Review

Physiological effects of vasopressin and atrial natriuretic peptide in the collecting duct

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Abstract

Vasopressin plays a primary role in the concentration of urine to maintain body fluid homeostasis. The collecting duct as well as thick ascending limb is a major target site of vasopressin. The antidiuretic action of vasopressin is mediated by the V2 receptor in the basolateral membrane of principal cells in the collecting ducts. The binding of vasopressin to V2 receptors causes an activation of adenylate cyclase and a synthesis of cAMP. Vasopressin regulates water and ion transport through V2 receptor-mediated ion channels and transporters. In contrast, the V1a receptor mainly in the luminal membrane of distal nephron regulates basolateral V2 receptor-mediated action with regard to water and ion transport through the activation of G_{q,11} and phosphoinositide turnover. Guanylate cyclase forms three types of ANP receptors, although NPR-A and B (GC-A and B) are biologically active and related to the synthesis of cGMP. Urodilatin, synthesized by the kidney, causes natriuresis by binding to GC-A in the collecting ducts. ANP causes diuresis and natriuresis, at least in part by inhibiting the V2 receptor-mediated action of AVP in the collecting ducts. The site of interaction of ANP and AVP is post cAMP synthesis, at least in the collecting ducts. The roles of AVP and ANP under pathophysiological conditions have been reported. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The role of the kidney is to maintain body fluid homeostasis. Vasopressin (AVP) is a key hormone in maintaining plasma osmolality. An increase as small as 2% in plasma osmolality stimulates thirst and the secretion of AVP from the postpituitary gland, followed by water ingestion and water reabsorption in the kidney, respectively, after which the plasma osmolality returns to normal. The secretion of AVP is also stimulated by reductions in the effective circulating blood volume. A decrease in the effective circulating blood volume increases the plasma AVP concentrations leading to a concentration of urine to prevent further loss of body fluid. The action of AVP on the kidney is affected by various factors, including atrial natriuretic peptide (ANP), endothelin, adrenomedullin, glucagon and oxytocin. ANP is a hormone secreted from the atrium in response to cell stretch occurring primarily as a result of volume expansion. ANP provides a negative feedback against AVP in the central nervous system (CNS) and the kidney. In the CNS, the release of AVP, principally through its vasopressor action, may stimulate the release of ANP [1], with ANP in turn inhibiting the release of AVP. In the kidney, ANP inhibits the effect of AVP on water and ion transport [2], thereby modulating the control of body fluid homeostasis by AVP. Since the collecting duct is a primary site of the action of AVP and ANP, we will focus on the physiological effects of AVP and ANP in the collecting duct.

2. Localization of vasopressin and ANP receptors in the kidney

2.1. Vasopressin receptors

Three vasopressin receptors have been characterized...
thus far. V1a (vascular/hepatic) and V1b (anterior pituitary) receptors are selectively coupled to the Gq/11 family [3], mediating the activation of distinct isoforms of phospholipase Cβ, and resulting in the breakdown of phosphoinositide lipids. The V2 (kidney) receptor, on the other hand, is coupled to Gs [3], resulting in the activation of adenylate cyclase.

V2 receptor mRNA, detected by RT-PCR using microdissected tubules from the rat, was heavily expressed in the cortical, outer medullary and inner medullary collecting duct (CCD, OMC and IMCD, respectively) and was weakly but significantly expressed in the inner medullary thin limbs, and the medullary and cortical thick ascending limbs (MAL and CAL, respectively) [4]. Immunohistochemistry using a specific polyclonal antibody showed the presence of V2 receptor protein in the basolateral membrane of the thick ascending limbs and the principal cells in CCD, OMC and IMCD [5]. Early studies measuring AVP-dependent adenylate cyclase activity carried out primarily by Morel’s group support these recent findings [6].

