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The axon initial segment in nervous system disease and injury

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Abstract

The axon initial segment (AIS), with its dense clusters of voltage-gated ion channels decorating the axonal membrane, regulates action potential initiation and modulation. The AIS also functions as a barrier to maintain axodendritic polarity, and its precise axonal location contributes to the fine-tuning of neuronal excitability. Therefore, it is not surprising that mutations in AIS-related genes, disruption of the molecular organization of the AIS and altered AIS ion channel expression, function, location and/or density are emerging as key players in neurological disorders. Here, we consider the role of the AIS in nervous system disease and injury.

Keywords

action potential; axon initial segment; disease; ion channel

Introduction

Neurons are highly polarized cells with multiple distinct membrane domains. The subcellular localization and molecular compositions of these domains are essential to their functions. For example, dendritic synapses are highly enriched in neurotransmitter receptors that respond to pre-synaptic input. The axon initial segment (AIS) is another unique domain with high densities of ion channels that integrates the input from thousands of synapses to generate an action potential (AP). The AP is directionally propagated along the axon toward the axonal terminal where, at chemical synapses, neuronal output is mediated by the release of neurotransmitter. Therefore, the AIS functions at the intersection between neuronal input and axonal output. Given the importance of the AIS for a neuron's input–output relationship, it is easy to understand how perturbations of AIS organization or integrity can have profound effects on nervous system function.

Several genes encoding proteins found at the AIS are emerging as risk factors for neurological diseases (Scheffer *et al.*, 2007; Alarcón *et al.*, 2008; Arking *et al.*, 2008; Williams *et al.*, 2011). Furthermore, calpain-mediated disassembly of the AIS cytoskeleton was recently identified as an early consequence of ischemia-induced neuronal injury (Schafer *et al.*, 2009). Here, we provide a brief overview of the function and molecular organization of the AIS, and its role in maintaining neuronal polarity. We also discuss recent work demonstrating AIS plasticity in response to activity deprivation during nervous system development. We then consider how diseases including channelopathies, developmental neuropsychiatric conditions like autism and schizophrenia, and autoimmune disorders could impact AIS function. Finally, we speculate how AIS integrity could be compromised during aging and how these insults may contribute to cognitive decline.

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Role of the axon initial segment

The AIS is a specialized membrane domain situated in the proximal axon. The protein complex assembled at the AIS is characterized by a high density of voltage-gated ion channels, cytoskeletal adaptor proteins and cell adhesion molecules (CAMs) (Grubb & Burrone, 2010a) (Fig. 1). Many of the AIS proteins implicated in human disease directly contribute to its two central functions – controlling the initiation of APs and maintaining neuronal polarity (Fig. 2).

The site of action potential initiation

Early intracellular recordings in motor neurons identified the AIS as the spike initiation zone (Coombs *et al.*, 1957). In these studies, AIS spike activity always preceded, at a predictable interval, the generation of a somatodendritic spike element. This finding was attributed to the special electrical properties of the AIS associated with its more hyperpolarized AP threshold potential relative to the somatodendritic domain (Coombs *et al.*, 1957). In 1981, autoradiographic experiments using an Na_v channel-binding neurotoxin (^{125}I-scorpion toxin) revealed a non-uniform distribution of Na_v channels in neurons with the highest densities observed at the AIS (Catterall, 1981). Elevated Na_v channel density alone, based on the statistical probability of channel opening and the fraction of channels needed to elicit the all-or-none response, could explain the reduced AP threshold at the AIS relative to the soma. Several studies support the conclusion that the AIS is the site of AP initiation in a variety of central nervous system neuron types (Stuart & Sakmann, 1994; Mainen *et al.*, 1995; Khaliq & Raman, 2006; Palmer & Stuart, 2006; Atherton *et al.*, 2008; Kole *et al.*, 2008; Kole & Stuart, 2008; Foust *et al.*, 2010; Popovic *et al.*, 2011). Nevertheless, the precise Na_v channel density at the AIS remains controversial (Colbert & Johnston, 1996; Kole *et al.*, 2008; Fleidervish *et al.*, 2010; Lorincz & Nusser, 2010).

At one extreme, patch-clamp studies revealed no difference in Na_v channel density between the AIS and the somatodendritic domain (Colbert & Johnston, 1996). Consistent with this idea, Fleidervish *et al.* (2010) recently reported high-resolution Na^+ imaging data supporting a mere threefold increase in Na_v channel density at the AIS. Instead of Na_v channel density setting the low AP threshold at the AIS, the authors suggest that Na_v channel gating kinetics may differ here and claim that channel density estimates based on immunofluorescent labeling may be misleading due to the detection of a non-functional pool of channels. However, it is difficult to imagine mechanisms that lead to a non-functional pool of channels on the cell membrane. In contrast to these observations, measurement of Na_v channel density using freeze-fracture immunogold electron microscopy (Lorincz & Nusser, 2010), immunofluorescent labeling (Wollner & Catterall, 1986) and patch-clamp recording following depolymerization of the actin-based cytoskeleton (Kole *et al.*, 2008) revealed an AIS Na_v channel density 50-fold that of the soma and proximal dendrites.

It is likely that both channel density and specialized gating kinetics contribute to the low AP threshold at the AIS. Active regulation of either property provides a plausible mechanism for altering neuronal excitability in an activity-dependent manner. Post-translational modification of AIS Na_v channels (e.g. phosphorylation) could change the local AP threshold by altering open channel probability (Cantrell & Catterall, 2001; Baek *et al.*, 2011). If a non-functional pool of channels exists, dysregulation of the balance between functional and non-functional Na_v channel populations may contribute to the pathogenesis of certain epilepsies and developmental disorders as well as hyperexcitability following injury.

