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Chloride secretion by renal collecting ducts

Madhumitha Rajagopal[1,3] and **Darren P. Wallace**[1,2,3]

[1]Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, United States

[2]Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, Kansas, United States

[3]The Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas, United States

Abstract

Purpose of review—Renal collecting ducts maintain NaCl homeostasis by fine-tuning urinary excretion to balance dietary salt intake. This review focuses on recent studies on transcellular Cl^- secretion by collecting ducts, its regulation and its role in cyst growth in autosomal dominant polycystic kidney disease.

Recent findings—Lumens of non-perfused rat medullary collecting ducts collapse in control media but expand with fluid following treatment with cAMP, demonstrating the capacity for both salt absorption and secretion. Recently, inhibition of apical epithelial Na^+ channels (ENaC) unmasked Cl^- secretion in perfused mouse cortical collecting ducts (CCD), involving Cl^- uptake by basolateral NKCC1 and efflux through apical Cl^- channels. AVP, the key hormone for osmoregulation, promotes CFTR-mediated Cl^- secretion. In addition, prostaglandin E2 stimulates Cl^- secretion through both CFTR and Ca^{2+}-activated Cl^- channels.

Summary—Renal Cl^- secretion has been commonly overlooked because of the overwhelming capacity for the nephron to reabsorb NaCl from the glomerular filtrate. In ADPKD, Cl^- secretion plays a central role in the accumulation of cyst fluid and the remarkable size of the cystic kidneys. Investigation of renal Cl^- secretion may provide a better understanding of NaCl homeostasis and identify new approaches to reduce cyst growth in PKD.

Keywords

Cl^- transport; NKCC1; CFTR; ENaC; paracellular

INTRODUCTION

Glomerular filtration generates approximately 180 liters of fluid per day and robust tubular reabsorption reclaims all but a 0.5 to 1 liter back to the body. Urine is commonly thought of as left over fluid and solutes from incomplete tubular reabsorption. However, an

Correspondence to: Darren P. Wallace, Ph.D., The Kidney Institute, Department of Medicine, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160-3018, dwallace@kumc.edu.

CONFLICT OF INTEREST
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underappreciated amount of NaCl secretion, hidden within the reabsorptive transport of Na^+, may provide fine-tuning of the amount of NaCl excreted by the kidneys. It is reasonable to think that salt secretion by tubule segments that are distal to regions with high Na^+ absorptive capacity (i.e. proximal tubules and thick ascending limbs) would have the greatest impact on overall salt balance. We propose that regulation of NaCl absorptive and secretory processes expressed in renal collecting ducts, the last segments in contact with tubule fluid, adjust salt excretion to dietary intake.

Cl^- Secretion by Renal Collecting Ducts

Cl^- transport by the collecting ducts involves both transcellular and paracellular pathways. The cortical collecting duct (CCD), the most responsive segment to aldosterone, is an important site for net NaCl absorption predominantly due to amiloride-sensitive Na^+ absorption via the apical epithelial Na^+ channel (ENaC). In the CCD, ENaC-mediated Na^+ reabsorption creates a lumen negative potential that drives passive Cl^- reabsorption through the paracellular pathway [1]. Some evidence suggests that Cl^- permeable pores in the tight-junctions are formed by claudins 4 and 8 [2, 3]. Whereas, other studies have indicated that claudins 4 and 8 serve as barriers to cation permeation, preventing back-flux of Na^+ and maintaining the electrochemical gradient that drives paracellular Cl^- reabsorption [4–7]

Pendrin (*SLC26A4*), also known as the Na^+-independent Cl^-/HCO_3^- exchanger, is expressed in type B intercalated cells in aldosterone-sensitive regions of the collecting duct and provides a passive transcellular pathway for Cl^- reabsorption in CCDs [8]. In addition, passive Cl^- movement into cells may involve apical Cl^- channels when there are large lumen-negative transepithelial voltage differences [9]. In CCD cell monolayers, clamping transepithelial voltage difference to 20 mV (lumen negative) induced passive Cl^- reabsorption through ATP-stimulated Ca^{2+}-activated Cl^- channels (CaCCs) [9].

Given the presence of these multiple transcellular and paracellular pathways in the CCD for passive Cl^- permeation, Cl^- might be capable of being transported in either direction, resulting in net reabsorption or secretion, depending on the transepithelial voltage. Active Na^+ reabsorption via ENaC during periods of high aldosterone could establish lumen negative potentials favoring passive Cl^- absorption through both the paracellular and transcellular pathways. However, when aldosterone levels are low, reduced Na^+ absorption by ENaC would generate a lower transepithelial voltage across the epithelium, limiting Cl^- absorption.

