

## Review

**Science Review: Vasopressin and the cardiovascular system part 1 – receptor physiology**Cheryl L Holmes<sup>1</sup>, Donald W Landry<sup>2</sup> and John T Granton<sup>3</sup><sup>1</sup>Staff intensivist, Department of Medicine, Division of Critical Care, Kelowna General Hospital, Kelowna BC, Canada<sup>2</sup>Associate Professor, Department of Medicine, Columbia University, New York, New York, USA<sup>3</sup>Assistant Professor of Medicine, Faculty of Medicine, and Program Director, Critical Care Medicine, University of Toronto, and Consultant in Pulmonary and Critical Care Medicine, Director Pulmonary Hypertension Program, University Health Network, Toronto, Ontario, CanadaCorresponding author: John T Granton, [John.Granton@uhn.on.ca](mailto:John.Granton@uhn.on.ca)

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**Abstract**

Vasopressin is emerging as a rational therapy for vasodilatory shock states. Unlike other vasoconstrictor agents, vasopressin also has vasodilatory properties. The goal of the present review is to explore the vascular actions of vasopressin. In part 1 of the review we discuss structure, signaling pathways, and tissue distributions of the classic vasopressin receptors, namely V<sub>1</sub> vascular, V<sub>2</sub> renal, V<sub>3</sub> pituitary and oxytocin receptors, and the P<sub>2</sub> class of purinoreceptors. Knowledge of the function and distribution of vasopressin receptors is key to understanding the seemingly contradictory actions of vasopressin on the vascular system. In part 2 of the review we discuss the effects of vasopressin on vascular smooth muscle and the heart, and we summarize clinical studies of vasopressin in shock states.

**Keywords** adrenergic agents, antidiuretic hormone, cardiac inotropy, hypotension, nitric oxide, oxytocin, physiology, potassium channels, receptors, septic shock, smooth muscle, vasoconstriction, vascular, vasodilation, vasopressin

**Introduction**

Arginine vasopressin (hereafter referred to as vasopressin), also known as antidiuretic hormone, is essential for survival, as attested by its teleologic persistence. Oxytocin- and vasopressin-like peptides have been isolated from four invertebrate phyla and the seven major vertebrate families, representing more than 120 species [1]. Therefore, the ancestral gene encoding the precursor protein appears to antedate the divergence of the vertebrate and invertebrate families, about 700 million years ago [2]. Virtually all vertebrate species possess an oxytocin-like and a vasopressin-like peptide, and so two evolutionary lineages can be traced. The presence of a single peptide, vasotocin ([Ile<sup>3</sup>]-vasopressin or [Arg<sup>8</sup>]-oxytocin), in the most primitive cyclostomata supports the notion that primordial gene duplication with subsequent mutations gave rise to the two lineages [2].

Vasopressin is essential for cardiovascular homeostasis. The vasopressor effect of pituitary extract, first observed in 1895, was attributed to the posterior lobe of this gland [3]. It was not until 18 years later that the antidiuretic effect of neurohypophyseal extract was demonstrated [4,5]. After isolation and synthesis of vasopressin in the 1950s, it was proven that the same hormone in the posterior pituitary possessed both antidiuretic and vasopressor effects [6,7]. The importance of vasopressin in osmotic defense is fundamental. Indeed, the antidiuretic effect of vasopressin has been exploited clinically for over half a century to treat diabetes insipidus. Only recently has vasopressin emerged as a therapy for shock states, renewing interest in the cardiovascular effects of vasopressin.

Shock states induce an increase in vasopressin levels from 20- to 200-fold [8–12]. These supraphysiologic levels cause

ACTH = adrenocorticotrophic hormone; DAG = diacylglycerol; DDAVP = 1-deamino-8-D-arginine vasopressin; GPCR = G-protein-coupled receptor; GRK = G protein-coupled receptor kinase; OTR = oxytocin receptor; PKC = protein kinase C; P<sub>2</sub>R = P<sub>2</sub> purinergic receptors; V<sub>1</sub>R = V<sub>1</sub> vascular receptor; V<sub>2</sub>R = V<sub>2</sub> renal receptor; V<sub>3</sub>R = V<sub>3</sub> pituitary receptor.

profound vasoconstriction and help to maintain end-organ perfusion [13,14]. Prolonged shock is associated with a fall in vasopressin levels [15–18], probably due to depletion of vasopressin stores [19,20], and may contribute to the refractory hypotension that is seen in advanced shock states. Paradoxically, vasopressin has also been demonstrated to cause vasodilation in some vascular beds [21–28], distinguishing this hormone from other vasoconstrictor agents.

The present review explores the vascular actions of vasopressin. First, a discussion of the signaling pathways and distribution of vasopressin receptors is necessary to gain an understanding of the seemingly paradoxical vasodilatory and vasoconstrictor actions of vasopressin. We discuss the structural elements responsible for the functional diversity found within the vasopressin receptor family. In part 2 of our review, we explore the mechanisms of vasoconstriction and vasodilation of the vascular smooth muscle, with an emphasis on vasopressin interaction in these pathways. We review the seemingly contradictory studies and some new information regarding the actions of vasopressin on the heart. Finally, we summarize the clinical trials of vasopressin in vasodilatory shock states and comment on areas for future research.

## Overview of vasopressin

### Structure of the hormone and the genes

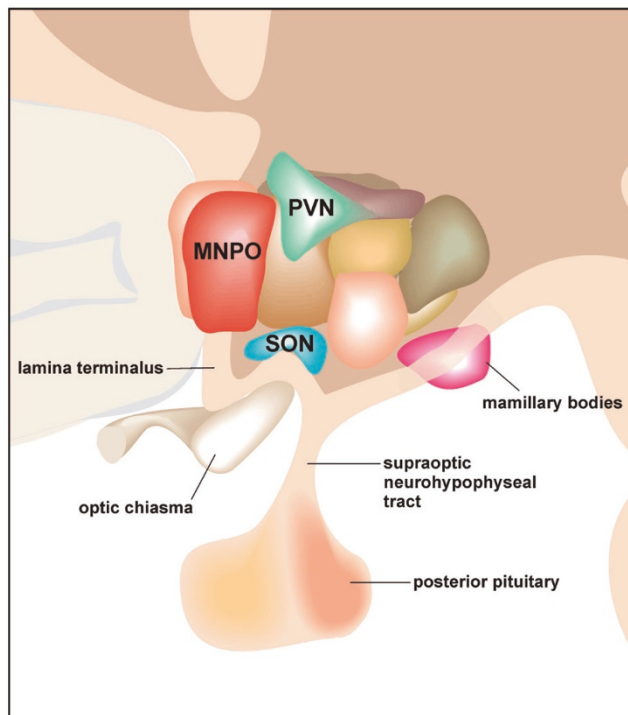
Vasopressin is a nonapeptide with a disulfide bridge between two cysteine amino acids [29] and is synthesized by the magnocellular neurons of the hypothalamus [30] (Fig. 1). Although oxytocin differs from vasopressin by only one amino acid (80% homology), they have clearly divergent physiologic activity. Vasopressin is involved in osmotic and cardiovascular homeostasis, whereas oxytocin is important in parturition, lactation, and sexual behavior.

