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Differential regulation of ion channels function by proteolysis☆

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ABSTRACT

Ion channels are pore-forming protein complexes in membranes that play essential roles in a diverse array of biological activities. Ion channel activity is strictly regulated at multiple levels and by numerous cellular events to selectively activate downstream effectors involved in specific biological activities. For example, ions, binding proteins, nucleotides, phosphorylation, the redox state, channel subunit composition have all been shown to regulate channel activity and subsequently allow channels to participate in distinct cellular events. While these forms of modulation are well documented and have been extensively reviewed, in this article, we will first review and summarize channel proteolysis as a novel and quite widespread mechanism for altering channel activity. We will then highlight the recent findings demonstrating that proteolysis profoundly alters Inositol 1,4,5 trisphosphate receptor activity, and then discuss its potential functional ramifications in various developmental and pathological conditions.

1. Introduction

Cells and intracellular organelles are bounded by biological membranes that function as electrical insulators. Ion channels are pore-forming protein complexes embedded in biological membranes that allow the rapid flux of ions in a direction dependent on their electrochemical gradient [1, 2]. By virtue of selectivity and exquisite control over activity, ion channels establish the resting cellular membrane potential and subsequently their behavior in response to cellular stimuli controls a multitude of physiological and pathological events [3–5].

In order to selectively control a diverse array of biological processes with fidelity and selectivity, ion channel activity is strictly regulated [1, 3]. Fundamentally, channel gating can be initiated following the binding of ligands, in response to changes in membrane potential or pH, together with sensing of mechanical stretch [1–3, 6] (Fig. 1A). Channel activity is also frequently further fine-tuned by a myriad of regulatory molecules and inputs. A common theme is that the activity of specific channels is selectively regulated by the binding of ions, nucleotides and accessory proteins, together with phosphorylation and redox status and additional post-translational modifications [3, 7, 8]. A further consideration is that many ion channels are protein complexes assembled from multiple individual channel subunits [9, 10]. Thus, the particular subunit composition and their specific regulation can be a major determinant of the overall biophysical properties of an individual channel [3, 9].

While these “conventional” forms of regulation are well documented, recently a less orthodox, novel form of regulation has emerged as an event, widely employed to alter ion channel activity. Intracellular proteases, including caspase and calpain introduce peptide cleavage at specific sites and result in channel and isoform specific regulation of channel activity. Although, intuitively it might be expected that proteolysis might simply always function as a binary switch to deactivate ion channels, proteolysis can also alter the biophysical properties of channels to enhance or attenuate activity or influence the pharmacological properties of specific ion channels [11–15]. With major reference to proteins involved in Ca^{2+} signaling, or where proteolysis is regulated by Ca^{2+}, we first highlight the diversity of ion channels subject to proteolysis as regulatory events and discuss the corresponding functional consequences of receptor cleavage. We then focus on recent findings which suggest that proteolytic cleavage of the ubiquitous intracellular Ca^{2+} release channel, the inositol 1,4,5 trisphosphate receptor (IP_3R), profoundly alters activity in a subtype-specific fashion.

2. Disabling channel activities by proteolysis

Somewhat instinctively, a major consequence of ion channel proteolysis is the abrogation of activity as the proteins are disabled

