Renal Chloride Transport and Diuretics

REABSORPTION OF SODIUM CHLORIDE by the renal tubules is the major factor controlling urinary salt excretion and the balance of salt in the body. Until recently, the process was believed to depend principally on active sodium transport. It was recognized that the details of sodium transport might differ between the nephron segments, but the primacy of sodium transport was not seriously questioned. With certain notable exceptions, investigators also believed that diuretic drugs acted by inhibiting active sodium transport. Efforts were made to elucidate mechanism of action of the diuretic drugs by testing their effect on sodium transport in various tissues. This approach was unsatisfactory, however, since it failed to explain how the diuretic drugs could have such a large effect on salt transport in the kidneys, with so little effect on salt transport elsewhere in the body.

Current studies continue to support the belief that active sodium transport is the basic process in proximal tubules, distal convoluted tubules, and the collecting ducts. The findings in the thick ascending limb of Henle’s loop (the “diluting segment”), however, are in striking disagreement with the traditional concept. In this segment it is now apparent that active chloride transport rather than sodium transport is the primary event, and that the major effect of several important diuretics is to inhibit this active chloride transport, rather than sodium transport, as previously believed.

Since the diluting segment does not approach the surface of the kidney, it could not be studied directly by micropuncture. Instead, the technique of dissection and perfusion of nephron segments in vitro was used. It was found that the diluting segment reabsorbed sodium chloride and was impermeable to water, resulting in dilution of the tubule fluid. The transepithelial voltage was oriented positive in the lumen, contrary to the expectation if sodium transport were the active process. It was concluded that chloride transport, being against the electrochemical gradient, was active and that sodium transport, following down the electrochemical gradient, was passive (fig. 1). The positive voltage was caused by the chloride transport. Removal of chloride (but not of sodium) from the experimental solutions caused the voltage to fall to zero.

Not all of the previous evidence had favored the view that diuretic drugs acted by inhibiting sodium transport. The additional urine excreted following the administration of mercurial diuretics contains a relative excess of chloride. Virtually no bicarbonate is excreted. Based on this finding, Schwartz and Wallace and Axelrod and Pitts proposed that the mercurials acted primarily to inhibit chloride reabsorption and that the inhibition of sodium reabsorption was secondary or a passive consequence. Although their theory was not generally accepted at the time, direct study of the diluting segment now substantiates it.

On the basis of clearance and micropuncture studies the most potent diuretics such as the organic mercurials, furosemide, and ethacrynic acid were known to inhibit reabsorption of sodium chloride in the diluting segment. Direct studies of isolated perfused diluting segments from rabbit kidney are confirmatory, and in addition provide insight into the mechanism of drug action. It was found that each of the three types of drug, when added in a low concentration to the perfusate, caused the reabsorption of salt from this segment to decrease reversibly. The drugs primarily inhibited active chloride transport. This caused the voltage to decrease. The decrease in voltage explained the accompanying decrease in sodium transport.

The characteristic action of the drugs occurred only when they were present in the lumen, which is where they are believed to act when given therapeutically. All three drugs are bound to plasma proteins, limiting their filtration at the glomerulus. They are secreted into the tubule fluid in the proximal tubule by the same organic acid transport system that is responsible for the secretion of p-aminomhippuric acid. When the secretion of furosemide in the proximal tubule was inhibited competitively by probenecid, the diuretic effect of the furosemide was prevented.

Ethacrynic acid and the organic mercurials are highly reactive and potentially toxic. Binding of these drugs to proteins in the serum, in addition to restricting glomerular filtration, probably also protects the cells from this toxicity. The active form of ethacrynic acid was found to be, not the drug itself, but its cysteine complex. The complex forms rapidly in the body and is the principal excretory product of the drug in the urine. Ethacrynic cysteine was found to be one hundred times more potent than pure ethacrynic acid as an inhibitor of active chloride transport in the diluting segment. Significantly, the other known cellular effects of ethacrynic acid which might cause toxicity (inhibition of respiration, of glycolysis, of Na and K activated ATPase, etc.) are prevented, not enhanced, by the presence of thiols. Thus, the formation of the ethacrynic cysteine complex both

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enhances the diuretic activity of ethacrynic acid and reduces its potential toxicity.

Although the most potent diuretic drugs act to inhibit chloride transport in the diluting segment, there are other, albeit less effective, diuretics that act to inhibit sodium transport in other nephron segments. For example, amiloride and acetazolamide inhibit sodium transport in the collecting tubules,12 and proximal tubules,9 respectively, but do not inhibit chloride transport in the diluting segment. Inhibition of the diluting segment results in a greater diuresis than does inhibition of other segments. Not only does the diluting segment reabsorb a large fraction of the filtered salt, but following inhibition of this segment there is not a compensating increase in reabsorption in the other segments. In contrast, inhibition of proximal tubules generally is compensated by increased reabsorption in the diluting segment,9 and relatively little salt is normally reabsorbed by the collecting tubules, so that diuretics affecting only these segments are relatively ineffective.

In summary, reabsorption of sodium chloride in the thick ascending limb of Henle's loop (the diluting segment) is due to active chloride transport, not sodium transport as previously believed. The most potent diuretic drugs such as organic mercurials, furosemide, and ethacrynic acid act specifically to inhibit this active chloride transport. The specificity to chloride transport in this segment explains how the drugs are able to inhibit reabsorption of salt in the kidney while having so little effect on active sodium transport processes elsewhere in the body.

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References

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Circulation. 1976;53:587-588
doi: 10.1161/01.CIR.53.4.587

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