Topical Review

Cell pH and Transepithelial H/HCO₃ Transport in the Renal Proximal Tubule

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Introduction

H/HCO₃ transporters have been identified on the cell membranes of both polar and nonpolar cells. In nonpolar cells, these transporters subserve functions such as cell pH and cell volume defense. In addition, these transporters have been demonstrated to be activated by signals which elicit cell growth. As a group, these functions have been referred to as "housekeeping" functions and the transporters as housekeeping transporters. In that polarized epithelial cells also must defend cell pH, defend cell volume, and grow, they also require the transporters capable of contributing to these housekeeping functions. In addition, certain epithelia effect transepithelial H/HCO₃ transport and thus require these transporters to subserve an additional function. By proper placement in a polarized epithelium, a single transport mechanism can contribute to transepithelial transport as well as to housekeeping functions.

Proximal Tubule Cells Possess H/HCO₃ Transporters Similar to, Yet Distinct from, Those Present in Nonpolar Cells

The proximal tubule is responsible for the reabsorption of 70–80% of HCO₃ filtered by the glomerulus. This is accomplished by apical membrane H secretion and basolateral membrane HCO₃ efflux. Here, we will briefly describe the important H/HCO₃ transport mechanisms which have been found in the proximal tubule. The interested reader is referred to a recent review for a more extensive discussion of these (Alpern, 1990). In the present review, emphasis will be placed on how these transporters serve to effect transepithelial H/HCO₃ transport in a regulated fashion, while at the same time maintaining a constant cell composition.

The major mechanism for apical membrane H secretion is an Na/H antiporter (Murer, Hopfer & Kinne, 1976). This antiporter is similar to that present in nonpolar cells in that it is inhibited by amiloride and allosterically activated by decreases in cell pH, but is different than the housekeeping Na/H antiporter in two ways. First, the apical membrane Na/H antiporter is less sensitive to amiloride and its analogues than is the housekeeping Na/H antiporter (Haggerty et al., 1988). Second, and most importantly, Na/H antiporters in nonpolar cells tend to be inactive at resting cell pH unless the cell is stimulated (Clark & Limbird, 1991). While such a pattern may be acceptable for housekeeping functions, it would not be acceptable if the antiporter is to mediate transepithelial H secretion. Thus, the apical membrane Na/H antiporter, while similar to housekeeping Na/H antiporters in that it is allosterically activated by decreases in cell pH, is different in that it functions at a significant rate at resting cell pH. Indeed, this may be responsible for the fact that resting cell pH in the proximal tubule is 0.15–0.3 pH units higher than in most nonpolar cells. The apical membrane Na/H antiporter has been shown to mediate approximately 2/3 of transepithelial H secretion (Preisig et al., 1987), and by functioning in parallel with Cl/base exchangers to mediate all of tranacellular NaCl absorption in the proximal tubule (Preisig & Rector, 1988). In addition to the apical membrane Na/H antiporter, a basolateral membrane Na/H antiporter is present in the most distal parts of the proximal tubule (S3 segment) and in some of the most juxtedudillary nephrons (Kurtz, 1989; Geibel, Giebisch & Boron, 1989). This basolateral membrane Na/H antiporter is presumably of the housekeeping variety, and does not contribute to transepithelial H/HCO₃ transport.
A cDNA encoding an amiloride-sensitive Na/H antiporter has been cloned (Sardet et al., 1989). This cDNA encodes a protein of 815 amino acids, with an aminoterminal hydrophobic domain including 10–12 transmembrane spanning regions and a carboxyterminal hydrophilic domain which represents the major cytoplasmic portion of the protein. Based on the tissue distribution of gene expression, as well as the amiloride sensitivity of the expressed protein, it is believed that the cloned Na/H antiporter gene encodes the housekeeping Na/H antiporter. This gene is now referred to as NHE-I. By reverse transcriptase PCR, its mRNA has been localized to those proximal tubular segments found to possess basolateral membrane Na/H antiporter (Krapf & Solioz, 1991). Additional isoforms of Na/H antiporter genes have recently been cloned by low stringency screening of intestinal and renal cDNA libraries (Sardet et al., 1991). These studies should yield the sequence of the apical membrane Na/H antiporter.

In parallel with the apical membrane Na/H antiporter, proximal tubule cells exhibit a Na-independent, amiloride-insensitive H transporting mechanism (Chan & Giebisch, 1981; Preisig et al., 1987). This mechanism is able to defend cell pH against an acid load and is responsible for approximately 1/3 of transepithelial H secretion (Kurtz, 1987; Preisig et al., 1987; Preisig, 1992). Based on immunocytochemical studies, this transport mechanism is most likely an H ATPase of the vacuolar type (Brown et al., 1988).

The major mechanism for base efflux across the basolateral membrane is a Na-coupled electrogenic transporter which carries one Na, one HCO₃, and one CO₂ (Boron & Boulpaep, 1983; Alpern, 1985; Yoshitomi, Burckhardt & Fromter, 1985; Soleimani & Aronson, 1989). Although first described in the proximal tubule, this transporter has now been found in numerous different polar epithelia and in some nonpolar cells. Its function in nonpolar cells has not been delineated, but it is able to defend cell pH against acid or alkali loads (see below).

Lastly, the proximal tubule possesses basolateral membrane Na-coupled and Na-independent Cl/HCO₃ exchangers (Alpern & Chambers, 1987). A Na(HCO₃)₂/Cl exchanger would be expected to function in the HCO₃ influx-Cl efflux mode, and thus could contribute to transepithelial NaCl absorption. While this transporter is present in many nonpolar cells where it participates in cell pH defense to an acid load, no such role has been demonstrated in the proximal tubule (Krapf et al., 1988). Lastly, a Na-independent Cl/HCO₃ exchanger on the basolateral membrane can contribute to base efflux. In nonpolar cells such Cl/HCO₃ exchangers have been shown to defend against an alkaline pH challenge. In order to accomplish this function, the transporter has been demonstrated in numerous cells to be allosterically activated by increases in cell pH. On the basolateral membrane, the transporter has the potential to contribute to base efflux mediating transcellular H transport, as well as to cell pH defense. In most of the proximal tubule, however, most of NaHCO₃ absorption independently of Cl, and base efflux is likely mediated by the Na/HCO₃/CO₂ cotransporter (Alpern, 1990). However, it has been suggested that the most distal parts of the proximal tubule as well as the most juxtamedullary located nephrons may rely on a different mechanism for base efflux such as a Cl/HCO₃ exchanger (Geibel et al., 1989, Kurtz, 1989; Nakhoul, Chen & Boron, 1990). Figure 1 summarizes the H/HCO₃ transporters present in the proximal tubule. Other H/HCO₃ transporters such as an apical Cl/base exchanger and apical and basolateral H leaks have not been discussed because their activities are very low (for review, see Alpern, 1990). The area within the dashed line in Fig. 1 includes those transporters believed to be the most important in cell pH defense and transepithelial H/HCO₃ transport.

**Proximal Tubule Cells Regulate Intracellular and Extracellular pH**

As the function of most proteins is affected by ambient pH, the regulation of cytoplasmic pH within narrow limits is key to cellular function. Maintenance of normal cell pH is accomplished in part through maintenance of extracellular pH in the nor-