An update on transcriptional and post-translational regulation of brain voltage-gated sodium channels

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Abstract Voltage-gated sodium channels are essential proteins in brain physiology, as they generate the sodium currents that initiate neuronal action potentials. Voltage-gated sodium channels expression, localisation and function are regulated by a range of transcriptional and post-translational mechanisms. Here, we review our understanding of regulation of brain voltage-gated sodium channels, in particular SCN1A (NaV1.1), SCN2A (NaV1.2), SCN3A (NaV1.3) and SCN8A (NaV1.6), by transcription factors, by alternative splicing, and by post-translational modifications. Our focus is strongly centred on recent research lines, and newly generated knowledge.

Keywords Voltage-gated sodium channel · Regulation · Transcription factor · Alternative splicing · Post-translational modification

Introduction

Voltage-gated sodium channels are essential proteins in brain physiology. Upon voltage-mediated activation, sodium channels produce sodium currents responsible for depolarisation of excitable cells, including neurons and cardiomyocytes. From the point of view of biomedical sciences and pathophysiology, brain disorders such as some forms of epilepsy have long been directly associated with voltage-gated sodium channel malfunction.

Sodium channels are thought to be macromolecular complexes composed of tens of different proteins (Abriel et al. 2015). The pore-forming protein is known as the α subunit, and is sufficient to generate sodium currents. All α subunits include a voltage sensor that promotes channel opening when the cell membrane is depolarized by a few millivolts. Sodium channels thus activate, generate the sodium currents that underlie the initial depolarisation phase of the action potential, and then inactivate within tens of milliseconds, critically shaping cell repolarisation (Zilberter et al. 1994).

There are nine isoforms of the voltage-gated sodium channel α subunit, and each form has distinct expression and electrophysiological patterns. In this review, we have considered the main sodium channel isoforms expressed in the central neuronal system (CNS), i.e., SCN1A (NaV1.1), SCN2A (NaV1.2), SCN3A (NaV1.3) and SCN8A (NaV1.6). Wherever relevant we have also included additional information regarding other isoforms, including SCN5A (generally known as the cardiac isoform, NaV1.5) and SCN9A (mainly expressed in the peripheral nervous system, NaV1.7), (Dib-Hajj et al. 2013).

Sodium channel α subunits are large (ca. 2000 residues), hydrophobic, integral membrane proteins that have been fascinating (and challenging) a range of scientific communities including biochemists, pharmacists, neuroscientists, and electrophysiologists for more than three decades (Catterall 2015). Although detailed mammalian voltage-gated sodium channel structures are not yet available, it is widely accepted that the topology of α subunits at the protein level consists of four homologous domains (termed DI to DIV), each consisting of six transmembrane helices, and joined by cytosolic interdomain linkers (Yu and Catterall 2003). The N and C termini of α subunits are also intracellular. Thus, cytosolic interdomain linkers, and N- and
C-terminal domains of α subunits are accessible to intracellular enzymes that catalyse post-translational modifications (PTM) of the channels.

In this review, we aim to integrate progress in our understanding of CNS voltage-gated sodium channel regulation at the transcriptional and post-translational level. The reader will find that much more is known on sodium channel PTMs than on the transcriptional mechanisms that regulate channel expression. Consequently, the weight of the review is balanced towards PTMs. Our focus is strongly centred on recent research lines, and newly generated knowledge. The goal is to facilitate dissemination of recent developments with a view on fostering further relevant research.

**Regulation of brain sodium channel expression at the transcriptional level**

In this section, we have considered the regulation of CNS voltage-gated sodium channels by transcription factors, and by alternative splicing. The regulation of sodium channels at the post-transcriptional level (e.g., by microRNAs) is out of the scope of the present review.

**Regulation by transcription factors**

Promoter regions of brain voltage-gated sodium channel genes have been described, including SCN1A (Dong et al. 2014; Long et al. 2008; SCN2A (Lu et al. 1998; Schade and Brown 2000), SCN3A (Martin et al. 2007), and SCN8A (Drews et al. 2005, 2007). Based on the sequence analyses and databases, several transcription factors have been proposed to control brain sodium channel expression (Long et al. 2008). Experimentally, a recent study has shown that SCN3A expression is regulated by promoter CpG methylation and Methyl-CpG-binding domain protein 2 (MBD2), (Li et al. 2015). MBD2 targets methylated CpG for demethylation, possibly leading to activated transcription. Consistently, knock-down of MBD2 decreased SCN3A mRNA levels in a neuroblastoma cell line. In seizure-induced mice, MBD2 expression was increased, which correlated with decreased CpG methylation, and enhanced SCN3A expression (Li et al. 2015).

Another recent development has been the identification of receptor for activated C kinase 1 (RACK1) as a repressor of SCN1A expression (Dong et al. 2014). The authors identified a transcriptional silencer in a region between +53 and +62 bp downstream of SCN1A promoter and used EMSA assays to uncover possible transcriptional regulators. RACK1 was found to bind to the silencer in NT2 cells (a pluripotent embryonal carcinoma cell line often used for differentiation into neurons). Knocking-down RACK1 in NT2 cells markedly increased SCN1A mRNA levels (Dong et al. 2014).

Sodium channel macromolecular complexes may incorporate proteins classically known as voltage-gated sodium channel β subunits. These include five different proteins termed β1, β1b, β2, β3, and β4. Many groups have studied the effect of β subunits on α subunit trafficking and electrophysiology, mainly from the point of view of protein–protein interactions (for a recent review, see Namadurai et al. 2015).

Additionally, sodium channel β subunits have been proposed to regulate α subunits at the transcriptional level. One of the first experimental observations was the increase in NaV1.1 mRNA and protein levels in the presence of proteases targeting the β2 subunit. The group of Kovacs, and others, has demonstrated the sequential mechanism by which, first, ADAM10 and BACE1 proteases cleave off the extracellular domain of the β2 subunit. Second, γ-secretase releases the β2 intracellular domain. And third, the β2 intracellular domain induces an increase in NaV1.1 mRNA and protein levels (Kim et al. 2005, 2007; Wong et al. 2005), although the precise pathways for β2 internalisation into the cell nucleus remain unknown. BACE1-dependent sodium channel expression seems to be specific for NaV1.1, and mRNA levels of other brain NaV isoforms including NaV1.2, NaV1.3 and NaV1.6 are relatively insensitive to BACE1 protease activity (Kim et al. 2007, 2011).