Overview of the molecular organization of the axon initial segment

The AIS consists of densely clustered voltage-gated ion channels supported by a specialized cytoskeletal scaffold. However, structural and molecular diversity can be seen among neuron classes. For example, differences in ion channel composition (Nusser, 2009) and synaptic innervation of the AIS (DeFelipe *et al.*, 1985; Huang *et al.*, 2007) contribute to the functional diversity of neurons. Even neurons responding to similar stimuli can strategically alter the axonal location of their AIS (Kuba *et al.*, 2006; Fried *et al.*, 2009). Additional examples of differences at the AIS among neuronal populations are discussed at greater length below.

Ion channel localization at the axon initial segment

Action potential generation depends on the density, availability and biophysical properties of Na_v and K_v channels (Bean, 2007). The distribution of these channels within the AIS and ion channel gene expression patterns underlie the variety of AP shapes observed between neuron classes (Lai & Jan, 2006; Bean, 2007; Nusser, 2009).

Sodium channels are recruited to the AIS through direct interaction with the cytoskeletal scaffolding protein ankyrin-G (ankG) (Zhou *et al.*, 1998; Garrido *et al.*, 2003; Lemaillet *et al.*, 2003) and are further promoted by casein kinase 2-mediated phosphorylation of two serine residues in the AIS-targeting motif (Garrido *et al.*, 2003) of Na_v channels (Bréchet *et al.*, 2008). A subset of K_v channels are also enriched at the AIS through interaction with ankG (Pan *et al.*, 2006). Channel distribution within the AIS can be further divided into proximal and distal subcompartments (Van Wart & Matthews, 2006a; Hu *et al.*, 2009). Modeling analyses performed by Hu *et al.* (2009) suggest that the dense clusters of $Na_v1.6$ channels at the distal AIS contribute to AP initiation, whereas proximal $Na_v1.2$ clusters regulate AP backpropagation to the soma and dendrites. Although $Na_v1.6$ is expressed in almost all central nervous system neuron types, it tends to be co-expressed with $Na_v1.1$ in inhibitory GABAergic neurons but with $Na_v1.2$ in excitatory glutamatergic neurons (Lorincz & Nusser, 2008).

Temporal control of channel expression is also thought to be important. For example, during early development, $Na_v1.2$ channel expression precedes that of $Na_v1.6$ in retinal ganglion cells (Van Wart & Matthews, 2006a). This is reflected in the observation that $Na_v1.2$ channels are the first Na_v channels enriched at the developing retinal ganglion cell AIS. $Na_v1.6$ channels cluster at later time points, just prior to eye opening between post-natal weeks 2 and 3 (Boiko *et al.*, 2003). This developmental switch is thought to be required for the generation of high-frequency AP trains that encode visual information (Wang *et al.*, 1997; Boiko *et al.*, 2003). Indeed, in mice lacking $Na_v1.6$, $Na_v1.1$ and $Na_v1.2$ channels are present at the retinal ganglion cell AIS and the $Na_v1.6$-deficient retinal ganglion cells can no longer sustain high-frequency bursts (Van Wart & Matthews, 2006b). Thus, maturation of the AIS protein complex is important for proper neuronal output.

Multiple K_v channels, including K_v1 and K_v7 subtypes, are enriched at the AIS of diverse central nervous system neurons (Kole *et al.*, 2007; Pan *et al.*, 2006). Similar to the subcompartmental arrangement of Na_v channels, the precise distribution of K_v channels within the AIS probably contributes to the diversity of AP shape and firing rates observed between neuron classes. For example, $K_v1.1$ and $K_v1.2$ immunoreactivity gradually increases toward the distal part of the AIS in cortical and hippocampal pyramidal cells, and may even extend distally beyond the $Na_v1.6$ channels in neocortical interneurons (Lorincz & Nusser, 2008). K_v1 channels carry low voltage-activated outward currents that can depolarize the AP threshold potential, making cells less excitable (Lu *et al.*, 2004). Interestingly, Kv1.1 and Kv1.2 are not expressed at detectable levels at the cerebellar

Purkinje neuron AIS, although they are enriched in the surrounding basket cell terminals and at the cerebellar interneuron AIS (Lorincz & Nusser, 2008). Although K_v1 channels are enriched at the juxtaparanode of myelinated axons through interactions with the CAM contactin-associated protein 2 (caspr2), K_v1 channel clustering at the AIS does not require caspr2 (Horresh *et al.*, 2008; Ogawa *et al.*, 2008, 2010). Intriguingly, the phosphorylation state of the auxiliary subunit $K_v\beta2$ determines the AIS targeting of K_v1 channels (Vacher *et al.*, 2011). However, with no ankG-binding capacity, the mechanism(s) of K_v1 channel localization and stabilization at the AIS remains an active area of investigation. In contrast to Kv1 channels, AIS clustering of the K_v7 channels KCNQ2 and KCNQ3 is mediated through an ankG-binding motif analogous to the Na_v1 channel AIS targeting motif (Pan *et al.*, 2006), a similarity that is a striking example of convergent molecular evolution (Hill *et al.*, 2008). K_v7 channels at the AIS carry a non-inactivating, subthreshold K^+ current (M current) and act as key regulators of neuronal excitability by controlling the resting membrane and AP threshold potentials (Shah *et al.*, 2008; Guan *et al.*, 2011).

