Is glycine effective against elevated blood pressure?

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Purpose of review

Glycine, a non-essential amino acid, has been found to protect against oxidative stress in several pathological situations, and it is required for the biosynthesis of structural proteins such as elastin. As hypertension is a disease in which free radicals and large vessel elasticity are involved, this article will examine the possible mechanisms by which glycine may protect against high blood pressure.

Recent findings

The addition of glycine to the diet reduces high blood pressure in a rat model of the metabolic syndrome. Also, glycine supplemented to the low protein diet of rat dams during pregnancy has a beneficial effect on blood pressure in their offspring. The mechanism by which glycine decreases high blood pressure can be attributed to its participation in the reduction of the generation of free radicals, increasing the availability of nitric oxide. In addition, as glycine is required for a number of critical metabolic pathways, such as the synthesis of the structural proteins collagen and elastin, the perturbation of these leads to impaired elastin formation in the aorta. This involves changes in the aorta's elastic properties, which would contribute to the development of hypertension.

Summary

The use of glycine to lower high blood pressure could have a significant clinical impact in patients with the metabolic syndrome and with limited resources. On the other hand, more studies are needed to explore the beneficial effect of glycine in other models of hypertension and to investigate possible side-effects of treatment with glycine.

Keywords

glycine, hypertension, metabolic syndrome, oxidative stress

Curr Opin Clin Nutr Metab Care 9:26–31. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Clinical Nutrition and Metabolic Care 2006, 9:26–31

Abbreviations

BP	blood pressure
GSH	reduced glutathione
NEFA	non-esterified fatty acid
ROS	reactive oxygen species
SFR	sucrose fed rat

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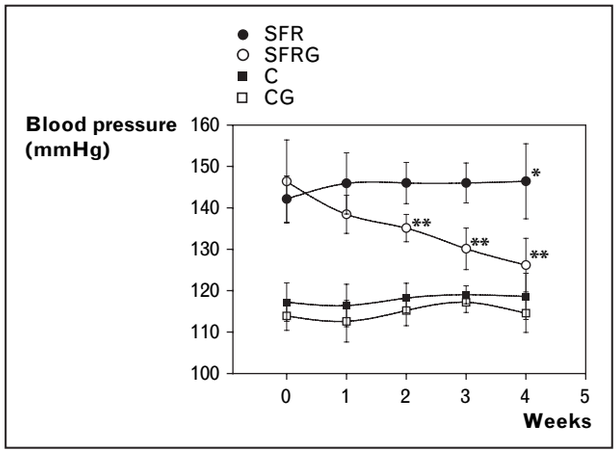
Introduction

It was recently found that glycine, which is both the simplest and a non-essential amino acid, when supplemented to the diet, lowers blood pressure (BP), triglycerides and intra-abdominal fat in experimental models of hypertension induced by an unbalanced diet [1•]. Such models are relevant to the human population in developing countries where the diet is high in fat, carbohydrates and salt, and where there is an increased incidence of the metabolic syndrome. Hypertension, like obesity and insulin resistance, is an important hallmark of the metabolic syndrome. Even the presence or absence of obesity in hypertensive patients appears to affect the prognostic effects of therapy. For instance, diuretics are far more effective in reducing major events in obese than in thin hypertensive patients [2]. Current recommendations in the therapy for the metabolic syndrome focus on correction of its components (i.e. hypertension, dyslipidemia, central obesity and glucose intolerance). As with dyslipidemia, the initial treatment of hypertension is non-pharmacological therapy, including sodium restriction and weight loss, through calorie restriction and exercise. Even though the success of lifestyle modification is limited, the importance of such therapy cannot be overemphasized. Drug intervention, however, must focus on treatment of the manifestations of the metabolic syndrome, with clearly defined targets for BP, weight, and levels of triglycerides. Evidence has accumulated that glycine protects in a variety of disease states in experimental models of hypertension, dyslipidemia and ischemia–reperfusion. Data from clinical trials also show a lowering effect of glycine on glycosylated haemoglobin in patients with type 2 diabetes. The aim of this review is to examine whether glycine can be used as a hypotensive agent and to discuss the possible mechanism by which it could exert this effect of lowering BP.

