The physiological and pathophysiological functions of renal and extrarenal vasopressin V2 receptors

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Juul KV, Bichet DG, Nielsen S, Nørgaard JP. The physiological and pathophysiological functions of renal and extrarenal vasopressin V2 receptors. Am J Physiol Renal Physiol 306: F931–F940, 2014. First published March 5, 2014; doi:10.1152/ajprenal.00604.2013.—The arginine vasopressin (AVP) type 2 receptor (V2R) is unique among AVP receptor subtypes in signaling through cAMP. Its key function is in the kidneys, facilitating the urine concentrating mechanism through the AVP/V2 type receptor/aquaporin 2 system in the medullary and cortical collecting ducts. Recent clinical and research observations strongly support the existence of an extrarenal V2R. The clinical importance of the extrarenal V2R spans widely from stimulation of coagulation factor in the endothelium to as yet untested potential therapeutic targets. These include V2R-regulated membranous fluid turnover in the inner ear, V2R-regulated mitogenesis and apoptosis in certain tumor tissues, and numerous other cell types where the physiological role of V2Rs still requires further research. Here, we review current evidence on the physiological and pathophysiological functions of renal and extrarenal V2Rs. These functions of V2R are important, not only in rare diseases with loss or gain of function of V2R but also in relation to the recent use of nonpeptide V2R antagonists to treat hyponatremia and possibly retard the growth of cysts and development of renal failure in autosomal dominant polycystic kidney disease. The main functions of V2R in principal cells of the collecting duct are water, salt, and urea transport by modifying the trafficking of aquaporin 2, epithelial Na+ channels, and urea transporters and vasodilation and stimulation of coagulation factor properties, mainly seen with pharmacological doses of 1-desamino-8-D-AVP. The AVPR2 gene is located on the X chromosome, in a region with high probability of escape from inactivation; this may lead to phenotypic sex differences, with females expressing higher levels of transcript than males.

vasopressin V2 receptor; arginine vasopressin V2 receptor; arginine vasopressin; desmopressin; extrarenal vasopressin V2 receptor

The purpose of this report is to review current evidence on the physiological and pathophysiological functions of renal and extrarenal arginine vasopressin (AVP) type 2 receptors, referred to as V2Rs (Fig. 1).

AVP is an important neurohypophysial nonapeptide that, via its three receptor types, is primarily responsible for regulating osmotic homeostasis of body fluids, volume homeostasis, and vasoconstriction in addition to an array of central functions such as memory and learning (17, 29). In addition to these endocrine functions, AVP also contributes to regulating mitogenesis, cell survival, and death (apoptosis) (77).

AVP is released from its storage site in the posterior pituitary (Fig. 2) by highly sensitive osmotic stimuli, specifically by a <1–2% increase in plasma osmolarity, as originally detailed in the 1940s through classic research by Prof. E. B. Verney (125). AVP release may also occur due to nonosmotic stimuli, e.g., orthostatic hypotension (134) or emetic reflexes as manifested in nausea and vomiting (99, 135).

The signal transduction pathways of AVP are mediated by three AVP receptors, referred to as V1a, V1b (or V3R owing to initial descriptions of its expression on corticotrophs of the anterior pituitary), and V2R (50). The difference between V2R on one side and V1a, V1b, as well as oxytocin (OT) receptors on the other side is reflected in the sequence similarities, which are higher among V1a, V1b, and OT receptors than between any of these and V2Rs. In mammals, OT and vasopressin nonapeptides share a high degree of similarity, differing from each other at only two amino acid positions. It is likely that the OT and AVP genes, and their nonmammalian vertebrate lineages, arose due to a gene duplication event before vertebrate divergence. Consistent with similarity of the peptides, the OT receptor and the three AVP receptor subtypes share a high degree (35–50%) of sequence homology (26, 109). V1a receptors are expressed in vascular smooth muscle cells (92), hepatocytes (58), the brain (5), and other tissues and mediate signaling through Ca2+ and phosphatidylinositol transducer.