Recently, ENaC inhibition by addition of amiloride in the tubule perfusate unmasked a basolateral-to-apical Cl^- flux in isolated perfused mouse CCDs [10]. Cl^- secretion was blunted by basolateral bumetanide, an inhibitor of the Na,K,2Cl cotransporter NKCC1, and by gene knockout of NKCC1 [10]; and by the addition of a non-selective Cl^- channel blocker (DIDS) to the perfusate [11]. A selective inhibitor of cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channels failed to block Cl^- secretion suggesting that, at least, in the absence of cAMP agonists CFTR Cl^- channels were not involved. In split open CCDs, a Cl^- channel was observed that had conductance properties consistent with the ClC family of Cl^- channels; however, ClC-5 was ruled out as a primary pathway for Cl^- efflux

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from the cell. Additional studies will be needed to identify the Cl^- channels involved in unstimulated Cl^- secretion by the CCD and the response of this segment to cAMP agonists.

Medullary collecting ducts consist of an outer medullary collecting duct (OMCD) and initial and terminal regions of the inner medullary collecting duct (IMCDi and IMCDt, respectively). These segments are less responsive to aldosterone than the CCD and have lower net NaCl reabsorption. In vitro studies of isolated collecting duct segments revealed that the OMCD and IMCDi have a robust capacity to secrete Cl^- in response to elevated levels of intracellular cAMP and Ca^{2+}; whereas the IMCDt was less responsive [12]. Pharmacological inhibition of basolateral NKCC1 and Cl^-/HCO_3^- exchanger significantly decreased agonist-stimulated Cl^- secretion indicating that the cellular uptake of Cl^- involved these two Cl^- entry mechanisms [12–14]. Cl^- efflux across the apical membrane was mediated by cAMP-dependent CFTR Cl^- channels [12, 13, 15, 16] and CaCC [9, 15, 17]. While the specific CaCC channel has not been identified, anoctamin-1 (ANO1), a member of the TMEM16 family and a candidate protein for a CaCC, is highly expressed in rodent kidneys [18], renal epithelial cell lines [9, 17, 19] and in human renal collecting ducts [18].

Regulation of Cl^- Secretion by the Collecting Ducts

Cellular mechanisms for Cl^- secretion by renal collecting ducts are regulated by circulating hormones and paracrine factors binding to G-protein coupled receptors (GPCRs) and modulation of intracellular cAMP and Ca^{2+} levels.

Arginine Vasopressin (AVP) is the central hormone involved in the regulation of plasma osmolality by modulating water permeability of the collecting duct and is one of the most studied renal hormones. AVP binding to V2 receptors on the distal nephron and collecting ducts stimulates the production of intracellular cAMP by activation of adenylyl cyclase 6 [20–22]. Elevated cAMP promotes the membrane insertion and activation of aquaporin-2 water channels to the apical membrane, leading to increased water absorption. AVP has also been shown to stimulate Cl^- secretion through cAMP-dependent protein-kinase A (PKA) phosphorylation and activation of CFTR Cl^- channels and subsequent increase in NKCC1 activity. In cultured mouse CCD cells, basolateral AVP stimulated transcellular Cl^- and net fluid secretion [23, 24]. AVP was also shown to stimulate transcellular Cl^- secretion by primary cultures of human IMCDi cells that was blocked by inhibitors of NKCC1 and CFTR Cl^- channels [12, 13, 16]. In contrast to IMCDi cells, the capacity for AVP-induced Cl^- secretion by IMCDt cells was much lower [12, 13, 16], supporting the hypothesis that the initial region of the IMCD is a predominant site for renal salt secretion. AVP can also induce the release of autocrine factors by collecting duct cells, including ATP [25] and prostaglandin E2 (PGE2), which may further augment Cl^- secretion.