Effect of glycine on high blood pressure in experimental models of the metabolic syndrome

The metabolic syndrome is characterized by the co-occurrence of obesity, insulin resistance, dyslipidaemia and hypertension, which contribute to the development of cardiovascular diseases. The effect of glycine against high BP has been investigated in a hypertensive rat model induced by a high-calorie diet and in a model of early growth restriction induced by maternal protein deficiency. Both models show many features of the metabolic syndrome such as insulin resistance and hypertension.

Figure 1. Effect of glycine added to the diet on blood pressure in sucrose fed rats and control animals



After 20 weeks, the period necessary for the SFR to develop a significantly higher blood pressure than control animals, each group was divided into two subgroups. The first subgroup (control; C) continued to drink water ($n = 10$), the second subgroup (control + glycine; CG) received water supplemented with 1% glycine ($n = 10$). In parallel, the group that had received sucrose in its drinking water was also divided into two subgroups: one subgroup (sucrose-fed rats; SFR) continued to receive 30% sucrose in its drinking water ($n = 10$) and the other subgroup (SFR + glycine; SFRG) received sucrose supplemented with 1% glycine ($n = 10$). Data are expressed as mean ± SD ($n = 10$ different animals). *Significantly different from C ($P < 0.01$). **Significantly different from SFR ($P < 0.001$). Adapted with permission [1•].

Glycine and sucrose diet-induced hypertension

It was recently described that glycine protects against high BP induced in rats by long-term consumption of a refined carbohydrate in the diet (Fig. 1) [1•]. The mechanism by which glycine reduces high BP is not well established. Nevertheless, glycine has been found to reduce oxidative stress in many disease states [3,4]. In animal models of sucrose feeding, limited evidence suggests that a sucrose diet causes enhanced generation of reactive oxygen species (ROS) [5]. This allows us to hypothesize that glycine reduces oxidative stress, thus increasing the availability of nitric oxide. ROS, such as the superoxide anion, reacts with nitric oxide to form peroxynitrite, which can modify proteins and lipids to create nitrotyrosine, nitrosothiols and isoprostanes, which are also able to modulate vascular tone. Antioxidants and agents that interrupt nicotinamide adenine dinucleotide phosphate–reduced form (NADPH) oxidase-driven superoxide production regress vascular remodelling, improve endothelial function and decrease BP in hypertensive models [6•].

Glycine and low protein diet-induced high blood pressure

When pregnant rats are given a modest reduction in dietary protein during pregnancy (the diet low in protein contained 9% of casein as compared with the control diet which contained 18% of casein), the offspring develop high BP from 4 weeks of age, which remains higher than normal over their entire lifespan [7]. The addition of glycine at 3% to the low protein diet of rat dams during pregnancy has a beneficial effect on the high BP developed in their offspring whereas alanine supplemented to the diet low in proteins has no effect (Table 1). In addition the treatment of animals with glycine rectifies the abnormal vascular reactivity in both mother and offspring [8••]. The authors suggest that the rate of endogenous biosynthesis of glycine becomes inadequate in satisfying metabolic needs. This may be a limiting factor for the normal development of the fetus, mediated in part through developmental changes in the structure and function of the heart, kidneys and large vessels [9,10]. Glycine is required for a number of critical metabolic pathways, such as the synthesis of the structural proteins collagen and elastin. The impairment of elastin formation in the aorta induces permanent changes in the elastic properties of the large vessels, which would predispose to higher BP in the offspring and in hypertensive individuals [11,12].

Possible mechanisms of action of glycine as a hypotensive agent

Information about the exact mechanism by which glycine protects against high BP is limited. Several studies, however, have demonstrated the effect of glycine on intracellular calcium concentration through the activation of a glycine-gated chloride channel, on the generation of free radicals and on lipid metabolism. All these events are implicated in the regulation of vascular tone.