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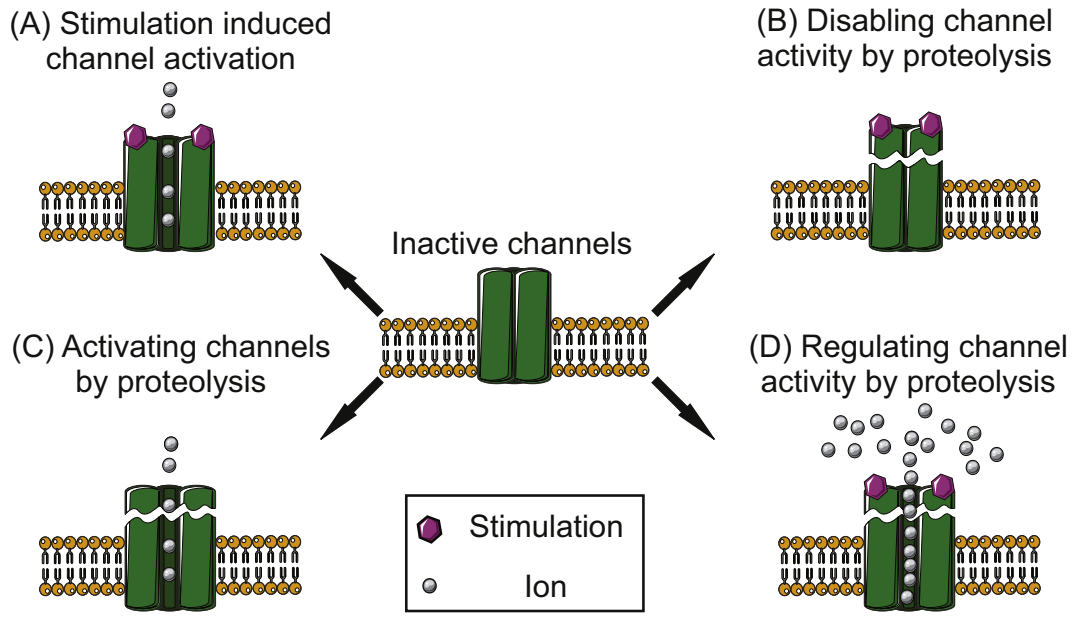

Fig. 1. Schematic diagram summarizing different potential forms of proteolytic regulation of ion channels. In normal condition, ion channels are activated by the corresponding stimulus (A). Proteolytic fragmentation functions as a regulatory event, which can disable (B), activate (C), or regulate (C) channel activity in a channel specific manner.

Table 1
Summary of the proteolytic regulation of ion channels.

Protein	Protease(s)	Cleavage site(s)	Functional outcome of proteolysis
hERG [16]	Calpain, proteinase K, proteinase XIV and XXIV	In the S5-pore linerGly-603 for calpain	Disable channel activity
NMDA receptor: NR2A subunit [20]	Calpain	After the amino acid 1051 in the C-terminal region	Disable channel activity
STIM1 [21, 22, 26]	Calpain, γ-secretase and casepase-3		Disable channel activity
CFTR [23]	Calpain	Between the first nucleotide-binding site and the regulatory domain	Disable channel activity
Voltage gated sodium channel: b2 subunit [89]	BACE1 and γ secretase		Disable channel activity
ENaC [90]	Furin	Arginine 205 and arginine 231 on the α subunit; arginine 143 on the γ subunit for furin	Activate the channel
TRPC5 [31]	Calpain	Threonine 857	Activate the channel
Nav. 1.6 [11]	Calpain		Decrease the activation threshold of I_{NaP} and increase its amplitude
ASIC-1a [12, 91]	Trypsin, chymotrypsin and proteinase K	Arginine 145 for trypsin	Shift both the pH dependence of channel activation and the steady-state channel inactivation to lower pH values; be resistant to the inhibition of venom of *P. cambridgei* and display faster recovery from inactivation than wild type channels
EAG2 [14]	Calpain		Decrease current density; a positive shift in voltage dependence of channel activation; a lack of EAG2 signature fast activation
Cav 1.2 [32, 34]	Calpain, proteasome		Alter channel voltage-current relationship and voltage-dependent channel inactivation
TRPM7 [13]	Caspase	Aspartic acid 1510	Potentiate TRPM7 channel activity
NMDA receptors: NR1 and NR2B subunits [39, 40]	Tissue plasminogen activator	Arginine 260 in NR1 Arginine 67 in NR2B	Enhance NMDA-mediated Ca^{2+} influx for NR1; reduce ifenprodil inhibition and increase glycine EC50 for NR2B
CNG channel [36]	Metalloproteinase 2 and 9		Increase the apparent affinity for cGMP and the efficacy of cAMP to regulate CNG channel activity
R1 [15]	Caspase and calpain	Aspartic acid 1891 for caspase; Glutamic acid 1917 for calpain	Increase the frequency of Ca^{2+} oscillations and augment single channel open probability; abolish the PKA regulation of R1
R2 and R3 [65]	Digestive enzymes	Third and fourth solvent exposed regions	Decrease the frequency of Ca^{2+} oscillations; decrease the single channel open probability.