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Physiology of Acid-Base Balance: Links With Kidney Stone Prevention

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Two processes permit the urine pH and the medullary interstitial pH to remain in an "ideal range" to minimize the risk of forming kidney stones. First, a medullary shunt for NH_3 maintains the urine pH near 6.0 to minimize uric acid precipitation when distal H^+ secretion is high. Second, excreting dietary alkali excreting alkali as a family of organic anions—including citrate—rather than as bicarbonate maintains the urine pH near 6.0 while urinary citrate chelates ionized calcium, which minimizes $CaHPO_4$ precipitation. In patients with idiopathic hypercalciuria and recurrent calcium oxalate stones, the initial nidus is a calcium phosphate precipitate on the basolateral membrane of the thin limb of the loop of Henle (Randall's plaque). Formation of this precipitate requires medullary alkalinization; K^+ -depletion and augmented medullary H^+/K^+ -ATPase may be predisposing factors.

KEYWORDS acid-base, citrate, kidney stones, renal medulla pH, urine pH

It is truly an honor to contribute to this issue of *Seminars in Nephrology*, which recognizes the many novel contributions of Neil Kurtzman that have provided insights into the renal regulation of acid-base balance and its broader physiologic impact. In this style, we examined the regulation of acid-base balance from the perspective of how to maintain acid-base balance while the urine pH is close to 6 to minimize the risk of precipitating calcium phosphate and uric acid in the urine (Fig 1).[1] Examining acid-base balance in this way led us to challenge some of the accepted dogmas and to suggest alternative interpretations of the physiology, with possible important clinical implications. We also extend our analysis to the regulation of the pH level in the medullary interstitial compartment because recent evidence suggests that the initial phase of calcium oxalate stone formation is the precipitation of calcium-phosphate ($Ca_3(PO_4)_2$) nidus in the medullary interstitium, a process that requires medullary alkalinization.[2] New insights for the renal regulation of potassium (K^+) homeostasis[3] were very helpful for this analysis.

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Acid Balance and Precipitation of Uric Acid Stones

Acid balance has 3 components: the production of H^+ in the liver from the oxidation of dietary proteins, titration of these H^+ by HCO_3^-,[4] and the addition of new HCO_3^- to the body when ammonium ions (NH_4^+) are excreted in the urine.[5] The major acids of dietary origin requiring renal disposal are phosphoric acid and H_2SO_4. Only the H^+ from H_2SO_4, which is derived from the oxidation of sulfur-containing amino acids in the liver, require NH_4^+ excretion to eliminate these protons because of the low affinity of SO_4^{2-} for H^+. Support for this version of acid balance is that the daily urinary excretion of NH_4^+ and SO_4^{2-} are very similar in milliequivalent terms.[6]

Traditional Analysis of the Excretion of NH_4^+

The major renal response to a large chronic acid load is to increase the rate of excretion of NH_4^+.[7] There are 2 sites where NH_4^+ is added to the lumen of the nephron: the proximal convoluted tubule (PCT) and the medullary collecting duct (MCD).[7] Our focus will be on the transfer of NH_4^+ from the lumen of the thick ascending limb of the loop of Henle (LOH) to the MCD, the medullary shunt of ammonia (NH_3).[8] In the traditional view, an increased secretion of H^+ in the distal nephron drives the medullary shunt of NH_4^+ because it de-

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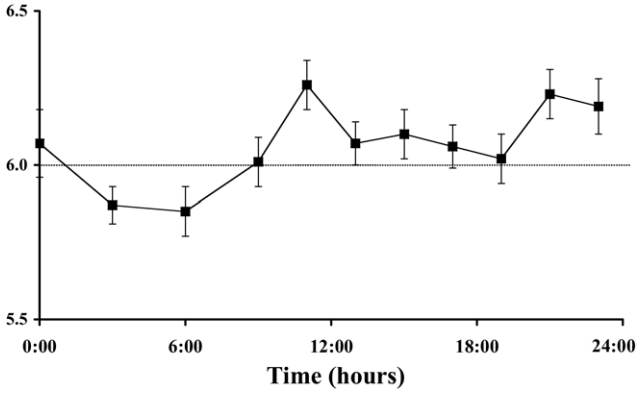

Figure 1 Diurnal variation in the urine pH in normal subjects. The solid line connecting the filled black squares depicts the values in normal volunteers (mean ± SEM). Note that urine pH is approximately 6.0 for most of the 24-hour period.

