V2 Receptor Antagonists in Cystic Kidney Diseases: An Exciting Step towards a Practical Treatment

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It is unusual in nephrology for the fruits of basic science research in genetics and cell biology to directly translate into a practical therapy for common renal diseases. Therefore it is with great anticipation that the clinical and research communities receive publications like the article by Wang *et al.* in this issue of the *Journal of the American Society of Nephrology*, which shows striking efficacy of a nonpeptide selective vasopressin 2 (V2) receptor antagonist in a rat model of autosomal recessive polycystic kidney disease (ARPKD) (1).

In the past decade, studies in animal models of the cystic renal diseases suggest a final common pathway for cystogenesis involving a major role for adenosine 3′,5′-cyclic monophosphate (cAMP)–stimulated signaling pathways in controlling the rate of epithelial cell growth and fluid secretion in cysts (2,3). These data are derived from studies in diverse models of autosomal dominant polycystic kidney disease (ADPKD), ARPKD, and the medullary cystic disease–nephronophthisis complex (4). If agonists of cAMP stimulate cell proliferation and fluid secretion and cause enlarging cysts, it follows that antagonists of cAMP-mediated processes would be logical therapeutic targets to reduce cyst volume. The elegant work of Gattone and Torres in this regard, which shows that inhibition of V2 receptors by V2 receptor antagonists blocking adenyl cyclase–mediated cyst growth as measured by renal structure and function in murine models of cystic kidney diseases, has been a major advance (5,6). Presumably, the inhibition of this pathway by V2 receptor antagonists is kidney-specific, as polycystic liver disease in these models was not affected consistent with the absence of V2 receptors in the liver (1).

Obviously, there are major species' differences between murine and human V2 antagonists. Many compounds with efficacy in rodents have failed in the clinic. Thus the current paper of Wang *et al.* is exciting, because it shows that a once-daily orally-administered compound which has already been given safely to humans for other indications favorably influences structure and function in the PCK rat, a model of autosomal recessive cystic kidney disease. Furthermore, inhibition of specific cAMP-mediated extracellular signal-regulated kinase (ERK) signaling pathways that correlate with anatomic and renal functional improvement provide more proof of principle for the central role of cAMP signaling. The anatomic location of cysts expressing V2 receptors in the cortical collecting duct of the kidneys in these models and in human cell cultures suggests that perhaps all cysts are not equal when it comes to producing renal volume increases and resultant morbidity and renal dysfunction. It is known that cysts in ARPKD and nephronophthisis are of collecting duct origin and thus may have upregulated V2 receptors. ADPKD contains a mixture of proximal tubule and distal nephron originating cysts. Recent data suggest that the actively proliferating cysts carry markers for vasopressin receptors, while cysts from epithelia from the proximal tubule are dedifferentiated and thus would not likely be affected by anti-V2 receptor drugs. This implies that early intervention before cell dedifferentiation is more likely to be effective.

Another interesting and practical aspect of the work of Wang *et al.* is that the vasopressin antagonist used, OPC-41061 (Tolvaptan), has already been tested in humans as a treatment for hyponatremia and congestive heart failure (7). It logically has been evaluated as a compound causing increased free water clearance by inhibition of vasopressin in states of hypoosmolality. This would obviously be of therapeutic benefit in various hyponatremic states, including the hyponatremia that accompanies congestive heart failure. That both Phase 1 and Phase 2 trials have already been done with this compound without major safety issues, besides possibly excessive water loss, is a major advantage in the timeline to drug approval by the Food and Drug Administration. In patients with severe congestive failure and ejection fractions $<40\%$, patients lost up to 2.1 kg in 24 h. All patients were also on maintenance diuretics (8). Severe water diuresis might be more of a problem in patients with normal GFR. When given to volunteers, another V2 antagonist, OPC-31260, increased urine volume dose dependently over 6 h up to 4 times placebo without natriuresis. Thus, excessive diuresis and thirst might be problems (7). An investigational new drug application has been filed by the manufacturer of the vasopressin antagonist Tolvaptan to examine use in clinical trials of cyst growth modification in ADPKD. These trials have recently started. Dose-ranging and pharmacokinetic studies are in progress. Questions of safety and efficacy with reduced GFR also need to be answered in addition to effects on renal blood flow and BP. Another major implication derived from the pivotal role of cAMP-mediated processes in cystogenesis is that

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agonists of cAMP likely enhance cyst growth. The clinical, anecdotal wisdom of reducing the intake of caffeine, a phosphodiesterace inhibitor which increases intracellular cAMP, may be a practical example of such a pathogenetic construct. There may also be other ways to reduce renal cyclic AMP such as β blockade.

Recent work from the Consortium of Radiologic Imaging Studies in PKD (CRISP) using MRI have shown that autosomal dominant polycystic kidney disease, the most common of the cystic renal disorders is characterized by progressive increases in renal and cyst volume well before declines in GFR take place (9). The cohort for this study had relatively preserved GFR at baseline. However, morbidity is observed while cysts are growing even though serum creatinine and GFR are maintained perhaps by hyperfiltration in noncystic nephrons. If vasopressin antagonists are used, it seems logical to use them early in the course of the disease before renal volume becomes excessively increased. This in turn would have major implications for genetic screening of family members and children for ADPKD. Until now, routine screening in people under the age of 30 with ADPKD has been discouraged because there is a 15 to 20% false negative rate for ultrasound diagnosis and no effective treatment available. Furthermore, making the diagnosis has impacts on employment and insurability. The presence of an effective treatment to prevent increases in renal volume will dramatically change the guidelines in this area.

In cystic kidney diseases, any effective therapy will likely need to be given chronically. This raises questions about what will happen if V2 receptors are downregulated by the drugs. Is efficacy lost? Should these drugs be given intermittently? Many such practical issues await clinical demonstration of efficacy. No doubt, the exciting magnetic resonance methodology of the CRISP trial regarding renal blood flow, total renal volume, and cyst volume will be applied to markedly reduce the time and patient numbers necessary to prove efficacy.

Clearly, the details of dose, frequency of administration, and long-term benefits and side effects in humans will need to be worked out, but this animal investigation, together with the early clinical experience with Tolvaptan, are very encouraging. The prospect of an effective therapy for the hundreds of thousands of sufferers of cystic renal diseases represents a bright light at the end of what now is a short tunnel. Further, nephrology can be proud of this beautiful translation of fundamental research to clinical trials and hopefully to effective therapy.

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See related article, "Effectiveness of Vasopressin V2 Receptor Antagonists OPC-31260 and OPC-41061 on Polycystic Kidney Disease Development in the PCK Rat," on pages 846–851.