Address for reprint requests and other correspondence: K. V. Juul, Medical Science Urology, Ferring Pharmaceuticals, 11 Kay Fiskers Plads, Copenhagen S DK-2300, Denmark (e-mail: kvj@ferring.com).
pathways. In situ hybridization studies have demonstrated that the bulk of V1a receptor expression in the kidney is associated with the vasculature, particularly the vas recta (92). However, it is clear that there is V1a expression in the cortical collecting duct (33), probably in intercalated cells (49). V1b receptors are prominent in the anterior pituitary (2) and are involved in adrenocorticotropic hormone secretion and also in cognitive functions in the brain (e.g., learning and memory, neuroendocrine reactivity, social behaviors, circadian rhythmicity, thermoregulation, and autonomic function) (14).

In contrast, V2R, which, uniquely among AVP receptor subtypes, signals through cAMP, has the key function of controlling fluid homeostasis. Its principal action is mediated through the AVP/V2R/aquaporin (AQP)2 system in medullary and cortical collecting ducts and other renal structures facilitating the urine concentrating mechanism and water, salt, and urea transport by modifying the trafficking of AQP2, epithelial Na\(^+\) channels (ENaC), and urea transporters (3, 4, 78). There are also V2Rs in the renal thick ascending limb of Henle, where they regulate NaCl transport and the countercurrent multiplication effects (42, 44, 80, 103).

The relative abundance of one of these three AVP receptor subtypes determines the actions of AVP on a specific organ. Due to the immediate antidiuresis (increased urinary osmolality, inversely proportional to urine production) observed in response to the administration of specific V2R agonists, such as 1-desamino-8-D-AVP (desmopressin), with no additional clear clinical signals from other organs, it was previously thought that V2 AVP receptors were exclusively present in the kidney: in patients with X-linked diabetes insipidus who possess a mutation in the V2R gene (AVPR2), desmopressin failed to cause an increase in circulating vWF (13). However, in patients with chronic renal failure, V2R agonist stimulation in high doses did raise plasma vWF even after bilateral nephrectomy (73).

These clinical observations strongly supported the existence of extrarenal V2Rs, and later studies positively confirmed V2R effects in the endothelium (55, 75): the endothelial V2R, activated by desmopressin in high doses and by equivalent blood concentrations of endogenous AVP (56), releases vWF and factor VIII from Weibel-Palade bodies (Fig. 2). The source of vWF and factor VIII released after V2R agonist stimulation in high doses remains to be established, but evidence suggests that they are synthesized and stored within the same cell (41).

Tight fluid homeostasis is critical not only at the whole body level but in most organs, tissues, and physiological systems. Thus, it is not unexpected that the AVP/V2R complex also turns out to play a significant role in local fluid homeostasis, for instance, by controlling the elimination/reabsorption of fluid in the inner ear through stimulation of V2Rs to mobilize AQP water channels, likely in much the same way as occurs in the kidney (Fig. 2) (114).

The role of V2R under malignant conditions is less known. Many tumors produce and secrete AVP, which has a mitogenic action on cellular growth (35, 105, 130). The presence of all AVP receptor subtypes, but particularly V2R, has been reported in transformed epithelial cells (86, 89). V2R is present in a wide panel of human tumor cell lines, including human breast cancer cells (47), cervical cancer (85), lung cancer (95), and in corticotrophinomas (126).

In addition to V2Rs being abundantly present in the kidneys, vascular endothelium, and inner ear endo-organ tissues, a recent systematic exploration of the human proteome using antibody-based proteomics (8, 121) showed staining for the
AVPR2 gene product in 29 of 75 cell types. This staining was most pronounced in the cytoplasm and membranes of the parathyroid. More moderate cytoplasmic staining combined with extracellular positivity was seen in the following cell types: the exocrine pancreas, nonkeratinized squamous epithelia, smooth muscle, salivary glands, breast, and Leydig cells. The physiological role of V2Rs in these tissues is yet to be determined. Furthermore, other groups have failed to replicate these findings (96), possibly raising queries about the specificity of the antibodies used in these experiments. Further investigation of expression and protein levels in these tissues using other techniques is necessary before firm conclusions can be drawn.

