pH sensors and ion Transporters: Potential therapeutic targets for acid-base disorders

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ABSTRACT
Regulation of pH is critical for physiological processes. Maintenance of acid-base homeostasis is tightly regulated by the renal and respiratory systems. However, fluctuations in extracellular pH are also sensed by other organ systems. Ion transporter activity to modify the amount of acid (H^+ and CO_2) and bicarbonate HCO_3^- is therefore actively maintained within the kidney and lung. This review describes acid-base disorders (acidosis and alkalosis) and highlights the importance of pH sensors and ion transporters that may be potential therapeutic targets for treatment of acid-base disorders. Specifically, the renal pH sensors proline-rich tyrosine kinase-2 (Pyk2) and G-protein coupled receptor-4 (GPR4) are discussed here.

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## RESPIRATORY AND RENAL REGULATION OF ARTERIAL PH

Regulation of physiological pH is very important since most biochemical processes occur only within a narrow pH range. Typically, intracellular pH is about 7.2 and extracellular (or arterial) pH is between 7.36 and 7.44. pH fluctuation can occur in many organs and triggers a response in multiple cell types. pH can change as a result of ischemia, inflammation, exercise, musculoskeletal pain, and normal metabolic and neuronal activity [1]. Acid base homeostasis is primarily maintained by the renal and respiratory systems, but pH is also sensed by the epididymis, osteoclast, myocyte, neuron, and acid/base-producing cells in the kidney, gut, and pancreas, among others. Within the cell interior and in the blood, the carbonic acid-bicarbonate buffering system works to maintain pH homeostasis by adjusting the amount of hydrogen and bicarbonate ions present. The reaction of the CO_2/HCO_3^- buffering system, catalyzed by carbonic anhydrase (CA), is as follows: $CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$ [2]. CO_2 can readily diffuse through the membrane without the aid of a transporter. The lipid bilayer however is impermeable to charged H^+ and HCO_3^-, thereby requiring transport proteins to allow these ions to cross. Regulation of the acid or base transporters occurs through signaling transduction cascades initiated by a pH sensor, which is a protein directly activated by fluctuations in arterial or intracellular pH. This article focuses on the ion transporters that regulate pH and the putative pH sensors that control H^+ and HCO_3^- influx and efflux within a cell.

Acid loads occur regularly due to metabolism of protein from a Western diet. Normal physiology is therefore in place to prevent acidemia after ingestion of dietary acids including compensatory mechanisms of the renal and respiratory systems. Excessive drops in pH (<6.8) is termed acidosis, and can occur as a result of the loss of an alkali load via diarrhea or vomiting [3].The kidney can compensate for acid loads by increasing proximal tubule bicarbonate reabsorption, increasing distal acid secretion, and/or increasing ammonia excretion [4]. Hyperventilation is another way the body prevents acidosis by decreasing P_{CO2} [4]. Alkali loads can be metabolic, due to excessive excretion of urinary (or gastric) acid or respiratory; it can also due to hyperventilation, which lowers P_{CO2}. To maintain a normal pH, the proximal tubule compensates for an alkali load by decreasing bicarbonate reabsorption; the pH can also be lowered through hypoventilation [4].

The respiratory system regulates pH by altering the amount of CO_2 in the blood versus that exhaled through breathing. There are respiratory compensatory mechanisms triggered by decreased blood pH that results in greater diaphragm contraction, therefore more CO_2 gets exhaled [5]. The equilibrium between CO_2 (gas) $\leftrightarrow$ CO_2 (dissolved) varies with partial pressure of CO_2, temperature, and pH [2]. Upon entering the low CO_2 concentration environment of the lungs, erythrocytes control the amount of CO_2 exhaled through regulation of the activity of CA and of ion transporter activity, specifically of AE1 (anion exchanger 1), which exchanges intracellular HCO_3^- for extracellular Cl^-. CA converts HCO_3^- to CO_2, which readily diffuses across the membrane and is exhaled [2]. This

