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Vasopressin antagonists in polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common of the inherited renal cystic diseases and a leading cause of ESRD (1). It is genetically heterogeneous with two genes identified, *PKD1* and *PKD2*. Autosomal recessive polycystic kidney disease (ARPKD) is less common than ADPKD, but together with nephrophthisis, is the leading cause of ESRD in childhood. It is caused by mutations to *PKHD1* (2). Currently there is no effective therapy for these diseases. Advances in the understanding of cystogenesis and availability of genetically related animal models provide unique opportunities to develop effective treatments. This article summarizes recent advances raising the hope that vasopressin V2 receptor antagonists will become a safe and effective therapy for PKD.

Pathogenesis of Polycystic Kidney Disease

The cloning of *PKD1* and *PKD2* in 1994 and 1996 (3–6) and of *PKHD1* in 2002(7–9) were major steps towards the understanding of polycystic kidney disease. The proteins encoded by these genes are membrane associated proteins. Polycystin-2 (PC2 or TRPP2), the protein encoded by *PKD2*, is a TRP channel with high permeability to calcium. Polycystin-1 (PC1) and fibrocystin/polyductin (FC/PD) are thought to be cell surface receptors that directly in the case of PC1 (10, 11) or indirectly in the case of FC (12) interact with and regulate the channel function of PC2. PC1 and FC/PD also have other functions, some of which are in turn regulated by PC2. For example, PC2 binding to PC1 reduces the ability of PC1 to constitutively activate G-proteins (13).

PCs and FC/PD are multifunctional proteins with numerous interacting partners that are essential to maintain the differentiated phenotype of the tubular epithelium (14). Reduction in one of these proteins below a critical level induces changes in protein trafficking and targeting, cell-matrix and cell-cell interactions, proliferation and apoptosis, planar polarity, and fluid secretion that result in the initiation and growth of cysts (15). The underlying molecular mechanisms are complex. The PCs and FC/PD participate in kinase cascades that connect interactions at cell-matrix and cell-cell contacts to the regulation of nuclear transcription and cell differentiation (16–18). PC1 and FC may also undergo regulated intra-membrane proteolysis, a process initiated by ligand binding that releases cytoplasmic peptide fragments that migrate to the nucleus and affect transcription (19–22).

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The role of the PKD proteins in primary cilia and regulation of intracellular calcium homeostasis has received the most attention. PC1, PC2 and FC/PD are located in primary cilia (23–25). In the primary cilia, the PC/FC complex senses and translates mechanical stimulation into Ca entry, which triggers calcium-induced calcium release from the ER (26–28). PC2 is also present in the ER where it interacts with other calcium channels, the IP3R and RR (29–32). Together, PC2, IP3R and RR are responsible for Ca release from intracellular stores. Reductions in the levels of PCs or FC below a critical threshold impair intracellular Ca homeostasis (33, 34). In renal tubular epithelial cells, intracellular calcium limits cAMP accumulation by inhibiting AC6 and stimulating PDE1 (35–37). This may account for the renal accumulation of cAMP in animal models of ADPKD and ARPKD (38–41). Cyclic AMP stimulates cell proliferation and chloride (CFTR-mediated) driven fluid secretion (42–44). While under normal conditions cAMP inhibits MAP kinase signaling and cell proliferation, in conditions of Ca deprivation such as in polycystic kidney disease it stimulates cell proliferation in a src, ras and b-raf dependent manner. This proliferative effect may be further enhanced by the stimulation of mislocalized Erb-B receptors by EGF-like factors present in cyst fluid (45). The signaling pathways activated downstream from mutated PC1 converge with those activated in tuberous sclerosis complex, possibly due to disruption of the physical interaction between PC1 and tuberlin or to phosphorylation of tuberlin by MAPK and Akt leading to activation of mTOR (46).

Opportunities for intervention

The increased understanding of the molecular mechanisms of polycystic kidney disease has provided a number of targets for therapeutic intervention (Figure 1). Triptolide binds to PC2, induces Ca release by a PC2 dependent mechanism, and ameliorates cystic disease in a Pkd1 animal model (47). Consistent with observations of milder disease in patients who have ADPKD and cystic fibrosis (48, 49), CFTR inhibitors inhibit the development of cysts by MDCK cells in collagen gels (50) and in metanephric organ cultures (51) by inhibiting chloride secretion. How to apply this strategy without inducing cystic fibrosis will be challenging. Erb-B tyrosine kinase inhibitors have been used successfully in a variety of models, but different Erb-B receptors seem to be important in different animal models (45, 52–55). These drugs have significant toxicity, which may limit their use for extended periods of time. The same can be said for src, mek and cdk inhibitors (56–58). This concern is less for mTOR inhibitors thanks to the extensive experience with this drug in transplantation (46, 59, 60).

