

# 1.13 Evolution of the Action Potential

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## Glossary

<i>A-type current</i>	A transient outward $K^+$ current that activates and inactivates rapidly. A-type currents are coded for by the Kv4 potassium channel gene subfamily. In addition, Kv1.4 and other Kv1 proteins can form A-type currents when complexed with accessory cytoplasmic proteins (e.g., $\beta$ -subunits). A-type currents contribute to the resting potential, participate in repetitive firing and spike repolarization, and prevent back-propagation of dendritic APs.	<i>anode break excitation</i>	Generation of an AP at the end of a long-duration depolarization or hyperpolarizing pulse.
<i>absolute refractory period</i>	The time interval during which a second AP cannot be elicited, regardless of stimuli intensity.	<i>conductance</i>	Property of a channel that characterizes its ability to conduct current.
<i>afterhyperpolarization (mV)</i>	A temporal slow hyperpolarization observed after a train of APs. Often plays a role in the regulation of the neuron's firing rate.	<i>delayed rectifier</i>	Outward $K^+$ currents that activate slowly (delayed with respect to activation of voltage-gated sodium current). These channels show little, if any, inactivation in the range of seconds. These channels play a predominant role in AP repolarization.
<i>amplitude (mV)</i>	Property of an AP that refers to the mV difference between the RMP and peak.	<i>depolarization</i>	Change that results in a more positive (less negative) MP.
		<i>duration (ms)</i>	A measure of the time that depolarization lasts during an AP (e.g., interval between threshold on the rising phase and recovering half of the AP amplitude on the falling phase).
		<i>hyperpolarization (mV)</i>	Change that results in a more negative (less positive) MP.

<i>inactivation</i>	A process that leads to a non-conducting channel state that does not respond to depolarization by opening of the channel.	<i>relative refractory period</i>	The briefest interval after which a second AP can be elicited, albeit with diminished amplitude.
<i>inward rectifier</i>	Also known as anomalous rectifiers (as opposed to normal outward rectification), these potassium channels pass inward currents at potentials more negative than the $K^+$ equilibrium potential of ( $E_K$ ). The Kir subfamily of voltage-gated ion channels (VGICs) codes for inward rectifiers. Inward rectifiers are strongly regulated by intracellular factors and second messengers and contribute to maintenance of the resting potential and $K^+$ homeostasis.	<i>repolarization</i>	Change that brings the MP back towards the resting value.
<i>ionic dependence</i>	Property of an AP that refers to the principal ion driving the depolarization.	<i>rheobase (nA)</i>	The minimum amount of current needed to generate at least one AP.
<i>outward rectifier</i>	A channel that allows current to flow in an outward direction more easily than an inward direction.	<i>sodium current (<math>I_{Na}</math>)</i>	Ion flux through a sodium-selective ion channel.
<i>peak (mV)</i>	The voltage at which the maximum AP amplitude is reached.	<i>threshold (mV)</i>	The minimum value of the MP at which an AP is initiated. Threshold can also be defined as the absolute depolarization magnitude from the RP required to initiate an AP.
<i>permeability</i>	Ion channel property that determines the rate at which ions pass through the pore.		
<i>potassium current (<math>I_K</math>)</i>	Ion flux through a potassium-selective ion channel.		
<i>rate of fall (<math>mV ms^{-1}</math>)</i>	Change in MP per unit time during the falling (repolarizing) phase of the AP. Used as an indirect measure of potassium current density.		
<i>rate of rise (<math>mV ms^{-1}</math>)</i>	Change in MP per time unit during the rising (depolarizing) phase of the AP. Used as an indirect measure of sodium current density.		
<i>rectifier</i>	In electronics, a circuit that converts bidirectional current (AC) to unidirectional current (DC). In physiology, a non-linear I/V relationship produced when a membrane conductance is dependent upon the direction of traffic of the permeant ion. As a result, a rectifying current preferentially flows in one direction and not the other.		
<i>refractory period (ms)</i>	A primary determinant of the maximal rate of firing of a neuron.		

### 1.13.1 Introduction

The nervous system collects, coordinates, integrates, and disseminates diverse types of information regarding both the external and internal environments. Processing of this information leads to appropriate physiological and/or behavioral responses. In order for stimuli to produce accurate descriptions of the environment, a variety of neural codes and operations arose during evolution that allow information exchange within and between neurons (for review, see [Perkel and Bullock, 1968](#); [Gerstner et al., 1997](#)). One mechanism, the action potential (AP), arose early during evolution and is essential for rapid signaling in the nervous system.

In this article, we focus on how embryonic neurons acquire the ability to fire APs. AP generation represents a significant challenge because of the requirement for function of several different membrane proteins. Further, there are several examples of neurons that fire APs with developmentally regulated properties. Consequently, the roles of APs in emerging nervous systems are not static and depend upon developmental stage. We review mechanisms that lead to the developmental regulation of excitability. We conclude by identifying key issues that remain unresolved and warrant being the focus of future study (see Neuronal Migration, Axon Pathfinding, A Tale of Two CPGs: Phylogenetically Polymorphic Networks).

### 1.13.2 What Are Action Potentials?

Electrically excitable cells share in common the ability to generate APs. During an AP, the membrane potential (MP) of an electrically excitable cell displays dramatic, stereotypic, and rapid changes. In

muscle cells, AP generation quickly leads to muscle contraction. In neurons, APs allow rapid intra- and intercellular communication.

The classic work of [Hodgkin and Huxley \(1952; Hodgkin, 1958, 1964\)](#) demonstrated that time-dependent changes in the membrane conductance to specific ions underlie the generation of APs. For more detailed treatment of the ionic basis of the MP and AP, we refer the reader to any of several excellent books ([Jack et al., 1988; Johnston and Wu, 1994; Kandel et al., 2000; Hille, 2001; Nicholls et al., 2001](#)). Below, we briefly review key aspects of AP generation. We have defined important terms in the glossary for readers who wish to read the primary literature.

Typically, all cells display an electrical difference across their membrane. This electrical difference, known as the MP, has values in the mV range. By convention, the inside of the cell is negative with respect to the outside. The predominant value of the MP is referred to as the resting MP (RMP).

Excitable cells generate APs (also referred to as spikes or impulses) in response to stimuli that bring the MP to a new, less negative value, known as threshold. Threshold values are not fixed and vary among excitable cells. Moreover, for any given cell, the value of threshold can change over time as a result of developmental regulation, activity, or cell-cell interactions. Stimuli that bring the MP to values less positive than threshold do not lead to AP generation and instead generate subthreshold responses. Thus, APs are not generated in a graded manner but rather as an all-or-none response of the membrane to stimuli of sufficient intensity ([Hodgkin and Huxley, 1952](#)).

Once threshold is achieved, the conductance to sodium and/or calcium ions increases, allowing rapid entry of positively charged sodium and/or calcium ions. The influx of positive charge results in a more positive MP. With further depolarization, more sodium channels open, resulting in greater sodium influx and even more positive MP values. When depolarization occurs, the membrane conductance to potassium ions also increases, but with a delay. The increased potassium conductance and inactivation of sodium channels repolarize the membrane to its original negative resting value, thereby terminating the AP.

In neurons, AP generation initiates near the cell body at a site known as the axon hillock ([Coombs et al., 1957a, 1957b](#)). Subsequently, APs propagate down the axon at constant velocity and amplitude. The ability to propagate APs without diminution in amplitude is an essential feature of neuronal cell-cell communication and guarantees that signals will be transmitted faithfully without failure.

### 1.13.2.1 APs are Neuronal Signatures

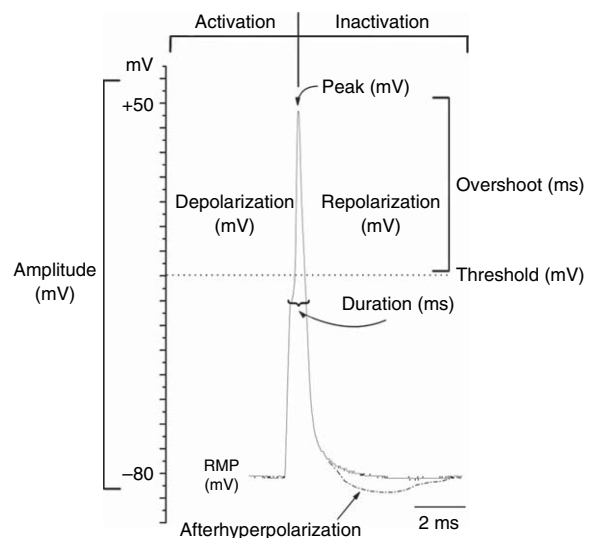
[Figure 1](#) presents an example of an AP fired by a mature neuron. Typically, adult neurons fire APs that are brief in duration and rely upon voltage-gated sodium channels for generation. However, APs fired by mature neurons vary significantly. Further, some neurons respond to stimulation by firing a single AP, while others fire multiple impulses in a characteristic pattern. Consequently, the type of AP or AP train fired in response to stimulation can serve as a signature of neuronal identity (for review, see [Contreras, 2004](#)).

### 1.13.2.2 AP Waveform Properties

The plot of the MP as a function of time during an AP is known as the AP waveform ([Figure 1](#)). Characterization of APs involves analysis of specific properties of the waveform that, in turn, reflect the complement of voltage-gated channels expressed by the cell (see ‘Glossary’).

During the AP, the MP achieves positive values near the equilibrium potential for sodium. The most positive MP achieved during an AP is known as the peak. The rapid depolarization leading to the peak reflects the activity of voltage-gated sodium channels. Thus, measuring the rate of rise provides an indication of sodium current density. In contrast, the activity of voltage-gated potassium channels contributes to the subsequent repolarization and the rate of fall.

After repolarization, the MP often becomes slightly more negative than the standard RMP,



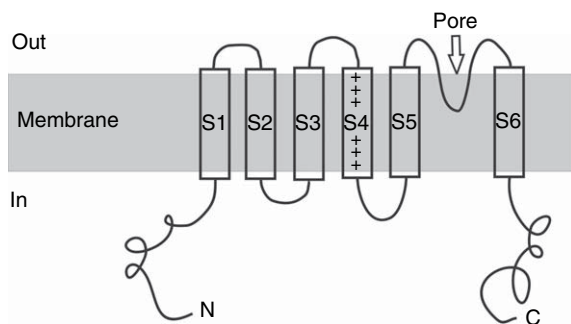
**Figure 1** Stereotypic AP of a mature neuron: an AP recorded from a Rohon-Beard cell of a 2-day-old zebra fish embryo is shown ([Pineda and Ribera, unpublished data](#)). Several AP properties that are defined in ‘Glossary’ are illustrated in the figure.

resulting in an afterhyperpolarization. Afterhyperpolarizations play important roles in determining the frequency of AP firing. Because information is often encoded by AP frequency, afterhyperpolarizations can greatly influence processing of information in the nervous system.

