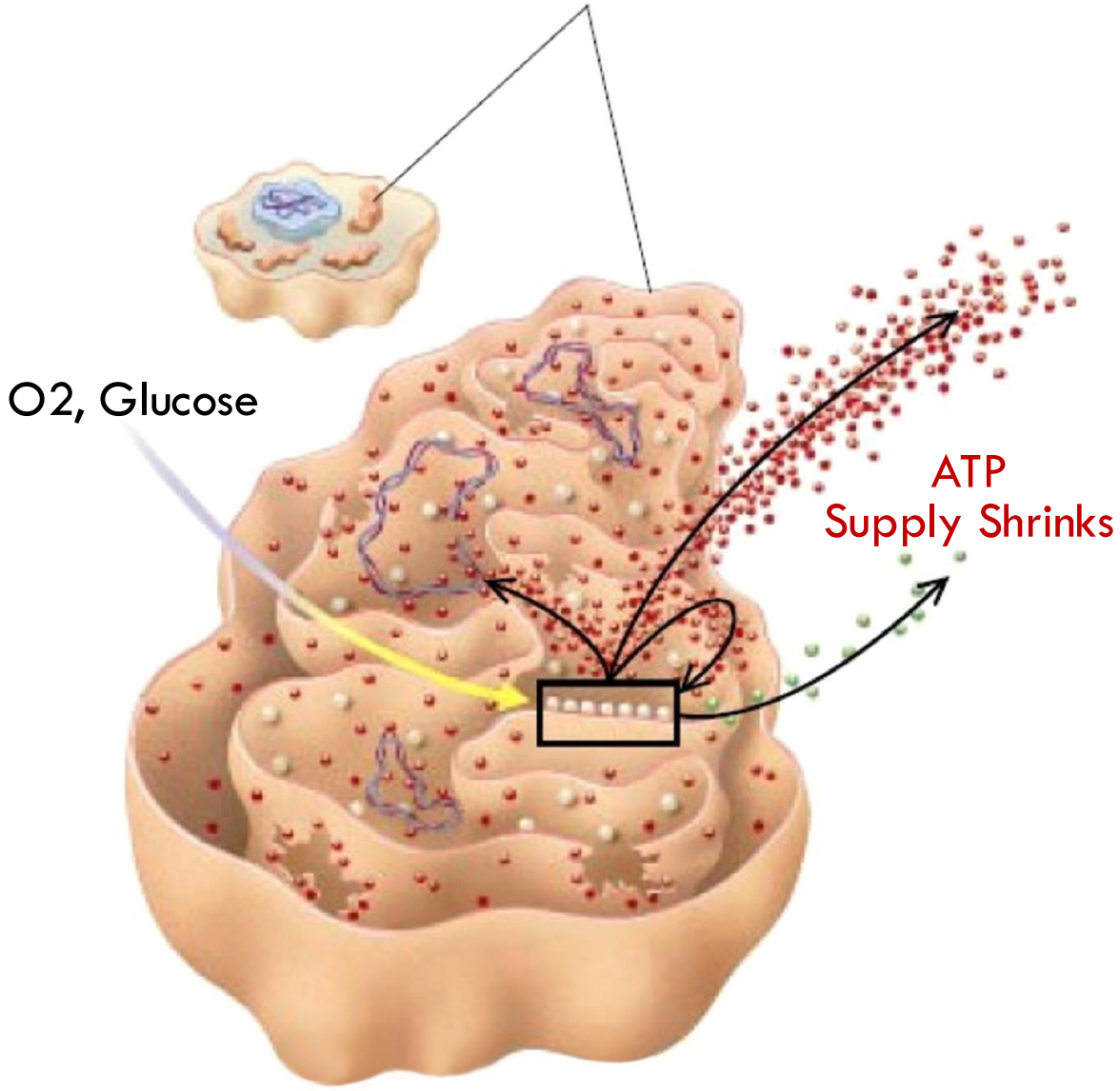
Damaged Mitochondria in
Distressed Old Cell



