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Abstract

The adverse effects of vasopressin (AVP) in diverse forms of chronic kidney disease have been well described. They depend on the antidiuretic action of AVP mediated by V2 receptors (V2R). Treatment with tolvaptan, a selective V2R antagonist, is now largely used for the treatment of patients with ADPKD. Another way to reduce the adverse effects of AVP is to reduce endogenous AVP secretion by voluntary increase in fluid intake. These two approaches differ in several ways, including the level of thirst and AVP. With voluntary increased drinking plasma osmolality will decline and so will AVP secretion. Thus, not only will V2R-mediated effects be reduced, but also those mediated by V1a (V1aR) and V1b receptors. In contrast, selective V2R antagonism will induce a loss of fluid that will stimulate AVP secretion and thus, increase AVP's influence on V1a and V1b receptors. V1aR are expressed in the luminal side of the collecting duct and in inner medullary interstitial cells, and their activation induces the production of prostaglandins, mostly PGE2. Intrarenal PGE2 have been shown to reduce sodium and water reabsorption in the collecting duct and to increase blood flow in the renal medulla, both effects contributing to increase sodium and water excretion and reduce urine concentrating activity. Conversely, non-steroidal anti-inflammatory drugs have been shown to induce a significant water and sodium retention and potentiate the antidiuretic effects of AVP. Thus, during V2R antagonism, V1aR-mediated actions may be responsible for part of the diuresis observed with this drug. These V1aR-dependent effects do not take place with voluntary increase in fluid intake. In summary, while both strategies may have beneficial effects, the information reviewed here lead us to assume that the pharmacological V2R antagonism, with resulting stimulation of V1aR and increased PGE2 production, may provide greater benefit than voluntary HWI. The influence of tolvaptan on PGE2 excretion rate and the possibility to use somewhat lower tolvaptan doses than presently prescribed remain to be evaluated.

Keywords

Thirst, Prostaglandin, Polycystic kidney disease, Sodium excretion, Medullary insterstitial cells, Chronic kidney disease

Bullet points

What is already known about this subject

--- Vasopressin, by activation of its V2 receptors, promotes kidney disease progression in a variety of nephropathies, beyond its direct involvement in autosomal dominant polycystic kidney disease.
--- This influence on CKD in general is mediated, indirectly, by modifications of the composition of the tubular fluid at the macula densa and resulting changes in the tubulo-glomerular feedback control of GFR.
--- It is thus important to reduce V2 receptor-mediated actions in ADPKD, as well as in all forms of CKD; this can be achieved either by a treatment with a selective V2 receptor antagonist, or by a voluntary increase in fluid intake.

What this study adds

--- Although rarely discussed, V2 receptor blockade or voluntary increase in fluid intake differ in their consequences on endogenous vasopressin secretion: vaptans increase vasopressin secretion while high water intake reduces it.
--- As a result, an increased stimulation of V1a receptors occurs with vaptans and is absent with voluntary increase in fluid intake. V1aR stimulation is known to increase PGE2 production in the collecting duct and in insterstitial cells of the inner medulla.
--- Because these actions reduce urine concentrating activity (by mechanisms that have been well described several decades ago), they probably contribute to amplify the aquaresis induced by V2 receptor antagonism.

What impact this may have on practice or policy

--- We suggest measurements of urinary PGE2 excretion in patients submitted to each of these two treatments.
--- If indeed, this excretion is significantly greater with vaptans than with voluntary increase in water intake, it will support the hypothesis that vaptans could provide a greater benefit than voluntary increase in fluid intake by reducing V2 effects both directly and indirectly.
--- Moreover, targeting a urine osmolality close to that of plasma, rather than significantly below it, which could improve tolerability without much disadvantage, deserves to be evaluated.

Abbreviations

AVP	Vasopressin or antidiuretic hormone
dDAVP	Desmopressin = 1-deamino 8D-arginine vasopressin
V2R, V1aR, V1bR	AVP V2, V1a, and V1b receptors, respectively
CKD	Chronic kidney disease
ADPKD	Autosomal dominant polycystic kidney disease
HWI	Voluntary increase in water intake
CD	Collecting duct
CCD	Cortical collecting duct
IMCD	Inner medullary collecting duct
TAL	Thick ascending limb
RMIC	Renal medullary interstitial cells
PGE2	Prostaglandin E2

1. Introduction

The adverse effects of vasopressin (AVP) and urine concentrating activity in chronic kidney disease (CKD) in general [1, 2], and more specifically in diabetic kidney disease [3] and autosomal dominant polycystic kidney disease (ADPKD) [4, 5] have been well described. Experimental studies *in vivo* and *in vitro* have provided some insight into the mechanisms of these adverse effects. They depend on the antidiuretic action of AVP, mediated by V2 receptors (V2R). The selective non-peptide orally active V2R antagonist tolvaptan is now largely used for the treatment of patients with rapidly progressing ADPKD [6] after it was proved to bring significant benefits in the Tempo 3:4 trial [7-10].

Glomerular hyperfiltration is known to be associated with further kidney dysfunction, adverse cardiovascular events and/or death [11-17]. Experimental studies and clinical investigations have shown that the sustained action of the selective V2R agonist dDAVP induces a chronic hyperfiltration and a rise in urinary albumin excretion [18, 19] while the suppression of AVP secretion by a water load results in a decrease in GFR [18, 20, 21]. Vasopressin contributes to CKD progression and to diabetic nephropathy by V2R-depedent actions [22, 23]. In ADPKD, the adverse effects of AVP depend on two independent and additive mechanisms: 1. the well understood influence of AVP on cyst growth mediated by its second messenger, cAMP; and 2. the hyperfiltration imposed on the kidney, as described above for all forms of CKD [24].

Thus, in order to reduce AVP-dependent V2R-mediated adverse consequences in renal patients (with ADPKD and with CKD in general), a voluntary high water intake (HWI) has been proposed, instead of a pharmacologic approach [4, 25-30]. Both V2R antagonism or voluntary HWI increase urine volume and decrease urine osmolality. However, they are fundamentally different. Drinking more will reduce AVP secretion and thirst. In contrast, V2R antagonism will induce a water loss and thus, will increase AVP secretion and thirst.

The aim of this review is to comparatively describe the direct and indirect consequences of these two approaches and explain how their differences may affect the outcomes.

2. AVP receptors

The three AVP receptors, the V1a, V1b, V2 receptors (V1aR, V1bR, V2R) are strikingly similar in both size and amino acid sequence. The V1aR and V1bR are selectively coupled to G-proteins of the Gq/11 family, leading to the breakdown of phosphoinositide lipids. The V2R preferentially activates the G-protein Gs, resulting in the activation of adenylyl cyclase.

The AVP receptors are widely distributed in different tissues in the body, as listed in **Table 1**. **V2R** are expressed in the kidney, the vascular endothelium where they play a role in coagulation, pneumocytes, and the inner ear [31]. They are also expressed in mouse, rat and human cholangiocytes and in polycystic liver epithelium [32]. **V1aR**, besides their well-known expression in vascular smooth muscle, are expressed in the kidney, in the liver where they may influence glucoregulation [33-36] and other organs [37, 38]. **V1bR** are present in the anterior hypophysis, pancreatic islets, adrenal glands [37, 39]. With so many different target sites, it is obvious that all tissues cannot respond simultaneously and indistinctly to AVP. Differences in the level of AVP required to stimulate each of them, and possible associated permissive or antagonizing factors may allow organ-selective responses. However, the V2R-dependent antidiuretic response is by far the most sensitive of all. In healthy volunteers undergoing water diuresis, a very low rate of AVP infusion induced a significant reduction in diuresis with no influence on other target organs or even on other intrarenal target sites [40].

Within the kidney (**Table 2**), V2Rs are located in the principal cells of the collecting duct (CD) and in the thick ascending limb (TAL). Less well-known, V1aRs are expressed in the luminal membrane of CD intercalated cells [41] and in interstitial cells of the inner medulla [42]. Binding studies with a V1aR antagonist and molecular studies

[43-45] suggest V1aR expression in thin descending limbs of short looped-nephrons, which also express the urea transporter UT-A2 (**Figure 1**).

