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Chemical Chaperones: Mechanisms of Action and Potential Use

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Abstract An increasing number of studies indicate that low-molecular-weight compounds can help correct conformational diseases by inhibiting the aggregation or enable the mutant proteins to escape the quality control systems, and thus their function can be rescued. The small molecules were named chemical chaperones and it is thought that they nonselectively stabilize the mutant proteins and facilitate their folding. Chemical chaperones are usually osmotically active, such as DMSO, glycerol, or deuterated water, but other compounds, such as 4-phenylbutiric acid, are also members of the chemical chaperone group. More recently, compounds such as receptor ligands or enzyme inhibitors, which selectively recognize the mutant proteins, were also found to rescue conformational mutants and were termed pharmacological chaperones. An increasing amount of evidence suggests that the action of pharmacological chaperones could be generalized to a large number of misfolded proteins, representing new therapeutic possibilities for the treatment of conformational diseases. A new and exciting strategy has recently been developed, leading to the new chemical group called folding agonist. These small molecules are designed to bind proteins and thus restore their native conformation.

Keywords Chemical chaperones · Pharmacological chaperones · Conformational diseases · Protein misfolding · Quality control machinery

1 Chemical Chaperones

Chemical chaperones are small molecules with a common feature mimicking the chaperone function of molecular chaperones. Many osmolytes as well as compounds with the ability to bind to hydrophobic surfaces can rescue mutant proteins from aggregation or can help them to escape from quality

control and subsequent degradation (Sitia and Braakman 2003; Conn et al. 2002). This feature can be very helpful in the so-called folding diseases (Selkoe 2003). In this group of diseases, the disorder results from a mutation of one specific protein (Kopito and Ron 2000). The symptoms can result from the aggregation of the protein, such as the beta-amyloid plaques in Alzheimer's disease (Soto et al. 2003), as well as problems resulting from the loss-of-function of the protein in question, such as Cl^- ion transport deficiency in cystic fibrosis, where a point mutation in the gene of CFTR (cystic fibrosis transmembrane conductance regulator) protein results in its capturing by the quality control system within the endoplasmic reticulum and its quick degradation by the proteasomal machinery (Denning et al. 1992). Absence of this channel results in an imbalance of ion concentrations across the cell membrane, which leads to the onset of many severe symptoms, such as chronic inflammation and fibrosis of the lung, problems with all the secretory glands, especially with the pancreas, resulting in the devastation of beta cells, and promotes diabetes. Diseases in which the combination of both types of the above-mentioned disturbance occur are also known. In alpha-1 antitrypsin deficiency a serum elastase inhibitor, alpha-1 antitrypsin (AAT) is mutated. The specific point mutation often referred to as Z type AAT results in fatal folding deficiency of the protein. The uncovered hydrophobic surface of the protein leads to its prompt aggregation inside the lumen of the endoplasmic reticulum, forming large insoluble aggregates in the organelle. The loss-of-function of AAT results in emphysema in human patients and, additionally, the protein deposits in the endoplasmic reticulum of the liver cells generates cirrhosis, hepatitis, and elevated sensitivity to hepatocellular carcinoma (Needham and Stockley 2004). Chemical chaperones are widely used in experimental systems (Smith et al. 1998); however, their use in human patients is limited due to their general impact on the whole organism. The main groups of classical chemical chaperones, their mechanism of action, and new findings in models of various diseases are discussed below.

1.1 Osmolytes

The most common chemical chaperones are usually osmolytes, such as glycerol, or trimethylamines, e.g., trimethylamine N-oxide (TMAO), and amino acid derivatives, such as proline. Osmolytes are the ancient members of stress responses. Prolin as well as glycine betaine are known osmoprotectors, defending bacterial and plant cells against osmotic and freezing stress. These osmolytes exert their beneficial activity by limiting the free movement of proteins by elevating the density of the solvent, thus preventing aggregation of unfolded proteins. Their ability to reduce the frequency of "folding-detours" to nonproductive folding pathways has been proved for several mutant proteins involved in conformational diseases (Table 1).