Likewise β2, the β1 subunit has been shown to regulate NaV expression, and mouse models show changes in brain NaV expression and localization upon β1 deletion (Chen et al. 2004). In a recent development, β1 subunit silencing has been shown to result in decreased NaV1.1, NaV1.3 and NaV1.6 (but not NaV1.2) mRNA and protein levels in cells models (Baroni et al. 2014), although the mechanism underlying this regulation was not investigated. Although β1 subunit is a target for BACE1 in vitro, the question remains whether this is physiologically relevant (Wong et al. 2005).

**Regulation by alternative splicing**

The first evidences for alternative splicing of brain sodium channels were reported more than 20 years ago (Sarao et al. 1991; Gustafson et al. 1993), and splicing mechanisms are thought to be common to most brain NaV isoforms (Copley 2004). In particular, SCN1A alternative splicing has been extensively studied due to its relevance in CNS disorders such as epilepsy (Lossin 2009; Schlachter et al. 2009; Le Gal et al. 2011; Thompson et al. 2011).

The best studied SCN1A splicing variants are often referred to as the adult and neonatal forms, although both forms are expressed in adults. They result from the mutually exclusive expression of either exon 5A (adult) or 5N
Regulation of brain sodium channels at the post-translational level

From biochemical assays in vitro to targeted purification of proteins from tissues, research in sodium channel PTMs has recently expanded from (immuno) chemical methods to embrace mass spectrometry and proteomics. Here, we review our current understanding of some of the best known sodium channel PTMs. As before, we have included Na\textsubscript{V}1.1, Na\textsubscript{V}1.2, Na\textsubscript{V}1.3, and Na\textsubscript{V}1.6. Where relevant, Na\textsubscript{V}1.5 has also been considered because of the wealth of available Na\textsubscript{V}1.5 PTM data. In particular, Na\textsubscript{V}1.5 phosphorylation, ubiquitylation, and arginine methylation have been studied in detail ("Phosphorylation", "Ubiquitylation" and "Arginine methylation", respectively).

Previously in "Regulation by transcription factors", we have reviewed our knowledge of sodium channel \(\beta\) subunit processing by proteases, leading to transcriptional regulation of \(\alpha\) subunits. In "Regulation of brain sodium channels by proteases", we have included available data on direct proteolysis of \(\alpha\) subunits. Although proteolysis is in most cases associated with degradation, it can also be regarded as PTM if it is limited and specific (Rogers and Overall 2013).

Phosphorylation

Phosphorylation is the most experimentally observed PTM at the proteome-wide level, and it is certainly thought to be the most abundant PTM along with N-glycosylation (Khoury et al. 2011). Sodium channels are no exception to the rule and phosphorylation is the most studied and observed sodium channel PTM.

Identified phosphorylation sites

The aim of this subsection is to comprehensively collect and update the repertoire of sodium channel ‘phosphorylatable’ sites (Table 1). These include phosphosites identified by the use of in vitro assays and heterologous expression experiments, as well as those identified in sodium channels isolated from native sources. Data in Table 1 are taken from classical papers (Berendt et al. 2010), and previous reviews (Cerda et al. 2011; Baek et al. 2011), and updated to include recent original articles that described novel phosphosites (Marionneau et al. 2012; Baek et al. 2014; Herren et al. 2015). Functional consequences of Na\textsubscript{V} phosphorylation are discussed below.

Is it safe to assume that if a Na\textsubscript{V} isoform is phosphorylated at a certain residue, then our favourite isoform will also be, provided the site is conserved? The general answer is No. Visual analysis of phosphosite conservation in Table 1 leaves little room for hope, at least according to the data currently available. The exception is the interdomain linker between domains I and II, which is considered the PTM hot-spot (Cantrell and Catterall 2001), and where one can find phosphosites conserved among 3, sometimes 4, of the considered Na\textsubscript{V} isoforms. Nevertheless, due to the substoichiometric and labile nature of phosphorylation, the failure to detect a protein modification does not imply that a residue is not phosphorylated. Perhaps future comprehensive proteomic studies will demonstrate higher degree in phosphosite conservation among Na\textsubscript{V} isoforms.

Specificity of the functional effect of phosphorylation among Na\textsubscript{V} isoforms

Most of the phosphosites included in Table 1 were identified by proteomics and mass spectrometry methods, and we currently lack information on which protein kinase may catalyse phosphorylation of many of the Na\textsubscript{V} phosphosites. Nevertheless, it has long been known that protein kinase C (PKC) and cAMP-dependent kinase (PKA) can phosphorylate brain Na\textsubscript{V} channels (West et al. 1991; Numann et al. 1991; Li et al. 1992, 1993). Other kinases involved in regulating brain Na\textsubscript{V} phosphorylation are glycogen synthase kinase 3 (GSK3) (James et al. 2015), protein kinase CK2 (Hien et al. 2014), A kinase-anchoring protein 15 (Few et al. 2007), Fyn tyrosine kinase (Beacham et al. 2007), and p38 mitogen-kinase activated protein kinase (Wittmack et al. 2005).

