Global Academic Journal of Pharmacy and Drug Research
Website: https://www.gajrc.com
DOI: 10.36348/gajpdr.2020.v02i02.001

OPEN ACCESS

ISSN (P): 2706-9044
ISSN (O): 2707-255X

Review Article

Pharmacoperones Role in Nephrogenic Diabetes Insipidus

Dr. Mohd Faheem Mubeen*
Associate Professor, Ayaan Institute of Medical Sciences, Hyderabad India

***Corresponding Author**
Dr. Mohd Faheem Mubeen

Article History
Received: 25.01.2020
Accepted: 16.02.2020
Published: 13.12.2020

Abstract: "Pharmacoperones," or Pharmacological chaperones correct the folding of misfolded proteins, allowing them to go throughout the cell's quality-control system and makes it correctly fold of a protein. In the distal convoluted tubule, and the collecting ducts of the kidney the vasopressin type 2 receptors (V2R) is present as a G protein-coupled receptor (GPCR), a seven-transmembrane protein. V2R normally responds to vasopressin and activates mechanism that concentrates urine and maintains water homeostasis. Mutation of the V2R which leads to mistrafficking of the receptor, which in turn results in vasopressin unresponsive cells. This insufficiency leads to nephrogenic diabetes insipidus (NDI). Recently, a novel aquaretic, Pharmacoperones - Tolvaptan, is a selective, competitive VPR2 antagonist used to target hyponatremia (low blood sodium levels) associated with congestive cardiac failure (CCF), cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH).

Keywords: Pharmacoperones, G protein-coupled receptor (GPCR), congestive cardiac failure (CCF), Diabetes.

"Pharmacoperones," or Pharmacological chaperones correct the folding of misfolded proteins, allowing them to go throughout the cell's quality-control system and makes it correctly fold of a protein [1]. Chaperones are a heterogeneous class of proteins that make correct folding and assemblage of nascent polypeptides as well as refolding of unfolded or misfolded proteins. During mutations usually misfolding and misrouting of protein which in turn causes various diseases, pharmacoperones are one of the best therapeutic agents, since they correct this defect [2].

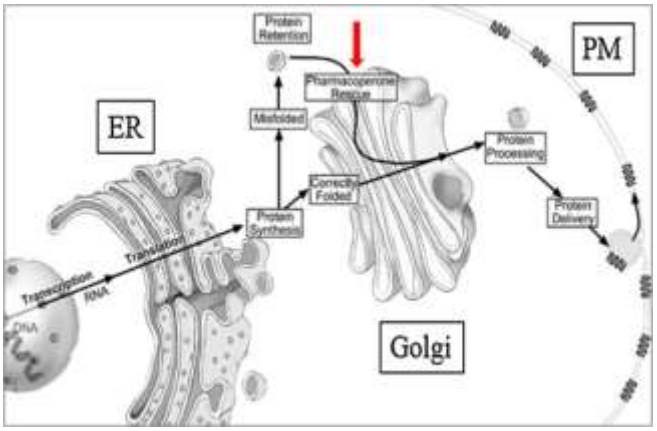

Fig-1: Emphasizing misfolded proteins are retained in the cell (endoplasmic reticulum) and rescued by target-specific pharmacoperone drugs (gray arrow) that correct misfolding and restore function. Redrawn from Conn *et al*.

Protein folding and its importance: An embryonic polypeptide chain is synthesized on the ribosome and in the sequence of protein synthesis, the most important folded state is polypeptide chain undergoes through various chemical modification till folding completes to the native state. The chemical alteration regulates the final state, movement, lifespan, or cellular position of protein.

Sometimes, the protein may not completely reach to the native state, or it may get misfolded before its completion to the native state. Some of the factors to manipulate, such as misfolding consist of defective chaperoning, genetic mutations which in turn results in altered amino acid series, exposure to heat, excesses of pH, cellular stress, and other chemicals such as urea or guanidine hydrochloride can interrupt the weak non-covalent bonds and weaken the native conformation of protein [3].

