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Glycine can prevent and fight virus invasiveness by reinforcing the extracellular matrix

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ABSTRACT

The extracellular matrix, mainly composed of collagen, is a mechanical barrier against infective agents, including viruses. High glycine availability is needed for a healthy collagen turnover. Glycine produced by human metabolism is much lower than the cell's needs giving a general glycine deficiency of 10 g/day in humans. This effect was tested for three years in 127 volunteers who had virus infections usually once or more times every year. 85 of them took glycine 10 g/day; 42 did not take glycine. Among those who took glycine, only 16 (12 of whom had infections two or more times each year) had the flu just in the first year –but much reduced in severity and duration– while those who did not take glycine, were infected as often and as severely as before. Glycine intake at the afore-mentioned dose prevents the spread of viruses by strengthening the extracellular matrix barriers against their advance.

1. Introduction

1.1. The extracellular matrix

The extracellular matrix, mainly composed of collagen, is not only the mechanical support of the tissues, but also a mechanical barrier that impedes or blocks the invasion of infective agents, such as bacteria (Lemichez, Lecuit, Nassif, & Bourdoulous, 2010), protozoa (Piña-Vázquez, Reyes-López, Ortíz-Estrada, de la Garza, & Serrano-Luna, 2012), fungi (Allert et al., 2018) and viruses (Stavolone & Lionetti, 2017). In fact, many invasive agents secrete proteases to destroy the collagen of the cellular matrix to allow or improve their advance and proliferation through the tissues. Collagenases and other proteases have been found in bacteria (Harrington, 1996), protozoa (Piña-Vázquez et al., 2012; Santana et al., 1997), fungi (Allert et al., 2018), and even viruses (Makarova et al., 2000; Gorbalenya et al., 1989); some viruses increase the protease activity of invaded tissues (Yeo et al., 1999; Wang et al., 2010) or decrease collagen synthesis (Levinson, Bhatnagar, & Liu, 1975). Inhibition of tissue MT1-MMP collagenase did protect the tissue from influenza-related structural and compositional tissue damage without significantly altering the immune response or cytokine expression (Talmi-Frank et al., 2016).

The extracellular matrix must be continuously regenerated and remodeled, which involves the body's own proteases in order to eliminate old damaged collagen, which accumulates deteriorations in its structure (glycation and others), and to resynthesize new molecules (Kielty et al., 2002; Verzijl et al., 2000; Birkedal-Hansen, 1995). Collagen constitutes approximately 25–33% of the total protein in mammalian organisms. Glycine is the main component of collagen (one-third of its amino acid residues (Meléndez-Hevia and de Paz-Lugo, 2008; Meléndez-Hevia et al., 2009), which implies a high availability of this amino acid to support a healthy turnover of collagen, as a protein-deficient diet causes a poor turnover of proteins, especially collagen (Gibson, Jahoor, Ware, & Jackson, 2002).

1.2. Restriction of glycine synthesis

Glycine has been long been considered a non-essential amino acid, as it is synthesized by human metabolism. However, in previous work (Meléndez-Hevia and de Paz-Lugo, 2008; Meléndez-Hevia et al., 2009) we have shown that there is a limit to its synthesis in metabolism that cannot be surmounted, as it is explained in Fig. 1.

Abbreviations: 3-PGA, 3-phosphoglycerate; AdoMet, adenosyl-methionine; THF, tetrahydrofolate; THF-[C_1], N^5,N^{10}-methylene tetrahydrofolate.

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1.3. Glycine deficiency causes a weak mechanical system

In a previous work we have calculated the fluxes of glycine synthesis and its expenditure (Meléndez-Hevia, de Paz-Lugo, Cornish-Bowden, & Cárdenas, 2009). The results shown in Table 1 give a deficit of glycine of about 10 g daily for a human of 70 kg body mass, even taking into account its regular intake from a common diet. Therefore glycine must be considered to be an essential or indispensable amino acid because, although it can be synthesized by human metabolism, the body's capacity for its synthesis does not satisfy the needs of the cells, especially for collagen synthesis. Neither can glycine be considered "conditionally essential" as its need is a general requisite, independent of any particular circumstances.