The functional effects of channel phosphorylation on Na\textsubscript{V} electrophysiology often depend on the specific isoform of interest. For instance, phosphorylation by PKA and PKC results in attenuation of Na\textsubscript{V}1.2 currents due to defective channel trafficking to the cell surface (Li et al. 1992). But Na\textsubscript{V}1.6 channels are relatively insensitive to PKA/PKC regulation (Chen et al. 2008), and Na\textsubscript{V}1.5 currents are enhanced by PKA activation due to increased Na\textsubscript{V}1.5 expression at the cell surface (Hallaq et al. 2006). Subtle variations in the primary sequence of Na\textsubscript{V} isoforms must underlie such differences. For instance, it is thought that...
| Table 1 | Phosphosities of different NaV isoforms |
|---------|-----------------------------------------|
| MEOTLVFPPD | PGDSPFPFTE | SLAIAERRIA EEAANNKPD | ----- | KKDDDE | NaV1.1 mouse (N terminus) |
| MARSLYVPDP | PGSRFPFTRE | SLAIAERQIA EEAKRPKQE | ----- | KRDDEDD | NaV1.2 rat (N terminus) |
| MALLQVFPDP | PESFRFTFTE | SLAIAERKRA EEAAPKPEK | ----- | QDNODE | NaV1.3 human (N terminus) |
| MAARLVPDP | PGDFFPFTPE | SLANIERRIA ESLLKPPPA DGSHREDDE | 50 | NaV1.6 mouse (N terminus) |
| NGKPKNSDLLE | AGKNLFFPYG | DIPPMVSEP LEDDPYVIN KKFIVLNVK | 96 | NaV1.1 mouse (N terminus) |
| NGKPKNSDLLE | AGKSLPFTYG | DIPPMVSEP LEDDPYVIN KKFIVLNVK | 97 | NaV1.2 rat (N terminus) |
| NGKPKNSDLLE | AGKNLFFPYG | DIPPMVSEP LEDDPYVIN KKFIVMNNK | 96 | NaV1.3 human (N terminus) |
| MAAPQPDLPQ | ASKLPDPDLQ | NPQFLGELIEP LEDDPFYSY QKTFIVLNVK | 99 | NaV1.4 human (N terminus) |
| SKKPKNSDLLE | AGKSLFPPYG | DIPQLVAVP LEDDFFYILT QKTFVNLNRG | 100 | NaV1.6 mouse (N terminus) |
| KAIFRFSATS | ALYILTFPNP | LKIAAIKILV HLSMSLIMC TILTNCVFMT | 146 | NaV1.1 mouse (N terminus) |
| KAISRFSATS | ALYIFTPNPK | IRKIAAIKILV HLSFVNLIMC TILTNCVFMT | 147 | NaV1.2 rat (N terminus) |
| KAIFRFSATS | ALYILTPFNL | VRKIAAIKILV HLSMSLIMC TILTNCVFMT | 146 | NaV1.3 human (N terminus) |
| KTIFRFSATN | ALYVTLPFNP | IRRAAIKILV HLSFVNLIMC TILTNCVFMT | 149 | NaV1.4 human (N terminus) |
| KTFLFRSPAT | ALYILSPFNL | IRRIAIIKILV HLSFMSLIMC TILTNCVFMT | 150 | NaV1.4 human (N terminus) |
| EFQMLEQKLK | KQKEAAQQA AATTAE---- | -HREE---- | PS | AAGRLDDSSS | 484 NaV1.1 mouse (Linker DI-DII) |
| EFQMLEQKLK | KQKEAAQAA AAAAAA---- | -EERDFSGAG GIGVFSSSSS | 488 | NaV1.2 rat (Linker DI-DII) |
| EFQMLEQKLK | KQKEAAQAA AAAAAA---- | -A5RDFSGIG GLGLELLSSS | 486 | NaV1.3 human (Linker DI-DII) |
| RFQEMMEMLK | KEHAI---- | - -------- | -IR | QVTVSRLS | 461 | NaV1.5 human (Linker DI-DII) |
| EFKAMLQKLK | KQKEAAGQA- AAATMAGTVS EDAIEEEGED GVGSEPRSSS | 478 | NaV1.6 mouse (Linker DI-DII) |
| EA5KLSKSA | KERRNRRKKK KQKRSQGGEE K--EDAVRK | 533 | NaV1.1 mouse (Linker DI-DII) |
| VASKKLSSKSE | KELHRKRKKK KQKEGAEKKE --EDAVRRK | 536 | NaV1.2 rat (Linker DI-DII) |
| EA5KLSKSA | KERRNRRKKK KQKRSQGGEE K--EDAVRK | 533 | NaV1.1 mouse (Linker DI-DII) |
| EMLSLAPVNS | HERRSRKKR ----MSSSTE | ECGRDRPLPS ESDPFDPR | 504 | NaV1.4 human (Linker DI-DII) |
| EL5KLSKSA | KERRNRRKKK KQKRSQGGEE K--EDAVRK | 528 | NaV1.8 mouse (Linker DI-DII) |
| FRPSNQGRNL | TYERKSSPH QSLSSPRLSL FSSPRNRTS | LCSRFR-- | G | 581 | NaV1.1 mouse (Linker DI-DII) |
| FQPSNQGRLS | TEYRSFSPH QSSLSSPRLSL FSSPRNRTS | LSFPR-- | G | 584 | NaV1.1 mouse (Linker DI-DII) |
| FLPSMGQRNL | TSDKKFSFPH QSLSSPRLSL FSSPRNRTS | LSFPR-- | G | 584 | NaV1.1 human (Linker DI-DII) |
| FRPSNQGRNL | TYERKSSPH QSLSSPRLSL FSSPRNRTS | LSFPR-- | G | 581 | NaV1.1 mouse (Linker DI-DII) |
| FR--LPDRNL | G--RKFSPIMN QSLRSSPLS FSFSRPGGPF | 574 | NaV1.6 mouse (Linker DI-DII) |
| KDVGENDFA | DDEHHFTEDN ESRRSFILVP | RHRGERRRN-- | ---- | SNSQGTS | 626 | NaV1.1 mouse (Linker DI-DII) |
| KDVGENDFA | DDEHHFTEDN ESRRSFILVP | RHRGERRRN-- | ---- | SNSQGTS | 626 | NaV1.1 mouse (Linker DI-DII) |
| KDVGENDFA | DDEHHFTEDN ESRRSFILVP | RHRGERRRN-- | ---- | SNSQGTS | 629 | NaV1.2 rat (Linker DI-DII) |
| RDQGEADFA | DDEHHFTEDN ESRRSFILVP | RHRGERRRN-- | ---- | SNSQGTS | 629 | NaV1.3 human (Linker DI-DII) |
| RDQGEADFA | DDEHHFTEDN ESRRSFILVP | RHRGERRRN-- | ---- | SNSQGTS | 629 | NaV1.3 human (Linker DI-DII) |
| RSSRMAVPF | ANKMHSTVD CNGVVSLVG | GSFVTSPVPG QLLPEVIIDD | 675 | NaV1.1 mouse (Linker DI-DII) |
| RSSRMAVPF | ANKMHSTVD CNGVVSLVG | GSFVTSPVPG QLLPEVIIDD | 675 | NaV1.1 mouse (Linker DI-DII) |
| MRRSAIGPL | ANKMHSTVD CNGVVSLVG | GSFVTSPVPG QLLPEVIIDD | 673 | NaV1.3 human (Linker DI-DII) |
| RSSRMAVPF | ANKMHSTVD CNGVVSLVG | GSFVTSPVPG QLLPEVIIDD | 673 | NaV1.3 human (Linker DI-DII) |
| PGTS-AHGA | LHGLKNNST | GDPEATSPGS HLLRFVLMLEH | 626 | NaV1.5 human (Linker DI-DII) |
| RSSRMAVPF | ANKMHSTVD CNGVVSLVG | GSFVTSPVPG QLLPEVIIDD | 675 | NaV1.1 mouse (Linker DI-DII) |
| RSSRMAVPF | ANKMHSTVD CNGVVSLVG | GSFVTSPVPG QLLPEVIIDD | 675 | NaV1.1 mouse (Linker DI-DII) |
| PATTEDGTTT | ETEMRKRGSS | SIVSHVMDLE DPFRQRAMS IAISILNTV-- | 724 | NaV1.1 mouse (Linker DI-DII) |
| PATTEDGTTT | ETEMRKRGSS | SIVSHVMDLE DPFRQRAMS IAISILNTV-- | 724 | NaV1.1 mouse (Linker DI-DII) |
| ELEESQKRC | PCCWKFSN | FLINDCSFPY LVKIVHVNLV VMDFPVDLAI | 774 | NaV1.1 mouse (Linker DI-DII) |
| ELEESQKRC | PCCWKFSN | FLINDCSFPY LVKIVHVNLV VMDFPVDLAI | 774 | NaV1.1 mouse (Linker DI-DII) |
| ELEESQKRC | PCCWKFAMN | CLINDCCPKW LVKIVHVNLV VMDFPVDLAI | 775 | NaV1.2 rat (Linker DI-DII) |
| ELEERQKRC | PCCWFRPAD | FLINDCCDAW LVKIVHVNLV VMDFPVDLAI | 776 | NaV1.3 human (Linker DI-DII) |
| ELEESRRKHC | PCCWNLARQ | YLWEECCTPLW MS1QKVGLVL VMDFPDTLTI | 723 | NaV1.3 human (Linker DI-DII) |
| ELEESQRKRC | PCCWYKFHNT | FLINECHPYW ILKIEIVNLI VMDFPVDLAI | 757 | NaV1.6 mouse (Linker DI-DII) |
NaV1.5 phosphorylation by PKA at S528 masks an endoplasmic reticulum retention signal (RRR535), thereby promoting NaV1.5 trafficking to the membrane (Zhou et al. 2002). This endoplasmic reticulum signal is absent in NaV1.2 (RVK585) and modified in NaV1.6 (RFR575).