Misfolding comes in contact with hydrophobic domains on the protein, which makes them tremendously wobbly and reactive. Once misfolded, the proteins might go through either denature with the help of chaperones or continue misfolding of proteins, with formation of toxic compounds, injurious consequences like aggregation and accumulation of toxic composites, leading to cell death especially neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and prion disease [4]. Embryonic polypeptides, misfolded protein are identified as atypical by the cells' highly efficient 'Quality Control System' (QCS) in the Golgi apparatus/endoplasmic reticulum not reaching to its native state e.g., receptors do not reach to the plasma membrane, and enzymes do not reach to the lysosome, i.e., they are misrouted. The chaperones correct the folding defect, but if unsuccessful, they generate an 'Unfolded Protein Response' (UPR), thereby misfolded protein is ubiquitinated and thereby proteasome or non-proteasome degradation occurs. This avoids accumulation of cytotoxic aggregates. Thus, misfolding of proteins is ultimately cytotoxicity and waste of proteins [5].

Recently, it has been identified that an increase in the number of genetic defect of protein synthesis because of lysosomal enzyme defects, ion channel, or receptor are in fact, whereby the altered amino acid series disturb with the suitable folding of the protein to its native state. As an end result, though functionally satisfactory, these proteins are identified by the cellular QCS as anomalous and disallowed from attainment their last site of action. Such misrouting of functionally satisfactory proteins results in the beginning of a whole group of hereditary disorders that are now identified to be 'Conformational Disorders [6]. Certain cases of nephrogenic diabetes insipidus, cystic fibrosis, familial hypocalciuric hypercalcemia, retinitis pigmentosa, hypogonadotropic hypogonadism, obesity, Hirschsprung's disease, congenital hypothyroidism, and lysosomal storage disorders are conformational disorders [7].

Pharmacoperones appear to be one of the most promising therapeutic methods to target conformational diseases. In contrast with chemical chaperones, pharmacoperones have the advantage of *target* binding to the misfolded protein, which allows the advantageous (normal) degradation of other misfolded proteins that necessitate being eliminated from the cell as part of the normal progression in synthesis of protein [8].

Mechanism of action of Pharmacoperones

In general, advantageous characteristics of molecules that could function as pharmacoperones for misfolded proteins consist of *i.* Ability to reach physiologically adequate concentrations; *ii.* Permeability of cell; *iii.* Ability to reach and intervene at the endoplasmic reticulum and/or post-endoplasmic reticulum compartments where the misfolded protein is retain; *iv.* Ability to remain undegraded long enough to become constant the target mutant; *v.* Specificity for the target protein; and *vi.* To reversibly bind the misfolded protein, so they may detach from the target molecule after its localization at the exact cellular target (*e.g.,* the plasma membrane) or, alternatively, do not competitively bind to the natural ligand binding site [9].

Whereas, defective proteins can corrected by Pharmacoperones allowing that the mutant could get away from endoplasmic reticulum quality-control system and transfer to the plasma membrane or be interfering with its aggregation or degradation [10]. The mechanisms by which pharmacoperones stabilize and rescue plasma membrane expression of the target receptor is still provisionally and present information is mostly based on imaginary guess of protein arrangement and drug interactions. Two mechanisms have been anticipated to give an explanation of the capability of pharmacoperones to become stable misfolded proteins [11]. Pharmacoperones may bind to and increase the strength of the native or native-like state of the target protein for which they have high attraction than for intermediates, undeveloped forms (*i.e.,* non-native structures) or, alternatively, they may bind to the fewer folded, non-native folding intermediates and serve as a scaffold for the following folding, raising the speed at which these intermediates are transformed to the native form.

This would prevent the protein from being recognized by the endoplasmic reticulum quality-control system as defective, allowing it to escape degradation and promoting its transfer to the Golgi apparatus for supplementary processing [12].

