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Review

Defective interactions of protein partner with ion channels and transporters as alternative mechanisms of membrane channelopathies☆

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ABSTRACT

The past twenty years have revealed the existence of numerous ion channel mutations resulting in human pathology. Ion channels provide the basis of diverse cellular functions, ranging from hormone secretion, excitation–contraction coupling, cell signaling, immune response, and trans-epithelial transport. Therefore, the regulation of biophysical properties of channels is vital in human physiology. Only within the last decade has the role of non-ion channel components come to light in regard to ion channel spatial, temporal, and biophysical regulation in physiology. A growing number of auxiliary components have been determined to play elemental roles in excitable cell physiology, with dysfunction resulting in disorders and related manifestations. This review focuses on the broad implications of such dysfunction, focusing on disease-causing mutations that alter interactions between ion channels and auxiliary ion channel components in a diverse set of human excitable cell disease. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. Guest Editor: Jean Claude Hervé

Contents

1. Introduction

Most ion channels are recognized as central players of larger multi-subunit complexes. Ion channels associate with a number of scaffolding, anchoring, regulatory, and signaling proteins. Co-targeting of these auxiliary subunits to the channel complex has evolved to allow for rapid and localized regulation of ion channels in response to specific stimuli. Electrophysiological properties of cells, once thought to be

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exclusively attributed to ion channels, have expanded to include these auxiliary subunits. While mutations in ion channel genes can cause dysfunction, a growing number of ion channel-associated proteins have come to the forefront in the study of human excitable cell pathology. This new paradigm has emerged based on growing evidence demonstrating variants in genes involved in the expression, localization, and regulation of ion channels also result in excitable cell disease. These findings have expanded the view of excitable cell disease, uncovered new mechanisms for ion channel regulation, and provided novel targets for pharmacological treatment of aberrant ion channel activity in excitable cells.

2. Liddle syndrome: dysregulation of Nedd4-2-mediated regulation of ENaC and hypertension

The last, and rate-limiting, step in Na^+ reabsorption by the kidney occurs in the distal convoluted tubules, connecting tubules, and collecting ducts where the epithelial sodium channel (ENaC) regulates Na^+ absorption [1,2]. ENaC selectively transports Na^+ down an electrochemical gradient established by the Na^+/K^+ ATPase at the basolateral membrane of polarized epithelial cells [3]. Consequently, the directional movement of Na^+ produces an osmotic gradient that drives the movement of water in the same direction [4–6].

ENaC is selectively expressed at the apical membrane in a variety of epithelia, such as the kidney, lung, and colon [7]. Since entry of Na^+ through ENaC is the last and rate-limiting step for Na^+ absorption, [3,7,8] regulation of this channel is vital to the regulation of extracellular fluid volume, blood volume, and blood pressure. The activity of ENaC is tightly controlled by a number of hormones (aldosterone, vasopressin, and insulin) and intracellular mediators (Na^+, Ca^{2+}, pH, cAMP, protein kinases A and C, and extracellular proteases) [3,9]. The necessity of this tight regulation is illustrated by the number of human diseases that have been linked to dysfunction in ENaC, including Liddle syndrome, [10,11] cystic fibrosis, [12] pseudohypoaldosteronism type I (PHA-I), [13,14] and pulmonary edema [15,16].

Liddle syndrome, first described in 1963, was originally determined to be an autosomal dominant form of endocrine hypertension [17]. Activating mutations of the epithelial sodium channel (ENaC) were initially described, resulting in increased sodium reabsorption/potassium wasting in the distal nephron. As a result, affected patients experience hypertension, hypokalemia, low aldosterone and renin levels, salt sensitivity volume expansion, and metabolic alkalosis [17]. ENaC is composed of three similar subunits, α, β, and γ. While the stoichiometric ratio of these subunits in a channel complex is debated, the current view is a ratio of 1:1:1 [18]. Each subunit consists of intracellular N- and C-termini, two transmembrane domains, and an extracellular loop [19]. The C-terminal region of each subunit contains a conserved proline-rich sequence, called the PY motif [19]. The original gene variants (frameshifts and premature stop codons) identified in the etiology of Liddle syndrome were found to result in the truncation of the C-terminus, with specific deletions of the PY motifs (PPxY) of the β (*SCNN1B*) and γ (*SCNN1G*) subunits [10,11].