Adenosine triphosphate (ATP) is released into the luminal fluid in response to a high dietary salt intake [26], in addition to the action of AVP [25]. Once released, ATP and its breakdown products ADP and AMP bind to P2Y purinergic receptors to induce Cl^- secretion [17, 27, 28]. P2Y receptors are a family of purinergic receptors consisting of 12 known isoforms. ATP binding to G_q coupled puringeric receptors (P2Y1, 2, 4, 6 and 11),

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present on IMCD cells, activates phospholipase C (PLC), which increases production of inositol triphosphate (IP_3). IP_3 binding to its receptors causes the release of Ca^{2+} from intracellular stores [17], leading to inhibition of ENaC [26, 29] and stimulation of Cl^- secretion via apically localized CaCCs [9, 17, 27]. Purinergic receptors are localized to both membranes of collecting duct cells. In murine CCD cells, ATP addition to either membrane elicited an increase in Cl^- secretion; and apical and basolateral application of hexokinase, an ATP scavenger enzyme, blocked anion secretion [27]. Several studies have demonstrated that inhibition of P2Y receptors by suramin abrogates the ATP-mediated rise in intracellular Ca^{2+} and CaCC-mediated Cl^- secretion [9, 30, 31]. Inhibition of P2Y1 and P2Y2 receptors significantly reduced ATP-mediated Cl^- secretion in murine IMCD cells. Cl^- secretion was also inhibited by CaCC blockers and PLC inhibitors, and treating cells with a Ca^{2+} chelator [17]. Recently, knock-down of CaCC candidate protein Ano1, decreased ATP-induced Cl^- secretion by M1 cells, despite an elevation in intracellular Ca^{2+} levels [30]. ATP has also been shown to activate Ca^{2+} influx across the plasma membrane by activating luminal ATP gated Ca^{2+} channels (called P2X receptors). ATP binding to these channels stimulates Ca^{2+} influx into the cell and activation of CaCC-mediated Cl^- secretion [32, 33]. In mIMCD-3 cells, blocking of P2X receptors with gadolinium, a non-selective cation channel blocker, and P2X antagonists PPADS and PPNDS significantly inhibited ATP-induced rise in intracellular Ca^{2+} levels [33], consistent with a role for P2X in the regulation of Cl^- secretion.

Prostaglandin E2 (PGE2) is a paracrine factor produced by collecting duct cells in response to an increase in dietary salt intake [34] and ATP activation of P2Y2 receptors [35, 36]. PGE2 can bind four GPCR designated EP_1-EP_4 [37]. Activation of EP_1, a $G_{\alpha i}$ receptor, has been shown to inhibit aldosterone induced, ENaC-mediated Na^+ reabsorption within the renal medulla [38]. Several studies have shown that activation of EP_2 or EP_4 ($G_{\alpha s}$ receptors) in collecting ducts activates cAMP and enhances CFTR-mediated Cl^- secretion [13, 39–41]. In mIMCD-K2 cells, which were derived from the initial IMCD of a murine kidney, PGE2 binding to basolateral EP_4 receptors stimulated transcellular Cl^- secretion and this effect was mediated by cAMP activation of CFTR Cl^- channels. In addition, PGE2 also caused PKA activation of IP_3 receptors that lead to an elevation in intracellular Ca^{2+} and stimulation of Cl^- secretion via CaCC [41]. Interestingly, PGE2 activation of CFTR Cl^- channels appeared to be modulated, in part, by the rise in intracellular Ca^{2+}, since the intracellular Ca^{2+} chelator BAPTA-AM and 2-APB, an IP_3 receptor antagonist, reduced CFTR-mediated Cl^- secretion, in parallel with a decrease in CaCC-mediated current [41]. Intracellular Ca^{2+} has been shown to be required to maintain CFTR conductance in airway epithelium [42].

Catecholamines binding to β-adrenergic receptors (β-AR) were also found to promote transcellular Cl^- secretion by IMCD cells. Epinephrine, norepinephrine and isoproterenol individually increased cAMP levels and induced anion secretion by human IMCDi cell monolayers [43]. Immunohistochemistry of human kidney tissue revealed a greater expression of β_2-AR than β_1-AR in the medullary collecting ducts, and Cl^- secretion was blocked by inhibition of β_2-AR, but not β_1-AR. Conversely, activation of α_2-AR, a receptor coupled to $G_{\alpha i}$, with guanabenz inhibited isoproterenol-induced anion secretion.

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There are other potential agonists that have been shown to modulate cAMP and Ca^{2+} signaling in collecting duct cells and may regulate transcellular Cl^- secretion. Interestingly, the IMCD is a major site for the production of endothelin-1 (ET-1) [44], which is capable of binding four $G_{\alpha q}$ coupled GPCR isoforms ETA, ETB1, ETB2 and ETC. In the collecting duct, ET-1 binding to ETA or ETB decreases ENaC activity [45, 46]; however, it role in Cl^- secretion has not been examined. Recently, glycogen synthase kinase 3β (GSK 3β), a kinase in the Wnt signaling pathway, was shown to stimulate cAMP production by activating adenylyl cyclase in collecting duct cells. In CCD cells, GSK-3β inhibition reduced cAMP production and CFTR-mediated Cl^- secretion [47], raising the question if signaling molecules that utilize the GSK 3β signaling pathway modulate collecting duct Cl^- secretion.

