Therapy for Polycystic Kidney Disease? It's Water, Stupid!

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Water, which is preeminent among all biomolecular compounds, creates more complexities than implied by simple H_2O. Humans are more than 50% water and die in a few days without it. Space scientists eagerly search dry planets for traces of water. Nephrologists spend most of their time thinking and worrying about urine, which is mostly water. When the heart fails, we drown from too much water. Now we are confronted by the bizarre prospect that water is the "cure" for hereditary diseases that grotesquely bloat the kidneys with . . . water.

In autosomal dominant and autosomal recessive polycystic disease (ADPKD and ARPKD, respectively, or PKD when referring to both), the kidneys often grow larger than footballs. They are composed of innumerable fluid-filled cysts varying in size from a pinhead to a grapefruit. Cysts arise in renal tubules when epithelial cells focally proliferate, leading to tiny out-pouchings, or hernias, that progressively expand. Aberrant cell differentiation and sustained proliferation initiate the formation of the cysts, and upstream fluid from glomerular filtrate fills the budding cyst cavity. Later, after they separate from the parent tubules, fluid is transported across the epithelium in conjunction with active chloride transport into the lumens of autonomous cysts. Thus, two ordinarily quiescent renal processes, epithelial cell proliferation and solute-driven fluid secretion, come storming out of hiding and push a relatively small number of cystic segments to take over eventually the parenchymal landscape, driving functional glomeruli and tubules into oblivion.[1]

We knew this much about PKD for more than a decade. We also knew, without the benefit of specific genetic molecular information about these hereditary disorders, that abnormal growth of cyst epithelial cells and the transepithelial transport of chloride and fluid are increased dramatically in polycystic kidneys by our old friend cAMP, the "second messenger" of a host of G-protein–linked hormone and autacoid receptors.[2] cAMP stimulates cell proliferation in mural epithelial cells from polycystic kidneys but not in cells from normal kidney tubules. Renal tubules harbor receptors for a swarm of adenylyl cyclase agonists (vasopressin, parathyroid hormone, epinephrine, norepinephrine, secretin, vasointestinal polypeptide, prostaglandin E_2, adenosine, and forskolin), bringing with them the potential to activate many normal and abnormal physiologic processes that could also drive the enlargement of renal cysts.[3]

In a seminal study, Gattone *et al.*[4] tested in living animals the idea that endogenous vasopressin has a role in promoting cyst growth through its action to stimulate adenylyl cyclase production of cAMP. *Cpk/cpk* mice with a rapidly progressive form of recessive PKD were administered a vasopressin V_2 receptor inhibitor (OPC-31260), and an impressive decrease in renal enlargement and preservation of renal function followed. OPC-31260 also dramatically slows renal enlargement and preserves function in three more genetically different forms of cystic diseases in rodents (*Pkd2/Pkd2*$^{-tm1Som}$, *pcy/pcy*, and PCK).[5,6] OPC-41061, a highly specific V_2 blocker with a higher affinity for the V_2 receptor, also diminishes renal enlargement and protects renal function.[7] These findings suggest that in all renal cystic disorders, AVP, acting through cAMP, has a commanding role in promoting cyst growth. Nagao *et al.*[8] further reasoned that if blockade of V_2 receptors is beneficial in PKD, then reducing plasma vasopressin levels should be effective as well. PCK rats, encouraged to drink enough water to reduce urine osmolality below that of plasma, show a marked reduction in renal enlargement with preservation of renal function.