$GABA_A$-$\alpha2$ receptors are enriched along the distal AIS of cortical and hippocampal pyramidal neurons. Classically, chandelier neurons, GABAergic interneurons that exclusively synapse onto the AIS, were thought to negatively regulate AP initiation in the cortex; however, GABA release leading to depolarization of the post-synaptic cell has been reported (Szabadics *et al.*, 2006; Khirug *et al.*, 2008; Molnár *et al.*, 2009). Thus, although GABA neurotransmission at the AIS is inhibitory in the hippocampus (Glickfeld *et al.*, 2009), it may be excitatory in the neocortex (Szabadics *et al.*, 2006; Khirug *et al.*, 2008; Woodruff *et al.*, 2009).

Ankyrin-G-organized assembly of the axon initial segment

In vivo and *in vitro* experiments suggest that ankG is the first region-defining protein to become concentrated at the AIS and is required for all subsequent protein enrichment here during development and throughout life (Jenkins & Bennett, 2001; Hedstrom *et al.*, 2008; Sobotzik *et al.*, 2009). The relationship between ankG and the specialized microtubule (MT) network at the AIS is the subject of several current studies. Recent work shows that some MT-related proteins, such as casein kinase 2, contribute to ankG stabilization within the proximal axon during early AIS development (Sanchez-Ponce *et al.*, 2008; Sanchez-Ponce *et al.*, 2011). The AIS MTs themselves, existing mostly in an acetylated-form, are highly stable; in contrast, MTs in the distal axon are in a dynamic, deacetylated (mediated by histone deacetylase-6) state during axon outgrowth (Tapia *et al.*, 2010). This differential post-translational modification of tubulin between the proximal and distal axon is necessary for the establishment of functional neuronal polarity (Tapia *et al.*, 2010). Interestingly, although the AIS cytoskeleton is typified by fasciculated MT bundles (Palay *et al.*, 1968), these bundles are conspicuously absent from the Purkinje neuron AIS in a cerebellum-specific ankG knockout mouse (Sobotzik *et al.*, 2009), suggesting a cooperative link between ankG enrichment and the post-translational modification of MTs within the proximal axon.

The local actin-based cytoskeleton also contributes to AIS function. βIV spectrin, an actin-binding cytoskeletal protein, is recruited to the AIS through interaction with ankG (Yang *et al.*, 2007). This interaction is thought to link ankG to the local actin-based cytoskeleton. In βIV spectrin mutant mice, $Na_v1.6$ immunoreactivity is reduced at the AIS (Yang *et al.*, 2007). The AIS cytoskeleton is linked to the extracellular matrix through the CAM neurofascin-186 (Nfasc186) (Hedstrom *et al.*, 2007). AIS assembly is normal in the absence of Nfasc186 expression *in vitro* and *in vivo*; however, Nfasc186 is required for the long-term maintenance and function of the AIS (Hedstrom *et al.*, 2008; Zonta *et al.*, 2011), and for the assembly of the brevican-based extracellular matrix at the AIS (Hedstrom *et al.*, 2007).

The axon initial segment as a post-synaptic domain

Synaptic connections where the AIS is the post-synaptic domain are termed 'axo-axonic' synapses (Fig. 1C) (Fairen & Valverde, 1980; Huang *et al.*, 2007). These inputs are strategically positioned to modulate synaptic integration and AP initiation. Axo-axonic synapse assembly is thought to be experience-independent and to depend on the expression of transmembrane CAMs (Di Cristo *et al.*, 2004). Nfasc186 has been suggested to play an important role in regulating the assembly of GABAergic synapses. For example, Pinceau synapse formation at the Purkinje neuron AIS follows the establishment of an ankG-dependent, distally-increasing Nfasc186 gradient along the AIS (Ango *et al.*, 2004). Similarly, in hippocampal pyramidal neurons, loss of the Nfasc186 gradient disrupts localization of gephyrin, a scaffolding protein at inhibitory synapses, and interferes with GABA receptor clustering at the post-synaptic membrane (Burkarth *et al.*, 2007). However, work by Koticha *et al.* (2005) shows that the mucin-like domain of Nfasc186 inhibits cell adhesion. Investigation into axo-axonic synapse formation in newly available Nfasc186 conditional knockout mouse lines (Zonta *et al.*, 2011) may help to clarify the role of transmembrane CAMs in axo-axonic synapse assembly.

Neuronal polarity and axon initial segment stability

Maintaining neuronal polarity

The AIS maintains the electrical and physical separation of the axon from the somatodendritic domain by functioning as a 'selectivity filter' to permit axonal cargoes to enter the axon while excluding somatodendritic cargoes (Winckler *et al.*, 1999; Song *et al.*, 2009; Rasband, 2010). Polarized transport of axonal cargoes through the AIS is thought to be facilitated by the unique properties of the local MT cytoskeleton. Nakata & Hirokawa (2003) reported that the kinesin KIF5 associates with axonal-membrane-bound cargoes; however, neuron-wide MT stabilization prevents KIF5 from distinguishing between dendritic shafts and the AIS, resulting in mislocalization of the targeted proteins. Variable post-translational modification of tubulin also aids in the targeted delivery of cargoes; by virtue of its inability to bind tyrosinated tubulin, the kinesin-1 motor domain is limited to proceeding through the AIS to deliver axonal membrane components (Konishi & Setou, 2009). The maintenance of axodendritic polarity also depends, directly or indirectly, on ankG. Silencing ankG after AIS formation results in the dispersion of the ion channels, CAMs and other cytoskeletal proteins enriched at the AIS (Hedstrom *et al.*, 2008). Without the selectivity filter established by the AIS cytoskeleton, dendritic proteins can enter the axon leading to the acquisition of both molecular and structural features of dendrites, including spines. These results were confirmed *in vivo* using a cerebellum-specific ankG knockout mouse (Zhou *et al.*, 1998; Sobotzik *et al.*, 2009).