Rationale for therapies targeting the AVP-V2 receptor axis and renal cAMP

Targeting strategies that minimize the effects of a medication on normal cells are essential in chronic diseases that require long-term treatments. The central role of cAMP in the pathogenesis of PKD and the ability to hormonally modulate cAMP in a cell-specific manner provide opportunities for such strategies in PKD. Among various hormonal systems that may influence the development of PKD, a combination of favorable factors make the arginine vasopressin (AVP)- AVP V2 receptor axis a particularly attractive target:

- A. The cysts in PKD derive predominantly from vasopressin sensitive tubular segments expressing V2 receptors, i.e. the collecting duct and the distal nephron. While there is general agreement that the cysts in ARPKD and nephronophthisis derive from collecting ducts, a careful review of the literature indicates that cysts in ADPKD and in slowly progressive Pkd1 and Pkd2 animal models derive predominantly from collecting duct and distal nephron (61). The expression of V2 receptors is strong in the medullary thick ascending limb, macula densa, and medullary collecting duct, intermediate in connecting tubule and cortical collecting duct, and low in cortical thick ascending limb and distal convoluted tubule (62).

- B. Vasopressin acting on V2 receptors is the main hormonal regulator of adenylyl cyclase activity in freshly dissected collecting ducts (63). The V2 induced effects on cAMP and water permeability may be limited by the action of AVP on V1a receptors on apical and basolateral membranes, stimulating phospholipase C, phosphoinositide hydrolysis and Ca^{2+} release from the endoplasmic reticulum (64).
- C. To avoid dehydration mammals live under the constant tonic action of AVP on the distal nephron and collecting duct (65–68). Only after drinking large volumes of liquid do plasma AVP levels decrease enough to render the urine more dilute than plasma. Thus, during most of the day, cyst epithelial cells are persistently stimulated to proliferate and secrete fluid.
- D. The circulating levels of AVP are increased in human ADPKD and in all animal models where it has been ascertained (69–71). This may be due to a central defect (72) or, more likely, to compensate for the reduced concentrating capacity of the polycystic kidneys. This concentrating defect may be due to the disruption of the corticomedullary architecture by the cysts, early development of tubulointerstitial disease or directly linked to the PKD cellular phenotype (73). The upregulation of aquaporin 2 (AQP2) in polycystic kidneys (38–40, 73), in sharp contrast to other forms of nephrogenic diabetes insipidus, suggest enhanced vasopressin activity and a defect distal to the production of AQP2.
- E. In contrast to the V2 receptor downregulation in other conditions with persistently elevated AVP (74), the V2 receptor is overexpressed in polycystic kidneys (38–40, 73). This is probably due to the upregulation of the V2 receptor promoting activity by cAMP (75).
- F. The restricted expression of V2 receptors to epithelial cells of the distal nephron and collecting duct (62) and on endothelial cells, where it has been implicated in the secretion of von Willebrand factor (76), suggest that V2 antagonists are likely to be well tolerated. Indeed, there is already considerable experience with these compounds in clinical trials for congestive heart failure and hyponatremia. These have as main side effects an expected mild to moderate thirst and dry mouth, and increased urination that are all generally well tolerated (77–81).

Preclinical trials of Vasopressin V2 receptor antagonists

Gattone et al initially reported that administration of an AVP receptor antagonist ameliorated the cystic enlargement and azotemia in a mouse model of rapidly progressive renal cystic disease (73). To test the effects of AVP V2 receptor antagonists in animal models orthologous to human diseases, we have used two compounds, OPC-31260 and tolvaptan. OPC-31260, a strong antagonist of the V2 receptor in rodents that is 82 times more selective for rat V2 receptors than for rat V1a receptors (82). Because OPC-31260 is a relatively weak antagonist of the human V2 receptor, we have also used tolvaptan, a stronger antagonist for the human receptor (K_i value 22 times higher than that for OPC-31260), which is 29 times more selective for human V2 receptors than for human V1a receptors (82).