Role of Pharmacoperones in nephrogenic diabetes insipidus (NDI)

In the distal convoluted tubule, and the collecting ducts of the kidney the vasopressin type 2 receptors (V2R) is present as a G protein-coupled receptor (GPCR), a seven-transmembrane protein [13]. V2R normally responds to vasopressin and activates mechanism that concentrates urine and maintains water homeostasis. Mutation of the V2R which leads to mistrafficking of the receptor, which in turn results in vasopressin unresponsive cells. This insufficiency leads to nephrogenic diabetes insipidus (NDI) [14]. There are no drugs able to reversing receptor-mediate misfolding coupled with NDI, and existing management options are limited to alleviating symptoms. Whereas, 70 allelic variants or mutations found in the V2R beyond 188 have been reported to result in traffic-defective receptors [14]. The cell-based assay described here and in another place incorporates the use of the L83Q mutation, which leads to misfolded V2R and subsequently loss of receptor function. While another mutants are predicted to work, the alternative to use the L83Q mutant for high-throughput screening (HTS) was based on its ability to lead to NDI and because the intensity of receptor function, when in the presence of vasopressin, goes from basal (unrescued) to wild-type (rescued) activity when previously treated with the pharmacoperone [15].

Pharmacoperones are minute molecules that go into cells and act as a “molecular scaffold” to correct the folding of misfolded proteins [16]. SR121463, a pharmacoperone of V2R, has been demonstrated by many labs to restore a mutated V2R’s response to vasopressin. Notably, the binding affinity of this molecule to V2R demonstrates incredible selectivity and relatively constant low-nanomolar Ki profiles, regardless of species tested. SR121463 was also previously reported to be active on at least eight NDI associated V2R mutants. Unfortunately, this compound has the limitation of also being a V2R antagonist, which limits its potential for therapeutic translation [17].