Radioautographic studies using V1a receptor antagonists revealed the presence of V1a binding sites on the thin descending limbs of short loop nephrons and IMCD [7]. V1a receptor mRNA detected by RT-PCR using microdissected renal tubules from the rat was most abundant in CCD [8]. The expression was decreased in the deeper collecting duct and not detectable in the terminal IMCD [8], in agreement with a previous report by Ecelbarger et al. [9]. In addition, low expression was observed in the glomeruli and thick ascending limbs. We have recently developed a specific polyclonal antibody against the V1a receptor protein to clarify the localization of this protein in rat kidney [8]. The labeling was seen in the glomeruli, the luminal membrane and cytoplasm of MAL, CAL, CCD, OMC and initial IMCD. In contrast to the localization of the V2 receptor in the principal cells, the V1a receptor was present both in the principal and intercalated cells in the collecting ducts. The luminal localization of the V1a receptor may provide additional evidence for AVP action from the luminal side, which will be discussed later in this review.

V1b mRNA detected by RT-PCR is present in the medulla in rat kidney [10-12]. In the terminal IMCD, the increase in intracellular calcium concentration, [Ca2+], by AVP is not completely abolished by the simultaneous administration of antagonists for V1a, V2 and oxytocin receptors [13]. Furthermore, the V1b agonist [deamino9,10-(3-(pyridyl)Ala1,Arg8]vasopressin transiently increased [Ca2+] in this segment, suggesting the presence of V1b receptor [13]. However, RT-PCR failed to show the expression of V1b mRNA in IMCD [9], indicating no or very little expression. Thus, the presence and physiological role of the V1b receptor is not clear at present. Whether V1b mRNA and protein are expressed in other portions of the collecting ducts is not yet known.

It has been reported that oxytocin like AVP has an antidiuretic activity by direct action to the tubules. Chou et al. clearly demonstrated that oxytocin increases osmotic water permeability in isolated perfused rat IMCD [14]. Specific oxytocin binding sites have been demonstrated in IMCD [15], the thin limbs of Henle’s loop [16], the macula densa [16,17], and the paraglomerular structure [18] as the result of autoradiographic studies of the rat kidney. In addition, RT-PCR has revealed the expression of the oxytocin receptor in IMCD [19]. It has been reported that AVP binds the oxytocin receptor with high affinity, followed by phosphoinositide hydrolysis in cultured rat IMCD cells [20]. These data suggest that the action of AVP in IMCD may, at least in part, be through binding to the oxytocin receptor.

2.2. ANP receptors

The natriuretic effect of ANP was first reported by De Bold et al. 20 years ago [21]. ANP binds to a membrane form of guanylate cyclase; in other words, a membrane form of guanylate cyclase is a natriuretic peptide receptor [22]. Guanylate cyclase has two different molecular forms: a soluble hem-containing enzyme and a non-hem-containing transmembrane enzyme [23]. The ANP receptor is the membrane form of guanylate cyclase. Three types of ANP receptors are known: NPR-A, B and C (GC-A, B and C). NPR-A (GC-A) is a biologically active receptor that is activated primarily by ANP and, to a lesser extent, by brain natriuretic peptide (BNP) [24-26]. Another type of ANP receptor, NPR-B (GC-B), cannot be stimulated by either ANP or BNP. C-type natriuretic peptide (CNP) selectively stimulates NPR-B [27]. NPR-C (GC-C) has a homologous extracellular domain with NPR-A and B, but has a short cytoplasmic domain without guanylate cyclase activity. Therefore, the binding of ANP, BNP, or CNP to NPR-C does not stimulate cGMP production. NPR-C acts as a clearance receptor that regulates circulating levels of ANP and has been reported to decrease synthesis of cAMP by unclear mechanisms [28,29].

NPR-A is located throughout the entire nephron: from glomeruli to IMCD [30-34]. We have shown that ANP-induced cGMP accumulations can be observed throughout entire nephron segments [31]. The highest stimulation of cGMP accumulations by ANP have been observed in glomeruli and IMCD. Low concentrations of ANP (10^-9 M) stimulate cGMP accumulation in IMCD but not in glomeruli, suggesting a physiological significance of ANP action in IMCD. RT-PCR has demonstrated almost the same distribution of NPR-A mRNA in nephron segments [35]. NPR-B mRNA has also been detected in entire nephron segments [36]. Higher expression has been observed in glomeruli and collecting ducts. In contrast, NPR-C is located primarily in glomeruli, but not in tubules [29,36,37].

