REVIEW

Water in health and disease: new aspects of disturbances in water metabolism

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ABSTRACT

Vasopressin is a critical regulator of water homeostasis. There are two major receptors for vasopressin: V1 and V2 receptors. Disturbances in water balance are commonly encountered in clinical practice and can be divided into disorders of urinary dilution and concentration. The major representatives of such disorders are diabetes insipidus and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
Recent studies show that genetic forms of nephrogenic diabetes insipidus are due to mutations in the genes coding for the vasopressin V2 receptor (V2R) or aquaporin-2 (AQP2). Identification of the genes involved and analysis of the cellular fate of the V2R and AQP2 mutants are relevant for understanding the functioning of the V2R and AQP2 protein. These developments also have implications for future therapeutic options.
The development of nonpeptide vasopressin receptor antagonists (VRAs) offers prospects for the treatment of euvolaemic (SIADH) or hypervolaemic hyponatraemia (congestive heart failure or cirrhosis). Several nonpeptide VRAs are now in various stages of clinical trials. At present, only conivaptan is registered by the FDA for intravenous treatment of euvolaemic and hypervolaemic hyponatremia. A recent long-term study comparing tolvaptan with placebo in patients with chronic heart failure showed no reduction in risk of death and hospitalisation.

KEYWORDS

Conivaptan, diabetes insipidus, SIADH, tolvaptan, vasopressin, water homeostasis

INTRODUCTION

Water is essential for living organisms. Human water balance is tightly regulated by the integrated action of osmoreceptors and volume receptors, thirst, vasopressin, and the excretion of water by the kidney.[1] Disturbances in water metabolism are frequent in clinical practice and include well-known syndromes such as diabetes insipidus and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In recent years the pathophysiology of these water metabolism disorders has been largely unravelled, which has increased the prospects for new treatment modalities.

In this review we will discuss normal water regulation and specifically address recent advances in the understanding of the role of mutations in the vasopressin receptor and their relevance for future treatment strategies.

CURRENT CONCEPTS IN WATER REGULATION

The maintenance of human water balance depends on the regulation of water intake (which is governed by the sensation of thirst and the availability of water) and of water excretion in the kidney, which is under the control of the antidiuretic hormone arginine vasopressin (AVP), and dependent on the presence of a hypertonic medulla and functioning vasopressin type-2 receptors (V2R) and aquaporin-2 (AQP2) water channels.

In normal physiology, arginine vasopressin (AVP) is synthesised in the hypothalamus and is secreted into the circulation by the posterior pituitary gland, in response to an increase in serum osmolality or a decrease in effective circulating volume. In general, the plasma sodium concentration is the primary osmotic determinant of AVP release. The osmoreceptors (specialised hypothalamic cells) are extremely sensitive and respond to alterations in the plasma osmolality of as little as 1%.[2] The osmotic threshold for AVP is about 280 mosmol/kg. This system is so efficient that plasma osmolality does not vary by more

than 1 to 2%, despite wide fluctuations in water intake.[3] Although relatively stable in a healthy person, the set point of the osmoregulatory system may be lowered by pregnancy, the menstrual cycle, and relatively large, acute reductions in blood pressure or circulating volume.

The sensitivity of the volume receptors is different to that of the osmoreceptors. AVP is only secreted nonosmotically in humans if there is a large enough change in the effective arterial blood volume (approximately 5-10%), usually leading to a reduction in (standing) blood pressure.[4] In case of such large, significant blood volume changes, signals originating from the volume receptors override those originating from the osmoreceptors.[3] AVP secretion may also be stimulated by nausea, acute hypoglycaemia, glucocorticoid deficiency and smoking.[5] The primary stimulus for water ingestion is thirst, which is mediated by an increase in plasma osmolality (threshold 295 mosmol/kg) or a decrease in blood pressure or extracellular volume. Various hormones such as AVP and angiotensin II are involved in the stimulation of thirst.

AVP is rapidly metabolised in the liver and excreted by the kidney, with a half-life in the circulation of only 15 to 20 minutes. There are two major receptors for AVP: the V1 and the V2 receptors.

