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Ionic Channel Function in Action Potential Generation: Current Perspective

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Abstract Over 50 years ago, Hodgkin and Huxley laid down the foundations of our current understanding of ionic channels. An impressive progress has been made during the following years that culminated in the revelation of the details of potassium channel structure. Nevertheless, even today, we cannot separate well currents recorded in central mammalian neurons. Many modern concepts about the function of sodium and potassium currents are based on experiments performed in nonmammalian cells. The recent recognition of the fast delayed rectifier current indicates that we need to reevaluate the biophysical role of sodium and potassium currents. This review will consider high quality voltage clamp data obtained from the soma of central mammalian neurons in the view of our current knowledge about proteins forming ionic channels. Fast sodium currents and three types of outward potassium currents, the delayed rectifier, the subthreshold A-type, and the D-type potassium currents, are discussed here. An updated current classification with biophysical role of each current subtype is provided. This review shows that details of kinetics of both sodium and outward potassium currents differ significantly from the classical descriptions and these differences may be of functional significance.

Keywords Sodium channels · Potassium channels · Activation kinetics biophysical properties · Kv1, Kv2, Kv3, Kv4 Potassium channel genes · A-type current · D-type current · Delayed rectifier current

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Introduction

Neurons are electrically excitable cells, and a rapid spike in the membrane potential that lasts less than a couple of milliseconds, an action potential (AP), is thought to be an elementary information unit in the brain. Ionic channels define electrical properties of neurons, and as such, they play a vital role in the brain function.

The foundations of modern knowledge of ionic channels function have been laid down 50 years ago by an elegant work of Hodgkin and Huxley presented in a series of seminal papers in late 1940s and early 1950s [1–4]. At that time, few people believed in the existence of membrane pores formed by proteins, and Hodgkin and Huxley were careful not to use the word "channel." Although now we know that currents are indeed carried out by membrane channels and we understand much better the function of ionic channels, many ideas of the Hodgkin and Huxley model (HH model) that described the kinetics of sodium and potassium currents in the squid giant axons are still in use.

It is clear that even a book may not suffice to cover all basic facts on all ionic channels [5]. Thus, it will be focused here on the role of native voltage-gated fast sodium and outward potassium currents in the generation of APs in the *soma* of central mammalian neurons. Several comprehensive reviews on the topic appeared over 15 years ago [6, 7], and only the data of the last 10–15 years will be discussed.

Because of very limited data on the molecular composition of dendritic and axonal ionic currents (with a notable

exception of the subthreshold A-type potassium current [8]), these currents will not be reviewed here. Similarly, the precise location of AP initiation in central mammalian neurons is still a matter of debate, and little is known which currents control these events. Thus, this review is limited to the currents that control AP generation in soma.

Currents discussed here are closely related to the original set of ionic currents described by Hodgkin and Huxley, the fast sodium current, the delayed rectifier current and the leakage current. Leakage or background currents are not gated by voltage, have been recently reviewed [9–12], and their role in AP generation is thought to be the same as described in HH model. Thus, these currents are not described here. In contrast, several new features of mammalian fast sodium channels, such as non-HH-like activation [13] and slow inactivation and the resurgent current, are important during AP generation, and they are discussed in this paper. Potassium channel genes and the relationship between the behavior of potassium channel and its structure have been extensively reviewed [14–16]. However, very scant attention has been given to the roles of a multitude of delayed rectifier currents in the AP generation in real neurons. This is quite surprising given the fact that the identification of the fast delayed rectifier current in neurons showed that delayed rectifier channels can differ substantially in their function from the classical description [17].

For completeness, all subtypes of the delayed rectifier current including the fast one will be reviewed. In addition, the so-called A- and D- types of potassium currents are described here because it is difficult to define the delayed rectifier current without the description of these other two types of outward potassium currents. Finally, because of space limitations, no discussion is provided for the fourth type of outward potassium currents, the M-type, that has a well-established function [18] recently confirmed with modern pharmacological and molecular biology tools [19–23].

Two goals are pursued by this review. First, although these potassium currents have been identified a long time ago [6, 18, 24–26], the biophysical data accumulated during the last decade alter significantly many widely used assumptions about kinetics of the native currents. Second, an attempt is made to group outward potassium currents recorded in central mammalian neurons into the classes according to our knowledge about the genes encoding these channels. The presented scheme can be considered as an extension of the existing classification of outward potassium currents that has been in use for over 15 years [6, 18]. Currents are divided according to the potassium channel gene families that presumably are responsible for these currents. Because of large diversity seen among Kv1 currents, a further subdivision based on the functional role of a current is suggested. Although the presented scheme may be altered in the future as a result of the appearance of new data, there is a clear need to relate genetic data to the ability of currents to control electrical behavior of neurons. The author hopes that this paper will, in part, fill such a need.

Several recent reviews were dedicated to the ionic channel knockouts in mice and to the diseases associated with the voltage-gated ionic channels, the so-called channelopathies [27–29]. Because the expression of ionic channels is very plastic and a number of compensatory mechanisms exist [30–34], the data obtained from such knockouts and channelopathies require careful and extensive analysis before any conclusion about the channel function can be drawn [35]. Such an extensive analysis is beyond the scope of this review, and an interested reader is referred to the above-mentioned papers.

Fast Sodium Currents

According to Hodgkin and Huxley, sodium (Na) currents are responsible for the membrane potential depolarization that results in the AP (Fig. 1). Today we know that fast, tetrodotoxin (TTX)-sensitive Na currents are responsible for the vast majority of APs generated in the brain (however, see, for instance, [36]). As of today, two additional types of Na currents have been identified. The

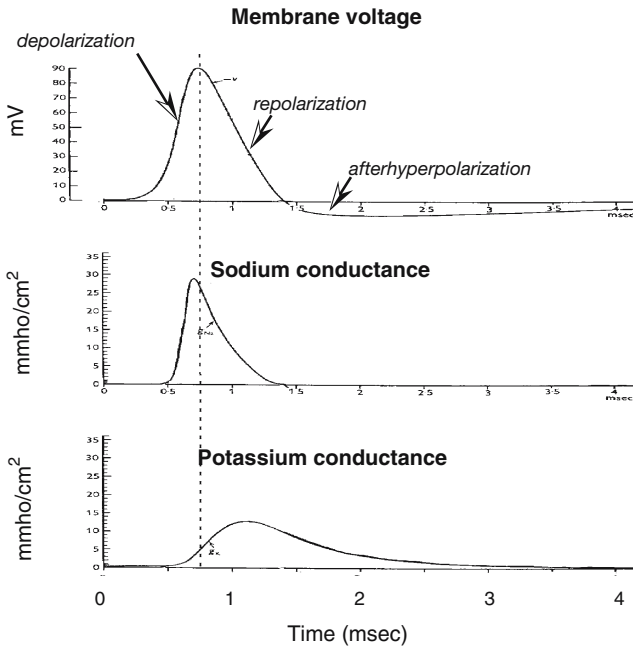

Fig. 1 AP obtained during simulations employing Hodgkin and Huxley model of membrane currents. The *dashed line* marks the peak of membrane potential reached during this AP. Note that, whereas sodium conductance reached maximum before the AP peak, potassium conductance reached maximum during the repolarization phase. Modified from [4]