3. Major differences between voluntary increase in water intake or treatment with a V2R antagonist

Table 3 shows the similarities and differences induced by either a voluntary HWI or a treatment with a V2R antagonist. The main differences reside in the level of thirst and AVP. With voluntary HWI, thirst is largely abolished, plasma osmolality declines, and so will AVP secretion. Thus, not only will V2R-mediated effects be reduced, but also those mediated by V1a and V1b receptors. In contrast, the V2R antagonism induces a loss of water that increases thirst, plasma osmolality and AVP secretion. Tolvaptan has been shown to increase plasma AVP and its surrogate marker copeptin, about 3 to 4-fold, [46-48]. Thus, effects mediated by V1aR and V1bR should be enhanced while V2R effects are, at least largely, abolished.

During the development of V2R antagonists, a serious concern was the risk of hypertension due to V1aR-mediated vasoconstriction. The use of a mixed V1aR/V2R antagonist was proposed [49-51]. However, princeps and long-term follow-up studies with tolvaptan did not reveal any significant rise in blood pressure [7, 9]. Actually, two recent studies revealed that blood pressure declined slightly in ADPKD patients after several months or years of tolvaptan treatment, compared to placebo [52, 53]. This effect was assumed to result from the beneficial effect on disease progression and on a higher fractional excretion of sodium and urea.

Another, more recent concern was a possible rise in glycemia via hepatic V1aR [33-35]. In epidemiologic studies, AVP is associated with obesity and metabolic syndrome [36, 54, 55]. However, princeps and long-term follow-up studies with tolvaptan disclosed no significant rise in glycemia. This confirms that the concentration of AVP required to induce a sustained vasoconstrictive or a metabolic response is significantly higher than that responsible for its antidiuretic action. Similarly, increased concentration of vasopressin in ADPKD patients at baseline and during tolvaptan

treatment did not result in activation of the hypothalamic-pituitary-adrenal axis. The impaired glucocorticoid production in these patients was found to be related to their degree of kidney function impairment [56].

In addition to the differences explained above, the two treatment approaches lead to quantitatively different urine volumes. Tolvaptan given for three weeks (90/30 mg in the last week) to 27 patients with ADPKD induced an average urine volume of 5,930 mL/d , vs 2,584 mL/d at baseline. Twenty four hour osmolar excretion was strongly associated with 24-hour urine volume [57]. In contrast, in patients with voluntary HWI, much lesser water intake and urine volumes were observed. In ADPKD patients with voluntary HWI for one year, urine volume rose only from 2.048 ± 648 to 2691 ± 710 mL/d [58]. In CKD patients coached for one year to increase their water intake by 1.0 to 1.5 L/d above their usual consumption, urine volume went up from 1.9 to 2.5 L/d, a change distinctly lower than intended in the design of the study [28].

The discussion about tolvaptan versus voluntary HWI is only valid for counteracting vasopressin's actions in kidney patients. The situation is different for patients with metabolic diseases (diabetes mellitus, metabolic syndrome) in which adverse V1aR- or V1bR-mediated effects are suspected [54, 55, 59]. In the absence of selective V1aR and V1bR antagonists, a voluntary increase in fluid intake is the only option.

4. AVP and the renal handling of sodium : opposite roles of V2 and V1a receptors. Role of V1a receptors in chronic kidney disease

AVP or dDAVP (selective V2R agonist) increase permeability of the collecting duct to water via their influence on aquaporin 2 (AQP2). They also increase sodium reabsorption by activating ENaC. dDAVP or relatively low doses of AVP reduce sodium excretion in both rats [60] and humans [61, 62]. This effect is dependent on ENaC since it is abolished by prior administration of amiloride [63]. This sodium retention was not observed in patients with nephrogenic diabetes insipidus with loss-of-function of the

V2R, but was intact in patients with AQP2 mutations, thus showing that it is mediated by V2R [61].

Paradoxically, many studies reported a strong natriuretic action of AVP when infused *in vivo* in experimental animals or in humans (see review in [62]). How can these observations be reconciled with the sodium-retaining effect of AVP or dDAVP via ENaC? Perucca et al performed dose-response studies of AVP effect on sodium excretion in conscious rats [60]. With increasing doses, AVP turned from being antinatriuretic to being natriuretic. The natriuretic effect was prevented by a selective V1aR antagonist (**Figure 2)**. This demonstrates that V1aR activation induces a natriuretic effect that, with increases in AVP secretion, overcomes the antinatriuretic V2R-dependent action [60].

In rats with chronic kidney disease (CKD) induced by renal mass reduction, Perico et al reported that treatment with the dual AVP V1aR and V2R antagonist RWJ-676070, combined with angiotensin II blockade, lowered blood pressure, proteinuria, and glomerulosclerosis only marginally over angiotensin II blockade alone [64]. Surprisingly, no increase the 24-h urine volume was observed [64]. The simultaneous blockade of V1aR and V2R thus prevented the aquaretic effect expected in response to V2R antagonism. This suggests that, in patients treated with tolvaptan, the stimulation of V1aRs by the elevated AVP might participate to the observed aquaretic effect.

In patients with CKD, the fractional urinary excretion of AVP was shown to be the major determinant of the fractional excretion of sodium [65]. This strongly suggested a role for luminal AVP (thus most likely on V1aR) as an intrinsic diuretic/natriuretic factor [65], as confirmed by in vitro studies (see below).

5. V1aR-dependent prostaglandin production and actions within the kidney

5. 1. Evidence for vasopressin-prostaglandin interaction in the kidney

Prostaglandins are involved in the regulation of hormonal actions in various tissues. In the 1980s-2000s, many articles and reviews described the synthesis of prostaglandins by the kidney and their possible role in the regulation of kidney function [66-74]. But these mediators did not receive much attention in recent years.

Cyclooxygenases 1 and 2 (COX-1 and COX-2), the rate-limiting enzymes for prostaglandin synthesis from arachidonic acid, are expressed in several structures within the kidney that are targets of AVP: COX-2 in the thick ascending limb (TAL) and medullary interstitial cells (RMIC), and COX-1 in the collecting duct (CD) [75, 76]. Prostaglandins interact with G protein-coupled receptors (EP1 to EP4) [77]. EP3 is expressed in TAL and the outer medullary CD, EP1 in the inner medullary CD, and EP4 in descending vasa recta [75], sites that also express AVP receptors or may influence the antidiuretic action of AVP.

Urinary prostaglandin excretion is considered to reflect renal synthesis [78]. Inhibitors of prostaglandin synthesis have been used for elucidating their influence on kidney function. They include non-steroidal anti-inflammatory drugs (NSAID) indomethacin, meclofenamate, aspirin (acetyl salicylic acid), and more recently, selective inhibitors of either COX-1 or COX-2 [79] or selective antagonists of the different receptors [80, 81].

The natriuretic effect of AVP has been shown to depend on a V1aR-mediated influence on prostaglandin production [82]. PGE2 exerts at least two main actions in the kidney. It reduces sodium reabsorption in the collecting duct and increases blood flow in the renal medulla [71, 72, 83], both effects contributing to increase sodium excretion and reduce urine concentrating activity. Conversely, NSAID induce a significant water and sodium retention, and potentiate the antidiuretic effects of AVP [70, 84-88]. In rats, PGE2 infusion depressed the cortico-medullary gradient of NaCl, whereas indomethacin lead to a rise in medullary NaCl concentration [89, 90] without any change in renal hemodynamics. Prostaglandin synthesis may thus regulate the cortico-medullary osmotic gradient and increase natriuresis. Therefore, PGE2 produced in response to V1aR stimulation may account for the natriuresis induced by AVP.

Prostaglandins have been shown to interfere with the antidiuretic and antinatriuretic actions of AVP [91, 92]. As shown in **Figure 3,** inhibition of prostaglandin synthesis in water diuretic dogs, by indomethacin or meclofenamate, markedly potentiated the antidiuretic response to a bolus of vasopressin, without any change in GFR and solute excretion [92]. Similar results were observed in humans [93, 94]. Intrarenal prostaglandins inhibit the AVP-dependent generation of cyclic AMP *in vivo*, as previously demonstrated *in vitro* [92], an effect mediated by EP3 receptors [95]. Altogether, these observations establish the important role of prostaglandins in modulating the action of AVP.

