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Review

Intrinsic neuronal excitability: implications for health and disease

Rajiv Wijesinghe and Aaron J. Camp*

Discipline of Biomedical Science, School of Medical Sciences, Sydney Medical School, University of Sydney, L226, Cumberland Campus C42, East St. Lidcombe, NSW 1825, Australia

*Corresponding author
e-mail: Aaron.Camp@Sydney.edu.au

Abstract

The output of a single neuron depends on both synaptic connectivity and intrinsic membrane properties. Changes in both synaptic and intrinsic membrane properties have been observed during homeostatic processes (e.g., vestibular compensation) as well as in several central nervous system (CNS) disorders. Although changes in synaptic properties have been extensively studied, particularly with regard to learning and memory, the contribution of intrinsic membrane properties to either physiological or pathological processes is much less clear. Recent research, however, has shown that alterations in the number, location or properties of voltage- and ligand-gated ion channels can underlie both normal and abnormal physiology, and that these changes arise via a diverse suite of molecular substrates. The literature reviewed here shows that changes in intrinsic neuronal excitability (presumably in concert with synaptic plasticity) can fundamentally modify the output of neurons, and that these modifications can subserve both homeostatic mechanisms and the pathogenesis of CNS disorders including epilepsy, migraine, and chronic pain.

Keywords: excitability; homeostatic; intrinsic plasticity; long-term potentiation; synaptic plasticity.

Introduction

Neurons in the central nervous system (CNS) convert inhibitory and excitatory inputs into a specific output, encoded as defined action potential (AP) patterns and/or frequencies propagated along the axon of the neuron. This 'input/output' relationship is referred to as 'neuronal excitability'. Most authors agree that the ultimate output of a single neuron is defined by the combination of both excitatory and inhibitory synaptic inputs, and intrinsic membrane properties (1, 2).

The modification of the input/output relationship of a neuron at the synapse is termed synaptic plasticity and has been the focus of most studies investigating neuronal excitability. Changes associated with the efficacy of excitatory or inhibitory connections have been defined under two major headings: long-term potentiation (LTP) and long-term depression (LTD), characterized by sustained increases or decreases in synaptic strength, respectively (1). Both LTP and LTD have generated much interest because evidence has shown that similar synaptic changes can be induced following behavioral training, and that learning is impeded following LTP/LTD interference (3, 4) [for review, see (2, 5)].

Although synaptic mechanisms are clearly important regulators of neuronal excitability, intrinsic membrane properties also impinge on neuronal input/output functions. For example, *in vivo*, the input/output function of rat motor cortex neurons can be modified by conditioning with a short burst of APs (6). *In vitro*, this modification can be related to changes in the number or kinetics of voltage-gated ion channels present in the plasma membrane in a compartment-dependent manner (i.e., axon, soma, and dendrite). Although the first voltage-clamp experiments by Hodgkin and Huxley described only two voltage-dependent conductances underlying the AP in the squid giant axon (7), it has become clear that the AP of mammalian neurons is subserved by a number of different voltage-dependent ion channels, each with the potential to be differentially expressed and/or localized in response to changes in physiological circumstance or experience. Furthermore, recent evidence suggests that changes in intrinsic neuronal properties contribute to both homeostatic and pathological phenomena. For example, changes in the intrinsic excitability of vestibular nucleus neurons have been temporally linked with subsidence of symptoms associated with unilateral vestibular trauma (8), whereas several CNS disorders including epilepsy have been linked to ion channel dysfunction (2). In this review, we briefly discuss the mechanisms underlying changes in neuronal excitability with a particular emphasis on intrinsic membrane properties *in vitro*, and how recent research provides a better understanding of the functional implications of these changes in health and disease.

Intrinsic membrane properties and intrinsic excitability

Experience driven changes in neuronal excitability (including LTP/LTD) arise from the combination of synaptic and intrinsic modifications. Although the capacity of the synaptic model for memory storage is large, and thereby attractive as a neuronal basis for behaviors such as learning and memory, this does not imply that the contribution of intrinsic neuronal

modifications are irrelevant to these behaviors, or, that they do not play a role during pathology of the CNS. Indeed, several lines of evidence suggest that changes in the density of voltage-gated ion channels are associated with CNS dysfunction [for review, see (2)] (Table 1). Here, we briefly describe the contribution of the major classes of voltage-gated ion channels to neuronal excitability.

Potassium channels

Neurons express several potassium-selective ion channels, the diversity of which is highlighted by the 40+ genes encoding the different subunit families that comprise them (9, 10). These channels include calcium-dependent and voltage-gated channels, each crucial for the regulation of membrane excitability. Activation of these channels repolarizes the neuron or attenuates the impact of depolarization by shifting the membrane potential towards the potassium equilibrium potential and away from AP threshold (11). Thus, altering the conductance of these channels effectively alters the excitability of the neurons endowed with them.

Voltage-gated potassium channels

Although all voltage-gated potassium (K_V) channels contribute to stabilization of the membrane potential, two of these channels have been shown to be particularly important regulators of neuronal excitability: the $K_V4.2$ channel that confers the fast transient (A-type) K current (12, 13) and the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel that passes the so-called 'h' current (14–17).