**V2R Compared With Other Receptors in the AVP/OT Family**

V2R shares the typical structure of G protein-coupled receptors (GPCRs): as shown in Fig. 1, three intracellular loops and three extracellular loops connect seven transmembrane helices. There is an extracellular NH2 terminus, which is involved in ligand binding, and the signaling activity of the GPCR is enabled by the intracellular COOH terminus and the third intracellular loop (100, 101, 104, 117). The receptor has a complex three-dimensional structure that is generated in the endoplasmic reticulum (ER) and Golgi apparatus by posttranslational sugar moieties at N22, COOH-terminal serines, and/or threonines (100) as well as two conserved cysteine residues (putative disulfide bonds) between C112 in the first extracellular loop and C192 in the second extracellular loop (104). In addition, V2R is palmitoylated at cysteines C341 and C342, stabilizing the protein in the membrane (101). When the receptor is correctly folded, it will transit via the intracellular membrane systems to the cell surface (117).

The processes of synthesis and breakdown of V2R are maintained in equilibrium at steady state. In the ER and the ER-Golgi intermediate compartment are localized, newly synthesized, immature V2Rs. Mature receptors are located in the Golgi network and at the plasma membrane. To maintain stable levels of V2Rs, redundant receptors from the plasma membrane are internalized and degraded in the lysosomes (15, 31, 34).

As mentioned above, all four neurohypophysial receptor subtypes share a high degree (35–50%) of sequence identity (26, 109). However the V1a, V1b, and OT receptors are selectively coupled to G proteins of the Gq/11 family (68), whereas only V2R preferentially signals via the Gs and cAMP pathway. Coupling of V2Rs to adenylyl cyclase takes place after AVP binding and increases catalysis of ATP into cAMP, activating protein kinase substrates (e.g., PKA). An increasing understanding of the modalities involved in V2R signaling indicates that V2R also increases intracellular Ca2+ (20, 33,
Review

Functions of Renal and Extrarenal V2Rs

Recent research has focused on basic cellular mitogenic and antiapoptotic properties of AVP in the kidney via V2R activation. AVP can inhibit apoptosis through V2Rs and downstream cAMP-mediated pathways in the mammalian kidney (77). In rats with elevated AVP levels, it has been found that kidney cell proliferation is unaffected by selective V1a or V1b receptor antagonists. However, upon administration of a selective V2 antagonist, kidney cell proliferation is inhibited, whereas it is mimicked when a V2 agonist is administered (1). The molecular mechanisms triggering kidney cell proliferation via V2R activation remain to be established.

Deficiencies of any part of the renal AVP-V2R-AQP2 axis, as described above, have profound clinical and pharmacological implications, being responsible for the development of central (11) or nephrogenic diabetes insipidus (NDI) (10).

V2Rs in polycystic kidney disease. Polycystic kidney disease is a ciliopathy characterized by renal cysts and altered fluid and electrolyte transport in the collecting duct. V2R mRNA levels are elevated compared with healthy subjects, and the binding of AVP to V2Rs in the collecting ducts increases cAMP and accelerates cyst growth by stimulating cell proliferation and Cl−-dependent fluid secretion (93). It has recently been shown that clia(−) cells grown on culture dishes formed domes after apical AVP treatment, leading to the hypothesis that in these patients, V2Rs may have been mislocalized to the apical membrane (102). The nonpeptide V2R antagonist tolvaptan, indicated for the treatment of hyponatremia with heart failure, has in recent years been studied as a therapy to delay the progression of autosomal dominant polycystic kidney disease in both short-term (48) and long-term studies (45, 119).

V2Rs in the inner ear. The expression of V2Rs in the inner ear has been debated in the literature. RT-PCR studies revealed V2R mRNA in the cochlea and endolymphatic sac (37), but de Minteguiaga et al. (27) reported that it was only minimally expressed, if at all, in microdissected rat stria vascularis. In situ hybridization experiments demonstrated that V2R was expressed throughout the neonatal rat cochlea, whereas none was detected in the adult cochlea (119). On the other hand, chronic application of AVP reduced V2R mRNA expression in the adult rat cochlea (113). This phenomenon can, in many ways, be compared with the so-called “vasopressin escape” that, under certain conditions, allows free water excretion despite inappropriate secretion of vasopressin (124).

V2R has been detected in human (65, 111) and rat (59) inner ear endo-organ tissues. In the luminal epithelium of the human endolymphatic sac, V2Rs are distributed together with AQP2 (65). Unlike the effect in rat kidneys, the physiological interactions between AVP and V2R in the endolymphatic sac reduce membranous fluid turnover. Also unlike the mode of action in the human kidney, AQP2 is translocated from the luminal side to the basolateral side of the endolymphatic sac (Fig. 2) (112).