Cl^- secretion in cyst expansion in polycystic kidney disease

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common renal disorder characterized by the progressive enlargement of numerous fluid-filled cysts that disrupt the normal architecture, leading to nephron loss, fibrosis and decline in function. The kidneys expand 4–8 times normal size due to cyst growth involving aberrant cell proliferation and fluid accumulation within the cyst. Transepithelial fluid secretion, driven by active Cl^- secretion, is responsible for the remarkable appearance of the ADPKD kidneys. In the absence of Cl^--dependent fluid secretion, the small amount of abnormal cell proliferation would lead to small benign neoplasms in the kidney that would likely have minimal impact on overall renal function.

The role for cAMP on renal cyst growth is well established [48]. In ADPKD, cAMP activates apical CFTR Cl^- channels and subsequent Cl^- efflux from the cell causes indirect activation basolateral NKCC1, driving Cl^- entry [24, 49]. Inhibition of CFTR prevents cAMP-dependent anion secretion across human ADPKD cell monolayers [50], slows cyst-like dilations in embryonic kidneys [51] and delays disease progression in PKD mice [52]. AVP binding to V2 receptors on cystic epithelial cells maintains cAMP at elevated levels, activating pathways involved in cell proliferation and Cl^-dependent fluid secretion [49, 53]. Tolvaptan, a V2 receptor antagonist, blocks the renal effects of AVP and inhibits Cl^- secretion and in vitro cyst grown of human ADPKD cells [50]. In preclinical studies, tolvaptan delayed the progression of cystic disease in four different animal models of PKD [54–57], providing the rationale for the TEMPO trials in PKD patients. The results of the TEMPO trial demonstrate that V2 receptor antagonism effectively slowed total kidney volume increase and the decline in estimated glomerular filtration rate in ADPKD patients [58, 59]. Clearly, AVP is the major factor for cyst growth in PKD; however other factors may contribute to both cell proliferation and fluid secretion. PGE2 was shown to induce Cl^- secretion to a greater level in PKD1 deficient IMCD cells, compared to wild-type cells [60]. This effect of PGE2 was mediated by both cAMP activation of CFTR Cl^- channel and Ca^{2+} activation of CaCC. ATP has also been shown to augment fluid secretion induced by cAMP in three-dimensional “cyst” models of MDCK-1 cells [19]. Furthermore, inhibition or knock-down of ANO-1, a potential CaCC, reduced fluid secretion and cyst-growth in MDCK cysts, as well as in cultured mouse metanephric kidneys treated with forskolin [61]. In addition, endogenous concentrations of ouabain, a steroidal hormone synthesized by the adrenal gland, were found to bind to its receptor Na-K-ATPase and cause a synergistic effect

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on cAMP-mediated Cl^- secretion in human ADPKD cells [62]. The effect of ouabain on Cl^- secretion was prevented by inhibitors of EGF receptor, Src and MEK, suggesting a novel pathway for modulating CFTR Cl^- channels. Other agonists shown to contribute to Cl^- secretion by ADPKD cells include ATP and β2-AR agonists [43, 63]. A better understanding of renal hormones and autocrine factors that promote cAMP- and Ca^{2+}-mediated Cl^- secretion will allow for development of targeted therapies to reduce fluid accumulation within renal cysts.

CONCLUSION

The role of renal Cl^- secretion in salt balance has been proposed for many years, but it has been difficult to demonstrate in vivo because of the exuberant NaCl reabsorption by the kidney. Several lines of evidence suggest that renal collecting ducts, particularly the initial region of the IMCD, retain cellular machinery for regulated Cl^- secretion that shares aspects of salt elimination by insect Malpighian tubules [64] and aglomerular nephrons of the hagfish and lamprey [65].The capacity for renal Cl^- and fluid secretion is revealed in the progressive expansion of cysts in genetic forms of PKD.

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- Renal collecting ducts have the capacity for regulated NaCl secretion to make the final adjustments to salt excretion.
- Renal Cl^- secretion involves Cl^- uptake by basolateral NKCC1 and Cl^- efflux by apical CFTR and Ca^{2+}-activated Cl^- (CaCC) channels.
- In polycystic kidney disease, cAMP-dependent Cl^- secretion drives transepithelial fluid secretion and the accumulation of fluid within renal cysts.

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