pH Modulation of Voltage-Gated Sodium Channels

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Contents

Abstract

Changes in blood and tissue pH accompany physiological and pathophysiological conditions including exercise, cardiac ischemia, ischemic stroke, and cocaine ingestion. These conditions are known to trigger the symptoms of electrical diseases in patients carrying sodium channel mutations. Protons cause a diverse set of changes to sodium channel gating, which generally lead to decreases in the amplitude of the transient sodium current and increases in the fraction of non-inactivating channels that pass persistent currents. These effects are shared with disease-causing mutants in neuronal, skeletal muscle, and cardiac tissue and may be compounded in mutants that impart greater proton sensitivity to sodium channels, suggesting a role of protons in triggering acute symptoms of electrical disease.

In this chapter, we review the mechanisms of proton block of the sodium channel pore and a suggested mode of action by which protons alter channel gating. We discuss the available data on isoform specificity of proton effects and tissue level effects. Finally, we review the role that protons play in disease and our

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own recent studies on proton-sensitizing mutants in cardiac and skeletal muscle sodium channels.

Keywords
Acidosis · Extracellular pH · Ischemia · Proton block · Voltage-gated sodium channel

1 Introduction

The transient sodium current through voltage-gated sodium channels initiates action potentials in neurons, skeletal muscle, and cardiac muscle. Voltage-gated sodium channels are heterotetrameric proteins formed by a single transcript that encodes four 6-transmembrane segment domains. The voltage-sensor is formed by the first four transmembrane segments of each domain and the pore is formed by the 5th and 6th segments as well as the extracellular P-loop connecting them. Any changes to the gating properties of these channels, and consequently the current passed during an action potential, can cause potentially fatal abnormalities in electrical signaling. Both gain-of-function and loss-of-function in sodium channels disrupt electrical signaling. Interestingly, several mutants display both gain- and loss-of-function, leading to multiple disease phenotypes (Webb and Cannon 2008; Makita et al. 2008).

In the primary sodium channel isoforms of the central nervous system, $Na_V1.1$, 1.2, 1.3, and 1.6, gain- and loss-of-function elicit epilepsy syndromes (Estacion et al. 2010; Catterall 2012; Veeramah et al. 2012). These include relatively mild epilepsies, like benign familial neonatal-infantile seizures, and more severe forms, such as Dravet syndrome (Heron et al. 2002; Scalmani et al. 2006; Dravet 2011). In the skeletal muscle sodium channel, $Na_V1.4$, mutants elicit myotonic and paralytic syndromes, causing an inability to relax the muscle or contract the muscle, respectively (Cannon 1996). Long QT syndrome is due to an increase in the fraction of $Na_V1.5$ cardiac sodium channels that fail to inactivate and, consequently, an increased persistent sodium current throughout the action potential plateau that delays repolarization (Wang et al. 1995). Conversely, mutants that decrease peak $Na_V1.5$ sodium current cause Brugada syndrome and other diseases of conduction (Antzelevitch et al. 2005).

Sodium channel mutants are present from birth, but interestingly these diseases can remain symptomless into adulthood. In many of these diseases, symptoms are elicited when patients perform specific activities, including exercise or use of specific drugs (Littmann et al. 2000; Miller et al. 2004; Antzelevitch et al. 2005; García-Borbolla et al. 2007; Ruan et al. 2010; Postema et al. 2011). In fact, similar symptoms and phenotypes to those found in patients with congenital sodium channel mutants can be elicited by changes to the body's internal environment in the absence of a corresponding channel mutant (McClelland et al. 2009; Anselm et al. 2014). Thus, physiological and pathophysiological changes to the body's internal environment may play an important role in triggering electrical diseases. One such change is acidaemia.