V1a receptors are located in vascular smooth muscle cells, cardiomyocytes, platelets, hepatocytes and myometrium.[6] The effect of activation of V1a receptors depends on their location. V1a receptor activation mediates vasoconstriction, vascular smooth muscle cell proliferation, platelet aggregation, glycogenolysis and uterine contraction in accordance with the above-mentioned locations. The V1a receptor also promotes hypertrophic growth of myocardial cells. Antagonism may result in increased cardiac output, reduced total peripheral resistance and reduced mean arterial blood pressure. V1b receptors are localised in the anterior pituitary gland and facilitate the release of ACTH. V2 receptors are located in the vascular endothelium and in the basolateral membranes of the principal cells in the cortical and medullary collecting tubules. Activation of the endothelial V2 receptor increases the release of factor VIII and von Willebrand factor, an effect which is used to attenuate an increased bleeding tendency by administering the V2 receptor agonist dDAVP. Binding of AVP to the V2 receptor in the kidney activates a G-protein mediated signalling pathway, involving activation of adenylate cyclase and the formation of cyclic adenosine monophosphate (cAMP). The subsequent activation of protein kinase A promotes the translocation of AQP2 water channels from cytoplasmic vesicles to the apical membrane (*figure 1*). Consequently, this usually watertight membrane becomes water permeable, thereby allowing the transcellular passage of water along the favourable osmotic gradient, and through the aquaporin-3 and aquaporin-4 water channels, which are present in the basolateral membrane. In response to decreased blood AVP levels, the AQP2 water channels are modified by ubiquitination, a process in which ubiquitin peptides are attached to AQP2 proteins.

Figure 1. *Regulation of renal water homeostasis by vasopressin (original figure from reference 15, reprinted with permission of the American Physiological Society)*
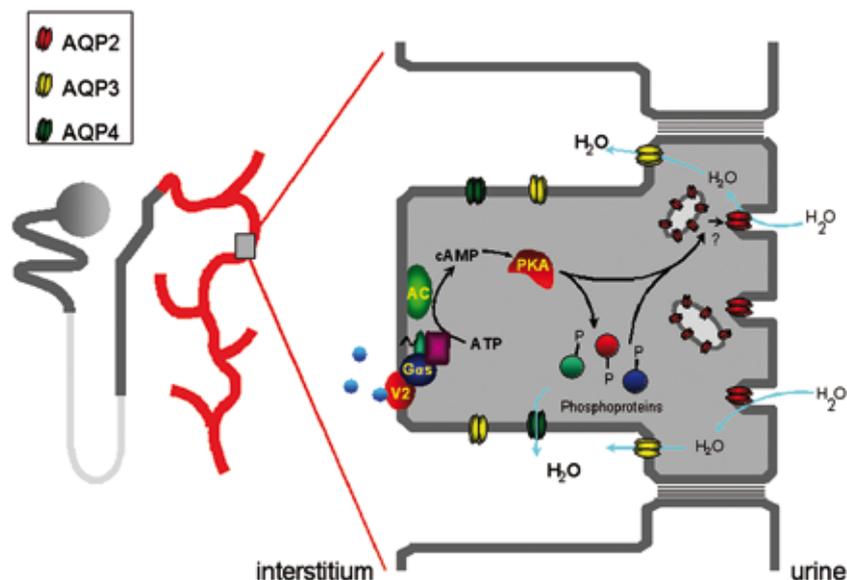
A nephron with a magnified principal cell is shown. Binding of AVP to the V2 receptor in the kidney activates a G-protein mediated signalling pathway, involving activation of adenylate cyclase and the formation of cyclic adenosine monophosphate (cAMP). The subsequent activation of protein kinase A promotes the translocation of AQP2 water channels from cytoplasmic vesicles to the apical membrane in the cell. The membrane becomes water permeable, thereby allowing transcellular passage of water along the favourable osmotic gradient and through AQP3 and AQP4 water channels (which are present in the basolateral membrane). For further details, see text.

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Ubiquitin is a small protein designed to mark other proteins for intracellular destruction. Destruction, or more precisely proteolysis, occurs in a barrel-shaped structure, the proteasome. Ubiquitin can also mark transmembrane proteins, such as receptors, for removal from membranes. Thus, AQP2 water channels are removed from the luminal membrane by endocytosis and returned to cytoplasmic vesicles.[7] Apart from this direct effect on water transport, AVP also increases sodium transport via the epithelial sodium channel (ENaC) and urea transport through the UT-A1 transporter.[8,9]

DISORDERS OF WATER METABOLISM

Disturbances in water homeostasis can be divided into disorders of urinary concentration and disorders of urinary dilution (*table 1*). The major examples of such disorders are SIADH and diabetes insipidus.