A recent study (115) went even further and found that three types of AQP, AQP1, AQP2, and AQP3, as well as V2R contribute to fluid transport in the inner ear.

Judging by the evidence cited above, it now seems beyond doubt that V2R does exist and contributes to the regulation of membranous fluid turnover in the inner ear, as shown in Fig. 2. The clinical implications of this may be that V2R-mediated activation of AQP2 is involved in the pathogenesis of Ménière’s disease. It has been suggested that elevated plasma
concentrations of endogenous vasopressin may stimulate the V2R-AQP2 system in the inner ear, causing endosomal internalization of apical membrane AQP2 and overflow of endoplasmic fluid, leading to endolymphatic hydrops (69).

**V2Rs in the endothelium.** Extrarenal V2Rs, primarily located in endothelial cells (Fig. 2), have been shown to increase the circulating levels of coagulation factor VIII, vWF, and tissue plasminogen activator (56, 75).

Clinically, this hematological action of desmopressin has been used in the treatment of hemophilia A, a condition characterized by a reduction in factor VIII complex in human blood (108). Factor VIII serves as a cofactor for factor IX in the activation of factor X in the coagulation cascade and is essential for plasmatic coagulation. Lack of this factor results in the formation of fibrin-deficient clots, which makes coagulation much more prolonged and the clot more unstable. The normal physiological importance of this property is not known since its absence does not appear to be detrimental in patients with NDI. As demonstrated by Bichet et al. (12), patients with NDI bearing mutations of the AVPR2 receptor exhibit a normal capacity to release coagulation factors after epinephrine infusions.

**V2Rs in the brain.** AVP is an important neuromodulator/neurotransmitter regulating an array of central nervous system (CNS)-mediated functions (e.g., learning and memory, neuroendocrine reactivity, social behaviors, circadian rhythmicity, thermoregulation, and autonomic function). However, most of these central actions of AVP are mediated by the so-called pituitary AVP receptor, referred to as V1b or V3R. In general, V2R is much less abundant in the brain than V1a and V1b, and very little is known regarding the role of V2R in the brain (98).

Little data exist on the possible function of V2R in the CNS. RT-PCR studies have shown that V2Rs are expressed in the hippocampus of adult rats (46) and in epithelial cells and vascular endothelial cells of the choroid plexus (54). Kato et al. (54) demonstrated using RT-PCR that V2R mRNA was present in the cerebellum of both newborn and adult rats and in the cerebrum of newborn but not adult rats. In situ hybridization revealed dense localization of V2R mRNA in the choroid plexus and neurons of the hippocampus and granular layer of the cerebellum. Expression in the hippocampus of the newborn rat decreased with age to undetectable levels at >2 wk old, but expression in the cerebellum was stable with age. The authors postulated that V2Rs may play a role in the development of the CNS. The consensus seems to be that vasopressin-induced brain edema is mediated primarily by the V1a receptor (67). Nonetheless, Kozniewska et al. (63) found that intracarotid administration of desmopressin in seven rats increased cerebral blood flow by 43% and cerebral O2 consumption by 29% and decreased cerebrovascular resistance by 29% of the control value, suggesting that the vasopressin-induced cerebral blood flow increase is, at least partly, mediated by V2 or V2-like receptors.

In another study (32), intraventricular administration of desmopressin in rats increased the brain water content from 78.2% to 79.2–79.5%. While the water content of the hemispheres increased by 1.3%, that of the olfactory bulbs did so by 1.7% (32). In some recent Russian studies, patients with affective disorders were treated with an intranasal application of desmopressin. In aphasic patients, desmopressin had a positive influence primarily on simple forms of speech and secondarily on composite forms. It was also found to be effective in correcting both apatoadynamic and anxious depression when used as a selective agonist of vasopressin V2R in the treatment of post-stroke depression (7, 120).

Desmopressin also stimulated adrenocorticotropic hormone release in patients with Cushing’s disease, indicating a V2R-sensitive response in these patients. However, there was no such response in most normal, obese, or depressed subjects (24, 70, 71).