TTX-resistant Na channels activate and inactivate three to five times slower than the fast, TTX-sensitive Na channels [36]. A persistent TTX-sensitive Na current inactivates even slower (τ>100 ms), and probably, a fraction of this current does not inactivate at all [37]. TTX-resistant Na channels are largely found in a subset of nociceptive neurons in the spinal cord and dorsal root ganglia, and they are encoded by two genes, NaV1.8 and NaV1.9 [38, 39]. A persistent Na current is detected in many or all neurons [40–44], and it is likely that a complex gating of fast, TTX-sensitive Na channels produces this current ([40, 41], cf [45]).

The fast type of sodium currents was among the first ionic currents described quantitatively by Hodgkin and Huxley, and one may believe that this type of current will not present any surprise after years of research. Nevertheless, three developments are worthwhile to note. First, it has been discovered that, in many central mammalian neurons, fast sodium currents activate without a Hodgkin and Huxley-type delay (the HH delay, [13]). Thus, in the soma of central mammalian neurons, sodium currents turn on faster than predicted by the HH model. This faster activation time-course suggests that the speed of information transfer in central neurons is higher than has been thought previously [46, 47]. Second, during the last decade, it has been shown that a slow inactivation of fast sodium currents is an ubiquitous phenomenon and might explain such diverse observations as the dynamics of high frequency AP firing in dendrites [48] and the modulation of sodium currents by neurotransmitters [49]. Finally, the discovery of the "resurgent" sodium current should be mentioned [50]. The last two phenomena have been reviewed [29, 51], and because of space limits, only a brief comment on the phenomena will be provided. Meanwhile, differences in the kinetics of axonal and somatic sodium currents were identified very recently and these results will be discussed in depth here.

The presence of delay during activation of sodium currents can be explained by relatively simple channel gating models. These models will be used here to describe the functional consequences of the absence of the HH delay. A more detailed mathematical treatment of these models can be found in Appendix.

In the simplest model, a channel has an open and a closed states, and the current is proportional to the number of open channels:

$$\begin{aligned} &\mathrm{C} \leftrightarrow \mathrm{O} \\ &I = N_{\mathrm{open}} \times i_{\mathrm{channel}} = N \times m \times i_{\mathrm{channel}} \end{aligned} \tag{1}$$

where C and O denotes the closed and open states, respectively; I is the sodium current amplitude; N_{open} and N are the numbers of open and all sodium channels respectively; i_{channel} is the single channel current amplitude; m is the probability that a channel will be in the open state.

In such a model, it is usually assumed that the transition rate from the closed to the open state is proportional to the number of closed channels and a certain rate constant, α. Similarly, the transition rate from the open to the closed state is proportional to the number of open channels and a closing rate constant β.

$$\begin{aligned} &\mathrm{d}\left(N_{\mathrm{open}}\right)/\mathrm{d}t = \alpha \times N_{\mathrm{closed}} - \beta \times N_{\mathrm{open}} \\ &\mathrm{d}(N \times m)/\mathrm{d}t = \alpha \times [N \times (1-m)] - \beta \times [N \times m] \end{aligned} \tag{2}$$

or

$$\mathrm{d}m/\mathrm{d}t = \alpha \times (1-m) - \beta \times m \tag{3}$$

where N_{closed} is the numbers of closed sodium channels.

A general solution of the first order differential Eq. 3 is

$$A + B \times \exp(-t/\tau_{\mathrm{m}})$$

where τ_m=1/(α+β) is the activation time constant and t is time from the start of the voltage step.

Coefficients A and B are determined by initial conditions. If, before a depolarizing test pulse, m was 0, that is, all channels were closed and the depolarizing test pulse promotes the open state probability, the starting rate of current increase will be proportional to $\alpha \times N \times i_{\mathrm{channel}} > 0$. This notion is confirmed by the solution of Eq. 3 for these initial conditions:

$$m = m_V \times (1 - \exp(-t/\tau)) \tag{4}$$

where m_V is the steady state value of m at the test voltage V.

The derivative of this function that corresponds to the speed of current increase is expressed as

$$\mathrm{d}m/\mathrm{d}t = m_V/\tau \times \exp(-t/\tau) \tag{5}$$

At $t = 0$, $\mathrm{d}m/\mathrm{d}t = m_V/\tau$. Thus, according to Eq. 1, at t= 0, the expression for current is:

$$\mathrm{d}I/\mathrm{d}t = N \times i_{\mathrm{channel}} \times m_V/\tau = I_V/\tau$$

where I_V is the steady state current at the test voltage (no inactivation).

This analysis shows that such a simple two-state model predicts a mono-exponential time-course of current activation without any delay. However, in their original paper of 1952 [4], Hodgkin and Huxley showed that sodium current in the squid giant axon activates with a delay (Fig. 2a). The time-course of the sodium current activation could be well fit with a cube function, and Hodgkin and Huxley assumed that, in fact, three independent "particles" (gates) have to be in the open position before the current can flow. In their model, the kinetics of each particle was governed by the

same first order differential Eq. 3. For independent events, the probability that all gates will be open is equal to the multiple of probabilities that each gate will be open. Thus, the expression for current becomes:

$$I = N \times i_{\text{channel}} \times m^3 \times h \tag{6}$$

where m is the probability that an activation gate will be in the open position, h is the probability that an inactivation gate will be in the open position.

The addition of an inactivation gate was necessary to explain the sodium current decay while the command voltage remained constant (Fig. 2) [2]. In short, Eq. 6 states that current can pass the channel when all gates are open. Thus, by combining Eqs. 6 and 4, for the depolarizing test pulses starting from membrane potentials at which all channels are closed and not inactivated, one can obtain the following expression for the current time-course:

$$I(t) = N \times i_{\text{channel}} \times m_V^3 \times h_V \times [1 - \exp(-t/\tau_m)]^3 \times \exp(-t/\tau_h) \tag{7}$$

$$I(t) = I_{\text{Na}V} \times [1 - \exp(-t/\tau_m)]^3 \times \exp(-t/\tau_h), \tag{8}$$

here $I_{\text{Na}V} = N \times i_{\text{channel}} \times m_V \times h_V$ where t is time from the start of the voltage step, τ_m and t_h are the activation and inactivation time constants, respectively, at the test voltage. The term $\exp(-t/\tau_h)$ represents channel inactivation process that, in sodium channels, is about ten times slower than activation process.