The V1aR-dependent prostaglandin production in the kidney may explain the paradoxical observations reported in the following three studies. 1. In Brattleboro rats (lacking AVP) with 5/6th nephrectomy, AVP infusion (V2R + V1aR-mediated effects) induced much less severe signs of CKD progression than did dDAVP (V2R only). The deleterious effects of V2R activation were markedly blunted when associated with V1aR activation (**Table 4)** [96]. 2. In rats with hypertension induced by blockade of NO formation, AVP secretion is increased. Contrary to expectations, the selective V1aR antagonist worsened the rise in blood pressure and increased urinary albumin excretion [97] (**Figure 4A)**. 3. The facilitated urea transporters UT-A2 and UT-A1 are expressed in the rat kidney. Infusion of dDAVP induced a marked increase in UT-A2 and UT-A1 expression, whereas almost no change was observed with an infusion of AVP [98] (**Figure 4B**). This suggests that the presence of V1aR agonism with AVP attenuated the influence of V2R agonism induced by dDAVP. Retrospectively, the effects observed in these three studies may be attributed to an influence of prostaglandins produced under the stimulation of intrarenal V1aR, that was not considered by the authors at that time.

V1aR are expressed in the intercalated cells of the CD and interstitial cells of the inner medulla (RMIC) [42]. In these two cell types, AVP stimulates the synthesis of PGE2 which is released locally. PGE2 then induces specific paracrine actions on CD principal cells (reduction of V2R-dependent osmotic water permeability and ENaC-mediated Na reabsorption), thick ascending limbs (inhibition of sodium reabsorption) and inner medullary vasculature (increase in medullary blood flow) [99]. These actions contribute to reduce the antidiuretic and antinatriuretic response mediated by V2R and to reduce

the urine concentrating ability. The simplified diagram of **Figure 5** shows the different actions of AVP, via its V2R and V1aR.

5. 2. Collecting duct

PGE2 attenuates the AVP-dependent effects on the CD in animals and humans [92, 93] and impairs AVP-dependent water transport in isolated perfused rabbit CCD [100] by inducing a faster degradation of cAMP. V1aRs are expressed in the lumen of the CD. Addition of AVP to the luminal perfusate of isolated perfused CDs inhibited the hydro-osmotic effect of AVP [101], and induced a sustained decrease in Na and Cl net fluxes [102]. This inhibitory action was prevented by meclofenamate, thus showing the role of PGE2 biosynthesis. A downregulation of V2R in the CD, via a V1aR-dependent pathway, represents an additional mechanism by which V1aR activation may reduce the antidiuretic action of AVP [103]. Taken together, the effects reported above explain how AVP, via its luminal V1aR in intercalated cells, significantly interferes with V2R-mediated antidiuretic action in the CD.

How high may be the concentration of AVP in the CD luminal fluid? AVP is far more concentrated in urine than in plasma. The urine/plasma ratio of AVP concentrations was 42 in a study of healthy humans [104]. When the urine concentrating ability is reduced and the rate of tubular fluid flow rate in the CD lumen is increased (by V2R antagonism or other causes), AVP concentration in the CD lumen may still be significantly higher than in plasma. Thus, luminal AVP may still induce a significant influence on V1aR in the CD.

5.3. Thick ascending limb

V1aR and V1aR-mediated actions of AVP have not been reported in the TAL. However, TAL transport proteins and/or transport functions are regulated by prostaglandins. A paracrine influence on the TAL by PGE2 released by medullary CDs in the inner stripe interstitium can be favored by the close proximity of these two structures. PGE2 reduces cell cAMP content [105] and ion transport in MTAL cells by

inhibiting AVP-dependent cAMP formation [106, 107]. In isolated perfused TALs, PGE2 reduced chloride transport [108] and transepithelial voltage [109], and increased HCO_3^- reabsorption [110]. *In vivo*, endogenous PGE2 reduced fractional chloride reabsorption [111]. In mouse medullary TAL cells in culture. PGE2 inhibited the Na- and Cl-dependent, bumetanide-sensitive K influx, probably by downregulating the number of Na-K-2Cl cotransporters [112]. Conversely, cyclo-oxygenase inhibition increased the abundance of the Na-K-2Cl cotransporter. Thus, cyclooxygenase inhibitors enhance urinary concentrating ability in part by abolishing the inhibitory effect of PGE2 on AVP-dependent cAMP production [113]. Altogether, these studies suggest that PGE2 may act as a counter-regulatory factor to maintain a stable function in the MTAL during antidiuresis, when circulating AVP levels and medullary osmolality are elevated.

5. 4. Inner medullary interstitial cells and medullary blood flow

Renal medullary interstitial cells (RMICs) are very abundant in the inner medulla [114, 115]. These "lipid-laden" cells exhibit abundant lipid droplets of arachidonic acid, the precursor of prostanoids. They express COX-1, COX-2 and PGE synthase [116] and produce PGE2 and PGF2 alpha [117-120]. These cells also express abundantly V1aR [42]. PGE2 production in RMIC is stimulated by AVP, an effect abolished by a selective antagonist of the V1aR [119, 120]. This AVP-stimulated PGE2 production thus results from V1aR activation. The stimulation of V1aRs in RMIC may be very significant because AVP concentration is 20-30 times higher in medulla and papilla than in peripheral blood [121]. Urinary PGE2 excretion rate is considered to reflect largely the intrarenal PGE2 production by RMICs [78]. PGE2 induce a significant vasodilation of the vasa recta by activation of EP2 and EP4 receptors, resulting in an increase in medullary blood [122-124].

An increased blood flow in the medullary vasa recta compromises the accumulation of solutes in the inner medulla and thus, decreases the intra-renal osmotic gradient, a crucial requirement for the urine concentrating mechanism. Urea is accumulated in the inner medulla by an AVP-dependent increase in urea permeability of the terminal inner medullary CD permitted by the activation of the facilitated urea transporter UT-A1 [125-127]. If urea accumulation in the medulla is compromised,

water reabsorption and thus urine concentration will be reduced. An increased medullary blood flow will wash out the medullary urea in ascending venous vasa recta, and thus reduce inner medullary urea concentration [99]. Moreover, PGE2 may interfere with V2R-mediated influence on UT-A1 and thus, let more urea be excreted in the urine, thus reducing further its accumulation in the inner medulla and the urine concentrating capacity [128].

Intriguingly PGE2 in the renal medulla exhibit a strong sex-related difference. PGE2 excretion is about twice higher in female than in male rats, and ovariectomy lowers this production to the level observed in males [129]. High PGE2 in females is responsible for a twofold higher medullary blood or plasma flow in female than in male rats[130, 131]. Indomethacin reduced these flows in females to values similar to those in control males [131].

Altogether, the facts described above provide evidence that AVP, through actions initiated by V1aRs, attenuates the antidiuretic and antinatriuretic effects mediated by peritubular V2Rs and that these counter-regulatory actions are mediated by PGE2 (**Figure 5)**. The rise in AVP secretion induced by V2R antagonism thereby participates in the "aquaretic" effect observed during V2R antagonism. These V1aR-mediated effects in the kidney probably represent a safeguard against an excessive urine concentration that would compromise the excretory function of the kidney. Actually, a low urine flow rate markedly reduces the fractional excretion (FE) of urea [132] as well as that of other solutes, although to a lesser extent [18, 62]. In healthy humans undergoing a clinical investigation with renal clearance measurements, the FE during high and low hydration conditions (in the same subjects) were respectively 64 and 46 % for urea, 2.14 and 1.42 % for Na, and 19.3 and 15.7 % for K [21]. The FE of these solutes would most likely be even more significantly reduced without the counterbalancing influence of V1aR activation.

6. Possible role of AVP, via V1aR, in the high PGE2 production and the high polyuria observed in monogenic tubulopathies

In several mendelian diseases involving transporters or regulatory proteins expressed in the TAL, like antenatal Bartter syndrome, an intense polyuria is accompanied by a marked increase in PGE2 urinary excretion. Inhibitors of prostaglandin synthesis significantly ameliorate the urine concentrating defect of these patients [133, 134].Thus, in addition to the loss of function mutations in the Na-K-2Cl cotransporter [135], PGE2 also contributes largely to this excessive urinary dilution [133, 134, 136].