Oxytocin and vasopressin are encoded by separate genes but they lie on the same chromosome, at 20p [31], separated by a segment of DNA only 12 kilobases long [32]. The similarities in structure as well as the close apposition are suggestive of recent gene duplication [33]. Despite ample documentation of cell-specific expression and physiologic regulation of the vasopressin gene, there is striking lack of progress in identifying transcription factors that act on the vasopressin promoter [34].

### Structure of the receptor

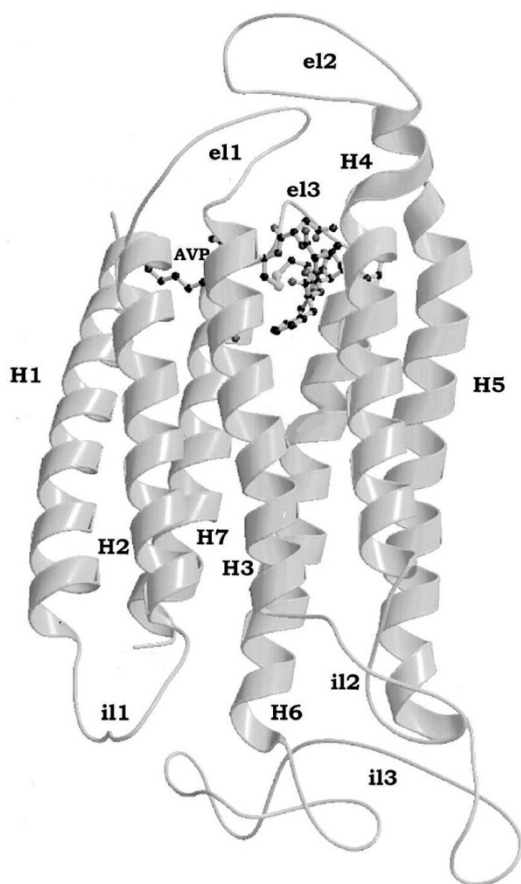
The actions of vasopressin are mediated by stimulation of tissue-specific G-protein-coupled receptors (GPCRs), which are currently classified into V<sub>1</sub> vascular (V<sub>1</sub>R), V<sub>2</sub> renal (V<sub>2</sub>R), V<sub>3</sub> pituitary (V<sub>3</sub>R) and oxytocin (OTR) subtypes [35] and P<sub>2</sub> purinergic receptors (P<sub>2</sub>R) [36]. The GPCRs are comprised of seven hydrophobic transmembrane  $\alpha$ -helices joined by alternating intracellular and extracellular loops, an extracellular amino-terminal domain, and a cytoplasmic carboxyl-terminal domain (Fig. 2) [29]. The actions of vasopressin are signaled through pathways that are similar to extracellular agents such

Figure 1



Hypothalamic nuclei involved in vasopressin control. The hypothalamus surrounds the third ventricle ventral to the hypothalamic sulci. The main hypothalamic nuclei subserving vasopressin control are the median preoptic nucleus (MNPO), the paraventricular nuclei (PVN), and the supraoptic nuclei (SON), which project to the posterior pituitary along the supraoptic–hypophyseal tract. Afferent nerve impulses from stretch receptors in the left atrium (inhibitory), aortic arch, and carotid sinuses (excitatory) travel via the vagus nerve, and neural pathways project to the PVN and the SON. These nuclei also receive osmotic input from the lamina terminalis, which is excluded from the blood–brain barrier and is thus affected by systemic osmolality. Vasopressin is synthesized in the cell bodies of the magnocellular neurons located in the PVN and SON. The magnocellular neurons of the SON are directly depolarized by hypertonic conditions (hence releasing more vasopressin) and hyperpolarized by hypotonic conditions (hence releasing less vasopressin). Finally, vasopressin migrates (in its prohormone state) along the supraoptic–hypophyseal tract to the posterior pituitary, where it is released into the circulation. Used by permission from *Chest* [95].

as hormones (glucagon, luteinizing hormone, and epinephrine [adrenaline]), neurotransmitters (acetylcholine, dopamine, and serotonin) and chemokines (interleukin-8). Local mediators signal to the four main G protein families to regulate cellular machinery such as metabolic enzymes, ion channels, and transcriptional regulators [37]. The extracellular signals are routed to specific G proteins through distinct types of receptors. For example, epinephrine's signal is transmitted through the  $\beta$ -adrenergic receptor coupled to G<sub>i</sub>, and the  $\alpha_1$ -adrenergic receptor coupled to G<sub>q</sub> and G<sub>11</sub>. Many important hormones, including epinephrine, acetylcholine, dopamine, and serotonin, interact with the G<sub>i</sub> pathway, which is characterized by inhibition of adenylyl cyclase [37].

**Figure 2**

Vasopressin docking and transmembrane topology of the human  $V_1$  vasopressin receptor ( $V_1R$ ). A model of arginine vasopressin (AVP), as bound to the human  $V_1R$ , is depicted. Vasopressin is shown in ball-and-stick representation and the receptor is shown in ribbons. The intracellular loops of the receptor are labeled il1, il2, and il3, and the extracellular loops are labeled e1, e2, and e3. The transmembrane segments are labeled H1–H7. Reprinted from Thibonnier M, Coles P, Thibonnier A, Shoham M: **Molecular pharmacology and modeling of vasopressin receptors**. *Prog Brain Res* 2002, **139**:179-196. © 2002, with permission from Elsevier [96].