The membrane potential activation range of the A-type current, or I_A, is below that required to generate APs and its activation results in the attenuation of excitatory postsynaptic potentials (EPSPs) (18) and backpropagating APs (19). The '*h*' current or I_h, is a slow, non-inactivating conductance active at resting membrane potential and augmented by hyperpolarization (20). Activation of I_h results in reduced EPSP summation (14, 17). Both I_A and I_h are modified following activity including tetanic stimulation of afferent fibers (a common protocol used to induce LTP) (21). For I_A this modification manifests in at least two ways: as a shift in voltage-dependence following channel phosphorylation by protein kinases A (PKA) and C (PKC), as well as mitogen-activated protein kinase (MAPK) (22), and/or a downregulation of the $K_V4.2$ channel. For I_h the major consequence of tetanic stimulation is a downregulation of protein and mRNA levels of HCN subunits (23) and concomitant increase in hyperpolarization amplitude. These changes have also been shown to occur in models of CNS disorders including epilepsy (24), Alzheimer's disease, and febrile seizures. For example, downregulation of both the $K_V4.2$ and HCN channels is associated with chronic epilepsy and other CNS disorders with neuronal hyperexcitability as a phenotype (1).

Table 1 Voltage-gated conductances in CNS disorders.

Current	Channel	CNS disorder	Direction of change and cell type	Cellular effects
I_A	$K_V4.2$	Epilepsy, Alzheimer's	Downregulation in CA1 dendrites	Altered firing mode, enhanced AP backpropagation
I_h	HCN1, HCN2	Epilepsy, febrile seizures	Downregulation in models of epilepsy, upregulation during development of CA1 neurons	Enhanced EPSP summation, hyperpolarization of resting membrane potential, increased input resistance
I_{CaT}	$Ca_V3.1$, $Ca_V3.2$	Epilepsy, chronic pain	Upregulation in DRG neurons	Burst-firing/change in firing mode
I_{CaL}	$Ca_V1.2$, $Ca_V1.3$	Epilepsy	Downregulation in CA1 neurons	Increased discharge rate, reduced post-burst AHP
I_{CaR}	$Ca_V2.3$	Juvenile myoclonic epilepsy	Upregulation in CA1 neurons	Enhanced ADP, burst-firing/change in firing mode
I_{CaN}	$Ca_V2.2$	Hyperalgesia, allodynia	Upregulation in dorsal horn neurons	Increased spontaneous activity
I_{Na}, I_{NaP}	$Na_V1.1$–1.9	Epilepsy, febrile seizures, migraine, Dravet's syndrome	Upregulation in CA1 neurons	Enhanced ADP, burst-firing

DRG, dorsal root ganglion; ADP, afterdepolarization; AP, action potential.

Voltage-gated calcium channels

Calcium is a signaling ion that contributes to a large ensemble of cellular activities including gene transcription, apoptosis, synaptic transmission, secretion, as well as modulation of intrinsic excitability. Each of these diverse processes requires tight regulation of intracellular calcium concentration (25, 26). For example, voltage-gated Ca channels (Ca_V) regulate movements of calcium across the neuronal cell membrane in response to membrane depolarization. The pore-forming subunits of Ca_V channels are encoded by 10 different genes, with several subtypes for each class made possible by a substantial degree of alternative splicing. In general, Ca_V channels are grouped into two major classes: low-voltage activated (LVA or 'T-type'; Ca_V3) and high-voltage activated (HVA) [for review, see (27, 28)]. The HVA class is further subdivided based on pharmacology and biophysical properties into L- ($Ca_V1.2$ and $Ca_V1.3$), N- ($Ca_V2.2$), P/Q- ($Ca_V2.1$), and R-type ($Ca_V2.3$) channels (11). Adding further complexity to the Ca_V channel family, a further 16 genes encode for accessory subunits to the HVA class, although the precise stoichiometry is not well understood for all HVA subtypes (27).

Although still incomplete, progress has been made towards unraveling the functional role(s) of each member of the Ca_V channel family including their contribution to intrinsic excitability and to various pathological states [for a comprehensive review, see (27)]. For example, the low-voltage activated 'T-type' channel, and in particular the fast-inactivating $Ca_V3.1$ isoform, which is expressed throughout the dendritic tree, has been shown to contribute to the bistable excitability states exhibited by thalamocortical relay cells (29, 30) (Figure 1). Furthermore, upregulation of I_{CaT} (parsed by $Ca_V3.2$ channels) has been shown to underlie burst-firing in dorsal root ganglion neurons in models of chronic pain (31), and CA1 neurons in models of epilepsy (32, 33), whereas knockout of the gene encoding $Ca_V3.2$ abolishes acute hyperalgesia associated with constriction injury in rats (34).