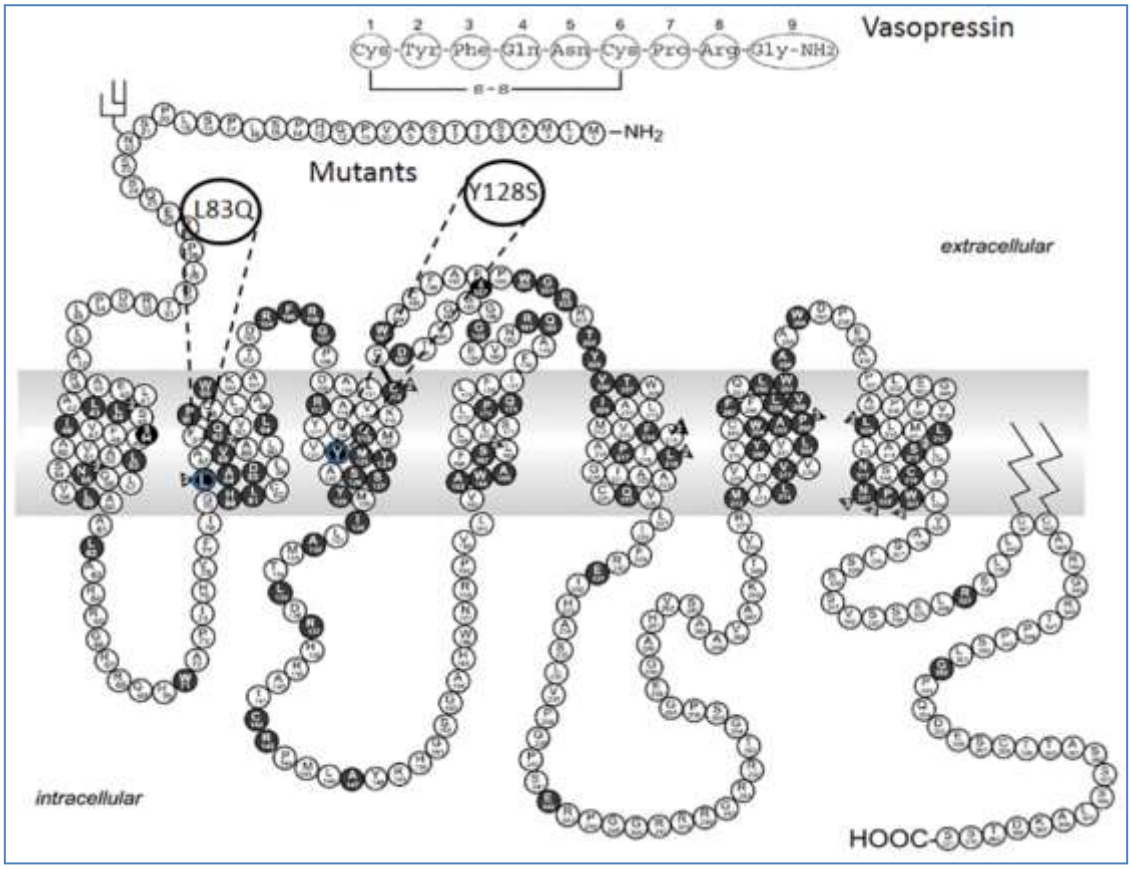

Fig-2: Vasopressin 2 receptor showing mutants associated with nephrogenic diabetes insipidus in black. The location of L83Q and Y128S, the mutants used, are shown. The amino acid sequence of the naturally-occurring ligand, vasopressin, is shown at the top. When there are multiple mutations at a single site, the number of mutations is noted in a triangle. The mutants in this study are a blue circle so they stand out. Bernier *et al.*

A non-peptide antagonist has proved that the pharmacoperones, there are conformational defective GPCRs in which these drugs have been beneficial in efficacy in rescuing function or preventing an irregular buildup of the defective molecule, (Satavaptan, Tolvaptan, Relcovaptan) [18]. About the V2R, it has been shown that distinct cell membrane permeable antagonists effectively rescue *in vitro* function of several misfolded, traffic-defective mutants which in turn cause diabetes insipidus in persons [19]. These findings are one of the important since the majority (~70%) of V2R mutations leading to disease are due to receptor misrouting [20]. Recently, the effect of the peptidomimetic $V1_AR$/V2R antagonist SR49059 to rescue function of $R^{137}H$, $W^{164}S$, and $des^{185–193}$ V2R mutants in patients with nephrogenic diabetes insipidus has been examined [21]. This short trial, that had to be interrupted during the study as a result of possible interference with the cytochrome P450 metabolic pathway, formation of a drop of urine production and intake of water as well as a significant increase in urine osmolarity in response to this particular compound [22].