For $t \ll \tau_m$, Eq. 8 can be approximated by the following function:

$$I(t) = I_{\text{Na}V} \times (t/\tau_m)^3$$

Hence, in the HH model, for $t \ll \tau_m$, the time-course of the sodium current activation follows closely the cube function and fits well the time-course of sodium currents recorded in the squid giant axons. It can be shown that the delay described by Eq. 8 is equal to $\ln(3) \times \tau_m \sim \tau_m$ (see Appendix). In the original HH model, the voltage dependence of current amplitude is associated with the voltage dependence of τ_m and is approximately six times steeper than the voltage dependence of τ_m (see Appendix).

In the following years, it became apparent that, in expression 5, raising m to the power of 3 was not always the best fit for the time-course of sodium current activation [7, 52]. Furthermore, other experimental data indicated that more elaborate schemes were necessary [7, 53–55]. However, for the data obtained from mammalian central neurons, the m^n function was universally used to describe

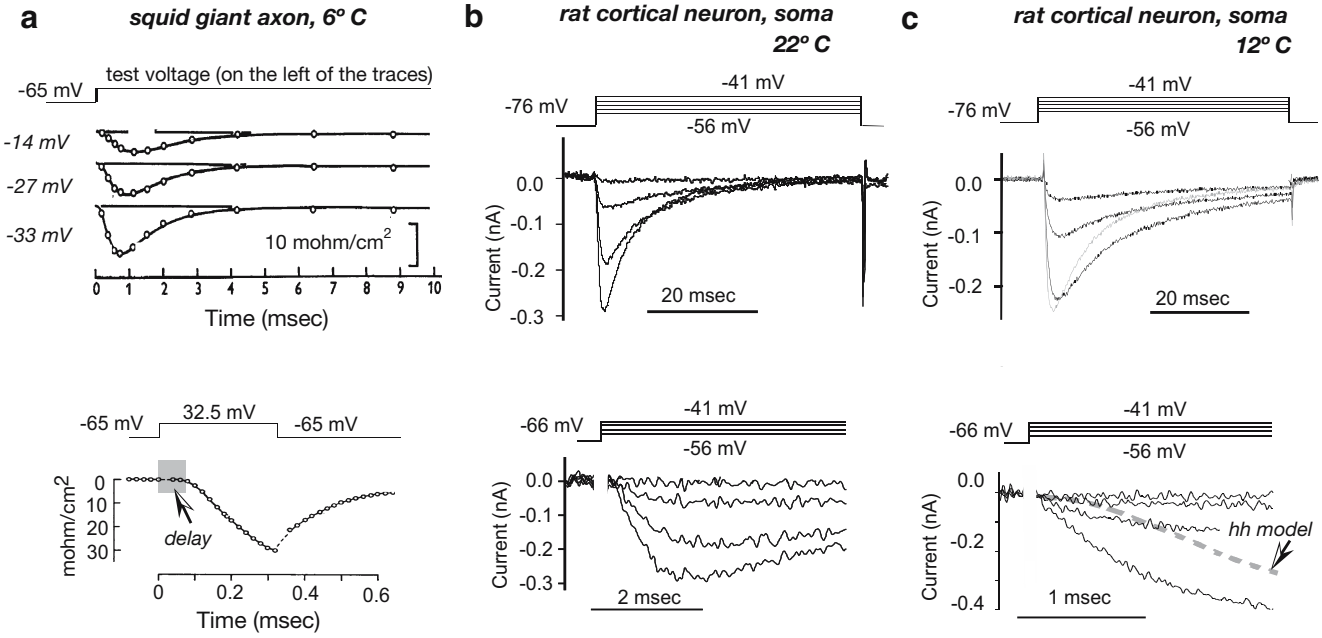

Fig. 2 Examples of sodium currents from a non-vertebrate (the squid giant axon) and vertebrate preparations (rat prefrontal cortex pyramidal neuron). **a** Sodium currents obtained from the original traces by digital subtraction by Hodgkin and Huxley [4]. The voltage of the applied command pulses is indicated *on the left of the traces*. A *gray-shaded area in the bottom panel* indicates the delay when no current is detected at the beginning of the test voltage command of 32.5 mV. Modified from [4]. **b** and **c** Sodium currents recorded from acutely dissociated prefrontal cortex pyramidal neurons at two different temperatures indicated *above the traces*. Voltage commands are shown on the *top of the traces*. Although at room temperature there is an indication of the presence of a delay, recordings at lower 12°C temperatures show that the delay is largely the membrane-charging artifact. This conclusion is confirmed by the tail current analysis, and these data were presented in [13]

the activation time-course of sodium currents and n was almost always assumed to be equal to 3 [56–59].

The explanation is that, during the majority of recordings from the soma of central mammalian neurons, the voltage clamp speed was no match to the one achieved in the classical preparations that provided data to construct the HH-type models of sodium currents. For instance, usually, it was impossible to discriminate well the recorded current during the first 0.5 ms after the start of the test command. Such voltage clamp quality was insufficient to determine the time-course of sodium current activation at room temperature because the expected delay ($\sim\tau_m$) was usually less than 0.5 ms ([56], see also Fig. 2b). In contrast, Hodgkin and Huxley were able to resolve current 0.1 ms after the start of the voltage command and cooling was employed to slow down the sodium current (Fig. 2a). In the few instances when the technique, the nucleated patch from slices, might have permitted the delay measurements, no appropriate analysis has been performed.

Thus, a recent study on the time-course of sodium current activation is the first and the only of its kind performed on sodium currents recorded from the soma of central mammalian neurons [13]. A combination of high quality voltage clamp recordings with cooling revealed that, in several types of central mammalian neurons, sodium currents activate without the HH-type delay (Fig. 2c). A brief delay observed in that study was clearly distinct from the HH-type delay, as it was much shorter (>3 times) than predicted by the HH model and almost voltage independent. These observations and a number of other features (activation and deactivation time constants were similar at the same voltage, the slope factor of the voltage dependence of current amplitude was half of the τ_m slope factor) were consistent with a model in which one gate controlled most of the sodium channel kinetics (see Appendix for details). For that reason, further in the text, this model will be called "the single gate" model.

A comparison of traces generated by the HH model with the recorded sodium currents (Fig. 2c) shows that the difference is clear only at the very start of the voltage command. The real sodium currents start abruptly, whereas the HH model traces start very smoothly. This difference is reflected in AP shape. Computer simulations show that the rising phase of the AP is much steeper in the simulations incorporating the single gate model than the HH model of sodium currents (Fig. 3).

Interestingly, for the single gate model, AP shape is much more sensitive to the sodium channel distribution than it is predicted by the HH model. For instance, when the HH model was used, the increased sodium channel density in the axonal compartment changed very little the steepness of the AP rising phase (Fig. 3b). Meanwhile, for the single gate model, such a change in the sodium channel density increased the steepness of the AP rising phase severalfold (Fig. 3c).