Agonist stimulation of vasopressin receptors leads to receptor subtype-specific interactions with G-protein-coupled receptor kinases (GRKs) and protein kinase C (PKC) through specific motifs that are present in the carboxyl termini of the receptors [38]. Guanine nucleotide-binding proteins (G-proteins) are signal transducers, attached to the cell surface membrane, that connect receptors to effectors and thus to intracellular signaling pathways [39]. Functional characterization of the G-proteins, including  $G_s$ ,  $G_{i/o}$ ,  $G_{q/11}$ , and  $G_{12/13}$  [37], indicates that a single receptor can activate multiple second messenger pathways through interaction with one or more G-proteins [40–42].

Vasopressin's signal is transmitted through both  $G_s$  and  $G_{q/11}$  subtypes [37]. The  $G_s$  pathway is characterized by inhibition of adenylyl cyclase, leading to increased levels of cAMP that in turn connects to multiple cellular machines, including ion channels, transcription factors, and metabolic enzymes. Both  $\beta$ -adrenergic receptors and vasopressin receptors regulate  $G_s$  protein signaling. The  $G_{q/11}$  pathway is the classical pathway that is activated by calcium-mobilizing hormones and stimulates phospholipase- $\beta$  to produce the intracellular messengers inositol trisphosphate and diacylglycerol (DAG) [37]. Inositol trisphosphate triggers the release of calcium from intracellular stores and DAG recruits PKC to the membrane and activates it. The  $\alpha$ -subunit of  $G_q$  also activates the transcription factor nuclear factor- $\kappa B$  [43].

### The $V_1$ receptor

The  $V_1R$  gene is located on chromosome 12 and maps to region 12q14-15 [44]. Functionally, the  $V_1R$  activates G-proteins of the  $G_{q/11}$  family. The  $\alpha$ -subunits regulate the activity of the  $\beta$ -isoforms of phospholipase C [29]. A variety of signaling pathways is associated with the  $V_1R$ , and these pathways include activation of calcium influx, phospholipase  $A_2$ , phospholipase C, and phospholipase D [45].

$V_1R$ s are found in high density on vascular smooth muscle and cause vasoconstriction by an increase in intracellular calcium via the phosphatidyl-inositol-bisphosphate cascade. Cardiac myocytes also possess the  $V_1R$  and are discussed in part 2 of the review. Additionally,  $V_1R$ s are located in brain, testis, superior cervical ganglion, liver, blood vessels, and renal medulla [46]. The exact physiologic role of vasopressin in many of these diverse tissues remains unknown.

Platelets express the  $V_1R$ , which upon stimulation induces an increase in intracellular calcium, facilitating thrombosis [47]. However, there appears to be tremendous variability in the aggregation response of normal human platelets to vasopressin [48]. Based on kinetic studies and the effects of PKC inhibition on the aggregation response to vasopressin, significant heterogeneity in the aggregation response of normal human platelets to vasopressin has been demonstrated, which is probably related to a polymorphism of the platelet  $V_1R$  [49].

$V_1R$ s are found in the kidney, where they occur in high density on medullary interstitial cells, vasa recta, and epithelial cells of the collecting duct. Vasopressin acts on medullary vasculature through the  $V_1R$  to reduce blood flow to inner medulla without affecting blood flow to outer medulla [50].  $V_1R$ s on the luminal membrane of the collecting duct probably exerted through  $V_{1a}$  receptors located on luminal membrane limit the antidiuretic effects of vasopressin [50]. Interestingly, cyclosporine A induces upregulation of  $V_1R$  mRNA in vascular smooth muscle [51], increasing the number of  $V_1R$ s by twofold [52], which could be a key mechanism by which cyclosporine A causes both hypertension and reduced glomerular filtration. Addition-

ally, vasopressin selectively contracts efferent arterioles [53], probably through the  $V_1R$ , but not the afferent arteriole. This selectivity, which is not shared by catecholamine vasopressors, would tend to increase glomerular filtration, probably accounting for the paradoxical increase in urine output observed when this antidiuretic hormone is administered to patients in vasodilatory shock [54,55].

There is considerable interspecies variation in the  $V_1R$ . For instance, although rat and human vasopressin are identical, the human  $V_1R$  is only 80% homologous with the rat  $V_1R$  [1]. This must be kept in mind when interpreting animal studies aimed at interpreting receptor subtypes based on the use of specific receptor inhibitors.

### The $V_2$ receptor

The  $V_2R$  differs from the  $V_1R$  primarily in the number of sites susceptible to N-linked glycosylation; the  $V_1R$  has sites at both the amino-terminus and at the extracellular loop, whereas the  $V_2R$  has a single site at the extracellular amino-terminus [56]. Despite structural similarities, the  $V_2R$  differs functionally from the  $V_1R$ . Mutagenesis experiments involving the  $V_1R$  and  $V_2R$  have confirmed that the short sequence at the amino-terminus of the cytoplasmic tail confers  $V_2$  receptor- $G_s$  coupling selectivity. The efficiency of  $V_2R$ - $G_s$  coupling can be modulated by the length of the central portion of the third intracellular loop [57], whereas the second intracellular loop of the  $V_1R$  is critically involved in selective activation of  $G_{q/11}$  [58].

The well known antidiuretic effect of vasopressin occurs via activation of the  $V_2R$ . Vasopressin regulates water excretion from the kidney by increasing the osmotic water permeability of the renal collecting duct – an effect that is explained by coupling of the  $V_2R$  with the  $G_s$  signaling pathway, which activates cAMP [59]. The increased intracellular cAMP in the kidney [60,61] in turn triggers fusion of aquaporin-2-bearing vesicles with the apical plasma membrane of the collecting duct principal cells, increasing water reabsorption [62]. Vasopressin regulates water homeostasis in two ways: regulation of the fast shuttling of aquaporin 2 to the cell surface and stimulation of the synthesis of mRNA encoding aquaporin 2 [63]. Most cases of diabetes insipidus can be explained by mutations in the  $V_2R$  gene, which is located on chromosome region 10q28 [64]. For example, an Arg137→His mutation in the  $V_2R$  abolishes coupling to the  $G_s$  protein, causing a complete phenotype of nephrogenic diabetes insipidus [65].

