Glycine metabolism in skeletal muscle: implications for metabolic homeostasis

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Abstract:

Purpose of review: The review summarises the recent literature on the role of glycine in skeletal muscle during times of stress.

Recent findings: Supplemental glycine protects muscle mass and function under pathological conditions. In addition, mitochondrial dysfunction in skeletal muscle leads to increased cellular serine and glycine production and activation of NADPH-generating pathways and glutathione metabolism. These studies highlight how glycine availability modulates cellular homeostasis and redox status.

Summary: Recent studies demonstrate that supplemental glycine effectively protects muscles in a variety of wasting models including cancer cachexia, sepsis and reduced caloric intake. The underlying mechanisms responsible for the effects of glycine remain unclear but likely involve receptor mediated responses and modulation of intracellular metabolism. Future research to understand these mechanisms will provide insight into glycine's therapeutic potential. Our view is that glycine holds considerable promise for improving health by protecting muscles during different wasting conditions.

Introduction

The cellular and molecular mechanisms regulating skeletal muscle mass involve an intricate network of signalling pathways. To coordinate protein synthesis and protein breakdown simultaneously these signalling pathways interact and modulate one another at numerous levels. Anabolic factors (e.g. amino acids, growth factors and hormones) inhibit protein breakdown and stimulate protein synthesis, while catabolic factors (e.g. reactive oxygen species, pro-inflammatory cytokines, and energy depletion) stimulate protein breakdown and inhibit protein synthesis (1). During extended periods of metabolic challenge, muscle protein degradation may exceed synthesis and compromise muscle mass and function. To restore homeostasis, skeletal muscle requires additional amino acids to promote protein synthesis.

Essential amino acids, the branched-chain amino acid (BCAA) leucine in particular, strongly stimulate muscle protein synthesis in healthy muscle (2). Leucine does not just act as a substrate for muscle protein synthesis, but as an important signalling molecule that directly modulates activity of the mechanistic target of rapamycin complex 1 (mTORC1), thereby enhancing the initiation of mRNA translation and promoting protein synthesis (1). Interestingly, leucine cannot stimulate protein synthesis in models of acute inflammation, such as lipopolysaccharide (LPS) (3) or caecal ligation and puncture (4). These observations indicate that impaired leucine sensing by mTORC1 reduces anabolic responses (in skeletal muscle) to food intake during inflammatory conditions. This phenomenon, called 'anabolic resistance' is considered a major contributor to muscle wasting (1).

We have proposed that restoring the normal anabolic response to nutrition in disease states is an effective means of preventing skeletal muscle wasting and weakness (2). Our recent work highlights the potential of glycine to enhance protein synthesis after leucine administration during inflammatory conditions and attenuate muscle wasting in mouse models of cancer cachexia and short-term caloric restriction (3, 5, 6). In this review, we focus on our current understanding of the anti-inflammatory and cytoprotective effects of glycine that alter muscle protein synthesis and homeostasis to identify gaps in our knowledge and the implications for future research.

The anti-inflammatory and cytoprotective properties of glycine

Glycine is a simple non-essential amino acid consisting of a single carbon molecule attached to an amino and a carboxyl group. In the central nervous system, glycine acts as an inhibitory neurotransmitter, but also modulates homeostasis in a variety of cell types via both a receptor-mediated response and its intracellular metabolism (Figure 1).

Glycine receptor mediated effects

Glycine inhibits inflammatory cell activation, thereby modulating systemic and tissue inflammation (7). Glycine directly activates glycine-gated chloride (Cl^-) channels (GlyR) expressed in inflammatory cells such as macrophages, which promotes Cl^- influx, hyperpolarising the cell membrane and preventing intracellular Ca^{2+} accumulation. Indeed, GlyR activation normalises intracellular $[Ca^{2+}]$ in inflammatory cells, thereby blunting NFκB activation and reducing pro-inflammatory cytokine (i.e. TNFα) production after haemorrhagic shock or LPS challenge (7). Although glycine administration effectively reduces systemic inflammation, it remains to be established

whether glycine also modulates skeletal muscle inflammation and homeostasis directly via this mechanism.