An independent study has recently shown that a rapid initiation is characteristic to the APs recorded in central neurons [47]. Furthermore, the authors could not attain such a steep rise with the HH model [47]. In neurons, the information transfer speed is associated with the steepness of the AP rising phase [46]. Thus, the HH model heavily underestimated the information transfer capability of mammalian central neurons. Interestingly, to explain the observed AP shape, the authors suggested a cooperative behavior *between sodium channels*. The single gate model of Baranauskas and Martina may be the consequence of a cooperative behavior between the domains of *a single sodium channel* [7]. Thus, these two models are very similar in behavior, and it is difficult to say whether the single channel model is sufficient to explain all features of APs in central neurons including a variable threshold of APs [47]. It should be noted that the single gate model predicts less steep voltage dependence of current amplitude on the membrane potential ([13], see also Appendix). Consequently, small variations in the amplitude of other currents and/or rate of membrane potential depolarization are more likely to change AP threshold in the single gate model than in the HH model of sodium currents.

The number of gates influences stochastic noise generated by spontaneous channel openings [60], and noise

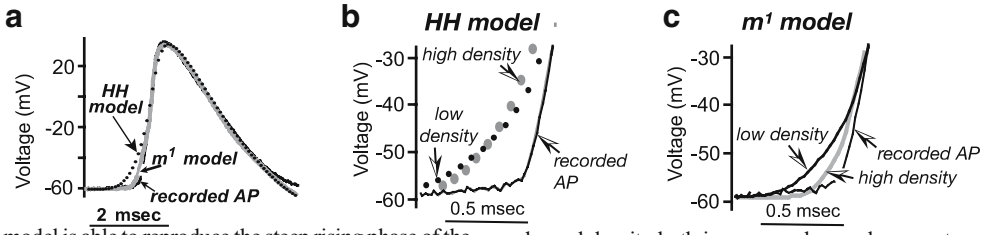

Fig. 3 Single gate model is able to reproduce the steep rising phase of the recorded AP. **a** *Thin black line* indicates the recorded action potential, *wide gray line* is the simulated AP employing the single gate model, and *dotted line* represents the AP obtained employing the three-gate HH model. **b** and **c** Show in the expanded time scale the initial phase of the AP. Low density corresponds to the model that assumes equal sodium channel density both in soma and axonal compartment, and high density corresponds to the model that assumes approximately eight times higher sodium channels density in the axonal compartment than in the soma. In **b**, simulations employed the HH model and, in **c**, simulations employed the single gate model. The data were presented, and details of simulations can be found in [13]

affects information processing in a number of ways [61, 62]. It is likely that a model in which sodium current kinetics is dominated by a single gate will predict different noise levels and spectrum compared to the HH model. However, a detailed study is required to evaluate these differences quantitatively.

As mentioned above, two additional important properties of fast sodium currents have been revealed during the last 10–15 years. First, it has been shown that a slow inactivation of fast, TTX-sensitive sodium currents is detected not only in the axonal and muscle channels, but also in the majority of channels from central neurons [63–66]. Second, it has been discovered that a fraction of sodium channels can reopen during the recovery from inactivation process constituting a slow "resurgent" current at membrane potentials close to AP threshold [50, 51].

The slow inactivation of sodium currents has been shown to contribute to the long burst formation [65] and to the AP amplitude attenuation and slow adaptation of AP firing frequency [63], especially in dendrites [48]. In addition, sodium current modulation by some neurotransmitters can modify slow inactivation [49, 67] and may serve as a mechanism to control sodium channel availability [67]. In contrast, the resurgent sodium current can be important for brief burst generation, although alternative mechanisms do exist [30, 50, 68].

Although slow inactivation seems to be inherent to all sodium channels, it is less clear how ubiquitous the resurgent current is [51]. The original proposal that NaV1.6 (formerly Scna8a) subunits are largely responsible for the resurgent current [69] has been replaced by the hypothesis that β_4 subunit confers this property to α subunits of the sodium channels [70].

Both phenomena extend the history of the membrane potential that sodium channels can "remember." The resurgent current will be generated if APs occurred during the last 20–50 ms and slow inactivation will reduce the availability of sodium channels if during the last 10 s or so there was an increase in the firing rates in the neuron. Hence, in contrast to the classical HH sodium current, new forms and dimensions of plasticity are added by these two properties of sodium currents [29, 51].

Delayed Rectifier Currents

During AP generation, the membrane potential upswing ("depolarization") is followed by the downswing ("repolarization," Fig. 1). In the squid giant axon, the so-called delayed rectifier potassium current drives this repolarization. The name 'delayed rectifier current' ('the delayed outward current' in the original paper [71]) was chosen to indicate that this potassium current was largely detectable at depolarized membrane potentials (rectification), and it was activated after a delay. Similar to the squid fast sodium current (see Eq. 8), this delay could be sufficiently well described by an exponential variable raised to the power of 4:

$$I_{\mathrm{K}} = I_{\mathrm{K}V} \times [1 - \exp(-t/\tau_m)]^4$$

where I_{K} is the amplitude of the potassium current, $I_{\mathrm{K}V}$ has the same meaning as $I_{\mathrm{Na}V}$ (see above), t is time from the start of the voltage step, τ_m is the activation time constant at the test voltage (for details see Appendix). The original HH model of the delayed rectifier current did not include any inactivation gates.

In the squid giant axon, the main function of the delayed rectifier current during the AP generation is to rapidly repolarize membrane potential, thus limiting inactivation of the fast sodium channels. To do that, the delayed rectifier current has to be sufficiently rapid to be activated during the AP; that is, the activation rate of these potassium channels should match the inactivation rate of the fast sodium channels of the squid giant axon. Furthermore, because, following the AP, the open potassium channels do not close immediately upon repolarization, the membrane potential overshoots the resting potential and that overshoot or "afterhyperpolarization" (AHP, Fig. 1) speeds up the recovery of sodium channels from inactivation. Such a speeding-up occurs because, at more hyperpolarized membrane potentials, sodium channels recover from inactivation faster and more completely. The recovery from inactivation of the sodium channels will be significant only if the closing rate of the delayed rectifier potassium channels will be comparable to the deinactivation rate of the sodium channels. Because, at the same voltage, the inactivation and recovery from inactivation time constants are similar [4, 13], these considerations suggest that the activation/deactivation time constants of the delayed rectifier potassium channels should be comparable to the inactivation/deinactivation time constants of the sodium channels. Indeed, there was relatively close match between the activation/deactivation time constants of the delayed rectifier channels and the inactivation/deinactivation time constants of the fast sodium channels (Fig. 4a, [4]).

In addition, the delayed rectifier current contributed to the resting membrane potential. The threshold of activation of this current was very low, close to the resting potential of the squid giant axon of approximately −65 mV at which a significant fraction of the delayed rectifier channels were open and passed the current.