The PCK rat is a model of human ARPKD caused by a splicing mutation (IVS35–2A→T) that skips exon 36 and leads to a frameshift in *Pkhd1*. Administration of OPC-31260 to PCK rats between three and ten weeks of age reduced the renal accumulation of cAMP and Ras and ERK activation, and inhibited disease development, as reflected by lower kidney weights, plasma creatinine and BUN concentrations, renal cyst volumes, and mitotic and apoptotic indices (38, 40). By comparing the kidney weights of the treated and untreated PCK rats to those of 10 week-old wild-type Sprague-Dawley rats, the estimated degree of

protection was 60% to 75% depending on the dose. Administration of OPC-31260 from ten to eighteen weeks of age reduced the renal accumulation of cAMP and inhibited disease progression, as reflected by lower kidney weights, plasma creatinine and BUN concentrations, renal cyst and fibrosis volumes, mitotic and apoptotic indices, and systolic blood pressures. The weights of the kidneys at eighteen weeks of age in the treated rats were identical to those of the control PCK rats at 10 weeks of age, indicating that the administration of OPC-31260 completely halted disease progression. OPC-31260 did not have a significant effect on the fibropolycystic liver disease, consistent with the absence of VP-V2 receptors in the liver.

The *Pkd*^{-WS25} mouse is a double heterozygote for a *Pkd2* null allele and an unstable *Pkd2* WS25 mutation. It is a model of human ADPKD (*PKD2*) that reliably develops renal cysts within three months. OPC-31260, administered in the diet to *Pkd2*^{-WS25} mice between 3 and 16 weeks of age, reduced the renal accumulation of cAMP and inhibited disease development, as reflected by lower kidney weights, plasma BUN concentrations, renal cyst and fibrosis volumes, and mitotic and apoptotic indices (39). The kidney weights of treated *Pkd2*^{-WS25} mice were similar to wild-type, indicating that renal enlargement was prevented. OPC-31260 did not have a significant effect on polycystic liver disease.

The *pcy* mouse is a model of nephronophthisis caused by a missense mutation in *NPHP3*, the gene mutated in adolescent nephronophthisis. Administration of OPC-31260 to CD1/*pcy* mice between four and thirty weeks of age inhibited the renal accumulation of cAMP and disease development, as reflected by lower kidney weights, plasma BUN concentrations, renal cyst and fibrosis volumes, and mitotic and apoptotic indices (38). Administration of OPC-31260 to CD1/*pcy* mice between fifteen and thirty weeks of age also inhibited the renal accumulation of cAMP levels and disease progression, as reflected by the lower kidney weights, plasma BUN concentrations, renal cyst and fibrosis volumes, and mitotic and apoptotic indices. Kidney weights of mice started on treatment at fifteen weeks and killed at thirty weeks of age were significantly lower than those of untreated mice at fifteen weeks of age. This suggests that OPC-31260 not only halted disease progression but also induced disease regression.

To confirm that tolvaptan, a V2 receptor antagonist used in clinical trials for hyponatremia and congestive heart failure, is also capable of inhibiting the development of polycystic kidney disease, this compound was administered to the same animal models of polycystic kidney disease. In the three models, the administration of tolvaptan reduced the renal enlargement and cystic pathology (40, 83, 84).

Modulation of renal cystogenesis by circulating vasopressin

To confirm that the protective effect of V2 receptor antagonists is indeed due to V2R antagonism, we generated PCK *AVP*^{+/+}, PCK *AVP*^{+/-}, and PCK *AVP*^{-/-} rats, as well as wild-type and Brattleboro controls, by breeding F1 rats resulting from PCK (*Pkhd1*^{-/-}) and Brattleboro (*AVP*^{-/-}) crosses. Brattleboro rats are homozygous for a 1-bp deletion of a guanine nucleotide in the second exon of the *AVP* gene and lack circulating AVP. At 10 and 20 weeks of age PCK *AVP*^{-/-} rats exhibited polyuria and reduced renal cAMP compared to the PCK *AVP*^{+/+} rats (85). This was accompanied by a marked reduction in kidney weight and renal cyst and fibrosis volumes.