It has been postulated that the  $V_2R$  is also expressed in endothelium because the potent  $V_2R$  agonist 1-deamino-8-D-arginine vasopressin (DDAVP) causes both release of von Willebrand factor and vasodilation [21]. Previous studies of the localization and distribution of different vasopressin receptors have been hampered by the use of nonselective radioligands such as [ $^3H$ ]arginine vasopressin, which binds to all types of  $V_1R$  and  $V_2R$ , certain OTRs, and neurophysins.

When selective  $V_1R$  and  $V_2R$  radioligands with *in vitro* autoradiography were used to study  $V_1R$  and  $V_2R$  binding sites, no binding was demonstrated on endothelium or liver, where DDAVP might influence clotting factor release, or in the brain, spinal cord, sympathetic ganglia, heart or vascular smooth muscle – regions where DDAVP might cause vasodilation [46]. Specific binding was only identified in the kidney, which is consistent with the known distribution of antidiuretic  $V_2Rs$  on renal collecting tubules.

### The $V_3$ receptor

The human  $V_3R$  (previously known as  $V_{1b}R$ ) is a G-protein-coupled pituitary receptor that, because of its scarcity, was only recently characterized. The  $V_3R$  gene maps to chromosome region 1q32 [66]. The 424-amino-acid sequence of the  $V_3R$  has homologies of 45%, 39%, and 45% with the  $V_1R$ ,  $V_2R$ , and OTR, respectively [67]. However, the  $V_3R$  has a pharmacologic profile that distinguishes it from the human  $V_1R$  and activates several signaling pathways via different G-proteins, depending on the level of receptor expression [68]. Interestingly the  $V_3R$  is also over-expressed in adrenocorticotrophic hormone (ACTH)-hypersecreting tumors.

More than one G-protein appears to participate in signal transduction pathways linked to  $V_3Rs$ , depending on the level of receptor expression and the concentration of vasopressin [69]. For instance, vasopressin causes secretion of ACTH from the anterior pituitary cells in a dose-dependent manner through activation of PKC [70] via the  $G_{q/11}$  class [68]. Other cellular responses, including increased synthesis of DNA and cAMP, which are important in the induction and phenotype maintenance of ACTH-secreting tumors, are mediated through recruitment of several pathways, including  $G_s$ ,  $G_i$ , and  $G_{q/11}$  [68]. The  $V_3R$  has been inferred to exist in the pancreas [71] on the basis of antagonist studies; however, this conclusion may be suspect because significant homology exists between the  $V_3R$  and the  $V_1R$  [59].

### The oxytocin receptor

The OTR can be considered a 'nonselective' vasopressin receptor. The OTR has equal affinity for vasopressin and oxytocin, whereas the  $V_1R$  has a 30-fold higher affinity for vasopressin than for oxytocin [72]. OTRs are functionally coupled to  $G_{q/11}$  class binding proteins, which stimulate the activity of phospholipase C [73]. This leads to the generation of inositol trisphosphate and 1,2-DAG. Inositol trisphosphate triggers calcium release from intracellular stores, whereas DAG stimulates PKC, which phosphorylates unidentified target proteins [73]. A variety of cellular events are initiated in response to an increase in intracellular calcium. For example, the forming calcium-calmodulin complexes trigger activation of neuronal and endothelial isoforms of nitric oxide synthase. Nitric oxide in turn stimulates the soluble guanylate cyclase to produce cGMP, leading to vasodilation. In smooth muscle cells, the calcium-calmodulin system triggers the activation of myosin light chain kinase activity, which initiates smooth muscle con-

traction (e.g. in myometrial or mammary myoepithelial cells) [74]. In neurosecretory cells, rising calcium levels control cellular excitability, modulate their firing patterns, and lead to transmitter release. Further calcium-promoted processes include gene transcription and protein synthesis.

OTRs have been localized to a variety of reproductive and nonreproductive tissues [73]. Importantly, OTRs exist in high density on vascular endothelium, mediating nitric oxide dependent vasodilation [75]. Recently, the oxytocin/OTR system has been discovered in the heart. Activation of cardiac OTR stimulates the release of atrial natriuretic peptide, which is involved in natriuresis, regulation of blood pressure, and cell growth [76]. Embryonic stem cells exposed to oxytocin exhibit increased atrial natriuretic peptide mRNA and abundant mitochondria, and express sarcomeric myosin heavy chain, which is consistent with promotion of cardiomyocyte differentiation [77].

### Purinergic receptors

Recently, vasopressin was demonstrated to act on the  $P_2$  class of purinoreceptors ( $P_2$ Rs) [36].  $P_2$ Rs also belong to the seven-transmembrane-domain GPCR superfamily. ATP released from platelets and damaged cells bind endothelial  $P_2$ Rs [78]. ATP can act on either of the two subclasses of purinoreceptors, namely  $P_{2\gamma}$  and  $P_{2v}$ . In both cases, activation of phospholipase C leads to mobilization of intracellular calcium stores. This binding stimulates phospholipase  $A_2$  and nitric oxide synthase, resulting in increased synthesis and release of prostacyclin and nitric oxide, respectively, and causing vascular smooth muscle vasodilation [78].

Purinoreceptors may also have an important role in cardiac contractility. ATP released by platelets, endothelial cells, and damaged myocardium activates the  $P_2$ R, causing a large increase in cytosolic calcium and myocyte contractile amplitude [79]. ATP is also released as a cotransmitter with norepinephrine from sympathetic nerve endings and acts in a synergistic manner with  $\beta$ -adrenergic agents, increasing myocardial contractility [80]. In contrast to  $\beta$ -adrenergic agents, inotropy is not accompanied by a positive chronotropic effect. It is speculated that  $P_2$ R agonist-stimulated increase in contractility could occur without the expense of a rate-related increase in myocardial oxygen demand [79].

Recently, vasopressin was shown to exert cardiac effects through activation of  $P_2$ Rs expressed on cardiac endothelium. Intracoronary infusion of vasopressin-dextran (confines vasopressin to the intravascular space) and vasopressin at maximal concentration in isolated perfused guinea pig hearts caused coronary vasoconstriction and negative inotropy – effects that were blocked with vasopressin antagonists and  $P_2$ R antagonist [36]. Caution must be exercised in interpreting this study because activation of  $P_2$ Rs and increased levels of ATP normally increase inotropy. Furthermore, the

same experiments performed in isolated perfused rat hearts demonstrated positive inotropy – an effect that was blocked by  $P_2$ R antagonists [36]. Further study is necessary to ascertain the significance of vasopressin  $P_2$ R activation in the human heart, but the discovery that vasopressin acts on  $P_2$ Rs is intriguing.

