

Supplemental Glycine as an “Antidote” to Fructose - Do GLP-1 and Glucagon Mediate This Protection?

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Abstract

By activating glycine-gated chloride channels in a range of cells types, supplemental glycine has been shown to exert anti-inflammatory, immunomodulatory, cytoprotective, platelet-stabilizing and anti-angiogenic effects in rodents. Of particular interest are studies demonstrating that glycine administered in drinking water opposes the adverse effects of a sucrose-rich diet on the liver, adipose stores, and vascular system of rats. These findings might be clinically pertinent, as high-fructose diets are suspected to be a mediator of metabolic syndrome and non-alcoholic fatty liver disease in humans; fructose acts within the liver to inhibit fatty acid oxidation, stimulate *de novo* lipogenesis, and boost triglyceride synthesis and secretion. It is proposed that the ability of glycine to oppose the negative impact of fructose on the liver reflects a glycine-mediated increase in the secretion of glucagon-like peptide-1 (GLP-1) by intestinal L-cells, as well as an increase in pancreatic glucagon secretion. Acting via intracellular mediators cAMP and AMPK, these hormones act to promote hepatic fatty oxidation, while opposing lipogenesis. If supplemental glycine can indeed provoke a physiologically meaningful increase in GLP-1 activity, its implications for health may be broader than currently recognized, as GLP-1 agonists appear to have utility for weight control, cardioprotection, and neuroprotection. The potential efficacy of glycine in these regards might be complemented by concurrent administration of DDP-4 inhibitory drugs, which prolong the half-life of endogenously produced GLP-1.

Protective Properties of Supplemental Glycine

Supplemental glycine, via activation of glycine-gated chloride channels that are expressed on a number of types of cells, including Kupffer cells, macrophages, lymphocytes, platelets, and endothelial cells, has been found to exert anti-inflammatory, immunomodulatory, cytoprotective, platelet-stabilizing, and anti-angiogenic effects in rodent studies that may be of clinical relevance.¹⁻¹⁷ Although the possibility that glycine might exert an anti-atherosclerotic effect by hyperpolarizing vascular endothelium¹⁸ has not yet been tested in rodents, it does exert an anti-inflammatory effect on human coronary arterial cells exposed to TNFalpha *in vitro*.¹⁹ Glycine is a biosynthetic precursor for creatine, heme, nucleic acids, and the key intracellular antioxidant glutathione. A recent clinical study reports that concurrent supplementation of elderly subjects with glycine and cysteine (100 mg/kg/day of each, cysteine administered as its N-acetyl derivative) reverses the marked age-related reduction in erythrocyte glutathione levels while lowering serum markers of oxidative stress;²⁰ the authors however did not prove that the supplemental glycine was crucial for this effect.

Of particular interest are studies showing that high glycine intakes can counteract many of the adverse effects of a high-sucrose diet on the liver, adipose mass, and vascular function in rats.^{21, 22} Glycine decreased the elevated non-esterified fatty acid content of the liver of sucrose-fed rats, increased the state

IV oxidation rate of hepatic mitochondria, corrected an elevation of blood pressure, normalized the serum triglycerides and insulin, prevented an increase in abdominal fat mass, and, in the vasculature, boosted glutathione, decreased oxidative stress and normalized endothelium-dependent vasodilation. Of likely relevance to these findings is a recent clinical report that supplemental glycine (15 g daily in 3 divided doses) administered to patients with metabolic syndrome lessened indices of oxidative stress in erythrocytes and leukocytes, while lowering systolic blood pressure.²³ These findings are of considerable interest, particularly in light of evidence that high dietary fructose intakes can promote metabolic syndrome and non-alcoholic fatty liver disease in humans.^{24, 25}

