Vasopressin-2 receptor antagonists in autosomal dominant polycystic kidney disease: from man to mouse and back

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Keywords: ADPKD; PKD1; renal cysts; Tolvaptan

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited nephropathy, with an estimated prevalence of 1:1000. The disease is characterized by the development of multiple cysts from all nephron segments leading to the enlargement of both kidneys and replacement of normal parenchyma (see [1]). Change in total kidney volume over time is the strongest predictor of renal function decline in ADPKD [2]. Glomerular filtration rate remains preserved up to the age of 40 years in most patients because glomerular hyperfiltration in functioning nephrons compensates for the ongoing loss of renal tissue, until end-stage renal failure ensues in >50% of patients, usually in their fifth decade. Mutations in the PKD1 gene account for ~85% of the affected families, whereas the remaining cases are caused by mutations in PKD2. PKD1 encodes polycystin-1, an integral membrane protein with a large extracellular domain that probably functions as a receptor and/or an adhesion molecule, whereas PKD2 encodes polycystin-2, a non-selective cation channel belonging to the family of transient receptor potential channels. The polycystins are located in the primary cilium and interact to form a mechanosensory complex that is involved in intracellular Ca2+ homeostasis and various signalling pathways. Disruption of the complex leads to cyst development and enlargement resulting from tubular cell proliferation and transepithelial fluid secretion. The progressive understanding of these pathways has led to spectacular advances in the prospective treatment for ADPKD, including the blockade of vasopressin 2 receptor (V2R) to decrease the intracellular level of 3′-5′-cyclic adenosine monophosphate (cAMP) in cyst-lining tubular cells [1].

Vasopressin and cAMP in ADPKD

The V2R is the major regulator of adenylyl cyclase activity and of cAMP production in the principal cells of the collecting ducts. Increased levels of cAMP and high expression of cAMP target genes have been observed in the cystic kidneys of various rodent models. These changes could arise from decreased intracellular Ca2+ concentration caused by mutations in polycystins 1/2, via the down-regulation of phosphodiesterase and stimulation of the Ca2+-inhibitable adenylyl cyclase 6 [1]. In turn, the increased production of cAMP stimulates proliferation and growth of ADPKD cells and drives Cl-/Na+ fluid secretion via protein kinase A-stimulated CFTR and, potentially, other transport processes located in the apical and basolateral membranes [3].

The importance of the V2R–cAMP pathway has been demonstrated by the spectacular effects of the V2R antagonists (V2RA) OPC-31260 and OPC-41061 (Tolvaptan) on lowering renal cAMP levels, slowing renal cyst growth and improving renal function in various models of autosomal recessive (PCK rat) and autosomal dominant (Pkd1+/− mouse) polycystic kidney disease [4]. Similar protection has been observed when vasopressin secretion is inhibited by high water intake in PCK rats [5]. Furthermore, the deletion of vasopressin in these PCK rats (by crossing them to Brattleboro rats) led to lower renal cAMP levels and an almost complete inhibition of cystogenesis, whereas administration of dDAVP recovered the cystic phenotype [6]. Based on these pre-clinical studies, a Phase III clinical trial investigating the effect of Tolvaptan in ADPKD patients (TEMPO 3/4) has been initiated in 2007 [7]. This trial enrolled >1400 ADPKD patients with relatively preserved kidney function (baseline estimated creatinine clearance ≥60 mL/min), aged 50 years or younger and with total kidney volume ≥750 mL (magnetic resonance imaging measurement). Blockade of V2R is hypothesized to inhibit cyst growth, thereby delaying ADPKD-associated complications including kidney function decrease, blood pressure control and flank pain.