There are multiple ways in which acid-base homeostasis is maintained in the human body, including renal, ventilation, and buffering mechanisms. Under normal physiological conditions, the extracellular pH is maintained at approximately 7.4, with the intracellular pH ranging from 7.2 to 7.4. Acidaemia accompanies many physiological and pathophysiological conditions including exercise, cardiac ischemia, and hypoventilation (Hermansen and Osnes 1972; Cobbe and Poole-Wilson 1980; Epstein and Singh 2001). These conditions are known risk factors for neurological, skeletal muscle, and cardiac disorders, particularly in those with channel function compromised by the presence of a mutation (Constantinou et al. 1989; Miller et al. 2004; Di Diego et al. 2005; García-Borbolla et al. 2007; Zhan et al. 2007). During exercise, skeletal muscle tissue pH can drop to pH 6.5 (Hermansen and Osnes 1972). Postmortem measurements show SIDS cases with brain tissue pH below pH 6.5 (Constantinou et al. 1989; Butterworth and Tennant 1989). Cocaine ingestion can decrease arterial pH below pH 6.4 (Hick et al. 1999; Allam and Noble 2001; Ortega-Carnicer et al. 2001). And ischemia can cause cardiac tissue acidaemia to pH 6.0 (Cobbe and Poole-Wilson 1980; Fleet et al. 1985; Yan and Kléber 1992).

During acidaemia, protons directly block the pore of the sodium channel, alter the movement of the voltage-sensors leading to changes in channel activation, fast inactivation, and slow inactivation, and increase the fraction of non-inactivating sodium channels (Fig. 1) (Woodhull 1973; Jones et al. 2011, 2013a). The effects of protons are dependent on the channel variant, with $Na_V1.4$ being relatively resistant to changes in extracellular pH compared to $Na_V1.5$ (Vilin et al. 2012). Furthermore, mutant sodium channels may be more susceptible to changes in pH than wild-type channels, leading to an even greater exacerbation of disease symptoms (Cheng et al. 2011; Peters et al. 2016; Ghovanloo et al. 2017). To date, the effects of protons have

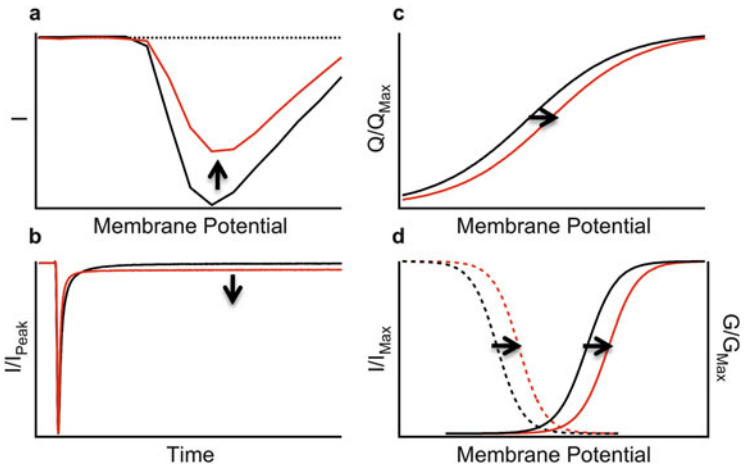

Fig. 1 Lowering extracellular pH reduces peak sodium current amplitude (**a**) and increases the fraction of channels which fail to inactivate and pass a persistent sodium current (**b**). Extracellular protons depolarize the charge-voltage relationship (**c**) as well as the conductance-voltage relationship and steady-state fast inactivation voltage-dependence of cardiac sodium channels (**d**)

not been characterized on all sodium channel variants, nor have all residues which impart proton-sensitivity been identified.

2 Molecular Mechanisms of Proton Block

Based on single channel data from guinea pig cardiomyocytes, protons decrease the conductance of individual channels (Zhang and Siegelbaum 1991). Early experiments on the effects of increasing extracellular protons indicated that proton current block is voltage-dependent based on the observation that proton block is decreased at positive potentials. Thus, Woodhull proposed that protons bind within the channel pore approximately 25% across the distance of the extracellular and intracellular membranes (Woodhull 1973). This was later disputed by Campbell, who suggested that, based on tail current analysis, proton block was independent of membrane potential and the binding site of protons lies outside the electrical field across the membrane (Campbell 1982). It is now known that a multitude of proton binding sites exist including residues in the selectivity filter, the outer charged ring, and residues C373 and H880 in cardiac sodium channels (Sun et al. 1997; Khan et al. 2002, 2006; Jones et al. 2013b).