The glycine receptor (GlyR) is found in a variety of cell and tissue types, including the central nervous system and inflammatory cells (7). GlyRs are inhibitory Cl^- channels composed of three different types of subunits: 1) the ligand binding α subunits (GLR α1-α4); 2) a structural β subunit (GLRB); and 3) a cytoplasmic anchoring protein known as gephyrin (GPHN) (8). Subunit combinations specifically dictate the pharmacokinetics, pharmacodynamics and binding affinity profiles of individual GlyR channels. While the effect of GlyR on intracellular Ca^{2+} accumulation has been well-characterised in neural and inflammatory cells (9), less is known about their role in muscle. Functional GlyRs (including α and β subunits) have been identified in guinea pig and human smooth muscle (10) as well as in rat cardiomyocytes (11). Glycine administration (1 mM) also facilitates smooth muscle cell relaxation *in vitro*, but not in the presence of the GlyR antagonist strychnine (3 µM), which inhibits all known GlyR isoforms. Similarly, α1 and β subunits were identified in cardiomyocytes and glycine (0.5-2.5 mmol) inhibits LPS-(8, 9) and hypoxia/regeneration-induced increases in cytosolic $[Ca^{2+}]$. Co-treatment with strychnine under LPS conditions completely prevented the cellular protection conferred by glycine (9). These studies demonstrate the existence of functional GlyRs in smooth and cardiac muscle.

Besides functioning as a regulator of intracellular Ca^{2+}, the GlyR and its scaffolding protein could form an active signalling complex (8). Gephyrin is an anchoring protein that provides the scaffolding needed for GlyR mediated cell-cell communication via cytoplasmic GlyRβ binding. Interestingly, it has been suggested that mTORC1 signalling

requires gephyrin, which contributes to its intracellular localisation in a variety of cell types (12, 13). Indeed, in HeLa cells, mutations within gephyrin's mTORC1 binding domain disrupt mTORC1 localisation and inhibit activation of its downstream targets p70S6K and 4E-BP1 (14).

To date, no in-depth studies of the role of glycine-receptor (and gephyrin) associated signalling in skeletal muscle has been performed. While functional GlyRs have yet to be identified in skeletal muscle, their demonstrated role in smooth and cardiac muscle suggests this may be one of the mechanisms by which glycine directly modulates skeletal muscle homeostasis.

Glycine metabolism

As a non-essential amino acid, glycine can be synthesised in tissues and is generally thought not to be involved in the regulation of protein turnover during healthy conditions. Interestingly, skeletal muscle glycine levels are lower in mouse models of diabetes and muscular dystrophy (15, 16). In addition, intracellular glycine levels are lower in older humans, with the most pronounced decreases associated with frailty (17). These observations suggest that during these conditions either tissue demand for glycine exceeds dietary intake, or glycine metabolic breakdown increases.

Glycine is not only needed for general protein synthesis but also as a precursor for the production of a variety of molecules. Glycine can deliver carbon units to the folate cycle, thereby mediating the production of purines (DNA), heme, glutathione, creatine and

NADPH (7). Through these mechanisms glycine modulates the balance between oxidised (GSSG) and reduced glutathione (GSH), a crucial regulator of cellular redox status. Therefore, the intracellular availability of glycine is critical for preserving homeostasis. Indeed, glycine (combined with L-cysteine) supplementation effectively and safely increases glutathione content in red blood cells, and reduces ROS and inflammatory cytokines (18). Intracellular glycine concentration can be regulated both by cellular uptake, via a glycine transporter, or synthesised within the cell from L-serine, which itself can be synthesised from glycolysis intermediates and L-glutamate. The metabolic pathways of glycine in animals and humans have been recently reviewed in detail elsewhere (7).

The importance of glycine (and serine) for the regulation of cellular homeostasis was first demonstrated in a variety of cancer cells, showing that rapidly proliferating cells have increased activity of the biosynthetic pathways of these amino acids (19). The role of glycine, L-serine and 1-carbon metabolism in skeletal muscle homeostasis has only recently received attention with two studies demonstrating that mitochondrial dysfunction leads to upregulation of the pathways for glycine, L-serine and 1-carbon biosynthesis (20, 21). Ost and colleagues (2015) demonstrated that compromised mitochondrial function, in uncoupling protein 1 transgenic (UCP1-TG) mice, led to increased mRNA and protein expression of regulatory enzymes in the serine/glycine and 1 -carbon biosynthesis pathway, and the trans-sulfuration pathway (20). These adaptations increase serine and glycine production and the activity of pathways that generate NADPH and glutathione as a defence mechanism against increased oxidative stress. Similarly, Mitochondrial DNA replication disorders are associated with changes in serine/glycine biosynthesis (21).