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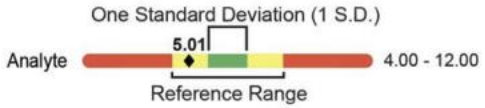
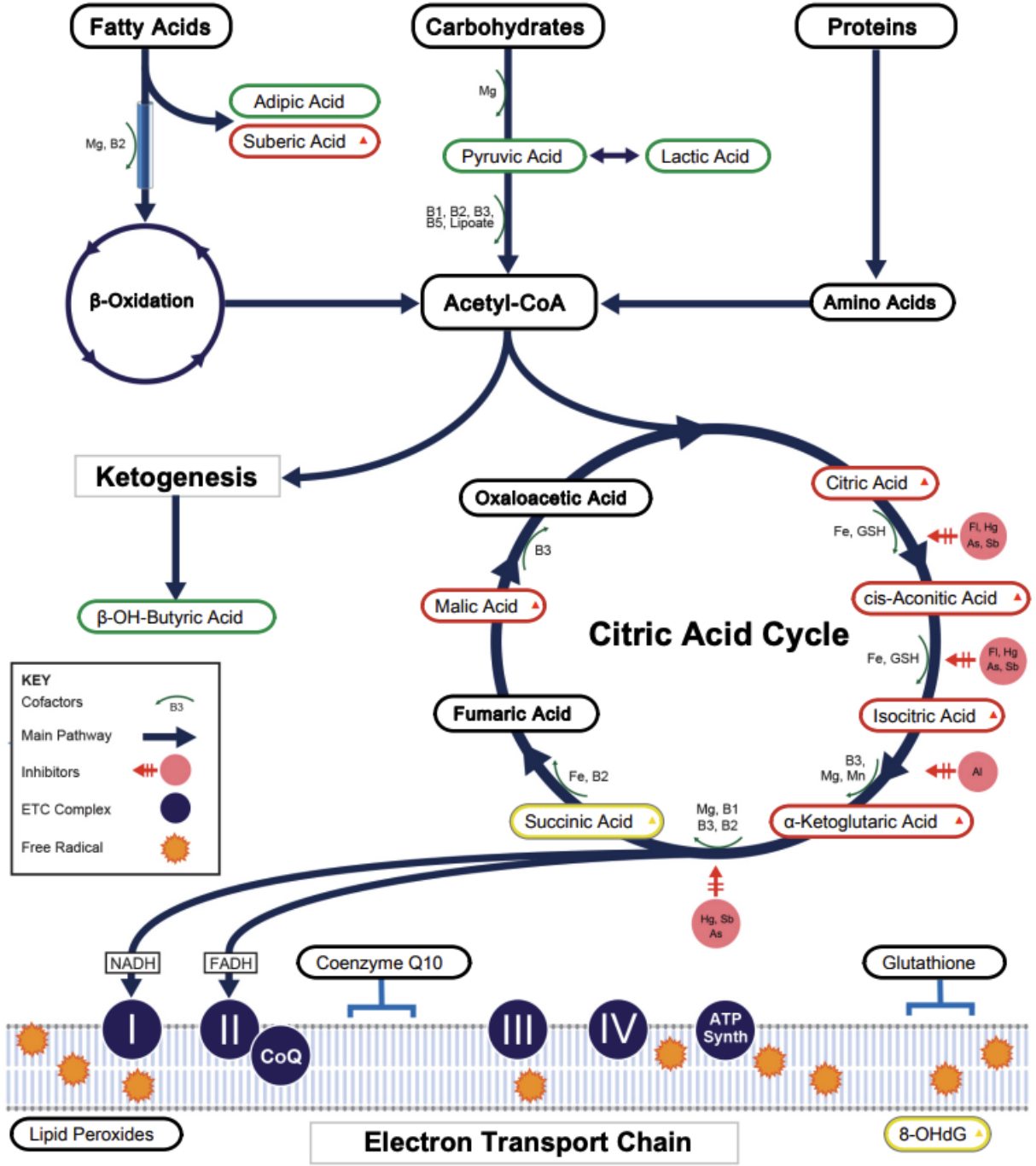