Although the foregoing studies clearly implicate a central role for vasopressin and cAMP in promoting kidney enlargement and reducing renal function in PKD, a study from the Mayo laboratory in this issue of the *JASN*[9] provides definitive proof. PCK rats with ARPKD (*Pkhd1*$^{-/-}$) were crossed with Brattleboro rats (AVP$^{-/-}$) with diabetes insipidus and then backcrossed to create double-homozygous null animals. *Pkhd1*$^{-/-}$ rats developed progressive renal enlargement as a result of cysts in the collecting tubules, and AVP$^{-/-}$ animals were born with diabetes insipidus and required supplemental water to survive. The AVP$^{-/-}$/*Pkhd1*$^{-/-}$ double-null rats also had diabetes insipidus and drank large amounts of water; moreover, there was a dramatic reduction of cyst formation in the kidneys. When exogenous AVP V2 agonist (dDAVP) was given to these animals by osmotic minipump, cysts developed within the kidneys, fulfilling Koch's postulates.

These are astounding results in this field of study! All of the cells in the collecting ducts of these animals carry mutated copies of *Pkhd1* genes in both alleles. Thus, the cells are "primed" to

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form cysts, yet cysts develop and enlarge only when under pressure from exogenous dDAVP. dDAVP increases cAMP within collecting duct cells, leading to activation of the BRAF/MEK/extracellular signal–regulated pathway for mitogenesis and increased numbers of epithelial cells.[10] The dramatic results in this report are consonant with the view that epithelial cell growth is of paramount importance to the *formation* of the cyst as well to the overall *increase of renal size* in ARPKD.

In view of the fact that so many hormones with receptors in renal tubules have the potential to generate increased amounts of cAMP, why did the singular removal of AVP produce such a dramatic suppression of cyst formation? The answer probably rests in the physiology of terrestrial animals that must conserve water to survive. Of the hormones and autocoids capable of increasing cAMP production in collecting ducts, only AVP is persistently elevated in the plasma of free-range animals, including human. Where do the cysts form in ARPKD? In collecting ducts. Land-based animals are normally antidiuretic for most hours of the day and night, except for short periods when relatively large volumes of water are imbibed. Therefore, plasma AVP levels are usually high enough to activate adenylyl cyclase, generate cAMP, activate aquaporin-2, increase collecting duct permeability to water, and concentrate urinary osmolality above that of plasma. Thus, cyst growth is "clamped" by vasopressin.

Recent studies have shown that cells cultured from the walls of renal cysts of patients with ADPKD and ARPKD respond to AVP in the range of plasma levels observed in patients.[11] AVP, through the generation of cAMP, promotes epithelial cell growth and stimulates transepithelial chloride and fluid secretion in cyst epithelial cells. OPC-41061 inhibits with high affinity the formation of cAMP in response to AVP and decreases the rate of cellular proliferation caused by the hormone.

If rodent kidneys were human counterparts in all respects, then there would be no need to do a clinical trial to determine whether inhibition of AVP reduces renal volume in patients with ADPKD. Sadly, man does not mimic rodents in every way, and we shall not know for sure whether the AVP inhibitor works until an ongoing clinical trial is completed in a few years. Until then, nephrologists must grapple with a question that their highly informed patients will undoubtedly ask: How much water should I drink now? Patients have already figured out that if extra water decreases vasopressin and cAMP levels, then why isn't plain old water a useful therapy? No one can give an informed, definitive answer to that question, but common sense leads me to think that sufficient water should be drunk to keep plasma vasopressin levels near a point that renders urine osmolality equal to or modestly lower than that of plasma. It would be impossible to meet the mark of the Brattleboro rat unless patients drank approximately 20 L of water daily. In the short term, a more moderate target would seem to be in order. To know for certain how much of the "water cure" is prudent therapy, a carefully controlled clinical trial seems justified.

What began approximately 25 yr ago as "blue-collar" science has progressed to optimistic clinical trials. With the assistance of more advanced molecular-based research strategies, we should expect to move much faster toward other highly targeted therapies for PKD.

DISCLOSURES

J.J.G. has consultancies with Otsuka Corp. and Genzyme Pharmaceuticals.

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See related article, "Vasopressin Directly Regulates Cyst Growth in Polycystic Kidney Disease," on pages 102–108.

Feast and Famine: Epidemiology and Clinical Trials in Chronic Kidney Disease

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