ESSAYS ON APS CLASSIC PAPERS

Renal potassium transport: the pioneering studies of Gerhard Giebisch

Bruce A. Stanton
Department of Physiology, Dartmouth Medical School, Hanover, New Hampshire

This essay looks at the historical significance of six APS Classic Papers that are freely available on line:


In the early 1960s, most of what was known about urinary potassium excretion was derived from clearance studies and stop-flow experiments that provided an indirect insight into the potassium transport properties of each nephron segment. Although the micropuncture technique, which allows the direct study of the transport properties of individual nephron segments, had been developed by A. N. Richards and his colleagues in 1924, most micropuncture studies performed before 1964 were limited to examining the function of the proximal tubule. However, in the early 1960s Gerhard Giebisch (Fig. 1) and Gerhard Malnic, with Ruth Klose, a gifted research associate, perfected the method of performing micropuncture and microperfusion studies on the distal tubule, which led to a series of six seminal papers published in the *American Journal of Physiology* that elucidated the role of each nephron segment in determining urinary potassium excretion (4–8, 12). These studies were made possible by the technical skill and imagination of Giebisch, Malnic, and Klose, and by the development by this group of a refined microflame photometer that allowed for very accurate measurements of sodium and potassium in nanoliter samples of tubular fluid.¹ These six beautifully detailed papers with thoughtful discussions unequivocally demonstrated that potassium is reabsorbed by the proximal tubule and the loop of Henle, that potassium reabsorption by these nephron segments is constant in a variety of experimental and metabolic conditions, and that it is the distal tubule that primarily determines the amount of potassium excreted in the urine by either continuing potassium reabsorption, or by secreting potassium into the tubular fluid. Furthermore, they provided the first insight into the cellular mechanisms of potassium transport by the distal tubule. Although the first paper was published in 1964, our

¹ The development of the refined microflame photometer was assisted by Dr. Paul Muller (11), who had built a similar device to measure the concentrations of sodium and potassium in single Ranvier nodes. Similar devices would be developed in other laboratories, with the assistance of Dr. G. Giebisch, enabling micropuncture to become commonplace in many laboratories throughout the world.

Address for reprint requests and other correspondence: B. A. Stanton, Dept. of Physiology, Dartmouth Medical School, Hanover, NH 03755 (e-mail: bas@Dartmouth.edu).

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Fig. 1. Gerhard Giebisch, M.D., with a backdrop of the mountains he so loves to climb.
basic understanding of renal potassium transport that was derived from this series of papers is as true today as it was 45 years ago (2, 9, 10).

These classic papers also provided additional, novel insights into potassium transport by the distal tubule. First, they characterized the effects on distal potassium transport of a variety of metabolic conditions (e.g., acidosis and alkalosis) and diuretics (e.g., amiloride and furosemide), and, second, they provided the first direct examination of the cellular mechanisms of potassium transport by the distal tubule.

As noted above, these elegant studies revealed that in essentially all conditions the proximal tubule and loop of Henle reabsorbs a constant fraction of the potassium filtered by the glomeruli, that potassium transport by the distal tubule depends on the metabolic state, and that potassium is reabsorbed by downstream nephron segments, later shown to be the medullary collecting duct. These results were in general agreement with clearance and stop-flow studies performed by Berliner and colleagues (1, 2) and Mudge and colleagues (reviewed in Refs. 2 and 10), who postulated that potassium is reabsorbed by the proximal tubule and that urinary potassium excretion is determined by distal potassium secretion.

Using microelectrodes to measure the electrical potential difference across the distal tubule, combined with measurements of potassium concentrations in tubular fluid and plasma, Giebisch and colleagues demonstrated that potassium is secreted down its electrochemical gradient, and thus, its secretion is passive and linked indirectly to the rate of sodium reabsorption, which is about 10 times the rate of potassium secretion (10). They also proved in these manuscripts that the rate of sodium reabsorption was not limiting for potassium secretion, a common notion at the time, and that potassium secretion did not depend on the rate of sodium reabsorption per se, but on the electrical potential difference (PD) across the distal tubule, which is determined in part by sodium reabsorption. Thus they showed that when sodium reabsorption is stimulated the increase in the PD enhanced the electrochemical driving force and stimulated potassium secretion. By contrast, inhibition of sodium reabsorption by amiloride reduces the PD and thereby decreases potassium secretion. These observations were seminal, because it was thought at the time that potassium secretion was coupled to sodium reabsorption by a 1:1 exchange mechanism. These papers also set the stage for a subsequent, more refined series of studies over the next several decades, which revealed that potassium secretion is a two-step process: uptake across the basolateral membrane via the Na\(^{+}\)-K\(^{+}\)-ATPase, and passive diffusion across the apical membrane via potassium channels (10). Moreover, in their study on potassium adaptation they clearly demonstrated that although potassium and hydrogen ion excretion are inversely related, the majority of potassium secretion is not tightly coupled with hydrogen in the distal tubule, a contradiction of the dogma at the time. Finally, based on the observation that there was less potassium in the urine than at the end of the distal tubule, Giebisch and colleagues proposed that potassium was reabsorbed downstream of the distal tubule, most likely by the collecting duct (4–8, 12). Many years later (1997), active potassium reabsorption, mediated by a K\(^{+}\)-H\(^{+}\)-ATPase, was identified by Doucet (3) in the medullary collecting duct.

In conclusion, these six studies published by Giebisch and colleagues (4–8, 12) in the American Journal of Physiology led to a paradigm shift in the field by unequivocally demonstrating that the distal tubule plays a major role in determining the amount of potassium excreted in the urine, and by elucidating the basic mechanism of potassium secretion by the distal tubule as well as its regulation by a variety of metabolic factors and drugs. Although Dr. Giebisch has studied many aspects of renal physiology throughout his stellar career, his fascination with and keen insight into renal potassium transport has continued since 1964 with the publication of ~250 manuscripts, many with his close friends, Gerhard Malnic and Steve Hebert. Each paper is a classic.

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DISCLOSURES

No conflicts of interest are declared by the author.

REFERENCES