In the following years, four additional classes of potassium currents were identified. Channels of the first class, the inward rectifier channels, allow potassium ions to enter the cell at hyperpolarizing potentials, whereas very little outward current is generated upon depolarization [9,

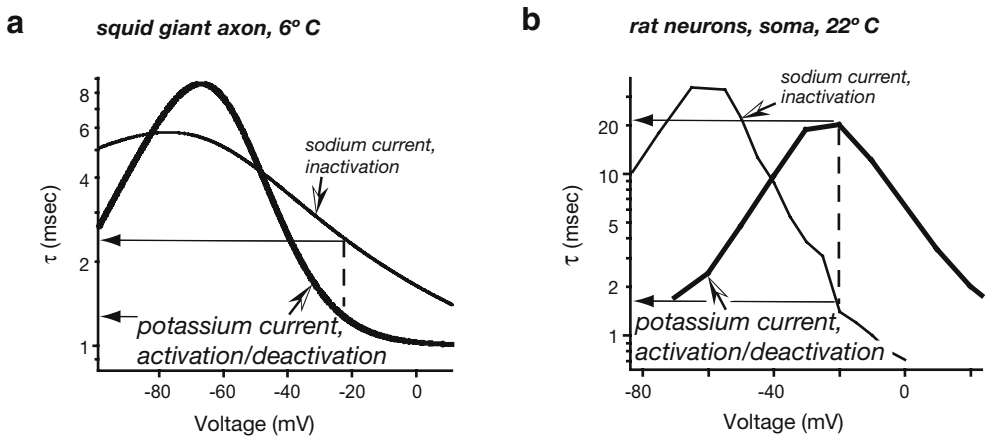

Fig. 4 A comparison of the inactivation/deinactivation time constants of sodium current and the activation/deactivation time constants of delayed rectifier currents in two systems: the squid giant axon (**a**) and rat central neuron (**b**). In the case of the squid giant axon, fits of experimental data are shown [4]. In the case of rat neuron, an averaged data on the fast delayed rectifier data [90] and sodium currents [13] are shown

72, 73]. The second class, the calcium-dependent potassium channels, are largely or exclusively gated by intracellular calcium ions [74–76]. The third and the fourth class of currents, the rapidly decaying ("inactivating") A-type potassium current and the slowly inactivating, highly sensitive to 4-aminopyridine (4-AP) and dendrotoxin (DTX) D-type current, are discussed in the following section of this review. Potassium currents that could not be assigned to any of these classes were frequently termed "delayed rectifier currents," although it was clear from early on that a large diversity exists among this class of potassium currents [6, 77]. However, few pharmacological tools, poor quality of voltage clamp data, especially regarding the activation/deactivation kinetics, and limited knowledge about the proteins-forming potassium channels prevented any reasonable classification of the delayed rectifier-like currents.

In the last 10–15 years, there was a dramatic improvement both in quality and quantity of data on potassium channels. Cloning and characterization of genes encoding the channels helped to understand the diversity of potassium currents [15]. Several new techniques such as whole-cell recordings in acutely dissociated cells [78] and nucleated patch from slices and primary cultures [79] provided high quality voltage clamp data on current kinetics in central neurons [13, 56, 80]. An extensive work on scorpion and snake venom toxins helped to significantly increase the number of pharmacological agents available for potassium current characterization [81–84]. Although many gaps in our knowledge about the composition of native potassium channels remain, a new picture of outward potassium current classification is emerging. This review will provide such an up-to-date classification of outward delayed rectifier-like potassium currents.

In this section, data on two subtypes of delayed rectifier currents will be discussed. These two subtypes, the fast and the slow delayed rectifier currents, are likely to comprise the vast majority of slowly inactivating outward potassium currents in central neurons. The third type of currents, DTX-sensitive/low threshold currents, is discussed in the following section. Such a choice was dictated by two reasons. First, it will be shown that these currents are very diverse. Second, it will be argued that the slowly inactivating D-type current is, in fact, a member of the delayed rectifier group of potassium currents.

Cloning of the first members of the mammalian Kv3 (formerly Shaw) family of genes immediately draw attention of neurophysiologists. Many properties of Shaw currents were rather unusual. First, these currents were highly sensitive to both tetraethylammonium (TEA) and 4-AP [17], two pharmacological agents widely used to block outward potassium currents. Originally, 4-AP was shown to preferentially block the A-type potassium currents (half maximal inhibitory concentration [IC_{50}] ~2 mM) [85], and millimolar concentration of TEA reduced the amplitude of the delayed rectifier-like currents in many neurons [6]. However, for both TEA and 4-AP, the estimated IC_{50} of Shaw current block was well below 1 mM. None of peptidergic toxins such as DTX or charybdotoxin, highly potent blockers of certain types of potassium currents, were affecting Shaw currents to any detectable degree [15]. This property distinguished Shaw currents from the slowly inactivating D-type potassium current that was highly sensitive to 4-AP and DTX [18]. Another distinct feature of Shaw channels was their extremely quick closing at negative membrane potentials. For instance, at −70 mV, the deactivation time constant of the Kv3.1 current was less than 1 ms [86].

Because of such a unique set of properties, Kv3 currents were the first delayed rectifier-like channels linked to a particular current in central mammalian neurons. It was found that certain classes of interneurons posses a component of outward potassium currents that is highly sensitive to the application of either TEA or 4-AP [87]. An application of solution containing sub-millimolar concentration of any of these two substances was sufficient to block most of the current. A concerted effort of several labs employing a combination of techniques, such as immunohistochemistry,

electrophysiology, and single cell reverse transcriptase-polymerase chain reaction (RT-PCR) [87–92], led to a firm conclusion that a specific type of delayed rectifier currents, the high-threshold or the fast delayed rectifier current (a more common name now), is present in certain classes of neurons and the Kv3 family proteins form the channels responsible for this current [17].

A number of studies have shown that fast delayed rectifier channels serve almost exclusively to repolarize APs and, consequently, speed up the recovery from inactivation of sodium channels [90, 91, 93]. It is interesting to note that, compared to fast sodium currents, fast delayed rectifier current activates much slower than the classical delayed rectifier found in the squid giant axons. As it has been explained above, to efficiently repolarize APs, the activation and deactivation time constants of a delayed rectifier potassium current should be close to the inactivation/deinactivation time constants of fast sodium channels. Figure 4b shows that the activation τ of the fast delayed rectifier channels is much slower (approximately tenfold) than the inactivation τ of fast sodium channels of the same cell. Thus, fast delayed rectifier currents do not significantly prevent the inactivation of sodium channels; rather, these currents speed up the recovery of sodium channels from inactivation. It has been shown that such properties of Kv3 currents are optimal for enabling fast spiking in neurons [93].

There are two additional important differences between fast delayed rectifier currents and the classical delayed rectifier current of the squid giant axon.