Affected muscles have altered cytoplasmic 1-carbon cycle, as well as increased glucose uptake and *de novo* serine and glutathione biosynthesis (21). Combined, these recent papers conclusively demonstrate that glycine/serine metabolism is part of an important compensatory stress signalling network that preserves cellular function during conditions of increased mitochondrial stress.

Glycine supplementation to prevent muscle wasting and metabolic disorders

As glycine can affect skeletal muscle homeostasis via direct and indirect mechanisms, we and others have performed studies to determine whether glycine administration can prevent skeletal muscle wasting and preserve protein synthesis.

Effect of glycine administration on C2C12 muscle cells

To our knowledge only one study has investigated whether glycine availability directly modulates Akt/mTORC1 signalling in muscle cells (22). These experiments were restricted to proliferating myoblasts and showed cell viability and proliferation were impaired when cells were incubated in glycine-free media. While glycine availability was required for cell viability, increasing glycine concentrations beyond physiological concentrations (0.25 mM) did not further improve cell viability. To determine changes in the phosphorylation status of key enzymes in the AKT/mTOR signalling pathway, myoblasts were serum- and glycine-starved for 6 hours to reduce intracellular concentrations, prior to re-introduction of glycine (0.25, 0.5, 1.0 mM). Phosphorylation of Akt, mTOR and P70S6K1 was elevated following 30 min of glycine exposure, an effect blocked by specific Akt inhibitors. Consistent with these observations, protein synthesis rates were higher in cells exposed to glycine compared with cells incubated in glycine-free media, suggesting that glycine modulates the mTOR signalling pathway.

However, since an appropriate non-essential control amino acid (e.g. L-serine, L-alanine or L-cysteine) was not used to confirm these effects were glycine specific, these results should be interpreted with caution. Although this study suggestsed that glycine impacts anabolic signalling in myoblasts, confirmatory studies are needed to determine the effect of glycine in myotubes or single fibres and assess whether the effects are attributable to a receptor mediated response or via glycine's intracellular metabolism, by incubating cells with strychnine or GlyT inhibitors, respectively.

Effect of glycine administration during wasting conditions in vivo

We have performed a series of *in vivo* studies in mice to assess whether glycine administration protects muscles from wasting during inflammatory conditions. Inflammation is likely the primary driver of defective protein metabolism that leads to muscle wasting in many diseases and conditions. We examined whether glycine administration (1 g/kg/day) could prevent muscle wasting in tumour-bearing mice (6). Glycine reduced tumour growth by 30% and attenuated the loss of muscle mass and strength by 50%. Glycine treatment also suppressed the cancer-induced production of reactive oxygen species and expression of genes associated with muscle inflammation and macrophage infiltration. We also observed attenuated muscle *Atrogin-1* mRNA expression in glycine treated tumour bearing mice and a reduction in eIF3f, a factor that controls translation initiation. These factors combined suggest that glycine helps maintain the machinery that controls protein synthesis in skeletal muscle. Blunted tumour growth was consistent with results from cell culture experiments showing higher levels of extracellular glycine (>1 mM) inhibited nucleotide synthesis and proliferation of colon cancer cells (23). Although the reduced tumour growth likely impacted food intake,

inflammation, and muscle wasting, direct effects of glycine on skeletal muscle cannot be ruled out. Despite the specific mechanism proving elusive, glycine has clear therapeutic potential in cancer cachexia (6).

Based on our observations that glycine treatment attenuates the cancer-induced loss of eIF3f, we investigated the effect of glycine on protein synthesis, and the anabolic response to leucine intake in mice exposed to LPS. Administration of LPS in mice is a well-characterised endotoxemic model of acute inflammation associated with oxidative stress, reduced basal (fasted) muscle protein synthesis and an impaired anabolic response to leucine (3). Treatment of mice with glycine (1 g/kg), 30 minutes prior to LPS injection counteracted the LPS-induced increase in superoxide and the anabolic resistance to leucine (0.5 g/kg) (3). These observations were specific to glycine, since pretreatment with the non-essential amino acid L-alanine did not change the protein synthesis responses to L-leucine in LPS treated mice. The glycine-induced alterations in protein synthesis were associated with changes in the phosphorylation status of mTOR, S6 and 4EBP1. These observations are in agreement with a recent study showing glycine pre-feeding protected skeletal muscle (4 hrs) after LPS injection in 28 day old pigs (24). Pretreatment with dietary glycine reduced circulating levels of TNFα and cortisol and largely prevented LPS-induced suppression in Akt and mTOR phosphorylation. In this pig model, glycine attenuated increases in *Foxo1, Atrogin-1,* and *Murf* mRNA expression and reduced *Tlr4* mRNA and its downstream targets, *Myd88, Irak1* and *Traf6* in gastrocnemius muscle compared to LPS treated piglets. These observations seemingly contradict our finding that glycine administration does not change the inflammatory response to LPS in mice (3). The mRNA expression of *Il-6, Tnfα, Socs3, Ccl2* and *Ccl5*