A number of pharmacologic observations have suggested the existence of vasopressin receptor/OTR subtypes beyond the five described above [72]. These include receptors for the metabolites of vasopressin and oxytocin (VP4-9 R and OT4-9 R) [72], and a cAMP-coupled vasopressin receptor with a  $V_1$ -like pharmacologic profile termed  $V_{2b}$  [81]. A novel ‘vasotocin-like’ receptor subtype has also been proposed [82].

### Vasopressin/oxytocin receptor downregulation

Upon ligand binding, GPCRs undergo activation followed by a decrease in receptor responsiveness (desensitization). Agonist-dependent desensitization of these receptors can reduce their signaling responsiveness to maximum stimulation by up to 70–80% [83]. Receptor desensitization occurs when activated receptors become phosphorylated and bind to  $\beta$ -arrestin proteins, inhibiting further interaction with G-proteins [84,85]. Receptor responsiveness is also limited by the degradation of cAMP by phosphodiesterases.  $\beta$ -Arrestins coordinate both phosphorylation of receptors and the rate of cAMP degradation by phosphodiesterases [85].

Exposure to vasopressin leads to desensitization of the  $V_1$ R, which occurs quickly and is accompanied by sequestration of receptors inside the cell [59]. The  $V_1$ R can also be desensitized by angiotensin II [86]. Compared with  $V_1$ Rs and  $\beta_2$ -adrenergic receptors, which are known to recycle and resensitize rapidly, the  $V_2$ R recycles and resensitizes slowly [87]. Mutagenesis experiments demonstrate that the interaction of  $\beta$ -arrestin with a specific motif in the GPCR carboxyl-terminal tail dictates the rate of receptor dephosphorylation, recycling, and resensitization [87,88]. The clinical importance of vasopressin desensitization of the vasopressin receptor/OTR family in human disease states is currently unknown.

Despite the clinical importance of the vasopressin receptors and OTRs, little is known about the mechanisms by which they undergo internalization and desensitization. Agonist activation of all vasopressin receptor/OTR subtypes leads to a specific physical association of the receptors with GRKs and/or PKC, following different time courses that are specific to the receptor subtype [38]. The pattern of interaction with GRKs and PKC is also unique to each vasopressin receptor subtype and occurs at the level of their carboxyl-termini [38].

Vasopressin is known to modulate the effect of other vasoactive agents [89,90] – an interaction that may be explained by arrestin trafficking. Isoproterenol-dependent internalization

of  $\beta_2$ -adrenergic receptors is specifically blocked (>65% inhibition) by vasopressin-induced activation of  $V_2$ Rs coexpressed at similar levels [42].  $\beta_2$ -Adrenergic receptors caused no detectable effect on  $V_2$ R internalization in the same cells. There is evidence to suggest that this nonreciprocal inhibition of endocytosis is mediated by receptor-specific intracellular trafficking of  $\beta$ -arrestins [42]. Interestingly, interaction of vasopressin with arrestins and resistance of vasopressin receptors to downregulation may explain the reported ability of vasopressin to bypass desensitized myocardial adrenergic receptors in an experimental model of congestive heart failure [91]. The clinical importance of vasopressin upregulation of adrenergic receptors in critically ill humans is an important area for further study.

## Conclusion

During the past 10 years, considerable progress has been made in our understanding of vasopressin receptor structure and function. The physiologic significance of the various receptors has been elucidated by the development of specific agonists and antagonists, particularly by Dr Maurice Manning's group [92–94]. An understanding of the molecular basis of receptor function will greatly aid in the development of new molecules with high selectivity for the different subtypes of receptors, and will have potential therapeutic significance, not only for conditions as diverse as hypertension, diabetes insipidus and premature labor, but also in vasodilatory shock with organ dysfunction. In part 2 of the review, we discuss the interaction of vasopressin with its various receptors in vascular smooth muscle and the heart, and its potential utility in vasodilatory shock states.

## Competing interests

None declared.