The role of desmopressin as a nootropic and in particular on memory function remains disputed. In healthy young males hearing six narrative passages of prose presented at differing rates, treatment with 60 µg desmopressin intranasally facilitated recall for both high and medium importance idea units, indicating some kind of V2R-mediated effect on human memory (6). An increase in short-term memory after desmopressin treatment was seen in children with nocturnal enuresis, indicating the CNS as a possible target involved in the pathogenesis of nocturnal enuresis (81). In a study of four patients with major affective illness, three patients showed highly significant and consistent improvements in memory function upon treatment with desmopressin (40). In addition, two patients showed some amelioration of depressive symptoms. However, a larger study (51) in normal subjects and patients with memory disorders using desmopressin found no beneficial effects on memory during treatment. Furthermore, there exist contradictory reports as to whether desmopressin can pass through the blood-brain barrier (36, 51, 107, 110). Further research is therefore needed in this area.

**V2Rs in other tissues.** Although not found in the lung until recently, it is now known that the V2R is functionally expressed in lung epithelial cells (56). A study (16) in mice found that AVP decreases the lipopolysaccharide-induced pulmonary inflammatory response, as measured by IL-6 levels, through NF-kB signaling by V2R stimulation. In addition to V2R expression in cultured lung endothelial cells, Kaufmann et al. (55) also reported a wide V2R distribution notably in the heart, lung, and skeletal muscle, indicating that desmopressin can activate endothelial nitric oxide synthase in human endothelial cells. This mechanism most likely accounts for desmopressin-induced vasodilation (55).

There have been a few reports of the presence of V2R in human lymphocytes (128, 132). One study demonstrated that desmopressin bound reversibly to untransformed lymphocytes. The binding was inhibited in the presence of pitressin or AVP, leading the authors to conclude that there are surface receptors for vasopressins on human peripheral blood lymphocytes that also react with desmopressin (128). Yamaguchi et al. (132) also detected V2R expression in human lymphocytes using RT-PCR. They reported increased levels of fibrinolytic activity in samples after incubating human peripheral blood lymphocytes obtained from desmopressin-infused volunteers, possibly due to urokinase-type plasminogen activator released from lymphocytes.

The presence of an AQP2-cAMP-V2R mechanism in epithelial cells of the colon has been suggested. Cristia et al. (25) demonstrated that specific V2R antagonism inhibits the effect of vasopressin in the rat distal colon.
**V2Rs in tumor cells.** AVP has been shown to induce a dose-dependent (from 1 nM) and time-persistent increase of tumor cell proliferation. V2 receptors are present in human breast cancer (47), cervical cancer (85), and lung cancer (95) cells and in corticotrophinomas, with V2Rs varying greatly, being lower in macroadenomas than in microadenomas (126). An abnormal truncated V2R was also detected in MCF-7 cells, although it appeared to be nonfunctional (87–89).

Interestingly, desmopressin has mild cytostatic properties against human breast carcinoma cell cultures expressing V2Rs (57), likely due to V2R signaling, which activates adenylate cyclase and elevates cAMP (116). Hydrophobicity at the cyclic part of desmopressin seems to improve its antiproliferative activity (72).

**AVPR2 and the Genetic Basis for Sex Differences**

The AVPR2 gene, which codes for V2R, is located on the X chromosome in the region Xq28, centromeric to the adjacent Rho GTPase-activating protein 4 gene and ~29 kb telomeric to the L1 cell adhesion molecule gene (Fig. 3 and Table 1). The gene’s three exons and two introns are contained within 2.3 kb, of which 1,113 nucleotides code for 371 amino acids.

To achieve a balanced gene expression between males (XY) and females (XX), a compensatory mechanism known as X inactivation randomly inactivates one of the female X chromosomes. X chromosome inactivation occurs early in female embryogenesis, at about the 32- to 64-cell stage (43, 129). X inactivation is irreversible, and all descendants of any given cell will have the same X chromosome inactivated. Since the process is random, it results in a normal distribution of skewing, with most females expressing maternally and paternally inherited X chromosomes with a 50:50 ratio. However, the Xq28 region is known to have a high probability of escape from inactivation; this would lead to phenotypic sex differences, e.g., in antidiuretic function and other V2R-mediated physiological functions, with females expressing higher levels of transcript than males (9, 19).