The sodium channel selectivity filter is formed by a single residue in each of the P-loops in the four domains: D372, E898, K1419, and A1710 (Sun et al. 1997). The permeation rate of sodium is further determined by a series of carboxylate residues, E375, E901, D1423, and D1714, which form the outer charged ring (Terlau et al. 1991). These two motifs are fully conserved across all human voltage-gated sodium channels. Mutation of residues in the selectivity filter or outer charged ring shifts the pKa of proton block to more acidic pH (Sun et al. 1997; Khan et al. 2002). In particular, replacement of the selectivity filter carboxylates with alanines increases the fraction of proton independent sodium current by 25% (Sun et al. 1997). Although protonation of these carboxylates is one of the primary drivers of proton block of sodium channel conductance, proton sensitivity is not fully abolished by replacement of the entire selectivity filter with alanines or by any mutations in the outer charged ring (Sun et al. 1997; Khan et al. 2002). This suggests that other residues in the outer vestibule of the channels may play a role in proton block of sodium channels.

One such residue, which is also important in determining isoform specificity of proton block in sodium channels, is residue C373 in $Na_V1.5$ and its analogous residues Y401 in $Na_V1.4$ and F385 in $Na_V1.2$. In $Na_V1.5$ proton block nears completion at pH 4.0. By contrast, in $Na_V1.4$, 12–17% of the current is resistant to proton block (Khan et al. 2006; Jones et al. 2013b). The C373Y mutant in $Na_V1.5$ imparts a similar fraction of proton resistant current as that in $Na_V1.4$. Conversely, the Y401C mutant in $Na_V1.4$ abolishes the proton insensitive sodium current (Khan et al. 2006).

Given that the pKa of proton block is approximately 6.0, similar to the pKa of histidine, extracellular histidines may also play a role in determining proton block. Our lab previously tested two histidines in the $Na_V1.5$ domain II P-loops: H880Q

and H886Q. H886Q did not produce functional channels. The H880Q mutant, however, imparts proton insensitivity to a fraction of sodium current, similar to that imparted by C373F (Jones et al. 2013b).

3 Proton Modulation of Channel Gating

The effects of acidification on sodium channel gating have been studied best in $Na_V1.5$ and to a lesser extent in $Na_V1.1$, 1.2, and 1.4. As with proton block of conductance, the effects of protons on channel gating are isoform dependent, with $Na_V1.5$ being the most sensitive (Vilin et al. 2012). Results in cardiomyocytes and heterologous expression systems show that extracellular acidification depolarizes the voltage-dependence of activation and fast inactivation in $Na_V1.5$ (Yatani et al. 1984; Vilin et al. 2012; Jones et al. 2013b). Protons also increase the fraction of non-inactivating current in $Na_V1.5$ and decrease the fraction of immobilized charge (Jones et al. 2011, 2013a; Peters et al. 2016). Protons speed recovery from, and slow onset of, fast and slow inactivation in cardiac sodium channels (Jones et al. 2011; Vilin et al. 2012). Interestingly, in heterologous expression systems intracellular acidification does not impact the gating of WT sodium channels, suggesting that protons interact with specific extracellular residues in the channel as opposed to interacting with the cell membrane to induce a charge-screening effect (Cheng et al. 2011; Hu et al. 2015).

