GLYCINE

The most important role of Glycine is combining with N-Acetyl-Cysteine (NAC) intracellularly to produce Glutathione, "The Master Antioxidant". [Read our article on Glutathione.] Glutathione can also be thought of as "The Master REJUVENIN" --- which is the purpose of Rejuvenator.

When Glycine availability is too low to sustain a normal rate of Glutathione synthesis, there is a consequent rise in gamma-glutamyl cysteine, a metabolic waste product that is further metabolized and then eliminated in the urine. Urinary excretion of this metabolite is elevated in vegetarians and others on low-protein diets --- strongly suggesting that dietary Glycine can be rate-limiting for Glutathione synthesis.

Confirmation of Glycine's fundamental role in Glutathione synthesis is that NAC supplementation without Glycine supplementation does not raise Glutathione as effectively as does combining the two --- and administering Glycine alone, will raise Glutathione intracellularly.

----- Glycine is an important methyl group donor. Methyl groups are abundant in DNA and are important components of multiple cellular reactions.

Glycine is also important for normal brain function. Thus, providing Glycine could contribute to multiple benefits attributed to Glutathione.

In addition to its fundamental role in intracellular Glutathione production, consider the many other metabolic effects of Glycine:

- Glycine is required in purine metabolism for DNA synthesis.

- Glycine is an important component of cartilage. ----- Glycine constitutes approximately 1/3 of the amino acids in collagen and elastin, and is thus a fundamental component of connective tissues, and of the extra-cellular matrix.

  Since collagen and elastin are so rich in Glycine and thus critical to connective tissue strength and protection against inflammation --- it is not surprising that supplemental Glycine promotes healing and inhibits inflammation in Achilles Tendonitis. ----- The essentiality of Glycine for connective tissue extends to the connective tissue of the cardiovascular system.

- Glycine is a precursor for porphyrins, creatine, sarcosine, and bile salts. ----- Bile salts are a critical link between gut microbiota and the brain in the Gut-Brain Axis.

○ Glycine acts as a neurotransmitter in the brain, as glycinergic receptors are an important controller of the sleep/wake cycle.

○ Glycine is a co-agonist for N-methyl-D-aspartate receptors in the brain.

○ Glycine inhibits protein glycation.

○ Glycine increases liver production of pyruvate, an effective scavenger of hydrogen peroxide.

○ Glycine is an agonist for Glycine-gated chloride channels.

And more: Supplemental Glycine may have the potential for …

- improving endothelial function,
- improving resistance to cardiac INFLAM-AGING,
- aiding control of Metabolic Syndrome,
- preventing complications of hyperglycemia,
- inhibiting inflammation,
- limiting INFLAM-AGING of the liver,
- promoting effective sleep.

Glycine protects against the adverse metabolic effects of a high-fructose diet --- with favorable effects on insulin sensitivity, blood pressure, serum free fatty acids, and intra-abdominal fat deposition. These benefits may be partly due to up-regulation of enteral production of glucagon-like peptide-1 (GLP-1).

Dietary gelatin --- extremely rich in Glycine --- boosts GLP-1 levels.

FGF-21(Fibroblast Growth Factor 21) has been referred to as the "Pro-longevity Hormone". Fibroblast Growth Factor 21 (TGF-21) is produced mainly in hepatocytes and adipocytes. It promotes leanness, insulin sensitivity, and vascular health, while down-regulating hepatic IGF-1 production. Transgenic mice overexpressing FGF-21 enjoy a marked increase in median and maximal longevity --- comparable to that evoked by calorie restriction, but without a reduction in food intake.

Factors promoting hepatic FGF-21 expression include fibrate drugs, elevated lipolysis, moderate protein diets, growth hormone, and bile acids. Butyrate (produced by healthy microbiota in response to Immuno-Synbiotic) also increases FGF-21 expression. GLP-1 (Glucagon-like peptide-1) also increases FGF-21 and increases Lifespan in mice.

Increased glucagon secretion can be evoked by supplemental Glycine, if administered during post-absorptive metabolism.

Glycine administered in a morning fasting state provokes increased glucagon secretion, likely reflecting a direct or indirect stimulatory effect on pancreatic alpha cells. Because both GLP-1 and glucagon boost hepatic fatty acid oxidation, these two hormones likely collaborate in mediating the protective benefits of supplemental Glycine on fructose-fed rats.

Of particular interest is that high Glycine intake can counteract many of the adverse effects of a high-sucrose (fructose) diet on the liver, adipose tissue, and vascular function. Glycine …

- decreases the elevated non-esterified fatty acid content of the liver on high-sugar diets,
- increases the oxidation rate of hepatic mitochondria,
- normalizes elevated blood pressure,
- decreases serum triglycerides and insulin,
- prevents an increase in abdominal fat mass,
- boosts the Glutathione level intracellularly,
- decreases Oxidative Stress,
- normalizes endothelium-dependent vasodilation.