is shown in the diagram in (**Figure 1 and Panel B**). Anion exchangers (AEs) (AE1, AE2, AE3, and AE4) are important bicarbonate transporters in nearly all acid sensitive cells, as shown in (**Figure 1**). AE1 is a bicarbonate/chloride exchanger expressed in the erythrocyte and collecting duct (**Figure 1 and Panel D**). AE2 is another important bicarbonate/chloride exchanger expressed in gastric parietal cells and osteoclasts (**Figure 1 and Panel C**). AE3 is important in myocyte acidification. AE4, a sodium/bicarbonate cotransporter, is important in the brain (**Figure 1 and Panel A**) and in B-IC cells of the collecting duct (**Figure 1 and Panel D**). Other important bicarbonate transporters include NBCe1, Ndcbe, and Pendrin described in more detail in (**Table 1**).
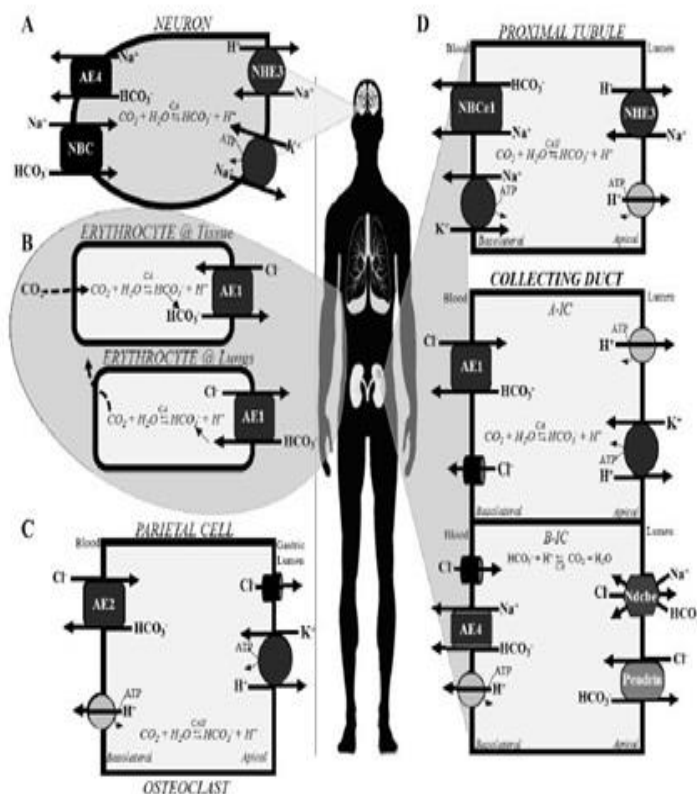
The diagram shows the main six cell types involved in pH sensing and/or regulation of arterial pH and the acid (H^+) and base (HCO_3^-) transporters expressed on the plasma membrane of each cell type. **(A)** The neuron senses and responds to changes in pH through regulation of bicarbonate transporters AE4 (HCO_3^- efflux) and NBC (HCO_3^- influx). **(B)** Respiratory regulation of pH occurs primarily through AE1 in erythrocytes, which interestingly reverses the direction of its normal HCO_3^-/Cl^- transport when in the lungs. Bicarbonate secretion occurs when the blood is at the body's tissues. When at the lungs, bicarbonate absorption occurs through AE1. Once inside the cell, bicarbonate is converted to CO2, diffuses through the membrane and is exhaled. **(C)** The gastric parietal cell and osteoclast exhibit similar ion transporter expression, with basolateral bicarbonate absorption through AE2 and proton extrusion through the basolateral H^+ ATPase and apical H^+,K^+-ATPase activity. **(D)** The three polarized epithelial cells diagramed on the right show renal acid- and base-secreting cells of the proximal tubule (top) and collecting duct (middle and bottom). Two types of intercalated cells are shown; Type A acid-secreting (A-IC) cells (middle) and type B bicarbonate-secreting (B-IC) cells (bottom). In the proximal tubule, basolateral bicarbonate reabsorption occurs via NBCe1 and apical acid secretion occurs via NHE3 and the H^+-ATPase. In A-ICs of the collecting duct, basolateral bicarbonate reabsorption occurs via AE1 and apical acid secretion occurs via H^+,K^+-ATPase and V-ATPase. In B-ICs of 15 the collecting duct, basolateral bicarbonate reabsorption occurs via AE4 and apical bicarbonate transport occurs via Ndcbe and Pendrin. Proton reabsorption also occurs in B-ICs across the basolateral membrane via active transport of the V-ATPase.