To confirm that the protective effect of AVP deficiency on the development of polycystic kidney disease is due the lack of stimulation of the renal V2 receptors, PCK *AVP*^{-/-}, PCK *AVP*^{+/-}, and wild type rats were treated with the V2 agonist 1-deamino-8-D-arginine vasopressin (DDAVP) administered via osmotic minipumps at a dose of 10 ng/hr/100 gm body weight between 10 and 20 weeks of age (85). This dose is the minimal dose necessary

to achieve urine osmolalities in Brattleboro rats similar to those observed in wild type Sprague Dawley rats. Administration of DDAVP to PCK *AVP*^{-/-} corrected the polyuria, increased the renal concentration of cAMP, recovered the full cystic PCK phenotype as reflected by the kidney weights, and cyst and fibrosis indices, and significantly increased the plasma BUN concentrations. Administration of DDAVP to PCK *AVP*^{+/-} rats increased the severity of polycystic kidney disease, as reflected by significantly higher kidney weights, cyst and fibrosis indices, and plasma BUN concentrations. Administration of DDAVP to wild type rats at the dose used in this study caused a slight but significant increase in renal mass per unit of body weight without inducing cystic changes or fibrosis. This is consistent with previous reports of selective AVP-induced hypertrophy of the medullary thick ascending limb in Brattleboro rats (86, 87).

A non-genetic approach to suppress vasopressin action also supports the importance of vasopressin in the modulation of renal cystogenesis. Addition of 5% glucose in the drinking water increased fluid intake and urine output 3.5-fold, reduced urinary AVP excretion, AVP V2 receptor expression and ERK activation, inhibited proliferation, reduced the severity of the cystic disease, and improved renal function (88).

Other observations supporting an effect of vasopressin on renal cystogenesis

The long-acting somatostatin analogue octreotide and the endothelin ET_B receptor antagonist A-192621 have been reported to have opposing effects in animal models orthologous to human polycystic kidney disease that may be mediated by opposing effects on vasopressin stimulated cAMP accumulation in the kidney. The administration of octreotide to PCK rats lowers cAMP levels and inhibits the development of polycystic kidney disease, while the administration of A-192621 to *Pkd2*^{-/WS25} mice increases urine osmolality and renal cAMP and aggravates the severity of the cystic disease (89, 90). At physiological concentrations somatostatin inhibits vasopressin induced cAMP generation and water permeability via Gi coupled SSTR1 and SSTR2 receptors which are predominantly located in the distal nephron and collecting tubule (91–93). On the other hand, endothelin-1 acting *via* ETB receptors, the predominant endothelin receptor subtype in the collecting tubules, inhibits vasopressin action and promotes diuresis (94).

Other potential benefits of AVP V2 receptor antagonists in polycystic kidney disease

In addition to its effects on cystogenesis, AVP may have effects on blood pressure and renal function that may be relevant to the progression of polycystic kidney disease:

- A. Effects on blood pressure. The inverse correlation between urine concentrating capacity and average 24-hour blood pressures in children with ADPKD (71) and the correlation between urine volume and mean arterial blood pressure in MDRD study participants with ADPKD(95) suggest that the increased circulating levels of AVP observed in ADPKD may contribute to the development of hypertension, one of the most common manifestations of this disease. AVP effects on blood pressure are mediated by V1a and V2 receptors. V1a receptor activation may increase blood pressure by a direct effect on vascular smooth muscle and by reducing medullary renal blood flow and pressure natriuresis (96). V2 receptor activation enhances beta and gamma epithelial sodium channel (EnaC) expression and EnaC function and acts synergistically with aldosterone in the cortical collecting duct (97–99). On the other hand V2 receptor activation may also exert an antihypertensive effect by inducing NO synthesis in collecting ducts and increasing medullary blood flow

(100). Impaired NO synthesis, which has been reported in human ADPKD and in animal models of polycystic kidney disease (101, 102), may be a prerequisite for the pro-hypertensive effect of vasopressin.

- B. CKD progression.** AVP levels are increased in CKD (103) and Bankir et al. have proposed that this contributes importantly to disease progression (104–107). AVP (or exogenous dDAVP) elevates urea and lowers NaCl concentrations in the thick ascending limb of Henle and at the macula densa by increasing intrarenal urea recycling. This results in a suppression of tubuloglomerular feedback and a stimulation renin secretion that may lead to glomerular hyperfiltration, albuminuria, renal hypertrophy, and tubulointerstitial disease. In support of this hypothesis, suppression of circulating AVP in 5/6 nephrectomized rats by doubling the daily water ingestion has been shown to reduce proteinuria, blood pressure, renal hypertrophy, glomerulosclerosis, and tubulointerstitial fibrosis (106, 108). The attenuation of renal disease progression in 5/6 nephrectomized Brattleboro is reversed by the administration of dDAVP, suggesting that V2 receptors play a major role in the deleterious influence of vasopressin on disease progression (105). Contrary to these observations, a retrospective analysis of Modification of Diet in Renal Disease (MDRD) patients with baseline GFRs 25 to 55 mL/min/1.73 m² raised the possibility that a high fluid intake could be detrimental to patients with chronic renal insufficiency, particularly to those with ADPKD (95). The patients with the greater urine volumes and the lowest urine osmolalities experienced the fastest GFR declines. Since they tended to have lower serum sodium concentrations and had urines hypotonic to plasma, the authors concluded that excess water intake and not a renal concentrating caused the high urine volume. Further studies will be necessary to elucidate the potential beneficial or detrimental effects of high fluid intake in ADPKD patients with renal insufficiency.