Neurofascin-186 also plays a critical role in maintaining polarity (Zonta *et al.*, 2011), at least in cerebellar Purkinje neurons. Using an inducible Cre to silence the expression of Nfasc186 in mature neurons, as soon as 1 week after silencing Nfasc186 expression, Na_v channels, along with ankG, βIV spectrin and neuron glia-related CAM, were completely lost from the Purkinje neuron AIS. As a consequence, the AP amplitude decreased, spontaneous firing all but ceased and the mice displayed motor deficits. These results are consistent with the idea that maintenance of neuronal polarity depends on the integrity of the AIS; however, no information was provided about the stability of the AIS of other neuron types. Silencing of NF-186 expression *in vitro* did not affect the molecular organization of the AIS in cultured hippocampal neurons (Hedstrom *et al.*, 2008). It is possible that Purkinje neurons are especially sensitive to alterations in AIS function, due to their unique physiology, and axons themselves may be damaged or degenerating in this model. It will be important to look at

other classes of neurons in the inducible Nfasc186 knockout mouse to establish whether the importance of Nfasc186 extends across neurons of all types.

Axon initial segment plasticity

Activity-dependent changes are the hallmark of neuronal plasticity. Long-term memory formation, facilitated by synaptic plasticity, involves dynamic restructuring of synapses supported by proteolysis (Bingol & Sheng, 2011), new protein synthesis (Klann & Sweatt, 2008) and cytoskeletal rearrangements (Kasai *et al.*, 2010). Over 40 years ago, Palay *et al.* (1968) postulated that structural changes in AIS shape could be a mechanism for exercising dynamic control over neuronal excitability. Local proteolysis and the incorporation of newly synthesized AIS proteins could also contribute to structural plasticity at the AIS.

Homeostatic axon initial segment plasticity

One way in which neurons fine-tune their excitability is by controlling the position and length of the AIS (Kuba *et al.*, 2006; Grubb & Burrone, 2010b; Kuba *et al.*, 2010). For example, neurons in the avian nucleus laminaris can be divided into three groups based on the range of critical frequencies that they respond to – low, medium or high (Kuba *et al.*, 2006). AIS length and localization along the axon within the same group of neurons are relatively uniform, but differ substantially between groups. Modeling analysis showed that AIS length and axonal location were optimized to reduce the AP threshold and accurately encode the interaural time differences at each critical frequency (Kuba *et al.*, 2006). Information processing can therefore be regulated at the level of AIS morphology.

Recently, it was shown that neurons can modify the structure and/or axonal location of the AIS in response to changes in activity levels (Grubb & Burrone, 2010b; Kuba *et al.*, 2010). For example, chronic depolarization of cultured hippocampal neurons leads to a distal shift in AIS position along the axon and reduced excitability (Grubb & Burrone, 2010b). Although voltage-gated Ca^{2+} channel blockers completely abolish AIS relocation during chronic depolarization (Grubb & Burrone, 2010b), little is known about how axonal translocation of the AIS occurs and whether this phenomenon occurs *in vivo*. Thus, it will be interesting to examine AIS length and axonal position in neurons that are chronically depolarized by disease or injury, or to determine if AIS plasticity also occurs in the normal brain.

Neurons can also change their AIS properties in response to decreases in synaptic input. For example, in response to loss of cochlear afferent innervation, neurons in the nucleus magnocellularis of birds increase their AIS length (Kuba *et al.*, 2010). Recordings revealed a compensatory increase in the intrinsic excitability of the input-deprived cells. Thus, sensory deprivation during critical periods of development initiates adaptive mechanisms to stabilize neuronal output (Kuba *et al.*, 2010). This phenomenon is qualitatively similar to homeostatic synaptic plasticity (Turrigiano & Nelson, 2004). Injuries or diseases that affect this adaptive response at the AIS may prevent proper integration of synaptic inputs. Furthermore, altered AIS plasticity following injury could also prove maladaptive and actually exacerbate pre-existing pathological conditions (Offord & Catterall, 1989; Waxman, 2001). Studies in animal disease models with abnormal network activity should improve our understanding of the molecular mechanisms underlying homeostatic AIS plasticity in adaptive compensation.

Ion channel expression and axon initial segment plasticity

Action potential firing properties are also controlled by the temporal regulation of ion channel expression. For example, $Na_v1.6$ channels are present at the mature cerebellar granule cell AIS but absent from the developing granule cell AIS. Studies in $Na_v1.6$ knockout mice revealed that the transition to an $Na_v1.6$-dominated granule cell AIS drives

an increase in persistent Na^+ current and improves firing reliability during sustained depolarization (Osorio *et al.*, 2010). It is possible that some nervous system insults could induce a reversion to early developmental expression patterns that would alter AIS composition and, consequently, neuronal excitability. The reversion in Na^+ channel subtype expression has previously been observed after demyelination (Rasband *et al.*, 2003; Craner *et al.*, 2004). Presumably, changes in the types of channels expressed in axons would involve the control of AIS protein component expression, particularly ion channels or the cytoskeletal scaffolds that regulate their retention at the AIS; however, little is known about the transcriptional and translational events that lead to changes in ion channel expression (Waxman, 2001).

