THE INFLUENCE OF VARIOUS VITAMINS UPON DIURESIS INDUCED BY DRUGS AND THE POSSIBLE CHANGES THAT HAPPEN IN ELECTROLYTES IN THE URINE BY COMBINING THE VITAMIN WITH THE DIURETIC AGENT

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ACTION OF VARIOUS DIURETICS ON URINARY ELECTROLYTES AND THE CHANGES BROUGHT BY DRUGS AND THE POSSIBLE CHANGES THAT MAYBE IN ELECTROLYTES IN THE URINE BY COMBINING THE VITAMIN WITH THE DIURETIC AGENT

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CONTENTS

INTRODUCTION

The vital activity of any organism is dependent upon various chemical and physical reactions occurring in its cells. Such activity may be modified by pharmacological agents which may act either by stimulation or depression, or by removing adverse conditions and establishing favourable circumstances. Thus the normal functioning of the body may be aided and its natural recuperative powers encouraged. The important homeostatic role of the kidney in maintaining the volume and the composition of the body fluids is well known. It is not surprising, therefore to find that drugs which alter renal function comprise a major and indispensable group of therapeutic agents. As knowledge of the fundamental physiological mechanisms of renal function has expanded, the number of drugs that can affect this function has grown in a parallel fashion especially those drugs having a diuretic activity.

The volume and composition of urine formed by the kidney is influenced by the three important processes: glomerular filtration, tubular reabsorption, and tubular secretion. Experience has demonstrated that one can alter the rate of excretion of many substances much more

effectively by drugs that alter tubular function than by those that change filtration rate. In fact renal plasma flow and glomerular filtration rate tend to remain relatively constant in normal humans, and the diuretic drugs ordinarily have no important effect on these functions. However, alterations in glomerular filtration and renal plasma flow may be of primary importance in the development of oedema, and this knowledge helps to define objectives in therapy. The mechanisms of filtration and reabsorption have little in common. The former is a physical process in which the hydrostatic energy is provided by the heart for transport of water, permeative solute ions and molecules, across a permeable membrane. Tubular reabsorption on the other hand is achieved by active transport of electrolytes and certain molecules from tubular urine to tubular cells and thence to the extracellular fluid. The tubular reabsorptive transport mechanisms in general may be subdivided into proximal and distal mechanism with the realization, however, that they do not necessarily have discrete anatomical correlations.

Thus in the proximal tubule reabsorption of sodium with an attendant fixed anion, usually chloride, takes place by active cellular processes susceptible to inhibition by drugs. The active transport of sodium, as illustrated in

(Fig. A), so that, through the side of the epithelial cell membrane adjacent to the peritubular fluid; while the brush border of the cell is highly permeable to the diffusion of sodium. The active transport of sodium out of the cell and into the peritubular fluid diminishes the concentration of sodium inside the cell; and creates an electrical potential of -70 mv. inside the cell; so sodium ions diffuse from the lumen of the tubule to the interior of the cell. Once there, the active transport process carries the sodium the rest of the way into the peritubular fluid. And the diffusion of sodium from the lumen of the tubule into the interior of the epithelial cell decreases the electrical potential of the tubular lumen to approximately -20 mv. Thus, there is an electrical gradient of 50 mv. between the lumen of the tubule and the interior of the epithelial cell, being more negative inside the cell. This electrical gradient acts as a force to pull sodium ions into the epithelial cell from the tubular lumen. Obviously, this is a second factor in addition to the concentration differences that cause diffusion of sodium from the tubular lumen to the interior of the cell. Therefore, both a concentration gradient, the chemical gradient, and an electrical gradient move sodium through the brush

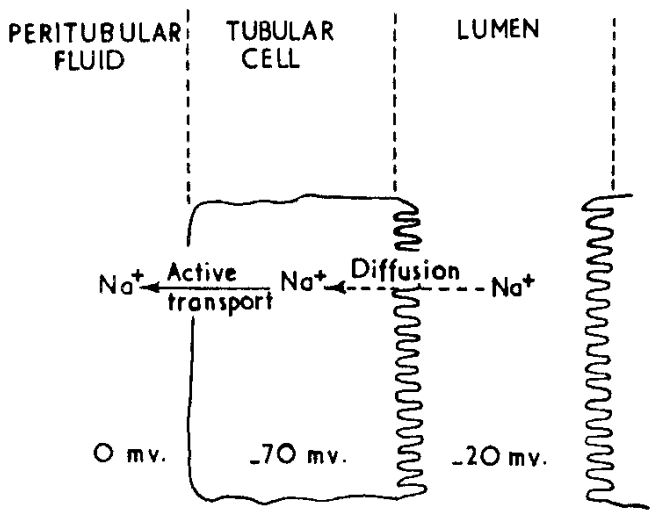

Fig. (1) Mechanism for active transport of sodium from the tubular lumen into the peritubular fluid, illustrating active transport at the base of the epithelial cell and diffusion through the lumenal border of the cell.

border of the cell. This combined effect is the electro-chemical gradient. The basic mechanism for active transport of sodium through the cell membrane is that sodium combines with a carrier in the substance of the membrane and in this form diffuses to the opposite wall, where it is released. Metabolic processes supply the energy for the chemical reactions that cause sodium to be transported through the membrane. Thus energy could cause combination of the carrier with sodium or it could cause splitting of the sodium away from the carrier. Regardless of which of these is true, the energy is probably supplied to the transport system at the inside surface of the cell membrane; because it is inside the cell that large quantities of the energy giving substance adenosine triphosphate are available for promoting chemical reactions. The energy required is proportional to the logarithm of the degree that the substance is concentrated. Several different carrier systems exist in cell membranes, each of which transports only certain specific substance. One carrier system, for instance, transports sodium to the outside of the membrane and probably transports potassium to the inside at the same time. The transport processes of the endoplasmic reticulum, have generally the same properties of both

diffusion and active transport as the cell membrane (Guyton (1967). Under normal conditions, this active reabsorption of sodium taking place in the proximal tubule, accounts for about 80% of the filtered sodium. The renal epithelium in this area is freely permeable to the diffusion of water so that, as solute is reabsorbed, an iso-osmotic equivalent of water is also reabsorbed so that the tubular fluid remains iso-osmotic with plasma.