The reason why prostaglandin synthesis is markedly increased in these diseases is not elucidated. AVP secretion is elevated in these patients, due to the loss of fluid induced by the high diuresis. Thus, the increased prostaglandin production may be explained by enhanced AVP-induced activation of renal V1aR in RMIC. This situation is similar to that observed in response to treatment with tolvaptan. Thus, the urine concentrating defect in these tubulopathies is likely due to two cumulative factors: 1, the genetic defect that impairs urine concentrating ability; 2, the influence of increased V1aR-stimulated prostaglandin synthesis that reduces the residual V2R-mediated antidiuretic action. In a mouse model of late-onset type I Bartter syndrome [137], urinary prostaglandin E2 is increased, as in the human disease, and the urine concentrating defect is largely attributed to a defect in urea concentration in the urine, likely attributable to a high medullary blood flow [137].

An enhanced secretion of AVP and its resulting action on renal V1aR bring a novel pathophysiological explanation for the markedly elevated PGE2 excretion rate and high diuresis observed in these monogenic diseases. V1aR antagonism could possibly represent an alternative to NSAID for reducing the urinary concentrating defect.

7. Complex effects of vasopressin on vascular smooth muscle cells and endothelial cells

In arteries, V1aR are expressed on vascular smooth muscle cells [138-140] and V2R on endothelial cells [31, 141]. *Ex vivo* studies have shown that AVP can induce opposite vasomotor effects : vasoconstriction via V1aR [140 , 142], and vasodilation via V2R [141]. *in vitro* studies of human HUVEC endothelial cells with heterologous V2R

expression, showed that dDAVP activates the endothelial NO-synthase eNOS via cAMP [143]. This explains the endothelial NO-dependent vasodilatation elicited by high concentrations of AVP.

Independent of its hemodynamic implications, desmopressin increases blood concentration of vWF, Factor VIII and plasminogen activator inhibitor-1 [144-146]. These effects are present in patients with bilateral nephrectomy, and abolished in patients with inactivating mutations of V2R (X-linked diabetes insipidus), which demonstrates the direct implication of extrarenal V2R [147].

In spite of the effects reported above, it seems unlikely that the pharmacological inhibition of V2R could lead to a clinically significant disturbance of vascular physiology, because patients with X-linked diabetes insipidus do not present with hematological or vascular disorders. In addition, both randomized controlled trials and follow-up studies of tolvaptan in ADPKD did not report a significant increase in blood pressure or cardiovascular events (a small decline in blood pressure is even observed on the long term (see above). Nevertheless, detailed studies of the effects of vaptans on the cardiovascular system, and comparison with increased hydration are lacking and are currently insufficient to suggest prioritizing either attitude in this setting. In particular, whether vaptans may improve or aggravate endothelial function may be particularly relevant in ADPKD patients, in which endothelial dysfunction is present as a consequence of the disrupted polycystin complex in arteries [148].

8. Which strategy should be most effective for reducing V2R-mediated adverse effects?

In ADPKD, reducing vasopressin V2R-mediated effects is a major issue because of their direct influence on cyst growth induced by V2R-dependent formation of cAMP. More generally, in CKD, reducing V2R-mediated effects is also relevant because they participate in glomerular hyperfiltration and increased albuminuria [22, 24]. It is currently difficult to conclude which of the two strategies (selective V2R antagonist or recommendations to voluntarily increased water intake) would be more effective to

slow progression of all forms of CKD. Moreover, very few results are yet available from trials based on a voluntary HWI.

A few recent trials showed the feasability of voluntary HWI. However, they concerned only small numbers of subjects and for short durations [26, 29, 30]. A one-year trial in Canadian patients with CKD showed no benefit of HWI for kidney protection in spite of monthly coaching [28]. In this and several other HWI trials, fluid intake was lesser than prescribed [28, 149, 150]. This is also the case in patients with recurrent urolithiasis, in spite of their painful symptoms [151, 152]. There are wide inter-individual differences in the tendency to concentrate urine and thus probably in usual beverage consumption among subjects [153]. Future "HWI" studies could select "low drinkers" with high baseline copeptin and U_{osm} [35].

V1aR-mediated actions of AVP were assumed for a long time to be potentially harmful, but no related adverse effects have been reported in the long-term follow-up studies of V2R antagonists. The rise in AVP secretion induced by tolvaptan is apparently not large enough to impact extra-renal tissues expressing V1aR. However, the influence of AVP on V1aR may be significant within the kidney because AVP gets concentrated in the luminal fluid of the CD by water reabsorption, and in the medullary vasa recta supplying the RMIC because of counter-current exchanges between descending and ascending vasa recta.

A recent review described how tolvaptan treatment should be proposed in the category of patients who can best benefit of this treatement [154]. Compared to HWI, limitations of tolvaptan include the risks of some adverse effects (liver toxicity, fatigue, hyperuricemia) and cost. A modest hyperuricemia was reported in 14.8% of the patients in the Japanese branch of the TEMPO 3/4 trial [155]. The intense polyuria and nocturia are responsible for some treatment discontinuation. As discussed recently, increasing the tolerability of this treatment is a major challenge [154]. Interestingly, the doses used up to now may possibly be reduced. Indeed, an important question that has rarely been addressed is how low should U_{osm} be reduced. In a small trial in ADPKD patients, tolvaptan given for three weeks (with 90/30 mg in the last week) reduced urine osmolality from 359 {IQ 289-425} mosm/kg H_2O at baseline to 139 {IQ 126-173}

mosm/kg H_2O on the third week [57]. In the TEMPO 3/4 trial, the mean U_{osm} observed over the course of the study was 220-230 mosm/kg H_2O (figure 3A in [156]). Based on early dose-finding studies of tolvaptan, in which efficacy was defined as the capacity to achieve U_{osm}<300 mosm/kg H_2O, Torres et al deduced that further lowering of U_{osm} below 300 may provide no significant additional benefit, while decreasing quality of life [6]. It is important to note that, in this range of low U_{osm}, the difference in daily urine volumes between U_{osm} of 220 or 300 mosm/kg is very large. For a given osmolar load of 900 mosm/d, it drops by more than 1 liter (from 4.1 to 3.0 L/d). Thus, treatments with lower doses than used in previous trials [7] could antagonize V2R-mediated actions while inducing less intense side effects (thirst, polyuria, nycturia [7]), allow better compliance (and could be less expensive).

Another reason why a lower dose of tolvaptan might be appropriate is because the adverse influence of vasopressin on kidney function (including the induction of glomerular hyperfiltration) appears to be biphasic. It is restricted to situations in which urine is still concentrated above plasma osmolality. It is not observed when urine is hypo-osmotic [21, 22, 157, 158]. A recent study in 1265 CKD patients suggests that either low or high water intake may not be beneficial in CKD: the association between the rate of eGFR decline and water consumption was U-shaped [159]. These observations thus suggest that the dose of tolvaptan might be adjusted to target an U_{osm} close to that of plasma, but not significantly below it. Given the benefits in terms of quality of life and adherence to the treatment, it might be worth testing in a clinical trial if a lower dose of tolvaptan would be as efficient as the doses prescribed presently.

During V2R antagonism, we assume that a significant part of the aquaresis may result from V1aR-mediated effects and resulting PGE2 production. Unfortunately, urinary PGE2 excretion has never been evaluated in patients treated with tolvaptan. A new clinical trial could evaluate the differences in urinary PGE2 excretion rate in healthy subjects, and/or in kidney patients treated with either tolvaptan or a placebo, or in patients recommended to increase their water intake. If a significantly greater PGE2 excretion rate is observed in the tolvaptan group, and the lowest excretion rate in the group with voluntary HWI, it will suggest that PGE2 do indeed participate in the aquaresis (as it does in monogenic diseases characterized by a high PGE2 production).

In summary, while both strategies may have beneficial effects, the information reviewed above lead us to assume that the pharmacological V2R antagonism, with resulting stimulation of V1aR and increased PGE2 production, may provide greater benefit than voluntary HWI. The influence of tolvaptan on PGE2 excretion rate and the possibility to use somewhat lower tolvaptan doses than presently prescribed remain to be evaluated.