The protective effects of glycine in sucrose-fed rats, and in humans with metabolic syndrome, are not readily explained on the basis of the known metabolic effects of glycine. Fructose is known to exert its adverse effects via its impact on liver metabolism; it is catabolized exclusively in the liver, and its oxidation, unlike that of glucose, is not regulated by metabolic need.^{24, 26} As a result, a high intake of fructose suppresses hepatic fatty acid oxidation, while promoting *de novo* lipogenesis and triglyceride synthesis; increased generation of malonyl-coA is responsible for the first two effects, whereas an increase in glycerol-3-phosphate contributes importantly to fructose's stimulatory impact on triglyceride synthesis. The increased triglyceride content of fructose-exposed hepatocytes can be expected to stabilize apoB100 and accelerate secretion of VLDL particles;^{27, 28} this phenomenon may explain the elevation of LDL cholesterol induced by high fructose intakes.²⁹ The increased hepatic secretion of VLDL triglyceride presumably is responsible for the increase in visceral fat observed in rodents and humans fed high-fructose diets.²⁴ This in turn can induce metabolic syndrome, including an increase in blood pressure.

How does glycine intervene in this process? We propose that glycine-stimulated secretion of glucagon-like peptide-1 (GLP-1) and of glucagon itself plays a key role in this regard.

Glycine May Stimulate GLP-1 and Glucagon Release

Gamerio and colleagues, working with the GLUTag cell line derived from intestinal L-cells – the cell type specialized for GLP-1 production in the intestinal mucosa – have found that glycine provokes an increase of GLP-1 secretion in these cells.³⁰ This reflects an activation of glycine-gated chloride channels that triggers a reduction in membrane polarization, leading to an increase in cytoplasmic free calcium and a consequent release of GLP-1. The ability of these chloride channels to decrease membrane polarization in these cells reflects the fact that they concentrate chloride via a $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ transporter. Drugs which inhibit either the glycine-gated channels or the chloride uptake mechanism prevent glycine from stimulating GLP-1 release in GLUTag cells. Since the apical microvilli of L-cells face the intestinal lumen, they are ideally positioned to detect an increase in glycine in the luminal contents. Hence, glycine supplementation could be expected to boost GLP-1 production.

Oral administration of glycine in humans (1 mmol glycine/kg lean mass) has also been reported to stimulate an increase in glucagon secretion by pancreatic alpha-cells.³¹ This response is negated if glucose is ingested simultaneously, likely reflecting the impact of glucose-evoked secretion of somatostatin from islet delta-cells.³² The contention that oral glycine stimulates GLP-1 production is difficult to square with glycine's impact on glucagon, as GLP-1 is known to inhibit alpha-cell glucagon secretion, either directly or by provoking delta-cell secretion of somatostatin.³³ However, there is recent evidence that glycine may act directly on alpha-cells as a glucagon secretagogue – and perhaps this effect overrides that of GLP-1. (The impact of GLP-1 on somatostatin secretion might be minor when glucose

is at basal levels, and GLP-1 receptor expression on alpha-cells is very low.³³) Li and colleagues have shown that alpha-cells express glycine-gated chloride channels that, when activated, trigger an influx of calcium and glucagon release.³⁴ This suggests that alpha-cells, like L-cells, have a mechanism for concentrating chloride intracellularly, such that a receptor-mediated increase in membrane permeability triggers chloride efflux and membrane depolarization. Since the affinity of glycine-gated channels for glycine is close to the fasting concentration of glycine in plasma,³⁰ it can be anticipated that a rise in plasma glycine induced via supplementation will cause an increase in glucagon secretion. One rather old study failed to observe an increase in glucagon secretion when glycine was infused intravenously, until the glycine reached supraphysiological levels;³⁵ it is not clear why the results of this study appear discordant with those of the two studies previously cited.