The effects of ANP and endothelium-derived relaxing
factor (EDRF) or nitric oxide (NO) are mediated by cGMP. Cyclic GMP modulates cGMP-gated channels, cGMP-dependent phosphodiesterase, and cGMP-dependent protein kinases (cGK). cGK exists as two major forms, cGK I and cGK II [38]. In the study by Gambaryan et al., cGK II was localized in juxtaglomerular cells, the thin ascending limbs, and, to a lesser extent, the brush border of proximal tubules in rats [39]. Neither cGK I nor cGK II, however, are endogenously present in the collecting ducts, suggesting that the effects of cGMP may be carried out by other mediators. However, another report has shown the presence of cGK II in freshly isolated connecting tubules and CCD in rabbit [40]. Although the species are different, the differences in the localization of cGK in these studies need more investigation.

3. Actions and roles of AVP in the collecting duct

The main target site of AVP is the collecting duct in the kidney. In the absence of AVP, the water permeability in the collecting duct is relatively low compared to the proximal tubule and the thin descending limb of Henle’s loop, where water channel, aquaporin 1 (AQP1), is constitutively expressed both in the apical and basolateral membrane [41]. In the presence of AVP, the water permeability of the collecting duct can be dramatically increased (within a few minutes) [42,43], and is mediated by cAMP production via V2 receptors in the basolateral membrane of the principal cells [44]. The binding of AVP to the V2 receptor induces the translocation of AQP2 from a store in intracellular vesicles to the apical plasma membrane of the principal cells in the collecting duct [45].

Because water transport is passive, the driving force, i.e. the osmotic gradient between the lumen and interstitium in the renal medulla, is necessary for the movement of water through this channel. The medullary osmotic gradient is produced primarily by the loop of Henle, which plays an important role in the countercurrent multiplication system together with the collecting duct. The thick ascending limb is impermeable to water because of the absence of a water channel and possesses a secondary active Na⁺–K⁺–2Cl⁻ cotransporter (NKCC2, or bumetanide-sensitive cotransporter 1, BSC1) in the apical membrane [46], allowing the dilution of urine. In contrast, absorbed sodium accumulates in the interstitium in the medulla because of the slow blood flow and the presence of a countercurrent exchange between the descending and ascending vasa recta in this area. These processes create an osmotic gradient between the urine and the interstitium and allow the reabsorption of water in the collecting duct until the osmolality of the urine reaches an equilibrium with that in the interstitium. Urea is impermeable in the collecting duct except for terminal IMCD [47,48] so that urea concentrations increase as urine passes through the collecting duct. If terminal IMCD is also impermeable to urea, concentrated urea creates an osmotic gradient so that water moves back to the lumen, greatly disturbing the urine concentrating capacity of the kidney, indicating that a urea transporter is also important to the water balance of the body. Indeed, UTA-1, vasopressin-regulated urea transporter, is present in the apical membrane and intracellular vesicles in the subapical portion of this segment [49]. In addition, the epithelial sodium channel (ENaC) present in the collecting duct [50,51] also plays an important role in creating a sodium gradient for water reabsorption. In Liddle syndrome, in which ENaC is constitutively activated, hypernatremia and hypertension due to volume expansion are usually seen. AVP regulates all of these channels and transporters to effectively concentrate urine in the kidney.