One Standard Deviation (1 S.D.)
Analyte
5.01
4.00 - 12.00
Reference Range


Fatty Acids
Carbohydrates
Proteins
Adipic Acid
Suberic Acid
Mg, B2
Mg
Pyruvic Acid
Lactic Acid
B1, B2, B3, B5, Lipoate
β-Oxidation
Acetyl-CoA
Amino Acids
Ketogenesis
β-OH-Butyric Acid
Oxaloacetic Acid
B3
Malic Acid
Citric Acid
Fe, GSH
Fl, Hg As, Sb
cis-Aconitic Acid
Citric Acid Cycle
Isocitric Acid
B3, Mg, Mn
Al
α-Ketoglutaric Acid
Mg, B1 B3, B2
Succinic Acid
Fe, B2
Fumaric Acid
KEY
Cofactors
Main Pathway
Inhibitors
ETC Complex
Free Radical
Hg, Sb As
NADH
FADH
Coenzyme Q10
Glutathione
I
II
CoQ
III
IV
ATP Synth
Lipid Peroxides
Electron Transport Chain
8-OHdG

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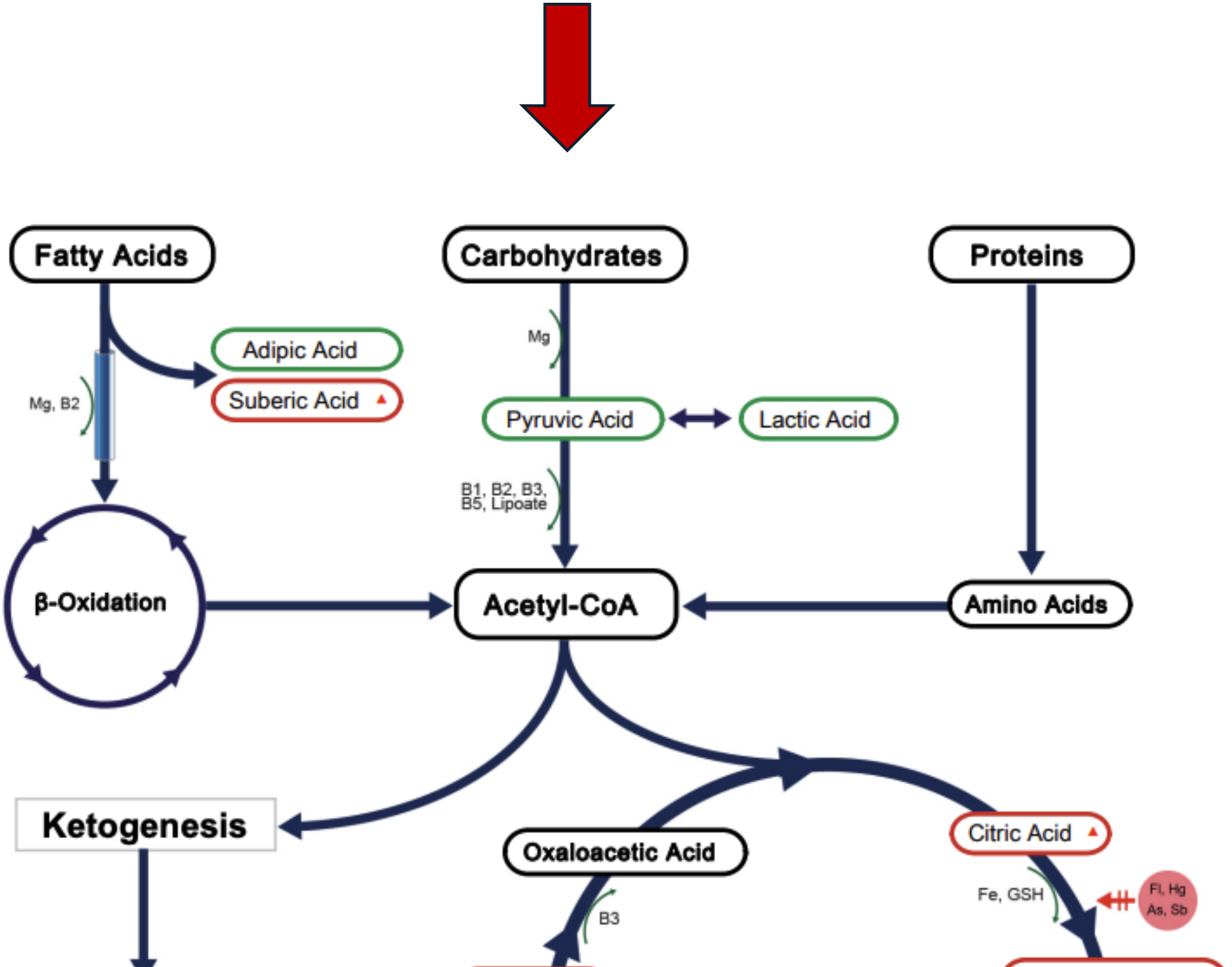
Fatty Acids
Carbohydrates
Proteins
Adipic Acid
Suberic Acid
Mg, B2
Mg
Pyruvic Acid
Lactic Acid
B1, B2, B3,
B5, Lipoate
β-Oxidation
Acetyl-CoA
Amino Acids
Ketogenesis
Oxaloacetic Acid
B3
Citric Acid
Fe, GSH
Fl, Hg
As, Sb