V2RA in Pkd1 mice

The aim of the TEMPO 3/4 trial is to examine whether tolvaptan at a high dose is able to slow renal cystic
progression in a pre-selected ADPKD population at a relatively early stage of disease and with a risk of progression to kidney failure. Independent of the final study outcome, this trial will leave important questions open, in particular the potential interest of V2RA for patients with more advanced disease and their efficacy at lower doses which should decrease the side effects (polyuria and nycturia) and thus improve tolerance. The investigations performed in a Pkd1 mouse model by Meijer et al. [8] provide interesting insights into these issues. This study is based on the oral administration of OPC-31260 at a high (0.1% w/w in ground rodent chow) or low (0.05%) dose, 10 days after the specific deletion of Pkd1 in renal tubular epithelium in 11-day old mice (using a tamoxifen-inducible Cre system). After a 3-week or 6-week treatment (late versus early intervention, respectively), the mice were sacrificed and sampled to monitor renal function parameters and kidney cyst growth.

The first finding is that an early (starting at 3 weeks of age) and short-term (3 weeks) treatment of this Pkd1 mouse model with high dose of V2RA resulted in a significant aquaretic effect and attenuation of the renal cystic phenotype (estimated by relative cyst area and kidney weight) as compared with untreated Pkd1-deleted mice. These results confirm some of the V2RA effects observed in other polycystic mouse models [4], although the treatment did not ameliorate renal function and was not shown to lower cAMP levels and decrease the expression of target genes in this Pkd1 model [8]. Secondly, the protective effect on the renal cystic phenotype is no longer observed after long-term (6 weeks) administration of the V2RA, even at a high dose. This treatment escape is paralleled by a lower aquaretic response to the V2RA, as attested by less marked changes in the urinary volume, urinary osmolality and water intake parameters at Week 6 versus Week 3. It must be noted that the intake of V2RA remained similar between the two time points, whereas the messenger RNA (mRNA) expression of V2R was significantly decreased at Week 6. The third finding of the study is the fact that administration of V2RA at a more advanced stage of disease (6 weeks of age, late intervention) induced a lower aquaretic response and showed no effect on cyst growth. Based on these findings, the authors conclude that intervention with V2RA should be initiated early in the course of the disease, at high dose, and that combination therapy may be needed to reduce cystogenesis at a later stage.

From Pkd1 mice to ADPKD patients

The results of Meijer et al. [8] raise several points regarding the translation of animal study results to human ADPKD. The discordance between encouraging pre-clinical studies and disappointing results of two clinical trials using mTOR inhibitors [9, 10] has pointed to issues such as drug dosage, time of treatment initiation, duration of administration, choice of end-point and surrogate markers and, most importantly, relevance of the pre-clinical models used to test drugs and predict human outcomes [11]. The mouse model used by Meijer et al. arises from the deletion of the Pkd1 gene (orthologous to human PKD1) in the mouse. However, the kidney-specific loss of Pkd1 occurs at once, in the early postnatal phase, and it is segment-specific, reflecting the expression of Cre recombinase [8]. These characteristics are very different from the two-hit model, which remains the most commonly accepted explanation for the focal and clonal nature of cystogenesis in human ADPKD [1]. Elegant studies have also demonstrated that the very timing of Pkd1 inactivation plays a major role in the cystogenesis profile in mouse models [12]. These factors probably explain the significant phenotype variations observed in different models. For instance, the Pkd1 mice used by Meijer et al. show a majority of cysts stained for uromodulin, a specific marker of the thick ascending limb of Henle’s loop [13], whereas only 20% of cysts, generally smaller, are positive for aquaporin-2 (AQP2), and no cysts positive for proximal tubule markers [8]. This profile is clearly distinct from what is observed in other models of Pkd1 or Pkd2 inactivation [14, 15]. In human ADPKD, Bachinsky et al. [16] located AQP1 in a majority (~70%) of cysts of proximal tubule origin (gp330 positive), whereas a minority of the cysts, negative for AQP1 and gp330, expressed AQP2. Devuyst et al. [17] confirmed the selective and mutually exclusive expression of AQP1 and AQP2 in various stages of ADPKD. In end-stage ADPKD, two-thirds of the cysts expressed either AQP1 or AQP2, but the two water channels never co-localized in the same cyst. Of note, the proportion of AQP2-positive cysts significantly increased with cyst size, supporting a role for vasopressin in cyst enlargement [17].