Glycine effect through the glycine-gated chloride channel

Glycine can exert its effect by binding to a glycine-gated chloride channel which has been described as present in

Table 1. Blood pressure at 4 weeks of age in male and female offspring of rats given one of four experimental diets for the duration of pregnancy

BP (mmHg)	CON	MLP	MLPA	MLPG
Male	103.7 ± 4.8	122.5 ± 3.7	113.3 ± 4.0	99.1 ± 4.2
Female	109.0 ± 4.2[a]	122.9 ± 4.1[b]	127.6 ± 4.3[b]	104.5 ± 2.0[a]

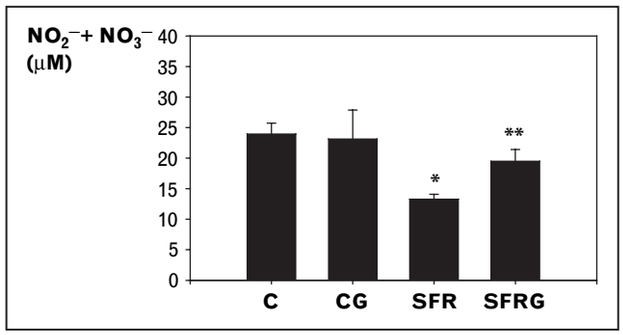
Values are means ± SEM. Differences among dietary groups were sought using one-way ANOVA. Groups that share the same superscript are not significantly different from each other. CON, control diet containing 18% (w/w) casein; MLP, low-protein diet containing 9% casein; MLPG, low-protein diet supplemented with 3% glycine or alanine (MLPA). Adapted with permission from reference [7•].

endothelial cell membranes and whose activation by glycine reduces intracellular calcium influx [13]. The increased intracellular calcium ions stimulated by phenylephrine, prostaglandin E_2 or vascular endothelial growth factors [14] are blocked by glycine in the presence of chloride ions [15]. The mechanism proposed by Zhong *et al*. [16] suggests that the activation of the glycine-gated chloride channel in the plasma membrane causes the influx of chloride ions, which hyperpolarizes the cell membrane. It is hypothesized that hyperporalization decreases the probable opening of calcium channels, thereby blocking the movement of calcium across the membrane and the subsequent event of vasoconstriction. It is well known that calcium plays an important role in the regulation of vascular tone. In addition, the increased intracellular calcium induces several events such as the activation of phospholipase A_2, which increases production of lipid-derived vasoactive substances such as eicosanoids and platelet-activating factors [17]. Glycine inhibits phospholipase A_2 activation caused by hypoxia in renal tubule cells, decreases arachidonic acid release and protects against cell injury [18].

Glycine and oxidative stress

The beneficial effects of glycine in several pathological situations other than hypertension are well reviewed by Zhong *et al*. [16]. The protective effects of glycine have been observed in experimental conditions of hypoxia/reoxygenation that are associated with increased generation of free radicals. We cite some of these in which glycine protects kidney proximal tubules [19,20], hepatocytes [21,22] and cardiomyocytes [23•] against hypoxia/reoxygenation. It has been reported that glycine protects endothelial cells against hydrogen peroxide injury [24] and against cyclosporin A-induced free radical formation in kidney [25]. Thus glycine may induce different effects to prevent ROS formation by minimizing the impairment of the activity of antioxidant enzymes and by inhibition of the activation of nuclear factor κB, as described in liver injury induced by hemorrhagic shock [3]. ROS activate phospholipase A2, which increases the release of arachidonic acid, a precursor of several vasoactive substances that modulate the vascular tone. In addition the enhanced ROS production (especially superoxide anion) causes diminished nitric oxide bioavailability and leads to endothelial dysfunction, which induces impaired vasorelaxation. The treatment of hypertensive sucrose-fed rats (SFR) with glycine increases plasma nitrites and nitrates (nitric oxide metabolites) to the normal level found in control animals (Fig. 2). In animals with a low protein diet, glycine supplementation reversed the reduced nitric oxide levels and improved the acetylcholine relaxation in mesenteric arteries, having no effect on endothelial nitric oxide synthetase expression [8••]. This suggests that the enhanced nitric oxide release in animal vasculature is probably due to the increased bioavailability of nitric oxide by the protective role of glycine against oxidative stress, through its participation in the glutathione biosynthesis pathway.