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Figure Legends

Figure 1. A and **B.** Autoradiographies showing binding of a radio-iodinated selective V1aR antagonist in adult rat kidney. Reproduced from [43]. **A.** The four kidney zones are indicated: C, OS, IS, and IM = cortex, outer stripe and inner stripe of the outer medulla, and inner medulla, respectively. V1aR labeling is observed in the cortex, the lower half of the IS, and the IM. Calibration bar = 1 mm. **B.** Higher magnification of a tangential section through the IS shows labeled thin descending limbs of short looped-nephrons (h) apposed at the periphery of unlabeled vascular bundles (vb). In the lower part of the figure, intense labeling is also observed in collecting ducts (cd) in the upper part of the IM. Calibration bar = 200 µm. **C** and **D.** Expression of the urea transporter UT-A2 in the inner stripe. **C.** Epon section of a mouse kidney through the deep IS, labeled for UT-A2. The thin descending limbs of short loops (S), lying around a vascular bundle, are labeled for UT-A2, whereas those of long loops (L), in the interbundle regions, are not. This study concludes that UT-A2 expression is restricted to the last 28% to 44% of the descending thin limbs of all short looped-nephrons. Magnification, x 80. Reproduced from [45]. **D.** In situ hybridization of UT-A2 in a rat kidney. Transverse section through the deep IS showing UT-A2 positive short loops gathered around negative vascular bundles (courtesy of Matthias Hediger, Boston Mass, USA; 1997). Note the similar pattern of labeling of UT-A2 (in D) and of V1aR (in B) in tubules gathered around vascular bundles. This suggests a possible co-localization of V1aR and UT-A2 in the thin descending limbs of short loops [43-45].

Figure 2. Effects of AVP (15mg/kg BW) on sodium excretion rate without or with the co-administration of the V1aR antagonist SR49059 (10 mg/kg BW). The effect of the antagonist alone and of dDAVP (selective V2 agonist) are also shown. Results of the experimental day are expressed as percentage of values observed during the previous basal day (with sham injections) in the same rats. Paired t test, experimental versus basal day : ** $P < 0.01$; *** $P < 0.001$. AVP injection at 15 mg/kg induced a significant rise in Na excretion, but injections at 1 or 5 mg/kg did not (not shown here). The V1aR antagonist induced a modest significant rise in urine osmolality (not shown here) and abolished the rise in sodium excretion rate due to AVP. dDAVP induced a

significant decline in sodium excretion, most likely due to increased ENaC-dependent Na reabsorption. Modified from [60].

Figure 3. Evidence for in vivo influence of prostaglandins on the antidiuretic response to vasopressin. Anesthetized, water diuretic dogs received a bolus of 100 mU vasopressin, twice at about a 120 min interval. The second bolus was given after the administration of 2 mg/kg indomethacin. Reproduced from [92].

Figure 4. A. Systolic blood pressure (SBP) in rats during an eight-week treatment with the NO synthase inhibitor N^G-nitro-L-arginine (L-NNA), the selective V1aR antagonist SR 49059, or both in combination. Data are means ± SEM. L-NNA induced a significant progressive rise in SBP; 2-way ANOVA: *** P<0.001. The V1aR antagonist alone had no effect on SBP but, contrary to expectations, it significantly worsened the rise induced by L-NNA (red double arrows). This suggests that the normal activation of V1aRs is actually protective. Significant interaction of L-NNA and SR 49059: # P<0.001. Adapted from [97]. **B.** Influence of a chronic infusion of AVP (acting on both V2Rs and V1aRs) or dDAVP (acting selectively on V2Rs) on mRNA expression of facilitated urea transporters in the four medullary zones of the Brattleboro rat kidney (superficial and deep inner stripe, and base and tip of inner medulla). Adapted from [98]. Exp = Experimental, after a 5 day infusion of AVP or dDAVP. * : $p < 0.05$ for dDAVP vs basal condition. dDAVP induced a marked increase in UT-A2 expression in the deep IS, and of UT-A1 in the upper IM, whereas almost no change was observed with an infusion of AVP. This suggests that the activation of the V1aRs (during AVP infusion) attenuated the influence due to activation of the V2Rs.

Figure 5. Effects of AVP, via V1a and V2 receptors, on different cell types in the kidney and their consequences on the urine concentrating ability. Not shown are additional effects on the thick ascending limbs via V2Rs (direct) and V1aRs (indirect, mediated by paracrine effects of PGE2 issued from surrounding CCDs). CCD and IMCD = cortical and inner medullary CDs, respectively. PG-R = PGE2 receptor.

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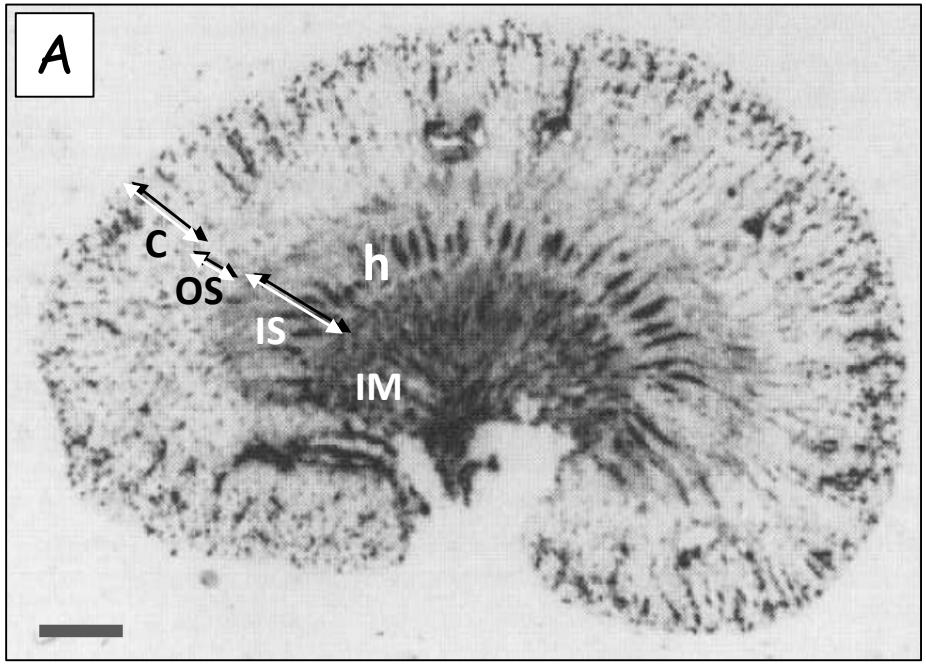
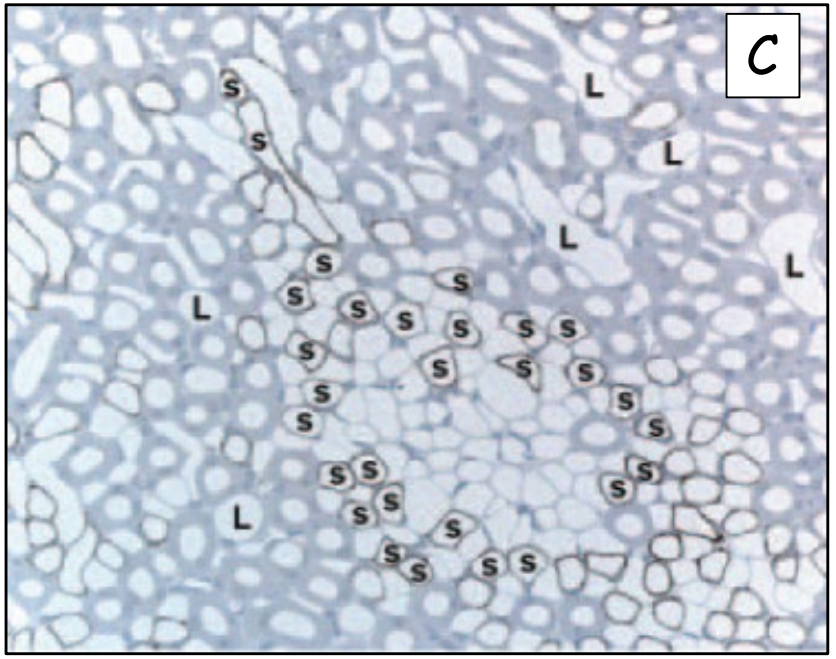
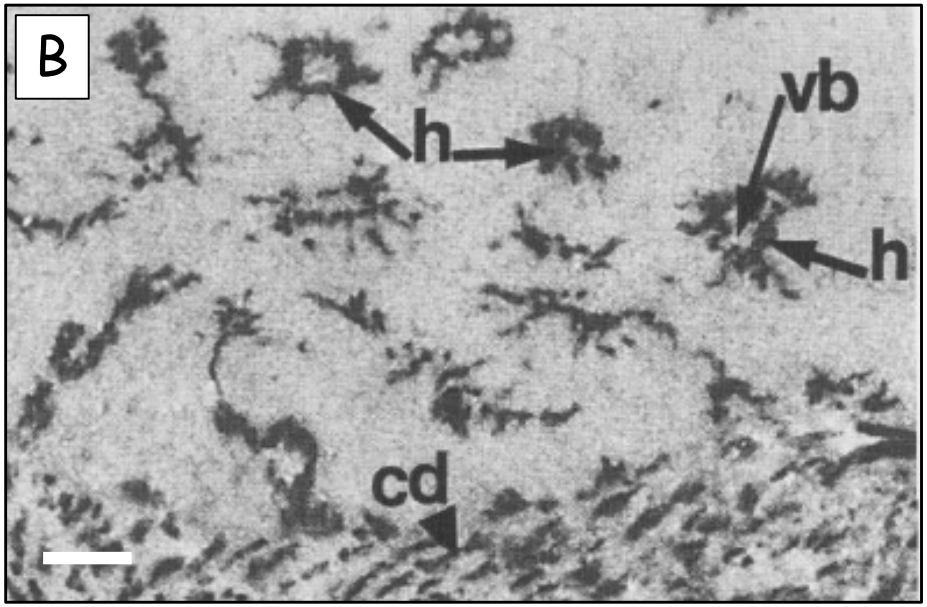
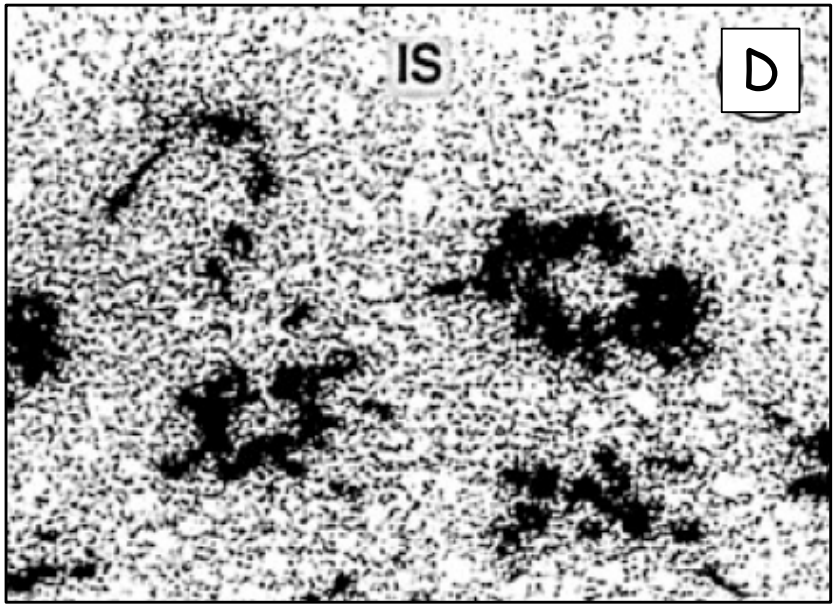
Bankir et al. Figure 1