First, because of the steep voltage dependence of current amplitude (the slope factor is approximately 6 mV) and the high activation threshold of > -30 mV, fast delayed rectifier currents do not contribute significantly to the resting membrane potential. Calculations show that, even at −60 mV, which is significantly above the resting membrane potential in the majority of neurons, less than 0.02% of channels will remain open. For a typical current density of 1–10 nS/pF [88, 89], such an open channel probability would result into the conductance density of 0.2–2 pS/pF. For a medium-sized cell of 15 pF, such a conductance density corresponds to the input resistance of approximately 40–400 GΩ, at least 40 times higher than the input resistance of a neuron (0.1–1 GΩ). Hence, although, similar to the classical HH delayed rectifier current, fast delayed rectifiers do repolarize APs but do not contribute to the resting membrane potential.

Because of such a discrepancy in the voltage dependence between the HH and fast delayed rectifier currents, the functional consequences of current block are different. A partial block of the HH delayed rectifier current leads to the increased number of evoked APs (Fig. 5a), whereas a partial block of the fast delayed rectifier current decreases the number of evoked APs [91] (Fig. 5b). Although both currents speed up the recovery from inactivation of sodium channels after the AP, only the HH delayed rectifier channels can open frequently below AP threshold and, thus, interfere with the following AP generation. So, the smaller HH delayed rectifier current may result in the increased number of generated APs (Fig. 5a). In contrast, fast delayed rectifier channels close quickly after the AP, and these channels remain closed until the next AP is generated. Hence, a single function of fast delayed rectifier channels is to have more sodium channels ready to open after the AP. The more Kv3 channels are expressed by a neuron, the higher maximal firing frequency that neuron can sustain (Fig. 5b, [91]). Dynamic current clamp experiments confirm that Kv3 channels are kinetically optimized for high-frequency AP generation [93].

Such a specific role of fast delayed rectifier currents explains why Kv3 channels are largely expressed in the fast spiking neurons that are able to fire continuously at frequencies above 100 Hz at 36°C [17, 87, 89, 90]. In addition, because of the high activation threshold, even

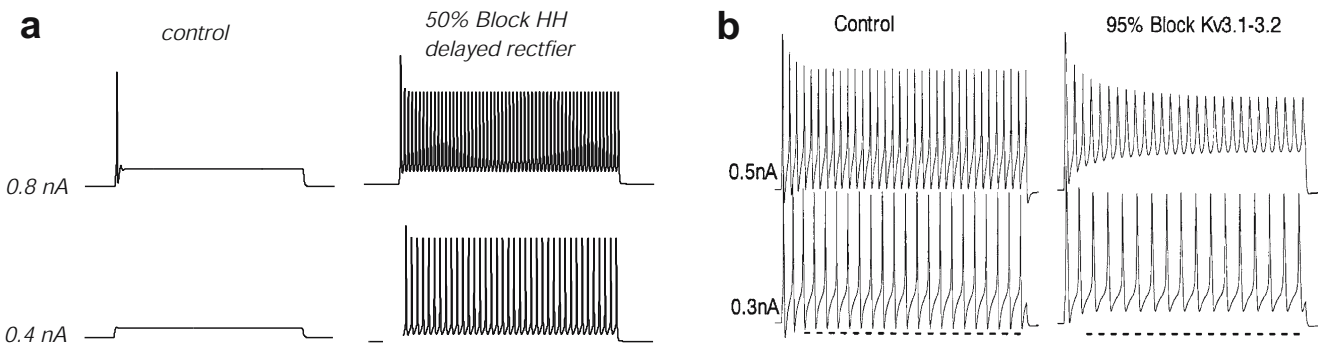

Fig. 5 Computer simulations show that, while the classical delayed rectifier current suppresses excitability (**a**), the fast delayed rectifier current increases the number of generated APs (**b**). Current clamp traces are shown. APs were evoked by current steps of the amplitude indicated on the left of the traces. **b** is modified from [91] and **a** is simulation data obtained by the author employing the publicly available HH model in the Neuron simulation software package

high densities of these channels do not decrease the input resistance of such fast spiking neurons allowing them to be very sensitive to the synaptic inputs.

However, fast spiking interneurons are not the only cell type expressing Kv3 channels. In hippocampal CA1 pyramidal neurons from young rats, a small fraction of delayed rectifier currents had properties of Kv3 channels, possibly, to minimize calcium entry during the AP [88]. In these cells, the presence of Kv3 channels was supported by the detection of Kv3.1 messenger RNA (mRNA) with single cell RT-PCR [88].

The second important difference between the classical HH and the fast delayed rectifier currents can be found in the kinetics of activation. As it has been mentioned above, the HH delayed rectifier current activates with a significant delay. According to the HH model (see above and Appendix), this delay is related to the activation time constant and depends strongly on membrane voltage. In contrast, fast delayed rectifier channels activate with a delay that is voltage independent and, for physiological range of membrane potentials, much shorter than the delay found in the current from the squid giant axon [93]. Thus, the activation kinetics of fast delayed rectifier current resembles the activation kinetics of fast sodium currents in central mammalian neurons [13] and can be described by the first order of kinetics [93]:

$$I_{\mathrm{K}} = g_{\mathrm{K}V} \times [1 - \exp(-t + \delta)/\tau_m)]$$

where I_{K} is the amplitude of the potassium current, $g_{\mathrm{K}V}$ is a constant that has the same meaning as $I_{\mathrm{Na}V}$ in Eq. 8, t is time from the start of the voltage step, δ is the voltage independent delay, τ_m is the activation time constant at the test voltage.

A number of other properties, such as similar time constants of activation and deactivation at the same voltage, good correspondence between the slope factors of voltage dependence of the current amplitude, and activation/deactivation time constants (see Appendix for further explanation), suggest that a single gate model can explain most kinetic properties of Kv3 channels [93].

Nevertheless, it is not clear how these differences in current kinetics affect neuronal responses. In contrast to sodium channels, there are no simulations that would directly address this question. It is known that current fluctuations depend on channel gating mechanisms [60], but because very few channels may open at resting potential, these fluctuations are unlikely to affect the subthreshold signals. It is not clear whether a single gate in the model corresponds to a unique gate in the channel structure. Currents similar to the ones of the single gate model can be produced by a number of mechanisms such as cooperative transitions or relatively slow last transition from the closed to the open state [7]. Most of the work on the mechanisms of potassium channel gating was performed with Shaker/Kv1 channels that seem to encode the major fraction of the classical delayed rectifier current (see below). Data from central neurons indicate that many details of the gating mechanisms in Shaw/Kv3 channels are very different from the ones in Shaker/Kv1 channels and future experiments in heterologous expression systems should explore these differences.