An intriguing observation made by Meijer et al. is the decreased efficacy of the high-dose V2RA over time, with no significant protection observed after 6-week treatment. The authors show that this is not due to a lower intake of the drug (as estimated by food intake), nor to increased endogenous vasopressin levels (as estimated from unchanged co-peptin precursor) and the global mRNA expression of the V2R was actually lower at this stage [8]. Differences in pharmacokinetics and timing and/or insufficient inhibition of the V2R in this model constitute a potential explanation. Indeed, significant effects on renal cystogenesis and function were observed in the Pkd2 mouse model after 12 weeks of treatment with 0.05% OPC31260 [15]. Changes in downstream effectors of vasopressin action in the collecting duct cells, which can be affected by polycystin-1 dosage, could also play a role [18]. Another hypothesis would be that the extent of the V1a receptor (V1aR) antagonistic effect on V2R signalling, which could contribute to the initial aquaretic effect of the V2RA, could decrease over time (due to e.g. the progressive down-regulation of V1aR) [19]. These findings may also suggest that the timing of Pkd1 inactivation in this model triggers cystogenesis via temporally and spatially distinct pathways in different tubular segments so that the effect of V2R blockage on cysts arising from the collecting ducts may only be partial and limited in time. If proved true, this mechanism of cystogenesis would necessitate combining various drugs targeting these segment-specific pathways of cystogenesis.

Two final considerations should be made when extrapolating these mouse studies to man. Firstly, the timing of intervention (treatment started at 3 weeks of age in the early
intervention group) is in fact very early when considering that significant changes in renal tubular maturation occur up to 6–8 weeks of age in mouse [20, 21]. In man, such an early intervention would mean to treat young children, with potential long-term consequences due to among others, prolonged polyuria [22]. Secondly, there are species differences in the functional effect of vasopressin in the distal nephron (thick ascending limbs and collecting ducts), which probably sustain the much higher urinary concentrating capacity of the rodents as compared to man [23]. The latter is explained by considerable differences in both renal anatomy (e.g. proportionally much longer loops of Henle in the inner medulla and papilla of the mouse) and metabolic rate (much larger amount of osmoles needed to be excreted in mouse). Furthermore, the segmental distribution of the V2 receptors in mouse and human kidneys remains debated [24, 25]. The effect of V2R blockade in any rodent model should thus be interpreted carefully in view of these potential differences.

Conclusions

Since cyst expansion is a major factor for the progressive deterioration and loss of renal function in ADPKD, therapies targeting fluid secretion and, thereby, cyst enlargement are of major clinical interest. The study of Meijer et al. [8] provides further support for the effect of V2RA on slowing cyst growth in ADPKD, shown for the first time in a PKD1 orthologous model. Although this effect is not reflected by protection in terms of renal function and fibrosis in this model, these findings suggest that the V2RA treatment should be initiated very early in the disease and with a high dose inducing a strong aquaretic effect. The fact that V2RA effect is not sustained supports the view that cystogenesis may be a dynamic process involving different segments during the disease course. Moreover, these results emphasize the need for better characterization of disease mechanisms and species differences when considering the pre-clinical models used to investigate new therapeutic targets.

Acknowledgements. The support of the Exchange Program between the Universität Zürich and the Shanghai Changzheng Hospital SSSTC projects: EG 14-032009 and IP-17-092009 and that of the National Centre of Competence in Research (NCCR) Kidney.CH are gratefully acknowledged.

Conflict of interest statement. O.D. is a member of the Steering Committee and investigator for clinical trials of tolvaptan in ADPKD sponsored by Otsuka Corp. (See related article by Meijer et al. Therapeutic potential of vasopressin V2 receptor antagonist in a mouse model for autosomal dominant polycystic kidney disease: optimal timing and dosing of the drug; Nephrol Dial Transplant 2011; 26: 24452453.)

References


Received for publication: 19.4.11; Accepted in revised form: 6.6.11