can this trajectory be modified using UCDA? The influence of cholic acid on DNA methylation in the agouti mouse model very likely occurred during embryogenesis, since all germ layers showed equivalent changes in methylation. If ICP is truly specific to the second or third trimester, the effects in the agouti model may be very different from any epigenomic effects elicited by ICP. The mouse model of cholestasis will be useful in future work to more fully characterize these epigenomic effects and to identify the particularly relevant windows of exposure.

Understanding the roots of metabolic dysfunction may provide inroads to improved treatment options involving the specific genes whose expression is altered by cholestatic programming. Obesity has major ramifications for overall health and well-being and is at epidemic proportions in the United States. This cholestatic mouse model may also provide insights that are generalizable to other factors that predispose to metabolic dysfunction.

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Address correspondence to: Susan K. Murphy, Duke University Medical Center, 226 B Wing, Levine Science Research Center, Box 91012, Research Drive, Durham, North Carolina 27708, USA. Phone: 919.681.3423; Fax: 919.684.5336; E-mail: susan.murphy@duke.edu.

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Mitochondrial TCA cycle intermediates regulate body fluid and acid-base balance

János Peti-Peterdi

Department of Physiology and Biophysics and Department of Medicine, Zilkha Neurogenetic Institute, University of Southern California, Los Angeles, California, USA.

Intrarenal control mechanisms play an important role in the maintenance of body fluid and electrolyte balance and pH homeostasis. Recent discoveries of new ion transport and regulatory pathways in the distal nephron and collecting duct system have helped to better our understanding of these critical kidney functions and identified new potential therapeutic targets and approaches. In this issue of the *JCI*, Tokonami et al. report on the function of an exciting new paracrine mediator, the mitochondrial the citric acid (TCA) cycle intermediate α-ketoglutarate (αKG), which via its OXGR1 receptor plays an unexpected, nontraditional role in the adaptive regulation of renal HCO_3^- secretion and salt reabsorption.

The distal nephron and collecting ducts are the final segments of the renal tubular network, which enable fine-tuning of systemic NaCl, water, K^+, and acid-base balance. According to the classical view, the principal cells respond to systemic hormones like aldosterone and vasopressin to modulate transport of salt, water, and K^+, while intercalated cells can excrete either H^+ (type A cells) or HCO_3^- (type B cells), depending on the body's acid-base status (1). Type B intercalated cells extrude H^+ through a basolateral vacuolar H^+-ATPase and secrete HCO_3^- into urine via the apical Cl^-/HCO_3^- exchanger pendrin (1). Another intercalated cell subtype, non-A–non-B cells, expresses both the H^+ pump and pendrin at the apical membrane (2). These intercalated cell types and transport mechanisms play an important role in maintaining the normal plasma pH of 7.4 (acid-base balance) via their corrective response to an acid or alkali load. For example, increased dietary acid intake (an example of metabolic acidosis) causes a reversal of polarity of HCO_3^- flux in the distal nephron and collecting duct, as HCO_3^--secreting type B intercalated cells are remodeled to become H^+-secreting type A intercalated cells (3). Conversely, dietary alkali load (an example of metabolic alkalosis) triggers an adaptive response by intercalated cells in which their population density is shifted to the B (HCO_3^--secreting) type (4).

However, in addition to their apparent role in pH balance, a new paradigm of the distal nephron and collecting duct is currently emerging in which, via newly identified functions of intercalated cells and paracrine mechanisms, this structure plays a critical role in renal physiology, body electrolyte and water homeostasis, and blood pressure control (5). For example, the Eladari and Chambrey groups recently demonstrated the expression of the Na^+-driven Cl^-/HCO_3^- exchanger NDCBE (Slc4a8) in