## References

1. Hoyle CH: **Neuropeptide families and their receptors: evolutionary perspectives.** *Brain Res* 1999, **848**:1-25.
2. Acher R, Chauvet J, Chauvet MT: **Man and the chimaera. Selective versus neutral oxytocin evolution.** *Adv Exp Med Biol* 1995, **395**:615-627.
3. Oliver H, Schaefer EA: **On the physiological action of extracts of the pituitary body and certain other glandular organs.** *J Physiol (Lond)* 1895, **18**:277-279.
4. von den Velden R: **The renal effects of hypophyseal extract in humans [in German].** *Berl Klin Wochenschr* 1913, **50**:2083-2086.
5. Verney EB: **The antidiuretic hormone and the factor which determines its release.** *Proc R Soc Lond (Biol)* 1947, **135**:25-106.
6. Turner RA, Pierce JG, Du Vigneaud V: **The purification and the amino acid content of vasopressin preparation.** *J Biol Chem* 1951, **191**:21.
7. Du Vigneaud V, Gash DT, Katsoyannis PG: **A synthetic preparation possessing biological properties associated with arginine-vasopressin.** *J Am Chem Soc* 1954, **76**:4751-4752.
8. Arnauld E, Czernichow P, Fumoux F, Vincent JD: **The effects of hypotension and hypovolaemia on the liberation of vasopressin during haemorrhage in the unanaesthetized monkey (*Macaca mulatta*).** *Pflugers Arch Eur J Physiol* 1977, **371**:193-200.
9. Cowley AW Jr, Switzer SJ, Guinn MM: **Evidence and quantification of the vasopressin arterial pressure control system in the dog.** *Circ Res* 1980, **46**:58-67.
10. Wilson MF, Brackett DJ, Hinshaw LB, Tompkins P, Archer LT, Benjamin BA: **Vasopressin release during sepsis and septic shock in baboons and dogs.** *Surg Gynecol Obstet* 1981, **153**:869-872.
11. Wilson MF, Brackett DJ: **Release of vasoactive hormones and circulatory changes in shock.** *Circ Shock* 1983, **11**:225-234.
12. Wang BC, Flora-Ginter G, Leadley RJ Jr, Goetz KL: **Ventricular receptors stimulate vasopressin release during hemorrhage.** *Am J Physiol* 1988, **254**:R204-R211.
13. Schwartz J, Reid IA: **Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs.** *Endocrinology* 1981, **109**:1778-1780.
14. Abboud FM, Floras JS, Aylward PE, Guo GB, Gupta BN, Schmid PG: **Role of vasopressin in cardiovascular and blood pressure regulation.** *Blood Vessels* 1990, **27**:106-115.
15. Errington ML, Rocha e Silva M Jr: **The secretion and clearance of vasopressin during the development of irreversible haemorrhagic shock.** *J Physiol (Lond)* 1971, **217**:43P-45P.
16. Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA: **Vasopressin pressor hypersensitivity in vasodilatory septic shock.** *Crit Care Med* 1997, **25**:1279-1282.
17. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA: **Vasopressin deficiency contributes to the vasodilation of septic shock.** *Circulation* 1997, **95**:1122-1125.
18. Morales D, Madigan J, Cullinane S, Chen J, Heath M, Oz M, Oliver JA, Landry DW: **Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock.** *Circulation* 1999, **100**:226-229.
19. Landry DW, Oliver JA: **The pathogenesis of vasodilatory shock.** *N Engl J Med* 2001, **345**:588-595.
20. Sharshar T, Carlier R, Blanchard A, Feydy A, Gray F, Paillard M, Raphael JC, Gajdos P, Annane D: **Depletion of neurohypophysial content of vasopressin in septic shock.** *Crit Care Med* 2002, **30**:497-500.
21. Bichet DG, Razi M, Lonergan M, Arthus MF, Papukna V, Kortas C, Barjon JN: **Hemodynamic and coagulation responses to 1-desamino[8-D-arginine] vasopressin in patients with congenital nephrogenic diabetes insipidus.** *N Engl J Med* 1988, **318**:881-887.
22. Walker BR, Haynes J Jr, Wang HL, Voelkel NF: **Vasopressin-induced pulmonary vasodilation in rats.** *Am J Physiol* 1989, **257**:H415-H422.
23. Evora PR, Pearson PJ, Schaff HV: **Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide.** *Chest* 1993, **103**:1241-1245.
24. Suzuki Y, Satoh S, Oyama H, Takayasu M, Shibuya M: **Regional differences in the vasodilator response to vasopressin in canine cerebral arteries in vivo.** *Stroke* 1993, **24**:1049-1053; discussion 1053-1044.
25. Rudichenko VM, Beierwaltes WH: **Arginine vasopressin-induced renal vasodilation mediated by nitric oxide.** *J Vasc Res* 1995, **32**:100-105.
26. Tamaki T, Kiyomoto K, He H, Tomohiro A, Nishiyama A, Aki Y, Kimura S, Abe Y: **Vasodilation induced by vasopressin V2 receptor stimulation in afferent arterioles.** *Kidney Int* 1996, **49**:722-729.
27. Okamura T, Toda M, Ayajiki K, Toda N: **Receptor subtypes involved in relaxation and contraction by arginine vasopressin in canine isolated short posterior ciliary arteries.** *J Vasc Res* 1997, **34**:464-472.
28. Okamura T, Ayajiki K, Fujioka H, Toda N: **Mechanisms underlying arginine vasopressin-induced relaxation in monkey isolated coronary arteries.** *J Hypertens* 1999, **17**:673-678.
29. Barberis C, Mouillac B, Durroux T: **Structural bases of vasopressin/oxytocin receptor function.** *J Endocrinol* 1998, **156**:223-229.
30. Swaab DF, Nijveldt F, Pool CW: **Distribution of oxytocin and vasopressin in the rat supraoptic and paraventricular nucleus.** *J Endocrinol* 1975, **67**:461-462.
31. Riddell DC, Mallonee R, Phillips JA, Parks JS, Sexton LA, Hamerton JL: **Chromosomal assignment of human sequences encoding arginine vasopressin-neurophysin II and growth hormone releasing factor.** *Somat Cell Mol Genet* 1985, **11**:189-195.