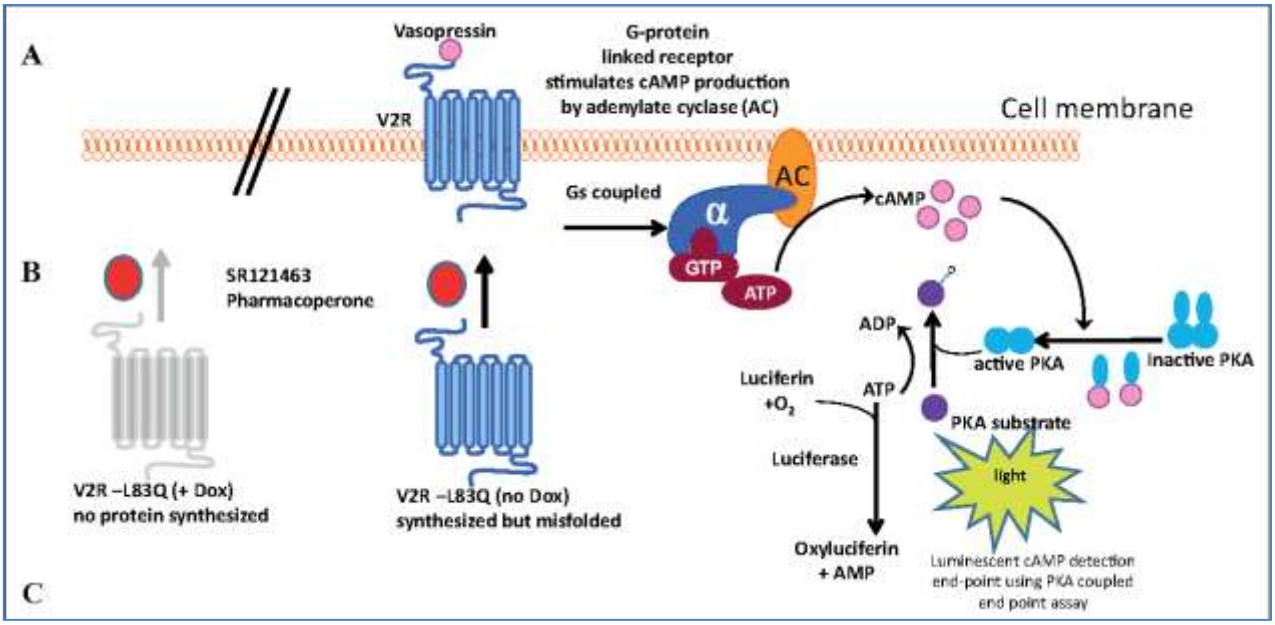

Fig-3.A) Representation of pharmacoperone rescue of mutant vasopressin receptor function. In wild-type V2R responses, vasopressin initiates Gαs activation of adenylate cyclase which increases the concentration of cAMP. Then after cAMP binds to protein kinase A, and the regulatory subunits undergo a conformational change to release the catalytic subunits. The free catalytic subunits then catalyze the transfer of the terminal phosphate of ATP to a protein kinase A substrate, consuming ATP in the process. The level of remaining ATP is determined using the luciferase-based ATP detection reagent. Luminescence is inversely proportional to cAMP levels. Thus, as cAMP concentration increases, luminescence decreases. B) Untreated cells "no Dox" have an active Tet promoter resulting in expression of a misfolded mutant protein. Upon treatment of the cells with vasopressin the pharmacoperone (SR121463), receptor folding is corrected and function is rescued, resulting in a Gs-coupled response which is readily monitored. In "+ Dox" cells, the Tet minus promoter is inactive and no protein is made, thus cells are non-responsive to SR121463 and V2R. Janovick *et al*.

Examples of pharmacoperons are AVPR2 and its antagonists SR49059, SR121463, OPC31260, and OPC41061 So far, there were only a few clinical trials were conducted in which five patients were treated with an antagonist SR49059 (Relcovaptan). As a result of the clinical trial, decreased levels of daily urine were observed. Vaptans class of drugs (for example Tolvaptan) are used in the treatment of hypernatremia. Their use in the treatment of NDI is still in the research phase [23].

Recently, a novel aquaretic, Pharmacoperones - Tolvaptan, is a selective, competitive VPR2 antagonist used to target hyponatremia (low blood sodium levels) associated with congestive cardiac failure (CCF), cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH) [24]. Tolvaptan was also in fast-track clinical trials for polycystic kidney disease. In a 2004 clinical trial, tolvaptan was administered with conventional diuretics, at the time was distinguished that increase excretion of excess fluids and improve blood sodium levels in CCF patients without producing side effects such as hypokalemia or hypotension and without producing a side effect or adverse effect on renal function [25].

