



Review

Vasopressin receptors and pharmacological chaperones: From functional rescue to promising therapeutic strategies



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ABSTRACT

Conformational diseases result from protein misfolding and/or aggregation and constitute a major public health problem. Congenital Nephrogenic Diabetes Insipidus is a typical conformational disease. In most of the cases, it is associated to inactivating mutations of the renal arginine-vasopressin V2 receptor gene leading to misfolding and intracellular retention of the receptor, causing the inability of patients to concentrate their urine in response to the antidiuretic hormone. Cell-permeable pharmacological chaperones have been successfully challenged to restore plasma membrane localization of the receptor mutants and to rescue their function. Interestingly, different classes of specific ligands such as antagonists (vaptans), agonists as well as biased agonists of the V2 receptor have proven their usefulness as efficient pharmacochaperones. These compounds represent a potential therapeutic treatment of this X-linked genetic pathology.

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Contents

1. Introduction: the X-linked genetic disease cNDI.....	74
2. Antagonists to the rescue: known compounds with novel pharmacological chaperone activity.....	75
3. Agonists and biased agonists: better pharmacological chaperones than antagonists?.....	76
4. Clinical trials.....	77
5. Conclusions and perspectives.....	77
Conflict of interest.....	77
References.....	77

1. Introduction: the X-linked genetic disease cNDI

Regulated water excretion by the kidney is crucial to preserve water homeostasis of our body. The adjustment of water renal reabsorption, to respond to increase in blood osmolality (hypernatremia) or decrease in blood volume (hypovolemia), mainly depends on the release of the antidiuretic hormone arginine-vasopressin (AVP) from the pituitary [1–3]. Binding of AVP to the vasopressin type 2 receptor (V2R), a Gs protein-coupled receptor

(GPCR) localized at the basolateral membrane of the principal cells of the kidney collecting duct, results in an intracellular cAMP-dependent signaling cascade of events. Among them, phosphorylation of the water channel aquaporin-2 (AQP2) and its translocation from storage compartments to the apical surface of the cells are of primary importance. Water from pro-urine which enters the cells exits *via* aquaporin-3 and aquaporin-4 at the basolateral side, leading to water reabsorption and urine concentration. Upon restoration of water balance, the level of plasma AVP drops and AQP2 is internalized, leaving the apical membrane watertight again.

Disorders that interfere with proper urine concentration can be life-threatening, especially in children. One such disease is the congenital form of Nephrogenic Diabetes Insipidus (cNDI) [4]. Indeed, cNDI is a rare inherited disease, characterized by insensitivity of the kidney to AVP and absence of water reabsorption. It results in polyuria and compensatory polydipsia, and may lead to severe

Abbreviations: AVP, arginine-vasopressin; AQP2, aquaporin-2; cNDI, congenital Nephrogenic Diabetes Insipidus; GPCR, G protein-coupled receptor; PC, pharmacological chaperones; V2R, vasopressin type 2 receptor.

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dehydration and electrolyte imbalance (hypernatremia) in the case of inadequate water supply.

The X-linked form of cNDI is caused by mutations in the V2R gene [5]. To date, over 200 different V2R mutations have been described. V2R mutations are divided into five different classes. Class II mutations (the most prevalent, more than 50%) are most frequently missense mutations (amino acid substitutions). These mutations result into misfolded, trafficking-deficient receptors that do not reach plasma membrane of the basolateral side of the principal cells of the kidney collecting duct. Indeed, most of the mutants are retained in the endoplasmic reticulum (ER) and in the ER-Golgi intermediate compartment. Consequently, V2R mutants are unable to interact with circulating AVP [6]. These V2R mutants, rather than resulting in nonfunctional proteins (mutants from classes III and IV) are intrinsically functional, as demonstrated by overexpression in heterologous cell expression systems [7].

cNDI-untreated adult patients may have a daily output of 15–20 L of highly dilute urine. Newborn infants often suffer from hypernatremic dehydration with symptoms of irritability, poor feeding and weight gain. In addition, repeated periods of brain dehydration may result in permanent brain damage, mental retardation and seizures can occur. The main strategy for treating cNDI patients consists of a sufficient water supply to replace the urinary water loss, but this can seriously impact on the quality of life due to excessive drinking and urine voiding. Some diuretics, like hydrochlorothiazide, amiloride or the cyclooxygenase inhibitor indomethacin, have been proven effective to reduce urine output by up to 50% [8]. However, diuretics may affect the sodium and potassium balance in patients and therefore these treatments require tight monitoring of serum electrolytes and osmolality.

Although understanding of cNDI from molecular and cell biological point of view has largely increased since the cloning of the V2R gene in 1992 [9–11], developing alternative strategies to manage water homeostasis and induce antidiuresis in cNDI patients is still obvious. The V2R is a “natural” target for establishing new forms of therapies, and rescue of its function is a very elegant and specific approach. Here starts the story of pharmacological chaperones (PC).