Phosphorylated residues are shown bold and shadowed.

Table 1 continued

| Sequence | Linker | Species | C terminus |
|----------|--------|---------|------------|
| AVGESDFEN | NTEDFS | NaV1.1 mouse | (Linker DII-DIII) |
| AVGESDFEN | NTEDFS | NaV1.2 rat | (Linker DII-DIII) |
| MKKLG | MKKLG | NaV1.5 human | (Linker DIII-DIV) |
| MKKLG | MKKLG | NaV1.6 mouse | (Linker DIII-DIV) |
| MKKLG | MKKLG | NaV1.1 mouse | (Linker DIII-DIV) |
| AVGESDFEN | NTEDFS | NaV1.1 mouse | (Linker DII-DIII) |
| AVGESDFEN | NTEDFS | NaV1.2 rat | (Linker DII-DIII) |
| MKKLG | MKKLG | NaV1.5 human | (Linker DIII-DIV) |
| MKKLG | MKKLG | NaV1.6 mouse | (Linker DIII-DIV) |
| MKKLG | MKKLG | NaV1.1 mouse | (Linker DIII-DIV) |

| Sequence | Linker | Species | C terminus |
|----------|--------|---------|------------|
| KELNYLRDG | NGTTSG | NaV1.3 human | (Linker DII-DIII) |
| KELNYLRDG | NGTTSG | NaV1.2 rat | (Linker DII-DIII) |
| KELNYLRDG | NGTTSG | NaV1.1 mouse | (Linker DII-DIII) |
| AVGESDFEN | NTEDFS | NaV1.1 mouse | (Linker DII-DIII) |
| AVGESDFEN | NTEDFS | NaV1.2 rat | (Linker DII-DIII) |
| MKKLG | MKKLG | NaV1.5 human | (Linker DIII-DIV) |
| MKKLG | MKKLG | NaV1.6 mouse | (Linker DIII-DIV) |
| MKKLG | MKKLG | NaV1.1 mouse | (Linker DIII-DIV) |

Opposite functional effects of post-translational modifications on distinct NaV isoforms have also been observed after phosphorylation by Fyn kinase. Fyn kinase phosphorylates essential tyrosine residues within the inactivation gate of sodium channels, including the equivalent Y1498...
(Na\textsubscript{v}1.2) and Y1495 (Na\textsubscript{v}1.5). Yet, the functional effect of phosphorylation by Fyn on channel inactivation is a negative (Na\textsubscript{v}1.2) or positive (Na\textsubscript{v}1.5) shift in the voltage dependence of inactivation (Beacham \textit{et al.} 2007; Ahern \textit{et al.} 2005). The simplest explanation is that Fyn phosphorylates other Tyr residues within Na\textsubscript{v}1.2 and Na\textsubscript{v}1.5, (Beacham \textit{et al.} 2007). Nevertheless, recent work has reported that distinct splicing variants of the same Na\textsubscript{v} isoform show different electrophysiological behaviour upon phosphorylation by Fyn, which introduces another level of complexity (Iqbal \textit{et al.} 2015).

**Ubiquitylation**

Protein ubiquitylation (or ubiquitination) is a post-translational modification that involves the orchestrated function of three types of enzymes. First, ubiquitin activating enzyme (E1) catalyses thioester formation between the C terminus of ubiquitin and an internal cysteine. Second, activated ubiquitin is transferred to the ubiquitin conjugating enzyme (E2). Third, ubiquitylation of the substrate protein is catalysed by ubiquitin ligases (E3), which covalently attach ubiquitin molecules to lysine residues within the target sequence. Ubiquitylation is often associated with protein degradation.