Similar to the LVA calcium channels described above, HVA calcium channels have also been shown to contribute to intrinsic neuronal excitability under normal conditions and during pathology. For example, R-type ($Ca_V2.3$) channels are a source of calcium during backpropagating APs (35) and synaptic plasticity (36), and have been shown to contribute to the afterdepolarization (ADP) underlying burst-firing in CA1 neurons (37), and in juvenile myoclonic epilepsy (38). Furthermore, L-type channels ($Ca_V1.2$ and $Ca_V1.3$) have been the focus of a significant amount of attention with regard to intrinsic excitability because they have been linked to the slow afterhyperpolarization (sAHP) (39–41). Thompson et al. showed that blockade of L-type calcium channels increase the firing rate of CA1 neurons *in vivo* (42), whereas others have shown that this increased intrinsic excitability is via (at least in part) a reduction in L-type-mediated post-burst AHP (40, 43–45). In addition, N-type ($Ca_V2.2$) channels distributed along dendrites, cell somas, and some nerve terminals (46) have been implicated in increased spontaneous activity in primary afferent fibers with associated hyperalgesia and allodynia (47, 48), as well as neuronal excitability of dorsal horn neurons following spinal nerve ligation (49), such that expression of these channels is increased in lamina II of the spinal cord (50).

Voltage-gated sodium channels

Voltage-gated sodium channels primarily function to provide an explosive, regenerative inward current during the rising phase of the AP. In the brain, voltage-gated sodium channels are formed by the combination of two β subunits and a cen-

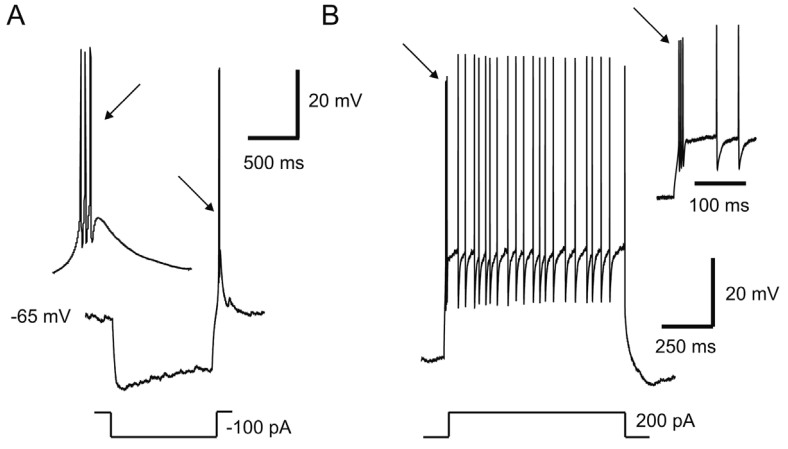

Figure 1 Low-voltage activated (T-type) calcium channels contribute to burst firing in thalamocortical neurons.
Panel (A) shows the characteristic burst-firing phenotype of thalamocortical relay neurons. Hyperpolarization activates low-voltage activated (LVA, T-type) calcium channels, which when released from hyperpolarization result in a burst of high-frequency action potentials (arrows) that ride on a low-threshold calcium spike (LTS). (B) Thalamocortical relay neurons show bistable discharge patterns. Following rapid depolarization of the membrane for rest, thalamocortical relay neurons display the characteristic burst phenotype (arrows) before switching to a more regular firing mode. (R. Wijesinghe and A.J. Camp, unpublished data.)

tral α subunit (27). The α subunits are further classified into nine subtypes ($Na_V1.1$–1.9), the expression of which is both cell-and tissue-specific (27). The main subtypes expressed in the brain are the $Na_V1.6$ localized in the axonal initial segment, nodes of Ranvier, cell somas and dendrites; $Na_V1.1$ is found in the cell soma; and $Na_V1.2$ is in unmyelinated axons and myelinated axons during development (51).

Currently, there is substantial evidence to suggest that abnormal expression of voltage-gated sodium channels contribute to the changes in intrinsic neuronal excitability that underlie several neurological disorders including epilepsy and migraine [for review, see (51)]. For example, changes in mRNA and protein levels of $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.6$, as well as β subunits have been shown in animal models of epilepsy and in human brain tissue in acquired epilepsy (52–55). In addition, changes in the $Na_V1.2$ subtype have been shown to be sufficient to cause chronic seizures in transgenic mice that have a mutation in the sodium channel gene Scn2a (56). The most compelling evidence for the role voltage-gated sodium channels in epileptogenesis, however, comes from the observation that mutations in several sodium channel genes lead to inherited epileptic syndromes ranging in severity from mild forms such as febrile seizures (57) through to severe disorders including Dravet's syndrome (58, 59). The $Na_V1.1$ subtype has also been implicated in the pathogenesis of a severe inherited type of migraine (familial hemiplegic migraine type 3). In human embryonic cell lines, expression of mutations in $Na_V1.1$ subtype channels result in both gain-of-function and complete loss-of-function (60, 61). Although the precise mechanism underlying this form of migraine are not well understood, one hypothesis is that changes in $Na_V1.1$ channels lead to cortical hyperexcitability, enhanced neurotransmitter release, accumulation of K^+, and subsequent stimulation of meningeal sensory afferents resulting in pain (62). Although some patients with $Na_V1.1$ mutations present with seizures, suggesting a common pathophysiology with epilepsy, others develop one or the other disorder, indicating that other factors contribute to both disease states.