32. Summar ML, Phillips JA III, Battey J, Castiglione CM, Kidd KK, Maness KJ, Weiffenbach B, Gravius TC: **Linkage relationships of human arginine vasopressin-neurophysin-II and oxytocin-neurophysin-I to prodynorphin and other loci on chromosome 20.** *Mol Endocrinol* 1990, **4**:947-950.
33. Ruppert S, Scherer G, Schutz G: **Recent gene conversion involving bovine vasopressin and oxytocin precursor genes suggested by nucleotide sequence.** *Nature* 1984, **308**:554-557.
34. Burbach J: **Regulation of gene promoters of hypothalamic peptides.** *Front Neuroendocrinol* 2002, **23**:342-369.
35. Thibonnier M, Conarty DM, Preston JA, Wilkins PL, Berti-Mattera LN, Mattera R: **Molecular pharmacology of human vasopressin receptors.** *Adv Exp Med Biol* 1998, **449**:251-276.
36. Zenteno-Savin T, Sada-Ovalle I, Ceballos G, Rubio R: **Effects of arginine vasopressin in the heart are mediated by specific intravascular endothelial receptors.** *Eur J Pharmacol* 2000, **410**:15-23.
37. Neves SR, Ram PT, Iyengar R: **G protein pathways.** *Science* 2002, **296**:1636-1639.
38. Berrada K, Plesnicher CL, Luo X, Thibonnier M: **Dynamic interaction of human vasopressin/oxytocin receptor subtypes with g protein-coupled receptor kinases and protein kinase c after agonist stimulation.** *J Biol Chem* 2000, **275**:27229-27237.
39. Ross EM, Gilman AG: **Biochemical properties of hormone-sensitive adenylate cyclase.** *Annu Rev Biochem* 1980, **49**:533-564.
40. Birnbaumer M: **Mutations and diseases of G protein coupled receptors.** *J Recept Signal Transduct Res* 1995, **15**:131-160.
41. Zhu X, Gilbert S, Birnbaumer M, Birnbaumer L: **Dual signaling potential is common among Gs-coupled receptors and dependent on receptor density.** *Mol Pharmacol* 1994, **46**:460-469.
42. Klein U, Muller C, Chu P, Birnbaumer M, von Zastrow M: **Heterologous inhibition of G protein-coupled receptor endocytosis mediated by receptor-specific trafficking of beta-arrestins.** *J Biol Chem* 2001, **276**:17442-17447.
43. Shi CS, Kehrl JH: **PYK2 links G(q)alpha and G(13)alpha signaling to NF-kappa B activation.** *J Biol Chem* 2001, **276**:31845-31850.
44. Thibonnier M, Graves MK, Wagner MS, Auzan C, Clauser E, Willard HF: **Structure, sequence, expression, and chromosomal localization of the human V1a vasopressin receptor gene.** *Genomics* 1996, **31**:327-334.
45. Briley EM, Lolait SJ, Axelrod J, Felder CC: **The cloned vasopressin V1a receptor stimulates phospholipase A2, phospholipase C, and phospholipase D through activation of receptor-operated calcium channels.** *Neuropeptides* 1994, **27**:63-74.
46. Phillips PA, Abrahams JM, Kelly JM, Mooser V, Trinder D, Johnston CI: **Localization of vasopressin binding sites in rat tissues using specific V1 and V2 selective ligands.** *Endocrinology* 1990, **126**:1478-1484.
47. Filep J, Rosenkranz B: **Mechanism of vasopressin-induced platelet aggregation.** *Thromb Res* 1987, **45**:7-15.
48. Vittet D, Launay JM, Chevillard C: **Homologous regulation of human platelet vasopressin receptors does not occur in vivo.** *Am J Physiol* 1989, **257**:R1400-R1405.
49. Lachant NA, Smith MR, Xie ZJ, Romani WR: **Heterogeneity of the aggregation response of human platelets to arginine vasopressin.** *Am J Hematol* 1995, **49**:56-66.
50. Bankir L: **Antidiuretic action of vasopressin: quantitative aspects and interaction between V1a and V2 receptor-mediated effects.** *Cardiovasc Res* 2001, **51**:372-390.
51. Cottet-Maire F, Avdonin PV, Roulet E, Buetler TM, Mermod N, Ruegg UT: **Upregulation of vasopressin V1A receptor mRNA and protein in vascular smooth muscle cells following cyclosporin A treatment.** *Br J Pharmacol* 2001, **132**:909-917.
52. Lo Russo A, Passaquin AC, Ruegg UT: **Mechanism of enhanced vasoconstrictor hormone action in vascular smooth muscle cells by cyclosporin A.** *Br J Pharmacol* 1997, **121**:248-252.
53. Edwards RM, Trizna W, Kinter LB: **Renal microvascular effects of vasopressin and vasopressin antagonists.** *Am J Physiol* 1989, **256**:F274-F278.
54. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA: **The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series.** *Intensive Care Med* 2001, **27**:1416-1421.
55. Patel B, Chittock D, Walley K: **Vasopressin infusion in SIRS and septic shock: a randomized controlled trial.** *Am J Respir Crit Care Med* 1999, **159**:A608.
56. Innamorati G, Sadeghi H, Birnbaumer M: **A fully active nonglycosylated V2 vasopressin receptor.** *Mol Pharmacol* 1996, **50**:467-473.
57. Erlenbach I, Wess J: **Molecular basis of V2 vasopressin receptor/Gs coupling selectivity.** *J Biol Chem* 1998, **273**:26549-26558.
58. Liu J, Wess J: **Different single receptor domains determine the distinct G protein coupling profiles of members of the vasopressin receptor family.** *J Biol Chem* 1996, **271**:8772-8778.
59. Birnbaumer M: **Vasopressin receptors.** *Trends Endocrinol Metab* 2000, **11**:406-410.
60. Orloff J, Handler J: **The role of adenosine 3',5'-phosphate in the action of antidiuretic hormone.** *Am J Med* 1967, **42**:757-768.
61. Dousa TP, Walter R, Schwartz IL, Sands H, Hechter O: **Role of cyclic AMP in the action of neurohypophyseal hormones on kidney.** *Adv Cyclic Nucleotide Res* 1972, **1**:121-135.
62. Harris HW Jr, Zeidel ML, Jo I, Hammond TG: **Characterization of purified endosomes containing the antidiuretic hormone-sensitive water channel from rat renal papilla.** *J Biol Chem* 1994, **269**:11993-12000.
63. Knepper MA, Inoue T: **Regulation of aquaporin-2 water channel trafficking by vasopressin.** *Curr Opin Cell Biol* 1997, **9**:560-564.
64. Kambouris M, Dlouhy SR, Trofatter JA, Conneally PM, Hodes ME: **Localization of the gene for X-linked nephrogenic diabetes insipidus to Xq28.** *Am J Med Genet* 1988, **29**:239-246.
65. Rosenthal W, Antaramian A, Gilbert S, Birnbaumer M: **Nephrogenic diabetes insipidus. A V2 vasopressin receptor unable to stimulate adenylate cyclase.** *J Biol Chem* 1993, **268**:13030-13033.
66. Rousseau-Merck MF, Rene P, Derre J, Bienvenu T, Berger R, de Keyser Y: **Chromosomal localization of the human V3 pituitary vasopressin receptor gene (AVPR3) to 1q32.** *Genomics* 1995, **30**:405-406.
67. Sugimoto T, Saito M, Mochizuki S, Watanabe Y, Hashimoto S, Kawashima H: **Molecular cloning and functional expression of a cDNA encoding the human V1b vasopressin receptor.** *J Biol Chem* 1994, **269**:27088-27092.
68. Thibonnier M, Preston JA, Dulin N, Wilkins PL, Berti-Mattera LN, Mattera R: **The human V3 pituitary vasopressin receptor: ligand binding profile and density-dependent signaling pathways.** *Endocrinology* 1997, **138**:4109-4122.
69. Thibonnier M, Berti-Mattera LN, Dulin N, Conarty DM, Mattera R: **Signal transduction pathways of the human V1-vascular, V2-renal, V3-pituitary vasopressin and oxytocin receptors.** *Prog Brain Res* 1998, **119**:147-161.
70. Liu JP, Engler D, Funder JW, Robinson PJ: **Arginine vasopressin (AVP) causes the reversible phosphorylation of the myristoylated alanine-rich C kinase substrate (MARCKS) protein in the ovine anterior pituitary: evidence that MARCKS phosphorylation is associated with adrenocorticotropin (ACTH) secretion.** *Mol Cell Endocrinol* 1994, **101**:247-256.
71. Lee B, Yang C, Chen TH, al-Azawi N, Hsu WH: **Effect of AVP and oxytocin on insulin release: involvement of V1b receptors.** *Am J Physiol* 1995, **269**:E1095-E1100.
72. Peter J, Burbach H, Adan RA, Lolait SJ, van Leeuwen FW, Mezey E, Palkovits M, Barberis C: **Molecular neurobiology and pharmacology of the vasopressin/oxytocin receptor family.** *Cell Mol Neurobiol* 1995, **15**:573-595.
73. Gimpl G, Fahrenholz F: **The oxytocin receptor system: structure, function, and regulation.** *Physiol Rev* 2001, **81**:629-683.
74. Sanborn BM, Dodge K, Monga M, Qian A, Wang W, Yue C: **Molecular mechanisms regulating the effects of oxytocin on myometrial intracellular calcium.** *Adv Exp Med Biol* 1998, **449**:277-286.
75. Thibonnier M, Conarty DM, Preston JA, Plesnicher CL, Dweik RA, Erzurum SC: **Human vascular endothelial cells express oxytocin receptors.** *Endocrinology* 1999, **140**:1301-1309.
76. Gutkowska J, Jankowski M, Lambert C, Mukaddam-Daher S, Zingg HH, McCann SM: **Oxytocin releases atrial natriuretic peptide by combining with oxytocin receptors in the heart.** *Proc Natl Acad Sci USA* 1997, **94**:11704-11709.
77. Paquin J, Danalache BA, Jankowski M, McCann SM, Gutkowska J: **Oxytocin induces differentiation of P19 embryonic stem cells to cardiomyocytes.** *Proc Natl Acad Sci USA* 2002, **99**:9550-9555.

