1: J Am Soc Nephrol. 2002 Nov;13(11):2723-9. Related Articles, Links

The effect of caffeine on renal epithelial cells from patients with autosomal dominant polycystic kidney disease.

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Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder characterized by the progressive enlargement of cysts derived from tubules. Tubule cell proliferation and chloride-dependent fluid accumulation, mechanisms underlying cyst expansion, are accelerated by adenosine 3':5'-cyclic monophosphate (cAMP). This study examined the extent to which caffeine may stimulate the production of cAMP by cyst epithelial cells, thereby adversely increasing proliferation and fluid secretion. Mural epithelial cells from ADPKD cysts and normal human kidney cortex cells (HKC) were cultured, and cAMP levels were determined in response to caffeine and receptor-mediated agonists linked to adenylyl cyclase. Caffeine, a methylxanthine, slightly increased basal levels of cAMP, as did other nonselective phosphodiesterase (PDE) inhibitors, 1-methyl-3- isobutyl xanthine and theophylline and rolipram, a specific PDE IV inhibitor. More importantly, clinically relevant concentrations of caffeine (10 to 50 micro M) potentiated the effects of desmopressin (DDAVP), prostaglandin E(2) (PGE(2)), and isoproterenol to increase cAMP levels in both ADPKD and HKC cells. By contrast, at concentrations that augmented the DDAVP response, caffeine attenuated cAMP accumulation by adenosine, implicating an action apart from the inhibition of PDE. Caffeine enhanced the effect of DDAVP to stimulate transepithelial short-circuit current of polarized ADPKD monolayers, reflecting an increase in chloride secretion. Caffeine potentiated the effect of DDAVP and PGE(2) to increase the levels of phosphorylated extracellular signal-regulated kinase (P-ERK). By contrast, P-ERK levels in HKC cells were not raised by increased intracellular concentrations of cAMP. It is concluded that PDE inhibition by caffeine increases the accumulation of cAMP, and through

this mechanism activates the ERK pathway to cellular proliferation and increases transepithelial fluid secretion in ADPKD cystic epithelium. Caffeine is, therefore, a risk factor for the promotion of cyst enlargement in patients with ADPKD.

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