There are hundreds of E3 ubiquitin ligases, usually classified into two groups: HECT (homologous to E6-AP C terminus) ligases, and RING (really interesting new gene) ligases (Goel \textit{et al.} 2015). Until 2015, it was thought that only HECT ligases could catalyse sodium channel ubiquitylation (see below).

The most studied molecular mechanism for sodium channel ubiquitylation involves channel recognition by Nedd4-2 ubiquitin ligases (HECT-type ligases) via protein–protein interaction between the WW4 domain of Nedd4-2, and the PY motif of neuronal and cardiac sodium channels (Fotia \textit{et al.} 2004; van Bemmelen \textit{et al.} 2004). Ubiquitylation by Nedd4-2 has been shown to tag sodium channels for internalisation from the cell surface, including Na\textsubscript{v}1.2 (Fotia \textit{et al.} 2004), Na\textsubscript{v}1.6 (Gasser \textit{et al.} 2010), and Na\textsubscript{v}1.5 (Rougier \textit{et al.} 2005). However, in most cases, the precise modification site(s), i.e., the Lys residues that are ubiquitylated, remain to be confirmed.

Very recently, compelling evidence has been presented that shows ubiquitylation of sodium channels in zebra fish CNS by RNF121, a member of the RING family of E3 ubiquitin ligases (Ogino \textit{et al.} 2015). From the initial observation that zebrafish bearing mutations in RNF121 present defective Na\textsubscript{v} trafficking in neurons and skeletal muscle, the investigators moved on to perform heterologous expression of Na\textsubscript{v}1.6 and RNF121 in HEK 293T cells. Results showed increased Na\textsubscript{v}1.6 degradation upon co-expression of RNF121 but, intriguingly, enhanced Na\textsubscript{v}1.6 membrane localization when co-expressed with RNF121 \textit{and} auxiliary Na\textsubscript{v} \beta subunits (Ogino \textit{et al.} 2015).

**Arginine methylation**

Arginine methylation consists on the addition of methyl groups to arginine residues of proteins. Arginine methylation is catalysed by protein arginine methyl transferases (PRMTs) that transfer a methyl group from S-adenosyl-l-methionine (SAM) to the target arginine. Arginine methylation has recently been reported as a novel post-translational modification of the voltage-gated sodium channel family using Na\textsubscript{v}1.5 as a model system (Beltran-Alvarez \textit{et al.} 2011).

The groups of Comb and Trimmer have described arginine methylation of brain sodium channels. Using a proteomic approach and bespoke antibodies that recognise peptides bearing methylated arginine, the group of Comb reported arginine methylation of Na\textsubscript{v}1.1, Na\textsubscript{v}1.2 and Na\textsubscript{v}1.5 in the mouse brain (Guo \textit{et al.} 2014). In parallel, the group of Trimmer described arginine methylation of Na\textsubscript{v}1.2 purified from rat brain (Baek \textit{et al.} 2014). We analysed the methylation sites reported by the three referenced articles (Beltran-Alvarez \textit{et al.} 2011; Guo \textit{et al.} 2014; Baek \textit{et al.} 2014), and found that three sites have been observed by at least two independent studies (Table 2).

The functional consequences of sodium channel modification by arginine methylation have been documented. Available electrophysiological data are consistent with an increase in sodium current density, most likely due to enhanced Na\textsubscript{v} membrane expression (Beltran-Alvarez \textit{et al.} 2013; Baek \textit{et al.} 2014). Additionally, the group of Trimmer reported considerable acceleration in Na\textsubscript{v}1.2 recovery from inactivation when arginine methylation was enhanced (Baek \textit{et al.} 2014). Remarkably, arginine methylation is an example of PTM conservation among Na\textsubscript{v} isoforms, even if catalysed by different enzymes: Na\textsubscript{v}1.2 is methylated by PRMT8 (mostly expressed in the CNS), while Na\textsubscript{v}1.5 methylation is catalysed by PRMT3 and -5 (ubiquitously expressed).

**Other known post-translational modifications**

We would like to mention that sodium channels have long been known to undergo cysteine modifications including S-palmitoylation (Schmidt and Catterall 1987; Bosmans \textit{et al.} 2011), and S-nitrosylation (Renganathan \textit{et al.} 2002). Methionine oxidation of sodium channels has previously been reviewed (Cui \textit{et al.} 2012). SUMOylation of the Na\textsubscript{v}1.7 isoform has been described, but available data suggest that SUMOylation may not be conserved in CNS Na\textsubscript{v} isoforms (Dustrude \textit{et al.} 2013).
Another well-known PTM, N-glycosylation, has been mostly studied in the cardiac isoform of the sodium channel, and several excellent reviews have recently been published (Baycin-Hizal et al. 2014; Marionneau and Abriel 2015). Perhaps the latest studies are those from the Chatelier and the Decosterd–Abriel groups, which have proposed alternative trafficking pathways for differentially glycosylated \( \text{Na}_\text{v} \) using \( \text{Na}_\text{v}1.5 \) and \( \text{Na}_\text{v}1.7 \) as study models (Mercier et al. 2015; Laedermann et al. 2013, respectively).

**Other possible post-translational modifications?**

The advent of large-scale proteomics including the publication of human proteome maps is revolutionising life sciences. The ion channel field can also benefit from the analysis of big data to anticipate and identify challenges and opportunities, particularly in the field of PTMs. With this in mind, we searched Phosphositeplus (Hornbeck et al. 2015) for PTMs of \( \text{Na}_\text{v} \) isoforms. The database contains potentially novel sodium channel modifications including Lys acetylation, which is reported for \( \text{Na}_\text{v}1.1 \), \( \text{Na}_\text{v}1.2 \), \( \text{Na}_\text{v}1.3 \), \( \text{Na}_\text{v}1.5 \) and \( \text{Na}_\text{v}1.6 \), and Lys methylation, which is included for \( \text{Na}_\text{v}1.2 \) and \( \text{Na}_\text{v}1.6 \).

Although promising at first sight, available data must be regarded with care. Conservation of the reported post-translationally acetylated or methylated Lys site among \( \text{Na}_\text{v} \) isoforms was very low. The finding worth mentioning was interspecies conservation of \( \text{Na}_\text{v}1.1 \) acetylation at K1948 in human and mouse samples. Although K1948 acetylation was observed in unrelated experiments, it must be noted that the source of tissue was not brain but colon cancer.