78. Boarder MR, Weisman GA, Turner JT, Wilkinson GF: **G protein-coupled P2 purinoceptors: from molecular biology to functional responses.** *Trends Pharmacol Sci* 1995, **16**:133-139.
79. Mei Q, Liang BT: **P2 purinergic receptor activation enhances cardiac contractility in isolated rat and mouse hearts.** *Am J Physiol Heart Circ Physiol* 2001, **281**:H334-H341.
80. Zheng JS, Christie A, De Young MB, Levy MN, Scarpa A: **Synergism between cAMP and ATP in signal transduction in cardiac myocytes.** *Am J Physiol* 1992, **262**:C128-C135.
81. Diaz Brinton R, Brownson EA: **Vasopressin-induction of cyclic AMP in cultured hippocampal neurons.** *Brain Res Dev Brain Res* 1993, **71**:101-105.
82. de Wied D, Elands J, Kovacs G: **Interactive effects of neurohypophyseal neuropeptides with receptor antagonists on passive avoidance behavior: mediation by a cerebral neurohypophyseal hormone receptor?** *Proc Natl Acad Sci USA* 1991, **88**:1494-1498.
83. Freedman NJ, Lefkowitz RJ: **Desensitization of G protein-coupled receptors.** *Recent Prog Horm Res* 1996, **51**:319-351; discussion 352-313.
84. Chuang TT, Iacovelli L, Sallase M, De Blasi A: **G protein-coupled receptors: heterologous regulation of homologous desensitization and its implications.** *Trends Pharmacol Sci* 1996, **17**: 416-421.
85. Perry SJ, Baillie GS, Kohout TA, McPhee I, Magiera MM, Ang KL, Miller WE, McLean AJ, Conti M, Houslay MD, Lefkowitz RJ: **Targeting of cyclic AMP degradation to beta 2-adrenergic receptors by beta-arrestins.** *Science* 2002, **298**:834-836.
86. Zhang M, Turnbaugh D, Cofie D, Dogan S, Koshida H, Fugate R, Kem DC: **Protein kinase C modulation of cardiomyocyte angiotensin II and vasopressin receptor desensitization.** *Hypertension* 1996, **27**:269-275.
87. Oakley RH, Laporte SA, Holt JA, Barak LS, Caron MG: **Association of beta-arrestin with G protein-coupled receptors during clathrin-mediated endocytosis dictates the profile of receptor resensitization.** *J Biol Chem* 1999, **274**:32248-32257.
88. Innamorati G, Sadeghi H, Birnbaumer M: **Phosphorylation and recycling kinetics of G protein-coupled receptors.** *J Recept Signal Transduct Res* 1999, **19**:315-326.
89. Karmazyn M, Manku MS, Horrobin DF: **Changes of vascular reactivity induced by low vasopressin concentrations: interactions with cortisol and lithium and possible involvement of prostaglandins.** *Endocrinology* 1978, **102**:1230-1236.
90. Noguera I, Medina P, Segarra G, Martinez MC, Aldasoro M, Vila JM, Lluch S: **Potential by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery.** *Br J Pharmacol* 1997, **122**:431-438.
91. Laugwitz KL, Ungerer M, Schoneberg T, Weig HJ, Kronsbein K, Moretti A, Hoffmann K, Seyfarth M, Schultz G, Schomig A: **Adenoviral gene transfer of the human V2 vasopressin receptor improves contractile force of rat cardiomyocytes.** *Circulation* 1999, **99**:925-933.
92. Hibert M, Hoflack J, Trumpp-Kallmeyer S, Mouillac B, Chini B, Mahe E, Cotte N, Jard S, Manning M, Barberis C: **Functional architecture of vasopressin/oxytocin receptors.** *J Recept Signal Transduct Res* 1999, **19**:589-596.
93. Bankowski K, Manning M, Haldar J, Sawyer WH: **Design of potent antagonists of the vasopressor response to arginine-vasopressin.** *J Med Chem* 1978, **21**:850-853.
94. Manning M SWH: **Discovery, development, and some uses of vasopressin and oxytocin antagonists.** *J Lab Clin Med* 1989, **114**:617-632.
95. Holmes CL, Patel BM, Russell JA, Walley KR: **Physiology of vasopressin relevant to management of septic shock.** *Chest* 2001, **120**:989-1002.
96. Thibonnier M, Coles P, Thibonnier A, Shoham M: **Molecular pharmacology and modeling of vasopressin receptors.** *Prog Brain Res* 2002, **139**:179-196.