e-ISSN:2322-0139
p-ISSN:2322-0120

Research & Reviews: Journal of Pharmacology and Toxicological Studies

PHARMACOPERONES- From Genes to Pharmacological Agents

Daswani BR*, Chandanwale AS

BJ Government Medical College, Pune, India.

Editorial

Received date: 20/10/2015
Accepted date: 04/11/2015
Published date: 11/11/2015

***For Correspondence**

Daswani BR, Associate Professor, Department of Pharmacology, BJ Government Medical College, Pune, India, Tel: 919421965337

E-mail: daswani_bharti@rediffmail.com

A NOVEL CONCEPT

'Pharmacoperones' as the name suggests are pharmacological chaperones. Chaperones are a heterogeneous class of proteins that facilitate folding and assembly of nascent polypeptides as well as refolding of unfolded or misfolded proteins [1, 2]. The role of a pharmacoperone is similar, but instead of being proteins, pharmacological chaperones are small molecules; and instead of assisting in folding, they usually bind to an already folded macromolecule (usually a protein) and stabilize it against thermal denaturation and proteolytic degradation.

Protein folding and its significance: A nascent polypeptide chain is synthesized on ribosomes and in the process of protein synthesis, the polypeptide chain undergoes chemical modification and folding till it achieves the native state, which is also the most stably folded state. The chemical modification determines the final state, activity, life span, or cellular location of proteins. Occasionally the protein may not achieve the native state or it may get misfolded after initially achieving the native state. Factors that predispose too such misfolding include defective chaperoning; genetic mutations resulting in an altered amino acid sequence; cellular stress; and exposure to heat, extremes of pH, chemicals such as urea or guanidine hydrochloride, that can disrupt the weak non-covalent bonds and destabilize the native conformation of a protein [3].

Misfolding results in exposure of hydrophobic domains on the protein, making them highly unstable and reactive. Once misfolded, the proteins may either renature with the help of chaperones or remain misfolded, with deleterious consequences like aggregation and accumulation of toxic compounds, leading to cell death as in Alzheimer's disease, Parkinson's disease, and Prion disease. Nascent polypeptides, if misfolded, are identified as abnormal by the cells' highly efficient 'Quality Control System' (QCS) in the endoplasmic reticulum/ Golgi apparatus and prevented from reaching the functional destination eg receptors may not reach the plasma membrane, and enzymes may not reach the lysosome, i.e., they are misrouted. The chaperones try hard to correct the folding defect, but if unsuccessful, they generate an 'Unfolded Protein Response" (UPR), whereby the misfolded protein is ubiquitinated and marked for proteosomal or non-proteosomal degradation. This avoids accumulation of cytotoxic aggregates. Thus, misfolding of proteins is a cause of cytotoxicity as well as wastage of proteins [3].

Recently, it has been recognized that a large number of genetic defects that present as ion channel, receptor or lysosomal enzyme defects are actually disorders of protein synthesis, whereby the altered amino acid sequence hinders with appropriate folding of protein to its native state. As a result, though functionally adequate, these proteins are recognized by the cellular QCS as abnormal and prevented from reaching their final site of action. Such misrouting of functionally adequate proteins results in genesis of a whole group of genetic disorders that are now considered to be 'Conformational Disorders'. Certain cases of nephrogenic diabetes insipidus, hypogonadotrophic hypogonadism, retinitis pigmentosa, obesity, familial hypocalciuric hypercalcemia, congenital hypothyroidism, Hirschsprung's disease, cystic fibrosis, and lysosomal storage disorders are examples of such conformational disorders [1, 3].

The only rational means to treat such patients is genetic modification of mutant proteins. This approach is not only costly, but is also as unfeasible as gene replacement therapy, and therefore impracticable.

Nearly 15 years ago, Conn et al serendipitously observed that misrouting of human gonadotropin releasing hormone receptor (GnRHR) mutants was a cause of loss-of-function in patients suffering from hypogonadotropic hypogonadism [4]. This contradicted the prevailing view that mutant receptors lacked the ability to bind ligand or couple to effector proteins. They observed that certain chemicals corrected the defective trafficking of receptors and re-routed them to their functional location with reversal of the phenotype. This suggested that chemicals could bind to mutant proteins and bring about changes in their conformation so that they can pass the cell's QCS. This was a powerful idea, as a single drug could be therapeutic for genetic disorders, bypassing the need for the gene based therapy, at least for such trafficking related conformational disorders. A large number of strategies have been tried for such disorders since then. Chemicals like glycerol, trimethylamine n-oxide, 4-phenylbutyric acid, and deuterated water can assist re-routing of functional proteins by modifying their chemical structure but are nonspecific, required in very high concentrations and may themselves promote polymerization/ aggregation of certain conformationally defective proteins [5].

The concept of re-routing proteins by chemicals coupled together with the specificity of agonists / antagonists brought to light the idea that drugs with specific affinity for certain proteins and ability to help misfolded proteins to pass the QCS could generate a whole new class of drugs called 'Pharmacoperones'.

The term 'Pharmacoperone' was coined by Conn et al4 and was defined by them as "a small molecule that enters cells and serves as molecular framework in order to cause otherwise-misfolded mutant or wild type proteins to fold and route correctly within the cell." Two mechanisms have been proposed to explain the ability of pharmacoperones to stabilize misfolded proteins. Pharmacoperones may bind to and enhance the stability of the native or native-like state of the target protein for which they have higher affinity than for intermediate, immature forms (i.e., non-native structures) or, alternatively, they may bind to the less folded, non-native folding intermediates and act as a scaffold for subsequent folding, increasing the rate at which these intermediates are converted to the native form. This would prevent the protein from being recognized by the ER QCS as defective, allowing it to escape degradation and promoting its transport to the Golgi apparatus for further processing [5].