were not different between the alanine and glycine treated animals, suggesting glycine does not interfere directly with pathways in skeletal muscle cells responsible for cytokine production and perhaps indicating that the receptor mediated response is not the main mechanism in skeletal muscle. Overall these data indicate glycine may restore the anabolic sensitivity of muscle to leucine during times of stress and protect muscles from wasting during acute inflammation.

Based on our observations that glycine preserves muscle mass and function during wasting conditions we also assessed the effect of glycine supplementation during short-term calorie restriction (CR), designed to mimic short-term dieting. Although reduced dietary energy intake is an effective strategy for stimulating weight loss it is also associated with loss of muscle mass, thereby potentially increasing the risk of developing metabolic diseases and weight regain (25). Interventions that preserve muscle mass during dieting are therefore needed. We demonstrated that glycine (1 g/kg/day) administered to obese mice undergoing short-term CR (40% for 10 days and 30% for the next 10 days) enhanced the loss of whole-body fat mass (14%) and epididymal fat mass (26%) compared with control mice treated with L-alanine (5). A similar protective effect has been reported in sucrose-fed obese rats, with glycine supplementation effectively reducing adiposity, blood pressure and vascular reactivity which was associated with normalized glutathione availability (26). Interestingly, We also observed a protection of lean mass (27%) upon glycine administration during CR, but did not observe changes in the phosphorylation states of AKT/mTOR signaling proteins, nor did we observe changes in gene expression of key factors in inflammation or protein breakdown. The lack of difference in mRNA expression between the alanine and glycine treated mice was not

surprising since most changes in mRNA expression would have occurred in the early stages of CR and not at the time of muscle sampling (after 20 days of CR). Combined, these studies highlight the potential of glycine to attenuate muscle wasting during dieting or fasting. Despite the lack of a definitive mechanism of action, glycine supplementation has therapeutic potential as an effective nutritional intervention to promote loss of fat mass and spare skeletal muscle during CR.

Conclusion and Perspectives

Glycine is a precursor for a range of important metabolites including creatine, heme, purines and glutathione. Glycine is a functional amino acid that can alter cellular homeostasis either through its metabolism or its receptor. Supplemental glycine effectively protects muscles in a variety of wasting models including cancer cachexia, sepsis and dieting. Future studies should focus on the underlying mechanisms responsible for the effects of glycine and enhance our understanding of the role of serine/glycine/1-carbon biosynthesis pathways that confer protection against cellular stress. Our view is that glycine holds considerable promise for improving health by protecting muscles during different wasting conditions.

Key points:

- Glycine is a non-essential amino acids with anti-inflammatory and cytoprotective properties.

- Glycine can modulate homeostasis in a variety of cell types via a receptor-mediated response and via intracellular metabolism.

- Dietary supplementation with glycine can effectively protect muscles in a variety of wasting models including cancer cachexia, sepsis and calorie restriction.

Acknowledgements

Conflicts of interest

None.