Figure 1: Cell-specific transporters involved in regulation of acid-base homeostasis.

Table 1: Transport proteins involved in pH regulation. The following transporters in the regulation of acid-base homeostasis are activated by changes in arterial pH. The cells expressing each protein and the function of each transporter are shown.

	Ion Transporter	Gene	Cell type	Ion efflux	Ion influx	Function	Refs
AE1	Anion exchanger 1; B and 3 protein	SLC4A1	Collecting duct (AIC)	Cl^-	HCO_3^-	Bicarbonate reabsorption (Cl^-/HCO_3^- exchanger)	[4]
AE2	Anion exchanger 2	SLC4A2	Gastric parietal cells and osteoclasts	Cl^-	HCO_3^-	Cl^-/HCO_3^- exchanger	[24]
AE3	Anion exchanger 3	SLC4A3	Cardiac myocyte	Cl^-	HCO_3^-	Myocyte acidification (Cl^-/HCO_3^- exchanger)	[2]
AE4	Anion exchanger 4	SLC4A9	Collecting duct (BIC) and Neuron	Na^+	HCO_3^-	Bicarbonate reabsorption	[4]
HKα1	α-subunit of gastric H^+,K^+-ATPase		Gastric parietal cells and Collecting duct (A-IC)	H^+	K^+	Urinary and intestinal acidification	
HKα2	α-subunit of colonic H^+,K^+-ATPase	ATP1A2	Colonic and Collecting duct (AIC)	H^+	K^+	Urinary and intestinal acidification	[8,2]
KCC4	KCl cotransporter	SLC12A7	Collecting duct	Cl^-	K^+	Urinary acidification	[4]
NBCe1	Sodium bicarbonate cotransporter-1	SLC4A4	Proximal tubule	HCO_3^-	Na^+	HCO_3^- absorption (Electrogenic Na^+/HCO_3^- cotransporter)	[4]
Ndcbe	Sodium-Driven Chloride/Bicarbonate Exchanger	SLC4A8	Collecting duct (B-IC)	Cl^-	Na^+ and HCO_3^-	HCO_3^- secretion (Na^+/HCO_3^- cotransporter)	[4]
NHE1	Na^+/H^+ exchanger 1		Cardiac myocyte Neuron	H^+	Na^+	Cardiac hypertrophy Epilepsy	[2]
NHE3	Na^+/H^+ exchanger 3		Proximal tubule and Neuron	H^+	Na^+	Urinary acidification	[26]
NHE6	Na^+/H^+ exchanger 6		Neuron	H^+	Na^+	Epilepsy and brain disorders	[19,26]
NHE9	Na^+/H^+ exchanger 9		Neuron	H^+	Na^+	ADHD	[26]
Pendrin			Collecting duct (B-IC)	HCO_3^-	Cl^-	Bicarbonate secretion	[4]
SLC26A7			Gastric parietal cells, CCD and OMCD	Cl^-	HCO_3^-	Basolateral HCO_3^- reabsorption (Cl^-/HCO_3^- exchanger)	[27]
V-ATPase	Vacuolar-type H^+-ATPase		Collecting duct and Epididymal clear cells	H^+		Urinary acidification	[8,13]