**Cross-talk between sodium channel PTMs**

Cross-talk, or interplay, between PTMs includes the regulatory mechanisms by which PTMs work together to determine protein function. Cross-talk between sodium channel phosphorylation, and arginine methylation, has been reported. The group of Trimmer reported cross-talk between \( \text{Na}_\text{v}1.2 \) arginine methylation and phosphorylation (Baek et al. 2014). In this study, the authors studied \( \text{Na}_\text{v}1.2 \) PTMs in the rat brain. \( \text{Na}_\text{v}1.2 \) was immunopurified, digested and subjected to mass spectrometry analysis. An initial observation was that detected \( \text{Na}_\text{v}1.2 \) peptides harboured either arginine methylation or phosphorylation, but not both PTMs on the same peptide. Convincingly, these two PTMs were reciprocally regulated in response to acute seizure: e.g., R563 methylation (see also Table 2) increased but S554 and S568 phosphorylation decreased after induction of seizure in rats (Baek et al. 2014). The most likely mechanism for this interplay between sodium channel arginine methylation and phosphorylation is the modification of kinetic specificity constants of serine phosphorylation.
upon methylation of a neighbouring arginine, and vice versa (Beltran-Alvarez et al. 2015). Nevertheless, the functional consequences of phosphorylation—arginine methylation cross-talk remain to be elucidated.

Additionally, cross-regulation between Na\textsubscript{v}1.6 phosphorylation, and ubiquitylation, has been observed. On the one hand, Na\textsubscript{v}1.6 is phosphorylated by p38 MAPK at position S553. On the other, Na\textsubscript{v}1.6 is ubiquitylated by Nedd4-2 after recognition of the PY motif (Pro-Ser-Tyr) at the C terminus of the channel. Results from the group of Dib-Hajj suggested that S553 phosphorylation enables further Na\textsubscript{v}1.6 ubiquitylation and internalisation of the channel (Gasser et al. 2010). A similar mechanism has recently been proposed for Na\textsubscript{v}1.2 whereby phosphorylation of T1966 by GSK3 primes recognition by Nedd4-2 via the Na\textsubscript{v}1.2 PY motif (PPSY\textsubscript{1973}), (James et al. 2015).

**Regulation of brain sodium channels by proteases**

Voltage-gated sodium channel density has long been known to be regulated by proteases under normal (Paillart et al. 1996) and stress conditions (Iwata et al. 2004). Among the most important proteases in mammalian cells stand the calpains, which target hundreds of proteins (Grimm et al. 2012). The group of Meany has revealed the bases of calpain-dependent proteolysis of Na\textsubscript{v}1.2.

Using rat brain homogenates, they showed that calpain cleaves Na\textsubscript{v}1.2 (but not Na\textsubscript{v}1.1) at two sites, i.e., the interdomain linkers between domains I and II, and between domains II and III (von Reyn et al. 2009). Intriguingly, most of the calpain sodium channel fragment products localise at the plasma membrane 6 h after calpain activation, and possibly interact (von Reyn et al. 2009). Perhaps the simplest explanation is that distinct sodium fragments still retain the protein–protein interactions that hold the sodium channel macromolecular complex together, and thus control the break-down of the complex. A more thought-provoking alternative is that sodium channel post-translational proteolysis creates new proteins with modified biological activities.

The group of Meany has dissected the mechanisms of Na\textsubscript{v}1.2 proteolysis in cellular and mouse models of neuronal injury (von Reyn et al. 2012; Schoch et al. 2013), opening opportunities for treatment and therapy of traumatic brain injury. In this line, other researchers have recently described the beneficial effect of calpain inhibitors on brain sodium channel expression and electrophysiology in a model of diabetic neuropathy (Kharatmal et al. 2015).

The other example of sodium channel processing by proteases is the excision of the initiation methionine by aminopeptidases. This has been shown for Na\textsubscript{v}1.5 (followed by N-terminal acetylation of the resulting initiation alanine) in cardiac disease (Beltran-Alvarez et al. 2014). Whether Na\textsubscript{v}1.5 or other Na\textsubscript{v} isoforms are devoid of Met residues (or post-translationally acetylated) in normal tissue is unknown.

**Conclusions and perspective**

Research in the voltage-gated sodium channel field has grown linearly for the last 20 years. While the interest in transcriptional mechanisms regulating sodium channel expression has also grown steadily, we have observed an exponential trend in the number of publications related to sodium channel post-translational regulation. We predict that this growth will keep pace over the coming years. The aim of this review was to provide the current state of the art of the transcriptional and post-translational regulation of sodium channels, and thus set the ground for further research opportunities and discoveries.

Our understanding of transcriptional mechanisms governing brain sodium channel expression is far from comprehensive, and the ongoing research efforts of the ENCODE Consortium will surely encourage groups around the globe to dissect the molecular mechanism controlling Na\textsubscript{v} transcription. Analogously, there are new questions in the field of PTM of sodium channels, in particular related to cross-talk among co-occurring types of PTM. As an example, the functional consequences of the interplay between phosphorylation and arginine methylation are intriguing, because the latter is thought to be a rather stable PTM (Bedford and Clarke 2009). The dynamic sequence of PTM events, thus, acquires vital relevance. Our incomplete understanding of proteolysis and degradation pathways of sodium channels also warrants further research in the area.

From the point of view of cell biology, biochemistry and electrophysiology, we predict that major advances in our understanding of Na\textsubscript{v} regulation will be made in two main directions. First, systems biology approaches will integrate knowledge on Na\textsubscript{v} biology, including transcriptional and post-translational regulation. This may be done using mathematical models and simulations of protein expression, function and degradation at the single molecule level, or, e.g., at the level of action potentials. Second, structural insights into whole sodium channel proteins, or isolated domains, will provide the framework to rationalise possible interactions between PTMs.

Additionally, research on Na\textsubscript{v} is intrinsically associated to biomedical sciences, given the prominent relevance of these channels in a range of neurological and cardiac disorders. In this respect, in the following years we expect reports on quantitative experiments identifying changes in PTM patterns in disease (some recent examples include Baek et al. 2014; and Herren et al. 2015). The effect of sodium channel proteolysis in major neurological diseases
is also an emerging field of research (Corbett et al. 2013), which includes the identification of genetic mutations in proteases affecting sodium channel levels (Kim et al. 2014).

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest. This review contains data published previously only. This article does not contain any studies with human participants or animals performed by any of the authors.