2. Antagonists to the rescue: known compounds with novel pharmacological chaperone activity

Chemical chaperones, like glycerol and DMSO, were shown for instance to correct mutants of the AQP2 water channel, as assessed by protein maturation, cellular targeting and water permeability [12]. Taking the concept of chemical chaperones further, artificial mutants of the multidrug resistance P-glycoprotein-1, a cell surface transporter which interacts with a panel of cytotoxic agents, were functionally rescued. Indeed, ER-retained mutants were targeted to the plasma membrane and their functional rescue was demonstrated using specific substrates or inhibitors like vinblastin, cyclosporin or verapamil [13]. These compounds were proposed to stabilize a specific native-like conformation of the transporter, allowing its release from the ER quality control cell system.

The concept was applied to the mutants of V2R responsible for cNDI, based on the idea that pharmacological ligands act by binding to and stabilizing specific conformations of their receptors. Selective cell-permeant nonpeptidic V2R antagonists (which block the V2R in an inactive conformation) were assessed to check whether they could facilitate the folding of mutant receptors that are retained in ER and unable to interact with AVP [14]. The experiments were successful. Given that these antagonists are specific to the V2R and that they perform chaperone-like activity, Drs. Bichet and Bouvier termed these compounds pharmacological chaperones (PC) [15]. Other names like pharmacochaperones or pharmacoperones have then been proposed.

The first antagonist (or inverse agonist) to be used was SR121463, a selective high-affinity V2R ligand [14]. An overnight treatment of the cells retaining different V2R mutants into an intracellular compartment converted precursor forms into fully glycosylated mature receptors that were targeted to the cell surface. Once correctly localized at the plasma membrane, these mutants were able to differentially bind AVP and produce a correlated cAMP intracellular signal. Interestingly, V2R membrane-impermeable peptidic antagonists were unable to mimic the SR121463 effect, indicating a PC intracellular effect. The PC-driven V2R mutant rescue was not limited to SR121463, because another nonpeptidic antagonist, VPA985, reproduced equivalent results. Since the publication of this outstanding study, SR121463 was used to rescue a larger panel of V2R mutants [16–19] and different other antagonists (or inverse agonists) were tested for their PC properties, such as the V1AR-selective SR49059 [17,20], the mixed V1A/V2R YM087 [21] and the V2R-selective OPC31260 and OPC41061 [22]. A list of the different PC used to rescue cNDI V2R mutants is presented in Table 1, as well as the different receptor mutants for which the PC beneficial effect was proven. Very importantly, the PC effect was also reproducible in polarized renal cells where V2R mutants were appropriately targeted to the basolateral membrane, the natural localization of the wild-type V2R [23]. In addition, because of their target specificity, the PC compounds are active at nanomolar concentrations on cultured cells [22]. This is a tremendous advantage, compared to chemical chaperones which are active at micromolar concentrations or even more.

Interestingly, the concept of PC developed for V2R mutants responsible for cNDI was applied to other GPCR families [24] but also to the V1A and V1B subtypes of the vasopressin receptor family, strengthening the idea that PC action can be generalized to many intracellular-retained misfolded mutant receptors. Regarding vasopressin receptor family, SSR149415, which is a specific nonpeptidic antagonist for V1B was demonstrated to rescue plasma membrane localization and function of the V1B mutant 341FN(X)₂LL(X)₃L350 [25]. Then, the selective nonpeptidic antagonist SR49059 was shown to rescue the functional properties of surface-impaired D148A/N/E mutants of the V1A receptor subtype [26]. To date, no more study has been investigated using PC to rescue other artificial mutants of V1AR, V1BR or the vasopressin-related oxytocin receptor.

Although very promising, using antagonists for rescuing function of the V2R and more generally GPCRs responsible for inherited conformational diseases is somehow paradoxical. First of all, because these antagonists specifically block (inhibit) their receptors, they cannot directly stimulate receptor-associated signaling pathways. Regarding patients who suffer from cNDI, the therapeutic beneficial effect would be antidiuresis, through activation of a cAMP-dependent signaling cascade and particularly membrane translocation of AQP2. Indeed, using the PC antagonist strategy, functional rescue of mutants of the V2R is a subtle balance between the ability of the ligand to target cell-surface expression of the mutants and its possibility to be displaced by AVP for receptor activation [27]. In this regard, considering the antagonist affinity is an important feature for this challenge, and therefore low-affinity antagonists (those which are easily displaced by AVP) may possess a highest clinical value [28]. However, the efficiency of such low-affinity antagonist ligands in rescuing receptor function is lower than that of high-affinity ligands (the higher the affinity, the better rescue will be obvious). Moreover, high concentrations of low-affinity antagonists to be administered for clinical efficiency might lead to unwanted side effects in patients (see below Section 4). In addition, compound-intrinsic factors other than affinity may influence their capacity to confer functional rescue and their extent to be displaced by AVP, like their localization in the binding pocket of the V2R, their intrinsic activity or their lipophilic value. Overall, it

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