It is notable that both GLP-1 and glucagon work in complementary ways to promote fatty acid oxidation and oppose lipogenesis in the liver.³⁶⁻⁴¹ The effects of glucagon appear to be mediated primarily by cAMP, whereas GLP-1 triggers activation of AMPK in hepatocytes. Joint action of GLP-1 and glucagon on the liver could readily account for the ability of supplemental glycine to counteract the excessive hepatic triglyceride synthesis promoted by sucrose or fructose feeding. Indeed, GLP-1 agonists have been shown to protect against hepatic steatosis in sucrose-fed rats, and to have clinical utility in non-alcoholic fatty liver disease.⁴²⁻⁴⁶ Fortuitously, although glucagon could be expected to promote hepatic gluconeogenesis, GLP-1 mediated AMPK activation would tend to offset this effect.⁴⁷

Broader Implications for Health

If supplemental glycine can promote a physiologically meaningful increase in GLP-1 production, it may have broader protective potential than is currently appreciated, reflecting the diverse and largely protective physiological effects of GLP-1.⁴⁸ GLP-1 agonist drugs exert cardioprotective effects in rodent models of myocardial infarction and congestive failure.⁴⁹⁻⁵² Clinically, they promote modest weight loss in diabetics and obese non-diabetics.⁵³ And particularly intriguing are studies showing that GLP-1 agonist drugs are neuroprotective in rodent models of stroke, traumatic brain injury, Alzheimer's and Parkinson's disease.⁵⁴⁻⁶⁸ Conversely, GLP-1-receptor-knockout mice are more susceptible to neuronal damage and have impaired cognitive function, revealing that this phenomenon is physiologically relevant.^{69, 70} GLP-1 is readily transported through the blood-brain barrier, so GLP-1 produced in intestinal L-cells has the potential to confer a measure of neuroprotection.

It should be noted, however, that glycine itself functions as a neurotransmitter in the brain, both as an inhibitory agonist, and as a cofactor for a metabotropic form of the NMDA receptor. Exceptionally high glycine intakes (0.8 g/kg/day has been widely tested) clinically; these appear to increase brain glycine levels, and have shown efficacy as an adjuvant strategy for control of negative symptoms in schizophrenia, likely owing to increased NMDA receptor function.⁷¹⁻⁷³ Although NMDA receptors play a key role in long-term potentiation and learning, high-dose glycine has not been found to influence cognitive function in humans.⁷⁴ Conversely, there does not appear to be any evidence that high glycine intakes can potentiate excitotoxicity, in which NMDA receptors likewise play a mediating role.⁷⁵ Recent reports indicate that modest doses (3 g) of glycine administered before bedtime may improve sleep quality in people complaining of insomnia.^{76, 77} Whether or how the direct brain effects of supplemental glycine might interact with the neuroprotective effects of GLP-1 is not clear at this time.

Could the increase GLP-1 production triggered by supplemental glycine be meaningfully neuroprotective? The increase in plasma and brain GLP-1 induced by glycine or by meals will be episodic, and GLP-1 has a plasma half-life of only several minutes, thanks to the avid proteolytic activity of plasma dipeptidyl peptidase-4 (DPP-4).⁷⁸ In contrast, GLP-1 agonist drugs are resistant to DPP-4, and hence produce sustained activity. The pattern of GLP-1 activity produced by glycine supplementation would be more analogous to that seen when DPP-4 inhibitors such as sitagliptin are administered; these prolong the half-life of physiologically secreted GLP-1. It is therefore reassuring to note that DPP-4 inhibitors, like GLP-1 agonists, have been reported to provide neuroprotection in rodent models.⁷⁹⁻⁸³ Ideally, when a strong neuroprotective effect – or other beneficial impact of GLP-1 – was sought, glycine could be administered in conjunction with a DPP-4 inhibitor. These are inherently more convenient and less expensive than GLP-1 agonists, as they are orally administrable, whereas the agonists must be administered by injection. Hence, the combination of supplemental glycine and a DPP-4 inhibitor might prove to have particular merit as a neuroprotective, hepatoprotective, or cardioprotective strategy. Fortunately, glycine powder is inexpensive, highly soluble, and has a pleasant sweet flavor. Clinically useful effects have been observed in patients with metabolic syndrome or diabetes with glycine intakes of 5 g, 3 times daily.^{23, 84}

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