SIADH is characterised by a nonphysiological release of AVP. It is a common problem that can be seen in a wide variety of clinical situations. SIADH manifests itself as an inability to excrete a free water load, with inappropriately concentrated urine, resulting in hyponatraemia and hypo-osmolality. The hyponatraemia is initially mediated by AVP-induced water retention, the ensuing volume expansion results in sodium losses. SIADH may result from enhanced hypothalamic secretion of AVP, ectopic production of AVP (malignancies), or the administration of exogenous AVP or oxytocin. Certain forms of drug-induced SIADH may be due to an increased susceptibility to AVP.[10] Recently a genetic form of SIADH was described, which could be attributed to a gain-of-function mutation of the vasopressin 2 receptor due to a point mutation in the V2R gene.[11] The result of this mutation is an AVP-independent continuous activation of the V2 receptor, which increases urinary concentration. This condition has been referred to as nephrogenic syndrome of inappropriate antidiuresis (NSIAD). Osmotically inappropriate antidiuresis may also be caused by stimuli such as hypovolaemia, hypotension (cirrhosis, congestive heart failure) or glucocorticoid deficiency. In patients with congestive heart failure (CHF) or cirrhosis, water retention is an initially beneficial defence against decreased cardiac output in CHF or the dilated splanchnic circulation in cirrhosis. Current and future treatment modalities in SIADH are presented in *table 1*. The very recent development and use of AVP type 2 receptor antagonists will extend our therapeutic armamentarium (see below).

Diabetes insipidus (DI) is characterised by the production of abnormally large volumes of urine that result from either a decreased secretion of AVP (central DI) or a diminished responsiveness to AVP (renal or nephrogenic DI). Patients complain of thirst and polyuria, but clinical signs of dehydration are uncommon unless fluid intake is impaired or prohibited. Central DI can be caused by a variety of congenital, acquired or genetic disorders, though in nearly 50% of cases it is idiopathic (*table 1*). Nephrogenic DI (NDI) is a congenital or acquired disorder in which hypothalamic function and AVP release are normal, but the ability to concentrate urine is reduced because of diminished or absent renal responsiveness to AVP. Acquired NDI is most often caused by electrolyte disturbances (hypocalcemia or hypokalaemia), urinary tract obstruction or exposure to certain drugs (e.g. lithium).

The genetic forms of NDI are related to mutations in the AVP V2 receptor or AQP2 gene.[12-15] The gene for the AVP V2 receptor is located on the X-chromosome, thus NDI caused by mutations in the V2 receptor gene are inherited and transmitted in an X-linked mode. The AQP2 gene is located on chromosome 12,[16] and NDI caused by mutations in the AQP2 gene is inherited in an autosomal mode. Both autosomal dominant and recessive forms have been described. Recent studies have provided more insight into the impact that various mutations have on the functioning of the V2 receptor and the AQP2 protein. Insight into these mechanisms provides clues for future therapeutic interventions, as is evident from the studies concerning the V2 receptor that will be addressed in the next section.

NEPHROGENIC DIABETES INSIPIDUS AND MUTATIONS IN THE V2 RECEPTOR

Likely due to its location on the X-chromosome, 90% of the patients suffering from congenital NDI have mutations in the V2R gene. Currently, more than 180 V2R gene mutations have been described,[17] and all these mutations result in severely disturbed receptor signalling that corresponds to an insensitivity of the renal principal cell for AVP. The molecular mechanism causing this insensitivity differs among mutants and recent data indicate that one of these underlying mechanisms might be treatable in the future.

The V2R belongs to the large family of G-protein coupled receptors (GPCR) and, based on the underlying mechanism, GPCR gene mutations in general and V2R gene mutations in particular were recently divided into five different classes according to their cellular fate (*figure 2*).[18,19]

Class I comprises mutations that lead to improperly processed or unstable RNA, resulting in the absence of a fully translated protein. Class II mutations are mainly missense mutations resulting in fully translated proteins, but due to a point mutation the receptors are misfolded. Instead of being transported to the plasma membrane, they are retained in the endoplasmic reticulum (ER). This

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Table 1. Overview of disorders in water metabolism