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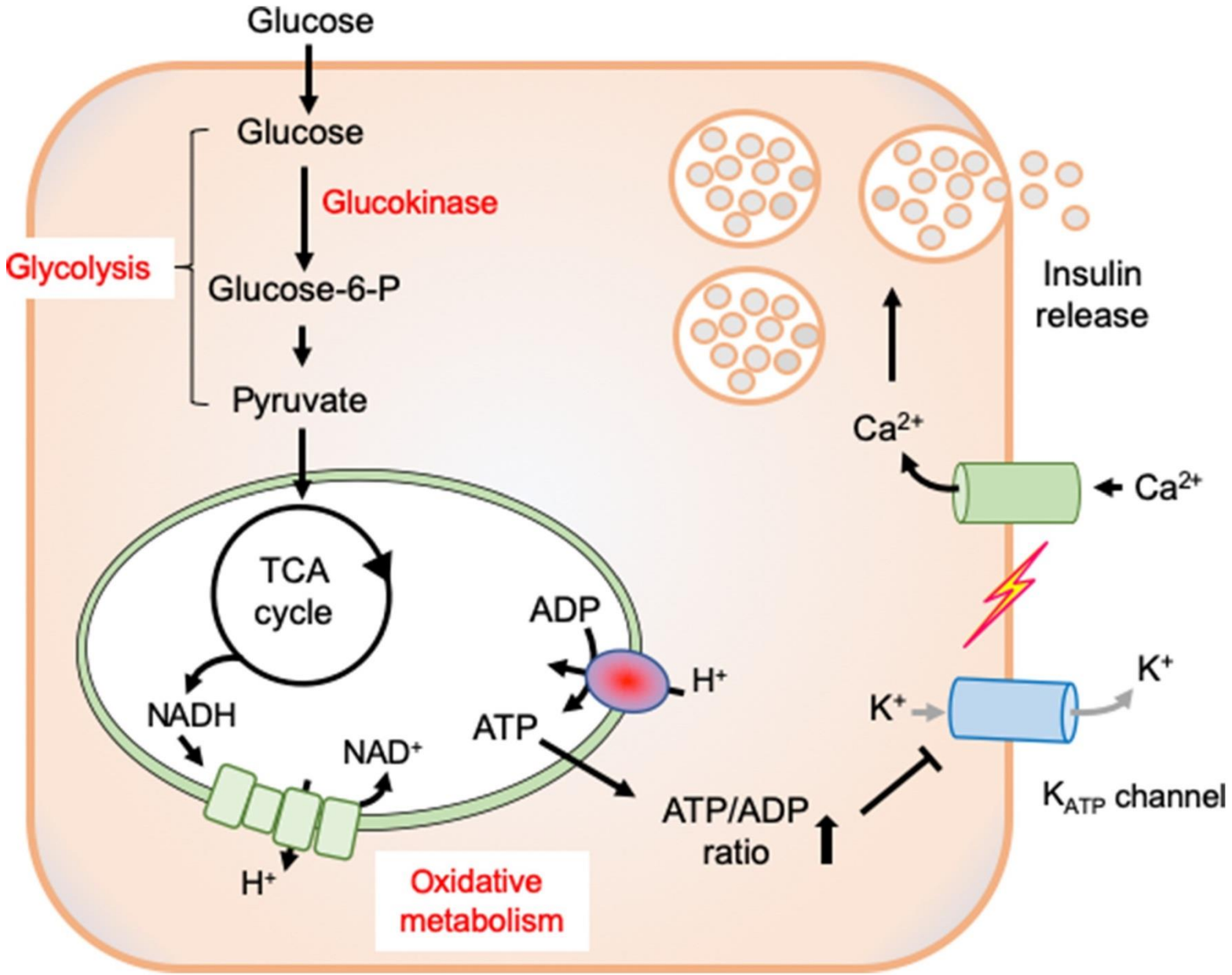

Trends in Endocrinology & Metabolism

Med Hypotheses. 1999 May;52(5):401-6. doi: 10.1054/mehy.1997.0682.