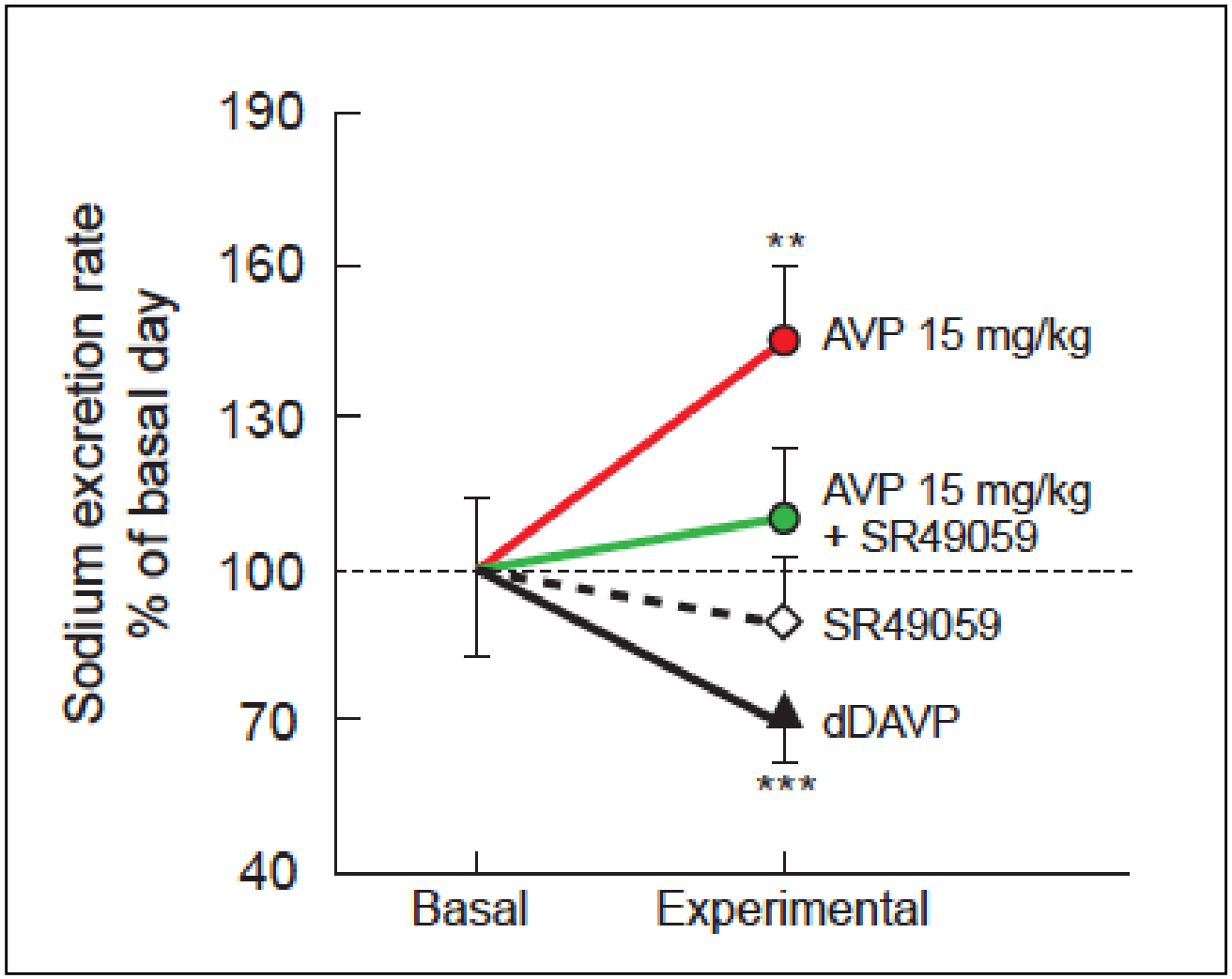








Bankir-Bichet. Figure 2



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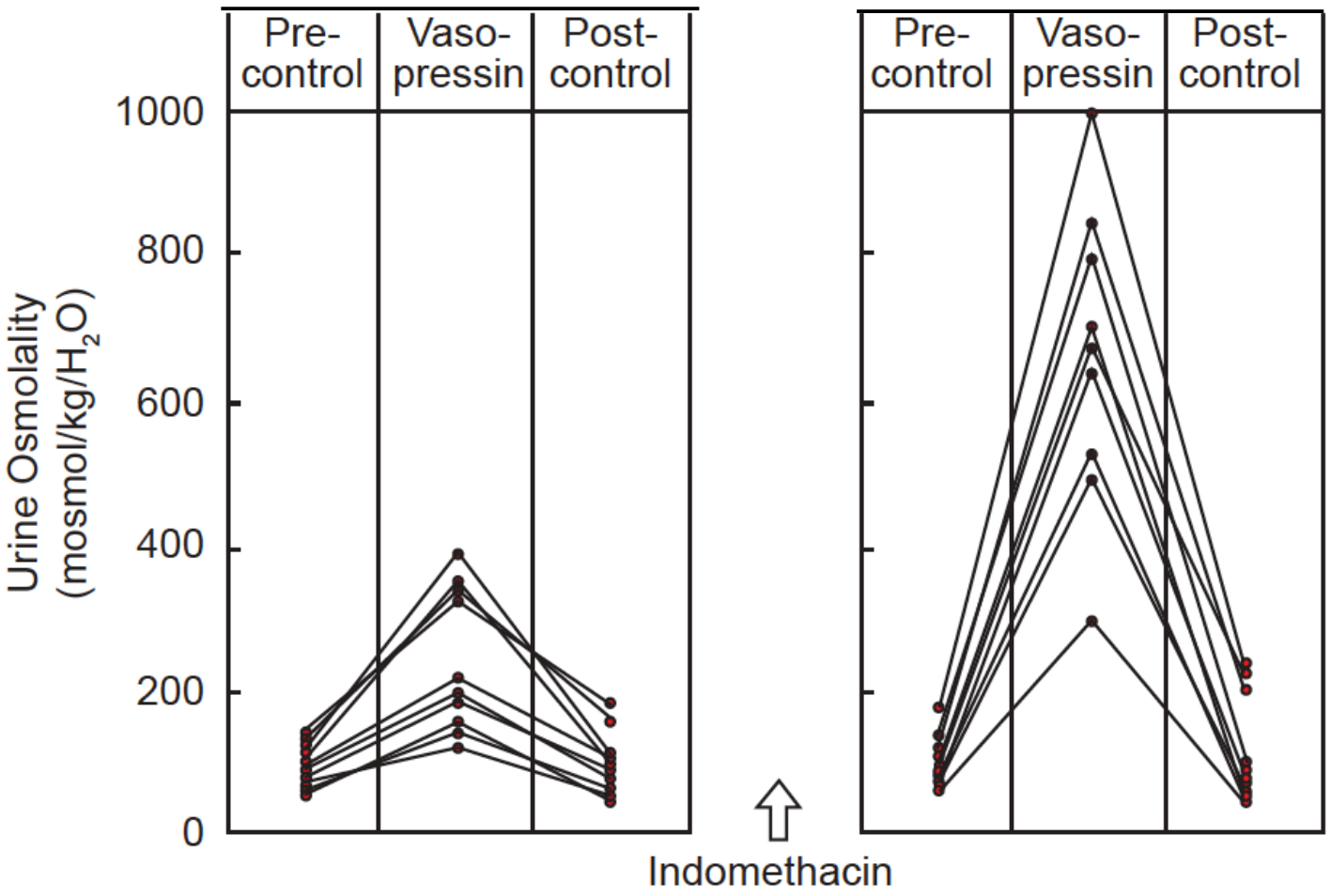