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References

Abriel H, Rougier JS, Jalife J (2015) Ion channel macromolecular complexes in cardiomyocytes: roles in sudden cardiac death. Circ Res 116(12):1971–1988
Ahern CA, Zhang JF, Wookalis MJ, Horn R (2005) Modulation of the cardiac sodium channel NaV1.5 by Fyn, a Src family tyrosine kinase. Circ Res 96(9):991–998
Baek JH, Cerda O, Trimmer JS (2011) Mass spectrometry-based phosphoproteomics reveals multisite phosphorylation on mammalian brain voltage-gated sodium and potassium channels. Semin Cell Dev Biol 22(2):153–159
Baek JH, Rubinstein M, Scheuer T, Trimmer JS (2014) Reciprocal changes in phosphorylation and methylation of mammalian brain sodium channels in response to seizures. J Biol Chem 289(22):15363–15373
Baroni D, Picco C, Barbieri R, Moran O (2014) Antisense-mediated post-transcriptional silencing of SCN1B gene modulates sodium channel functional expression. Biol Cell 106(1):13–29
Baycin-Hizal D, Gottschalk A, Jacobson E, Mai S, Wolozny D, Zhang H, Krug SS, Betenbaugh MJ (2014) Physiologic and pathophysiologic consequences of altered sialylation and glycosylation on ion channel function. Biochem Biophys Res 453(2):243–253
Beacham D, Ahn M, Catterall WA, Scheuer T (2007) Sites and molecular mechanisms of modulation of Na(v)1.2 channels by Fyn tyrosine kinase. J Neurosci 27(43):11543–11551
Bedford MT, Clarke SG (2009) Protein arginine methylation in mammals: who, what, and why. Mol Cell 33(1):1–13
Beltran-Alvarez P, Pagans S, Brugada R (2011) The cardiac sodium channel is post-translationally modified by arginine methylation. J Proteome Res 10(8):3712–3719
Beltran-Alvarez P, Espejo A, Schmader R, Beltran C, Mrowka R, Linke T, Battle M, Perez-Villa F, Perez GJ, Scorinivis FS, Bemendorf K, Pagans S, Zimmer T, Brugada R (2013) Protein arginine methyl transferases-3 and -5 increase cell surface expression of cardiac sodium channel. FEBS Lett 587(19):3159–3165

Beltran-Alvarez P, Tarradas A, Chiva C, Pérez-Serra A, Batlle M, Pérez-Villa F, Schulte U, Sabidó E, Brugada R, Pagans S (2014) Identification of N-terminal protein acetylation and arginine methylation of the voltage-gated sodium channel in end-stage heart failure human heart. J Mol Cell Cardiol 76:126–129
Beltran-Alvarez P, Feixas F, Osuna S, Díaz-Hernández R, Brugada R, Pagans S (2015) Interplay between R513 methylation and S516 phosphorylation of the cardiac voltage-gated sodium channel. Amino Acids 47(2):429–434
Berendt FJ, Park KS, Trimmer JS (2010) Multisite phosphorylation of voltage-gated sodium channel alpha subunits from rat brain. J Proteome Res 9(4):1976–1984
Bosmans F, Milescu M, Swartz KJ (2011) Palmitoylation influences the function and pharmacology of sodium channels. Proc Natl Acad Sci USA 108(50):20213–20218
Buchner DA, Trudeau M, Meisler MH (2003) SCN1M, a putative RNA splicing factor that modifies disease severity in mice. Science 301(5635):967–969
Cantrell AR, Catterall WA (2001) Neuroumodulation of Na+ channels: an unexpected form of cellular plasticity. Nat Rev Neurosci 2(6):397–407
Catterall WA (2015) Finding channels. J Biol Chem. doi:10.1074/jbc.X115.683383
Cerda O, Baek JH, Trimmer JS (2011) Mining recent brain proteomic databases for ion channel phosphosite nuggets. J Gen Physiol 137(1):3–16
Chen C, Westenbroek RE, Xu X, Edwards CA, Sorenson DR, Chen Y, McEwen DP, O'Malley HA, Bharucha V, Meadows LS, Knudsen GA, Vilaythong A, Noebels JL, Saunders TL, Scheuer T, Shrager P, Catterall WA, Isom LJ (2004) Mice lacking sodium channel beta1 subunits display defects in neuronal excitability, sodium channel expression, and nodal architecture. J Neurosci 24(16):4030–4042
Chen Y, Yu FH, Sharp EM, Beacham D, Scheuer T, Catterall WA (2008) Functional properties and differential neuromodulation of Na(v)1.6 channels. Mol Cell Neurosci 38(4):607–615
Copley RR (2004) Evolutionary convergence of alternative splicing in ion channels. Trends Genet 20(4):171–176
Corbett BF, Leiser SC, Ling HP, Nagy R, Breysse N, Zhang X, Hazra A, Brown JT, Randall AD, Wood A, Pangalos MN, Reinhart PH, Chin J (2013) Sodium channel cleavage is associated with aberrant neuronal activity and cognitive deficits in a mouse model of Alzheimer’s disease. J Neurosci 33(16):7020–7026
Cui JZ, Han ZQ, Li ZY (2012) Modulating protein activity and cellular function by methionine residue oxidation. Amino Acids 43(2):505–517
Dib-Hajj SD, Yang Y, Black JA, Waxman SG (2013) The Na(V)1.7 sodium channel: from molecule to man. Nat Rev Neurosci 14(1):49–62
Dong ZF, Tang LJ, Deng GF, Zeng T, Liu SJ, Wan RP, Liu T, Zhao QH, Yi YH, Liao WP, Long YS (2014) Transcription of the human sodium channel SCN1A gene is repressed by a scaffold- ing protein RACK1. Mol Neurobiol 50(2):438–448
Drews VL, Lieberman AP, Meisler MH (2005) Multiple transcripts of sodium channel SCN8A (Na(V)1.6) with alternative 5′- and 3′-untranslated regions and initial characterization of the SCN8A promoter. Genomics 85(2):245–257
Drews VL, Shi K, de Haan G, Meisler MH (2007) Identification of evolutionarily conserved, functional noncoding elements in the promoter region of the sodium channel gene SCN8A. Mamm Genome 18(10):723–731
Dustrude ET, Wilson SM, Ju W, Xiao Y, Khanna R (2013) CRMP2 protein SUMoylation modulates Na(V)1.7 channel trafficking. J Biol Chem 288(34):24316–24331
Few WP, Scheuer T, Catterall WA (2007) Dopamine modulation of neuronal Na(+)-channels requires binding of A kinase-anchoring
protein 15 and PKA by a modified leucine zipper motif. Proc Natl Acad Sci USA 104(12):5187–5192