Homeostatic changes in excitability

The rich variety of channels that neurons are able to utilize provides a flexible substrate with which to express excitability. Changes in excitability can be characterized as either those that contribute to the stabilization of neuronal output over time (homeostatic) (63–65) or those that produce a deviation from stability (non-homeostatic) [for review, see (2)]. Homeostatic changes in neuronal excitability usually arise in response to long periods of altered activity. One such model of homeostatic changes in excitability following altered neuronal activity is an extraordinary form of adult plasticity called vestibular compensation (8). Vestibular compensation follows injury to the balance organs of the inner ear or vestibular nerve. The normally tonic activity in the ipsilateral vestibular nucleus located in the brainstem is lost, leading to abnormal vestibulo-ocular and vestibulo-spinal reflexes. Remarkably, these behavioral signs abate over time and are temporally matched with a re-emergence in background discharge in the vestibular nucleus on the damaged side. In both rat and guinea pig, the increase in background discharge of ipsilateral vestibular nucleus neurons appears to be expressed as increased excitability of the so-called type B medial vestibular nucleus (MVN) neuron subpopulation, although these intrinsic changes are also accompanied by synaptic changes (66–69). Interestingly, this subpopulation has also been implicated in an opposite but nonetheless

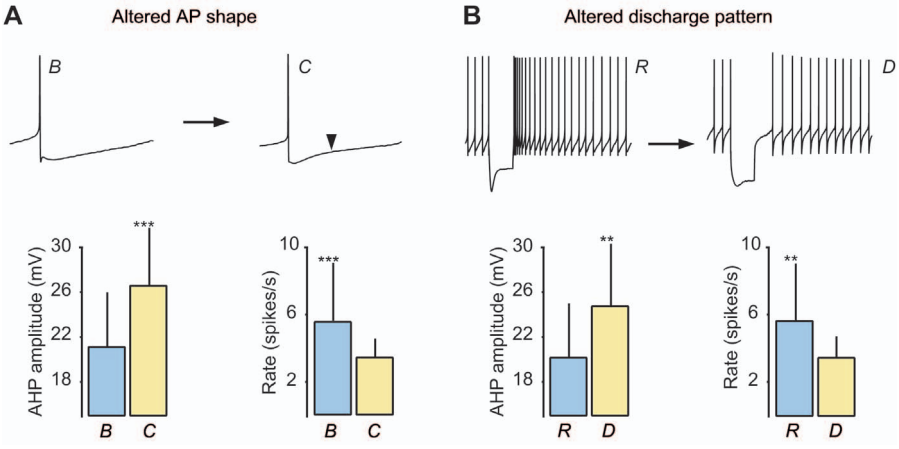

Figure 2 Homeostatic changes in MVN neuron excitability following attenuation of inhibitory drive.
(A) The two action potentials (upper traces) depict a change in action potential shape from the (*B*) to the (*C*) phenotype in response to chronically reduced inhibitory drive. This change is hypothesized to come about as a result of the addition or unmasking of a rate-dampening (I_A-like rectification; arrowhead) and manifests as alterations in excitability including larger AHPs and reduced discharge rates (bar plots). (B) The two action trains (upper traces) depict a change in discharge pattern following release from hyperpolarization from the responsive (*R*) to the deficient (*D*) phenotype in response to chronically reduced inhibitory drive. As in (A) this change is characterized by enhanced AHPs and associated reductions in discharge rate (bar plots). Adapted from Camp et al. (70).

homeostatic response in mice. In a recent study conducted by our laboratory, the type B MVN neuron subpopulation was shown to undergo changes in some AP and discharge properties following chronic reductions in glycine receptor-mediated inhibitory drive. These changes included reduced background discharge rate, lower neuronal gain, and larger AHPs (70). We concluded that the change in type B neuronal excitability could be explained by the addition or unmasking of a rate-dampening rectification (arrowhead in Figure 2A) similar to I_A that ultimately functions to stabilize the excitability of MVN neurons in the face of chronically reduced inhibitory drive (70) (Figure 2A).

As noted above, experience-dependent changes in neuronal excitability can also subvert network stability. For example, in the commonly used pilocarpine model of epilepsy where injection of the muscarinic agonist causes seizures similar to those observed in human temporal lobe epilepsy (71), downregulation of I_h has been observed in pyramidal neurons of the hippocampus (72), as well as entorhinal cortex (73). In these structures attenuation of I_h results in hyperpolarization of the resting membrane potential, increased cell resistivity (making the cell more sensitive to small voltage fluctuations), and increased EPSP summation (72, 73). Similarly, changes in the number of voltage-gated sodium (Na^+) channels have been demonstrated in animal models of chronic pain. In this example, the threshold required to elicit an AP from dorsal root ganglion (DRG) neurons was reduced following upregulated expression of voltage-gated Na^+ channels (74–76). In addition, downregulation of somatic I_A has been shown in DRG neurons following crush injury of the nerve root (77–80). These changes in DRG neuron intrinsic excitability presumably contribute to the hyperalgesia and allodynia commonly observed in chronic pain models.