3.1. Water channels

In isolated tubule perfusion studies, the administration of AVP to the basolateral side was dramatically found to increase collecting duct water permeability within a matter of minutes [43,52] (so-called short-term regulation), strongly suggesting the presence of water channel in this segment. With respect to this finding, AQP2 [53], a vasopressin-regulated water channel, and subsequently AQP3 [54,55] and AQP4 [56,57], both later known to be constitutively expressed in the basolateral membrane in the principal cells of the collecting duct, have been identified [54,55,58–60]. This rapid response to vasopressin is archived by at least two different mechanisms, i.e. the chemical modification of the water channel and a change in the number of functional water channels in the membrane. Immunohistochemistry using a specific antibody against AQP2 has shown strong labeling in the apical membrane and the subapical portion of the collecting duct, the latter of which present in small vesicles as confirmed by immunoelectron microscopy [61]. These observations favor the ‘membrane shuttle hypothesis’ [62], which proposes that water channels are stored in vesicles and inserted exocytically into the apical plasma membrane in response to vasopressin. This scenario has been clearly demonstrated by a combination of microperfusion and immunohistochemistry techniques using microdissected IMCD by Nielsen et al. [45]. AVP increases the water permeability of collecting duct cells by inducing a reversible translocation of AQP2 water channels from intracellular vesicles into the apical plasma membrane.

Because the AQP2 molecule possesses serines and threonines in hydrophilic domains [53] that are potential sites of phosphorylation by protein kinases, including protein kinase A, it is important to clarify whether the direct phosphorylation of AQP2 by cAMP-dependent kinase alters its transport characteristics. The changes in the water conductance of AQP2 by PKA-mediated phosphorylation (approximately 30%) [63] cannot explain the marked changes in collecting duct-water permeability in response to vasopressin treatment (3- to 10-fold increases).
Protein kinase A (PKA)-induced phosphorylation of AQP2 is more critical to the cellular localization of AQP2 [64–67]. Thus, collecting duct water permeability, and hence water balance, is acutely regulated by vasopressin-regulated trafficking of AQP2.

In addition to this short-term regulation, long-term regulation has also been emphasized recently. This regulation takes place over a longer period (hours to days) and results in changes in the total amount of AQP2 in the cells. In Brattleboro rats, an animal model manifesting a natural knockout of circulating vasopressin, chronic administration of AVP through osmotic minipumps has been observed to cause a threefold increase in AQP2 protein expression compared to controls [68]. In addition, AQP3, but not AQP4, protein expression is also upregulated by chronic exposure to AVP [69]. Uprogulation of these proteins by AVP primarily results in an increase in the transcription rates of the AQP2 and AQP3 genes, as AQP2 contains a cAMP-responsive element in its 5′-flanking region [70] and AQP3 has an Sp1 and AP2 cis-regulatory element associated with cAMP-mediated transcriptional regulation [71]. This long-term regulation may be more important under pathophysiological conditions, as under such conditions the cells face prolonged abnormalities.

3.2. Urea transporter

At least, four different isoforms of urea transporters (UTs) have been cloned from rat kidney so far (UT-A1, UT-A2, UT-A3 and UT-A4) [72]. UT-A1 (vasopressin-regulated urea transporter or VRUT) is present in intracellular vesicles as well as the apical plasma membrane in the IMCD [73] as with AQP2. This localization in cells leads to the possibility of dramatic increases in urea permeability by AVP as a result of the trafficking of UT-A1 to the apical membrane. However, physiological studies [74], immunocytochemical localization experiments, and surface biotinylation studies [75] do not support this view. Immunocytochemistry has revealed that AVP does not induce a major redistribution of UT-A1 labeling in IMCD cells. Surface biotinylation studies, although demonstrating a marked increase in AQP2 at the surface of IMCD cells in response to vasopressin, have failed to show any increase in the surface labeling of UT-A1. All of these studies indicate that the ability of vasopressin to activate UT-A1 does not depend on stimulation of trafficking to the cell surface.

The mechanisms of the short-term regulation of UT-A1 by vasopressin are not clear at present. One possibility is a cAMP-mediated phosphorylation of UT-A1. It has been reported that UT-A1 is phosphorylated in response to AVP stimulation in suspension of rat IMCD [76] and that serine-499, found in the middle loop of the UT-A1 protein, is important to the activation of UT-A1 by cAMP [77]. Further study to estimate a functional role for such phosphorylation in the regulation of UT-A1 is necessary.

Long-term regulation by AVP may not be a factor in the case of UT-A1. Northern blotting using RNA isolated from rat inner medulla has demonstrated that the abundance of the 4.0-kb collecting duct transcript is not regulated by AVP [78]. In agreement with this observation, the chronic administration of dDAVP to Brattleboro rats does not change the abundance of UT-A1 protein in the inner medulla [79].