Thus, a Pharmacoperone is a small molecule that enters cells, acts as template molecule that can induce mutant proteins to adopt native-type-like conformations instead of improperly folded ones, and allows them to pass through the cell's quality-control system. Unlike gene therapy, pharmacoperones need not be present at the time of protein synthesis as they can act to correct the conformation of pre-formed proteins. Therefore, they can potentially arrest or reverse conformation diseases. Similarly, certain pharmacoperones have the ability to bind to misfolded proteins that tend to aggregate. Thus, they can prevent such aggregation and accumulation of cytotoxic aggregates as in Alzheimer's disease, Prion disease, Parkinson's disease etc.

Progress so far:

Most of the findings are from in vitro studies and pharmacoperones have been identified for GnRH receptor mutants in hypogonadotrophic gonadism, FSH receptor mutants in infertility, V2R mutants in diabetes insipidus, rhodopsin mutants in retinitis pigmentosa, Fabry's disease, Gaucher's disease, mutant, PAH enzyme responsible for phenylketonuria, mutant CFTR responsible for cystic fibrosis, LQTS2 mutations in K+ channels of myocardium responsible for susceptibility to- Torsades de pointes, Defective ABC Transporters for hypercholestrolemeia [1,5].

In vitro studies have also identified pharmacoperones for aggregated proteins, e.g., Short β-sheet breaker peptides for neurodegenerative disorders [1].

Some pharmacoperones have also shown successful reduction in amyloid- deposition and fibril formation in experimental models of Alzheimer's disease [6, 7]. Similar success has been found with oral administration of 1-deoxygalactonojirimycin in transgenic mice model of Fabry's disease [8].

Clinical trials on utility of pharmacoperones are in the pipeline. A case report mentions that Galactose administered to a case of cardiac variant of Fabry disease, reduced cardiac mass and inproved ejection fraction. Clinical trials are being conducted for use of pharmacoperones in Fabry's, Gaucher and Pompe disease [9, 10]. In another clinical study, five patients with nephrogenic diabetes insipidus due to V2R mutations were assessed. Peptidomimetic SR49059 produced a drop in urine production and water intake as well as a significant increase in urine osmolarity [11].

Thus, pharmacoperones are a classical example of drugs where high-throughput screening can increase pace of primary drug research. They appear to be attractive drug development targets and a new class of therapeutic agents that can be specifically tailored for a certain genetic diseases. To qualify as a an effective pharmacoperone, the drug should be a small hydrophobic molecule that can enter the cell to reach ER; have affinity for the misfolded protein [usually an antagonist---may be agonist or partial agonist]; be specific for target protein; have a long half-life; and it should bind but not hinder with its normal function (in case of receptor and enzyme, it should bind allosterically or be displaced after correcting the conformational defect).

However, so far, they are of limited utility as they are still under development and yet to undergo several rounds of formal preclinical and clinical studies. Being of use in genetic disorders, there is apparently a large laboratory to clinic gap on account of inter-species variation. They are likely to be of use only where the defect is in protein trafficking. Mutants that affect functionality cannot be rescued with the use of pharmacoperones. It is also essential that pharmacoperones bind to a site that is distinct from the active moiety and should not themselves interfere with the function of the protein. Last but not the least, it is important to keep

in mind that nature has developed a very efficient QCS to seclude the mutant proteins. Although, these are functionally normal, they are biochemically abnormal. The long term impact of increasing expression of such proteins remains to be known and this may take several decades to manifest in a clinical setup. Nevertheless, pharmacoperones are a great scientific advancement that enable us to bypass the genetic code, at least sometimes, and it is definitely less challenging to correct defective folding, than replacing a mutant gene by a "healthy" one!

REFERENCES

1. Michael Conn P et al. G protein-coupled receptor trafficking in health and Disease: lessons learned to prepare for therapeutic mutant rescue in vivo. Pharmacol Rev. (2007); 59: 225–250.
2. Dagmar Ringe and Gregory A Petsko. What are pharmacological chaperones and why are they interesting? Journal of Biology. (2009); 8: 80.
3. Ulloa-Aguirre A et al. Pharmacoperones: Targeting Therapeutics Toward Diseases Caused by Protein Misfolding. Rev Inves Clin. (2015); 67: 15-9.
4. Michael Conn P et al. "Pharmacoperone": What's in a word? Pharmacological Research. (2014); 83: 1–2.
5. Ulloa-Aguirre A and Michael Conn P. Pharmacoperones: a new therapeutic approach for diseases caused by misfolded G protein-coupled receptors. Recent Pat Endocr Metab Immune Drug Discov. (2011); 5: 13-24.
6. Soto C et al. β-Sheet breaker peptides inhibit fibrillogenesis in a rat brain model of amyloidosis: implication for Alzheimer therapy. Nat Med. 1998; 4: 822–826.
7. Sigurdsson EM et al. In vivo reversal of amyloid-lesions in rat brain. J Neuropathol Exp Neurol. (2000); 59: 11–17.
8. Fan J-Q et al. Accelerated transport and maturation of lysosomal -1 galactosidase A in Fabry lymphoblasts by an enzyme inhibitor. Nat Med. (1999); 5: 112–115.
9. Parenti G et al. New strategies for the treatment of lysosomal storage diseases (review). Int J Mol Med. (2013); 31: 11-20.
10. Parenti G. Treating lysosomal storage diseases with pharmacological chaperones: from concept to clinics. EMBO Mol Med. (2009); 1: 268-79.
11. Bernier V et al. Pharmacologic chaperones as a potential treatment for X-linked nephrogenic diabetes insipidus. J Am Soc Nephrol. (2006); 17: 232-43.