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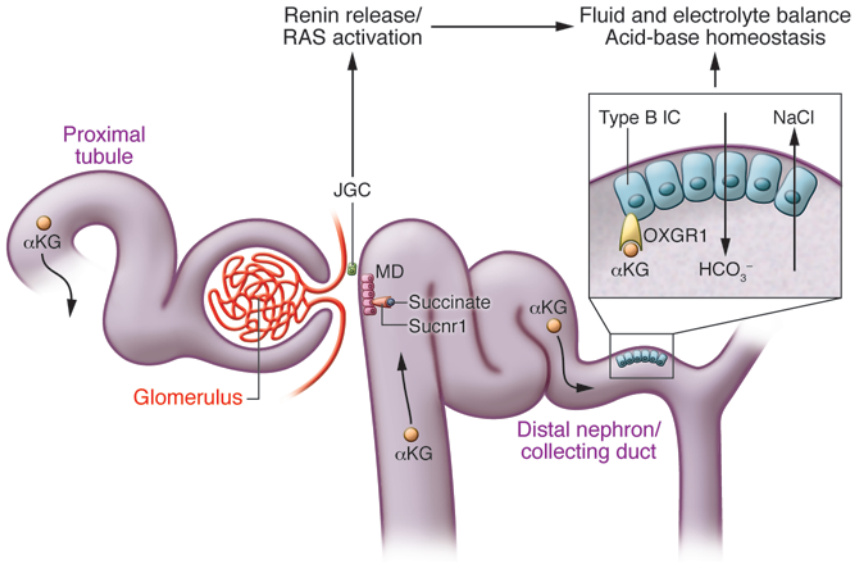

Figure 1

Illustration of the renal expression and functions of mitochondrial TCA cycle intermediates in the regulation of body fluid and acid-base balance. In addition to the collecting duct, Sucnr1 is expressed in the macula densa (MD) segment of the distal nephron and mediates succinate-induced renin release from the adjacent juxtaglomerular cell (JGC) via paracrine signaling. αKG in the tubular fluid mediates a paracrine crosstalk between proximal and distal nephron segments. Via OXGR1 expressed in type B (and also in non-A–non-B) intercalated cells (ICs) of the distal nephron and collecting duct, αKG regulates HCO_3^- secretion and electroneutral transepithelial NaCl reabsorption. These intrarenal mechanisms appear to play important new roles in the regulation of body fluid and electrolyte balance and acid-base homeostasis. Adapted with permission from *Physiology* (12). RAS, renin-angiotensin system.

type B intercalated cells, which upon functional coupling with pendrin performs electroneutral NaCl reabsorption (6). This finding revealed that type B intercalated cells are critical for acid-base transport but also play a role in NaCl reabsorption and, accordingly, blood pressure regulation.

Metabolic sensors modulate kidney function

One important piece of the puzzle in understanding these intrarenal control mechanisms was the finding that metabolic intermediates exert direct control over distal nephron and collecting duct function. He et al. demonstrated that the citric acid (TCA) cycle intermediates succinate and α-ketoglutarate (αKG) (also called 2-oxoglutarate) are ligands for the (previously) orphan GPCRs GPR91 and GPR99, respectively (7), structurally similar receptors that are now called Sucnr1 and OXGR1. Since then, the role of succinate/Sucnr1 in pathology has been established in diverse organs, including the kidney (8, 9), in which they regulate renin release and the activation of the renin-angiotensin system in certain conditions, including diabetes (10–12). He et al. demonstrated that OXGR1 was predominantly expressed in the renal distal tubules (7), but the (patho) physiological function of this receptor has remained unknown for the 9 years since its deorphanization. Beyond their traditional function in the TCA cycle, succinate and αKG may also play roles in various cellular responses to mitochondrial stress via their cell surface receptors. In fact, the accumulation of succinate in the local tissue environment was observed in various metabolic conditions in which there was an imbalance between energy supply and demand, e.g., hypoxia and diabetes (7, 9–11). It remains to be shown if a similar phenomenon exists for αKG.