Table 1 Osmolytes used in folding problem-related diseases

Disease	Protein	Agent used	References
Alzheimer's disease	Beta-amyloid	Glycerol, TMAO	Yang et al. 1999
Cancer	Ubiquitin-activating enzyme E1	Glycerol, TMAO, D^2O	Brown et al. 1996
	Glucocorticoid receptor	Glycerol, TMAO, D^2O	Baskakov et al. 1999
	p53	Glycerol, TMAO, D^2O	Brown et al. 1996
	pp60	Glycerol, TMAO, D^2O	Brown et al. 1996
Cystic fibrosis	CFTR	Glycerol, TMAO, DMSO	Sato et al. 1996
Emphysema and liver disease	Alpha-1-antitrypsin	Glycerol, TMAO	Burrows et al. 2000
Machado-Joseph disease	Ataxin-3	Glycerol, TMAO, DMSO	Yoshida et al. 2002
Maple syrup urine disease	BCKD complex	TMAO	Song et al. 2001
Menkes disease	MNK	Glycerol	Kim et al. 2002
Nephrogenic diabetes insipidus	Aquaporin-2	Glycerol, TMAO, DMSO	Tamarappoo et al. 1999
	V2R	Glycerol	Tan et al. 2003

The most frequently examined target among the conformational diseases is the cAMP-activated chloride ion channel protein, CFTR and its most common mutation, the D508F CFTR. Many cell lines used in laboratory experiments express this mutant protein. In most cases, the mutation does not lead to the aggregation of the protein, but the mutant CFTR is degraded rapidly. In a set of experiments carried out by Sato et al. (1996), it has been proved that glycerol and TMAO could increase the maturation of the mutant CFTR protein and rescue the cAMP-activated chloride conductance of cells expressing DF508 CFTR. DMSO, the well-known cryoprotectant, was also shown to have chemical chaperone activity, since it helped the transport of mutant CFTR in a cell culture model (Bebök et al. 1998).

The mutation of the water channel, aquaporin-2, is responsible for the development of nephrogenic diabetes insipidus. Its folding deficiency was correctable with chemical chaperones (Tamarappoo and Verkman 1998). The onset of diabetes insipidus is triggered by the mutation of a vasopressin receptor, V2R. The mutated V2R protein escaped from the quality control machinery, integrated to the membrane, and functioned as a normal vasopressin receptor with the help of the osmolyte glycerol (Tan et al. 2002). The sequestration of mutant alpha-1 antitrypsin Z can be enhanced by chemical chaperones, as was proven by Burrows et al. (2000).

Other types of diseases were also involved in the investigation of chemical chaperone effects. The central nervous system is sensitive to folding diseases due to its poor regenerating ability, making neurodegeneration diseases "hot spots" in chemical chaperone research. In Alzheimer's disease, where the beta-amyloid plaque formation causes the death of neuronal cells, which leads to mental deterioration, the effect of glycerol as well as TMAO was investigated. Both molecules successfully inhibited the formation of beta amyloid plaques. In Creutzfeldt-Jacob disease the prion protein, besides the specific action of doxycycline, quinacrine, and chlorpromazine, DMSO and glycerol was also found to revert the mutated form of PrP (Sc), the protein responsible for the onset of prion disease (Gu and Singh 2004), giving new hope of curing these folding disorders.

An entirely different group of diseases is cancer. In tumors, not one but many genes have to be mutated to exert oncogenic features. However, in more than 50% of tumor cells, the tumor suppressor protein p53 was found to be mutated. Mutation of the viral oncogene protein, pp60src, is also of key importance in tumors. The active osmolytes, glycerol, TMAO, and DMSO, corrected mislocalization of many of the oncogenic mutations of these proteins, such as p53, pp60src, or the ubiquitin-activating enzyme E1 (Brown et al. 1996).

The immune system can also improve its efficiency with the help of chemical chaperones. Glycerol, TMAO, and DMSO were also found to enhance antigen-presentation by promoting the folding of MHC molecules (Ghumman et al. 1998).

An interesting member of the often used osmolytes is prolin, which is a known agent protecting against high saline and freezing in yeast and also in *Escherichia coli* (Csonka 1989). However, prolin has controversial effects on protein folding. In *E. coli* prolin was found to increase thermotolerance and was able to substitute the chaperone DnaK in deficient strains (Chattopadhyay 2004). Low physiological concentrations of prolin had an activator effect on prokaryotic chaperons, while higher concentrations had a rather inhibitory effect on chaperone–protein interactions (Diamant et al. 2001). On the other hand, prolin strongly inhibited the refolding of denatured porcine lactate dehydrogenase, probably by limiting the interactions of the side chains of the protein amino acid backbone (Chilson and Chilson 2003). It is noteworthy that in this model system TMAO was also found to have anti-chaperone activity.

As an extraordinary chemical chaperon, deuterated water is also used as an osmolyte, since it can increase the viscosity of the fluids. Deuterated water was shown to stabilize the native conformation of the mutant CFTR and many proteins having oncogenic properties (Sato et al. 1996, Brown et al. 1996).

Osmolytes, is spite of the overwhelming data on their efficiency in many models, have relatively minor significance in clinical practice, due to their nonspecific means of action.