One property of APs that varies greatly between excitable cells is the duration. In some neurons, the AP duration is extremely brief and barely 1 ms (Storm, 1987). In contrast, skeletal muscle fibers fire APs that have slightly longer durations (~5–10 ms; Kuriyama *et al.*, 1970). Cardiac myocytes fire strikingly different impulses with durations that are often as long as 500 ms (Cavalié *et al.*, 1985; Hume and Uehara, 1985). As discussed further below, the duration of neuronal APs often undergoes substantial developmental regulation.

### 1.13.3 Molecular Determinants of APs

The membrane conductances that underlie the AP reflect the activities of several members of the voltage-gated ion channel (VGIC) superfamily of membrane proteins (Figure 2). VGICs respond to membrane depolarization with conformational changes that reveal an ion-selective pore through which specific ions pass in a diffusion-limited manner. Members of the VGIC superfamily have a positively charged transmembrane domain known as the S4 helix, the structure of which depends upon the transmembrane voltage (for review, see Gandhi and Isacoff, 2002).



**Figure 2** Proposed membrane topography of a voltage-gated potassium channel: the proposed disposition of a single voltage-gated potassium channel  $\alpha$ -subunit in the membrane is shown. The S4 transmembrane domain, thought to be critical for voltage-dependent gating, is indicated. Similar S4 domains are also found in voltage-gated sodium and potassium channels and are a hallmark of the VGIC superfamily. 'N' and 'C' indicate the amino- and carboxyl-termini, respectively. Reprinted by permission from Macmillan Publishers Ltd: *Nature* (Yellen, G. 2002. The voltage-gated potassium channels and their relatives. *Nature* 419, 35–42), copyright (2002).

VGICs exist in species throughout the animal and plant kingdoms, including prokaryotes, protozoa, yeast, vascular plants, coelenterates, nematodes, arthropods, mollusks, teleosts, and tetrapods (for review, see Hille, 2001). Not surprisingly, APs have been recorded from cells in a range of species spanning the animal and plant kingdoms (for review, see Hille, 2001). During the last 20 years, many genes and transcripts for a large variety of VGIC proteins have been cloned and characterized. Noda *et al.* (1984) reported the cloning of a voltage-gated sodium channel from the electric organ of the electric eel, *Electrophorus electricus*. The cloning of a voltage-gated calcium channel from rabbit skeletal muscle followed in 1987 (Tanabe *et al.*, 1987). That same year, several groups reported cloning of the *Drosophila Shaker* potassium channel gene (Kamb *et al.*, 1987; Papazian *et al.*, 1987; Pongs *et al.*, 1988; Schwartz *et al.*, 1988). Comparisons of the primary sequences of cloned VGIC genes have revealed a high degree of conservation among species that are distantly related (for review, see Jan and Jan, 1990; Coetzee *et al.*, 1999; Moreno-Davila, 1999; Goldin, 2001; Yu and Catterall, 2003). Such findings suggest that the key structural and functional properties of VGICs have been conserved during evolution.

Molecular cloning has revealed an unexpectedly large number of VGIC genes, many more than might have been expected on the basis of physiological recording. Current research seeks to identify the specific roles of the many VGIC genes that have been identified. A common finding has been that VGIC gene subfamilies may have multiple members in vertebrates (e.g., Kv1 family: Kv1.1–Kv1.9; Nav1 family: Nav1.1–Nav1.9, respectively) but only a single orthologous gene in invertebrates (e.g., *Drosophila Shaker*; *Drosophila para*, respectively).

Phylogenetic analyses suggest that VGICs evolved from an ancestral voltage-gated potassium channel (for review, see Hille, 2001; Yu *et al.*, 2005). Further, voltage-gated calcium, but not sodium, channels have been detected in unicellular organisms (DeHertogh *et al.*, 2002). APs recorded from species lacking voltage-gated sodium channels rely upon voltage-gated calcium channels for their initiation and typically are much longer-lasting events that signal via changes in intracellular calcium ion concentrations.

Phylogenetic analyses indicate that voltage-gated sodium channels evolved later than did voltage-gated potassium and calcium channels. Voltage-gated sodium channel function also enlisted a sodium pump that establishes a transmembrane

sodium gradient (Stein, 2002). Voltage-gated sodium channels underlie the ability of the AP to be a rapid spike, occur in bursts, and propagate rapidly. Thus, the later evolution of voltage-gated sodium channels introduced important changes into the AP waveform, allowing it to be a rapid spike. Further, voltage-gated sodium channels allow APs to occur repetitively at high frequencies. Thus, voltage-gated sodium channels significantly expanded the roles that APs can play in information processing and behavior.

### 1.13.4 Roles in Information Coding

During development, the roles that APs play in the nervous system vary substantially (Figure 3; see below). Interestingly, many neurons fire APs prior to synapse formation. Several lines of evidence indicate that early-appearing APs play a developmental role. After synapse formation, APs take part in mechanisms that select and/or eliminate specific connections. In the mature nervous system, APs contribute to plasticity mechanisms in addition to being essential for the rapid processing of information.

#### 1.13.4.1 Prior to Synapse Formation

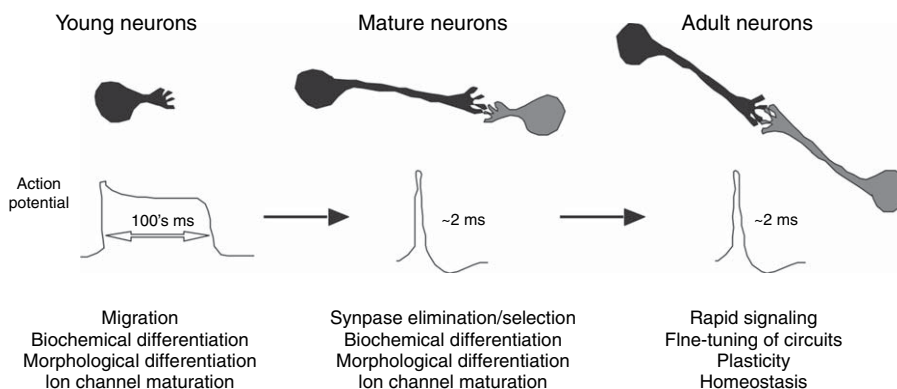
Many aspects of neuronal differentiation begin prior to synapse formation. Importantly, many neurons acquire electrical excitability prior to synapse formation, thus allowing neuronal activity to influence subsequent aspects of differentiation (Holliday and Spitzer, 1990). For example, soon after neurons exit the cell cycle and initiate postmitotic differentiation, they often migrate long distances and take up residence at distant sites. Blocking electrical activity can affect migratory patterns of embryonic neurons for both invertebrates and vertebrates

(Komuro and Rakic, 1992; Tam *et al.*, 2000). Neurons differentiate biochemically and often synthesize and secrete neurotransmitter prior to synapse formation. Perturbations of excitability alter biochemical differentiation of neurons, resulting in inappropriate neurotransmitter synthesis (Gu and Spitzer, 1995; Borodinsky *et al.*, 2004). Morphological differentiation also occurs during this period, notably axon outgrowth and initial contact of targets. Blockade of activity also perturbs this important aspect of neuronal differentiation (Cohan and Kater, 1986; Gu *et al.*, 1994). As discussed further below, electrical membrane properties are also developmentally regulated. Patterns of early activity influence acquisition of mature channel properties (Desarmenien and Spitzer, 1991; Gomez and Spitzer, 1999).

A common finding for effects of activity prior to synapse formation concerns its dependence on calcium ions. The majority of studies indicate that calcium ions act as intracellular messengers and participate in mechanisms that translate patterns of activity into developmental programs (for review, see Spitzer *et al.*, 2004). As we discuss below, many neurons fire long-duration calcium-dependent APs prior to synapse formation, thus accounting, at least in part, for the calcium dependence.

#### 1.13.4.2 During Synapse Formation and Early Circuit Activity

Synapses can form in the absence of neural impulses (Verhage *et al.*, 2000; Trachtenberg *et al.*, 2002; De Paola *et al.*, 2003). However, the maintenance of synapses requires transmitter secretion that normally depends upon impulse propagation (for review, see Sanes and Lichtman, 2001). Moreover, in several instances, after synapses initially form,



**Figure 3** AP roles change during development. In neurons, APs play several roles in addition to rapid processing of information. Prior to synapse formation, APs play developmental roles. During the early stages of synapse formation, APs function in mechanisms that eliminate or stabilize specific connections. In the adult nervous system, APs contribute to plasticity mechanisms.

there is a period of pruning or synapse elimination. For example, at the neuromuscular junction, muscle fibers that receive inputs from multiple axons become singly innervated (for review, see Colman and Lichtman, 1993). Also, in the cerebellum, Purkinje cells are initially innervated by more than one climbing fiber but later respond to inputs from only one (Mariani and Changeux, 1981). Similar observations have been made for developing synapses in the visual, auditory, and autonomic nervous systems (Lichtman, 1977; Shatz and Stryker, 1988).

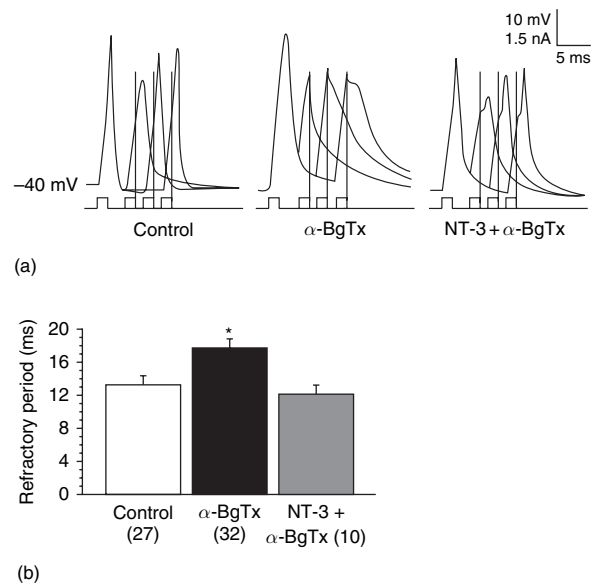
During development, activity regulates neuronal arbor growth by regulating branch lifetime in retinal ganglion cell axons and tectal dendrites of *Xenopus* and zebra fish larvae (Rajan and Cline, 1998; Rajan *et al.*, 1999; Lohmann *et al.*, 2002; Schmidt, 2004). Activity-dependent expression of structural proteins may also be involved in synapse stabilization and dendritic branch formation (Ziv and Smith, 1996; Lichtman, 2000; Star *et al.*, 2002; Fukazawa *et al.*, 2003; for review, see Steward and Schuman, 2001; Hua and Smith, 2004). Moreover, activity promotes secretion of neurotrophins that have multiple effects on synaptic development and function as well as ion channels (Nick and Ribera, 2000; for review, see Poo, 2001; Lu and Je, 2003; Figure 4).

