Prime time for polycystic kidney disease: does one shot of roscovitine bring the cure?*

E. Wolfgang Kuehn and Gerd Walz

Renal Division, University Hospital Freiburg, Hugstetter Strasse 55, 79104 Freiburg, Germany

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD), caused by either PKD1 or PKD2 mutations, relentlessly progresses to end-stage renal disease (ESRD) in more than half of the affected patients. Although the pathogenesis is still incompletely understood, several potential therapies are now emerging that promise to effectively prevent cyst formation and progression. In a lifelong disease, therapeutics with a long-lasting effect after a brief application appear particularly attractive. (R)-roscovitine, a protein kinase inhibitor with preferential selectivity for cyclin-dependent kinases (CDKs), may be just such a drug. A recent report demonstrates that roscovitine blocks cyst progression in two animal models of PKD, the jck (NEK8) and cpk (cystin) mouse. Roscovitine prevents phosphorylation of the retinoblastoma protein (Rb) through inhibition of CDKs, and normalizes the levels of several cyclins, thereby preventing cell proliferation. In addition, roscovitine ameliorates cyst progression, through inhibition of transcription and apoptosis. Perhaps most importantly, a 3-week course of therapy had a long-lasting beneficial effect on disease progression. In several clinical trials, roscovitine is reportedly well tolerated, adding yet another exciting approach to the list of putative therapies in ADPKD.

Subjects and methods

The pathogenesis of polycystic kidney disease

ADPKD and its much less common autosomal recessive siblings (e.g. ARPKD, nephronophthisis) were long considered untreatable hereditary defects. Over the last couple of years, several therapeutic approaches have surfaced that, in contrast to their predecessors, hold promise of a long-awaited cure [1]. ADPKD, caused by mutations of either PKD1 (polycystin-1) or PKD2 (polycystin-2), is characterized by progressive cyst formation leading to ESRD over the course of approximately five decades [2]. The pathogenesis of cyst formation has recently been linked to a ciliary defect. Deflection of the primary (non-motile) cilium that decorates most mammalian cells, causes an increase in intracellular calcium [3]. This calcium transient, which requires an intact polycystin-1/polycystin-2 complex and may be triggered by urine flow in vivo [4], appears to orient tubular cells along the anterior–posterior axis of the nephron [5,6]. Defective ciliary signalling results in confusion: rather than oriented divisions along the nephron, cells divide randomly and form cysts [7]. In ADPKD, <1% of all nephrons acquire a second somatic mutation that in combination with a germline mutation results in cystogenesis. Although mechanical compression, increased apoptosis of healthy tissue, and reactive fibrosis have been evoked to explain the progressive loss of renal function, why patients with ADPKD develop ESRD has remained largely elusive. This discrepancy may indicate that the pathogenesis of cyst formation and cyst progression differs, opening a window for therapeutic interventions.

Vasopressin-2-receptor antagonists and mTOR inhibitors

The cyst fluid contains several growth factors and hormones (e.g. antidiuretic hormone, ADH) that stimulate cyclic adenosine monophosphate (cAMP) accumulation and augment fluid secretion (Figure 1A). Many cyst cells express the vasopressin-2-receptor (V2R), and V2R antagonists, already tested in small clinical trials to increase water excretion in heart failure, showed spectacular effects in several animal models of PKD [8,9]. This benefit also holds up for the effects of rapamycin, an inhibitor of mTOR. Cells lining the cysts of human ADPKD kidneys, as well as several animal
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Cyclin T1
Cyclin E
mTOR
P
Cdk9
P
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CDK inhibitors
With two excellent therapeutic options at hand, how did roscovitine make it into prime time? (R)-roscovinine is a potent Cdk2-cyclin E inhibitor, but also inhibits Cdk7, Cdk9, Cdk5 and other targets (Figure 2A). In their article, Bukanov et al. [13,14] treated jck (NEK8-mutant) mice with 50 and 150 mg/kg roscovitine for a total of 5 weeks, starting at 26 days of age. Both doses dramatically inhibited cyst and kidney growth, and the higher roscovitine dose also normalized BUN concentrations. Similar results were obtained in a second model of polycystic disease, the cpk (cystin-mutant) mouse [15]. Surprisingly, and perhaps most promising, 150 mg/kg/day roscovitine, given either for the first three weeks or every other week, were almost as effective as the continuous 5-week application. Although neither NEK8 nor cystin mutations have been found to cause human disease, the efficacy in both mouse models supports the hypothesis that CDK inhibitors target yet another essential component.
of the final common pathway of cyst progression. In a careful analysis, the authors detail the effects of roscovitine on cyst progression, and outline some of the mechanisms that appear to explain the dramatic effect of this drug in PKD (Figure 2B). R-roscovitine, through inhibition of Cdk2, prevents phosphorylation of Rb, and maintains the transcription factor E2F in an inactive state. Roscovitine normalizes phosphorylation of cyclin D1, and decreases the up-regulated levels of cyclin D2 and D3 by blocking ERK1/ERK2 activation [16]. Roscovitine also inhibits Cdk7 and Cdk9, thereby preventing the activation of RNA polymerase II (RNA pol II) and RNA pol II-dependent transcription. Down-regulation of the pro-apoptotic Cdk5-p25 in combination with the up-regulation of Bcl-2 and Bcl-xL appears to block apoptosis in the kidneys of roscovitine-treated jck mice.

Discussion and conclusion

Can ADPKD patients benefit from CDK inhibitors?

An intermittent or short-term therapy is appealing in a chronic disease that progresses over the course of five decades, and likely requires lifelong treatment. Other cancer drugs, for example taxol [17], previously entered centre court of polycystic kidney research, but did not translate into clinical trials, since the anticipated rate of side effects was considerable. What is so different about roscovitine? Similar to taxol, roscovitine is an anticancer drug that is currently being tested in several phase I/II clinical cancer trials. Although lower doses of the drug are surprisingly well tolerated [19], hyponatraemia and severe hypokalaemia, as well as acute renal failure with decreased renal blood flow on radioisotope imaging, were observed at higher doses [18]. These are worrying features in a therapy aimed to slow progression of ADPKD. Nevertheless, kinase inhibitors add to our armamentarium of novel therapeutic options to maintain renal function in patients with ADPKD.

Conflict of interest statement. None declared.

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