Although the residues responsible for all proton-dependent changes in sodium channel gating have not been positively identified, structural studies and data from hERG channels suggest an important role of acidic residues in the voltage-sensing domain. The depolarization and slowed outward gating current movements in sodium channels suggest that protons directly impede the outward movement of the S4 voltage-sensors (Jones et al. 2013a). A depolarization in the movement of the S4 voltage-sensors by extracellular acidification is also seen in hERG channel voltage-sensor fluorescence recordings (Shi et al. 2014). In hERG, the effects of protons can be abolished by mutating a series of acidic residues in the voltage sensing domain: D456 and D460 in S2 and D509 in S3, which are accessible from the extracellular side (Shi et al. 2014). Crystal structures indicate that acidic residues in the voltage-sensing domains of voltage-gated sodium channels are also accessible from the extracellular fluid (Payandeh et al. 2011). Thus, like in hERG, protonation of the carboxylate residues in the voltage-sensing domains may depolarize the outward motion of the four voltage-sensors, which would depolarize the activation and fast inactivation voltage-dependence.

Currently, little is known about proton effects in $Na_V1.1$ with a single study showing only a block of current and depolarization of activation by protons (DeCaen et al. 2014). Interestingly, both $Na_V1.2$ and $Na_V1.4$ display relative insensitivity to protons compared to $Na_V1.5$. As in $Na_V1.5$, the conductance voltage-relationship in $Na_V1.2$ is depolarized by low extracellular pH (Vilin et al. 2012; Peters et al. 2013). Unlike in $Na_V1.5$, $Na_V1.2$ fast inactivation voltage-dependence is not altered by protons; however, the recovery from fast inactivation is faster and onset of fast

inactivation is slower at low extracellular pH (Vilin et al. 2012; Peters et al. 2013). The literature on proton-dependent changes in slow inactivation in $Na_V1.2$ is conflicting, with one report showing an increase in slow inactivation at low pH and another showing a decrease (Vilin et al. 2012; Peters et al. 2013). $Na_V1.4$ activation and fast inactivation are not sensitive to changes in pH, nor is $Na_V1.4$ use-dependent inactivation (Vilin et al. 2012; Ghovanloo et al. 2017). Thus, of the channels studied thus far, $Na_V1.5$ is the most proton-sensitive and $Na_V1.4$ the least.

As with proton-block, residue C373 (Y401 in $Na_V1.4$ and F385 in $Na_V1.2$) plays an important role in determining isoform specificity of proton effects on channel gating. Slow inactivation in sodium channels involves both the voltage-sensing domains and the extracellular P-loops (Vilin et al. 2001; Payandeh et al. 2012; Silva and Goldstein 2013a, b). The C373F mutant abolishes the proton sensitivity of slow inactivation onset and recovery in $Na_V1.5$ (Jones et al. 2013b). C373F also removes the proton sensitivity of use-dependent inactivation in $Na_V1.5$ (Jones et al. 2013b). This suggests that the presence of aromatic acids in these positions in $Na_V1.2$ (F385) and $Na_V1.4$ (Y401) are likely responsible, at least in part, for the different proton effects in these tissues.

Although all the residues responsible for isoform-dependent differences in proton sensitivity are not known, insensitivity may be a particularly important adaptation in $Na_V1.4$. During exercise, arterial blood pH shows relatively small changes. Capillary blood pH, however, may drop by 0.2 units and skeletal muscle tissue pH may drop as low as pH 6.4 (Hermansen and Osnes 1972). Relative insensitivity to changes in pH likely plays an important role in maintaining action potential generation in working muscle (Pedersen et al. 2005).

4 Effects of Protons on Tissues

Heterologous expression and characterization of sodium channels have yielded a wealth of information on the effects of extracellular acidosis; however, in vivo, sodium channels function within multi-protein signaling complexes and associate with various proteins that modify expression and regulate gating, cytoskeletal anchoring, and signaling cascades (Meadows and Isom 2005). Thus, studies in whole tissue preparations are necessary to understand the role proton modulation of sodium plays in altering electrical signals in the body.