REFERENCES

1. Conn, P.M., Janovick, J.A. (2009). Drug development and the cellular quality control system. *Trends Pharmacol Sci*, *30*(5):228-33.
2. Smithson, D.C., Janovick, J.A., Conn, P.M. (2013). Therapeutic Rescue of Misfolded/ Mistrafficked Mutants: Automation-Friendly High Throughput Assays for Identification of Pharmacoperone Drugs of GPCRs. *Methods Enzymol*, 521, 3–16.
3. Kapoor, H., Koolwal, A., Singh, A. (2014). Ivacaftor: A novel mutation modulating drug. J Clin Diagn. *Res,* 8:SE01-5.
4. Ulloa-Aguirre, A. (2015). Pharmacoperones: Targeting Therapeutics Toward Diseases Caused by Protein Misfolding. *Rev InvesClin*, 67: 15-9.
5. Michael, Conn, P. (2014). "Pharmacoperone": What's in a word? *Pharmacological Research*, 83: 1–2.
6. Bernier, V., Morello, J.P., Zarruk, A. (2006). Pharmacologic chaperonesas a potential treatment for X-linked nephrogenic diabetes insipidus. *J Am Soc Nephrol*, 17:232-43.
7. Conn, P.M., Smith, E., Hodder, P. (2013). High-ThroughputScreen for Pharmacoperones of the Vasopressin Type 2Receptor. *J. Biomol. Screen*, *18*(8): 930–7.
8. Morello, J.P., Salahpour, A., Laperriere, A. (2000). Pharmacological Chaperones Rescue Cell-Surface Expressionand Function of Misfolded V2 Vasopressin Receptor Mutants. *J. Clin. Invest, 105*(7): 887–95.
9. Daswani, B.R., & Chandanwale, A.S. Research & Reviews: Journal of Pharmacology and *Toxicological Studies*, *3*(4):1-6.
10. Conn, P.M., Janovick, J.A., Brothers, S.P., Knollman, P.E. (2006). 'Effectiveinefficiency': Cellular control of protein trafficking as a mechanismof post-translational regulation. *J Endocrinol*, 190: 13-6.
11. Mendes, H.F., Van, der, Spuy, J., Chapple, J.P., Cheetham, M.E. (2005). Mechanisms of cell death in rhodopsin retinitis pigmentosa: Implications for therapy. *Trends Mol Med,* 11: 177-85.
12. Robben, J.H., Sze, M., Knoers, N.V., Deen, P.M. (2006). Rescue of vasopressinV2 receptor mutants by chemical chaperones: Specificity and mechanism. *Mol Biol Cell*, 17: 379-86.
13. Janovick, J.A., Conn, P.M., Brothers, S.P., Knollman, P.E. (2006). 'Effective in efficiency': Cellular control of protein trafficking as a mechanismof post-translational regulation. *J Endocrinol*, 190: 13-6.
14. Conn, P.M., Knollman, P.E., Brothers, S.P., Janovick, J.A. (2006). Protein foldingas posttranslational regulation: Evolution of a mechanism forcontrolled plasma membrane expression of a G protein-coupledreceptor. *MolEndocrinol*, 20: 3035-4.
15. Maya-Nunez, G., Janovick, J.A., Conn, P.M. (2000). Combined modification on intracellular and extracellular loci on human gonadotropin releasing hormone receptor provides a mechanism for enhancedexpression. *Endocrine*, 13: 401-7.
16. Janovick, J.A., Patney, A., Mosely, R., Goulet, M., Altman, M., Rush, T. (2009). Molecular mechanism of action of pharmacoperone rescue of misrouted GPCR mutants: The GnRH receptor. *Mol Endocrinol*, 23: 157-68.
17. Bernier, V., Morello, J.P., Zarruk, A. (2006). Pharmacologic chaperones as a potential treatment for X-linked nephrogenic diabetes insipidus. *J Am Soc Nephrol*, 17:232-43.
18. Morello, J.P., Salahpour, A., Laperriere, A. (2000). Pharmacological Chaperones Rescue Cell-Surface Expression and Function of Misfolded V2 Vasopressin Receptor Mutants. J. Clin. Invest, 105: 887–95.
19. Bernier, V., Morello, J. P., Zarruk, A., Debrand, N., Salahpour, A., Lonergan, M., ... & Bichet, D. G. (2006). Pharmacologic chaperones as a potential treatment for X-linked nephrogenic diabetes insipidus. *Journal of the American Society of Nephrology*, *17*(1), 232-243.
20. Bartoszewski, R., Rab, A., Jurkuvenaite, A., Mazur, M., Wakefield, J., Collawn, J. F., & Bebok, Z. (2008). Activation of the unfolded protein response by ΔF508 CFTR. *American journal of respiratory cell and molecular biology*, *39*(4), 448-457.
21. Bernier, V., Morello, J. P., Zarruk, A., Debrand, N., Salahpour, A., Lonergan, M., ... & Bichet, D. G. (2006). Pharmacologic chaperones as a potential treatment for X-linked nephrogenic diabetes insipidus. *Journal of the American Society of Nephrology*, *17*(1), 232-243.
22. Bichet, D.G. (2006). Nephrogenic diabetes insipidus. *Adv Chronic Kidney Dis*, *13*(2):96-104.
23. Serradeil-Le, Gal. (1993). Biochemical and pharmacological properties of SR 49059, a new, potent, non-peptide antagonist of rat and human vasopressin V_{1a} receptors. *J. Clin. Invest*, *92* 224-6.
24. Tahtaoui. (2003). Identification of the binding sites of the SR 49059 nonpeptide antagonist into the V_{1a}vasopressin receptor using sulfydryl-reactive ligands and cysteine mutants as chemical sensors. *J.Biol. Chem*, *278-81.*
25. Torres, Vicente, E., Chapman, A.B., Devuyst, O. (2012). "Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease". *New England Journal of Medicine*, *367*(25): 2407-9.