In a number of neurons in which Kv3 currents are present, the second type of delayed rectifier is detected [88, 89]. These currents are insensitive to 4-AP ($IC_{50} \geq 5$ mM) and moderately sensitive to TEA (IC_{50}=1–5 mM). The deactivation time constant is approximately 60–100 ms at −40 mV, whereas the inactivation τ is about 3 s at +20 mV. Interestingly, at least in some cell types, these currents can be well described by the first order kinetics in much the same way as the fast delayed rectifier current ([94], Baranauskas, unpublished observations). Because of much slower activation kinetics, this subtype of delayed rectifier currents is sometimes called the slow delayed rectifier current [80, 88], and this name will be used further in the text. Properties of slow delayed rectifier currents are very similar to the properties of Kv2/Shab currents attained in heterologous expression systems.

There are two members in the Kv2 gene family: Kv2.1 and Kv2.2. In heterologous expression systems, properties of Kv2.1 and Kv2.2 currents are nearly identical. The activation threshold of Kv2 currents is approximately −30 mV, both types of currents inactivate slowly (τ ~5–10 s). The activation time constants are relatively slow (τ ~10 ms at 0 mV). Compared to Kv3 currents, at the same membrane potential, Kv2 currents deactivate approximately 20-fold slower (τ ~35 ms at −70 mV, [86]). Kv2 currents are modestly sensitive to TEA (IC_{50}=5–10 mM) and completely insensitive to a large number of toxins such as DTX and related peptides and charybdotoxin [95]. Although the first report suggested that 4-AP blocks the rat Kv2.1 (previously drk1) current with an IC_{50} of 0.5 mM, [96], later studies concluded that Kv2 currents are much less sensitive to 4-AP (IC_{50}>5 mM) [86, 95]. The picture is somehow complicated by the fact that electrically silent subunits of Kv5, Kv6, Kv8, and Kv9 families can associate with Kv2 subunits and significantly, although not dramatically, modify the original Kv2 currents [95, 97–99]. In addition, xMinK and xMiRP2 can alter the kinetics of Kv2 currents [100]. Nevertheless, a quick comparison between the properties of the original and modified Kv2 currents and Kv3 currents reveals two major differences: Kv2 currents always deactivate three- to tenfold slower and are ≥10 times less sensitive to TEA and 4-AP than Kv3 currents.

Experiments employing quantitative single cell RT-PCR, antibodies, and dominant negative subunits showed that the slow delayed rectifier current is indeed encoded by the Kv2

family genes [89, 101, 102]. Biochemical evidence suggests that, in the brain, Kv2.1 channels are largely homomers [103] and single cell RT-PCR supports such a notion [89]. In contrast to Kv3 currents, the gene expression data indicate that most, if not all, neurons possess variable numbers of Kv2 channels [104]. It is likely that all slow, TEA sensitive (5–10 mM) and 4-AP insensitive (IC_{50} >1 mM) delayed rectifier currents are because of channels formed by Kv2 subunits alone or in combination with Kv5–9 subunits.

Although, compared to Kv3 currents, Kv2 currents activate at slightly more negative membrane potentials, the three- to fivefold slower activation rates result in three to five times smaller fraction of the current activated during the AP (Fig. 6a). Consequently, in fast spiking globus pallidus cells and hippocampal interneurons, an application of low concentrations of TEA or 4-AP eliminated most of the outward current generated by the AP shape voltage command ([88], Baranauskas, unpublished observations).

Hence, AP repolarization is not the main function of Kv2 currents. Although only a small fraction of Kv2 currents is activated during the AP, slow deactivation at the membrane potentials close to AP threshold leads to two significant effects. First, current can accumulate during the AP trains of high frequency and may be responsible for the fast AP frequency accommodation [105]. Second, because Kv2 channels close slower than it is required to recover sodium currents from inactivation (Fig. 6b), the resultant slower AHP delays the appearance of the next AP. Because of the low threshold of the channel activation, this effect can be further enhanced by opening of a significant fraction of Kv2 channels below AP threshold (Fig. 6a), thus additionally reducing the probability of the following AP generation.

Computer simulations show that, in the absence of the fast delayed rectifier current and other fast, such as D-type and calcium-dependent potassium channels, the slow delayed rectifier current can participate in AP repolarization, although low efficiency and high current densities are required for this task [13]. Thus, it is more likely that the main function of Kv2 currents is to control intrinsic excitability and the usual effects of millimolar TEA on the number of evoked APs in neurons are probably attributable to the ubiquitous presence of slow delayed rectifier currents.

This view is supported by the fact that, under physiological conditions, neuronal activity modifies the phosphorylation state of Kv2 channels leading to the shift of the current voltage dependence [106]. Even a moderate shift of voltage dependence toward more negative membrane potentials would affect dramatically the ability of Kv2 currents to suppress APs because more channels would open before the AP generation.

Another gene family that is clearly contributing to the delayed rectifier-like currents in neurons is the Kv1 family. Because the D-type current is mediated by the channels composed of Kv1 subunits (see below), this current will be also discussed in the following section.

D-Type and Other Kv1-Like Potassium Currents

The current that delayed the appearance of the first spike for seconds was first detected in hippocampal CA1 pyramidal neurons, and it was termed the delay or D-type potassium current, I_D [24]. Voltage clamp experiments showed that I_D inactivated slowly (τ>200 ms), recovered extremely slowly from inactivation (5 s at −90 mV), and

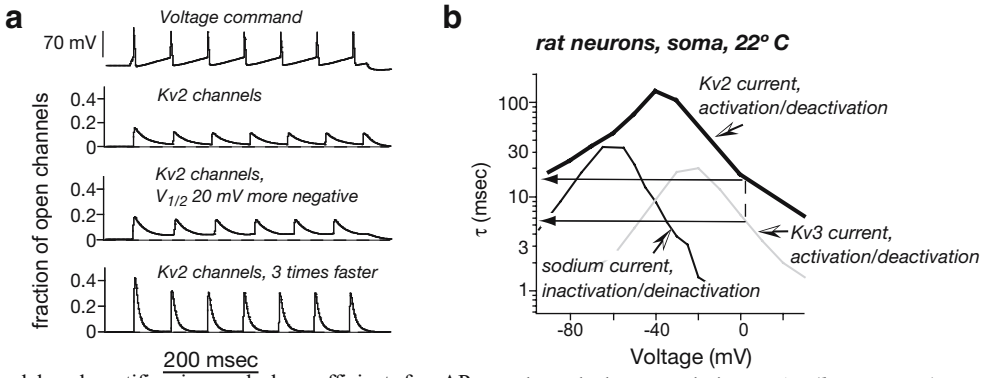

Fig. 6 The slow delayed rectifier is much less efficient for AP repolarization than the Kv3 current. **a** Only a small fraction (>1/6) of the original Kv2 channels open during an AP (*top trace*) and shifting voltage dependence to more negative membrane potentials does not increase much the fraction of channels that open during an AP (*middle trace*). Meanwhile, faster kinetics has a dramatic effect on the number of channels that open during an AP (*bottom trace*). Note also an increased background current in the middle trace. **b** A comparison of the activation/deactivation time constants of the fast delayed rectifier current ('Kv3 current'[90]) and the slow delayed rectifier current (Baranauskas, unpublished data). For comparison, the inactivation/deinactivation time constants of the sodium current are also shown [13]

activated below AP threshold (approximately −50 mV) [18]. Because of such a slow recovery from inactivation, even brief repetitive membrane potential depolarizations could gradually inactivate I_D, thus this current could integrate information about synaptic depolarizing potentials for a period of several seconds. In addition, there is convincing evidence that, in hippocampal pyramidal neurons, I_D participates in AP repolarization [24, 107, 108].