This glycine deficiency is universal and manifests itself in large animals from 25 to 30 kg of body mass such as the dog, where collagen is in a considerable amount, its deficiency being totally generalized in humans (Meléndez-Hevia et al., 2009). In a later work, we have demonstrated the effect of glycine increasing the synthesis of type II collagen of cartilage in chondrocytes cultured in vitro (de Paz-Lugo et al., 2018). Based on data on glycine flux and collagen synthesis in humans, we estimate that glycine deficiency is 10 g daily, and we therefore recommend its intake at this dose as a dietary supplement to prevent and solve health problems of the body's mechanical system such as osteoarthritis and osteoporosis. Furthermore, the worsening of the mechanical system due to the deterioration of collagen will affect not only cartilage, bone, tendons, ligaments, etc., but the entire connective system of the extracellular matrix that is found in all tissues.

In addition to its function in other processes such as the synthesis of the heme group, glutathione and nucleotides, glycine metabolism is closely related to other amino acids, particularly the essential lysine and methionine in the pathway to synthesize carnitine, and in general to C-1 metabolism, especially for the synthesis of creatine with methionine, see Ref. (Meléndez-Hevia et al., 2009) for details. Thus, a deficiency of glycine could also result ineffective function.

Table 1
Glycine balance sheet (Meléndez-Hevia et al., 2009).

Process	Glycine flux (g/day)
Synthesis in metabolism	3.0
Hydrolysis of dietary proteins	1.5–3.0
Synthesis of metabolites	–1.5
Synthesis of collagen	–12.0
Synthesis of other proteins	–1.0
Balance	**–8.5** to **–10.0**

The aim of this work was to check if the general glycine deficiency that makes a weak extracellular matrix was related with infections. This was investigated by a nutritional research supplying glycine to 85 volunteers, with a control group of 42 who did not take it during three years. Results showed that who taken glycine had not or very reduced infections (mainly by viruses) while no effect were seen in the control group. Thus we conclude that the general glycine deficiency solved by taken it as nutritional supplement can fight virus invasiveness.

2. Materials and methods

2.1. Previous data

Our treatment with glycine in the recommended doses (10 g/day) to fight mechanical problems has always yielded very good results in all the hundreds of patients attended usually in a time period of between