3.3. Epithelial sodium channel

The amiloride-sensitive epithelial sodium channel (ENaC) is a multimeric channel formed by an association of α-, β- and γ-subunits arranged around the pore in a tetrameric structure. The effect of AVP on ENaC is much different between the rat and rabbit collecting duct. Sodium transporter in rat CCD is activated synergistically by mineralocorticoids and AVP [80,81]. An electrophysiological study using microperfusion of rat CCD has revealed stable increases in sodium conductance in principal cells by AVP [82]. cAMP analog, isobutylmethylxantine (a phosphodiesterase inhibitor), and forskolin (a direct stimulator of adenylate cyclase) appear to mimic AVP action, which is blocked by amiloride, indicating that AVP stimulates ENaC by cAMP production, presumably via the V2 receptor [83]. In contrast, AVP action on ENaC is more complicated in the rabbit collecting duct. AVP causes transient increases in sodium absorption followed by a sustained decrease in it [84]. Using specific V1a and V2 antagonists, OPC-21268 and OPC-31260, Yoshitomi et al. [85] has tried to dissect the action of AVP through V1a and V2 receptors. AVP in the presence of V1a antagonist, i.e. pure V2 receptor-mediated action has been caused a sustained inhibition of sodium conductance, as does cAMP. In contrast, AVP in the presence of V2 antagonist, i.e. pure V1a receptor-mediated action causes a sustained activation of sodium conductance associated with [Ca^{2+}]i increases. It thus seems likely that the effect of AVP on sodium absorption in rabbit CCD is a complex of V1a and V2 receptor-mediated action. Although the mechanism by which AVP stimulates ENaC is not yet clearly understood, it may be, at least in part, dependent on the increase in the number of ENaCs in the apical membrane [86,87].

In addition to short-term regulation, the long-term regulation of AVP by ENaC has also been suggested. Chronic exposure to AVP significantly increases the amounts of mRNA and the translation rates of the β- and γ-subunits of the rat ENaC in the RCCD1 rat CCD cell line [88]. It has recently been confirmed by an in vivo study, in which quantitative immunoblotting was carried out with the polyclonal antibody against three subunits of ENaC, that there is an increase in the whole kidney abundance of β- and γ-subunits in Brattleboro rats infused with dDAVP for 7 days and in 7-day water restricted Sprague–Dawley rats [87].
3.4. \( \text{Na}^+ - \text{K}^+ - 2\text{Cl}^- \) cotransporter 1 (NKCC1)

Two types of bumetanide-sensitive \( \text{Na}^+ - \text{K}^+ - 2\text{Cl}^- \) co-transporters have been characterized. The absorptive type, NKCC2 (BSC1), is located in the luminal membrane in MAL and CAL [89–91] and is the main engine for counter-current multiplication system. In contrast, the secretory type, NKCC1 (BSC2) mRNA and protein, is expressed in the collecting duct in rat kidney [92]. The physiological role of NKCC1 in the collecting duct is not clear. The physiological role of NKCC1 may be related to the acid–base balance. Net acid excretion is the sum of ammonium and titratable acid excretion if there is no bicarbonate wasting. \( \text{NH}_4^+ \) has been shown to replace \( \text{K}^+ \) in NKCC1 [93]. The expression of NKCC1 (BSC2) mRNA and protein in OMCD are highest among the collecting duct [94], which is consistent with the high capacity for acid excretion in OMCD [95]. Ammonia is primarily produced in the proximal tubules by phosphate-dependent glutaminase and accumulates in the medullary interstitium [96]. The ammonium ion (\( \text{NH}_4^+ \)) is absorbed via NKCC2 in MAL and CAL by substituting itself for \( \text{K}^+ \) [96–98]. The luminal membrane of these segments is impermeable to \( \text{NH}_4^+ \) [97,98]. The non-ionic diffusion of \( \text{NH}_3 \) into the lumen of OMCD, which is stimulated by low luminal pH, has been thought to be the primary route of ammonium excretion, at least under control conditions [95]. It has been reported that the participation of NKCC1 in ammonium excretion in OMCD is only 6% under control conditions [99]. However, chronic metabolic acidosis upregulates NKCC1 mRNA and protein in OMCD of the rat, suggesting a contribution of NKCC1 to the acid–base balance under this chronic condition [94]. It is interesting that dehydration stimulates both NKCC1 mRNA and protein expression in OMCD [94]. The chronic exposure to AVP in the rat also increased NKCC1 mRNA and protein expression [100], suggesting some role of AVP in the regulation of NKCC1 expression in OMCD.