In ventricular cardiomyocytes, sodium channels pass a large transient current which causes the initial phase 0 depolarization. Studies in rat and canine ventricular myocytes show a similar proton-induced depolarization of conductance and decrease in peak sodium current as is seen in heterologous expression systems (Yatani et al. 1984; Watson and Gold 1995; Murphy et al. 2011). However, the effects of extracellular protons on fast inactivation differ between these studies. Furthermore, studies in rat ventricular myocytes differ from heterologous expression systems in suggesting that intracellular acidification may affect inactivation voltage-dependence and kinetics (Watson and Gold 1995). The overall effect in ventricular myocytes is a proton-induced decrease in the transient sodium current that is

predicted to decrease the rate of the phase 0 depolarization, which in turn decreases conduction velocity in the heart (Yatani et al. 1984; Kléber et al. 1986; Watson and Gold 1995; Murphy et al. 2011; Jones et al. 2011).

In ventricular myocytes, the persistent sodium current is active throughout the action potential plateau and in part determines the action potential duration (Kiyosue and Arita 1989). Disease or pharmacologically induced increases in the persistent current elongate the action potential while block of the persistent sodium current shortens the action potential (Kiyosue and Arita 1989; Wang et al. 1995; Shimizu and Antzelevitch 1999). In heterologous expression systems, decreases in extracellular pH increases the fraction of sodium channels which fail to inactivate. Thus, although protons lower the overall sodium conductance, the persistent sodium current is relatively well maintained (Jones et al. 2011; Peters et al. 2016). Experiments in ventricular myocytes suggest that persistent sodium currents are either increased by ischemia, or less sensitive than peak sodium current (Murphy et al. 2011; Tang et al. 2012). In conjunction with the block of the rapid delayed rectifier potassium current by extracellular protons, persistent sodium currents likely play a large role in the elongation of the cardiac action potential during ischemia (Fry and Poole-Wilson 1981; Komukai et al. 2002; Murphy et al. 2011; Van Slyke et al. 2012).

Unlike cardiac tissue, a consensus on the effects of protons on neural tissue is complicated by the large variety of neurons. At pH 6.0 isolated rat trigeminal mesencephalic nucleus (Vmes) neurons show a depolarization of the activation and, in contrast to studies in heterologous expression systems, a depolarization of fast inactivation voltage-dependence (Vilin et al. 2012; Peters et al. 2013; Kang et al. 2016). In rat pyramidal neurons, exposure to acidic pH 6.4 resulted in the reduction of peak sodium current, depolarization of the conductance voltage relationship, and no effect on steady-state fast inactivation (Tombaugh and Somjen 1996). In both GABAergic neurons and CA1 hippocampal interneurons, extracellular acidosis reduces spike frequency (Zhan et al. 2007; Huang et al. 2015). In contrast, acidosis stimulates a subset of serotonergic neurons in the medullary raphe that may act as chemosensors (Wang et al. 2001). Overall, these studies show that while the majority of neurons studied are inhibited by extracellular protons, this is not true for all.

$Na_V1.4$ is the least proton-sensitive of the sodium channels studied in heterologous expression systems, which may be an evolutionary adaptation as during exercise the pH of skeletal muscle can decrease considerably (Hermansen and Osnes 1972; Vilin et al. 2012). Skeletal muscle tissue pH studies suggest that protons may compensate for losses of excitability that occur when extracellular potassium is elevated during exercise. This occurs by proton-dependent reductions in the inhibitory chloride currents passed by the ClC-1 channel (Pedersen et al. 2005; Bennetts et al. 2007). The reduction in chloride current increases the skeletal muscle excitability. Authors of one study suggest that the sodium current must be relatively well maintained during extracellular acidification, a theory consistent with the relative pH insensitivity of the $Na_V1.4$ channel (Pedersen et al. 2005; Vilin et al. 2012). Thus in contrast to cardiac muscle and the majority of neurons, skeletal muscle electrical excitability appears to be relatively well maintained in the face of acidaemia.

These studies show that in native tissues and intact tissues, the direct effect of protons may cause complex effects on tissue excitability. While simulations using the data from heterologous expression systems may predict some of these effects, studies in intact tissue are necessary to fully understand the role of protons in human physiology and pathophysiology.