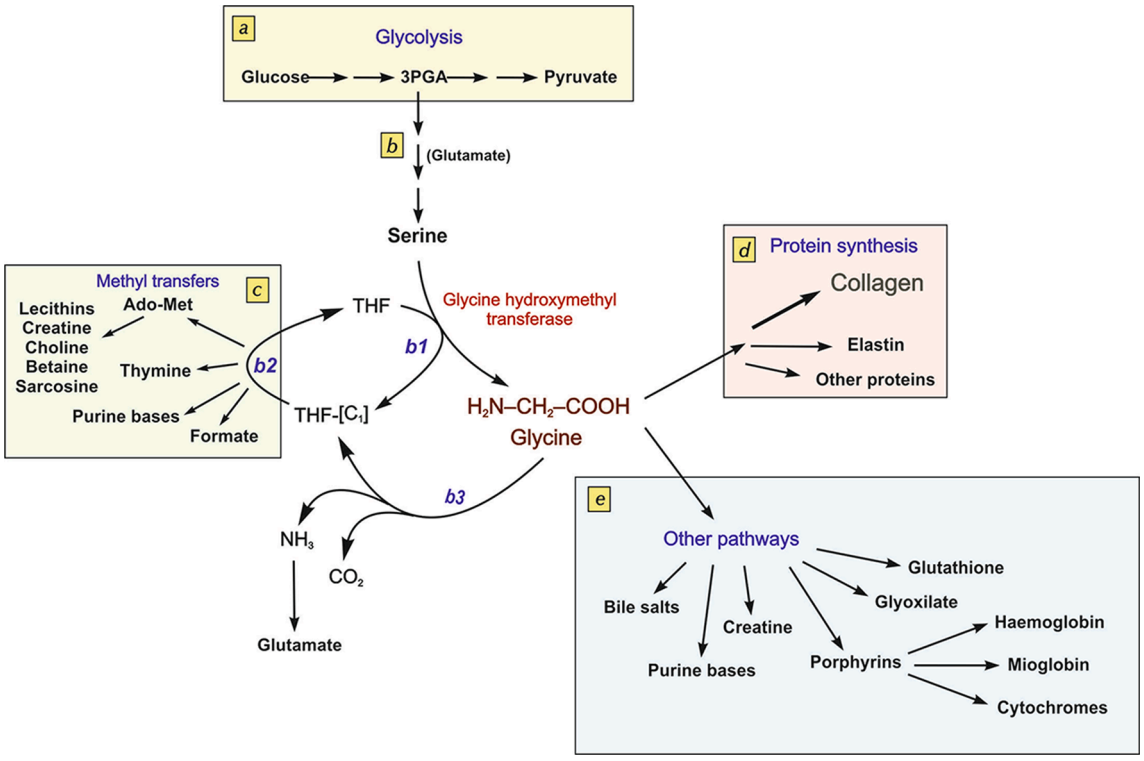

Fig. 1. Pathways of glycine and [C_1] metabolism (Meléndez-Hevia and de Paz-Lugo, 2008; Meléndez-Hevia et al., 2009). The glycine synthesis pathway starts from a bifurcation in glycolysis (**a**) at the 3-PGA intermediate level that leads to serine (**b**). The synthesis reaction of glycine from serine and THF (reaction b1) represents 87.4% of its metabolic production. This reaction establishes a branching link with fixed stoichiometry –not a bifurcation link– that restricts the ability of glycine synthesis to the equimolar use of the [C_1] fragment (Reactions b2). Therefore, the availability of glycine for its use in different processes (**d, e**) cannot be greater than the use of [C_1] (**c**). In fact, it is less because some is lost by the glycine cleavage system (Reaction b3). The fluxes of these processes in humans (Table 1) show a daily glycine deficit of approximately 10 g, mainly necessary for the synthesis and renovation of collagen[3]. 3-PGA, 3-phosphoglycerate; AdoMet, Adenosyl-methionine; THF, tetrahydrofolate; THF- [C_1], N^5,N^{10}-methylene tetrahydrofolate.

two weeks and four months and generally according to the participant's age and the nature of the afflicted joints. Most people under 40 years of age achieved some pain relief in the first week of treatment, while some people over 60 years old needed more than four month to see the first results. Osteoarthritis was reduced with a decrease in WOMAC index scores of >40%, after four weeks after starting our treatment to >70%, after four months. Osteoporosis was also reduced in all 65 female cases studied checked by bone densitometries, from about 20% loss of bone mass at starting time of the treatment to 10% in the first year and very close to normal state (3–5%) after the second year.

A number of patients of our nutritional center, after several months of treatment with glycine for osteoarthritis and/or osteoporosis with the same positive results mentioned above reported that, after starting the glycine treatment, they had fewer infectious diseases (e.g., sore throat, flu, or common cold) as compared to number of instances of such problems in prior years. The spontaneous declaration of such observations was unexpected, but possibly not unpredictable. Glycine intake increases the reinforcement potential of the body's connective tissues, which may conceivably impede the advance of invasive agents (viruses or bacteria), thereby enhancing the capability of the immune system to repel such invasive agents. As the patients were not advised of this possible effect, there was no possibility of a placebo effect, which gives further credence to the results.

2.2. Nutritional research

Consequently, in view of these results we undertook a nutritional study with a different group of 127 new subjects between the ages of 15 and 70, who usually had the flu and/or the common cold every year [17 of them two or more times each year), and who were to be treated for several health problems (osteoarthritis, osteoporosis, physical injuries, diabetes, obesity and hypertension). All of them were routinely asked about their general health (physical form, ailments, diseases, etc.) and regularly checked by a medical professional. None of them had started the treatment with glycine or other nutritional supplements. All of them volunteered for these nutritional treatments. An informed consent was obtained from every one, after the nature and possible consequences of the studies were explained, and the privacy of all of them was guaranteed.

They were divided into two groups. The first one (85 participants) included those who had only mechanical problems (osteoarthritis, osteoporosis and physical injuries). They were advised to take glycine as the only nutritional supplement, 10 g/day, divided into two doses of 5 g with breakfast and dinner. All were informed that glycine could produce more and different beneficial effects without specifying which, and without mentioning the possible benefit of our treatment for infectious diseases in order not to condition their results.

