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Review

Glycine betaine rather than acting only as an osmolyte also plays a role as regulator in cellular metabolism

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ABSTRACT

For many years, glycine betaine (GB) has been widely studied as an osmolyte in plants and bacteria. In animal cells, GB is an osmolyte mainly in the kidneys, but in humans many studies have shown its role as a methyl donor in homocysteine metabolism in the liver. GB is also a protein stabilizer, and thus, it became known as an osmoprotector. In many organisms GB is synthesized from choline and can also be obtained from some foods. Over the last twenty years GB has gone from being considered simply as an osmolyte to being known as a cytoprotector involved in cell metabolism and as a chemical chaperone. The aim of this review was to gather information about the role of GB in the metabolism of ethanol, lipids, carbohydrates and proteins in animals. The information generated thus far shows that GB regulates enzymes involved in the homocysteine/methionine cycle, sucrose, glucose, fructose and glycogen metabolism, in oxidative and ER-stress caused by ethanol abuse, likewise enzymes involved in lipogenesis and fatty oxidation. Besides, there are data supporting that GB regulates the transcription factors PPARα, NF-κB, FOX1, ChREBP and SREBP1 and this lets GB play a role in protein synthesis. One of the main mechanisms by which GB regulates the enzymes is by changes in their activity either because GB increases their expression or because it regulates changes in their phosphorylation status through specific kinases. GB modulates the expression of genes by changing the degree of methylation in the promoter of target genes. The exact mechanism by which GB modifies the methylation status of the promoter is not yet clear, but methyl transferases that use SAM as methyl donor and DNA methyl transferases are good candidates for this function.

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1. Introduction

Glycine betaine (N,N,N-trimethyl glycine, GB) is a zwitteronic quaternary amine with a $pK_a = 1.84$ that was first isolated from sugar beet by Scheibler in 1869 [1]. GB is an important component of several foods including wheat bran, clams, mussels, beetroot, amaranth, quinoa and spinach [2–4]. Bacteria, fungi, animals and plants are able to synthesize and/or transport and accumulate GB [5–9]. The cells of different organisms uptake GB via several transport systems (ProP, ProU, BetL, Gbu, OpuA, OpuC, OpuD or GABA/BGT), but GB can also be synthesized *de novo* [10–14].

There are several industrial applications of GB: it is used in the food and cosmetic industries for its zwitterionic, hygroscopic, and osmoprotective qualities [15]. GB has been widely used in livestock production [16], since GB can decrease fat accumulation in broilers [17,18], laying hens [19], meat ducks [20] and pigs [21–24]. GB promotes growth in pigs [22], and in rabbits GB, increases growth performance and improved the immune (humoral and cellular) response [25]. In aquaculture, GB has been used to facilitate the transfer of salmon from freshwater to sea water [26–28]. Additionally, GB stimulates appetite in fish and prawn [29–32].

For several years GB was studied as an osmolyte in bacteria and plants [6,33,34], and it was later found that GB possessed the ability to protect biomolecules under hydric stress [8]. Changes in cellular volume regulate GB synthesis and degradation [14,35,36]. GB is now known to be involved in a large number of cellular and biochemical processes, such as macromolecule stabilization, antioxidant activity, apoptosis, metabolism of homocysteine, ethanol and lipid, etc. Furthermore, due to GB's participation in many biochemical processes, it is thought to be involved in diseases such as diabetes, Alzheimer's, Parkinson's, Huntington's disease, etc. Because of the importance of GB as an osmolyte there are several excellent reviews describing the role of GB as an osmolyte in animals, plants and microorganisms [6–8,37–39]. In addition, GB has been studied for its importance in human nutrition, health and body performance and there are several illustrative reviews about GB's role in these aspects [40–46] so they were not included in this manuscript. The aim of this review is to summarize the knowledge garnered in recent years about the role of GB in ethanol, sugar, lipid and homocysteine metabolism and the possible mechanisms involved in the GB effect mainly in animals.