5 Acidosis and Disease

Acidosis may trigger symptoms in sodium channel-based diseases. Increases in extracellular protons may compound with the effects of sodium channel mutants, further compromising function in tissues throughout the body (Peters et al. 2016). Protons may also act to unmask biophysical defects in mutants that function normally at physiological pH (Cheng et al. 2011). Finally, protons may alter the effects of drugs such as, for example, Ranolazine, which is itself protonatable (Peters et al. 2013; Sokolov et al. 2013).

Interestingly, acidaemia may elicit symptoms of diseases normally associated with sodium channel mutants in the absence of underlying mutants in any of the voltage-gated sodium channel genes. Patients with glutaric aciduria type 1, propionic acidaemia, and methylmalonic acidaemia may all present with epilepsy (McClelland et al. 2009; Haberlandt et al. 2009; Ma et al. 2011). One study found that over 40% of patients with methylmalonic acidaemia, a disease caused by mutations in genes involved in amino acid and fat break down, presented with epilepsy (Ma et al. 2011). This phenomenon is not unique to epilepsy; acute acidaemia is implicated in Brugada phenocopy. In Brugada phenocopy, a Brugada syndrome-like electrocardiogram (ECG) is elicited in response to environmental or clinical conditions, and is resolved when the underlying condition is resolved (Baranchuk et al. 2012). The association of acidaemia and Brugada phenocopy is particularly strong with myocardial ischemia and cocaine induced acidaemia known to elicit the characteristic Brugada ECG (Littmann et al. 2000; Ortega-Carnicer et al. 2001; Anselm et al. 2014).

In both epilepsy and Brugada phenocopy, the presence of protons may mimic the effects of mutants. Protons decrease peak sodium current through direct block of channels and depolarization of channel activation (Zhang and Siegelbaum 1991; Jones et al. 2013b). Similarly, the most common causes of Brugada syndrome are mutations in SCN5A, the gene which encodes for $Na_V1.5$, which decrease peak sodium conductance, thereby decreasing conduction velocity and altering action potential morphology (Antzelevitch et al. 2005; Wilde et al. 2010). Although many epilepsies are caused by gain-of-function mutants in sodium channels, one form, the Dravet syndrome, is caused primarily by loss-of-function in $Na_V1.1$ (Yu et al. 2006). It is believed this loss of function decreases activity of GABAergic neurons leading to disinhibition of the brain and an overall increase in excitability. Acidaemia in turn appears to decrease excitability of GABAergic neurons (Li et al. 2011; Huang et al. 2015).

Protons are also known to act in conjunction with mutants, either unmasking biophysical defects, or preferentially effecting those already present. The S1103Y

polymorphism, which increases the risk of SIDS, does not produce significantly different currents at pH 7.4; however, intracellular acidosis elicits a persistent sodium current in S1103Y $Na_V1.5$, not seen in WT (Cheng et al. 2011). Similarly, the S1787N mutant in $Na_V1.5$ when expressed in conjunction with the Q1077del polymorphism produces a small persistent current that is exacerbated by decreasing intracellular protons (Hu et al. 2015). Our lab has since shown that the most common $Na_V1.5$ Brugada syndrome and long QT syndrome mutant, E1784K, is preferentially sensitive to changes in extracellular pH (Peters et al. 2016). Extracellular protons cause larger decreases in peak current and larger increases in the fraction of non-inactivating channels in the E1784K mutant compared to WT (Fig. 2), which represent exacerbation of the biophysical defects seen in Brugada syndrome and LQT3, respectively.

Preferential effects of acidosis may not be limited to cardiac sodium channels. Our lab recently studied P1158S in $Na_V1.4$, a channel mutant associated with both periodic paralysis and myotonia congenita (Webb and Cannon 2008). P1158 is a fully conserved residue located on the S4-S5 linker of DIII in $Na_V1.4$. In addition to myotonia and periodic paralysis, the mutation of this proline to leucine (P1308L) in $Na_V1.7$ also causes inherited erythromelalgia (Cheng et al. 2010).