Figure 2. Effect of glycine on plasma nitrites and nitrates concentration in both control and sucrose-fed rats



The treatment of animals was performed as described in the legend of Fig. 1. Nitrites and nitrates were determined using the Griess reaction. Data are expressed as mean ± SD ($n = 6$ different animals). SFR, sucrose-fed rats; C, control rats; SFRG, SFR + glycine; CG, control + glycine. **Significantly different from C ($P < 0.01$). *Significantly different from SFR ($P < 0.01$) (unpublished data).

Glycine, reduced glutathione biosynthesis and hypertension

The synthesis of reduced glutathione (GSH) from glutamate, cysteine, and glycine is sequentially catalyzed by two cytosolic enzymes, γ-glutamylcysteine synthetase and GSH synthetase. This pathway is present in all cell types, with the liver being the major producer and exporter of GSH [26]. GSH effectively scavenges free radicals and other reactive oxygen species directly (e.g. hydroxyl radical, lipid peroxyl radical, peroxynitrite, and hydrogen peroxide), and also indirectly through glutathione peroxidase which oxidizes GSH to form oxidized glutathione; this is then reduced to GSH by the NADPH-dependent glutathione reductase [27]. GSH/oxidized glutathione is the most important redox couple and plays crucial roles in antioxidant defence, nutrient metabolism and the regulation of pathways essential for whole body homeostasis. Glycine is a limiting factor for GSH synthesis when its availability is reduced in response to protein malnutrition [28,29], or when hepatic glycine oxidation is enhanced in response to high levels of glucagon or a diabetic condition [30].

Moreover, GSH deficiency contributes to oxidative stress and, therefore, may play a key role in the pathogenesis of hypertension. GSH has been found to conjugate with nitric oxide to form an S-nitrosoglutathione adduct. This is cleaved by the thioredoxin system to release GSH and nitric oxide which, in turn, diffuse to a site of bioactivity [31,32]. Recent evidence suggests that the targeting of endogenous nitric oxide is mediated by intracellular GSH

through the formation of S-nitrosoglutathione, which mediates cell signalling reactions [33]. In addition S-nitrosoglutathione appears to be effective for the treatment of hypertension [34].

Glycine and lipid metabolism

The addition of glycine to the diet of SFR or of alcohol-supplemented rats reduces circulating and liver triglycerides and non-esterified fatty acid (NEFA) concentrations [1•,35]. The mechanism by which glycine reduces these parameters remains to be elucidated. In SFR, high BP is, in part, associated with the high accumulation of intra-abdominal fat involved in an increased release of NEFA, due to the probable increase in lipolytic activity in this adipose tissue. NEFAs have been postulated to be responsible for the development of high BP, associated with central obesity, by inducing oxidative stress and by decreasing nitric oxide availability in endothelial cells in culture [36,37]. The study regarding the alcohol-supplemented model does not describe changes in BP, but hypertension has long been found to be directly associated with alcoholism [38]. Chronic alcohol administration to the rat induces high BP and alters vascular reactivity in isolated rat aorta [39].

Other possible mechanisms exist by which glycine could reduce high BP in SFR. Glycine, as a prominent neurotransmitter in the reflex control of cardiovascular activity, can act at the level of the sympathetic nervous system to modulate heart rate and BP, as described by Talman *et al.* [40]. These authors showed that the microinjection of glycine in the nucleus tractus solitarii increases acetylcholine release, reducing high BP and heart rate. Thus, glycine could also decrease BP in SFR by affecting the sympathetic nervous system, modulating lipid mobilization from adipose tissue that is regulated by catecholamines, which are the most potent regulators of lipolysis in human fat cells.