A control group was established with the remaining 42, who had to be treated for other health problems (obesity, diabetes, or hypertension) with L-aspartic acid 12 g/day divided into four doses of 3 g throughout the day as the only nutritional supplement, and who did not take glycine. The role of L-aspartic acid, as the immediate precursor to the anaplerotic oxaloacetate pathway, was to improve the functioning of the Krebs cycle by helping to eliminate excess fat, which is necessary to combat these health problems. l-Aspartic acid was always the acid form, not a salt, to avoid excessive consumption of sodium or another mineral cation. Both amino acids supplied as nutritional supplements were food grade in powder format to mix with any smooth liquid, such as water, fruit juice or yogurt.

This control group was also informed of the benefit of glycine for mechanical problems but they said that they did not need such treatment, as their problem was exclusively overweight, diabetes, or hypertension and they refused to take glycine. These agreements with the patients preferences allowed us to avoid a placebo group, which has been criticized for being unethical (Miller, 2002) and of dubious value (Bijlsma & Welsing, 2008). In fact, this study was not a 'clinical trial' since it was always carried out with nutritional supplements whose use was legal without requiring specific authorization, and in all cases our treatment with glycine or L-aspartic acid had been well tested in previous patients for their respective health problems, always with positive results.

The patho-physiological conditions of the two groups were different, as explained above (mechanical problems in the study group and problems related to metabolic syndrome in the control group), so each of them was subjected to a different protocol, but the incidence of viral disease was the same in both of them. Both groups belonged to the same demographic.

All of them were warned that they should maintain a diet rich in protein; otherwise part of the nutritional supplements (amino acids) would be used in metabolism for the synthesis of other non-essential amino acids that might be deficient and would therefore not give the expected result. All study protocols were approved by the Institutional Ethic Committee of the Instituto del Metabolismo Celular and were in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

The nutritional research program lasted three years for each patient. It was performed under medical supervision with check-ups every week of the first month, every 15–20 days for the following two months, every month for the rest of the first year, every two months during the last two years, and specific clinical check-ups when they had symptoms of infectious diseases. In all cases, in the follow-up medical consultations and reviews of treatment with nutritional supplements, the patients were asked about the diet they had followed (diet rich in protein and nutritional supplements at the recommended doses). The basic body parameters (weight, body fat and body perimeters) were taken according to the general protocol. The special complete clinical history of infectious study included the general assessment of infectious processes (fever, body pain, oropharyngeal symptoms, etc). In addition, the study-specific examination included cardiorespiratory auscultation, body temperature measurement, oropharyngeal examination, and lymph node palpation.

3. Results

Results of the nutritional research are shown in Table 2. Apart from the positive results for their specific problems mentioned in each case (osteoarthritis, osteoporosis, etc.), among the 85 who took glycine, only 16 (18.8%, 12 of them belonging to the group that usually contracted infectious diseases more than once a year) had infections once, only during the first year of treatment, and much less severe and for a briefer period of time (3–4 days instead of the habitual 6–7 days prior to treatment), while of the 42 that did not take glycine, 39 of them contracted infections in the same way as before. In no case were there any negative side effects.

Table 2
Sample and results of the nutritional assay with a 127 patients (Flu/Common cold).

Nutritional supplement	Glycine	L-Aspartic acid	Total
Frequency of diseases before the nutritional assay			
1/year	73	37	110
2–3/year	12	5	17
Total sample	85	42	127
Frequency of diseases after the nutritional assay (3 years)			
No infectious disease	69 (81.2%)	3 (7.1%)	72
1/year	16 (18.8%)*	35 (83.3%)†	51
2–3/year	0	4 (9.5%)	4
Total sample	85	42	127

* Only the first year, and less severe and shorter than usual.
† Every year with similar duration and intensity.

4. Discussion

These results confirm our proposition of the need for glycine to regenerate and strengthen collagen. Invasive agents (bacteria, fungi, protozoa, or viruses) advance in the body to invade new areas through the extracellular matrix, which acts as a mechanical barrier that prevents their expansion within the body. As this matrix consists mainly of collagen, whose renewal and regeneration is difficult due to the lack of glycine, its reinforcement thanks to an increase in glycine in the diet helps to prevent the entry and advance of infectious agents.