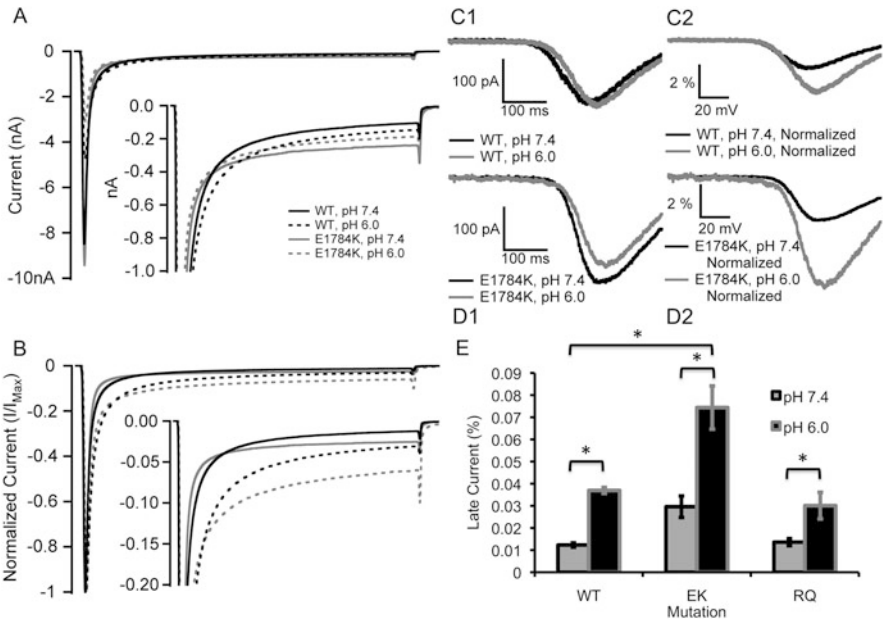

Fig. 2 Absolute (**a**) and normalized to peak (**b**) persistent current traces from wild type and E1784K $Na_V1.5$ channels at pH 7.4 and at pH 6.0. Insets show these persistent currents on a larger scale. Absolute (**c1** and **d1**) and normalized to peak (**c2** and **d2**) ramp current traces in wild type (**c**) and E1784K (**d**) $Na_V1.5$. The average percentage of persistent sodium current for wild type, R1193Q, and E1784K $Na_V1.5$ at pH 7.4 and pH 6.0 (**e**). Reprinted from Peters et al. (2016), with permission from Elsevier

We showed that the mutation of the "helix-breaker" proline to serine in the DIII S4-S5 imparts proton sensitivity to $Na_V1.4$. Action potential modeling suggests that, as proton concentrations are changed, AP morphology may shift from a periodic paralysis phenotype at physiological or alkalotic pH to a myotonia phenotype during acidosis (Ghovanloo et al. 2017).

6 Conclusion

Changes in proton concentration are associated with a wide range of physiological and pathophysiological conditions including exercise, sleep apnea, cardiac ischemia, stroke, metabolic diseases, and drug use. Protons block the pore of sodium channels and alter voltage-sensor movement to change channel gating. Protons decrease the peak sodium current while increasing the fraction of non-inactivating channels. The effects of protons can be measured at all levels of function, from single-channel recordings to electroencephalogram and electrocardiogram recordings. Protons act on both mutant and WT sodium channels and may trigger symptoms in those with congenital disease or elicit symptoms like those of the congenital disease in otherwise healthy patients. Sodium channels are not unique in this regard, as protons are known to alter the properties of both calcium and potassium channels. Thus, protons have a physiological impact whose effects are seen throughout the electrical systems of the body and whose actions alter cellular function and disease. Future studies will integrate these different effects and lead to a greater understanding of the physiological and pathophysiological roles of protons at the molecular, cellular, and tissue levels.

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