High-dose biotin, an inducer of glucokinase expression, may synergize with chromium picolinate to enable a definitive nutritional therapy for type II diabetes

Glucokinase (GK), expressed in hepatocyte and pancreatic beta cells, has a central regulatory role in glucose metabolism. Efficient GK activity is required for normal glucose-stimulated insulin secretion, postprandial hepatic glucose uptake, and the appropriate suppression of hepatic glucose output and gluconeogenesis by elevated plasma glucose. Hepatic GK activity is subnormal in diabetes, and GK may also be decreased in the beta cells of type II diabetics. In supraphysiological concentrations, biotin promotes the transcription and translation of the GK gene in hepatocytes; this effect appears to be mediated by activation of soluble guanylate cyclase. More recent evidence indicates that biotin likewise increases GK activity in islet cells. On the other hand, high-dose biotin suppresses hepatocyte transcription of phosphoenolpyruvate carboxykinase, the rate-limiting enzyme for gluconeogenesis. Administration of high-dose biotin has improved glycemic control in several diabetic animals models, and a recent Japanese clinical study concludes that biotin (3 mg t.i.d. orally) can substantially lower fasting glucose in type II diabetics, without side-effects. The recently demonstrated utility of chromium picolinate in type II diabetes appears to reflect improved peripheral insulin sensitivity--a parameter which is unlikely to be directly influenced by biotin. Thus, the joint administration of supranutritional doses of biotin and chromium picolinate is likely to combat insulin resistance, improve beta-cell function, enhance postprandial glucose uptake by both liver and skeletal muscle, and inhibit excessive hepatic glucose production. Conceivably, this safe, convenient, nutritional regimen will constitute a definitive therapy for many type II diabetics, and may likewise be useful in the prevention and management of gestational diabetes. Biotin should also aid glycemic control in type I patients.

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Front Nutr. 2022 Oct 31;9:1046800. doi: 10.3389/fnut.2022.1046800

Influence of biotin intervention on glycemic control and lipid profile in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

Yujia Zha

Author

PMCID: P

Current researches have demonstrated that biotin deficiency could impair energy production by decreasing glucose utilization and oxidative phosphorylation (25). Chuahan et al. (26) reported that biotin could regulate the glucokinase gene at the transcriptional stage in starved rats. In addition, insulin expression and secretion were found to be increased in response to biotin administration (18). On the other hand, excessive biotin intake may also ameliorate diabetic status. A study conducted in 43 Japanese T2DM patients demonstrated a decrease of approximately 45% of FBG concentration after one month of oral supplementation of 9 mg of biotin per day (15, 27). Similar effects were also observed in type 1 diabetic patients whose FBG levels decreased up to 50% after daily administration of 16 mg biotin for one week (28). High-dose biotin may compensate for subnormal insulin exposure by suppressing FOXO1 levels (29). Although the mechanism of hyperglycemia is different, biotin is effective in both type of diabetes mellitus (18, 30, 31). Moreover, many clinical trials have shown the hypoglycemic effect of biotin supplementation in overweight and obese individuals with T2DM (32, 33). A double-blind placebo-controlled trial including 348 participants reported a significant decrease in LDL-C, TC, HbA1c, and VLDL-C after 3 months intervention (34). However, another biotin intervention lasted for 4 weeks showed no significant change in plasma glucose, insulin, TG, TC or lactate concentration compared with placebos (35). The difference between these results may be caused by the small number of participants in one study and the specific conditions of the experiment such as the duration and dosage of the intervention.