The changes in intrinsic excitability described above can be broadly characterized as those that affect the properties of all-or-none APs. However, experience-dependent changes can also impact on the pattern of neuronal discharge, that is, the number or regularity of APs. Most neurons can be classified as either regular-firing or burst-firing. Regular-firing neurons are characterized by a single AP in response to brief membrane depolarization, and a series of regular but distinct APs in response to prolonged depolarization (1). In contrast, burst-firing neurons respond to suprathreshold depolarization with a variable length burst of high frequency (approx. 200 Hz) APs. Changes in these firing patterns have been observed during both homeostatic and pathophysiological conditions (1). For example, following chronic attenuation of inhibitory drive, there is a pronounced alteration in the discharge patterns of mouse MVN neurons *in vitro* (70). This change manifests as an increase in the proportion of neurons displaying the burst-firing phenotype following release from hyperpolarization. Interestingly, this phenomenon is accompanied by a presumed homeostatic change in excitability whereby there is also a pronounced increase in neurons with depressed firing rates following release from hyperpolarization (termed post-inhibitory rebound depression; PRD neurons by the authors) (70) (Figure 2B). Similarly, changes in firing mode have been reported in the pilocarpine model of chronic epilepsy (71), and in other epilepsy-associated disorders (81). These changes are brain region specific (82, 83), and cell specific, with neurons close to the CA1 subfield of the hippocampus showing opposing effects to those distal to this subfield, and no concomitant change in intrinsic properties of CA1 interneurons (84). Furthermore, increases in the number of neurons displaying burst-firing phenotypes have been shown electrophysiologically in several other CNS disorders including chronic stress (85), pain (86, 87), and neuroinflammation (88). Thus, changes in the discharge pattern could be a common feature of very different CNS disorders, but whether this feature plays a causative role has not yet been determined.

What underlies experience-dependent changes in firing mode? In regular-firing neurons a subthreshold depolarization (termed ADP) follows the all-or-none AP (32, 71). In burst-firing neurons, this ADP can exceed AP threshold and elicit a burst of high frequency APs. Changes in the ionic conductances underlying the ADP presumably contribute to the changes in firing mode observed under both homeostatic and pathological conditions. Indeed, a number of the voltage-gated channels described above have been shown to be important determinants of firing mode. For example, blockade of dendritic I_A (generated by the fast transient A-type K channels) increases the amplitude of the ADP in CA1 neuron dendrites beyond that required for AP generation and results in a burst-firing phenotype (89, 90). Similarly, alterations in the magnitude of I_{NaP} have also been shown to alter the magnitude of the ADP and thus contribute to firing mode (91). For example, in response to somatic blockade of I_{NaP} the ADP of CA1 neurons is reduced, whereas reduction of extracellular Ca^{2+} (known to facilitate I_{NaP}) leads to larger ADPs and burst-firing (92). In addition, there is substantial evidence for the involvement of other voltage-gated channels in regulating the magnitude of the ADP (and firing mode) including I_{CaT} channels, which, when upregulated as in the pilocarpine model of epilepsy or in response to ischemia, cause an increase in ADP magnitude and burst-firing (33, 92).

Although factors underlying the generation and discharge pattern of all-or-none APs clearly contribute to neuronal input/output functions, other intrinsic properties such as those that underlie the AHP can also shape neuronal output, particularly during prolonged stimulation. For example, Ca^{2+}-sensitive K^+ currents activated during repetitive firing can be modified by experience, including prolonged synaptic activity (93–95). In lateral geniculate nucleus (LGN) neurons, the sAHP, mediated by a Ca^{2+}-sensitive K^+ current, is reduced following *trans*-ACPD blockade of metabotropic glutamate receptors *in vitro*. In this preparation, the input/output function of LGN neurons becomes steeper, indicating an increase in neuronal sensitivity or gain (R. Wijesinghe and A.J. Camp, unpublished observations). Interestingly, the sAHP is also downregulated in models of epilepsy (96) and chronic pain (97–99), making it plausible to suggest that changes in intrinsic membrane properties underlying the AHP also contribute to the discharge phenotype observed in some CNS disorders (1).

Molecular substrates of intrinsic neuronal excitability

As described above, intrinsic membrane properties including the type and density of voltage-gated ion channels are crucial determinants of intrinsic excitability. In experimental models, upregulation or downregulation of these channels or their subunits can lead to behavioral phenotypes characteristic of several CNS disorders [for review, see (1)]. What are the mechanisms underlying these changes in intrinsic membrane properties? One explanation is kinase-dependent phosphorylation of gene transcription factors (78–80, 100, 101). Stimulus protocols that are commonly used to induce synaptic plasticity also trigger phosphorylation, making it an attractive candidate. Other possibilities include altered production and insertion of ion channels (i.e., channel trafficking to the neuronal plasma membrane) [for review, see (102)]. Evidence shows that in some models, upregulation or downregulation of ion channel mRNAs directly impinges on ion channel function (72, 73). Importantly though, the specific trigger(s) of this transcriptional modification of ion channel mRNA is not well understood, particularly when compared with other proteins under pathological conditions such as epilepsy (103, 104) [for review, see (105)].

