ESSAYS ON APS CLASSIC PAPERS

Two classic papers in acid-base physiology: contributions of R. F. Pitts, R. S. Alexander, and W. D. Lotspeich

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This essay looks at the historical significance of two APS classic papers that are freely available online:


The main charge of the kidney in maintaining acid–base balance is to secrete acid at a rate equal to that of nonvolatile acid production and to reabsorb almost all of the filtered bicarbonate to prevent depletion of the body’s alkali reserves. The topic of this short essay is two relevant landmark papers in renal physiology. The first paper (7), published in 1945, addressed and successfully resolved the problem of the nature of the mechanism by which renal tubules acidify the urine. The second paper, published a year later, defined the properties of renal excretion of bicarbonate (8). Importantly, these investigations also provided a conceptual framework and the strategies for noninvasive quantitative exploration of the kidney’s role in acid–base balance. The work was immediately recognized for its flawless experimental design, its faultless execution, and the intellectual strength of the data analysis. The clear style and the elegance of the writing were also admired. It established Robert F. Pitts as one of the leading investigators in renal physiology.

Prior to the publication of the first paper, titled “The nature of the renal tubular mechanism for acidifying the urine” (7), three mechanisms had been proposed to account for the tubules’ ability to acidify the urine and to excrete acid, but no evidence was available to choose among them. The first two were based on the suggestion of L. J. Henderson (4) and of J. Sendroy, S. Seelig, and D. D. Van Slyke (9), and the third was suggested by H. Smith, without direct experimental support, in his first monograph on The Physiology of the Kidney (10).

The most popular, the phosphate reabsorption theory, assumed that the glomerular filtrate contained both Na2HPO4 and NaH2PO4, but that only the acidic member of the buffer mixture, NaH2PO4, is excreted into the urine and that Na2HPO4 was effectively reabsorbed by the renal tubules and delivered to the postglomerular capillaries. The “carbonic acid theory” postulated that H2CO3 was the main source of acid in the urine, because the tubules are completely impermeable to H2CO3, which is thus copiously excreted; NaHCO3 was thought to be reabsorbed. The third mechanism postulates that hydrogen ions from tubule cells are exchanged for sodium ions in the tubule lumen where they convert dibasic phosphate to the monobasic form. The source of hydrogen ions was postulated to be H2CO3 produced in tubule cells and derived from CO2 and H2O in the postglomerular blood.

An important step in designing the experiments that clarified the issue of the mechanism of renal acidification, and that allowed a choice between the three competing theories, was the realization that each of the proposed mechanisms had inherent limitations for the amount of acid that could be excreted. The phosphate reabsorption theory and the carbonic acid filtration theory are intrinsically limited by the fact that the acid in the urine derives from phosphate or H2CO3, both of them filtered through the glomeruli. In contrast, acid is added to the tubule fluid by the renal tubule cells according to the ion exchange theory. The first two mechanisms are thus dependent on and limited by the amount of acid filtered, and the third is dependent on the amount of acid that the tubules secrete.

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The critical experimental design involved two maneuvers. First, acid excretion was maximally stimulated in unanesthetized dogs by feeding hydrochloric acid for several days. Second, a large amount of buffer, phosphate or creatinine, was administered to provide conditions favoring large amounts of titratable acid formation. The major finding was that the urine of the acid-loaded dogs contained such large amounts of titratable acid that it could only be explained by a mechanism involving the secretion of acid by tubule transport. Clearly, the quantity of acid filtered through the glomeruli did not suffice to account for the amount of acid excreted in the urine. Further support for the secretory tubular origin of hydrogen ions was the demonstrated inhibition of acid secretion by sulfanilamides. These are inhibitors of carbonic anhydrase, an enzyme known to accelerate the hydration of CO₂ and hence the formation of hydrogen ions in tubule cells.

Additional observations are noteworthy. First, experiments in which creatinine replaced phosphate as the major urinary buffer, and in which essentially no phosphate was excreted, showed comparably high rates of titratable excretion rates. This finding is strong evidence that the ability for effective excretion of titratable acid is not dependent on phosphate. Accordingly, the phosphate reabsorption theory can thus not explain the formation of large amounts of titratable acid.

A second observation has to do with previous studies by R. F. Pitts and R. S. Alexander that examined the effects of metabolic acidosis on urinary phosphate excretion (6). These studies showed that acidosis did not alter the excretion of phosphate. If phosphate had played a significant role in the acidification process, then an increase in urinary phosphate excretion would have been expected with the large observed enhancement of titratable acid excretion. Finally, comparison of the efficacy of different buffers in promoting acid excretion demonstrated considerable differences depending on their pK: those with lower pK values diminished acidification. This was explained by effects on the concentration gradients against which hydrogen has to be transported: the lower the pK, the greater the concentration gradient against which hydrogen ions have to move for a given amount of acid excreted.

An informative account of the circumstances surrounding this interesting paper can be found in an essay by R. S. Alexander titled “Pitts and urine acidification” (1), in papers dedicated to Pitts’ career (2, 3), and in a thoughtful autobiographical sketch of Pitts in which he expounds on “Some aphorisms on research and writing” (5).

The second paper, “Bicarbonate and the renal regulation of acid base balance,” coauthored by Pitts and Lotspeich (8), defined the properties of renal bicarbonate transport by examining the relationship between bicarbonate reabsorption and excretion at varying plasma bicarbonate levels. A renal threshold for bicarbonate excretion was defined at 24 mM. Bicarbonate reabsorption, measured as the difference between filtered and excreted bicarbonate, was essentially complete below the threshold but increased linearly with bicarbonate above the threshold plasma level. A limiting value of bicarbonate reabsorption, not unlike that found with glucose and phosphate, was observed at higher plasma bicarbonate levels. However, an interesting feature was observed when the bicarbonate transport was related to filtration rate. Whereas the maximal rate of glucose and phosphate transport above the plasma threshold had been found to be independent of glomerular filtration rate, that of bicarbonate varied directly with filtration rate, thus rendering the renal threshold independent of filtrate formation. Additional findings, later amply confirmed, established the kidney’s ability to generate significant transepithelial CO₂ gradients, which were explained by a lack of effective carbonic anhydrase activity in the lumen of distal nephron segments. Finally, an interesting relationship was established between bicarbonate transport and excretion of acid, based on the observation that during acidosis the excretion of titratable acid varied inversely with the amount of bicarbonate administered. It was argued that higher bicarbonate loads entering the distal tubule would compete with that portion of distal hydrogen ion secretion that otherwise is involved in the elimination of titratable acid. The importance of hydrogen ion secretion was underscored by the observation that both bicarbonate reabsorption and titratable acid excretion were reduced following administration of carbonic anhydrase inhibitors.

In conclusion, the two papers by Pitts, Alexander, and Lotspeich provided the ground on which modern renal acid-base physiology is based. Their studies provided early and novel insights into the mechanisms by which the kidney regulates buffer and acid transport. Moreover, their ideas provided a powerful framework for subsequent studies on the distribution of acid transporters along the nephron, their regulation, and molecular identification.

REFERENCES