#### 1.13.4.3 Mature Nervous System

In the mature nervous system, a principal role of the AP is transduction, conduction, and processing of information (Eggermont, 1998; Sanger, 2003). However, even at these stages, AP generation contributes to mechanisms that alter the nervous system both structurally and functionally. For example, activity sculpts the time course of elimination of Rohon–Beard cells from the spinal cord of larval zebra fish (Svoboda *et al.*, 2001). Neural activity also promotes both short- and long-term synaptic changes and affects the maintenance, synthesis, and release of neurotrophins (Madison *et al.*, 1991; Poo, 2001; Lu and Je, 2003).

#### 1.13.5 Regulation of Excitability during Embryogenesis

Developmental regulation of excitability occurs throughout embryogenesis. In the early 1970s, Takahashi and co-workers recorded the changes in electrical excitability that occur in the tunicate *Halocynthia roretzi* as it develops from an unfertilized egg to an adult with differentiated tissues (Takahashi, 1979; for review, see Takahashi and

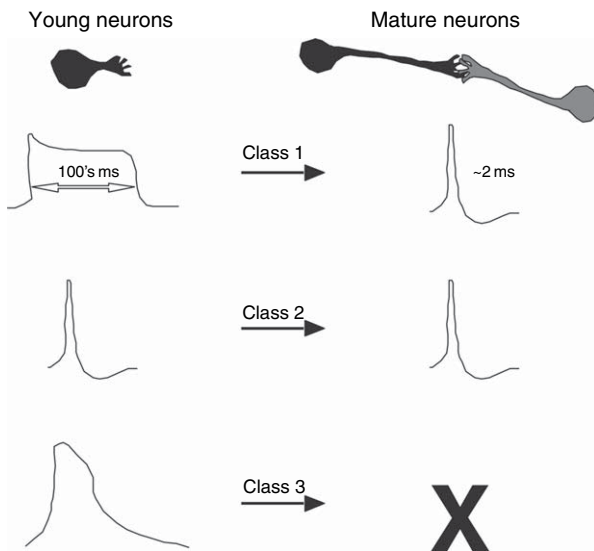


**Figure 4** Synaptic activity regulates presynaptic excitability. Muscle activation leads to release of retrograde factors that modulate excitability of the presynaptic neurons. These effects are mediated by the neurotrophin, NT-3. a, The refractory period was measured using a two-pulse protocol with a longer interpulse interval for each successive trial. Three trials are superimposed for each condition. In the presence of  $\alpha$ -BgTX, APs did not overshoot the stimulus artifact. b, Co-application of NT-3 with  $\alpha$ -BgTX rescued the effects of the toxin. Reprinted by permission from Macmillan Publishers Ltd: *Nat. Neurosci.* (Nick, T. A. and Ribera, A. B. 2000. Synaptic activity modulates presynaptic excitability. *Nat. Neurosci.* 3, 142–149), copyright (2000).

Okamura, 1998). Their results indicated that, in both the unfertilized and the newly fertilized egg, APs were generated. Further, AP generation required the function of voltage-gated sodium and/or calcium channels. In contrast, differentiated muscle fibers showed a predominantly calcium-dependent AP. These observations suggested that, during early embryonic differentiation: (1) some types of ion channels are eliminated; (2) some types of ion channels increase in density; and (3) new channel types appear.

#### 1.13.6 Developmental Regulation of the AP

The results of several studies reveal three general developmental patterns of APs (Figure 5). The first two patterns, classes 1 and 2, have been studied more frequently and are relevant to the vast majority of neurons that continue to fire APs in the nervous system. These two patterns are distinguished on the basis of the ionic dependence of the impulse initially fired by a differentiating excitable cell (for review, see



**Figure 5** Patterns of AP development. Three patterns have been described. In the first, APs are of long duration when first present, but mature in time to the more stereotypic brief spikes, characteristic of mature neurons. The second pattern consists of APs that show little developmental regulation and are brief and sodium-dependent from the time of first appearance. The third pattern, characteristic of some sensory neurons, consists of APs at early stages followed by the loss of AP generation. At adult stages, neurons of the class 3 pattern respond with graded depolarization or hyperpolarizations to sensory stimuli.

Spitzer, 1991; Ribera and Spitzer, 1992; Spitzer *et al.*, 2000). We discuss these two patterns in more detail below.

The third developmental pattern consists of an early period of electrical activity followed by loss of AP generation. This pattern appears to be unique to sensory cells and consists of an early transient period of excitability followed by the generation of graded potentials in response to sensory stimuli (Beutner and Moser, 2001). Interestingly, the available evidence implicates the transiently appearing APs in proper development of sensory neurons (Beutner and Moser, 2001; Brandt *et al.*, 2003).

#### 1.13.6.1 Class 1 Pattern of AP Development

The class 1 pattern of AP development consists of APs that are initially of long duration (5–500 ms; Spitzer and Lamborghini, 1976; Baccaglini and Spitzer, 1977). The early-appearing APs can be generated in the absence of extracellular sodium or in the presence of the sodium channel blocker tetrodotoxin and are eliminated by substitution of calcium in the extracellular media. Hence, these APs are described as calcium-dependent. In this respect, the class 1 pattern is similar to the third pattern mentioned above: the early APs that are transiently

expressed by sensory neurons are calcium-dependent (Beutner and Moser, 2001).

As development proceeds, the AP duration becomes progressively briefer. In addition, the AP acquires sensitivity to blockers of voltage-gated sodium channels (e.g., tetrodotoxin) and insensitivity to calcium channel blockers (e.g., cobalt). The later-appearing APs are hence considered to be sodium-dependent. Examples of excitable cells displaying the class 1 pattern of development include amphibian primary spinal neurons, neurons of the rat dorsal nucleus of the vagus, chick motor neurons, ferret lateral geniculate neurons, and rat nucleus accumbens neurons (Spitzer, 1976; Spitzer and Lamborghini, 1976; Baccaglini and Spitzer, 1977; McCobb *et al.*, 1990; Ramoa and McCormick, 1994; Belleau and Warren, 2000; for review, see Spitzer, 1991; Moody, 1995).

#### 1.13.6.2 Class 2 Pattern of AP Development

The class 2 pattern of AP development consists of APs that have brief durations from the time of their first appearance. The APs initially expressed are and remain sodium-dependent as differentiation proceeds. Further, the AP duration does not change significantly. Examples of cells displaying the class 2 pattern include chick ciliary ganglion neurons, quail mesencephalic neural crest cells, rat spinal and phrenic neurons, grasshopper interneurons, and amphibian myocytes (Goodman and Spitzer, 1981; Bader *et al.*, 1983, 1985; DeCino and Kidokoro, 1985; Henderson and Spitzer, 1986; Krieger and Sears, 1988; Ziskind-Conhaim, 1988a, 1988b).

#### 1.13.6.3 General Principles

Even though several different types of ion channel underlie AP generation, the principal difference between the three patterns of AP development concerns developmental regulation of potassium current (Barish, 1986; Krieger and Sears, 1988; O'Dowd *et al.*, 1988; McCobb *et al.*, 1989; Nerbonne and Gurney, 1989; Ribera and Spitzer, 1989, 1990). The class 1 pattern reflects a program of ion channel regulation in which voltage-gated potassium channels are present at low density and have slow activation properties when APs are initially expressed and of long duration. The subsequent developmental shortening of the AP duration is due to a progressive increase in potassium channel density with concomitant changes in channel activation properties (Barish, 1986; O'Dowd *et al.*, 1988; Ribera and Spitzer, 1989; Lockery and Spitzer, 1992; Harris *et al.*, 1998).

Computer reconstructions of the APs recorded from *Xenopus* spinal neurons support the view that the delayed rectifier potassium current plays the predominant role during AP maturation in amphibian spinal neurons (Barish, 1986; Lockery and Spitzer, 1992).

Regardless of the developmental pattern, calcium and sodium currents appear early in neuronal differentiation (O'Dowd *et al.*, 1988; Alzheimer *et al.*, 1993; Albrieux *et al.*, 2004). Once present, calcium currents may increase in density but often remain stable (Barish, 1986; Gottmann *et al.*, 1988; McCobb *et al.*, 1989). In contrast, sodium currents typically increase in density and undergo kinetic changes (Huguenard *et al.*, 1988; O'Dowd *et al.*, 1988; McCobb *et al.*, 1990; Alzheimer *et al.*, 1993; Pineda *et al.*, 2005).

### 1.13.7 Myelination

In the nervous system, developmental regulation of ion channels is not unique to neurons. Glial cells also display developmentally regulated properties of excitability (Sontheimer *et al.*, 1992; Kressin *et al.*, 1995; Bordey and Sontheimer, 1997; Maric *et al.*, 1998; Bringmann *et al.*, 2000; Pannicke *et al.*, 2002; for review, see Waxman *et al.*, 1993). The distribution of specific sodium and potassium channel isoforms in myelinated axons provides one of the most interesting examples of developmental regulation of ion channels. Recent studies have revealed that interactions between axons and glia during development play key roles in sculpting the differential localization of VGICs in the axonal membrane.

#### 1.13.7.1 Function

Glial cells wrap around axons and form several layers of membrane known as myelin (for review, see Sherman and Brophy, 2005). The identities of the glial cells that form myelin differ in the peripheral versus central nervous systems. In the central nervous system, oligodendrocytes form myelin. Schwann cells are the relevant glia for the peripheral nervous system.

Myelination of axons in both the peripheral and central nervous systems underlies the amazing ability of axons to propagate APs rapidly (for review, see Sherman and Brophy, 2005). Myelin provides insulation to the axon and current flow is restricted to nonmyelinated areas, known as nodes of Ranvier. Consequently, APs need not be conducted down the entire length of the axon but only to successive nodes of Ranvier, thereby accelerating AP conduction velocities. Further, the metabolic demands of

transmitting APs over long distances are diminished because impulses are only generated at nodes and not throughout the entire length of the axon.

Morphological studies indicate that myelin is present in jawed vertebrates but not lamprey or hagfish (Bullock *et al.*, 1984). In addition, a few copepod crustacean species that display rapid escape behaviors necessary for life in predator-rich ocean waters also have myelin (Davis *et al.*, 1999). The copepods that display rapid behaviors and myelin-like sheaths are thought to have evolved later than other members of their species. Thus, myelin represents a relatively recent evolutionary adaptation that results in rapid behavioral responses.