Trafficking of ion channels to the correct neuronal subcompartment and subsequently to the cell membrane is also a crucial factor in determining neuronal excitability (102) (Figure 3). For example, in a study by Misonou ion channel phosphorylation was shown to impact on insertion of the potassium channel $K_V2.1$ (106). Furthermore, the number of ion channels trafficked and inserted into the neuronal cell membrane is balanced by ongoing internalization and degradation of existing channels, usually through ubiquitination and/or sumoylation (107), and as such, these mechanisms can also contribute to intrinsic neuronal excitability. Yet another mechanism that might underlie excitability is proteolytic cleavage (108). Recent research has shown that the level of B-site amyloid precursor protein cleaving enzyme 1 (BACE1) is significantly increased in the brains of Alzheimer's disease patients, and that this affects neuronal excitability by cleaving the B2 Na^+ channel subunit. Subsequently, there is an increase in the production of NaV1.1 channels, although presumably owing to intracellular sequestering of these channels the density of the Na^+ current is actually decreased (108).

As described above, voltage-gated Ca^+ channels and calcium-dependent K^+ channels mediate at least some part of the AHP. As such, changes in Ca^+ buffering and sequestering

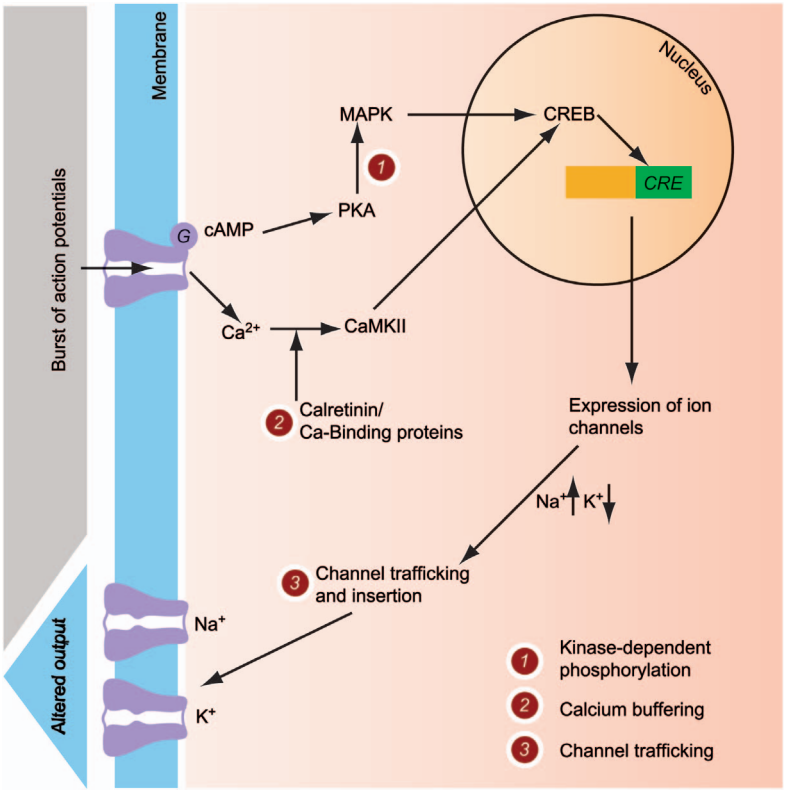

Figure 3 Putative molecular substrates of intrinsic excitability.
Several intracellular signaling molecules have been shown to contribute to intrinsic excitability. In this example, a burst of presynaptic action potentials produces both an influx of calcium ions across the neuronal cell membrane and activation of cAMP. Calcium/cAMP activate protein kinases A, C, and/or CaMKII to phosphorylate cAMP response element binding protein (CREB). Phosphorylation of CREB increases binding to a specific DNA sequence called the cAMP response element (CRE), present in the promoter of many genes, and subsequently initiates gene expression. CRE-driven gene expression has been shown to result in both synaptic and intrinsic modifications including altered regulation of sodium and potassium channel expression, and subsequent alterations in neuronal output.