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Influence of biotin intervention on glycemic control and lipid profile in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

Yujia Zhang [1], Yiwang Ding [1], Yawen Fan [1], Yenan Xu [1], Yuting Lu [1], Lingzi Zhai [1], Ling Wang [1,*]

Effects of biotin on FBG levels

All of the five included studies examined the effect of biotin supplementation on FBG levels. Overall, biotin supplementation significantly reduced FBG levels (MD: −1.21 mmol/L, 95% CI: −2.73 to 0.31, $P = 0.33$, $I^2 = 0\%$). Regarding on subgroup analysis, two trials with supplementation of biotin dosage ≥ 9 mg/d significantly decreased FBG levels (MD: −3.02 mmol/L, 95% CI: −8.15 to 2.46). Three trials with supplementation dosage of <9 mg/d biotin demonstrated no significant difference compared with placebos (MD: −0.10 mmol/L, 95% CI: −2.38 to 2.18) (Figure 3). In addition, although two trials used the combination of biotin and chromium, subgroup analysis showed no significant difference in the effects of supplementation between the groups with or without chromium (34, 39) (Supplementary Figure S2).

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Effects of biotin on insulin levels

Four studies (32, 34, 35, 39) investigated the effects of biotin supplementation on insulin levels. Overall, no significant difference was observed in this meta-analysis (MD: 1.88 pmol/L, 95% CI: −13.44 to 17.21) (Figure 4). Regarding on subgroup analysis, one trial involved 18 participants, ten of which took biotin at the dosage of ≥ 9 mg/d and the other eight took the placebo, both groups showed a significant decrease in insulin levels, while the decrease was more remarkable in biotin group (MD: −16.6 pmol/L, 95% CI: −41.65 to 8.45). However, three trials with supplementation dosage <9mg/d biotin presented a contrary trend where insulin levels were raised after intervention (MD: 6.79 pmol/L, 95% CI: −9.20 to 22.78). Besides, the combination of biotin and chromium supplementation did not show any significant difference with the subgroup of individual biotin supplementation (34, 39) (Supplementary Figure S3).

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PMCID: PMC9659605 PMID: 36386951

The effects of biotin on glycemic outcomes are mainly caused by two pathways. First, biotin can increase the activity and expression of glucokinase expressed in hepatocyte and pancreatic β cell (40). Glucokinase phosphorylates glucose to glucose 6-phosphate inside the hepatocyte, ensuring an adequate flow of glucose enters the cell to be metabolized (41). Glucokinase activity is essential for glucose-induced insulin secretion, post-prandial hepatic glucose uptake, and suppression of hepatic glucose output and gluconeogenesis by elevated plasma glucose (33). Diabetic patients often have subnormal hepatic glucokinase activities, which affects the rate at which glucose is converted into glucose-6-phosphate in the liver,

(net: higher serum glucose)