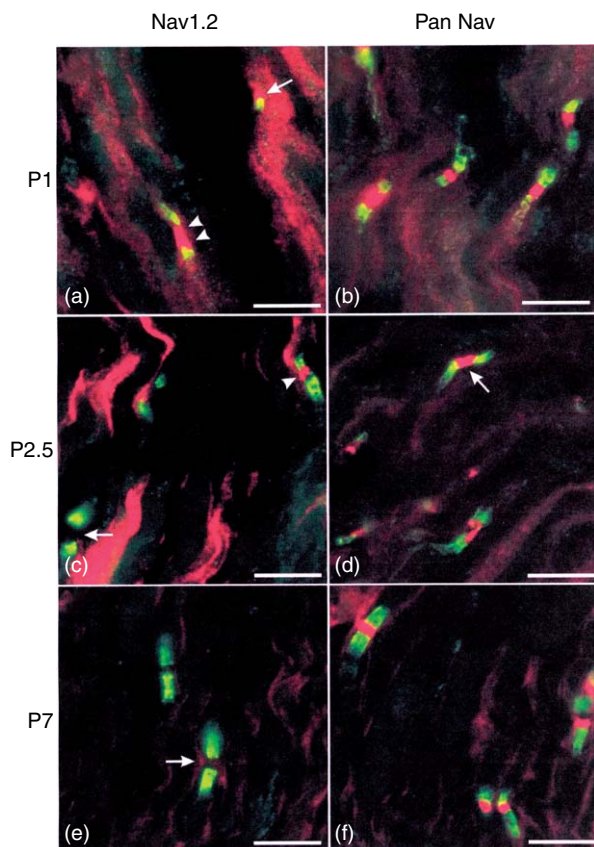
#### 1.13.7.2 Distribution of Ion Channels during Developmental Myelination

Toxin labeling studies indicated that axons have an overall low density of sodium channels, even though they can propagate APs (Waxman *et al.*, 1989). These studies raised the possibility that, in addition to myelin, the distributions of VGICs may be optimized for generation of APs at nodes of Ranvier. More recent immunocytochemical studies have demonstrated that sodium channels are maintained at high densities at nodes of Ranvier (for review, see Rasband and Trimmer, 2001; Figure 6). In contrast, specific potassium channel isoforms are maintained at high densities in nearby, non-nodal regions known as the juxtaparanodes. Moreover, the specific locations of the different ion channel types are specified during developmental myelination and require interactions between the axon and glia (Wu and Barish, 1994; Demerens *et al.*, 1996; Stevens *et al.*, 1998; Stevens and Fields, 2000).

In both the peripheral and central nervous systems, one sodium channel isoform, Nav1.2, appears early in unmyelinated zones (Westenbroek *et al.*, 1992; Gong *et al.*, 1999; Boiko *et al.*, 2001; for review, see Rasband and Trimmer, 2001). As nodes form, another isoform, Nav1.6, becomes the dominant sodium channel type (Caldwell *et al.*, 2000; Boiko *et al.*, 2001; for review, see Rasband and Trimmer, 2001).

Potassium channels also display stereotypic distributions in myelinated axons. Electrophysiological studies demonstrated that potassium current densities were not constant across the length of myelinated axons, suggesting nonhomogeneous, optimized distributions of potassium channels (Chiu and Ritchie, 1980; Chiu and Wilson, 1989; Roper and Schwarz, 1989). Immunocytochemical results have directly demonstrated the locations of specific potassium channel subtypes in myelinated axons. In myelinated axons, potassium channel





**Figure 6** VGIC distributions in axons. At nodes of Ranvier, the identity of the sodium channel  $\alpha$ -subunit changes during development in rat sciatic nerve. Panels (a), (c), and (e) present Nav1.2 immunoreactivity (red) data, whereas panels (b), (d), and (f) present pan-sodium channel immunoreactivity (red) data. Caspr immunoreactivity, a marker of the paranode, is shown in green. At all stages of development, nodes of Ranvier possess high densities of sodium channels (b, d, f). At early (a) but not late (e) stages, the predominant sodium channel isoform is Nav1.2. Scale bar: 10  $\mu$ m. Reproduced from Rasband, M. N. and Trimmer, J. S. 2001. Developmental clustering of ion channels at and near the node of Ranvier. *Dev. Biol.* 236, 5–16, with permission from Elsevier.

densities are especially high in the juxtaparanodal regions (Wang *et al.*, 1993; Arroyo *et al.*, 1999; for review, see Rasband and Trimmer, 2001).

In sum, recent studies are revealing the molecular organization of nodal, paranodal, and juxtaparanodal regions of myelinated axons. It is clear that interactions between the axon and myelinating glia are required to form and maintain these regions and the concomitant distributions of ion channels. A better understanding of the underlying mechanisms will provide insights about how ion channel expression and distributions are regulated during development. Moreover, the information could potentially be useful for intervention and treatment of conditions associated with demyelination or axon regeneration.

### 1.13.8 Mechanisms of Developmental Regulation

Even though developmental changes in potassium currents typically drive maturation of the AP, most VGICs show developmental regulation. Analyses of mRNA and protein indicate that regulation of ion channel expression occurs across both temporal and spatial domains (Table 1). Electrophysiological analyses further indicate that the properties of voltage-gated currents expressed by a given cell are not constant over time but change during differentiation and in response to activity (Table 2).

Developmental regulation of channel function could occur at transcriptional, post-transcriptional, translational, and post-translational levels. These levels of control are not mutually exclusive and several could be operating simultaneously (Giraud *et al.*, 1998; Blaine *et al.*, 2004).

In some cases, developmental regulation of ion currents occurs in the absence of interactions with other cells or factors (Henderson and Spitzer, 1986). Additionally, cell–cell interactions, often apparent at the onset of synaptogenesis, play important roles (Okado and Takahashi, 1990a, 1990b; Okamura *et al.*, 1994; Subramony *et al.*, 1996; Bahls *et al.*, 1998; Nick and Ribera, 2000; Martin-Caraballo and Dryer, 2002a). Growth factors and neurotrophins often mediate the effects of activity or cell–cell interactions (Subramony *et al.*, 1996; Rothe *et al.*, 1999; Martin-Caraballo and Dryer, 2002a; for review, see Dryer *et al.*, 2003).

Further, extrinsic cues affect functional expression of VGICs differently depending upon the neuron type. For example, growth factors regulate expression of currents post-translationally in ciliary ganglion neurons but their effects require new protein synthesis in lumbar motor neurons (Subramony *et al.*, 1996; Martin-Caraballo and Dryer, 2002a). Thus, both intrinsic and extrinsic cues operate to regulate ion currents during development (for review, see Dryer, 1998; Ribera, 1998).

In Table 1, we review the molecular bases of developmental regulation of ion channel expression and function in the developing nervous system.

#### 1.13.8.1 Transcriptional Regulation

Numerous stimuli, such as injury, electrical activity, growth factors, and development, modulate VGIC gene transcription (Beckh *et al.*, 1989; Ribera and Nguyen, 1993; Toledo-Aral *et al.*, 1995; Burger and Ribera, 1996; Gurantz *et al.*, 1996; Villeneuve *et al.*, 2000; Vega *et al.*, 2003; for review, see Levitan and Takimoto, 1998; Sashihara *et al.*, 1998; Black and Grabowski, 2003). Recent

**Table 1** Developmentally and spatially specific expression of ion channels

VGIC type	Molecular identity	Regulation	Neuron type	References
Sodium	Nav1.3	Expression of Nav1.3 was linked to acquisition of electrical excitability.	Murine preplate and Cajal–Retzius cells (E12–13)	Albrieux <i>et al.</i> (2004)
Sodium and potassium	Nav1.1, Nav1.2, Nav1.3, Nav1.6; Kv1.3, Kv1.4, Kv1.6; Kv2.1; Kv3.1, Kv3.3; Kv4.2, Kv4.3	RT-PCR analyses indicated that full-length variants of Nav1.1 and Nav1.3 were expressed. In contrast, variants of Nav1.2 and Nav1.6 coding for truncated subunits were expressed. Several potassium channel subunits were already expressed at these early stages of differentiation.	Rat spinal motor neurons <i>in vitro</i>	Alessandri-Haber <i>et al.</i> (2002)
Sodium	Nav1.1, Nav1.2, Nav1.3	<i>In situ</i> hybridization studies showed that: (1) Nav1.1 was predominant at late postnatal stages; (2) Nav1.2 was expressed at all stages studied with regional variability; and (3) Nav1.3 was predominantly expressed at fetal and early postnatal stages.	Rat CNS, E10–P90	Beckh <i>et al.</i> (1989)
Potassium	Kv 1.1, Kv2.1, Kv2.2	<i>In situ</i> hybridization studies revealed Kv2.2 and Kv1.1 mRNA in ventral and dorsal spinal cord, respectively. Both Kv2 genes were detected in RNA of developing embryos by RNAase protection assays.	<i>Xenopus</i> spinal cord, 1–3 days	Burger and Ribera (1996)
Potassium	Kv $\beta$ 1	<i>In situ</i> hybridization studies revealed developmentally and spatially regulated expression of the auxiliary subunit.	Mouse brain, E16–P7	Butler <i>et al.</i> (1998)
Potassium	Kv $\beta$ 1, Kv $\beta$ 2, Kv $\beta$ 3	Kv $\beta$ 1 expression was high at birth in all brain regions examined and decreased with age. Kv $\beta$ 2 expression was low at birth and increased with age, reaching adult levels by the third postnatal week.	Mouse CNS, spinal cord and dorsal root ganglia, E16–adult	Downen <i>et al.</i> (1999)
Calcium	Calcium channel isotypes A, B, and E	Expression of Ca <sup>2+</sup> channel transcripts are developmentally regulated <i>in vitro</i> and can be influenced differentially by transmembrane signaling via chronic depolarization and Ca <sup>2+</sup> entry.	Rat cerebellar cortex	Falk <i>et al.</i> (1999)
Potassium	Kv3.1	Kv3.1 transcripts were upregulated <i>in vivo</i> and <i>in vitro</i> during the period of maturation of <i>I</i> <sub>Kv</sub> .	<i>Xenopus</i> spinal neurons, 1–3 days	Gurantz <i>et al.</i> (1996)
Potassium	xKv $\beta$ 2, xKv $\beta$ 4	mRNA of both subunits is expressed during the period of impulse maturation in different neuronal populations.	<i>Xenopus</i> spinal neurons, 1–3 days	Lazaroff <i>et al.</i> (1999)
Sodium	TuNa I and TuNa II	Regional specific expression. Gene transcription is dependent on specific cellular contacts.	Ascidian embryo and neural cells ( <i>Halocynthia roretzi</i> )	Okamura <i>et al.</i> (1997)
Calcium	N and L type	Immunocytochemical and physiological analyses demonstrated developmentally regulated expression of calcium channel isotypes.	Rat hippocampal neurons, <i>in vitro</i>	Pravettoni <i>et al.</i> (2000)
Potassium	XSha2 (Kv1.2)	RNAase protection assays demonstrated that Kv1.2 expression is neural-specific. Further, Kv1.2 transcripts were first detected at the time of neural induction.	<i>Xenopus</i> spinal neurons <i>in vivo</i> and <i>in vitro</i>	Ribera (1990)

(Continued)

**Table 1** (Continued)

<i>VGIC type</i>	<i>Molecular identity</i>	<i>Regulation</i>	<i>Neuron type</i>	<i>References</i>
Potassium	XSha1	mRNA detection in neural crest derivatives and in both CNS and PNS glia.	<i>Xenopus</i> embryo, 1–3 days	Ribera and Nguyen (1993)
Sodium	Nav $\beta$ 3	<i>In situ</i> hybridization studies revealed developmentally regulated expression of Nav $\beta$ 3.	Rat CNS, E10–P14 and adult	Shah <i>et al.</i> (2001)
Potassium, sodium	Kv1.1, Kv1.2, Kv $\beta$ 2; Pan Nav1	Immunocytochemical analyses revealed progressive clustering of Kv subunits in axonal juxtaparanodes during developmental myelination. Nav1 subunits were in nodes of Ranvier.	Rat sciatic nerve, P3–21	Vabnick <i>et al.</i> (1996)
Calcium	P/Q, N, and R	Immunocytochemical analyses revealed cell-specific patterns of expression for calcium channel isotypes A, B, C, D, and E.	Adult rat spinal motor neurons, interneurons, and nerve terminals	Westenbroek <i>et al.</i> (1998)

RT-PCR, reverse transcriptase polymerase chain reaction; CNS, central nervous system; PNS, peripheral nervous system.