Clinical trials of vasopressin V2 receptor antagonists

The observations in animal models of polycystic kidney disease strongly suggest that AVP is a powerful modulator of cystogenesis and provide support for clinical trials of V2 receptor antagonists in this disease. TEMPO stands for Tolvaptan Efficacy and Safety in Management of PKD and Outcomes and consists of several studies. Two phase 2 studies on the safety, pharmacokinetics, and pharmacodynamics of tolvaptan tablets in ADPKD included 11 and 37 volunteers, 18–60 years old, with a serum creatinine <1.8 mg/dL, randomized to oral placebo or tolvaptan (109–111). Each study began with a 1 day baseline. Patients drank *ad lib* and recorded fluid intake and output.

Study A was a randomized placebo controlled (8 treatment, 3 placebo), ascending dose (0, 15, 30, 60, and 120 mg administered 72 hours apart) study. Urines were collected 0–4, 4–8, 8–12, 12–16, and 16–24 hours post-dosing. Tolvaptan caused dose dependent increases in urine output and reductions in urine osmolality and AQP2 excretion, without significant changes in cAMP excretion. AQP2 excretion changes paralleled those in UO. A significant increase in plasma AVP of 2- to 3-fold was seen at the highest dose of tolvaptan (<0.03 at 24 h post-120 mg), when compared to its own baseline although the difference from the P group only reached a trend (p=0.06). The maximum means observed at any time were 4.1 (tolvaptan) and 3.2 ng/L (placebo). Hypostenuria was sustained during 4–16 hours post-dosing, but UO increased above 300 mOsm/L in 5/8 (15 mg), 2/8 (30 mg) and 1/8 (60 mg) patients 16–24 hours post-dosing. These results indicate that cAMP production may not be inhibited beyond 16 hours post-dosing, AQP2 excretion is not superior to UO to monitor the response, and cAMP excretion is not a good marker of cAMP production in the renal medulla.

In Study B, subjects took tolvaptan at 15/15, 30/0, 30/15 or 30/30 mg twice daily (8 AM and 4 PM) administration for 5 days. Mean urine output increased an average from between 2974–4586 mL/day by a further 2974 to 4586 mL on day 1 declining to a further 1764 to 2274 mL on day 5. A negative fluid balance was seen on acute introduction of tolvaptan (–708 to –901 mL), however this equilibrated by day 5 of Study B (–99 to +558 mL). AVP increased dose-dependently with variable significance compared to baseline. For the highest dose, the mean level at day 5 remained in the mid-normal range 1–3 ng/L. Twice daily administration was necessary for adequate suppression of the vasopressin effect reflected by persistent urine hypotonicity and the best result was obtained with the administration of 30 mg twice daily.

In both studies, tolvaptan dose-dependently induced modest increases in serum sodium and osmolality, without changes in other electrolytes. No appreciable changes in vital signs were noted. Thirst appropriately maintained fluid intake. No serious adverse events were reported and no one discontinued tolvaptan in either study. In Study A, 21 mild and 3 moderate level side effects were reported in the tolvaptan (n=8) and 4 mild and 1 moderate level side effect in the placebo group (n=3). In Study B a total of 35 mild and 6 moderate side effects were reported in 21/37 subjects. Dry mouth was the most frequently reported side effect and was not clearly dose dependent.

The pharmacokinetic profile of oral tolvaptan in ADPKD individuals was similar to a healthy control population. In summary, tolvaptan was well tolerated throughout a range of doses and when administered once or twice a day in ADPKD individuals with normal renal function. Twice daily administration was necessary for adequate suppression of the vasopressin effect reflected by persistent urine hypotonicity.