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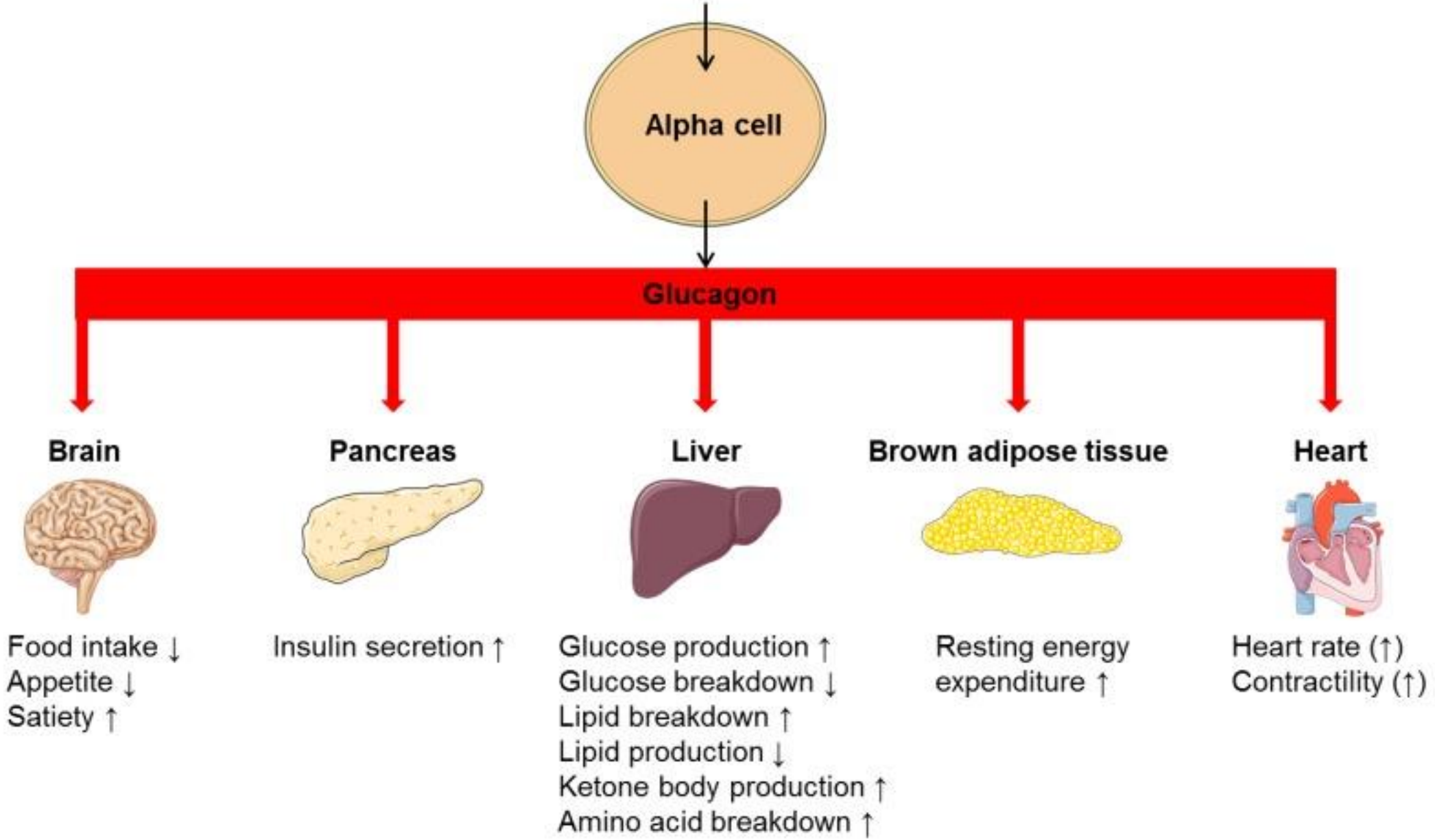
Insulin Receptor Inactivation



https://www.ncbi.nlm.nih.gov/books/NBK279127/bin/glucagon-physiology-Image006.jpg

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thus hindering the breakdown of glucose and hepatic glycogen. Biotin can stimulate glucokinase to accelerate the conversion of glucose into pyruvate, thereby reducing FBG levels (41, 42). Meanwhile, after the increase of glucokinase, the carbon from glucose are provided for *de novo* lipogenesis (43). Glucokinase mRNA expression has been proven to be associated with markers of *de novo* lipogenesis and liver triglyceride content in humans (44). The overexpression of glucokinase can promote pathways that convert glucose to fatty acids, which suggests that increased glucokinase activity may leads to reduced blood glucose and induces hypertriglyceridemia and hepatic steatosis (45, 46). Secondly, biotin acts as a key coenzyme for PC in gluconeogenesis. In biotin-deficient patients, biotin administration can increase PCC activity and maintain blood glucose stability (47). Biotin can also repress both the gluconeogenic genes and their transcription factors, such as phosphoenolpyruvate carboxykinase (PCK1), glucose-6-phosphatase (G6PC), forkhead box protein O1 (FoxO1) and hepatocyte nuclear factor 4α (HNF4α) through a pathway independent of insulin-signaling (48). The role of biotin in glucokinase and PC together make up for the efficacy of its potential clinical value.