2. Glycine betaine synthesis and degradation pathways

Different organisms capable of synthesizing GB have found various ways to do it, through different enzymes some of them specific either for animals, bacteria, fungi or plants. Animals, plants and some bacteria synthesize GB from choline via a two-step oxidation pathway (Fig. 1A). In animals and some bacteria, the first step is catalyzed by choline dehydrogenase (E.C. 1.1.99.1) [47–49] while in plants it is catalyzed by choline monooxygenase (E.C. 1.14.15.7) [50,51]; both enzymes oxidize choline to betaine aldehyde (BA) (Fig. 1A). The second step is BA oxidation to glycine betaine catalyzed by betaine aldehyde dehydrogenase (BADH EC 1.2.1.8) which uses $NAD(P)^+$ as coenzyme (Fig. 1A) [52]. BADH catalyzes that last step in animals, plants and bacteria [36,53]. BADH belongs to the aldehyde dehydrogenase (ALDH) super family and, phylogenetic studies have demonstrated that the BADH from animals, proteobacteria and fungi are grouped into the ALDH9 family whereas the BADH from plants is included in the ALDH10 family [53].

Bacteria such as *Arthrobacter globiformis and A. pascens,* and the fungus *Aspergillus fumigatus* oxidize choline to GB using only the enzyme choline oxidase (1.1.3.17). Choline (with BA as the intermediary) or BA as substrate is oxidized in the presence of O_2 to produce GB and hydrogen peroxide (Fig. 1B) [54–56]. The extremely halophilic bacteria *Actinopolispora halophilia* and *Ectothiorhodospira halocloris* synthesize GB from glycine via three methylation steps catalyzed by glycine sarcosine methyl transferase (GSMT) and sarcosine dimethylglycine transferase (SDMT), which use S-adenosylmethionine (SAM) as a methyl donor [57,58] (Fig. 1C). In plants, GB is synthesized in chloroplasts, the cytoplasm and/or peroxisome [59,60]; while in animals, it is made in the cytoplasm and mitochondria [61–63]. In mammals, GB is metabolized to methionine by betaine homocysteine methyl transferase (BHMT) which uses homocysteine and GB as substrates [64–66]

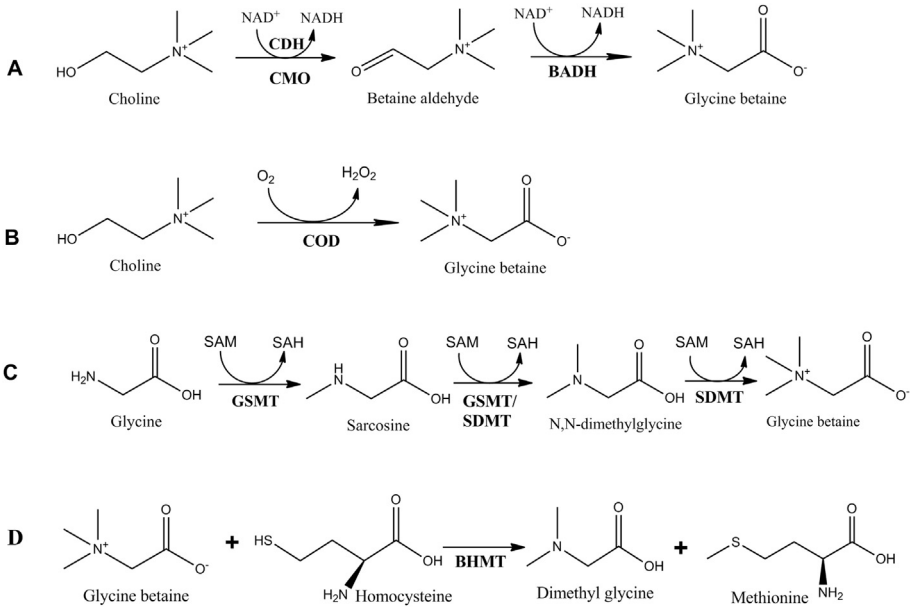

Fig. 1. Glycine betaine synthesis and degradation pathways. A) In plants, animals and some bacteria synthesis route. B) In some bacteria and fungi synthesis route. C) In extremely halophilic bacteria synthesis route. D) Degradation pathway. BADH, betaine aldehyde dehydrogenase; BHMT, betaine homocysteine methyl transferase; CDH, choline dehydrogenase; CO, choline oxidase; CMO, choline monooxygenase; GSMT, glycine sarcosine methyl transferase; SDMT, sarcosine dimethylglycine transferase.