capabilities within the cell cytosol have also been implicated in neuronal excitability (109) (Figure 3). For example, Roussel et al. showed that in cerebellar granule cells changes in calcium buffering capabilities can profoundly alter neuronal excitability (26). In that model, neurons loaded with high concentrations of the fast calcium buffer BAPTA (15 mM) exhibited the burst-firing phenotype, whereas those loaded with low concentrations (0.15 mM) never displayed burst-firing characteristics. The authors concluded that as cytosolic calcium levels so tightly modulate firing patterns, that calcium-binding proteins (proteins that function to localize and sequester intracellular calcium) could also play a crucial role in intrinsic excitability (26). Indeed, Schurmans et al. showed that LTP induction is impaired in mice deficient in the calcium-binding protein calretinin ($CR^{-/-}$) (110), whereas Gall et al. suggest that calretinin deficiency (and therefore in calcium buffering capability) leads to increased neuronal excitability and that this change can be abolished by the addition of BAPTA to the cytosol (111). In contrast, calretinin-expressing neurons in the mouse MVN display an altered firing pattern (away from a burst-firing phenotype) and reduced discharge rate when compared with neurons that do not express calretinin (A.J. Camp, unpublished observation). Because calcium is fundamental to cell signaling, it is perhaps not surprising that the maintenance of intracellular calcium concentrations, particularly the buffering and sequestering activities performed by calcium-binding proteins, are important for the regulation of intrinsic excitability. It is less clear, however, if similar binding and/or sequestering of other important ions contributes to changes in intrinsic excitability.

Several protein kinases including PKC, PKA, and calcium/calmodulin-dependent protein kinase II (CaMKII) have also been shown to be factors in determining intrinsic neuronal excitability (78–80, 100) (Figure 3). For example, in rat CA1 pyramidal neurons activation of PKA has been shown to reduce the magnitude of the post-burst AHP (parsed by a combination of I_h, I_M and calcium-dependent potassium channels described above) (101, 109, 112–114), whereas interruption of CaMKII activity reduces intrinsic excitability of mouse vestibular nucleus neurons by reducing the BK-type calcium-dependent potassium current associated with the early fast component of the AHP (100) [but also see (115)]. A common downstream target of both, and other, protein kinases is the cAMP-response element binding protein (CREB), a protein made famous by its title 'the memory gene'. Whereas early research identified a role for CREB in synaptic forms of plasticity, more recent research suggests that it also plays a role in modulating intrinsic neuronal excitability (116). Dong et al. showed that expression of a CREB variant in medium spiny neurons of the nucleus accumbens resulted in augmented intrinsic excitability (117). Specifically, they found that the numbers and or properties of voltage-gated sodium and potassium channels were altered such that the magnitude of the currents passing through these channels was increased and decreased, respectively (Figure 3). In addition, they reported a reduction in the threshold needed to elicit an AP (117). More recently, Viosca et al. showed that in pyramidal neurons of the basal nucleus of the amygdala enhancement of CREB reduced the AHP amplitude and increased discharge frequency (118). Similarly, Zhou et al. showed that overexpression of a CREB variant (wt-CREB) in the lateral amygdala reduced AP threshold, spike-frequency adaptation, and the post-burst AHP, while increasing the number of evoked APs (119). These results are consistent with microarray data showing that CREB promotes the transcription of the 1β sodium channel subunit while decreasing the expression of $K_V1.4$ potassium channel subunit (120). In addition to its role in the modulation of intrinsic neuronal excitability, altered regulation of CREB signaling could also be a factor underlying CNS disorders including epilepsy (121, 122) and depression-like behaviors (120). For example, mice expressing the artificial CREB inhibitor A-CREB were resistant to two common models of epilepsy (including kindling), whereas mice that have CREB regulators ICER and/or CREM knocked out (122) or absent (121) showed accelerated kindling and greater probability of spontaneous seizures after status epilepticus (121). Taken together, these results suggest that a major function of CREB in the CNS is the modulation of intrinsic neuronal excitability, and that disruption of CREB signaling could be a common underlying mechanism contributing to several disorders of the CNS. It should be noted, however, that CREB most probably acts in concert with other transcriptional factors [e.g., Sp1; a voltage-dependent potassium channel upregulator (123)] and that the relative importance of each of these to absolute changes in excitability are not yet known.

Development of channels that regulate intrinsic excitability

Voltage-gated ion channels are responsible for the output firing rate and pattern of neurons (11). Although neurons express ion channels throughout their lifetime, their characteristic firing properties emerge after a period of postnatal maturation. During this period there are profound changes in the type, density, and location of sodium, calcium, and potassium channels expressed at the neuronal membrane. For example, in mature mice fast-spiking neocortical interneurons (FS) are able to respond very rapidly to excitatory stimuli with single or high-frequency, non-adapting trains of APs (124–127). These characteristic firing features are not evident at birth, but instead emerge very rapidly during the second to third postnatal week (128). Okaty et al. showed that genes coding for voltage-gated ion channels are upregulated during the first four postnatal weeks. In their study, the two-pore domain, inwardly rectifying potassium channel, $K_V2.1$, undergoes monotonic increases in expression between P10 and P25, establishing the low input resistance exhibited by these cells (129). Similarly, the rapidly inactivating potassium channel subtype K_V 3.1 has been shown to undergo similar developmental upregulation, primarily during postnatal day 10 (P10) to P18 (128). In mature thalamocortical relay neurons, low-threshold T-type calcium channels ($Ca_V3.1$) mediate a burst of high-frequency APs [low threshold spikes,