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Regarding on lipid profile, biotin can regulate lipid metabolism by reducing the expression of adipogenesis genes in liver and adipose tissues. As the coenzyme of ACC1 and ACC2, biotin helps to catalyze the reaction of acetyl CoA to malonyl CoA in the synthesis of long-chain fatty acids, which is related to the synthesis of acetylcholine and cholesterol (49). Biotin supplementation can reduce lipogenesis by increasing cGMP content and activating AMP-activated protein kinase (AMPK) (50), thereby inactivating ACC1. It is also able to increase fatty acid oxidation by decreasing ACC2 activity (32). In patients with atherosclerosis and hyperlipidemia, decreased blood cholesterol concentration was found after biotin supplementation, especially those with exacerbated hyperlipidemia (51). The triglyceride-lowering effect of biotin was also reported in patients with T2DM (32). Meanwhile, another study suggested that biotin could also potentiate the suppression of appetite by upregulating ACC2 gene expression in the hypothalamus, which lead to the suppression of food intake and contribute to the prevention of diabetes (49).

Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Within range	3.1	ug/mg	0 - 3.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Within range	1.39	ug/mg	0.2 - 1.9
Kynurenate	Within range	5.3	ug/mg	1 - 6.6
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Above range	27.7	ug/mg	0 - 18
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Within range	52.6	ug/mg	38 - 83
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Within range	52.5	ug/mg	0 - 131
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	6.6	ug/mg	4 - 16
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	7.0	ug/mg	2.5 - 7.5
Neuroinflammation Marker				
Quinolinate	Above range	15.8	ug/mg	0 - 12.5
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Low end of range	22.6	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	4.2	ng/mg	0 - 8.8

65yo M, DM2, Hashimoto, HBP, Hypercholesterolemia

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Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Within range	1.9	ug/mg	0 - 3.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Within range	0.51	ug/mg	0.2 - 1.9
Kynurenate	Within range	1.7	ug/mg	1 - 6.6
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Above range	23.4	ug/mg	0 - 18
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Below range	27.6	ug/mg	38 - 83
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Within range	94.9	ug/mg	0 - 131
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Above range	158.0	ug/mg	4 - 16
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	5.3	ug/mg	2.5 - 7.5
Neuroinflammation Marker				
Quinolinate	Within range	6.3	ug/mg	0 - 12.5
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Above range	3619.2	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	2.6	ng/mg	0 - 8.8

62yo M, DM2, HBP, Hypercholesterolemia

Biogenetix

Glucostatic Balance

Supports Healthy Insulin and Blood Sugar Levels

SUPPLEMENT FACTS

Serving size: 2 Capsules Servings per container: 90	Amount Per Serving	% Daily Value
Vitamin E (as D-Alpha Tocopheryl Succinate)	42.88 mg	286%
Thiamin (as Thiamin HCl)	7 mg	583%
Riboflavin	7 mg	538%
Niacin (as Niacinamide and Nicotinic Acid)	32 mg	200%
Vitamin B6 (as Pyridoxine HCl)	4 mg	235%
Vitamin B12 (as Cyanocobalamin)	7 mcg	292%
Biotin	428 mcg	1,427%
Pantothenic Acid (as Calcium D-Pantothenate)	43 mg	860%
Choline (as Choline Bitartrate)	57 mg	10%
Magnesium (as Magnesium Citrate)	36 mg	9%
Zinc (as Zinc Glycinate)	7 mg	64%
Selenium (as Selenium Glycinate)	29 mcg	53%
Manganese Bisglycinate Chelate	4 mg	174%
Chromium (as Chromium Polynicotinate)	200 mcg	571%%
Proprietary Blend N-Acetyl L-Cysteine, Gymnema Leaf Extract, Berberine HCl, R-Alpha Lipoic Acid, L-Carnitine (as L-Carnitine L-Tartrate), Para-Aminobenzoic Acid (PABA), Inositol, Garcinia Fruit Powder, Rehmannia Glutinosa Root, Poria Cocos Root Extract, Lagerstroemia speciosa (Banaba) Leaf Powder, Bitter Melon Fruit Powder, Organic Cassia Bark Powder, Broad Bean Powder (Viciafaba), Fenugreek Seed Powder, Guggul Gum Resin Powder, Vanadium (Vanadium Sulfate)	487 mg	**

** Daily Value Not Established

Other Ingredients: Gelatin (Capsule), Cellulose, Silica, Magnesium Stearate.

KEYS

1. Demand Fat for Fuel
2. Stabilize Glucose with Macro-differentiation
3. Macro-Energy Limitations
4. Drivers and facilitators
5. Time

*Biotin: 1.284 mg/day. (2 per meal)

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