The protective effects of Glycine in humans with a high fructose intake in Metabolic Syndrome are not readily explained on the basis of known metabolic effects of Glycine. Fructose does exert its adverse effects primarily via its impact on liver metabolism. Fructose is catabolized almost exclusively in the liver, and its oxidation, unlike that of glucose, is not regulated by metabolic need. As a result, high intake of fructose floods the liver with substrate and suppresses hepatic fatty acid oxidation, while promoting lipogenesis and triglyceride synthesis.

These fructose effects also increase hepatic production of diacylglycerols, which impair hepatic insulin sensitivity. The increased triglyceride content of fructose-overloaded hepatocytes accelerates the secretion of very-low-density lipoprotein (VLDL) particles. This phenomenon may explain the elevation of LDL cholesterol induced by high-fructose intakes.

The increased liver secretion of VLDL triglyceride is responsible for the increase in visceral fat (and Tubby Tummy) observed in those consuming high-fructose diets. This process in turn, can induce Metabolic Syndrome, including an increase in blood pressure driven in part by hyperinsulinemia.

Oral administration of Glycine stimulates an increase in glucagon secretion by pancreatic alpha-cells. But this response is negated if glucose is ingested simultaneously. But Glycine ingestion also stimulates GLP-1 production, which inhibits alpha-cell glucagon secretion. The answer to that paradox is likely that Glycine acts directly/independently on alpha-cells as a glucagon secretagogue --- and that effect overrides that of GLP-1, especially when glucose is at basal level.

It is notable that GLP-1 and glucagon work in complimentary ways to promote fatty acid oxidation and oppose lipogenesis in the liver. The effects of glucagon are mediated primarily by cAMP, whereas GLP-1 triggers activation of AMPK in hepatocytes. Joint action of the two accounts for the ability of supplemental Glycine to counteract the excessive hepatic triglyceride synthesis promoted by sucrose/fructose feeding. Although glucagon could be expected to promote hepatic gluconeogenesis, GLP-1 mediated AMPK activation offsets this effect. Indeed, AMPK offsets the stimulatory impact of fructose-evoked cortisol in this regard.

To the extent Glycine does boost GLP-1, this may have implications on glycemic control, and for the preservation of vascular health. GLP-1 functions to potentiate glucose-stimulated insulin secretion.

The efficacy of Glycine supplementation in rodent models of alcohol-induced steatosis is traced to its ability to suppress Kupffer cell activation. Alcohol, by promoting intestinal permeability, enables portal influx of bacterial endotoxins. The resulting activation of Kupffer cells exposes hepatocytes to pro-inflammatory cytokines such as TNF-α, which play a key role in induction of fatty liver disease. Glycine antagonizes Kupffer cell activation.

High fructose diets in rats likewise impair the intestinal barrier function, leading to an activation of Kupffer cells that exacerbates fructose-induced steatosis. Glycine should be protective in this regard, as it is in rodent models of alcohol-induced steatosis.

Fructose markedly increases production of uric acid in the liver. Increased uric acid poses a risk for gout or gouty nephropathy, and is also a risk factor for coronary disease, hypertension, Type 2 diabetes and heart failure. (However, the uric acid impact appears weak when compared to other risk factors.)

Supplementing Glycine at 5 grams, 3 times daily, to patients with Metabolic Syndrome caused fasting glucose to rise from 101 to 114, yet glycated hemoglobin fell from 7.81 to 6.45. The increase in fasting glucose in these patients is likely explained by the Glycine stimulating glucagon secretion.

Notably, when 5 grams Glycine is administered along with 25 grams of glucose in an oral glucose tolerance test, the subsequent increase in plasma glucose is blunted compared to the response to glucose alone. Since Glycine has only a small impact on insulin secretion, this control of glucose is postulated to come from some unknown intestinal hormone capable of boosting insulin sensitivity.

When patients with poor glycemic control were given 5 grams of Glycine 4 times daily for 6 months, glycated hemoglobin fell from 9.6 to 6.9 --- as not only was glucose tolerance improved, but protein glycation was decreased. (--- Advanced Glycation End-products (AGE) are the major source of OxS in those with fading insulin sensitivity).

Glycine supplementation also resulted in significant reduction in systolic blood pressure as well as many markers of OxS.

Dietary Glycine can protect the livers of alcohol fed mice, and this effect is at least partly due to suppression of Kupffer cell activation that lessons the production of TNF-α. Similarly, Glycine supplementation improves liver status in rat models of liver INFLAM-AGING induced by a high-fat, high-sugar diet or by choline deficiency. Increased liver production of pyruvate might contribute to the protection shown in these studies.