Axon initial segment channelopathies

Action potential properties are defined by the coordinated activity of the voltage-gated ion channels at the AIS (Bean, 2007 and Nusser, 2009); consequently, changes in channel kinetics can have a profound impact on neuronal output. In some cases, widespread alteration in neuronal properties can even be attributed to single nucleotide polymorphisms (Wallace *et al.*, 1998). Several genes encoding AIS channels and channel auxiliary subunits are associated with human epilepsy, leading to the suggestion that the AIS may be a site of functional convergence in the pathogenesis of epilepsy (Wimmer *et al.*, 2010a).

Axon initial segment Na_v channels in epilepsy

Voltage-gated sodium channels consist of a single pore-forming α subunit and two auxiliary β subunits. Mutations in both α and β Na_v channel subunits enriched at the AIS can cause hyperexcitability and seizure activity. $Na_v1.1$ channels are enriched at the AIS of GABAergic interneurons (Ogiwara *et al.*, 2007; Duflocq *et al.*, 2008; Lorincz & Nusser, 2008; Wimmer *et al.*, 2010b). Loss of functional $Na_v1.1$ is associated with an early-onset form of epilepsy known as Dravet syndrome or severe myoclonic epilepsy in infancy (Oakley *et al.*, 2011). Experiments performed on severe myoclonic epilepsy in infancy model mice (*Scn1a*$^{-/-}$) revealed a substantial loss of Na^+ current and an increase in AP firing failures in GABAergic hippocampal interneurons (Yu *et al.*, 2006; Kalume *et al.*, 2007). Without any accompanying decrease in excitatory hippocampal pyramidal neuron activity, the loss of inhibitory control by GABAergic interneurons may underlie hyperactivity and seizure generation in severe myoclonic epilepsy in infancy (Yu *et al.*, 2006; Oakley *et al.*, 2011). Mutations that cause only mild functional impairment of $Na_v1.1$ are associated with less severe forms of epilepsy in the genetic epilepsy with febrile seizures plus spectrum (Mashimo *et al.*, 2010). A missense mutation affecting the voltage-sensing domain of $Na_v1.2$ also causes Dravet syndrome (Shi *et al.*, 2009).

The $Na_v1.6$ channels underlie AP generation in several neuron types (Royeck *et al.*, 2008; Hu *et al.*, 2009). Hippocampal CA3 pyramidal neurons respond to weak repetitive stimulation by increasing their $Na_v1.6$ mRNA and protein levels (Blumenfeld *et al.*, 2009). In this case, activity-dependent facilitation mediated by changes in $Na_v1.6$ expression contributes to hyperexcitability and presumably epileptogenesis. Consistent with this idea, decreasing $Na_v1.6$ expression in *Scn1a* mutants reduces seizure susceptibility by restoring threshold potential (Martin *et al.*, 2007). These results suggest that channel subtype-specific changes in channel expression differentially affect network activity levels and that normal nervous system function depends on balanced Na_v channel activity.

Auxiliary Na_v channel β subunits are also enriched at the AIS and function in cell adhesion, α subunit gating and α subunit trafficking (Isom *et al.*, 1992; Malhotra *et al.*, 2000; Brackenbury *et al.*, 2010; Patino & Isom, 2010). Similar to $Na_v1.1$, mutations in the gene encoding the Na_v channel subunit $\beta1$, *SCN1B*, cause Dravet syndrome and genetic epilepsy

with febrile seizures plus (Wallace *et al.*, 1998; Meadows *et al.*, 2002; Patino *et al.*, 2009). The regulatory role of the β subunits makes them a particularly intriguing target for antiepileptic therapies as the different β subunits can have distinct effects on Na_v channel kinetics depending on the cell type in which they are expressed (Brackenbury *et al.*, 2010).

Axon initial segment K_v channels in epilepsy

The influx of K^+ through slowly activating K_v channels dampens excitability following membrane depolarization and returns the neuron to the resting membrane potential. Aberrant K_v channel activity at the AIS could lead to alterations in the shape of the AP waveform and changes in intrinsic membrane properties. Genetic loci containing AIS K_v channel genes (KCNQ2 and KCNQ3) have been identified as risk regions for benign familial neonatal seizures in humans (Leppert *et al.*, 1989; Lewis & Faber, 1993; Browne *et al.*, 1994; Biervert *et al.*, 1998; Charlier *et al.*, 1998; Singh *et al.*, 1998, 2003).

It is important to note that channelopathies are not limited to mutations in the channels themselves; alterations in the trafficking, localization, stabilization and/or expression of ion channels may also result in pathological states. Furthermore, dysfunction of K_v or Na_v channels specifically at the AIS has yet to be causally linked to seizure induction. As there are low densities of these channels located in somatodendritic regions, it is also possible that channel dysfunction in the soma, dendrites or distal axons also contributes to epilepsy. However, recent sequencing efforts have revealed that even deleterious ion channel mutations do not necessarily translate into a pathologic state. Instead, the high degree of variability in manifestation of epilepsy (or lack thereof) depends on the combined activities of multiple mutant ion channels (Klassen *et al.*, 2011).

The axon initial segment in neuropsychiatric developmental disorders

Several AIS protein-encoding genes have been identified as risk factors for neuropsychiatric developmental disorders in multiple genome-wide association studies (Abrahams *et al.*, 2007; Alarcón *et al.*, 2008; Arking *et al.*, 2008; Ferreira *et al.*, 2008; Schulze *et al.*, 2009; Athanasiu *et al.*, 2010). Some of these loci are even emerging as common risk factors in conditions previously considered unrelated (Ferreira *et al.*, 2008; Burbach & van der Zwaag, 2009; Schulze *et al.*, 2009). Much of the work to identify the molecular basis of neuropsychiatric developmental disorders focuses exclusively on synaptopathies; however, evidence is now accumulating that the aberrant organization and function of the AIS may also contribute to the pathophysiology of neuropsychiatric diseases.