In this issue of the *JCI*, the study by Tokonami et al. (13) adds the newest chapter to the emerging view of the distal nephron and collecting duct, with the discovery of a paracrine regulatory loop between the proximal and distal nephron that controls acid-base balance. They found that OXGR1 expressed in type B and non-A–non-B intercalated cells of the distal nephron and collecting duct can detect αKG secreted by proximal tubule and loop segments and regulate Cl^--dependent HCO_3^- secretion and electroneutral transepithelial NaCl reabsorption. This novel paracrine mechanism is clinically relevant to the maintenance of body fluid homeostasis. The new data indicate that αKG directly controls intercalated cell electroneutral NaCl reabsorption and suggest that OXGR1-mediated distal NaCl reabsorption is required to compensate for the altered proximal reabsorption of salt under a body acid-base challenge.

OXGR1 signaling in the distal nephron

Tokonami et al. first established that the elements of OXGR1 signaling are present in the distal nephron and collecting duct. OXGR1 receptor expression was found in type B and non-A–non-B intercalated cells, and the ligand αKG was detected in physiologically and functionally relevant concentrations in the urine (reflecting its presence in distal tubular fluid) under base loading conditions (13). Subsequently, elegant in vitro tubule microperfusion studies demonstrated that luminal activation of OXGR1 by αKG stimulated pendrin activity (HCO_3^- secretion) and electroneutral reabsorption of NaCl by type B and non-A–non-B intercalated cells. This novel renal control mechanism was shown to be functionally important and relevant in vivo, since mice devoid of OXGR1 exhibited a reduced capacity to maintain body acid-base equilibrium under base load conditions (13).

Overall, the study by Tokonami et al. offers an important new contribution to the emerging view of distal nephron and collecting duct as a mediator of physiology and further emphasizes the role of intercalated cells in the maintenance of fluid and NaCl homeostasis and acid-base balance. In light of the recently established roles of succinate and SUCNR1, which like OXGR1 is predominantly expressed in the distal nephron and collecting duct (11, 14), this study adds to the understanding that mitochondrial TCA cycle intermediates directly regulate the intrarenal mechanisms of body fluid and acid-base balance (Figure 1).

Conclusions and future directions

Future research on OXGR1 may find other renal and extrarenal functions for αKG and its receptor beyond modulation of bicarbonaturia. The special conditions of the local tissue environment (e.g., hypoxia) and cell metabolism (e.g., high anaerobic glycolysis) in most parts of the distal nephron and collecting duct likely drive the local accumulation of TCA cycle intermediates (9).

Similar to the established consequence of succinate/SUCNR1 accumulation (8), OXGR1 activation and signaling may be present and have roles in hypoxic and metabolic stress-related disease conditions such as diabetes (8, 9). It will be important to identify and characterize the downstream signaling molecules of OXGR1 in type B intercalated cells to more fully understand its function. In principal cells, succinate/Sucnr1 signaling involves MAP kinases and the generation of prostaglandins (e.g., PGE_2), which is highly relevant to the control of renal salt and water transport (11, 14). OXGR1 is a Gq-coupled GPCR (7), suggesting the involvement of Ca^{2+} and PKC in the adjacent intercalated cells. Interestingly, various isoenzymes of PKC (e.g., PKC-α, PKC-β1), which control tubular ion and water transport but also signal the actions of hormones and growth factors on cell proliferation and differentiation, show distinct high level expression in type B and non-A–non-B intercalated cells (15). Whether OXGR1 signaling involves any of these PKC isoenzymes and what other intercalated cell functions OXGR1 may control need to be further investigated.

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Address correspondence to: János Peti-Peterdi, Department of Physiology and Biophysics and Department of Medicine, Zilkha Neurogenetic Institute, University of Southern California, 1501 San Pablo Street, ZNI 335, Los Angeles, California 90033, USA. Phone: 323.442.4337; Fax: 323.442.4466; E-mail: petipete@usc.edu.

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