Furthermore these results can also help to explain one of the benefits of vitamin C (L-ascorbate) against viruses and other infective agents (Pauling, 1974). Vitamin C plays a key role in collagen synthesis (Kivirikko, Myllylä, & Pihlajaniemi, 1989; Myllyla, Kaska, & Kivirikko, 1989). Ascorbate contributes to precise collagen synthesis by avoiding or eliminating collateral reactions in proline and lysine hydroxylation (Myllyla et al., 1989), but it cannot cover the need for glycine, which must be ingested additionally to make possible the synthesis and renewal of collagen necessary to maintain firm extracellular matrix. In accordance with our results, glycine intake as nutritional supplement at the dose of 10 g/day (a dose of 5 g every 12 h) is highly recommended to block the spread of infectious agents –particularly viruses– thus preventing their invasion of the tissues. According to our results for other mechanical problems such as osteoarthritis or physical injuries, the effect of glycine begins to be noticed after one to three weeks. It is important to note that glycine is not a direct weapon against viruses or bacteria, such as an antibiotic, nor of course, a vaccine, but a passive, albeit very effective, mechanical defense, which by promoting the restoration and renewal of collagen in the extracellular matrix, can prevent or block the invasion of infectious agents.

In agreement with our previous results (Meléndez-Hevia et al., 2009), glycine as a nutritional supplement should be taken at the recommended dose every day to avoid its deficiency and to maintain all mechanical systems in healthy conditions. As explained above, glycine should always be taken with a diet rich in protein to avoid its metabolic use synthesizing other non-essential amino acids that might be deficient in a low-protein diet, deviating glycine from its expected function and which would therefore not give the expected result.

We should also point out that although glycine is not a vaccine, its effect can be more important since vaccines are specific for an particular antigen, and continuous mutations of viruses –much more abundant in RNA-viruses like of CoVid-19– can alter their antigenic protein rapidly, rendering the vaccine ineffective in a short time (Novella et al., 1995; Lauring et al., 2013; Steinhauer and Holland, 1987). The enhancement of collagen in the extracellular matrix, however, will always be effective and steadfast against any invasive agent. The close relationship we have shown here between the consistency and strength of the extracellular matrix, based on healthy collagen, and resistance to viruses (Stavolone and Lionetti, 2017; Gorbalenya et al., 1989; Yeo et al., 1999; Wang et al., 2010; Levinson et al., 1975; Talmi-Frank et al., 2016; Kielty et al., 2002) highlights the need to maintain this structure in good condition, for which dietary glycine supplementation is necessary. We must remark that glycine treatment is not specific against any particular virus such as, e.g., Covid-19, but is much more general, against any infectious agent, which includes, of course, viruses. In cases where it is probably unrealistic to expect a thoroughly tested protocol to combat new viruses, such as the current of COVID-19, the treatment we propose here may be helpful, as glycine is harmless even in much higher doses than what we propose here, and it is a permitted dietary supplement. Therefore, the approach we propose is feasible and has no dangerous side effects unlike the suggested high doses of some antiviral drugs.

5. Ethics Statement

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. An informed consent was obtained from every one, after the nature and possible consequences of the studies were explained, and the privacy rights of all of them was guaranteed.

CRediT authorship contribution statement

Enrique Meléndez-Hevia: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft. **Patricia de Paz-Lugo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing - review & editing. **Guillermo Sánchez:** Formal analysis, Methodology, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

P.dP-L. and G.S. declare no competing interests. EMH, as President of the Instituto del Metabolismo Celular (IMC) hereby declares: IMC is a private non/profit organization whose sole purpose, according to its statutes, is Scientific Research in Biochemistry and Molecular Biology. IMC research is supported primarily with its own resources, although it may occasionally receive grants from other institutions. The IMC has been founded as an independent Scientific Research Institution in order to avoid dependency on governmental policies, which at times are not based on sound scientific criteria. The IMC runs a nutritional office in which patients are advised on adequate nutrition based on the results of our research, under medical supervision when necessary, offering the recommended products such as amino acids and vitamins, in accordance with current European and USA legislations. All income obtained from this activity is in its entirety dedicated to supporting our scientific research. This includes a patent of the European Office (EPO) awarded for the use of glycine in the treatment of osteoarthritis and osteoporosis, and another application pending approval for the use of glycine to prevent and fight viral infections. The IMC has also destined a large part of its resources to subsidize grants and fellowships for researches from other institutions. In no case have its proceeds been used for any financial profit for IMC members or other persons.

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