4. Modification of AVP action by AVP itself

4.1. Basolateral side

The action of cAMP produced by AVP through the V2 receptor is modified by phosphoinositide pathway activated by AVP itself. Much data has shown that intracellular calcium [13,101–104] and protein kinase C [105] are also increased by AVP, resulting in an inhibition of water permeability. Receptors responsible for this modification are presumably the V2 receptor in rat IMCD [9,13,101–103] and V1a receptor in rabbit CCD [106] and rat CCD [107,108].

4.2. Luminal side

AVP is distributed in a volume approximately equal to the extracellular space, and nearly all of this hormone in plasma is in an unbound form, which, because of its relatively low molecular weight, permeates peripheral and glomerular capillaries readily so that the urinary excretion rate of AVP is extraordinary high. According to currently available data, the urinary clearance of AVP in human is 0.1–0.6 ml kg\(^{-1}\) min\(^{-1}\) and may reach 2.0 ml kg\(^{-1}\) min\(^{-1}\) [109]. Thus, urinary concentrations of AVP range from 5 to 500 pM and may reach as high as 1700 pM. It has been reported that in the rabbit CCD, luminal AVP suppresses the increase in water permeability (Lp) induced by basolateral AVP [110]. Furthermore, a microperfusion study using isolated rat terminal IMCD has clearly demonstrated that luminal AVP inhibits osmotic and urea permeability by 30–65% in the presence of bath AVP by decreasing cAMP accumulations via V1a or oxytocin receptors and by an unknown mechanism via V2 receptors in the luminal membrane [5]. An electrophysiological study using microperfusion of rabbit CCD has revealed that luminal AVP inhibits the stimulation of basolateral \( \text{Cl}^- \) conductance by basolateral AVP [111]. These observations suggest that luminal AVP may participate in a feedback regulation for basolateral AVP. Based on these basic findings, we have clinically shown that urinary AVP is an intrinsic diuretic especially in patients with chronic renal failure [112].

5. Physiological role of ANP in the collecting ducts

The physiological effects of ANP involve an increase in the glomerular filtration rate (GFR), changes in hemodynamics, and an inhibition of the tubular reabsorption of NaCl [113,114]. Recent reports have shown that NPR-A (GC-A)-deficient mouse cannot show natriuresis in response to an isooncotic saline infusion, suggesting that NPR-A is essential for natriuresis [115]. However, NPR-A is not required for normal kidney function under non-isoncotic conditions. Micropuncture studies have suggested that the main site of ANP action is IMCD [116–122]. Regarding the direct tubular effects of ANP, Harris et al. were the first to report that ANP inhibits angiotensin-induced sodium and fluid absorption in proximal tubules perfused in vitro with the standing-droplet method [123]. However, most subsequent studies have not observed any inhibitory effects of ANP on angiotensin II-stimulated fluid absorption [124–127]. In the loop of Henle, we have found that ANP inhibits AVP-stimulated chloride transport in long-looped MAL [128]. Some studies have not found any inhibitory effects of ANP in the thick ascending limbs [129,130]. We have also observed effects of ANP on \( \text{HCO}_3^- \) transport in MAL [131].