**Table 2** Development and activity regulate VGIC properties

<i>VGIC type</i>	<i>VGIC molecular identity</i>	<i>Regulation</i>	<i>Neuron type</i>	<i>References</i>
Sodium	Nav1.3	Expression of Nav1.3 was linked to acquisition of electrical excitability.	Murine preplate and Cajal–Retzius cells (E12–13)	Albrieux <i>et al.</i> (2004)
Sodium	Persistent current	Persistent current density was upregulated during development.	Rat sensorimotor cortex, P2–21	Alzheimer <i>et al.</i> (1993)
Calcium, sodium, and potassium	ND	Potassium and sodium currents were detected at early stages. Calcium currents developed later. All were subsequently upregulated.	Quail embryonic mesencephalic neural crest cells <i>in vitro</i>	Bader <i>et al.</i> (1983)
Calcium, sodium, and potassium	ND	At the time of neurite appearance, functional Na <sup>+</sup> , Ca <sup>2+</sup> , and voltage-gated K <sup>+</sup> channels were present. However, $I_{Kv}$ amplitude increased during neural development. Changes in kinetic parameters were observed. $I_{Na}$ and $I_{Ca}$ amplitudes were also increasing to a lesser extent during differentiation.	Amblystoma spinal neurons	Barish (1986)
Hyperpolarization-activated	HCN1, HCN2, HCN4	Febrile seizures differentially altered expression patterns of several HCN channel genes and proteins.	Rat hippocampus, E10–11	Brewster <i>et al.</i> (2002)
Potassium	Large-conductance K channels	Electrical recordings demonstrated developmental changes in calcium and voltage sensitivities.	Rat embryonic rat telencephalon cortical slices, E12–14 and E21	Bulan <i>et al.</i> (1994)
Potassium	A-type	Spontaneous electrical activity, but not target tissues, regulated the normal developmental increase in potassium current density.	Chick lumbar motoneurons, E6 and E11	Casavant <i>et al.</i> (2004)
Potassium	Large-conductance Ca-activated K channels	The developmental expression of functional K <sub>Ca</sub> channels was regulated differentially in choroids versus ciliary cells.	Chick choroid and ciliary ganglion neurons, E9–13	Cameron and Dryer (2000)
Whole-cell conductance	ND	Development and hypergravity altered electrophysiological properties of hair cells.	Rat utricular hair cells, P0–8	Chabbert <i>et al.</i> (2003)

(Continued)

Table 2 (Continued)

VGIC type	VGIC molecular identity	Regulation	Neuron type	References
Calcium	LVA and HVA calcium channels	Large modifications in the expression of voltage-dependent calcium channels occurred during a developmental period associated with neuronal growth and the beginning of synaptogenesis.	Mouse vestibular ganglia, E14–17	Chambard <i>et al.</i> (1999)
Calcium and potassium	Calcium-dependent K current; inward rectifier; voltage-gated K current; Ca current	Spontaneous activity regulated functional expression of calcium-dependent K current. The effects were calcium-dependent and required <i>de novo</i> transcription.	Ascidian embryonic muscle	Dallman <i>et al.</i> (1998)
Potassium	Delayed rectifier	Calcium influx through voltage-dependent channels during early developmental stages regulated the differentiation of potassium current kinetics and modulated the ionic dependence of APs via a PKC-dependent pathway.	<i>Xenopus</i> embryonic spinal neurons <i>in vitro</i>	Desarmenien and Spitzer (1991)
Calcium	Calcium channel isotypes A, B, and E	Expression of Ca channel transcripts were developmentally regulated <i>in vitro</i> and modulated differentially by transmembrane signaling via chronic depolarization and calcium entry.	Rat embryonic cerebellar cortical neurons <i>in vitro</i>	Falk <i>et al.</i> (1999)
Calcium	LVA and HVA	Patterns of activity differentially regulated densities of LVA and HVA calcium currents.	Mouse dorsal root ganglion neurons <i>in vitro</i>	Li <i>et al.</i> (1996)
Calcium and potassium	Calcium-activated potassium current	A calcium-activated potassium current was not present in the cochlea of the chick embryo, although it is present at adult stages.	Chick cochlea, E14	Fuchs and Sokolowski (1990)
Several VGICs	Sodium, potassium, calcium, calcium-dependent potassium current	Developmental changes in APs waveforms and the onset of repetitive firing correlate with increase in the current density of existing VGICs.	Rat spinal motor neurons, E15–16 and P1–3	Gao and Ziskind-Conhaim (1998)
Potassium	Kv1 subfamily	Activity regulated the expression of some, but not all, Kv1 channel genes.	Mouse hippocampus <i>in vivo</i> and <i>in vitro</i> , E17, P2–6 and adult	Grosse <i>et al.</i> (2000)
Potassium	Delayed rectifier (single channels)	Single-channel recordings revealed three different potassium single-channel types. One type showed developmental changes in kinetic properties.	<i>Xenopus</i> spinal neurons <i>in vitro</i>	Harris <i>et al.</i> (1988)
Sodium	ND	Developmental changes in sodium current densities but not kinetic properties were observed.	Rat sensorimotor cortical neurons, E16–P50	Huguenard <i>et al.</i> (1988)
Potassium	BK (large-conductance) calcium-activated potassium (single-channel analysis)	Single channel analysis of large conductance calcium-activated potassium channels in neocortical pyramidal neurons indicated the presence of both fast- and slow-gating channels between P0 and P5. However, at later stages, only slow-gating channel was detected.	Neocortical pyramidal neurons, P1–28	Kang <i>et al.</i> (1996)
Sodium	Nav1.3, 1.8, and 1.9	Changes in neuronal activity altered the expression of sodium channel genes in a subtype-specific manner, via an NGF-independent mechanism.	Mice dorsal root ganglion neurons, E13.5 <i>in vitro</i>	Klein <i>et al.</i> (2003)

(Continued)

Table 2 (Continued)

VGIC type	VGIC molecular identity	Regulation	Neuron type	References
Potassium	ND	Developmental upregulation of potassium current occurred during acquisition of hearing.	Mouse hair cells	Kros <i>et al.</i> (1998)
Potassium	Kv1.5, Kv1.4, and Kv2.1	Membrane depolarization specifically inhibited Kv1.5 channel gene transcription.	Rat pituitary cell line	Levitan <i>et al.</i> (1995)
Potassium	Kv3.1	Elevated potassium induced increased Kv3.1 mRNA levels. The effect of the block was prevented by the addition of calcium channel blockers.	Rat inferior colliculus neurons, P3–30	Liu and Kaczmarek (1998)
Potassium	Kv1.1, Kv3.1	Perturbations of activity in the auditory system regulated the levels of Kv1.1 and K3.1 channel proteins in the nucleus magnocellularis. However, alterations in channel proteins did not linearly predict changes in current densities.	Chick auditory system neurons, P1–2 (electrophysiology) and P5–10 (immunocytochemistry)	Lu <i>et al.</i> (2004)
Sodium, calcium, and potassium	Sodium, calcium, and potassium	Developmental changes in voltage-gated currents led to the class 3 pattern of AP development. Initially, hair cells fired APs. However, at late stages, hair cells responded to stimulation with graded potentials.	Mouse cochlear inner hair cells, E14.5–P12	Marcotti and Kros (1999); Marcotti <i>et al.</i> (2003)
Potassium	Ca(v)1.3 and SK2	The appearance of the SK current coincided with their becoming responsive to acetylcholine. The transiently expressed SK channel was activated by Ca <sup>2+</sup> influx through both Ca <sub>v</sub> 1.3 channels and nicotinic receptors.	Mouse inner and outer hair cells, E14.5–P18	Marcotti <i>et al.</i> (2004)
Potassium	ND	During early stages of neuronal differentiation, potentiometric dye studies revealed developmentally regulated changes in RMP.	Rat cortical cells, E11–22	Maric <i>et al.</i> (1998)
Potassium	Large-conductance Ca-activated K (BK); delayed rectifier; inactivating A-type	Two BK channel variants were described. One variant was preferentially expressed during embryonic development. In addition, there were quantitative changes in $I_K$ expression, that underlied the overall increase in excitability of differentiating cells.	Embryonic rat telencephalic neuroepithelium, E12–21	Mienville and Barker (1996, 1997)
Potassium	rSlo and Kv3.1 transcripts; single-channel analysis	Molecular analyses revealed developmental upregulation of rSlo transcripts but uniform expression of Kv3.1. Upregulation required depolarization and calcium and occurred at the transcriptional level.	Rat cerebellum, E20 <i>in vitro</i> and P2–21 <i>in vivo</i>	Muller <i>et al.</i> (1998)
Calcium	ND	The density of HVA calcium current increases after cell death, during the period of synapse elimination.	Chick motor neurons	Mynlieff and Beam (1992)

