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Polycystic Kidney Disease (PKD)

Polycystic kidney disease (PKD) is a heritable form of cyst development on the kidney. The cysts are generally simple, but there are many of them. Symptoms of PKD include high blood pressure, abdominal, back or flank pain, hematuria, and polyuria. The risk for kidney stones and kidney failure is also increased.

PKD is generally easy to distinguish from simple cyst formation because affected patients often present with positive family history for the condition, blood in the urine, cyst infection, multiple cysts visible on scans, extra-large kidneys, and renal failure.

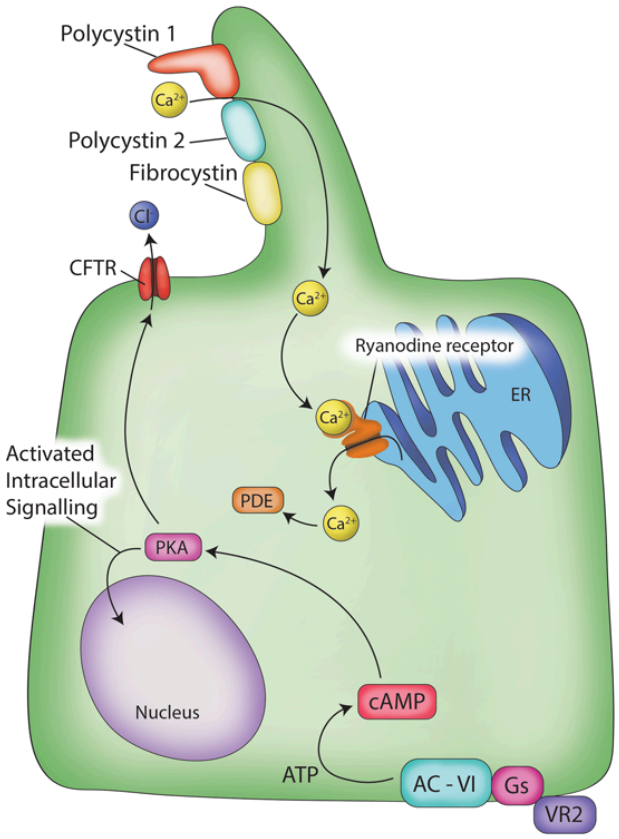
PKD is often characterized as one of two types – autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). Each type involves a mutated gene. ADPKD can develop if only one mutated gene (also called allele) is inherited. ARPKD requires the inheritance of both mutated genes.

ADPKD is the most common inherited kidney disease with around 6000 new cases diagnosed in the US annually. The condition affects both kidneys and can cause cysts in other organs like the liver, pancreas, colon, seminal vesicles and cerebral vessels.

Mutations within the **PKD1** and **PKD2** genes are responsible for ADPKD. These genes code for the **polycystin I** and **polycystin II** proteins, respectively. Mutated polycystin I accounts for 85% of ADPKD cases, while the remaining 15% is due to mutated polycystin II. Although the manifestations are almost identical with mutations in either gene, PKD1 gene mutations cause a more rapid progression of disease.

Most patients with ADPKD show no clinical symptoms of the disease until they are in the fourth or fifth decade of life. Individuals who inherit a single mutated PKD1 or PKD2 allele from one parent still have a normal gene from the other parent. Research suggests that two intact alleles are best for normal kidney health, but one intact gene can do a lot to promote normal function; however, some minor structural changes can be discovered even in young people with the inherited mutation. De novo mutation (not inherited, but acquired during life) from some type of mutagenic environmental event (e.g. DNA damage from radiation, chemical carcinogens, or cell division error) of one of the PKD genes is more challenging to diagnose because there is no family history. If both alleles of the PKD1 or 2 genes are mutated, the situation becomes even more dangerous as cyst formation progresses much more aggressively, ultimately leading to renal failure.

Polycystin I and II proteins are found in the membrane of the primary cilium of nephron tubule cells. This primary cilium projects into the nephron lumen where it bends in response to filtrate flow. The bending of the cilium helps regulate cell proliferation and growth. Polycystin I and II along with another protein called fibrocystin expressed on the cilium membrane help sense cilium movement (bending) and correspondingly activate membrane calcium channels. Calcium is an intracellular second messenger signal that leads to the activation of phosphodiesterase (PDE). PDE breaks down cAMP which is another intracellular second messenger that leads to increased growth and cell division as well as increased movement of Cl^- into the lumen of the nephron. If polycystin 1 or 2, or fibrocystin are dysfunctional due to gene mutation, Ca^{2+} influx is impaired and the activities of cAMP continue to increase cellular growth and division.