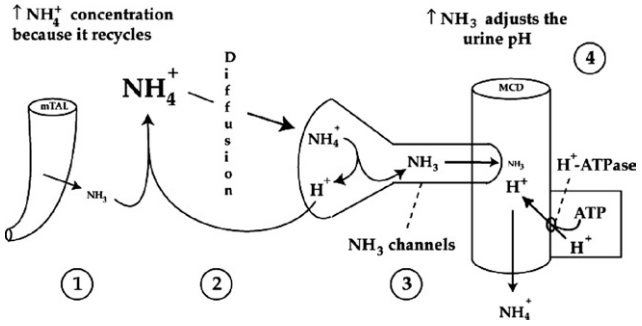

Figure 2 Hypothesis for the function of the medullary shunt pathway for NH_3/NH_4^+. The mTAL of the LOH is shown on the left and the MCD is shown on the right. The funnel-shaped structure in the MCD represents 2 different NH_3 channels, one in the basolateral membrane and the other in the luminal membrane of MCD cells. Reabsorption of NH_4^+ from the mTAL and its diffusion to the MCD permits NH_4^+ to enter the hydrophobic mouth of the NH_3 channel where it is converted to H^+ and NH_3. This increases the local $[NH_3]$, which diffuses into the lumen of the MCD if this channel is open. This entry of NH_3 increases the luminal pH despite continuing H^+ secretion by the H^+-ATPase. The net result is a higher urine pH and a somewhat higher rate of NH_4^+ excretion.

creases the urine pH and thereby the concentration of NH_3 in the lumen of the MCD, which allows for a more rapid rate of diffusion of NH_3 down its concentration difference from the medullary interstitium into the lumen of the MCD. This poses a conundrum because if a low urine pH were required to have high rates of excretion of NH_4^+, there would be an increased risk of precipitation of uric acid in the urine because the negative log of the dissociation constant (pK) of uric acid in the urine is approximately 5.3.[9] This led us to re-examine this traditional view of the physiology of NH_4^+ excretion.

Data in Conflict With the Traditional Interpretation of the Physiology of NH_4^+ Excretion

If a low luminal pH were needed to drive the diffusion of NH_3 into the MCD, one would expect to find a low urine pH when NH_4^+ excretion is increased markedly. Nevertheless, this is not the case because when human subjects were given a large chronic acid load the urine pH was close to 6.0 when the rate of excretion of NH_4^+ was greatly augmented.[10,11] In addition, when human beings were deprived of food for prolonged periods and developed chronic ketoacidosis, the urine pH was again close to 6.0 when the rate of NH_4^+ excretion was at its peak.[12]

Table 1 Concentration Difference of NH_3 in the Renal Medullary Interstitial Compartment

Lumen pH	Interstitial $[NH_3]$	Lumen $[NH_3]$	Difference in $[NH_3]$
7.0	20	10	10
6.7	20	5	15
6.3	20	2	18
6.0	20	1.0	19
5.0	20	0.1	19.9

In this calculation, we assumed that the interstitial fluid pH was 7.3. The concentration of NH_3 in the interstitial compartment is set at 20 in arbitrary units. Decreasing the urine pH toward 6.3 is the only pH range in which there may be a quantitatively important effect on the concentration difference for NH_3 between the interstitial compartment and the lumen of the MCD. In other words, only a large defect in the distal H^+ secretion (a very high urine pH) will have a large negative impact on the rate of diffusion of NH_3 into the MCD.

Another problem with the assumption that a low pH is important for augmenting the diffusion of NH_3 into the lumen of the MCD becomes evident when this process of diffusion is examined in quantitative terms (Table 1). Although diffusion depends on a concentration difference, the magnitude of the concentration difference for NH_4^+/NH_3 is almost exclusively a result of the high concentration of NH_4^+/NH_3 in the medullary interstitial compartment because changes in the concentration of NH_4^+/NH_3 in the luminal fluid of the MCD are very small at luminal pH values lower than 6.3.

There are 2 sets of data that provide insights on the quantitative importance of this medullary NH_3 shunt. The micropuncture data from studies in rats by Jaeger et al[13] and Sajo et al[14] revealed that 100% of the NH_4^+ to be excreted was present in the lumen of the PCT, whereas 33% to 50% of this NH_4^+ remained in fluid samples obtained from the earliest distal convoluted tubule. Hence, there was a large addition of NH_4^+ between this distal site and the final urine. If these were the only data evaluated, one would mistakenly conclude that the medullary NH_3 shunt accounted for the majority of NH_4^+ excreted. This, however, is not the case because in the study by Sajo et al[14] in which fluid also was sampled form the terminal cortical collecting duct, this fluid contained 75% of the NH_4^+ to be excreted in rats with chronic acidosis, and therefore only a small amount of NH_4^+ actually was added via the medullary NH_3 shunt.

To explore this issue further, we examined the rate of excretion of NH_4^+ and the concentration of NH_4^+ in the medullary interstitial compartment before and after inhibition of LOH function with a dose of furosemide that did not lead to