The kidneys are ultimately responsible for maintenance of acid base homeostasis through regulation of the HCO_3^- reabsorption and H^+ excretion into the urine. 90% of bicarbonate reabsorption occurs in the proximal tubule via transporters that are often Cl^- driven [6]. Acidification of the urine occurs primarily in the distal nephron via proton transporters that are often Na^+ or K^+ driven, such as the sodium/hydrogen exchangers (NHE) and Na^+, (H^+), K^+- ATPases. The apical membrane of the collecting duct is known to pump protons into the lumen via V-ATPases and H^+, K^+-ATPases to acidify the urine. The collecting duct (CD) is comprised of three segments, the cortical collecting duct (CCD), outer medullary collecting duct (OMCD), and inner medullary collecting duct (IMCD), each consisting of a different distribution of principal and intercalated cells. The three types of intercalated (IC) cells are acid-secreting Type A-ICs, bicarbonate-secreting Type B-ICs, and nonAnonB-ICs (not discussed in this article). (**Figure 1 and Panel D**) diagrams the transporters present in the apical and basolateral membranes of renal proximal tubule and intercalated cells. Many of the transporters responsible for the maintenance of pH are listed in (**Table 1**) along with the localization, physiological function, and ion specificity for each transporter.

CLINICAL MANIFESTATIONS AND PHARMACOLOGICAL IMPLICATIONS OF ACID-BASE DISORDERS

pH is indicative of acid-base status using the Henderson-Hasselbalch equation:

$$pH = pK + \log_{10} \frac{[Hco_3^-]}{Pco_2}$$

The acid dissociation constant is denoted as pK, bicarbonate concentration is in millimoles per liter and P_{CO2} is in millimeters of mercury [7]. Acid-base disorders involving abnormal CO_2 (changes in P_{CO2}) are termed respiratory disorders whereas those involving bicarbonate or acid are termed metabolic disorders [4]. Acidosis and alkalosis can each be either metabolic or respiratory. The methods for assessing acid-base disturbances depend on if the cause is respiratory or metabolic. Clinical evaluation includes analysis of any primary disease (pulmonary, cardiovascular, gastrointestinal) that may cause a secondary acid-base disturbance. Although these acid-base disorders are often due to genetic and/or physiological abnormalities, they can also be side-effects of certain medications or intoxications, as shown in (**Table 2**).

Table 2: Drug-induced acid-base disorders [6]. Acidosis (low pH) and alkalosis (high pH) can be due to dysregulation of H$^+$ or HCO$_3^-$, termed Metabolic, or due to abnormal CO$_2$ or P$_{CO2}$, termed Respiratory. These acid-base disorders can result from medications or intoxications.

	Metabolic		Respiratory
	Normal Anion Gap	**Elevated Anion Gap**	
Acidosis	Acetazolamide Topiramate Amphotericin B Ifosfamide	Linezolid Lorazepam Metformin Nitroprusside Nucleoside reverse transcriptase inhibitors Ethylene glycol Ethanol/Methanol	Opiates Benzodiazepines Propofol
Alkalosis	Diuretic therapy Bicarbonate administration Mineralocorticoids		Salicylates Nicotine Xanthine

Clinical evaluations of acid-base disorders involve measurement of blood pH, bicarbonate levels, and calculation of the urinary anion gap (AG), usually 10-12 mEq/L, and defined as follows:

AG = Na$^+$ - (Cl$^-$ + HCO$_3^-$). The AG is elevated in patients with metabolic acidosis (defined by arterial pH <7.35), which occurs due to excessive bicarbonate loss or acid loading. Symptoms of acidosis include weakness, headaches, shortness of breath, increased heart rate, nausea, vomiting, diarrhea, and sleepiness. Metabolic acidosis contributes to chronic kidney disease progression to end-stage renal disease [8]. Renal tubular acidosis (RTA) is a kidney disease that causes metabolic acidosis. Recent studies have shown that alkali treatment via sodium bicarbonate treatment slows the progression of CKD [9]. There are several types of RTA, including distal RTA (dRTA) and proximal RTA (pRTA), where distal and proximal refer to the segment of the nephron affected. Acid-base disorder treatment usually relies on treating the primary disease or problem that is contributing to the dysregulation of pH. In extreme cases of acidosis, bicarbonate infusions are used to regulate systemic pH. 7