Fotia AB, Ekberg J, Adams DJ, Cook DI, Poronnik P, Kumar S (2004) Regulation of neuronal voltage-gated sodium channels by the ubiquitin-protein ligases Nedd4 and Nedd4-2. J Biol Chem 279(28):28930–28935

Gasser A, Cheng X, Gilmore ES, Tyrrell L, Waxman SG, Dib-Hajji SD (2010) Two Nedd4-binding motifs underlie modulation of sodium channel Navi.6 by p38 MAPK. J Biol Chem 285(34):26149–26161

Gehman LT, Meera P, Stoilov P, Shiee L, O’Brien JE, Meisler MH, Ares M Jr, Otis TS, Black DL (2012) The splicing regulator RBfox2 is required for both cerebellar development and mature motor function. Genes Dev 26(5):445–460

Goel P, Manning JA, Kumar S (2015) NEDD4-2 (NEDD4L): the ubiquitin ligase for multiple membrane proteins. Gene 557(1):1–10

Grimm S, Höhn A, Grune T (2012) Oxidative protein damage and the proteasome. Amino Acids 42(1):23–38

Guo A, Gu H, Zhou J, Mulhern D, Wang Y, Lee KA, Yang V, Aguilar M, Kornhauser J, Jia X, Ren J, Beausoleil SA, Silva JC, Vemulpalli V, Bedford MT, Comb MJ (2014) Immunoaffinity enrichment and mass spectrometry analysis of protein methylation. Mol Cell Proteomics 13(1):372–387

Gustafson TA, Cleveinger EC, O’Neill TJ, Yarowsky PJ, Krueger BK (1993) Mutually exclusive exon splicing of type III brain sodium channel alpha subunit RNA generates developmentally regulated isoforms in rat brain. J Biol Chem 268(25):18648–18653

Hallag H, Yang Z, Viswanathan PC, Fukuda K, Shen W, Wang DW, Wells KS, Zhou Y, Ji Y, Murray KT (2006) Quantitation of protein kinase A-mediated trafficking of cardiac sodium channels in living cells. Cardiovasc Res 72(2):250–261

Heinzen EL, Yoon W, Tate SK, Sen A, Wood NW, Sisodiya SM, Goldstein DB (2007) Nova2 interacts with a cis-acting polymorphism to influence the proportions of drug-responsive splice variants of SCN1A. Am J Hum Genet 80(5):876–883

Herren AW, Weber DM, Rigor RR, Margulies KB, Phinney BS, Bers DM (2015) CaMKII phosphorylation of Na(V)1.5: novel in vitro sites identified by mass spectrometry and reduced S516 phosphorylation in human heart failure. J Proteome Res 14(5):2298–2311

Hien YE, Montersino A, Meiser TF, Zhang B, Murray B, Kornhauser JM, Latham V, Skr Hien YE, Montersino A, Castets F, Leterrier C, Filhol O, Vacher H, Herren AW, Weber DM, Rigor RR, Margulies KB, Phinney BS, Bers DM (2012) Oxidative protein damage and the proteasome. Amino Acids 42(1):23–38

Laedermann CJ, Syam N, Pertin M, Decosterd I, Abriel H (2013) β1- and β3-voltage-gated sodium channel subunits modulate cell surface expression and glycosylation of Nav1.7 in HEK293 cells. Front Cell Neurosci 7:137

Le Gal F, Salzmann A, Crespel A, Malafosse A (2011) Replication of association between a SCN1A splice variant and febrile seizures. Epilepsia 52(10):e135–e138

Li M, West JW, Lai Y, Scheuer T, Catterall WA (1992) Functional modulation of brain sodium channels by cAMP-dependent phosphorylation. Neuron 8(6):1151–1159

Li M, West JW, Numann R, Murphy BJ, Scheuer T, Catterall WA (1993) Convergent regulation of sodium channels by protein kinase C and cAMP-dependent protein kinase. Science 261(5172):1439–1442

Li HJ, Wan RP, Tang LJ, Liu SJ, Zhao QH, Gao MM, Yi YH, Liao WP, Sun XF, Long YS (2015) Alteration of Scn3a expression is mediated via CpG methylation and MBD2 in mouse hippocampus during postnatal development and seizure condition. Biochim Biophys Acta 1849(1):1–9

Long YS, Zhao QH, Su T, Cai YL, Zeng Y, Shi YW, Yi YH, Chang HH, Liao WP (2008) Identification of the promoter region and the 5′-untranslated exons of the human voltage-gated sodium channel Nav1.1 gene (SCN1A) and enhancement of gene expression by the 5′-untranslated exons. J Neurosci Res 86(15):3375–3381

Lossin C (2009) A catalog of SCN1A variants. Brain Dev 31(2):114–130

Lu CM, Eichelberger JS, Beckman ML, Schade SD, Brown GB (1998) Isolation of the 5′-flanking region for human brain sodium channel subtype II alpha-subunit. J Mol Neurosci 11(3):179–182

Marionneau C, Abriel H (2015) Regulation of the cardiac Na+ channel Nav1.5 by post-translational modifications. J Mol Cell Cardiol 82:36–47

Marionneau C, Lichit CF, Lindenbaum P, Charpentier F, Nerbomme JM, Townsend RR, Merritt J (2012) Mass spectrometry-based identification of native cardiac Nav1.5 channel α subunit phosphorylation sites. J Proteome Res 11(12):5994–6007

Martin MS, Tang B, Tsai N, Escayg A (2007) Characterization of 5′ untranslated regions of the voltage-gated sodium channels SCN1A, SCN2A, and SCN3A and identification of cis-converged noncoding sequences. Genomics 90(2):225–235

Mercier A, Clément R, Harnois T, Bourmeyster N, Bois P, Chatelier A (2015) Nav1.5 channels can reach the plasma membrane through distinct N-glycosylation states. Biochim Biophys Acta 1850(6):1215–1223
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