Primary defect	Reduced urinary concentration		Reduced urinary dilution			
Disorder	Central diabetes insipidus (CDI)	Nephrogenic diabetes insipidus (NDI)	Syndrome of inappropriate ADH secretion (SIADH)	Volume-dependent ADH secretion (SIADH-like)	Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)	
Pathogenesis	Complete or partial failure of vasopressin secretion	Reduced renal responsiveness to AVP due to defective V2 receptor Reduced renal responsiveness to AVP due to defective AQP2 Reduced renal responsiveness to AVP due to absence of medullary gradient	Enhanced secretion of vasopressin or potentiation of vasopressin effect	Enhanced secretion of vasopressin due to a decreased effective volume	Increased renal responsiveness to AVP due to a gain of function mutation of the V2 receptor	Impaired dilution due to decreased NaCl re absorption in the distal tubule
Causes	*Acquired* Idiopathic Neurosurgery Head trauma Neoplastic Hypoxic or ischaemic encephalopathy Other (sarcoidosis, histiocytosis X etc.) *Congenital* CNS malformations	*Congenital* X-linked loss of function mutation in V2 receptor gene *Congenital* Autosomal recessive or autosomal dominant mutations in aquaporin 2 gene *Acquired* Lithium Hypercalcaemia Hypokalaemia *Congenital* Defective Na-K-Cl cotransporter in thick ascending limb (Bartter) *Acquired* Sickle cell disease Urinary tract obstruction Loop diuretics Cisplatinum Sarcoidosis	Increased hypothalamic production (neuropsychiatric disorders, drugs, pulmonary disease, postoperative etc.) Ectopic production (carcinoma) Exogenous ADH Carbamazepine Chlorpropamide Hypothyroidism* Adrenal insufficiency*	Cirrhosis Congestive heart failure	Missense mutation of V2 receptor (R137C, R137L)	*Congenital* Defective Na-Cl cotransporter due to autosomal recessive mutation in SLC12A3 gene (M. Gitelman) *Acquired* Inhibition of NaCl reabsorption due to thiazide diuretic
Treatment	dDAVP Thiazide diuretic and/or amiloride Chlorpropamide Carbamazepine Clofibrate Future therapies **V2 receptor-antagonists acting as chaperones** Activation of cGMP kinase	*Congenital* Thiazide diuretic or amiloride Low sodium and protein diet NSAID (dDAVP) *Acquired* Resolve underlying disorder and see above *Congenital* NSAID *Acquired* Treat underlying disorder if possible or stop causative agent	Water restriction Intravenous administration of hypertonic saline NaCl tablets Loop diuretics High salt, high protein diet Demeclocycline Lithium Urea Vasopressin receptor antagonists	**V2 receptor antagonists** Loop diuretics Water restriction	Water restriction Demeclocycline Lithium Urea V2 receptor antagonist acting as inverse agonists (only tested *in vitro*)	Water restriction Withdrawal of thiazide diuretic

*Hypothyroidism and adrenal insufficiency cause SIADH-like syndrome, the exact mechanisms involved are unresolved but likely to include inappropriate ADH secretion or enhanced sensitivity to ADH.

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Figure 2. *Cellular fate of V2R mutants in congenital nephrogenic diabetes insipidus (NDI) and their rescue (original figure from reference 15, reprinted with permission of the American Physiological Society)*

A) Classes of V2R mutations in NDI. In the schematic view of the collecting duct cell, the fate of the different mutation classes is indicated by Roman numerals. Mutations can lead to incomplete proteins (I); endoplasmic reticulum (ER) retention of full-length proteins (II); impaired Gs coupling (III); impaired AVP binding (IV); and missorting in the cell (V). See text for details.
B) Rescue of class II V2R mutants by pharmacological chaperones. Class II V2R mutants are retained in the ER, but on binding of cell-permeable antagonists (CPA), the wild-type structure of the V2R mutant is stabilised, which allows them to exit the ER, mature in the Golgi complex, and subsequently translocate to the plasma membrane (1). At the membrane, displacement of the CPA by AVP will allow activation of the cAMP cascade (2), the missing step needed for translocation of AQP2 to the apical membrane.

organelle not only synthesises membrane proteins, but also assures that these proteins are properly folded and assembled. Misfolded proteins, including V2R mutants, are subsequently degraded by the proteasome.[20]

Class III and IV mutations also result in fully translated proteins. These proteins bypass the quality control performed in the ER and are transported to the plasma membrane. In the plasma membrane class III mutants disturb the binding of the stimulatory Gs protein, leading to reduced activation of adenylate cyclase and formation of cAMP, while class IV mutants are unable to bind AVP. Finally, class V mutations allow normal protein synthesis and maturation, but here the protein mutations direct the mutant receptor to another organelle in the cell. Due to mislocation, the V2R mutant is only briefly available for AVP binding.

