

Chemical Chaperones

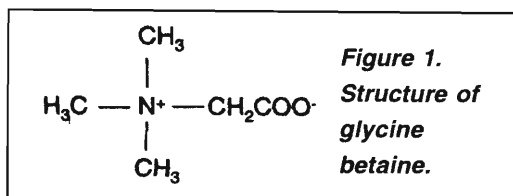
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The term 'molecular chaperone' was originally used to describe the function of nucleoplasmin, a nuclear protein that ensures correct assembly of nucleosomes from DNA and histones. Subsequently, the meaning of the term was extended to include a class of structurally unrelated proteins which mediate correct folding of other proteins but do not themselves form a part of the final structure. In a broader sense, they help determine the fate of a protein in the cell. Not only do they ensure correct folding, but also the correct assembly of the units of an oligomeric protein and transport of a protein to its particular subcellular compartment. During heat stress they assume the responsibility of quality control. They bind the heat denatured proteins and catalyze their renaturation.

In certain disease conditions, subtle mutations in some genes result in the formation of faulty proteins. As the degree of structural change is small, the proteins do not totally lose their biological properties but they are not properly processed and do not undergo their normal fate. Such is the case with the cystic fibrosis transmembrane conductance regulator protein. In the patients of cystic fibrosis, this protein gets improperly folded because of certain mutations in the gene. It is, therefore retained in the endoplasmic reticulum and not transported to the plasma

membrane where it normally performs its biological role. A couple of years ago it was found that a folding defect of this protein could be corrected by low molecular weight substances like glycerol and trimethylamine N-oxide. These substances, which help to stabilize proteins in their natural conformation, were termed 'chemical chaperones' by a group of investigators at the Department of Medicine, California University (San Francisco, USA). (*Cell Stress Chaperones*, Vol. 1, pp. 109-115, June 1996).

The protective effects of glycine betaine (*Figure 1*) and choline, two known chemical chaperones, on cellular proteins has subsequently been demonstrated by a group of workers led by Gilbert Richarme at Institut Jacques Monod (Paris University). They chose *Escherichia coli*, the colon bacteria, as a model. Exogenously added glycine betaine is taken up by *E.coli* cells and in certain strains, glycine betaine can also be synthesized from choline. *Dna K* protein is a molecular chaperone that is a part of the cellular machinery that is involved not only in folding of the nascent polypeptide chains but also in refolding of thermally denatured proteins. A *dna K* mutant is therefore unable to survive at higher temperatures. Gilbert and his colleagues had shown that the colony forming ability of a *dna K* mutant of *E.coli* at



42 °C could be restored in the presence of choline and glycine betaine. By measuring light scattering at 650 nm, they estimated the extent of the thermal denaturation of citrate synthase and β -galactosidase in the presence and absence of choline and glycine betaine. These two chemical chaperones were found to protect the enzymes from getting denatured and thus enabled the enzymes to retain their functional entities. The ability of these small molecules to reactivate citrate synthase, which was previously denatured by urea, was also demonstrated (*Microbiology*, Vol. 145, pp. 2543-2548, September 1999).

A couple of years ago, another group of researchers at the University of California, Davis reported the cryoprotective effects of glycine betaine in *Listeria monocytogenes*, the organism which is responsible for listeriosis and survives at low temperature in presence of salts. Colony forming ability of *L. monocytogenes* was significantly enhanced in presence of glycine betaine when the organism was grown at 7 °C. They also showed that at lower temperature, the rate of transport of

glycine betaine into the cell was facilitated compared to cells incubated at 30 °C (*J. Bacteriol.*, Vol. 176, pp. 426-431, January 1994).

The evidence of thermoprotective and cryoprotective effects of glycine betaine on two different bacteria is neither an enigma nor a riddle. The protective effects against two diametrically opposite types of stress (high and low temperature) may stem from its ability to maintain the native state of the essential cellular proteins which tend to aggregate under heat and cold stress. The ability of these molecules to maintain proteins in their native conformations may be helpful for survival of microorganisms under stress conditions, which threaten to coagulate the cellular proteins. The therapeutic potential offered by these compounds is also an interesting area to be explored. Chemical chaperones, therefore, offer new vistas in the areas of both, basic and applied research.

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... man will occasionally stumble over the truth, but usually manages to pick himself up, walk over or around it, and carry on.

Winston Churchill