1.2 Hydrophobic Compounds

In addition to the osmolyte effect detailed above, a new mechanism for chemical chaperones has been discovered. Different compounds with a shorter or longer hydrophobic part can be solved in different fluids and can bind to proteins. Accordingly, as lysophosphatidic acids or butyrate derivatives were found to mask mutations of proteins and stabilize their structure in the native conformation. The suggested mechanism of action is that these hydrophobic molecules have the ability to bind to the hydrophobic segments, which remain surface-exposed in unfolded proteins, and protect them from aggregation or degradation in this manner.

1.2.1 PBA

The most prominent member of this group is sodium 4-phenylbutyrate (PBA). Sodium 4-phenylbutyrate is an orally bioavailable short-chain fatty acid, which was originally used as an ammonia-scavenging agent in urea metabolism disorders. In recent years, PBA has also been shown to help the mutant CFTR protein to get to the membrane (Zeitlin et al. 2002). PBA appears to help in correcting the transport of mutant alpha-1 antitrypsin (AAT) in AAT-deficiency models. PBA enhances the secretion of mutant AAT in cell culture and also in transgenic mouse model (Burrows et al. 2000). Since mutant AAT has a significant residual elastase activity and since PBA can be used safely in human patients, this opens a promising, new therapeutic avenue for AAT deficiency.

Its ability to bind stretched hydrophobic surfaces of the protein, thus protecting it from aggregation and avoiding the check of the quality control system, was proposed as the mechanism of action, thus supporting its transport and integration into the plasma membrane. But the chaperone-like activity of PBA turned out to be much more complicated. In newer experiments, PBA was found to influence many levels of regulation. For example, PBA downregulated the general protein synthesis, but induced the synthesis of cellular chaperones in the case of mutant CFTR expressing the IBS-3 cell line (Wright et al. 2004). It was also shown that PBA activated the transcription of beta- and gamma-globin, which makes PBA a promising candidate in the treatment of thalassemias (Collins et al. 1995). In a recent study, PBA protected against cerebral ischemia through inhibition of ER stress-mediated apoptosis and inflammation (Qi et al. 2004).

Sodium phenylbutyrate (PBA) treatment seems to have no severe side effects, and it can be utilized with a good efficiency by oral supplementation. These features make PBA a promising chemical chaperone with hope of clinical use in the future.

1.2.2 Lipids and Detergents

In bacterial models, many short-chain fatty acids were found to have chaperone properties. Kern et al. (2001) found that lysophosphatidic acid can prevent *E. coli* strains from heat denaturation as well as facilitate the refolding of heat-denatured citrate-synthase. The nonionic detergent, Brij 58P was tested in many in vitro models (Krause et al. 2002). The group found that Brij 58P has a favorable effect on the refolding of denatured alpha-glucosidase, rhodanese, and citrate synthase in the presence of the aggregation-prone DnaJ molecule.

A series of cationic, zwitterionic, and nonionic detergents were tested on the course of the refolding of three different model proteins (Daugherty 1998). In this study, all types of detergents promoted the refolding of citrate synthase, unlike carbonic anhydrase B and lysozyme, which required zwitterionic detergent for the augmentation of successful folding.

2 Pharmacological Chaperones

The discovery that compounds selectively binding to intracellularly retained proteins can promote their proper folding and targeting opened the way to developing a new class of chemical compounds having chaperone activity. These specific molecules are called pharmacological chaperones. Table 2 shows the most important pharmacological chaperones used in different diseases. Pharmacological chaperones are similar to the chemical chaperones in their effect: they can promote the folding and transport of mutant proteins alleviating many folding disease (Bernier et al. 2004). The difference distinguishing these molecules from a separate group from chemical chaperones lies in their specificity. These molecules can bind to one definite protein, thus aiding its folding and transport. Pharmacological chaperones can be, for example, ligands for a receptor promoting its proper folding, or, more specifically, a molecule designed especially to bind the native conformation of the target protein, stabilizing its conformation and pushing the balance toward the native state.

2.1 Enzyme Antagonists

A study conducted on an energy-dependent transporter known as P-glycoprotein or multidrug-resistance gene-1 product (MDR1) showed that while synthetic mutations resulted in ER retention and rapid degradation of the protein (Loo and Clarke 1994), treatments with substrates (vinblastine and capsaicin) or inhibitors (cyclosporin and verapamil) of the transporter led to the appearance of functional MDR1 at the cell surface (Loo and Clarke 1995).