LTS (130–132); Figure 1]. Although T-type currents are evident from birth, relay neurons are only capable of firing LTS 14 days postnatal (133), suggesting a developmental shift in either the number or properties of T-type channels in this neuronal population. Finally, Benn et al. showed that the expression of $Na_V1.8$ and $Na_V1.9$ is increased between embryonic day 15 (E15) and E17, respectively, in rat DRG neurons, and that adult levels are reached at P7. The authors suggested that these changes underlie the excitability and specific temporal firing patterns observed in the DRG neuron development (134). Although not exhaustive, the examples described above make clear that the intrinsic excitability of a neuron (mediated by the expression of voltage-gated ion channels) is a dynamic property, whereby a single neuron can exist in several different stable excitability states throughout its finite lifetime. Ultimately, the changes in voltage-gated channel expression during development, and the resultant acquisition of specific firing patterns, make signal processing and output more efficient, and functional changes in these channels can also act to protect neuronal circuits from degenerating during aging.

Expert opinion

The neuronal components of brain circuitry are 'stable' throughout an animal's life except during times of growth and degeneration that occurs during development, aging, or pathology. To maintain this stability, neurons must find the balance between changing their output to meet new requirements and keeping output within a satisfactory operating range. This balancing act is done through the combination of synaptic plasticity and changes in intrinsic neuronal excitability. Although synaptic plasticity has been the focus of most research into neuronal excitability, growing evidence including that presented here, highlights the fact that changes in intrinsic membrane properties also shape the output of single neurons. One important consideration therefore is how are synaptic and intrinsic changes combined during homeostasis and disease? For example, calcium dynamics have been shown to be crucial to both synaptic plasticity and at least some component of intrinsic plasticity, therefore questions arise about whether the molecular substrates downstream from calcium are the same, complementary, or independent in each type of plasticity. A second point of interest is the impact of subthreshold synaptic noise on intrinsic neuronal excitability. Neurons are embedded within a complex architecture and are constantly subject to small synapse driven fluctuations of membrane potential. Recent reports have shown that the addition of subthreshold synaptic noise to depolarizing current steps can alter the input/output function of single neurons *in vitro*. Whether these alterations also result in the same or similar long-term alterations in the expression of voltage-gated ion channels and associated changes in excitability are yet to be determined. Finally, both changes in intrinsic excitability and synaptic plasticity have been observed in several CNS disorders. Elucidating how the interaction between synaptic and intrinsic plasticity maintains the excitability of individual neurons during homeostasis has implications for how individual neurons function as part of complex circuitry and during pathology.

Outlook

It is clear that changes in intrinsic neuronal excitability have the potential to account for several homeostatic phenomena including memory and learning. However, we are still only beginning to understand the importance of these changes during normal physiological events or indeed under pathological conditions. For example, in some CNS disorders such as epilepsy and chronic pain described above, a very clear schema of voltage-gated channel alterations has been shown to lead to well-characterized changes in neuronal output. In other CNS disorders including Alzheimer's, depression, and Parkinson's disease, this is not the case. Although most research on these disorders has focused on the role of synaptic transmission, with little emphasis on the intrinsic properties described here, it is probable that changes in intrinsic neuronal excitability also contribute to the underlying pathologies. Indeed, it is plausible to suggest that most, if not all, neuronal voltage-gated channels are targets of activity-dependent modulation. Advances in technology and/or techniques provide valuable tools to answer new questions about intrinsic neuronal excitability. For example, the development of second-generation multiphoton imaging allows changes in intrinsic excitability across neuronal populations to be assessed, whereas optogenetic approaches provide the opportunity to investigate the impact of intrinsic neuronal excitability on information processing in neural circuits. Furthermore, targeted electrophysiological recordings from transgenic animals can assess the contribution of changes in intrinsic excitability in models of CNS disorders, by correlating specific subcellular components with defined discharge phenotypes.

Finally, the key question remains: can we use this information to produce specific pharmacological treatments for neurological disease? The answer represents an exciting pursuit that could, over the coming years, reshape our understanding of how neurons function normally and in CNS pathology.

Highlights

- How do changes in intrinsic and synaptic properties combine to modulate overall neuronal and network excitability? And, how does this interaction affect both physiological and pathophysiological processes?
- Although both synaptic and intrinsic mechanisms underlying neuronal excitability have been demonstrated, the relative weighting of the two mechanisms is yet to be determined.
- Do intrinsic and synaptic mechanisms share common downstream CREB targets? And if so, which ones?

- Changes in intrinsic excitability have been observed in both homeostatic and pathological contexts. For example, changes in intrinsic excitability have been shown during vestibular compensation and in several models of epilepsy, chronic pain, and migraine.
- Changes in intrinsic excitability can be broadly characterized into two categories: (i) those that affect the properties of APs themselves and (ii) those that affect the discharge pattern of these action potentials.
- The molecular substrates of intrinsic excitability are as yet incompletely described. However, two putative mechanisms observed by several authors are the modulation of intracellular calcium, and, activation of CREB by one or more protein kinases.

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