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Review

The role of volume-sensitive ion transport systems in regulation of epithelial transport☆

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Abstract

This review focuses on using the knowledge on volume-sensitive transport systems in Ehrlich ascites tumour cells and NIH-3T3 cells to elucidate osmotic regulation of salt transport in epithelia. Using the intestine of the European eel (*Anguilla anguilla*) (an absorptive epithelium of the type described in the renal cortex thick ascending limb (cTAL)) we have focused on the role of swelling-activated K^+- and anion-conductive pathways in response to hypotonicity, and on the role of the apical (luminal) Na^+–K^+–$2Cl^-$ cotransporter (NKCC2) in the response to hypertonicity. The shrinkage-induced activation of NKCC2 involves an interaction between the cytoskeleton and protein phosphorylation events *via* PKC and myosin light chain kinase (MLCK). Killifish (*Fundulus heteroclitus*) opercular epithelium is a Cl^--secreting epithelium of the type described in exocrine glands, having a CFTR channel on the apical side and the Na^+/K^+ATPase, NKCC1 and a K^+ channel on the basolateral side. Osmotic control of Cl^- secretion across the operculum epithelium includes: (i) hyperosmotic shrinkage activation of NKCC1 *via* PKC, MLCK, p38, OSR1 and SPAK; (ii) deactivation of NKCC by hypotonic cell swelling and a protein phosphatase, and (iii) a protein tyrosine kinase acting on the focal adhesion kinase (FAK) to set levels of NKCC activity.

Keywords: *Fundulus heteroclitus*; *Anguilla anguilla*; Opercular epithelium; Intestine; RVD; RVI; NKCC; Na^+, K^+, $2Cl^-$ cotransport; SPAK; Protein kinase; Ussing chamber

Contents

Abbreviations: NKCC, Na^+, K^+, $2Cl^-$; RVI, volume regulatory increase; EATC, Ehrlich ascites tumour cells; SK, K channels having small conductance; IK, intermediate conductance; BK, large conductance; 2P-4TM, four transmembrane-spanning segments; TASK-2, acid sensitive potassium channel; LTD_4, leukotriene D4; EET, 5′,6′-epoxyeicosatrienoic acid; PGE_2, prostaglandin E_2; VRAC, volume regulated outward rectifying anion current; BAE, bovine aortic endothelial; PTPs, protein tyrosine phosphatases; PTKs, protein tyrosine kinases; PKA, protein kinase A; PKC, protein kinase C; CK2, casein kinase; MLCK, myosin light chain kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; Ste20, sterile 20; SPAK, sterile 20-related proline alanine-rich kinase; OSR1, oxidative stress response 1 kinase; ELA, Ehrlich Lettre Ascites; WNK, with no K (lysine) protein kinase; FW, freshwater; SW, seawater.

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1. Introduction

Swelling-activated K^+ and anion channels are important effectors during regulatory volume decrease (RVD after cell swelling, whereas a Na^+, K^+, $2Cl^-$ (NKCC) cotransporter and a Na^+/H^+ exchanger play major roles in the regulatory volume increase (RVI) following cell shrinkage. Transport pathways involved in RVD and RVI have been investigated in a wide variety of cell types (Hoffmann and Dunham, 1995; Lang et al., 1998; Wehner et al., 2003; Hoffmann and Pedersen, 2006). In the first part of this review we describe briefly the swelling activated channels and the shrinkage-activated NKCC and the signal transduction mechanisms involved in the activation of these transport systems by changes in cell volume. Other transport systems involved in rapid volume regulation and aspects of long-term adaptation to an anisosmotic environment are outside the scope of this review. In the second part of this review we will try to correlate this knowledge with the regulatory mechanisms involved in osmotic regulation of salt transport in epithelia using the killifish opercula epithelium and the eel intestinal epithelium as examples.

2. Volume-sensitive ion transport systems

2.1. Swelling-activated K^+ channels ($I_{K,vol}$)

Swelling activation of a K^+ leak pathway was initially established in lymphocytes (Roti Roti and Rothstein, 1973) and in Ehrlich ascites tumour cells (EATCs) (Hendil and Hoffmann, 1974). This swelling-activated increase in K^+ permeability has been established in different cell types to be related to a variety of swelling-activated K^+ channels including Ca^{2+}-activated channels of small conductance (SK), intermediate conductance (IK) or large conductance (BK); stretch-activated K^+ channels; voltage-dependent K^+ channels such as Kv 1.3 or Kv 1.5; KCNQ1/KCNE3 heterotetrameric channels and two-pore-regions, four-trans-membrane-spanning segment (2P-4TM) K^+ channels (Wehner et al., 2003; Stutzin and Hoffmann, 2006). The most likely candidate in EATCs is the 2P-4TM, acid-sensitive K^+ channel (TASK-2) (Niemeyer et al., 2000; 2001a,b). Many cloned K^+ channels have been found to be sensitive to cell volume changes when expressed in *Xenopus* oocytes or in HEK 293 cells including SK and IK channels, KCNQ1 and KCNQ4; HCN2 channels and TASK-2 channels (Calloe et al., 2005).

2.2. Activation and regulation of $I_{K,vol}$

Various eicosanoids seem to be involved in regulation of swelling-activated channels (Hoffmann, 2000; Stutzin and Hoffmann, 2006). In human platelets the 12-HPETE product, hepoxilin A activates $I_{K,vol}$ (Margalit and Livne, 1991, 1992) and in EATC, leukotriene D4 (LTD_4) activates $I_{K,vol}$ independent of any increase in cytosolic Ca^{2+} (Jørgensen et al., 1997; Hoffmann, 1999; Hougaard et al., 2000). A role for LTD_4 has also been shown in some other cell types but in several cell types the RVD response seems to be independent of LTD_4 (Stutzin and Hoffmann, 2006). The eicosanoids responsible for activation of RVD vary among cell types and the channels involved, but a common theme is that PLA_2 is activated during RVD, which releases arachidonic acid from the membrane phospholipids, as originally established in EATCs (Thoroed et al., 1997) and in IMCD cells (Tinel et al., 1997). In EATCs, activation of the 85-kDa Ca^{2+}-dependent $cPLA_2$ results in the release of arachidonic acid predominantly from the nuclear membrane (Pedersen et al., 2000). The