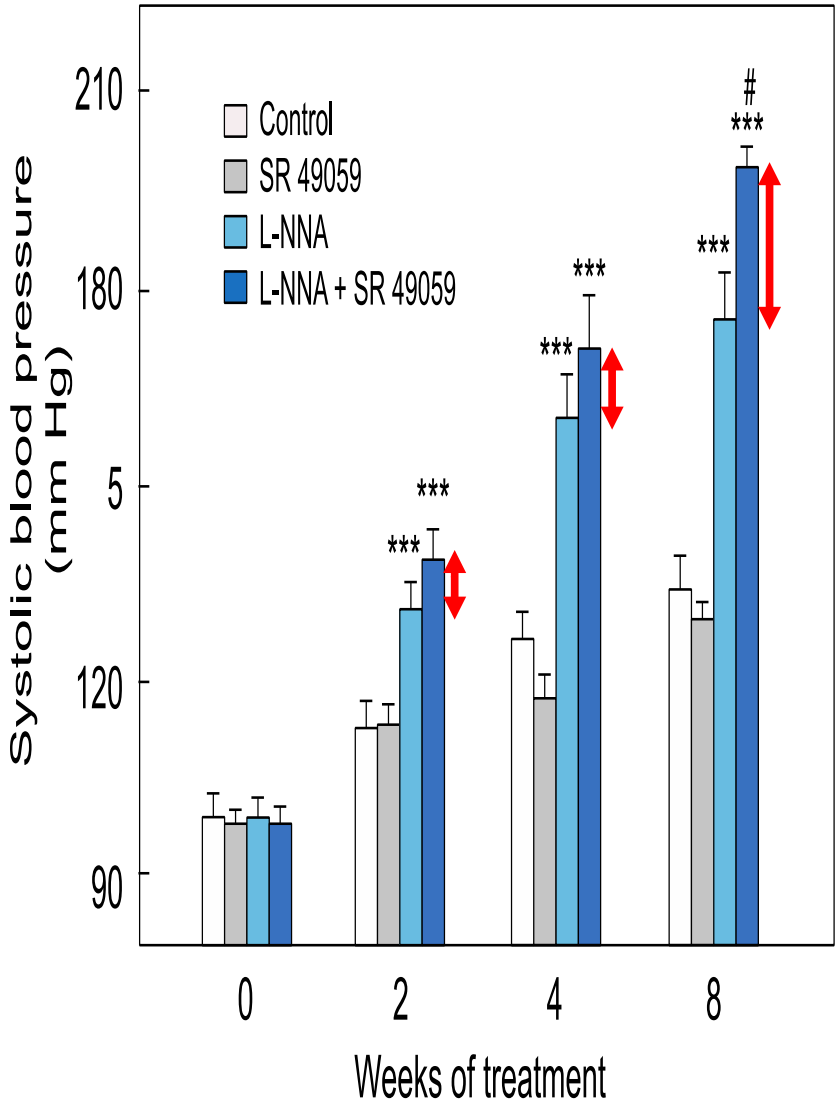


Bankir-Bichet. Figure 4

A



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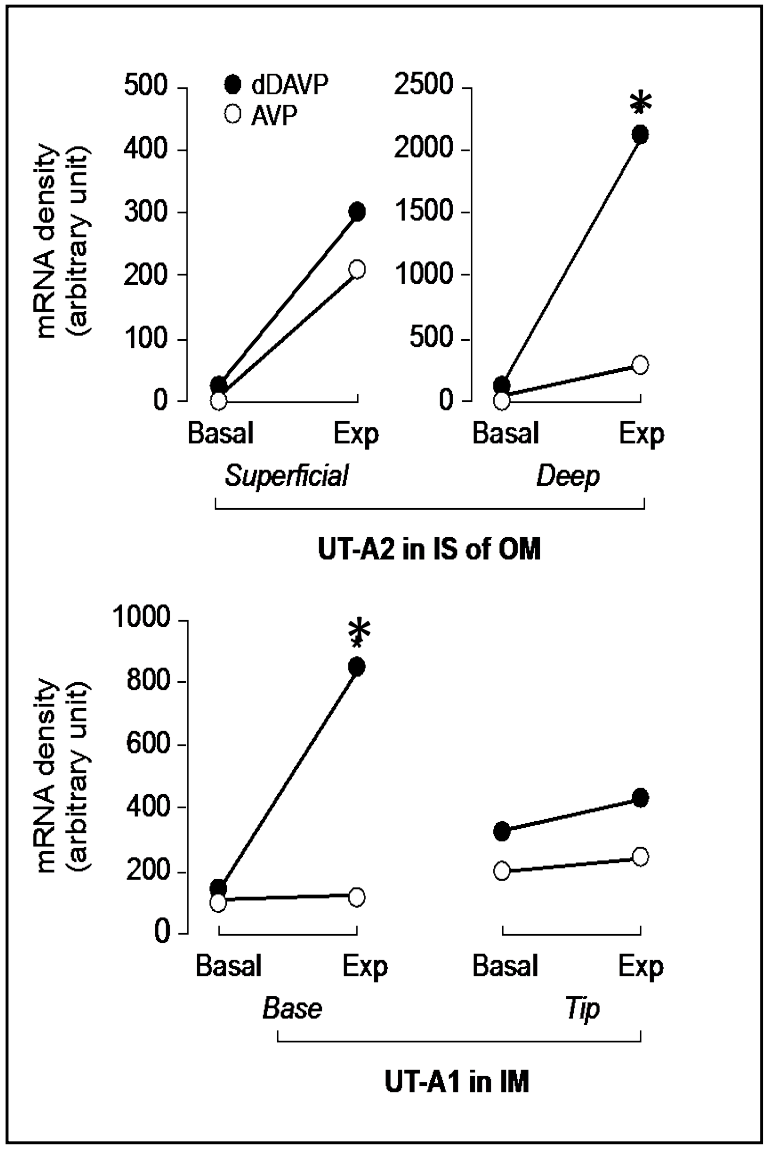