The contribution of the axon initial segment to working memory: implications in schizophrenia and bipolar disorder

Cognitive dysfunction in patients with schizophrenia has been attributed to altered cortical network activity (Van Snellenberg *et al.*, 2006). Schizophrenia and bipolar disorder are both thought to arise in part due to deficits in working memory (Raghavachari *et al.*, 2001; Altshuler *et al.*, 2004; Seidman *et al.*, 2002). Recent evidence suggests that some dysfunction may be due to aberrant axo-axonic synaptic activity at the AIS (Cruz *et al.*, 2009; Lewis, 2011). Early efforts to determine the molecular bases of schizophrenia identified a disruption in GABAergic circuitry (Bird *et al.*, 1978; Simpson *et al.*, 1989; Lewis *et al.*, 2005). Further studies revealed that a specific class of interneurons is particularly affected in schizophrenia – the parvalbumin-expressing chandelier cells that form axo-axonic synaptic connections exclusively onto the AIS of cortical pyramidal neurons (Lewis, 2011) (Fig. 1C). Post-mortem analysis of schizophrenic human brain tissue revealed abnormal axo-axonic synapse composition in layers II/III of the dorso-lateral prefrontal cortex (Cruz *et al.*, 2009). Specifically, $GABA_A$ receptor $\alpha 2$ subunit

immunoreactivity is increased at the post-synaptic AIS membrane of patients with schizophrenia (Volk *et al.*, 2002). This upregulation may be compensatory in response to decreased GABA release from apposed pre-synaptic terminals. Interestingly, and somewhat paradoxically (considering the increase in $GABA_A$-$\alpha 2$ receptor at the AIS membrane), ankG immunoreactivity is decreased at the schizophrenic AIS in the dorso-lateral prefrontal cortex. Presumably, decreases in ankG correspond to concomitant decreases in Na_v channel density at the AIS membrane and changes in neuronal excitability; however, this has not been explored experimentally. Decreases in Na_v channel availability at the AIS would be expected to impair AP initiation. This could interfere with the generation of normal cortical network oscillations and working memory (Wang, 2010). Thus, the interneuron-mediated regulation of AP generation at the cortical pyramidal neuron AIS may be a point of convergence between single-cell activity and whole network synchronization.

Schizophrenia and bipolar disorder share ANK3, the gene encoding ankG, as a common genetic risk factor (Ferreira *et al.*, 2008; Schulze *et al.*, 2009; Athanasiu *et al.*, 2010). However, nothing is known about changes that occur at the AIS in patients with bipolar disorder. It may be interesting to analyze axo-axonic synapse organization in postmortem human bipolar disorder tissue and AIS function in mouse models of bipolar disorder.

Autism spectrum disorders and the axon initial segment

Autism spectrum disorders are characterized by cognitive dysfunction of variable severity. Several hundred genes have been identified as autism spectrum disorder risk factors and the majority of these code for synaptic proteins and proteins involved in regulating synaptic plasticity (Bourgeron, 2009; Boda *et al.*, 2010). However, the gene encoding caspr2 (*CNTNAP2*) was recently identified as a genetic susceptibility factor in patients with autism (Alarcón *et al.*, 2008; Arking *et al.*, 2008; Bakkaloglu *et al.*, 2008; Rossi *et al.*, 2008). Interestingly, *CNTNAP2* is one of several autism spectrum disorder-linked genes that is also a genetic risk factor for schizophrenia, and mutations in caspr2 have also been shown to cause epilepsy (Friedman *et al.*, 2008; International Schizophrenia Consortium, 2008; Burbach & van der Zwaag, 2009; Strauss *et al.*, 2006). Caspr2 is enriched within the distal AIS of cortical pyramidal neurons and along myelinated axons at juxtaparanodes flanking nodes of Ranvier (Inda *et al.*, 2006; Ogawa *et al.*, 2008). At the juxtaparanode, caspr2 is required for K_v channel localization and regulates axoglial interactions (Poliak *et al.*, 2003). However, K_v channels accumulate at the AIS independently of caspr2 in *CNTNAP2* knockouts (Ogawa *et al.*, 2008). It is possible that caspr2 regulates the subcompartmental distribution of K_v channels within the AIS, strategically enriching them within the distal portion where GABAergic terminals make synaptic connections (Inda *et al.*, 2006). Changes in K_v channel distribution within the AIS could modify the generation of both the forward- and backward-propagating AP. Thus, the haploinsufficiency and single nucleotide polymorphisms in *CNTNAP2* implicated in schizophrenia and autism, respectively, may result in AIS dysfunction that contributes to the pathology of these disorders.

We speculate that primary genetic insults that impair synaptic formation, function and plasticity in autism spectrum disorder may drive secondary changes at the AIS. As described above, prolonged changes in neuronal activity can alter Na_v channel expression and AIS channel density (Waxman, 2001; Kuba *et al.*, 2010). Consistent with this idea, Kuba *et al.* (2010) showed that neurons can adjust the distribution of Na_v channels within the proximal axon, lengthening the AIS to increase neuronal excitability in response to decreased pre-synaptic input. Mouse models of neurodevelopmental disorders associated with autism may provide valuable systems in which to observe structural and functional AIS plasticity in response to altered synaptic and network activity *in vivo*.