Forty-six of the 48 participants in the previous phase 2 tolvaptan studies with a GFR >30 mL/min were enrolled in a 3-year, open label, phase 2 clinical trial to acquire tolerability, long-term safety and pilot efficacy data (112). Initially, tolvaptan was administered in ascending doses of 15/15, 30/15, 45/15, 60/30 or 90/30 mg PO twice daily (8 AM and 4 PM) beginning at 30/15 mg to establish maximal tolerated and minimum effective doses (titration phase); 96, 61 and 46% of subjects said they could tolerate 45/15, 60/30 and 90/30 doses for the rest of their life. Subjects were then randomized to a low (45/15, n=22) or a high (60/30, n=24) dose extended therapy. Sixteen of the planned 36-month followups had been completed at the time of the last report. Average daily doses have been 59.7 and 82.5 mg. Polyuria has been well tolerated. Median urine osmolalities have ranged 165–253, 123–154 and 108–152 mOsm/L before AM and PM doses and at bedtime. Serum creatinine increased from 1.20 and 1.36 mg/dL at baseline to 1.36 and 1.49 mg/dL at two months, but had returned towards the baseline level at sixteen months (1.27 and 1.39 mg/dL) in the low and high dose groups, respectively. The administration of tolvaptan was accompanied by slight, but sustained reduction in serum BUN and increase in serum uric acid. Serum sodium concentrations at 2 and 16 months were unchanged from baseline. Serious adverse events led to discontinuation of tolvaptan in 4 subjects: These included a reversible increase in serum creatinine from 1.4 to 1.7 mg/d, left periorbital swelling, atrial fibrillation with transient ischemic episode, and pituitary microadenoma. In summary, these preliminary results from this open label study suggest that a split dose regimen of tolvaptan is well tolerated, appears to be safe and is able to sustain urine hypotonicity.

A phase 3, multi-center, double-blind, placebo-controlled, parallel-arm trial of split dose regimens of tolvaptan has been initiated in 18–50 yr old patients, with relatively rapid progression, as indicated by a TKV >750 mL, and relatively preserved renal function as reflected by an estimated GFR >60 mL/min. The primary outcome measure is renal volume

change by MR. This clinical trial is expected to enroll 1200–1500 participants with 3 years duration of treatment (www.ClinicalTrials.gov Identifier NCT00428948_[fc1]).

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Figure 1.

Diagram depicting hypothetical pathways up- or down-regulated in polycystic kidney disease and rationale for treatment with triptolide, CFTR inhibitors, ErbB tyrosine kinase, src, ERK or cyclin dependent kinase inhibitors, mTor inhibitors, somatostatin, and V2 receptor antagonists. Dysregulation of $[Ca^{2+}]_i$, increased concentrations of cAMP, and mislocalization of ErbB receptors occur in cells/kidneys bearing PKD mutations. Increased accumulation of cAMP in polycystic kidneys may result from: (i) disruption of the polycystin complex, since PC1 may act as a Gi protein-coupled receptor; (ii) stimulation of Ca^{2+} inhibitable AC6 and/or inhibition of Ca^{2+} -dependent PDE1 by a reduction in $[Ca^{2+}]_i$; (iii) increased levels of circulating vasopressin due to an intrinsic concentrating defect; (iv) upregulation of vasopressin V2 receptors. Increased cAMP levels contribute to cystogenesis by stimulating chloride and fluid secretion. In addition, stimulates mitogen-activated protein kinase/extracellularly regulated kinase (MAPK/ERK) signaling and cell proliferation in a Src and Ras dependent manner in cyst derived cells or in wild type tubular epithelial cells treated with Ca^{2+} channel blockers or in a low Ca^{2+} medium. Activation of mislocalized ErbB receptors by ligands present in cystic fluid also contributes to the stimulation of MAPK/ERK signaling and cell proliferation. Phosphorylation of tuberlin by ERK and Akt (or inadequate targeting to the plasma membrane due to defective interaction with polycystin 1) may lead to the dissociation of tuberlin and hamartin and lead to the activation of Rheb and mTOR. AC-VI, adenylate cyclase 6; CFTR, cystic fibrosis transmembrane conductance regulator; ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PC1, polycystin-1; PC2, polycystin-2; PDE, phosphodiesterase; PKA, protein kinase A; R, somatostatin sst2 receptor; TSC, tuberous sclerosis proteins tuberlin (TSC2) and hamartin (TSC1); V2R, vasopressin V2 receptor; V2RA, vasopressin V2 receptor antagonists. Modified from Torres et al. Lancet 369, 1287–1301 (2007)