Glycine has a hyperpolarizing effect on airway smooth muscle that is broncho-dilatory. Ensuring optimal level of magnesium along with Glycine may modestly blunt the stimulatory effect of intracellular free calcium on bronchoconstriction.

To blunt the contribution of Oxidative Stress (OxS) to bronchoconstriction, use can be made of Glycine + NAC to promote the intracellular synthesis of Glutathione. Glutathione inducers such as lipoic acid, selenium, and zinc are also helpful in this regard. Hydrogen sulfide is also beneficial for bronchial INFLAM-AGING by several mechanisms. NAC + Taurine may boost hydrogen sulfide synthesis.

Macrophages, leukocytes, and Kupffer cells express Glycine-gated chloride channels, and in these cells, Glycine exerts a hyperpolarizing affect, inhibiting calcium influx through calcium channels, and thereby down-regulating their inflammatory activity.

Supplemental Glycine, via activation of Glycine-gated chloride channels expressed on many types of cells --- including Kupffer cells, macrophages, lymphocytes, platelets, cardiomyocytes and endothelial cells --- has been found to exert anti-inflammatory, immune-modulatory, cytoprotective, platelet-stabilizing and anti-angiogenic effects. The plasma concentration of Glycine in normal individuals is near the activation point for these channels, indicating that the large increases in plasma Glycine achievable with supplementation will further activate these channels.

Glycine activation of chloride channels tends to be a calcium channel blocker, and suppression of calcium influx may mediate many of the protective effects afforded by Glycine.

Platelets also express Glycine-responsive chloride channels, which have the hyperpolarization action that suppresses calcium infiltration and thus protects platelet stability.

In studies on rats, supplementation with Glycine, via its platelet-stabilizing effect, approximately doubled bleeding time, and the amplitude of platelet aggregation triggered by ADP or collagen was cut in half. Human platelets are just as responsive to Glycine's blood-thinning effect.

Glycine supplementation, via its hyperpolarizing effect on vascular endothelium and also via an anti-inflammatory impact on foam cells, is postulated to exert an anti-atherosclerotic affect (that has not yet been fully tested and confirmed). What has been shown very definitely is that Glycine hyperpolarization decreases superoxide production that comes from NADPH oxidase activation.

Glycine administration to aging rats in their drinking water for 2 months increased endothelium-dependent vasodilation, increased mRNA expression of endothelial nitric oxide, and down-regulated inflammatory prostaglandins, and TNF-α.

In consideration of the anti-inflammatory effects of Glycine, it is notable that c-reactive protein levels are nearly twice as high in patients in the bottom quartile of plasma Glycine as in the upper quartile.

In association with its impact on endothelial cells, Glycine opposes NADPH oxidase. NADPH is a key mediator of the signaling pathway whereby VEGF (Vascular Endothelial Growth Factor) promotes proliferation and migration of endothelial cells. Additionally, Glycine acts directly on hepatic cells, to inhibit expression of VEGF expression.

The anti-inflammatory effects of Glycine include benefits in cachexia, as Glycine supplementation blunts the loss of muscle and fat mass, and decreases inflammatory markers (particularly Tumor Necrosis Factor (TNF-α)).

- Glycine supplementation at bedtime (3 grams) in human volunteers with frequent unsatisfactory sleep ….

  --- improves subjective sleep quality
  --- improves sleep efficacy (sleep time to in bedtime ratio)
  --- shortens polysomnography latency both to sleep onset and to slow wave sleep, without changes in the sleep architecture
  --- lessens daytime sleepiness
  --- improves performance of memory recognition tasks.

  This improvement in sleep quality and in mental performance the next day was achieved by an entirely different mechanism and with none of the CNS depressant effects of traditional drugs such as benzodiazepines.

  Patients who suffer from insomnia associated with either a Sympathetic, a Glucogenic, or a Dysaerobic Imbalance, or from excess Histamine or Prostaglandin E2, generally benefit from supplementation with Glycine at bedtime. The Glycine activates the glycinergic receptors in the brain, thus ensuring deeper more restorative sleep, and awaking the next morning more fully refreshed. 3 grams (6, 500 mg capsules) shortly before bed.

  While Glycine supplementation at bedtime facilitates sleep via the glycinergic receptors in the brain, Glycine supplementation in the day does not cause drowsiness.

- Various neuronal populations are related to 2 biological rhythms --- the diphasic circadian rhythm of wake/sleep, and the periodic cycles of non-REM/REM sleep. Hypothalamic nuclei are the sources of circadian rhythm and sleep onset control. The control of periodic non-REM/REM cycling is within the pons.

- Glycinergic postsynaptic inhibition is responsible for the atonia of REM sleep --- During REM sleep, only receptors on alpha motoneurons in the trigeminal motor nucleus are excited. These receptors have been identified as glycinergic.