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Production of cAMP and Cl- secretion in nephron tubular cells:

You have likely learned of the effect of antidiuretic hormone (ADH) on water reabsorption within the collecting duct of the nephron. This process is mediated by ADH binding to a GPCR called the vasopressin 2 (V2) receptor, which increases the levels of intracellular cAMP to signal aquaporin protein translocation to the apical membrane. Another process stimulated by ADH involves the stimulation of adenylyl cyclase which increases cAMP concentrations in the cell. cAMP functions to promote cell growth and Cl^- secretion into the nephron tubule. Cell growth is signaled by activating gene transcription within the nucleus. Cl^- secretion is activated as cAMP activates a kinase known as protein kinase A (PKA) which phosphorylates, and activates the CFTR Cl^- channel located on the apical membrane of tubular cells. Cl^- then diffuses down its concentration gradient into the cell via the basolateral membrane sodium/potassium/chloride channel (NKCC1) and into the nephron lumen via the CFTR channel (which is the same protein that is mutated in cystic fibrosis).

Cl^- is negative and draws Na^+ into the nephron lumen by diffusion in-between tubular cells, a process known as paracellular solvent drag. The buildup of NaCl draws a lot of water to the inside of the lumen. The increased growth and division of nephron epithelial cells, combined with the extra sodium chloride and water entering the lumen leads to the development of cysts. Over time, the cysts grow larger and larger.

Many of the largest cysts are located in the collecting duct where there are lots of V2 receptors expressed. With ADPKD, tubular cells of the nephron begin to express more V2 receptors and aquaporin channels. These cells will respond to vasopressin and will therefore increase levels of cAMP and subsequently form cysts.

Caffeine inhibits phosphodiesterase and as a result will increase cAMP levels in the cells of the nephron. It is therefore critical for PKD patients to avoid caffeine. It is also important that these patients drink at least 3 liters of water a day to

keep the osmolality of their plasma down because increased plasma osmolality stimulates hypothalamus cells to raise ADH levels. ADH will bind and stimulate V2 receptors.

The use of V2 receptor antagonists is currently under investigation as a means of treatment to help reduce cyst growth. Ace inhibitors and Angiotensin II inhibitors are also used for treatment.

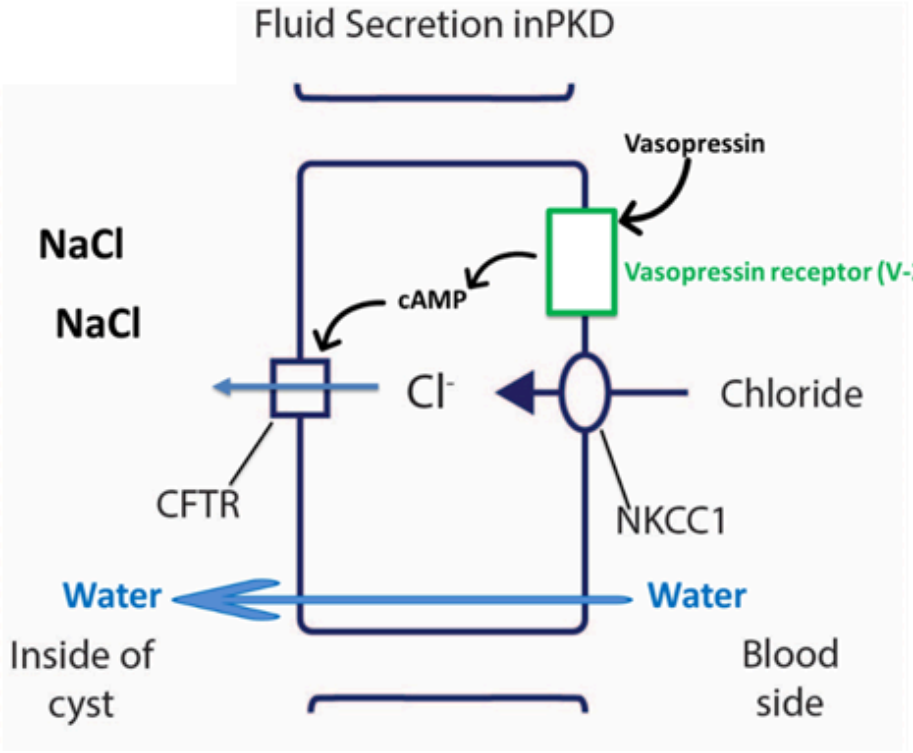

Image by Lanning B. BYU-I F17

Autosomal recessive polycystic kidney disease (ARPKD) appears to involve a mutation in the Polycystic Kidney and Hepatic Disease 1 (PKHD1) gene. This gene codes for the transmembrane protein called fibrocystin, also found in the primary cilium of the nephron tubule cells and functions in the sensory apparatus composed of the polycystin genes. It has other functions as well that are also tied to cell regulation. If one good copy of the PKHD1 gene is inherited, it is incredibly rare to develop ARPKD, although the person with the mutation will be a carrier of the mutation. If a person inherits two mutated alleles of PKHD1, then they will develop the symptoms of ARPKD early in life. For this reason, ARPKD is often referred to as childhood PKD. Manifestations of bilateral impaired lung development, flank masses, liver fibrosis, hypertension and renal failure can be noted even at birth. Nearly 75% of infants die just before or just after birth. Those who survive are treated with supportive measures that include respiratory support and dialysis. Kidney transplant is also pursued as a treatment option. Children who survive develop a specific kind of liver fibrosis that continues over time.