In the loop of Henle the reabsorption of sodium is quantitatively less significant than that occurring in the proximal tubule but it is of unique importance in determining the final solute concentration of the urine. This is accomplished by a countercurrent mechanism involving both the descending and ascending loops (Dipalma, 1965). Sodium is actively transported from the ascending limb of Henle's loop into the medullary interstitium whenever it diffuses into the descending limb. This establishes a small concentration gradient between the fluid contents of the ascending and descending limbs at each level along the course of the loop. The sodium concentration increases progressively down the descending limb because of countercurrent flow, and each unit of filtrate becomes more concentrated until it reaches the

loop itself. Thus is established the hypertonicity of the medullary interstitium which is maintained by the vasa-recta acting as a countercurrent exchanger. This process, which depends on the slow rate of medullary blood flow, maintains the 300/1200 mOsm. per Kg concentration differential between the cortex and the tip of the medulla. Only the water and sodium necessary to maintain the normal electrolyte concentration of the body pass into the systemic circulation. The countercurrent exchange system thus prevents the excessive loss of sodium from the medulla and papillae. The final determination of urinary solute concentration is achieved in the collecting ducts that run from the relatively iso-osmotic distal tubules in the cortex through the hyper-osmotic renal medulla to the papilla. So the osmolarity of the voided urine is established, primarily by the rate at which the water diffuses from the tubular fluid to the hyper-osmotic medullary tissue. This process, in turn, is determined by permeability of the renal epithelium to water. Agents such as antidiuretic hormone(ADH) have a direct effect on these permeability characteristics. Following the iso-osmotic reabsorption of the major portion of the glomerular filtrate in the proximal tubule, electrolyte reabsorption continues in

the ascending limb of Henle's loop, as well as, in the distal convoluted tubule and the collecting ducts. However, in the absence of antidiuretic hormone (ADH), the epithelium of the ascending limb, distal convoluted tubule, and collecting tubule is relatively impermeable to water. The fluid entering the distal convoluted tubule is already hypotonic and becomes steadily more dilute as electrolyte reabsorption continues. Thus, when the secretion of the hormone is completely suppressed by over hydration, 15% or more of the water of the glomerular filtrate may escape into the urine virtually free of electrolyte resulting in the formation of hypotonic urine. When levels of circulating antidiuretic hormone rise an increase in the permeability of the distal convoluted tubule and the collecting duct to water takes place, allowing more water to be reabsorbed along the osmotic gradient that has been supplied by the active reabsorption of electrolytes with formation of hypertonic urine. When maximally effective levels of antidiuretic hormone are present, the tubular urine leaves the distal tubule much reduced in volume and iso-osmotic with plasma, due to the continuing reabsorption of electrolyte and the diffusion of water out of the lumen along the osmotic gradient

thereby created. The final concentration of urine is then determined in the collecting ducts as they pass through the hypertonic interstitium of the renal papillae. During dehydration and maximal antidiuresis, water is passively abstracted from the lumen of the collecting duct into the hypertonic peritubular fluid so that the two fluids are in osmotic equilibrium, as the urine emerges from the tip of the papilla. Under these conditions, papillary osmotic pressure may reach 1200 mOsm or more per liter and thus urine having 4 to 5 times the osmotic pressure of plasma may be excreted. The amount of water abstracted and conserved in concentrating the urine to an osmotic pressure greater than that of plasma, is known as the negative free water clearance (TCH_2O), and is usually considered to have a maximal value of between 4 and 8 ml per minute in man, although higher figures have been recorded.

Many substances can be actively absorbed in the distal tubules and collecting ducts, especially sodium and probably chloride ions. In addition, these segments secrete large quantities of hydrogen, potassium ions and ammonia. An especially important feature of active transport here is that it can occur against greater electrochemical gradients than those occurring in the proximal tubules. On

the other hand, the total quantities of substances reabsorbed or secreted in the distal tubules and collecting ducts are much less than in the proximal tubules, averaging only to about 10-15%.

An important function of the kidney is the maintenance of the alkaline reserve of blood within normal limits, and this is effected through regulation of the pH of urine by means of three mechanisms, each of which is based fundamentally on an exchange of hydrogen ion secreted by tubular cell with sodium ion present in tubular urine. Firstly complete reabsorption of the filtered sodium bicarbonate, then acidification of urinary buffers and lastly the excretions of fixed anions in combination with ammonium ion rather than sodium ion.

The source of hydrogen ion secreted by tubular cell is carbonic acid derived from hydration of carbon dioxide through a reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3$ which is ionizable into hydrogen ion and bicarbonate ions. This reaction must proceed rapidly to supply the amount of hydrogen ion necessary for these exchange reactions and such an adequate rate is achieved by the activity of the enzyme carbonic anhydrase present in large amounts in the renal cortex.