In contrast to the small physiological effects of ANP in the proximal tubules and thick ascending limbs, large effects have been reported in the collecting ducts. In CCD, we have demonstrated inhibitory effects of ANP and cGMP on active chloride transport both in the presence
and absence of AVP [132]. Low concentrations of ANP 
\(10^{-10} \text{ M}\) inhibit fluid absorption by 50%, suggesting the 
physiological significance of ANP in this segment. These 
effects have been observed without changing the trans-
epithelial voltage, suggesting that ANP inhibits thiazide-
sensitive sodium chloride transport in rat CCD.

Many studies have shown that ANP inhibits NaCl 
transport in IMCD. ANP inhibits oxygen consumption and 
\(^{22}\text{Na}\) fluxes in IMCD cell suspensions, single channel 
currents in cultured IMCD cells as shown by patch-clamp 
technique, and NaCl absorption as shown by isolated 
tubule perfusion technique [133–138]. The first report of 
the effect of ANP on water permeability was presented by 
Dillingham and Anderson based on their observations of 
rabbit CCD [2]. We have demonstrated that ANP inhibits 
AVP-stimulated water permeability by 40–50% using 
isolated tubule perfusion [139], an effect that is mimicked 
by cGMP, and other investigators have confirmed these 
findings [140]. Although we have demonstrated the inhib-
itory effects of ANP on AVP-stimulated osmotic water 
permeability in IMCD, the effect was not observed in the 
presence of high doses of AVP \((10^{-5} \text{ M})\). An effect of 
ANP on water permeability has been observed only in the 
presence of low doses of AVP \((10^{-11} \text{ M})\). In contrast, ANP 
does not inhibit AVP-stimulated urea permeability in 
IMCD [139].

Urodilatin is identical to ANP except for a four-amino-
acid NH\_2-terminal extension. Urodilatin cannot be detected 
in plasma [141]. Urodilatin is synthesized by the kidney 
most likely in the connecting tubule and is secreted into 
the tubular lumen of collecting ducts, where it binds to 
GC-A and affects water and sodium transport [142,143]. 
These data suggest that urodilatin may be the predominant 
representative of natriuretic peptides in human kidney.

6. Role of AVP under pathophysiological conditions

The plasma AVP and ANP concentrations are altered 
under various chronic pathophysiological conditions, 
including congestive heart failure, liver cirrhosis and nep-
ritic syndrome. Recently, many investigators have pointed 
out that the chronic increase or decrease in AVP may play 
an important role in the abnormality of the body-fluid 
balance in some of these conditions.

6.1. Congestive heart failure

Congestive heart failure is associated with salt and water 
retention. Increased AQP2 expression and enhanced deliv-
ery to the apical plasma membrane play a significant role 
in water retention and the development of hyponatremia is 
associated with severe heart failure. Rats with congestive 
heart failure have significantly increased plasma vasopres-
sin levels, and the administration of the vasopressin-V2 
receptor antagonist OPC 31260 is associated with a 
significant reduction in AQP2 protein and mRNA levels 
[144].

6.2. Liver cirrhosis

Hepatic cirrhosis is another chronic condition associated 
with pathologic water retention and increased plasma 
levels of vasopressin. The changes in AQP2 expression 
differ significantly depending on the model of hepatic 
cirrhosis that is studied. Hepatic cirrhosis induced by 
chronic intraperitoneal administration of carbon tetra-
chloride is associated with an increased expression of both 
AQP2 protein and AQP2 mRNA [145,146]. Cirrhosis 
induced by ligation of the common bile duct [147,148] has 
demonstrated a significant reduction in AQP2 expression. 
Hepatic cirrhosis by carbon tetrachloride inhalation is 
associated with ascites and hyponatremia due to excessive 
water retention. However, no change in AQP2 expression 
has been observed in this model of cirrhosis, whereas 
AQP1 expression in the cortex is increased [149], sug-
gesting that the water retention is, in part, due to increased 
reabsorption in the proximal tubule, combined with a 
failure of the normal ‘vasopressin escape’ phenomenon. 
Additional studies are needed to fully clarify the role of 
adaptors and solute transporters in compensated and 
decompensated cirrhosis.