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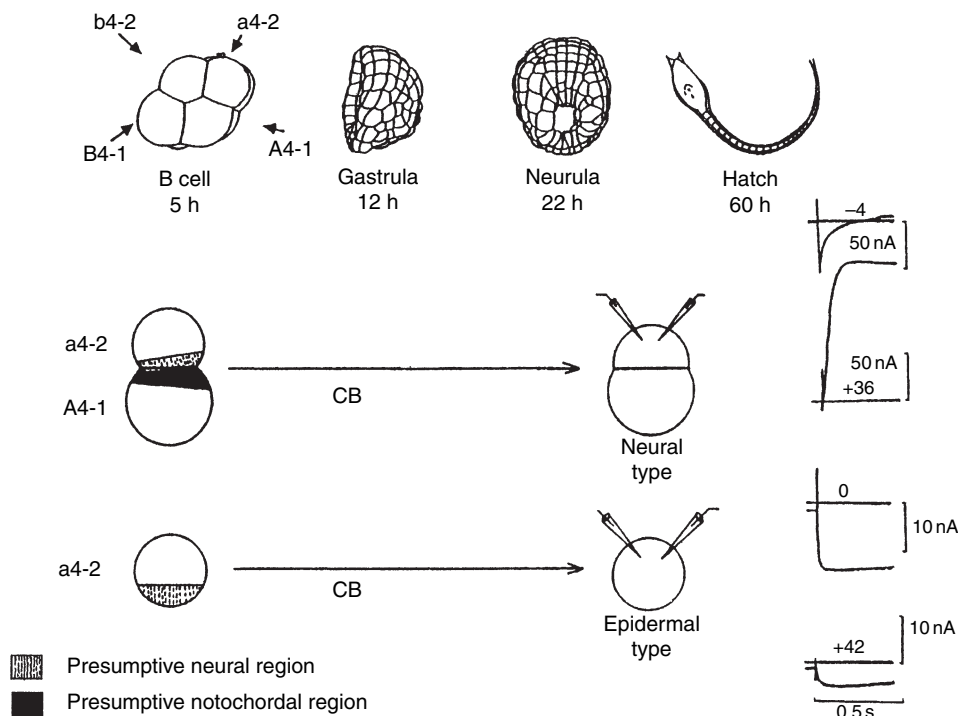
VGIC type	VGIC molecular identity	Regulation	Neuron type	References
Sodium and potassium	ND	Development of excitability in presynaptic motor neurons required synaptic activation of the postsynaptic muscle cells. The data suggested that muscle released a retrograde factor, perhaps NT-3.	<i>Xenopus</i> embryo spinal motor neurons <i>in vitro</i>	Nick and Ribera (2000)
Sodium, calcium, and potassium		During development, no changes in peak density or kinetics of $I_{Ca}$ were noted. $I_{Na}$ showed a twofold increase in its density with subtle changes in kinetics. In contrast, $I_{Kv}$ increased threefold in density and displayed changes in kinetic properties.	<i>Xenopus</i> spinal neurons <i>in vitro</i>	O'Dowd <i>et al.</i> (1988)
Sodium	ND	During this early developmental period, most outer hair cells expressed sodium current, in contrast to the situation in the adult.	Rat outer hair cells, P0–11	Oliver <i>et al.</i> (1997)
Sodium and potassium	ND	During late embryonic and early postnatal periods, $I_{Na}$ density was upregulated in cortical plate neurons. $I_K$ density showed subtle changes. The AP acquired a larger amplitude, shorter duration, and more negative value of threshold.	Mouse cerebral cortex – intermediate zone and cortical plate, E14–P17	Picken-Bahrey and Moody (2003)
Sodium and potassium	Nav1.1 and Nav1.6	Sodium current was developmentally upregulated. Morpholino antisense knockdown indicated that Nav1.1 and channels were more prevalent at early and late stages, respectively. Action potentials acquired larger overshoots and briefer durations as both sodium and potassium currents increased in density.	Zebra fish Rohon–Beard neurons, 16–48 h postfertilization	Ribera and Nüsslein-Volhard (1998); Pineda <i>et al.</i> (2005)
Potassium	Delayed rectifier and A-type currents	A critical period for the maturation of the delayed rectifier current required mRNA synthesis during a 9 h critical period. After transcriptional blockade, A-current development recovered but delayed rectified current did not.	<i>Xenopus</i> spinal neurons, <i>in vitro</i>	Ribera and Spitzer (1989)
Potassium	A-current	Maturation of A-current extended to times later than that for other voltage-dependent currents.	<i>Xenopus</i> spinal neurons, <i>in vitro</i>	Ribera and Spitzer (1990)
Potassium	ND	Extensive upregulation of $I_K$ current density occurred with changes in activation kinetics.	<i>Xenopus</i> embryonic myocytes, <i>in vitro</i>	Ribera and Spitzer (1991)
Sodium	ND	Changes in sodium channel mRNA and protein levels were followed, beginning during embryonic development. Although there were dramatic increases in sodium channel mRNA levels postnatally, the increase did not fully account for protein levels, suggesting other levels of regulation (translational or post-translational). Increased gene transcription and channel mRNA. Kinetic analysis suggests a requirement for a developmentally regulated translational or post-translational step in brain sodium channel expression.	Rat forebrain, E16–adult	Scheinman <i>et al.</i> (1989)

(Continued)

**Table 2** (Continued)

VGIC type	VGIC molecular identity	Regulation	Neuron type	References
Sodium	ND	During development, $I_{Na}$ increased in density and displayed kinetic changes. These developmental changes were largely restricted to the period of axon ingrowth (E30–38).	Cat retinal ganglion cells, E30–E55	Skalióra <i>et al.</i> (1993)
Calcium	LVA and HVA	The density of LVA $Ca^{2+}$ currents decreased during early stages of postnatal development, while the density of HVA increased.	Rat visual cortical neurons, P2–12	Tarasenko <i>et al.</i> (1998)

HVA, high-voltage-activated; LVA, low-voltage-activated; ND, not determined; E, embryonic; P, postnatal.



**Figure 7** Neural induction activates VGIC gene transcription. Cell–cell interactions between appropriate blastomeres of the tunicate *H. auratum* induce expression of voltage-gated sodium current. When anterior animal blastomeres (a4-2) are cultured with anterior vegetal blastomeres (A4-1) as a two-cell system, the a4-2 blastomere develops normally and expresses sodium channels and tetraethylammonium (TEA)-sensitive delay-rectifier potassium channels. In contrast, when a4-2 blastomeres are cultured in isolation, each cell autonomously develops long-duration calcium-dependent APs. Reproduced from Takahashi, K. and Okamura, Y. 1998. Ion channels and early development of neural cells. *Physiol. Rev.* 78, 307–337, used with permission from The American Physiological Society.

studies are providing insights into how these stimuli are transduced into signals that regulate VGIC gene transcription (Mori *et al.*, 1993; Dolmetsch *et al.*, 2001; Tao *et al.*, 2002; Chen *et al.*, 2003). Less is known about the promoter regions that control VGIC transcription.

A series of interesting studies using cleavage-arrested blastomeres of the tunicate *Halocynthia roretzi* indicated that neural induction leads to the appearance of voltage-gated sodium current in the cell that adopts a neural fate (Takahashi and Yoshii,

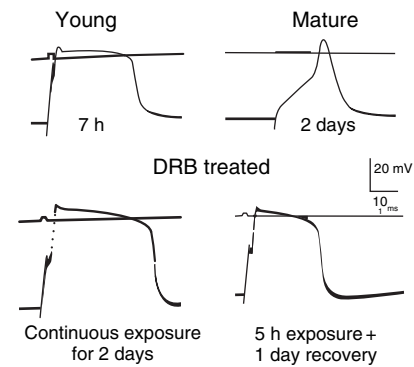
1981; Takahashi and Okamura, 1998; for review, see Okamura *et al.*, 1993; Figure 7). More recent studies have characterized the effects at a molecular level and demonstrated that neural induction leads to the expression of a specific voltage-gated sodium channel isotype, TuNa1 (Okamura *et al.*, 1997). Transcription of TuNa1 is activated during neural induction by interactions between specific blastomeres of the animal and vegetal poles during a critical period of time (Okado and Takahashi, 1988, 1990a, 1990b; Okamura *et al.*, 1994).

Inappropriate cell contacts lead to differentiation of alternate cell types and the expression of different ion channels (Okado and Takahashi, 1990b). Similarly, a specific potassium channel transcript begins expression at the time of neural induction in embryonic spinal neurons of the frog *Xenopus laevis* (Ribera, 1990).

While it is clear that cell–cell interactions during development can activate transcription of specific ion channel genes, the underlying mechanisms are poorly understood. Moreover, depending upon its identity, a neuron will express a specific repertoire of ion channels. It is possible to accelerate the expression of one type of channel by premature expression of another (Linsdell and Moody, 1994). Future work needs to address how transcription of the subset of ion channel genes expressed in any individual neuron is coordinated. For example, co-regulation of transient potassium and hyperpolarization-activated inward currents has been observed in lobster stomatogastric ganglion neurons (Maclean *et al.*, 2003).

In comparison to the vast number of ion channel genes that have been identified by molecular cloning, little is known about their DNA regulatory elements or the transcription factors that regulate transcription. The best-studied transcription factor for an ion channel gene is REST, or repressor element silencing transcription factor (also known as neuron-restrictive silencing factor or NRSF, Kraner *et al.*, 1992; Mori *et al.*, 1992; Schoenherr and Anderson, 1995a, 1995b). REST specifically controls expression of the voltage-gated sodium channel  $\alpha$ -subunit Nav1.2 (Chong *et al.*, 1995; Schade and Brown, 2000; Dallman *et al.*, 2004). REST binds to RE-1, a DNA element found in the regulatory region of many neuronal vertebrate genes (Kraner *et al.*, 1992; Schoenherr and Anderson, 1995b). Most non-neuronal tissues express REST. Overexpression of REST recombinant protein in neuronal cells prevents Nav1.2 expression (Huang *et al.*, 1999; Nadeau and Lester, 2002). Conversely, expression of a dominant negative REST in non-neuronal cells results in Nav1.2 transcription (Chong *et al.*, 1995). Thus, REST functions in a negative pathway and suppresses expression of Nav1.2 in non-neuronal cells.

Future work also needs to address what role transcriptional mechanisms play in the developmental upregulation of ion channels. For example, *Xenopus* spinal neurons display a threefold increase in potassium current density that underlies the developmental shortening of the AP duration (O'Dowd *et al.*, 1988; Lockery and Spitzer, 1992). A critical period of RNA synthesis is required for



**Figure 8** AP development requires a critical period of transcription. Blockade of transcription with an inhibitor of the RNA synthesis (DRB, 5,6-dichlorobenzimidazole 1- $\beta$ -D-ribofuranside) during a critical period of development prevents maturation of the AP and a voltage-gated potassium current. Reproduced from Ribera, A. B. and Spitzer, N. C. 1989. A critical period of transcription required for differentiation of the action potential of spinal neurons. *Neuron* 2, 1055–1062, with permission from Elsevier.

maturation of  $I_{Kv}$  (Ribera and Spitzer, 1989; Figure 8). Transient inhibition of RNA synthesis during a 9 h period prevents the normal threefold increase in density of  $I_{Kv}$ , even when a 48 h recovery period is allowed. Conversely, increasing the levels of potassium channel RNAs (e.g., Kv1.1 or Kv2.2) leads to premature maturation of  $I_{Kv}$  (Jones and Ribera, 1994; Blaine *et al.*, 2004). These findings are consistent with the notion that the critical RNA synthesized during the 9 h period codes for a potassium channel subunit.