Supplemental suggestions

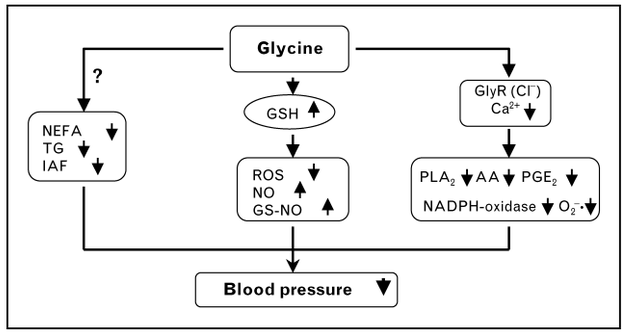
Glycine has several more beneficial effects than harmful ones. This would justify its clinical use: it can be administered in the diet without apparent side-effects, as suggested by Rosse *et al.* [41] and Carvajal-Sandoval *et al.* [42]. Many years ago it was reported that glycine given orally in amounts of 40–50 g/day causes a moderate reduction in blood glucose concentrations in healthy and diabetic adults: from 5.7 to 4 mmol/l in healthy subjects and from 14.2 to 8.9 mmol/l in diabetic patients [43,44]. Within the last decade Carvajal-Sandoval *et al.* [42] reported that type 2 and type 1 diabetic patients receiving daily doses of 20 g glycine dissolved in water, 5 g every 6 h, during variable times (3–56 months), show a reduction of non-enzymatic glycosylation of haemoglobin to the normal levels, without apparent side-effects.

In structural collagen, one in every three to four amino acids is glycine. When these structural proteins are subjected to denaturation by heating or alkaline and acid hydrolysis, they form gelatin, an ingredient commonly used in foods. Glycine is the major amino acid in gelatin, which strongly stimulates insulin secretion in patients with type 2 diabetes [45].

Glycine side effects

Information on the toxic properties of glycine is limited. Recently, Cupid *et al.* [46••] reported that glycine in the presence of nitric oxide induces the formation of a nitrozating agent, which reacts with 2′-deoxyguanosine (DNA compound) to produce O^6-carboxymethylguanosine and O^6-methylguanosine. These authors suggest that nitrozated glycine derivatives may be formed in the gastrointestinal tract from the reaction of dietary glycine and nitric oxide to produce a nitrozating agent. The detection of these O^6-guanine adducts in the DNA may indicate risk factors for gastrointestinal tract cancers. On the other hand Rose *et al.* [47] described that dietary glycine inhibits the growth of B16 melanoma in mice by 65%, indicating an anticancer property of glycine. To date, however, there is no data showing a carcinogenic property of glycine. More studies are therefore needed to investigate the range of doses that are effective without side-effects in different animal models of hypertension.

Figure 3. Proposed mechanisms by which glycine supplemented to the diet may lower high blood pressure



Glycine lowers non-esterified fatty acid (NEFA), triglycerides (TG) and intra-abdominal fat (IAF). How glycine reduced these variables remains to be elucidated. On the other hand, glycine via its receptor (GlyR) in the presence of the chloride ion (Cl^-) decreases intracellular calcium which acts as a signal for a variety of events such as the activation of phosphlipase A_2 (PLA_2) to release arachidonic acid (AA), a precursor of vasoactive substances such as prostaglandin E_2 (PGE_2). Calcium activates reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and generates superoxide anions ($O_2^{-\bullet}$) that reduce nitric oxide (NO) availability and produce peroxynitrites, a very reactive species. Glutathione, a product of the reaction between γ-glutamylcysteine and glycine, catalyzed by glutathione synthetase, scavenges the free radicals which induce vasoconstriction thus reducing the availability of NO.

Conclusion

The possible mechanisms by which glycine may reduce high BP are summarized in Fig. 3. The beneficial effect of glycine on high BP and dyslipidemia in experimental animals with metabolic syndrome, and on glycosylated haemoglobin in patients with type 2 diabetes, makes it a candidate drug to treat the metabolic syndrome. The use of glycine to lower high BP could have a significant clinical impact and could be effective, economical and simple for patients with metabolic syndrome and with limited resources. On the other hand, more studies could be designed to investigate the effect of glycine in different models of hypertension, such as spontaneously hypertensive rats (SHR), salt-induced, angiotensin-induced and others.

References and recommended reading

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 61).

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