Disassembly of the axon initial segment after injury

The pathophysiology of stroke is due in part to damage induced by excitotoxicity (Choi, 1996). The large and sudden influx of Ca^{2+} following an insult initiates several downstream effects, including the activation of proteolytic calpains (Siman *et al.*, 1984). Schafer *et al.* (2009) observed rapid, calpain-mediated degradation of the AIS ankyrin/spectrin cytoskeleton following middle cerebral artery occlusion. Importantly, disruption of the AIS cytoskeleton also resulted in loss of Na_v channel clusters. AIS disassembly was blocked by the calpain inhibitor MDL28170. Although both AIS disassembly and neuronal death are consequences of stroke, they are apparently separate events. Whereas application of the *N*-methyl-D-aspartate receptor antagonist MK801 in the oxygen–glucose deprivation cell culture model prevented cell death, it did not preserve the AIS (Schafer *et al.*, 2009). However, co-application of MK801 with MDL28170 both prevented AIS disassembly and significantly reduced cell death. As described above, the AIS is also essential to maintain neuronal polarity. Thus, disruption of the AIS cytoskeleton by calpain-mediated proteolysis after injury results in not only loss of ion channel clustering, but also loss of polarity. We propose that loss of neuronal polarity is a previously unappreciated consequence of nervous system injury, and that preserving the cytoskeleton would be expected to both preserve polarity and facilitate the retention of AIS membrane proteins, including Na_v channels, which would preserve a neuron's ability to generate APs. These observations suggest that neuroprotective strategies alone will not preserve nervous system function.

Autoimmune disorders and the axon initial segment

Several proteins common to both nodes of Ranvier and the AIS have been implicated in autoimmune-mediated pathology. Although the factors that lead to the immune system-mediated axonal degeneration in multiple sclerosis (MS) are not fully understood, recent evidence suggests that autoantibodies against the nodal and AIS CAM Nfasc186 are significantly increased in the serum of some patients with MS (Mathey *et al.*, 2007). Introduction of anti-Nfasc186 antibodies into hippocampal slice cultures activated the complement cascade resulting in AP conduction block and axonal injury (Mathey *et al.*, 2007). Similarly, antibody-mediated autoimmune channelopathies can affect neuronal excitability leading to nervous system dysfunction. For example, autoantibodies against K_v1 channels were found to be upregulated in the sera of patients with Morvan syndrome (Misawa & Mizusawa, 2010). The resulting hyperexcitability of neurons within the central nervous system is associated with epilepsy, short-term memory loss and insomnia (Misawa & Mizusawa, 2010; Cornelius *et al.*, 2011); patients suffer concomitant peripheral nervous system hyperexcitability. Thus, immune recognition of AIS and nodal proteins is a potential pathogenic mechanism for the neurological deficits observed in MS and other antibody-mediated neurological disorders.

To date, no studies have looked at the integrity of the AIS in postmortem MS tissue or in animal models of MS or other autoimmune diseases. In addition to degeneration, we speculate that irreversible loss of the AIS and neuronal polarity may contribute to the rapid, non-remitting progression of the secondary phase of MS. As axons that lose their AIS acquire a dendritic fate, and dendrites are not myelinated, it is also interesting to speculate that one potential cause for failure of remyelination is the loss of axon identity.

The aging brain

Neuronal death was thought to be the primary cause of cognitive decline during normal aging (Brody, 1970). However, more recent studies on cortical synaptic function, spine density and dendritic arbor complexity in aged animals suggest that age-related cellular changes contribute significantly to normal cognitive decline, even in the absence of

significant neuronal death (Peters, 2002; Peters *et al.*, 2008). Although changes in neuronal excitability have been shown to occur with age (Luebke *et al.*, 2004; Kumar & Foster, 2007), little is known about the concomitant changes in ion channel expression, trafficking, localization and stabilization. Altered neuronal excitability in aging cells could be due, in part, to changes in ion channel density, subcompartmental localization and modulation at the AIS.

Disruption of the molecular organization of the nodes of Ranvier has been shown to occur in normal aging, and this is thought to result primarily from age-related demyelination (Sugiyama *et al.*, 2002; Sloane *et al.*, 2003; Hinman *et al.*, 2004, 2006). As nodes of Ranvier and the AIS share a common molecular organization, we speculate that similar disruptions in AIS ion channel distribution, CAMs and/or cytoskeletal scaffolding proteins may occur in an age-dependent fashion resulting in altered excitability. These changes may be a consequence of dysregulation of internal Ca^{2+} levels (Toescu & Vreugdenhil, 2010) and/or mitochondrial dysfunction (Balaban *et al.*, 2005; Reddy & Reddy 2011). Finally, nothing is known about the AIS in age-related neurodegenerative diseases. Recently, however, tubulin deacetylation in the distal axon by histone deacetylase-6, a protein implicated in both Huntington's disease (Iwata *et al.*, 2005; Dompierre *et al.*, 2007) and Parkinson's disease pathology (Kawaguchi *et al.*, 2003; Du *et al.*, 2010), was shown to be required for proper AIS development (Tapia *et al.*, 2010).

Looking forward

Basic neuroscience has revealed the identities of several voltage-gated ion channels and supporting scaffolding proteins at the AIS that facilitate AP generation and maintain neuronal polarity. Furthermore, as described in this review, there is substantial circumstantial evidence linking the AIS to numerous neurological diseases. Nevertheless, many important questions remain unanswered. For example, we still have no direct evidence for a causal link between AIS channel mutations and epilepsy. Is disruption of the AIS a common feature of many nervous system diseases and injuries? Does the AIS undergo age-related degeneration or alteration? Does AIS plasticity only occur under pathological conditions, or is it a normal occurrence in the intact brain? Similarly, does AIS plasticity alter neuronal excitability to compensate for synaptic deficiencies in diseases like autism, and what are the molecular mechanisms underlying structural plasticity at the AIS? Is it possible to restore neuronal polarity after loss of the AIS? Does autoimmune-mediated attack of AIS proteins contribute to axonal degeneration?