### 1.13.8.2 Post-Transcriptional

Post-transcriptional mechanisms, such as alternative splicing, editing, mRNA stability, and localization, influence ion channel function. Neural activity can activate post-transcriptional effects, as is the case for stabilization of transcripts coding for specific calcium channel isoforms (Schorge *et al.*, 1999). Moreover, recent studies indicate that post-transcriptional control of ion channel function occurs throughout development of the nervous system.

**1.13.8.2.1 Alternative splicing** Alternative splicing influences translational efficiency as well as protein stability, transport, and localization (Black, 2003; Stamm *et al.*, 2005). Alternative exon usage constitutes a major mechanism to increase functional diversity of VGICs. Almost all aspects of VGIC function can be affected by alternative splicing: channel activation and inactivation, gating, kinetic properties, and sensitivity to blockers and

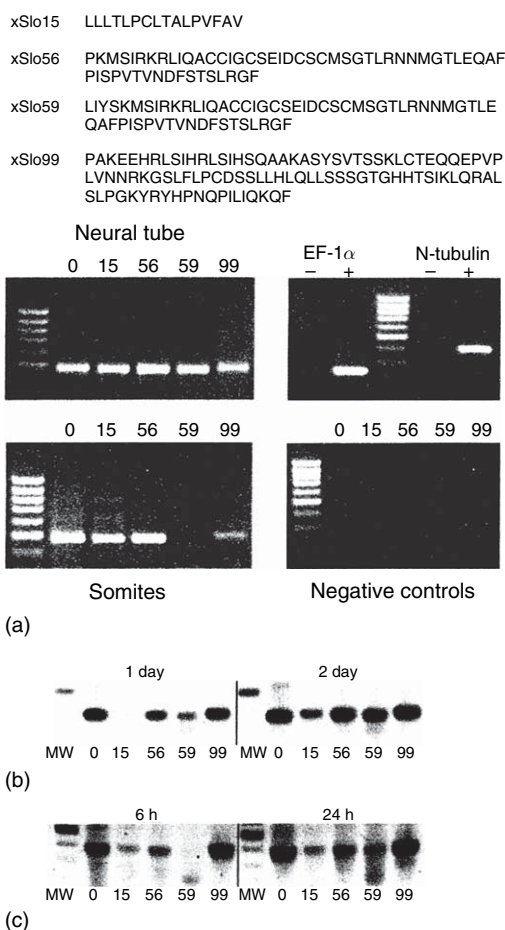


modulators (Iverson *et al.*, 1997; Chemin *et al.*, 2001; Decher *et al.*, 2001; Tian *et al.*, 2001a, 2001b). The effects range from subtle ones to complete loss of function.

Alternative exon usage can change dynamically in response to diverse stimuli, including growth factors, pH, and neural activity. Of particular interest, development influences alternative exon usage (Kaufer *et al.*, 1998; Oh and Waxman, 1998; Stamm *et al.*, 2005). For example, multiple sites for alternative splicing usage have been identified in voltage-gated potassium and sodium channels. In *Drosophila*, the major class of sodium channel is encoded by a single gene known as *para*. Alternative splicing of *para* generates several different channel isoforms. The isoforms display temporally and spatially distinct expression patterns (Thackeray and Ganetzky, 1994; Lee *et al.*, 2002). Alternative splicing also regulates sodium channels in the cockroach and results in mRNA variants coding for proteins with different activation, inactivation, and gating characteristics (Song *et al.*, 2004). Further, several of the isoforms display tissue-specific distribution and developmental specificity. Similar results have been obtained by the study of *Drosophila* genes coding for voltage-gated (i.e., *Shaker*) or calcium-dependent (i.e., *Slo*) potassium channels (Atkinson *et al.*, 1991; Adelman *et al.*, 1992; Butler *et al.*, 1993).

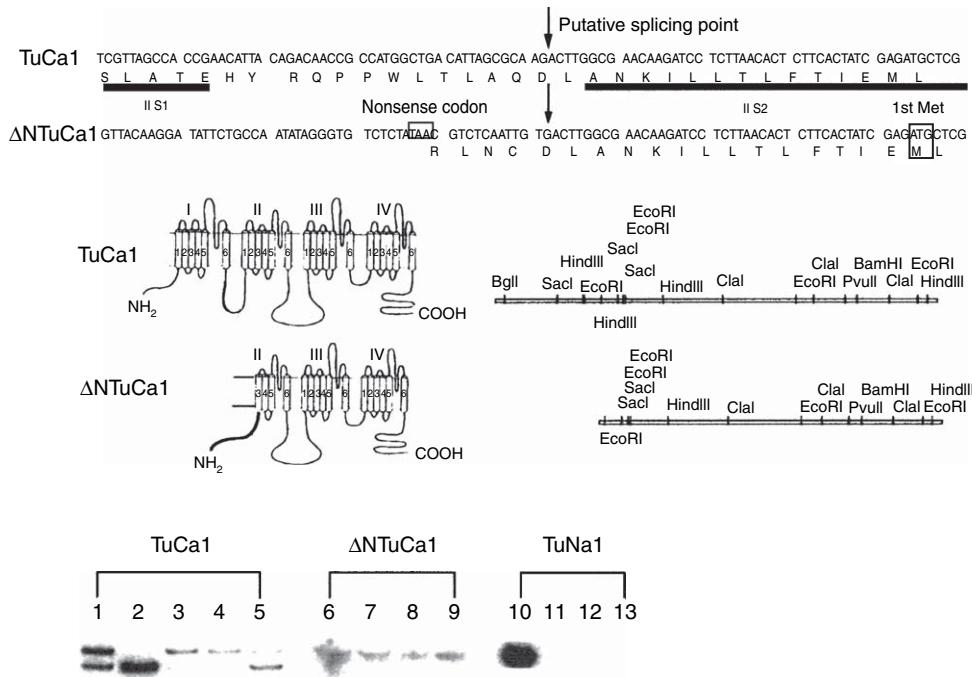
Ion channel gene families that are represented by a single gene in invertebrates often have undergone duplications during evolution and exist as multigene families in vertebrates (i.e., *Shaker* gene vs. Kv1 gene family; *para* gene vs. Nav1 gene family). Despite the increased functional diversity created by gene duplication, alternative splicing still operates to create molecularly diverse channel transcripts. For example, the mammalian sodium channel  $\alpha$ -subunit genes, Nav1.1, Nav1.2, Nav1.3, Nav1.6, and Nav1.9, are alternatively spliced (Sarao *et al.*, 1991; Gustafson *et al.*, 1993; Plummer *et al.*, 1997; Lu and Brown, 1998; Jeong *et al.*, 2000). Moreover, expression of specific splice variants is developmentally regulated. In *Xenopus*, alternative splicing of the *slo* (xSlo) gene generates variants that differ in their tissue and developmental expression patterns (Kukuljan *et al.*, 2003; Figure 9). Additionally, the variants code for channels that differ with respect to both voltage and calcium sensitivities.

Nav1.1, Nav1.2, and Nav1.6 genes display developmentally regulated patterns of alternative splicing (Sarao *et al.*, 1991; Plummer *et al.*, 1997; Alessandri-Haber *et al.*, 2002). Interestingly, the coding regions of neonatal variants of Nav1.2 and Nav1.6 genes



**Figure 9** Development regulation of splicing of xSlo transcripts. The xSlo gene of *X. laevis* displays both tissue-specific and developmentally regulated splice variants. a, Four alternative splice variants – xSlo15, xSlo56, xSlo59, and xSlo99 – were detected by reverse transcriptase polymerase chain reaction (RT-PCR) analysis of RNA isolated from 2-day-old *Xenopus* embryos. Three of the alternatively spliced variants were expressed in both embryonic spinal cord and somites. One variant, xSLO59, was only detected in spinal cord. Constitutively expressed EF-1 $\alpha$  and N-tubulin served as positive controls. Examination of 1- or 2-day-old embryo RNA indicated that the xSLO59 variant was developmentally upregulated (b) *in vivo* and (c) *in vitro*. Reproduced from Kukuljan, M., Taylor, A., Chouinard, H., Olguin, P., Rojas, C. V., and Ribera, A. B. 2003. Selective regulation of xSlo splice variants during *Xenopus* embryogenesis. *J. Neurophysiol.* 90, 3352–3360, used with permission from The American Physiological Society.

predict truncated proteins. Whether or not the predicted truncated proteins are expressed and what their potential roles are remain unknown. However, the existence of these splice variants that are developmentally regulated raises the interesting possibility of negative-feedback mechanisms implemented by alternative splicing. Developmentally regulated variants of calcium channels that code for truncated ion channel proteins have also been observed (Okagaki *et al.*, 2001; Figure 10).



**Figure 10** Alternative splicing generates transcripts for a voltage-gated calcium channel that code for truncated proteins. RT-PCR analyses indicate that the tunicate calcium channel gene expresses splice variants. One variant, TuCa1, codes for a full-length calcium channel  $\alpha$ -subunit. In contrast, the other variant,  $\Delta$ TuCa1, codes for a truncated subunit that lacks a substantial portion of the N-terminal region. Okagaki *et al.* (2001) demonstrate that the truncated subunit acts in a dominant-negative manner and inhibits function of the full-length protein. Lane 1 is a positive control with whole-tadpole RNA. RT-PCR analyses for a sodium channel gene TuNa1 are shown for comparison. Lanes 2, 6, and 10 present analyses done using neuronal RNA. Lanes 3, 7, and 11 present analyses done using RNA from epidermal (non-neuronal) cells. Lanes 4, 8, and 12 present analyses done using RNA from cells giving rise to motor neurons. Lanes 5, 9, and 13 present analyses done using muscle cell RNA. Reproduced from Okagaki, R., Izumi, H., Okada, T., Nagahora, H., Nakajo, K., and Okamura, Y. 2001. The maternal transcript for truncated voltage-dependent  $Ca^{2+}$  channels in the ascidian embryo: A potential suppressive role in  $Ca^{2+}$  channel expression. *Dev. Biol.* 230, 258–277, with permission from Elsevier.

**1.13.8.2.2 Editing** RNA editing leads to specific alterations in single nucleotides of mRNA transcripts (for review, see Simpson and Emerson, 1996). Selective mRNA editing of VGIC transcripts during development has been observed for sodium channels in invertebrates (Hanrahan *et al.*, 2000; Song *et al.*, 2004). The *Drosophila para* gene, in addition to being alternatively spliced, shows developmentally regulated patterns of RNA editing (Hanrahan *et al.*, 2000). In the German cockroach, editing of the sodium gene BgNav transcripts occurs in a developmentally specific manner (Song *et al.*, 2004). Furthermore, editing resulted in transcripts that coded for proteins that varied significantly in voltage-dependent activation and inactivation properties.

