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Invited review

Post-translational dysfunctions in channelopathies of the nervous system

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ABSTRACT

Channelopathies comprise various diseases caused by defects of ion channels. Modifications of their biophysical properties are common and have been widely studied. However, ion channels are heterogeneous multi-molecular complexes that are extensively modulated and undergo a maturation process comprising numerous steps of structural modifications and intracellular trafficking. Perturbations of these processes can give rise to aberrant channels that cause pathologies. Here we review channelopathies of the nervous system associated with dysfunctions at the post-translational level (folding, trafficking, degradation, subcellular localization, interactions with associated proteins and structural post-translational modifications). We briefly outline the physiology of ion channels' maturation and discuss examples of defective mechanisms, focusing in particular on voltage-gated sodium channels, which are implicated in numerous neurological disorders. We also shortly introduce possible strategies to develop therapeutic approaches that target these processes.

Contents

Ion channels are pore-forming trans-membrane proteins that control the movement of ions across cells' membranes, according to their electro-chemical gradients. The flow of ions through channels

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is regulated by specific stimuli and modulations, and generates electrical currents that in turn establish trans-membrane voltage and can modify ion concentration gradients, effects that are essential for diverse physiological functions: e.g. membrane potential generation and modulation, neurotransmitters release, signal transduction, hormone secretion, muscle contraction, etc. Channelopathies comprise heterogeneous diseases arising from defects of ion channels (Kullmann and Waxman, 2010; Curran and Mohler, 2015; Ptáček, 2015; Imbrici et al., 2016). The most common and direct cause are mutations in the encoding genes that alter channels' biophysical properties, thus producing gain or loss of function effects that compromise the function of the cell/tissue in which mutant channels are expressed. However, mutations impairing functional properties are not the only underlying mechanism for channelopathies. Indeed, decades of extensive research on the physiology of ion channels have shown that channels are not simply trans-membrane proteins with a pore that allows ions to flow, but rather heterogeneous multi-molecular complexes originating from a complex maturation process comprising numerous steps, which occur after that channels are translated. Perturbations of these processes can give rise to aberrant channels causing pathological conditions (Cobbold et al., 2003; Dib-Hajj and Waxman, 2010; Curran and Mohler, 2015).

Our review focuses on channelopathies of the nervous system associated with dysfunctions at the post-translational level: folding, trafficking, post-translational modifications, degradation, subcellular localization and protein interactions (see Table 1 and Fig. 1 for a summary). We will briefly outline the physiology of ion channels' maturation and then discuss examples of defective mechanisms, focusing in particular on voltage gated sodium channels (Na_v), which are implicated in numerous neurological disorders (Mantegazza et al., 2010a; Catterall, 2012; Eijkelkamp et al., 2012).

1. Maturation and functional modulation of ion channels

When mRNA translation begins to take place in a ribosome, the nascent peptide of an ion channel exposes specific aminoacidic sequences that target the peptide/ribosome complex to the endoplasmic reticulum (ER). Here, the synthesis continues, the tertiary structure is acquired and the developing channel is inserted into the lipid bilayer. The ER is also the first quality control check-point along the synthesis pathway by means of ER-associated chaperons that mediate the retention of not properly folded nascent ion channels within the ER compartment. Unfolded or misfolded channels can be either eliminated by ER-associated degradation (ERAD), through their retrotranslocation across the ER membrane and degradation by cytosolic proteasomes, or retained for further

Table 1
Summary of post-translational dysfunctions that we have reviewed and the affected ion channels.

Post-translational dysfunction	Channel	Reference
Folding/trafficking defects		
with negative dominance	$Ca_V2.1$	Pietrobon, 2010; Jeng et al., 2006; Mezghrani et al., 2008; Page et al., 2010; Dahimene et al., 2016; Raike et al., 2007
	Ca_V3	Mezghrani et al., 2008; Page et al., 2004
	Ca_V2	Mezghrani et al., 2008; Page et al., 2004
	$K_V1.1$	Chen et al., 2016
	$K_V1.2$	Syrbe et al., 2015; Helbig et al., 2016
	$K_V2.1$	Saitsu et al., 2015
	$K_V7.2$	Orhan et al., 2014; Maljevic et al., 2011
	$K_V7.4$	Gao et al., 2013
	TRESK	Lafrenière et al., 2010; Liu et al., 2013
	HCN1	Nava et al., 2014
	$Na_V1.5$	Sottas and Abriel, 2016; Mercier et al., 2012
	$Na_V1.2$	Kamiya et al., 2004
without negative dominance	$Na_V1.1$	Rusconi et al., 2007; Rusconi et al., 2009; Thompson et al., 2012; Bechi et al., 2015; Cestèle et al., 2013b
	$Na_V1.2$	Misra et al., 2008
	$Na_V1.6$*	Blanchard et al., 2015; Sharkey et al., 2009*
	$Na_V1.7$	Eijkelkamp et al., 2012
	$Ca_V1.4$	Hoda et al., 2006
	$Ca_V3.2$	Vitko et al., 2007; Eckle et al., 2014
Dysfunctional protein interactions	$Na_V1.1$*, $Na_V1.2$*, $Na_V1.3$, $Na_V1.6$* and Na_V β1	Wimmer et al., 2010*; Lucas et al., 2005; Rusconi et al., 2007; Patino et al., 2011
	$Na_V1.5$ and Na_V β2, 3, 4	O'Malley and Isom, 2015
	Ca_V1, 2 and Ca_V β4	Escayg et al., 2000
	$Na_V1.8$ and P11*	Okuse et al., 1997*
	$Na_{V1.1}$, $Na_V1.6$* and FGF14	van Swieten et al., 2003; Goldfarb et al., 2007*; Rusconi et al., 2009
	K_V7 and FGF14	Pablo and Pitt, 2017
	Na_V and AnkG*	Lopez et al., 2016*
	K_V and LGI1	Schulte et al., 2006
	AMPAr and LGI1*	Fukata et al., 2010*
	HCN1, HCN2 and TRIP8b*	Shin et al., 2008*
Dysfunctional PTMs		
Glycosylation	$K_V3.3$, $Na_V1.6$*	Gallego-Iradi et al., 2014; Jones et al., 2016*
Phosphorylation	$Na_V1.2$*, $Na_V1.7$#, Na_V 1.8#, Na_V 1.9#	Baek et al., 2014*; Laedermann et al., 2015#
Ubiquitylation	$Na_V1.1$, $Na_V1.7$*	Rusconi et al., 2009; Laedermann et al., 2013*
SUMOylation	$Na_V1.2$, $Na_V1.7$	Plant et al., 2016; Dustrude et al., 2016
Proteolysis	$Na_V1.2$*, $Na_V1.6$#, $Na_V1.8$§, $Na_V1.9$§, Na_V β subunits	Schoch et al., 2013*; Kharatmal et al., 2015§; Brocard et al., 2016#; Kovacs et al., 2010

Symbols (*, # and §) indicate experimental evidence from animal models.

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