Recently, it has been shown by Liu et al. (66) that female rats express significantly more V2R mRNA and protein in kidneys than male rats and that this results physiologically in a greater sensitivity to V2R agonist administration. In humans, the concept of a sex difference in renal sensitivity to desmopressin has been further supported by several studies in adult patients with nocturia (53, 127, 131).

Mutations in the factor VIII gene at the F8C locus (Fig. 3), also located at Xq28, cause hemophilia A, which is an X-linked recessive disorder. The functional gene for the V2R, AVP2R, is localized between DXS269 and F8C (123) and is flanked by DXS52, DXS15, and G6PD (the gene for glucose-6-phosphate dehydrogenase). Expression of the disease in heterozygous
females has been ascribed to skewed X inactivation. A study
(97) showed that factor VIII activity in hemophilia A heterozy-
gous females can be directly related to the degree of skewing
and low factor VIII activity in females is due to an unfavorable
skewing profile that preferentially inactivates the normal, func-
tional copy of the gene.

Recently, Nossent et al. (90) suggested that gain-of-function
variations in the AVPR2 gene would lead to increased vWF
secretion from Weibel-Palade bodies and to increased plasma
levels of vWF and factor VIII. They confirmed that variations
in AVPR2 single-nucleotide polymorphisms (SNPs) were
associated with increased levels of vWF propeptide and in-
creased mature vWF levels (90). Interestingly, a sex difference
was seen, with associations with levels of vWF propeptide for
three SNPs in male subjects and similar associations with vWF
and factor VIII levels, whereas these associations between the
three SNPs and coagulation factor levels were not present in
female subjects. However, these findings raise some questions,
since these gain-of-function variations were not associated
with hyponatremia compared with the gain-of-function muta-
tions R137C/L and F229V (18).

On the possible role of age-related skewing of X chromo-
some inactivation, a syndrome of late onset of X-linked disor-
ders has been described (39). While in general young women
have a mosaic of cells with either the maternal or paternal X
chromosome inactivated with a 50:50 ratio, a marked deviation
from this balanced expression may occur with aging, starting at
~55 yr of age and continuing to increase until 100 yr of age
(64). This may clinically manifest as late-onset X-linked disor-
ders; however, it remains to be shown if the AVPR2 gene
located at Xq28 is subject to this late onset skewing of
inactivation. It is plausible that this mechanism affects, at least
to some degree, the AVPR2 gene, since there exists both a
“gain-of-function” mutation leading to the syndrome of inap-
propriate antidiuretic hormone secretion (with one of the clin-
cal manifestations being hyponatremia) as well as a mutation
that leads to NDI, AVPR2” and AVPR2”, respectively (76). A
recent case report (28) described a woman developing transient
NDI associated with decreased AVPR2 for the first time at the
age of 55 yr (28), lending some support to the idea that AVPR2
expression may change with age, clinically manifested as
becoming either more or less sensitive to AVP/desmopressin.
Whether this is an extremely rare or more common clinical
event needs further research. A study (118) in rats also sug-
gested that a functional impairment of renal concentrating
ability with age may be related to impaired responsiveness of
the kidney to AVP secondary to a downregulation of renal V2R
expression and AQP2 abundance.

Conclusions

The key function of the V2R is to control fluid homeostasis.
The notion that the V2R is exclusively present in the kidney,
however, has in recent years been shown to be a misconcep-
tion, and the V2R is now known to be expressed in many
extrarenal tissues, including vascular and pulmonary endothe-
lial cells, inner ear endo-organ tissues, the parathyroid, nonke-
ratinized squamous epithelia, exocrine pancreas, salivary
glands, smooth muscle, breast cells, and Leydig cells. There is
also evidence to suggest that the V2R is expressed at low levels
in the brain and may mediate CNS effects after the adminis-
tration of desmopressin, a selective V2 agonist.

While the role of V2R in increasing factor VIII levels is well
established and has led to desmopressin being indicated for
hematological indications, the relevance and function of V2Rs
in many cell types have yet to be determined. Recent evidence
indicates that AVPR2 expression may be elevated in females
compared with males, contributing to phenotypic sex differ-
ences. It is clear, therefore, that there remains much to be
discovered about the pathophysiological and therapeutic po-
tential of V2R and its stimulation.

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