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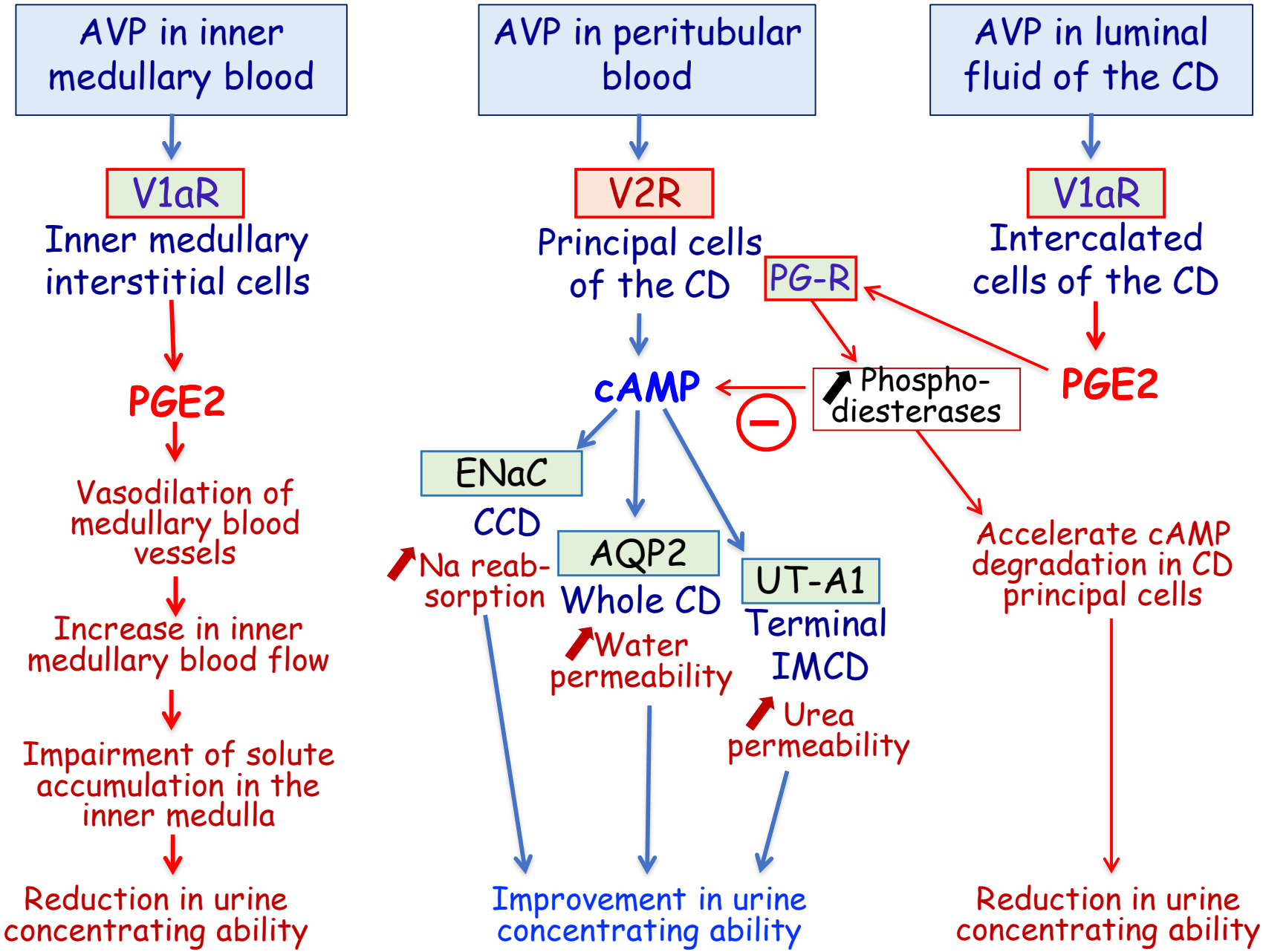

Table 1. Target sites of circulating vasopressin in the body and the receptors involved (target sites in the central nervous system are not considered here).

	V2 receptors	**V1a receptors**	**V1b = V3 receptors**
Vascular smooth muscle cells		Yes	
Endothelium	Yes		
Platelets		Yes	
Heart			Yes
Kidney	Yes	Yes	
Liver		Yes	
Adipocytes		Yes	
Spleen			Yes
Lung (pneumocytes)	Yes		
Inner ear	Yes		
Pancreatic islets			Yes
Adrenal gland		Yes	Yes
Anterior hypophysis			Yes
Thymus			Yes
Uterus			Yes
Breast			Yes

Table 2. Main structures expressing V2 and V1a receptors in the kidney, and resulting main effects

Structures	Main effects
V2 receptors	
Thick ascending limb (basolat. mbne)	Stimulation of Na-K-2Cl mediated transport
Connecting tubule (basolat. mbne)	Insertion of AQP2 in the luminal membrane
CD principal cells (basolat. mbne)	Insertion of AQP2 in the luminal membrane Stimulation of ENaC-mediated Na reabsorption Activation of UT-A1 in the terminal IMCD
V1a receptors	
Arterial vasa recta smooth muscle cells	Vasocontriction (not significant in vivo for usual AVP concentrations)
CD intercalated cells (luminal membrane)	Stimulation of prostaglandin production
Inner medullary interstitial cells	Stimulation of prostaglandin production, leading to vasodilation of medullary vasculature

basolat. mbne = basolateral membrane

Table 3. Similarities and differences induced by voluntary increase in hydration or treatment with a vaptan

	Voluntary Increase in Hydration	Treatment with a Vaptan
Water intake	Increased	Increased
Urine volume	Increased	Increased
Urine osmolality	Decreased	Decreased
Plasma osmolality	Decreased	Increased
Thirst	Decreased	Increased
Vasopressin secretion	Decreased	Increased
V1aR- and V1bR-mediated effects	Decreased	Increased
Cause of higher water intake	Voluntary	Increased thirst
Observance	Difficult to drink in excess of thirst	Easy to take a pill

V1aR and V1bR = vasopressin V1a and V1b receptors, respectively.

Table 4. Influence of either AVP or dDAVP infusion on CKD progression in Brattleboro rats. Results observed during the third month after 5/6th nephrectomy and initiation of the AVP or dDAVP infusion.

	Control (DI)	AVP (V1a & V2 agonism)		dDAVP (V2 agonism)	
Body weight (g)	339 ± 7	364 ± 12		370 ± 18	
Food intake (g/d)	13.8 ± 0.5	13.8 ± 1.4		14.5 ± 1.8	
Urine flow rate (ml/d)	105 ± 8	20 ± 3	§	32 ± 6	§
Urine osmolality (mosm/kg H_2O)	199 ± 13	997 ± 141	§	694 ± 129	§
Urinary protein excretion (mg/d)	23 ± 3	21 ± 4		49 ± 10	§ #
Systolic blood pressure (mm Hg)	194 ± 12	176 ± 15		204 ± 12	
Hematocrit (%)	43 ± 1	40 ± 2		36 ± 2	§
Plasma sodium concentration (mmol/L)	154 ± 1	146 ± 3	§	148 ± 2	§
Plasma potassium concentration (mmol/L)	3.36 ± 0.05	3.87 ± 0.17	§	3.95 ± 0.13	§
Plasma urea concentration (mmol/L)	15.4 ± 1	15.6 ± 2.0		30.9 ± 7.3	§ #
Plasma creatinine concentration (µmol/L)	107 ± 3	100 ± 6		127 ± 11	§ #
Kidney weight (mg/100g BW)	331 ± 16	541 ± 72	§	671 ± 50	§

Comparison of the three groups by a one-way ANOVA followed by Fisher post-hoc test.
AVP or dDAVP versus control : § = $p < 0.05$ or less; dDAVP versus AVP : # = $p < 0.05$ or less
Data from reference 24.