6.3. Chronic renal failure

Impairment of vasopressin-stimulated water reabsorption 
in the kidney collecting duct [150,151] is known in rats 
with chronic renal failure. Chronic renal failure induced by 
5/6 nephrectomy is associated with polyuria and a vas-
opressin-resistant downregulation of AQP2 and AQP3 
[152], suggesting that reduced AQP2 and AQP3 levels 
may be significant factors involved in the impaired collect-
ing duct water permeability and reduced or impaired 
avasopressin responsiveness in chronic renal failure. We 
have shown that urinary AVP is an intrinsic diuretic, 
especially in patients with chronic renal failure, based 
upon evidence that luminal AVP inhibits basolateral AVP-
stimulated water permeability [5,112].

7. Actions and roles of ANP in the collecting duct

7.1. Short-term regulation

As a mechanism of ANP action, cGMP acts as a second 
messeger. The stimulation of cGMP synthesis by ANP 
inhibits AVP (V2) action in IMCD. Since the second 
messeger of AVP is cAMP, the reduction in cAMP 
synthesis by ANP was considered. In fact, ANP reduces 
cAMP content by enhancing phosphodiesterase activity 
in human fibroblasts [153]. However, AVP-stimulated 
cAMP accumulations in IMCD nor MAL are not changed 
by ANP, suggesting that the site of ANP action on AVP is
distal to cAMP synthesis. It is not known whether the stimulation of cGK is a major effector of ANP action in the collecting ducts. Hyperosmolality reduces ANP-stimulated cGMP generation in IMCD, suggesting that the increase in medullary osmolality, such as in dehydration, reduces the natriuretic effects of ANP [154].

7.2. Long-term regulation

The expression of ANP receptors is regulated under various pathophysiological conditions. Congestive heart failure causes increased levels of circulating ANP and BNP, with a markedly blunted natriuretic response to ANP infusion [155]. Decreased NPR-A expression in IMCD in congestive heart failure has been reported. Cao et al. have shown that preincubation of IMCD cells with ANP reduces ANP-induced cGMP synthesis [156]. This inhibitory effect of ANP on its receptor activity (autoregulation) has also been observed in response to preincubation with BNP or urodilatin and is related to basal cGMP levels. ANP and cGMP cause a reduction of NPR-A mRNA expression. Furthermore, ANP reduces NPR-A gene promoter activity in transiently transfected IMCD cells, which is mimicked by 8-bromo-cGMP. These results suggest that increased cGMP levels, rather than ANP, are responsible for the downregulation of NPR-A gene and protein expressions such as those in congestive heart failure. The downregulation of ANP receptor expression by high circulating levels of ANP has also been observed during pregnancy [157] and diabetes mellitus [158]. It is interesting that sodium status affects NPR-B mRNA expression, but not that of NPR-A or C [159]. The upregulation of NPR-A mRNA expression in rats with reduced renal mass has been reported [160]. Upregulation of GC-A in renal papilla and GC-B in the aorta and mesenteric arteries was reported in DOCA–salt-treated rats [161].

NPR-C is a clearance receptor and regulates circulating levels of ANP [29,162]. NPR-C is dominantly expressed in glomeruli. Mice with inactivated NPR-C gene (Npr3) show a longer half life of injected ANP, although plasma levels of ANP and BNP are close to the wild type [162]. These mice have a reduced ability to concentrate urine, exhibit mild diuresis, and tend to have blood volume depletion, confirming that NPR-C modulates the availability of natriuretic peptides in the kidney. Recent reports suggest that NPR-C participates in the proliferation of mesangial cells by inactivating mitogen-activated protein kinase (MAPK) through the induction of MAPK phosphatase-1 (MKP-1) [163,164].

8. Conclusion

Vasopressin plays an important role in urine concentration through V2 receptor-mediated ion channels and transporters. In contrast, the V1a receptor, mainly in the luminal membrane of distal nephron, regulates basolateral V2 receptor-mediated action on water and ion transport through the activation of $G_{q/11}$ and phosphoinositide turnover. ANP causes diuresis and natriuresis, at least in part, by inhibiting the V2 receptor-mediated action of AVP in the collecting ducts.

References

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