In conclusion, the AIS is an essential regulator of neuronal output. The identities, density and modulation of voltage-gated ion channels enriched at the AIS exert powerful control over the excitability and firing patterns of neurons. We propose that disruption of the molecular organization of the AIS, due to disease, injury or aging, is a previously unappreciated focus for nervous system dysfunction. Nevertheless, additional experiments are clearly needed to define the roles of the AIS in nervous system disease. The results of these studies will enrich our perspective on how the AIS contributes to high-fidelity signal generation and activity-dependent adaptation of neuronal excitability in the developing, mature and diseased nervous system.

Abbreviations

AIS	axon initial segment
ankG	ankyrin-G
AP	action potential

CAM	cell adhesion molecule
caspr2	contactin-associated protein 2
MS	multiple sclerosis
MT	microtubule
Nfasc186	neurofascin-186

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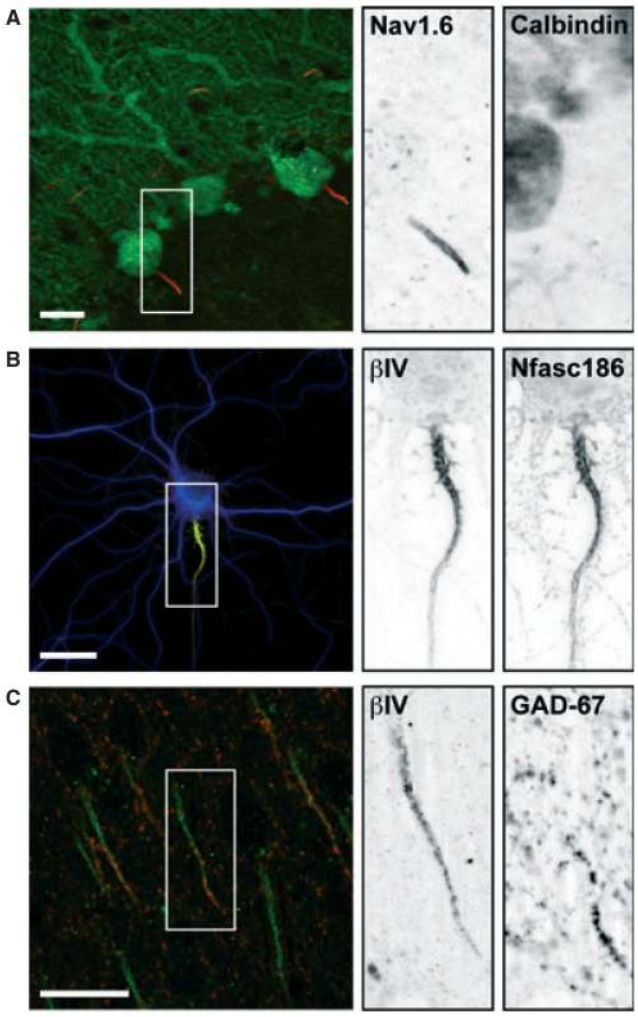

Fig. 1.

The AIS is decorated by dense clusters of voltage-gated Na^+ channels and is selectively innervated by GABAergic interneurons. (A) Voltage-gated Na^+ channel $Na_v1.6$ (red) is highly enriched at the AIS of cerebellar Purkinje neurons. Purkinje cell marker calbindin (green) is restricted to the somatodendritic domain. (B) AIS proteins βIV spectrin (green) and Nfasc186 (red) assemble within the proximal axon of a cultured hippocampal neuron independently of glial interaction or extrinsic factors. (C) Glutamic acid decarboxylase (GAD-67)-positive chandelier cell axonal cartridges (red) contact the distal AIS, denoted by βIV spectrin (green), in mouse neocortex. Scale bars: 20 μm.

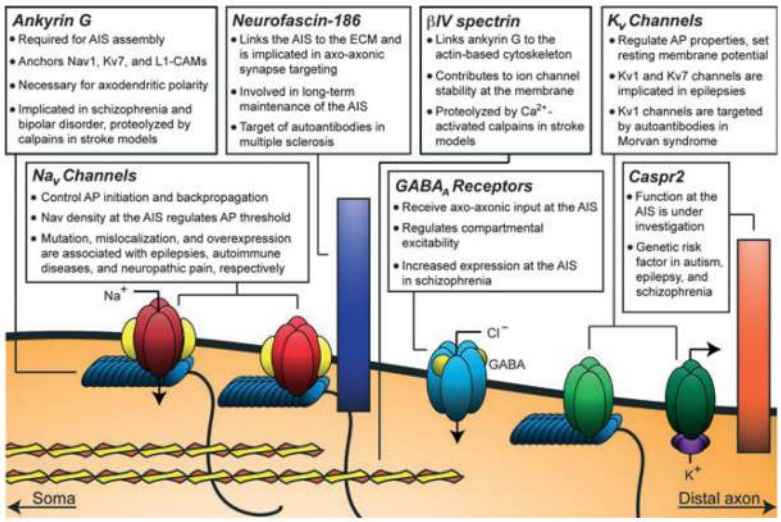

Fig. 2.

AIS protein association with nervous system pathologies and injuries. Ion channels, CAMs, neurotransmitter receptors and cytoskeletal adaptor proteins enriched at the AIS have been linked to neurological disorders including epilepsy, neuropsychiatric developmental disorders and autoimmune disorders. Nervous system injury can also cause disassembly of the AIS. ECM, extracellular matrix.