ANALYSIS OF VOLUME REGULATION IN AN EPITHELIAL CELL MODEL

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An epithelial cell is modeled as a single compartment, bounded by apical and basolateral cell membranes, and containing two nonelectrolyte solute species, nominally NaCl and KCl. Membrane transport of these species may be metabolically driven, or it may follow the transmembrane concentration gradients, either singly (a channel) or jointly (a cotransporter). To represent the effect of stretch-activated channels or shrinkage-activated cotransporters, the membrane permeabilities and cotransport coefficients are permitted to be functions of cell volume. When this epithelium is considered as a dynamical system, conditions are indicated which guarantee the uniqueness and stability of equilibria. Experimentally, many epithelial cells can regulate their volume, and such volume regulatory capability is defined for this model. It is clearly distinct from dynamical stability of the equilibrium and requires more stringent conditions on the volume-dependent permeabilities and cotransporters. For a previously developed model of the toad urinary bladder (strieter et al., 1990, j. gen. physiol. 96, 319–344) the uniqueness and stability of its equilibria are indicated. The analysis also demonstrates that under some conditions a second stable equilibrium may appear, along with a saddle-node bifurcation. This is illustrated numerically in a modified model of the epithelium of the thick ascending limb of Henle.

Introduction. Specific mechanisms for cell volume regulation have been examined in a variety of non-polar cells (e.g. erythrocytes, lymphocytes, ehrlich ascites tumor) (kregenow, 1981; siebens, 1985; grinstein et al., 1984; geck and pfeiffer, 1985) and epithelia (e.g. frog skin, gallbladder, proximal tubule, ascending Henle limb) (ussing, 1982; macknight, 1988; spring and ericson, 1982; reuss, 1988; dellasega and grantham, 1973; volkl et al., 1988; blumenfeld et al., 1989). Most commonly, these mechanisms are identified and studied during recovery from an osmotic shock: either volume regulatory decrease (VRD) following the cell swelling of a hypotonic shock, or volume regulatory increase (VRI) after the abrupt cell shrinkage of a hypertonic shock. Typically, VRD is mediated by loss of KCl, either via a neutral KCl cotransporter or via parallel K⁺ and Cl⁻ conductance channels. VRI can result from uptake of NaCl alone, either through a single cotransporter, or via parallel Na⁺/H⁺ and Cl⁻/HCO₃⁻ exchangers, or from the uptake of NaCl with KCl via a cotransporter (eveloff and Warnock, 1987; Montrose-Rafizadeh
The mechanisms by which these various transport systems are activated with the changes in cell volume are less well delineated. Nevertheless recent advances in the recording of single channel currents have permitted the identification and examination of stretch-activated K⁺ and Cl⁻ conductance channels (Sachs, 1987; Morris, 1990; Sackin, 1990).

Mathematical models of cell volume regulation have received relatively limited attention. As indicated by Jakobsson (1980), electrolyte models of even non-polar cells are sufficiently complex that few conclusions can be reached analytically. In his numerical calculations, Jakobsson noted that the presence of a Na⁺/K⁺-ATPase whose rate of ion transport was sensitive to the intracellular sodium concentration was sufficient to stabilize cell volume. By this he meant that steady state cell volume changed relatively little in response to changes in cell membrane ion permeabilities. VRD following hypotonic shock was first simulated in a model of the renal proximal tubule by Welling and Welling (1988). The critical feature of their model, suggested by their own prior experimental observations, was the incorporation of two water pores (a “small” pore with a high salt reflection coefficient, and a “large” pore with a low reflection coefficient) within the basolateral cell membrane. With the imposition of a hypotonic shock, inward water flows across the small pore were eventually balanced by outward flows across the large pore. Since the outward flows carried NaCl convectively and inward flow did not, cell volume declined. Such an arrangement of pores is mathematically equivalent to an NaCl cotransporter (Weinstein, 1987). Recently, Strieter et al. (1990) extended a previous electrolyte model of a urinary epithelium (Lew et al., 1979; Civan and Bookman, 1982) to one that could volume regulate. The key features, predicted by Ussing (1982), were the inclusion of an NaCl–KCl cotransporter to increase cell Cl⁻ content above electrochemical equilibrium, and a volume-activated chloride channel for which a 10% increase in cell volume increased Cl⁻ permeability 100-fold. Because baseline K⁺ channel permeability was already more than 200-fold greater than that of Cl⁻, only volume dependence of the Cl⁻ channel permeability was required to achieve stretch-activated KCl loss, and thus VRD. It was noted, however, that the inclusion of a volume-activated K⁺ channel enabled the model to better reproduce the experimentally observed changes in voltage (MacRobbie and Ussing, 1961).

The present work presents an approximate nonelectrolyte model of an epithelial cell in which the dynamics of cell volume regulation can be explored. The starting point is the erythrocyte model of Milgram and Solomon (1977) which is extended to a cell with distinct apical and basolateral membranes. To represent the effect of stretch-activated channels or shrinkage-activated cotransporters, transport coefficients are allowed to be functions of cell volume. When this model is examined as a dynamical system, conditions can be given for the stability and uniqueness of transport equilibria. The volume