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doi: 10.2306/scienceasia1513-1874.2007.33(s1).085

ScienceAsia 33 Supplement 1 (2007): **85-86**

Epithelial Transport of Electrolytes and Water in Tropical Diseases

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ABSTRACT: The role of ion transport through the epithelial cells in the pathogenesis of tropical diseases is often overlooked. This short communication brings to attention epithelial transporters of sodium, potassium, chloride, phosphate and water in snake bite, bee sting, cholera, pertussis, leptospirosis, and gossypol ingestion. The significance of dysregulation of these ion transporters in the kidney, intestine and lung in pathophysiology of the diseases is emphasized.

KEYWORDS: Ion channels, water channels, tropical diseases.

Several natural toxins exert effects through ion transport across neuronal and muscular membranes causing neuromuscular symptoms. Very few have the effect on the epithelial membranes. This article is a short communication on epithelial ion transport in tropical diseases which can be relevant for the better understanding of the disease mechanism. There are few studies in the area of animal toxins. Natriuretic peptides are present in the venoms of green mamba snake (Dendroaspis angusticeps), South American coral snake (*Micrurus corallinus*) and *Bothrops jararaca*[1-3]. Natriuretic peptide from the venom of green mamba snake induces natriuresis and diuresis by decreased distal tubular reabsorption of sodium through activation of cGMP by venom binding to the natriuretic peptide A receptor. Transient natriuresis, believed to be due to natriuretic peptides, has also been observed following envenomation of Russell's viper[4] and some crotalids[5]. The nature of the natriuretic peptides of these snake venoms and their site of action in the renal tubules have not yet been studied. Melittin and the water soluble fraction of bee venom inhibit the uptake of sodium, phosphate and a-methyl-D-glucopyranoside in the proximal renal tubules[6].

In the area of plant toxins, gossypol in the cotton seed oil consumed by the Chinese for birth control can cause hypokalemia, kaliuresis and decreased intracellular K[7,8]. The mechanism is not understood. There is no evidence of hyperaldosteronism. In guinea pigs, fed with gossypol for 5 to 9 weeks, Na-K ATPase activity of renal cortical tubules is decreased[7]. Gossypol also inhibits outward Na^+K^+ co-transport in human red cells[9].

Cholera toxin is best known for its effects on chloride transport in the intestinal epithelial cells. Cholera toxin binds to the membrane of epithelial cells. The A subunit is cleaved to A_1 which enters the cell and activates adenyl cyclase. ATP is converted to cAMP which stimulates Cl^- transport through the apical border of the intestinal epithelial cells to the intestinal lumen followed by Na^+, K^+ and water resulting in diarrhea[10]. Fluid loss in cholera diarrhea can be as high as 20 liters/day. Loss of electrolytes and water is nearly isoionic to the plasma, in contrast to diarrhea due to other diseases in which more water than sodium is lost[11, 12]. Zinc decreases cAMP with reduction in cholera toxin induced ion secretion[13]. Zinc supplement is therefore used in cholera. Pertussis toxin, through inactivation of Gi proteins, generates cAMP which opens Cl^- channels of epithelial cells of the trachea[10]. Mucus production is therefore increased.

In leptospirosis, renal expression of NHE3 and AQP2 is decreased, whereas NKCC2 expression is increased. Interestingly, Na^+ transport from the alveolar space through the apical border of the alveolar epithelium (ENaC) is downregulated, while Na^+, K^+ and Cl^- transport (NKCCl) from the lung interstitium to the alveolar epithelium through the basal border is upregulated[14]. Dysregulation of Na^+ transport both in the lung and the kidney may account for the development of acute respiratory distress syndrome (ARDS) especially with fluid overload. Pulmonary complications occur in over 20% of severe leptospirosis[15]. Furthermore, in ischemic acute renal failure pulmonary ENaC, Na-K ATPase and AQP5 are downregulated[16]. It should be noted that acute renal failure in tropical disease is mostly ischemic in type. The same ion transport dysregulation may occur. In adenovirus infected mice reduced levels of AQP1 and AQP5 protein have been demonstrated[17]. Since ARDS can complicate severe infectious diseases which share the same inflammatory cytokines and mediators as leptospirosis, it is possible that dysregulation of Na^+ and water channels in the lung is also present in those diseases. In the tropics, 21 to 24%

of severe malaria is complicated by ARDS. It is known that nitric oxide decreases lung sodium transport through a cGMP-mediated inhibition of epithelial cation channels[18]. In a number of inflammatory diseases, increased production of reactive oxygen-nitrogen intermediates such as peroxynitrite may damage alveolar epithelial cells, with dysregulation of and water channels[19]. Pulmonary ion transport channels in malaria have not been studied. Artesunate, an antimalarial agent, has been shown to decrease Na-K 2Cl transport (NKCC2) in the renal tubule causing natriuresis[20] which can be advantageous in avoiding fluid overload. Catecholamines, epidermal growth factor (EGF), tumor necrosis factor (TNFa) and transforming growth factor (TGFa) are among agents that can upregulate pulmonary ENaC[21]. The use of a combination of furosemide and renal dose dopamine in pre-renal or early renal failure in tropical diseases, a common practice in the rural tropics, appears rational[22]. Dopamine improves renal hemodynamics. Furosemide through NKCC2 inhibition promotes diuresis, and through inhibition of NKCCl would decrease basal Na^+ transport from the interstitium into the alveolar epithelial cell providing a better gradient for Na^+ transport from the alveolar lumen. Pulmonary edema can be prevented. In northeastern Thailand, the combination of dopamine and furosemide has been useful in the management of mild acute renal failure in leptospirosis, without any disadvantageous effects[23].

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