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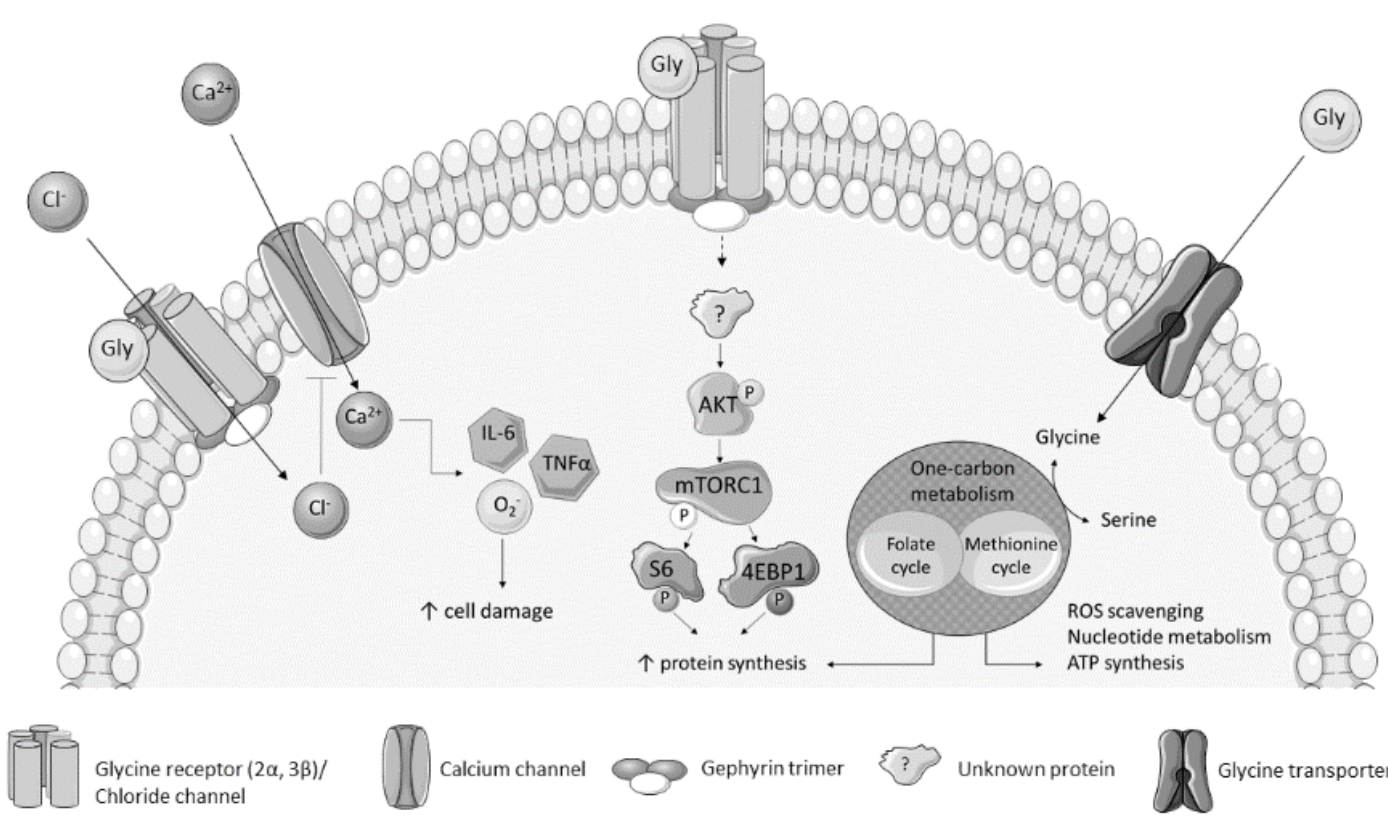
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FIGURE LEGENDS

Figure 1: Overview of the potential mechanisms by which glycine can modulate metabolic homeostasis. Glycine binding to the GlyR induces Cl^- influx which attenuates Ca^{2+}-induced increases in the production of cytokine and reactive oxygen species. In addition, activation of the GlyR has been associated with increased signalling via Akt and mTOR. Intracellular metabolism of glycine feeds pathways that produce NADPH and glutathione, which are important factors in anti-oxidant defence. This figure was produced using Servier Medical Art (http://www.servier.com/Powerpoint-image-bank).

Ca²⁺

Cl⁻

Gly

Gly

Gly

Ca²⁺

Cl⁻

IL-6

TNFα

O₂⁻

↑ cell damage

AKT ᴾ

mTORC1
ᴾ

S6
ᴾ

4EBP1
ᴾ

↑ protein synthesis

?

Glycine

One-carbon metabolism

Folate cycle

Methionine cycle

Serine

ROS scavenging
Nucleotide metabolism
ATP synthesis

Glycine receptor (2α, 3β)/ Chloride channel   Calcium channel   Gephyrin trimer   ? Unknown protein   Glycine transporter

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