pH SENSORS: REGULATION OF ION TRANSPORT

Regulation of the ion transporters that maintain pH homeostasis typically involves acid- or base activated signaling transduction mechanisms. Changes in pH may activate ion transporters directly, but more likely are sensed by an upstream pH sensor that regulates transporter activity, either directly or via a signaling cascade. Although a universal pH sensor has not been identified, several pH-sensitive signaling pathways that control acid-base transport have been elucidated. Putative pH sensors include pH-

sensitive G-protein coupled receptors (GPCRs) [10], H+-sensing ion channels [11], alkali-sensing receptor tyrosine kinases (RTKs), soluble adenylyl cyclase (sAC) [12], cyclic nucleotides, and intracellular non-RTKs [12,13]. It is expected that there must be a pH sensor, a protein activated by changes in extracellular pH, such as a membrane-spanning GPCR, ion channel, or receptor tyrosine kinase. In the cardiovascular system, acid-sensing ion channels (ASICs), relatives of Epithelial Sodium Channel (ENaC), may be responsible for sensing changes in pH in the blood, as well as regulating blood pressure [14]. There are also four known acid-stimulated GPCRs activated by the protonation of extracellular

histidine residues at low pH: GPR4 (G-protein coupled receptor-4) [3], OGR1 (ovarian cancer GPR1) aka GPR68 [15], TDAG8 (T Cell death-associated gene) aka GPR65 [16], and G2A aka GPR132 [10], shown in (**Table 3**). In the kidney, GPR4 is required for proper acid secretion [17]. GPR4-/- knockout mice develop metabolic acidosis due to reduced acid secretion, and also exhibit abnormal angiogenesis and increased insulin sensitivity [17]. GPR4 signals through a cAMP/PKA-mediated signaling mechanism and is required for H+, K+- ATPase activation in the CD [8]. Acid-sensing GPCRs have also been shown to be important in cancer cells, which often thrive in an acidic micro-environment [10].

Table 3: Putative Intracellular pH Sensors. The intracellular pH-sensitive proteins that have been identified are listed along with the particular cell types they are found, the downstream signaling proteins, and downstream targets.

Gene symbol	Protein Name	pH_o or pH_i	Localization	Signaling Mechanism	Target	Ref
Pyk2 (FAK)	Proline-rich tyrosine kinase-2 (Focal adhesion kinase)	pH_i	Proximal tubule collecting duct Osteoclast	$Ca^{++} \rightarrow$ ERK1/2	NHE3 V-ATPase	[13,18,19]
sAC	Soluble Adenylyl Cyclase	pH_i	Epididymis collecting duct	cAMP	V-ATPase ENaC	[22,23]
GPR4	G-protein coupled receptor-4	pH_o	Kidney, vasculature, pancreas	$G_s \rightarrow$ cAMP $\rightarrow$ PKA	AE1	[3,12,17]
OGR1 (GPR68)	Ovarian Cancer G-protein coupled receptor	pH_o	Bone, smooth muscle	$G_q \rightarrow$ PLC $\rightarrow$ Ca^{++}	V-ATPase	[15]
TDAG8 (GPR65)	T-Cell Death associated GPCR	pH_o	Immune and lymphoid cells	$G_s \rightarrow$ tmAC $\rightarrow$ cAMP $\rightarrow$ PKA	Inhibits MAPK	[16]
tmAC – transmembrane adenylyl cyclase						