Table 2 Pharmacological chaperones used in different diseases

Disease	Protein	Agent used	References
Misfolding/aggregation			
Gaucher disease	β-Glucosidase	*N*-(*n*-nonyl) deoxynojirmycin	Sawkar et al. 2002
β-Galactosidosis	β-Galactosidase	Galactonojirmycin derivatives	Matsuda et al. 2003
Long QT syndrome	HERG K*b* channel	Cisapride, E-4031, astemizole	Curran et al. 1995
Prion disease	Prion	IPrP13 quinacrine chlorpromazine	Soto et al. 2000; Korth et al. 2001
Misfolding/degradation			
Cancer	Smo	Cyclopamine	Chen et al. 2002
Cystic fibrosis	CFTR	Benzo(c)quinolizinium compounds	Galietta et al. 2001
Fabry disease	Alpha-Gal A	DGJ Galactose	Fan et al. 1999; Frustaci et al. 2001
Hyperinsulinemic hypoglycemia	SUR1	Sulfonylurea	Yan et al. 2004
Hypogonadotropic hypogonadism	GnRHR	GnRH peptidomimetic antagonist	Janovick et al. 2002
Drug resistance	P-glycoprotein	Cyclosporin, capsaicin, vinblastine, verapamil	Loo et al. 1995
Immunoglobulin secretion	Anti-phenyl-phosphocholine	Hapten p-nitrophenyl-phosphocholine	Wiens et al. 2001
Pain	dOR	Naltrexone	Petaja-Repo et al. 2002
Menkes disease	MNK	Copper	Kim et al. 2002
Nephrogenic diabetes insipidus	V2R	SR121463, VPA-985	Morello et al. 2000

This led the authors to propose that the drug-binding site forms early during MDR1 biosynthesis and that occupation of this site could stabilize a folding intermediate in a near-native conformation that can escape the quality control system (Loo and Clarke 1999). Similarly, an antagonist of the vasopressin receptor can increase the activity of mutant vasopressin receptor associated with nephrogenic diabetes insipidus (Morello and Bichet 2001). Potassium channel mutation associated with the long QT syndrome was also correctable with the help of selective inhibitors of the channel (Zhou et al. 1999).

A new concept of enhancing protein folding and secretion of immunoglobulins was to use hapten ligands as chemical chaperones. Secretion of antiphenylphosphocholine antibody was enhanced by phosphocholine treatment, suggesting that hapten binding can promote antibody maturation by stabilizing heavy- and light-chain assembly (Wiens et al. 2001). As an additional example of pharmacological chaperones, alpha-galactosidase A deficiency related to Fabry disease was correctable by administering galactose in a cell culture model (Okumiya et al. 1995).

2.2 Folding Agonists

The temperature-sensitive mutants of tumor suppressor p53 protein can be stabilized by a set of small molecule compounds, which can bind specifically to the p53 protein and help the folding into its active conformation (Foster et al. 1999). High throughput chemical screening led to new compounds that could stabilize p53 in its active conformation, opening a new chapter in tumor suppression strategies (Wang et al. 2003; Issaeva et al. 2003). As a result, a peptide designed to bind specifically to the native conformation of p53 could restore the activity of the R249S mutation of p53, which is the most frequent cause of cancer, especially in hepatocellular carcinomas (Friedler et al. 2004).

In Menkes disease, which is a congenital copper deficiency, results from the mutation of copper-ATPase. In this case, copper itself was found to be advantageous for the proper folding of the ATPase (Kaler et al. 1998; Kim et al. 2002).

A mutation in the sulfonylurea receptor, Sur is responsible for the onset of familial persistent hyperinsulinemic hypoglycemia (Thomas et al. 1995). Correction of the loss of function of the receptor was carried out by sulfonylurea (Yan et al. 2004) and also with diazoxide; however, the results are inconsequent at this point (Partridge et al. 2001; Yan et al. 2004). As an additional example, Dormer et al. found (2001) that benzoquinolizine derivatives can facilitate the folding of mutant CFTR in cystic fibrosis.

An interesting target of pharmacological intervention is pain. Opioid receptors were shown to fold in the endoplasmic reticulum. Still, the majority of the proteins is transported directly to the protein degradation system. Membrane permeable opioid ligands can stabilize the structure of the receptor and augment its insertion into the plasma membrane (Petaja-Repo et al. 2002)

Pharmacological chaperones, although their approach to the disease is similar to chemical chaperones, have the advantage of higher specificity. In this treatment, only the folding of the selectively targeted protein will be influenced. The specific mechanism of action of the pharmacological chaperones may be a significant advantage considering their potential use for disease-related folding deficiencies with clinical importance.

The growing pool of chemical and pharmacological chaperones opens a new field for applied research aimed to help in folding diseases. Supplementation of mutated proteins, as well as the emerging role of gene therapy, are also powerful tools for correcting dangerous mutations, but artificial chaperones constitute a real alternative in the course of folding disorders.

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