Intracellular retention of V2R missense mutants in the ER and their rapid degradation likely represent the main cause for NDI. The extent of ER retention may differ among mutants and may represent differences in their folding state. This was illustrated by Hermosilla *et al.*, who found that only three of eight V2R mutants in NDI were strictly kept in the ER, whereas the other five were transported to the ER-Golgi intermediate compartment, followed by retrograde transport to the ER.[21]

Although several mutants belong to one class only, others display characteristics of several classes. Some, for example, are partially ER retained (class II), whereas another fraction is expressed at the plasma membrane and exerts a reduced activity (class III or IV).[19] This partial expression of these mutants at the plasma membrane may explain the observed small antidiuretic response to high doses of desmopressin in NDI patients encoding these mutants.[23]

PHARMACOLOGICAL CHAPERONES TO RESCUE CLASS II V2R MUTANT

While cell biological studies have revealed that most V2R mutants in NDI are retained in the ER, other studies have proved that many of these ER-retained receptors are intrinsically functional (i.e. are able to bind AVP and generate a cAMP cascade). This means that ER retention is the main reason for these mutant receptors to cause NDI and that drugs that can rescue their cell surface expression may be of therapeutic value.[24-27] As such, the discovery that cell-permeable V1R and V2R antagonists are able to enter the cell, stabilise the V2R mutant and rescue its cell surface expression (*figure 2*) was widely hailed as a breakthrough. Most though not all ER-retained V2R

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mutants are rescued and re-expressed at the cell surface by these 'pharmacological chaperones'. To be of therapeutic use, the rescuing antagonist needs to be displaced by AVP after translocation of the V2R mutant to the basolateral membrane. Since the competition between AVP and the rescuing ligand at the plasma membrane determines functional rescue, low-affinity ligands are deemed to be more successful than high-affinity antagonists.[28] Indeed, Bernier *et al.* recently found that administration of a low-affinity V1R antagonist resulted in a small but significant reduction in urine production and water intake in five NDI patients with class II mutations, thereby proving in principle that pharmacological chaperones can also rescue V2R mutant activity *in vivo*.[29] Of great importance is that this treatment with relatively high blood concentrations of V1R antagonist came with a minimum of side effects. *In vitro* data show that at clinically relevant low concentrations of antagonists, V2R antagonists yield a better functional rescue of V2R mutants than V1R antagonists.[27] It is therefore anticipated that these drugs reduce NDI to a greater extent than V1R antagonists. As several of the V1R and V2R antagonists have been or are close to FDA approval, it will be exciting to discover to what extent they are able to relieve NDI caused by class II functional V2R mutants.

AVP RECEPTOR ANTAGONISTS

Conventional therapies for euvolaemic (SIADH) or hypervolaemic hyponatraemia (congestive heart failure (CHF), cirrhosis) including water restriction, hypertonic saline, democycline and urea are moderately effective and their use is limited by noncompliance or side effects. None of these therapies directly addresses the pathogenetic mechanism involved, i.e. elevated plasma AVP. Many patients with CHF develop hyponatraemia and hypervolaemia that is poorly responsive to conventional loop diuretics. Hyponatraemia in CHF is associated with increased morbidity and mortality, underlining the importance of adequate correction of this electrolyte disorder. The development of nonpeptide vasopressin receptor antagonists (VRAs) has opened a new era in the treatment of hyponatraemia. Several of these nonpeptide VRAs are now in various stages of clinical trials.