Sodium absorption through ENaC is altered in two non-mutually exclusive ways: altering the open probability (P_o) of the channel [20] or varying the membrane density of the channel [21–24]. There is overwhelming evidence to demonstrate that the most potent down-regulation of ENaC is via ubiquitination of the membrane channel and subsequent endocytosis. Liddle syndrome is linked to a defect in the ubiquitin-mediated down-regulation of β and γ ENaC. Specifically, it has been demonstrated that it is the Nedd4-2-mediated ubiquitination of ENaC that leads to endocytosis of the channel [25] and that dysfunction in the ability of Nedd4-2 to ubiquitinate ENaC results in enhanced Na^+ absorption and hypertension in Liddle syndrome (Fig. 1) [26]. Specifically, the E3 ubiquitin ligase Nedd4-2 binds to the PY motif in the C-terminal regions of ENaC subunits and facilitates ubiquitination of lysine residues located in the N-terminal domains of the β and γ ENaC subunits. Nedd4-2 has been shown to effectively suppress ENaC activity by enhancing the endocytosis of the channel from the apical membrane [27–30]. Liddle syndrome mutations effectively remove the PY motifs, resulting in an inability of Nedd4-2 to mediate the ubiquitination and endocytosis of ENaC. The result is an accumulation of active channels at the cell surface, sustained Na^+ (and fluid) absorption in the distal nephron, and hypertension. In summary, the dynamic relationship between ENaC and Nedd4-2 illustrates the complex mechanisms underlying human disease as well as potential new molecular targets to tune membrane excitability.

3. Yotiao and LQT1: PKA-mediated phosphorylation of KCNQ1 and the development of long QT syndrome

Late phase repolarization of the cardiac action potential is largely determined by the slow delayed rectifier current, I_{Ks} [31]. This cardiac membrane current is controlled by potassium channel comprised of

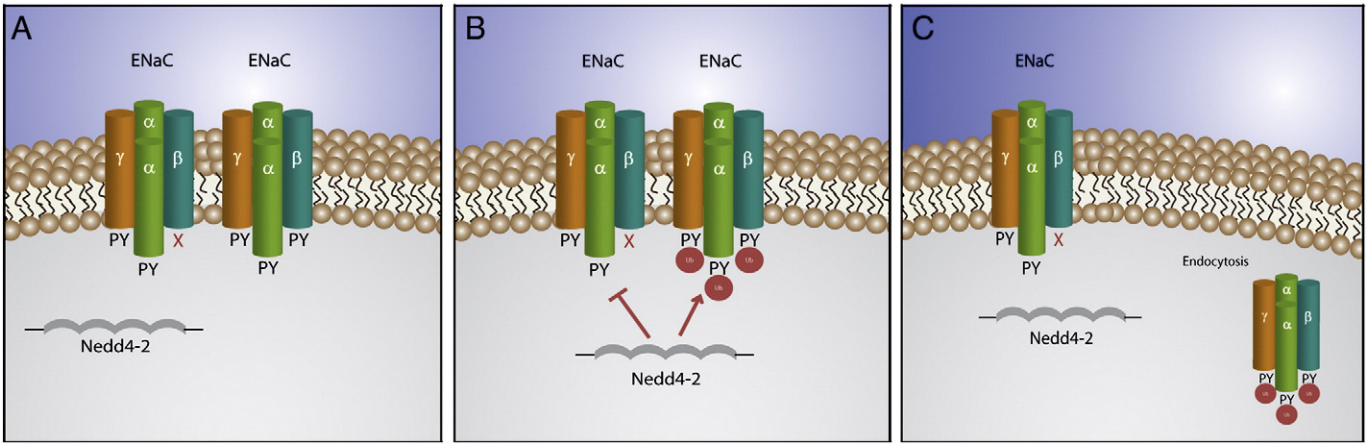

Fig. 1. Regulation of ENaC by Nedd4-2. A–B. The ubiquitin ligase Nedd4-2 recognizes PY motifs in wild type ENaC but not mutated forms of the β or γ subunits, which lack the PY motif. C. Ubiquitinated ENaC is endocytosed, leading to a reduction in ENaC at the plasma membrane, reducing activity. On the other hand, mutated forms of ENaC, that are resistant to ubiquitination, remain at the plasma membrane, and increase channel activity.