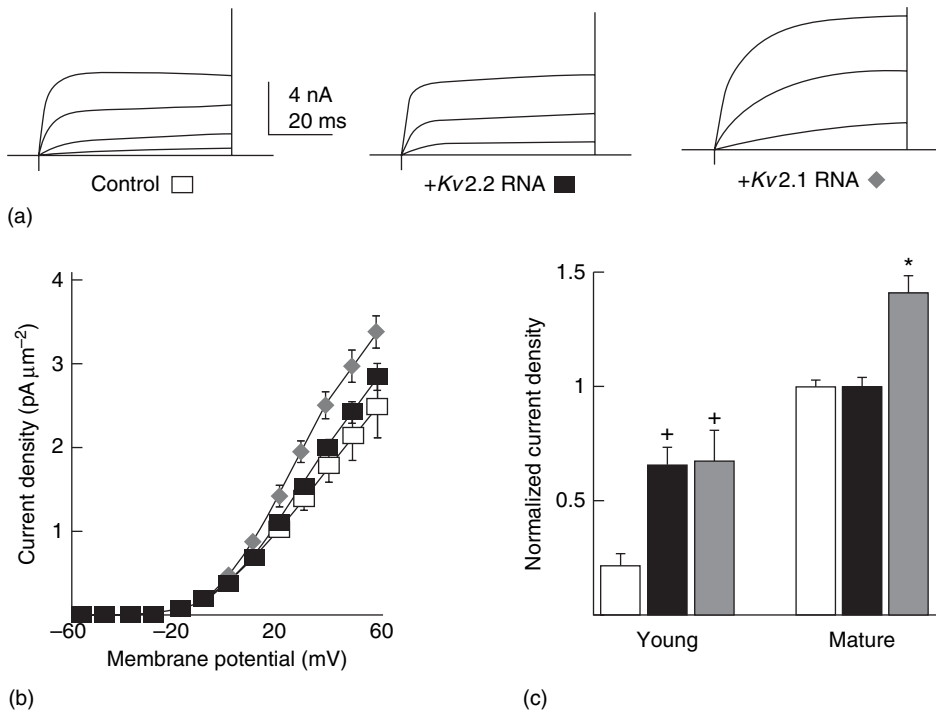
**1.13.8.3 Translational/Post-Translational**

Ion channels display many different types of post-translational modifications that are linked to specific functional consequences. Here, we summarize examples of developmentally regulated post-translational

modifications. For many cases, however, the potential physiological roles of post-translational modifications during development are poorly understood (but see Misonou *et al.*, 2004). Post-translation mechanisms might be involved in setting current density levels in mature neurons (Blaine *et al.*, 2004; Figure 11).

**1.13.8.3.1 Surface membrane insertion** One of the best-studied examples of post-translational control of excitability concerns regulation of large-conductance calcium-activated potassium ( $K_{Ca}$ ) channels of chick ciliary ganglion neurons (for review, see Dryer, 1998; Dryer *et al.*, 2003). Normal developmental upregulation of  $K_{Ca}$  channels requires interactions with both targets (iris) and inputs (afferent innervation provided by the Edinger–Westphal nucleus).

Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and  $\beta$ -neuregulin-1 mediate the effects of cell–cell interactions with targets and inputs, respectively, on  $K_{Ca}$  channels both *in vitro* and *in vivo* (Subramony *et al.*, 1996; Cameron *et al.*, 1998, 2001).



**Figure 11** Post-translational control of potassium current density. a, Potassium current density of mature neurons can be increased by excess Kv2.1 mRNA but not by excess RNA from another Kv2 isoform, Kv2.2. b, The mean  $I_{Kv}$  densities of +Kv2.1 but not +Kv2.2 neurons were significantly larger than those of control neurons. c, Overexpression of Kv2.2 RNA increased current density in young but not in mature neurons. In contrast, overexpression of Kv2.1 RNA increased current density in both young and mature neurons. Blaine *et al.* (2004) demonstrated that regulation of potassium channel density induced by excess Kv2.2 RNA required a proximal region of the carboxyl terminal, known as *proxC*. These studies indicate that post-translational mechanisms can regulate VGIC current density in neurons. Reproduced from Blaine, J. T., Taylor, A. D., and Ribera, A. B. 2004. Carboxyl tail region of the Kv2.2 subunit mediates novel developmental regulation of channel density. *J. Neurophysiol.* 92, 3446–3454, used with permission from The American Physiological Society.

Importantly, the effects of TGF- $\beta$ 1 and  $\beta$ -neuregulin-1 persist in the presence of protein synthesis inhibitors (Subramony *et al.*, 1996). These studies indicate that new protein synthesis is not required for the developmental upregulation of  $K_{Ca}$  channel expression mediated by TGF- $\beta$ 1 and  $\beta$ -neuregulin-1 in chick ciliary neurons. Interestingly, the effects of extrinsic factors on developmental regulation of current in chick lumbar motor neurons do require new protein synthesis (Martin-Caraballo and Dryer, 2002a, 2002b).

More recent studies suggest that the effects of TGF- $\beta$ 1 on ciliary ganglion neurons lead to surface membrane insertion of presynthesized  $K_{Ca}$  channels (Lhuillier and Dryer, 2002). This finding is especially significant because large intracellular pools of several different types of VGICs have been observed. Thus, for several different types of ion channels, post-translational control of surface membrane insertion would be an effective and possible way to regulate functional expression of current (for review, see Misonou and Trimmer, 2004).

Conversely, post-translational regulation of ion channels in the surface membrane could result in their removal. For example, activation of sodium channels and sodium influx leads to removal of these channels from the surface membrane (Dargent and Couraud, 1990; Dargent *et al.*, 1994). This type of regulation might function after circuit formation as a homeostatic mechanism to keep channel densities and electrical activity in an optimal range (for review, see Turrigiano and Nelson, 2004).

**1.13.8.3.2 Glycosylation** In the adult nervous system, glycosylation promotes proper protein folding, function, stability, intracellular sorting, and membrane targeting (Bar-Sagi and Prives, 1983; West, 1986; Marban *et al.*, 1998; Tyrrell *et al.*, 2001). For some plasma membrane sodium channels, removal of glycosylation leads to changes in the voltage dependence of gating (Recio-Pinto *et al.*, 1990; Bennett *et al.*, 1997; Zhang *et al.*, 2003). Notably, depolarizing shifts in the steady-state activation and inactivation curves are produced (Recio-Pinto *et al.*,

1990; Bennett *et al.*, 1997; Zhang *et al.*, 2003). Of particular interest is the finding that the glycosylation levels of voltage-gated sodium channels are developmentally regulated and linked to modulation of voltage-dependent properties (Tyrrell *et al.*, 2001). Further, glycosylation of sodium channels has been linked to developmentally regulated changes in single-channel conductance and steady-state activation (Castillo *et al.*, 1997, 2003). In comparison to sodium channels, much less is known about developmental regulation of glycosylation for other VGICs.

**1.13.8.3.3 Phosphorylation** Protein phosphorylation and dephosphorylation underlie modulation of the activity of ion channels and modulate neuronal excitability (for review, see Levitan, 1999). VGIC  $\alpha$ -subunits are common substrates for phosphorylation mediated by the major protein kinases, including cyclic adenosine monophosphate-dependent kinase (PKA), protein kinase C (PKC), calcium calmodulin kinase II (CAM kinase II), and tyrosine kinase. Moreover, electrophysiological studies indicate that key properties of VGIC can be modified by phosphorylation, at least in the mature nervous system (Brum *et al.*, 1983; Flockerzi *et al.*, 1983; Emerick and Agnew, 1989; Perozo and Bezanilla, 1990, 1991; Armstrong *et al.*, 1991; Hoyer *et al.*, 1991; Murphy and Catterall, 1992; Covarrubias *et al.*, 1994; Cohen, 1996; Cohen *et al.*, 1996; Roeper *et al.*, 1997; Beck *et al.*, 1998). Comparatively little is known about the role of phosphorylation in developmental regulation of ion channel function. However, expression of kinases, such as CAM kinase II, is developmentally regulated (Hanson and Schulman, 1992; Menegon *et al.*, 2002). Further, this kinase participates in developmental regulation of synapse formation (Zou and Cline, 1996; Wu and Cline, 1998). These findings motivate further study of the potential role of phosphorylation in the developmental regulation of VGIC function.

**1.13.8.3.4 Auxiliary subunits** Auxiliary (also known as accessory) subunits form complexes with the pore-forming subunits of VGICs. Pore-forming subunits are typically designated as  $\alpha$  whereas auxiliary ones are referred to by another Greek letter, such as  $\beta$ . Auxiliary subunits influence the kinetic properties and the voltage dependence of VGIC activation and inactivation (Isom *et al.*, 1992; Patton *et al.*, 1994; Rettig *et al.*, 1994; Morales *et al.*, 1995; Heinemann *et al.*, 1996) without major effects on ion conductance (for review, see Trimmer, 1998; Hanlon and Wallace, 2002). Further, auxiliary subunits have effects on the

assembly and expression of VGICs (Patton *et al.*, 1994; Isom *et al.*, 1995a, 1995b; Qu *et al.*, 1995; Shi *et al.*, 1996; for review, see Isom *et al.*, 1994; Striessnig, 1999; Goldin, 2001). Because many of these properties are developmentally regulated, the role of auxiliary subunits during differentiation of excitability is of interest.

Spatial and developmental regulation of VGIC auxiliary subunit expression has been observed in several types of excitable tissue, including brain, muscle, and heart (Butler *et al.*, 1998; Downen *et al.*, 1999; Lazaroff *et al.*, 1999; Franco *et al.*, 2001; Falk *et al.*, 2003; Grande *et al.*, 2003). Very little evidence exists linking auxiliary subunits to developmental regulation of excitability (but see Falk *et al.*, 2003).

### 1.13.9 Future Studies

Electrophysiological analyses have indicated three general patterns of development of excitability in neurons. Each pattern is associated with specific programs of development for underlying voltage-gated currents. Because ion channel genes have been and are being cloned, analyses of mechanisms can be approached at the molecular level. Regulation of excitability is complex and involves control of multiple VGIC genes at multiple levels.

Important issues for future research will be to identify transcription factors and DNA regulatory regions involved in the development control of VGIC gene transcription. It is likely that many VGIC genes will be coordinately controlled. At the other end of the spectrum, recent research suggests that an important post-translational mechanism for control of VGIC density involves regulation of plasma membrane insertion. This mechanism is not unique to VGICs as it is also crucial for regulation of postsynaptic function following periods of activity (for review, see Malinow, 2003).

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