Tolvaptan is a selective V2 receptor antagonist. Schrier *et al.* reported the combined data of two randomised trials evaluating 225 outpatients with euvolaemic or hypervolaemic hyponatraemia, who were given 15 and later 30 or 60 mg tolvaptan over a period of 30 days.[30] Tolvaptan increased average serum sodium concentration by 4 to 5 mmol/l throughout the entire treatment period. About 25% of the patients withdrew from the trial due to side effects. Similar results were obtained with conivaptan, which is the only combined V1a and V2 receptor antagonist that has been approved by the FDA for treatment of euvolaemic hyponatraemia. A randomised placebo-controlled trial in patients with euvolaemic or hypervolaemic hyponatraemia (n=74) showed that serum sodium normalised or increased >6 mmol/l within five days in 48% of patients who received placebo treatment, in 71% of patients who received 40 mg conivaptan, and in 82% of patients who were given 80 mg conivaptan.[31] In this short-term study, 5% withdrew from the trial because of side effects. Both studies noted hypotension, nausea, thirst, constipation, and dry mouth as the main side effects. Two other selective V2 antagonists, lixivaptan and SR121463, are currently being investigated in phase III trials.

From a clinical perspective, VRAs might become important new drugs for the treatment of patients with congestive heart failure. In patients with heart failure AVP is stimulated, thus causing hyponatraemia and impairment of diuresis. Two major randomised trials studying the effect of tolvaptan in CHF have been carried out. A randomised controlled trial studied 254 patients with CHF (NYHA II-III) and compared the effect of three different oral doses of tolvaptan for a duration of 25 days.[32] Tolvaptan-treated patients showed a decrease in body weight and had small, but significant increases in serum sodium concentrations. This effect gradually decreased over 25 days. Another major trial randomised 319 patients, who required hospitalisation for CHF, to receive placebo, 30, 60 or 90 mg tolvaptan for 60 days.[33] The primary endpoint was weight loss after 24 hours, which was greater in the tolvaptan group. Additional primary endpoints were worsening CHF, death or re-hospitalisation. Although there were no differences among the treatment groups, in post hoc analysis, 60-day mortality was significantly lower in the tolvaptan-treated patients with renal dysfunction or severe congestion at baseline. Considering these data, long-term benefits of VRAs in patients with CHF could be expected. The recent outcome of the EVEREST trial has therefore been somewhat disappointing.[34] The EVEREST trial tested the benefit of tolvaptan, given once a day (30 mg *vs* placebo) in two identical short-term studies and a longer-term safety and outcome trial. A total of 4133 patients were randomised. Although the short-term studies showed a change in body weight in favour of tolvaptan and modest improvement in dyspnoea and oedema, the long-term trial (treatment for a minimum of 60 days, median follow-up 9.9 months) demonstrated no reduction in risk of death or hospitalisation. A total of 537 patients in the tolvaptan group (25.9%) and 543 patients in the placebo group (26.3%) died (p=0.68). The other primary endpoint of hospitalisation or death from cardiovascular causes occurred in 871 patients in the tolvaptan group (42.0%) and 829 patients in the placebo group (40.2%, p=0.55). No significant worsening of renal function was observed; the

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main side effects of tolvaptan were dry mouth and thirst. Although tolvaptan can be safely used in patients with CHF, the lack of an effect on primary endpoints and the side effects advocate against its long-term use.

Theory and empirical evidence obtained from animal experiments indicate that dual vasopressin V1a and V2 receptor antagonists might provide greater benefits in patients with CHF than selective V2 receptor antagonists.[35] V1a receptor antagonists attenuate vascular smooth muscle contraction, resulting in vasodilatation and a decrease of systemic vascular resistance. As a consequence, the cardiac output may increase. Indeed in an acute study intravenously administered conivaptan lowered pulmonary capillary wedge pressure and right atrial pressure and increased urinary output in patients with CHF.[36] No animal or human experiments studying the haemodynamic effects of tolvaptan have been conducted so far, nor have there been trials comparing conivaptan with tolvaptan. Currently a large multicentre trial with hard endpoints is underway to examine the long-term benefits of conivaptan on exercise tolerance in patients with CHF.[37] It should be noted that conivaptan has only been approved for intravenous use by the FDA. Until data from additional clinical trials become available, VRAs are not recommended in patients with CHF.

CONCLUSION

In the past years our understanding of AVP-mediated urinary concentration has substantially improved with the elucidation of the crucial molecular mechanisms involved. Research on congenital NDI has led to promising therapeutic strategies that mediate an antidiuretic response. Advantageous effects of vasopressin antagonists have resulted in FDA approval of conivaptan for intravenous treatment of patients with euvolaemic or hypervolaemic hyponatraemia. However, in patients with congestive heart failure the expected beneficial effect of long-term use of a selective V2 receptor antagonist on risk of death or hospitalisation was not observed.

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