Intracellular pH sensors are localized inside the cell and activated by changes in intracellular pH (pH_i). Two potential intracellular pH sensors are proline-rich tyrosine kinase-2 (Pyk2) and sAC. Pyk2, an acid-activated non-RTK, is a putative intracellular pH sensor in the kidney that controls acid secretion through regulation of NHE3 and vacuolar V-ATPase activity in the proximal tubule and collecting duct, respectively [13,18,19]. In the case of Pyk2, mitogen-activated protein kinase (MAPK) signaling cascades involving extracellular signal-related kinase-1/2 (ERK1/2) control acid-activation of H+-secretion (via NHE3 and H+-ATPase) during pH recovery after an

acid load [13,20,21]. V-type H+-ATPase mobilization is regulated by sAC, an intracellular CO_2/HCO_3^- sensor directly activated by increased intracellular calcium and/or bicarbonate ions [22]. sAC stimulates cAMP/cGMP release via phospholipase C (PLC) and protein kinase C (PKC)-mediated signaling pathways to regulate V-ATPase recycling in the epididymis and Na+ reabsorption in the collecting duct [22,23]. Mineralocorticoids stimulate H+-ATPase activity in the medullary collecting duct. Mutations in genes that encode the α4 and β1 Isoforms of the V-ATPase lead to dRTA [6]. The importance of V-ATPase activity in acid-base balance, especially its regulation in the

kidney, makes it a possible therapeutic target for controlling systemic pH. Pharmacologically, the transporters of the distal nephron and the pH sensors that regulate their activity would be good therapeutic targets for the treatment of acidosis.

PHYSIOLOGY OF ACID-BASE STUDIES

Renal micropuncture, nephron microperfusion and various molecular and biochemical techniques have greatly contributed to our current understanding on the acid-base regulation. The use of transgenic mice has also allowed us to further comprehend the physiological roles of acid-base transports. A mutation in acid-base transport can result in neonatal death [24-27]. However, it is important to note that these mice also have other severe phenotypes in addition to acid-base imbalance. Other phenotypes include growth retardation, pulmonary edema, electrolyte imbalance, anemia, intestinal obstruction, and other organ abnormalities, making it hard to discern the cause of death in these mice. Interestingly, administration of sodium bicarbonate in one of the mouse models prolonged survival rate, indicating that acid-base balance could dampen the progression of organ damage [26]. Physiologically, the acid-base homeostasis is also known to be a redundant process. To better understand this, we will use NHE3 as an example. In NHE3 mutant mice, NHE8 plays a compensatory role in renal acidification [27,28]. Both NHE2 and NHE3 also share a redundant function [29]. Although NHE3 mutant mice may present mild absorptive defects [30,31], the resulting hypovolemia does not help in understanding the specific effects of NHE3 deficiency on kidney function [32]. Furthermore, there is co-regulation between NHE3 with different NHE isoforms [33,34], denoting a highly complex acid-base regulation. Given the significance of acid-base regulation in all tissues, it is not surprising that we have a redundant physiological system to compensate any acid-base imbalance in our body. Nonetheless, transgenic mouse models have provided a plethora of knowledge on acid-base transport in vivo. This includes a better understanding that NHE3 plays an important role in fluid and bicarbonate reabsorption in the proximal convoluted tubule but does not play an important role in NH4 excretion [31].

Despite the significant physiological complexity, much has been learned about acid-base regulation in vivo through animal models, including the molecular mechanism of different transporters (**Table 1**). For more information about animal models used to study acid-base regulation, please refer to a recent comprehensive review [35-39].

SUMMARY

In summary, the regulation of systemic (or arterial) pH is highly complex and involves different mechanisms in multiple cell types, various transporters, and pH sensors. Recent advances using transgenic animal models suggest no single genetic knockout mouse has caused a major disruption in acid-base homeostasis, indicating it is a highly complex and redundant process. Pharmacological control of pH may be accomplished by targeting ion transporters, pH sensors, or signaling molecules that regulate acid-base homeostasis. We have discussed the putative pH sensors and ion transporters that need to be examined as therapeutic targets, including but not limited to Pyk2, sAC, and GPR4.

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