The original D-type current had a peculiar pharmacological profile. DTX, a toxic peptide from the green mamba snake, was blocking I_D at 100 nM, and 30 μM of 4-AP was sufficient to eliminate most of the current. Meanwhile, the other inactivating A-type potassium current (see next section) was blocked by 4-AP only at concentrations well above 100 μM.

Interestingly, in the soma of several types of peripheral neurons [83, 109, 110] and in the axons of frog and *Myxicola* [77, 111, 112], a component of the delayed rectifier current was also sensitive to DTX and <100 μM of 4-AP. In contrast to I_D of hippocampal pyramidal neurons, these DTX-sensitive currents did not inactivate or inactivated incompletely and very slowly (seconds). Thus, their main functional role seemed to be rather than the slow integration of synaptic inputs for seconds, the control of intrinsic excitability, and adaptation of the AP firing frequency [109].

Further studies showed that DTX blocked a fraction of delayed rectifier currents in many central mammalian neurons [113–120]. All these DTX-sensitive currents shared a number of properties.

First of all, with one exception [117], the DTX-sensitive fraction of the delayed rectifier current had invariably lower threshold of activation than the DTX-resistant fraction of the current. This lower threshold of activation was detected in spite of large variability in the estimated $V_{1/2}$: from −47 mV in [118] to −8 mV in [113].

Second, in all cells tested, the application of DTX (~100 nM) increased the number of evoked spikes suggesting that the DTX-sensitive current controls intrinsic excitability of the neuron. The effect on the delay to the first spike was very variable, and only in hippocampal pyramidal neurons and striatal medium spiny cells was the DTX-sensitive current responsible for the delays of over 200 ms long, the feature emphasized in the first description of I_D [24, 108, 114].

Third, in all cells tested, an application of <100 μM of 4-AP was sufficient to reduce significantly the amplitude of the DTX-sensitive current.

DTX is known for several decades, and it has been extensively tested against a number potassium channel subunits [81, 82, 84, 109, 110, 121]. So far, high sensitivity has been reported only toward Kv1.1, Kv1.2 and Kv1.6 subunits; and current consensus is that the sensitivity of a specific current to DTX is strong evidence that the Kv1 family subunits are present in the channels mediating the current. Thus, further in the text, the name 'Kv1 currents' will be used as a general name to all DTX-sensitive currents including I_D. If no I_D is implied, the term 'DTX-sensitive' current will be used.

Although many features of Kv1 currents in central mammalian neurons were similar, clear differences were also evident.

Among the reported properties of Kv1 currents, the activation/deactivation time constants show the largest variability even when the temperature effects are taken into account (Fig. 7). For instance (all data in this paragraph refers to room temperature), in ventral cochlear nucleus, the activation constant of the DTX-sensitive current was less than 5 ms for voltages above −60 mV, and it was approximately equal to 1.5 ms at 0 mV [122]. The same fast kinetics has been reported for the DTX-sensitive current in visual cortex pyramidal neurons [105]. In contrast, in striatal medium spiny neurons, the activation τ was close to 30 ms at 0 mV [114]. Similarly, large differences were detected for the deactivation time constants. At −60 mV, the deactivation time constant was 6 ms in ventral cochlear nucleus cells, whereas it was close to 50 ms in striatal medium spiny neurons [114].

As mentioned before, further differences were detected in the voltage dependence of current amplitude. The range

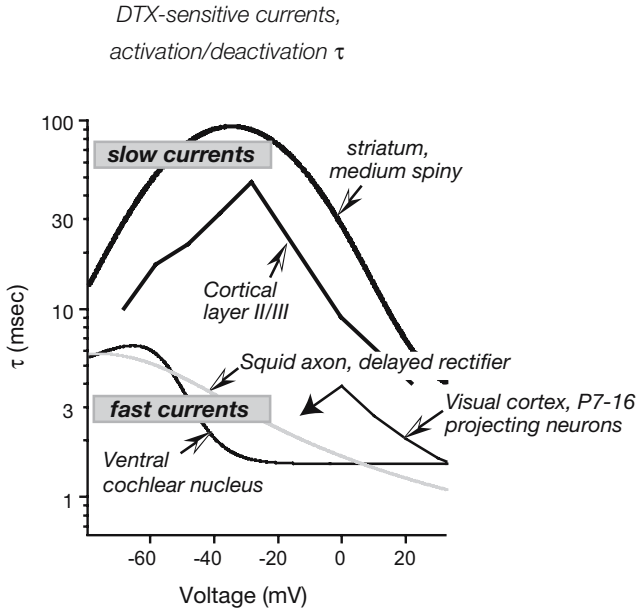

Fig. 7 A comparison of the activation/deactivation time constants of Kv1 currents. The data of DTX-sensitive currents from striatal medium spiny neurons [114], cortical layer 2–3 pyramidal neurons [113], visual cortex projection neurons [117], and ventral cochlear nucleus cells [122] are shown. All these data were obtained at room temperature. In addition, the activation/deactivation time constants of the classical delayed rectifier current of the squid giant axon for T= 6°C are shown [4]

of $V_{1/2}$ is so wide (−47 to −8 mV) that it is very likely that different subunits of the Kv1 family underlie these currents. Indeed, the use of more specific toxins that act only on one to two subunits, such as margatoxin (Kv1.3), tityustoxin (Kv1.2), agitoxin (Kv1.1, Kv1.3, Kv1.6), DTX-related peptide DTX-K (Kv1.1), has revealed the existence of subtypes of Kv1 currents, often in a single neuron [113, 120]. A combined application of several such toxins showed that at least a fraction of Kv1 currents is insensitive to DTX [113]. In addition, these pharmacological studies corroborated the notion that Kv1 channels are indeed encoded by the Kv1 family genes.

Thus, both pharmacological and biophysical data confirm the existence of several subtypes of Kv1 channels, and at least in some neurons, several subtypes are present in a single cell. However, in spite of large differences in the kinetics and voltage dependence of these currents, the presence of almost any Kv1 channels decreases the excitability of a neuron because of the low threshold of activation of these currents.

The fast Kv1 channels ($\tau_{-60\ mV}<10$ ms) deactivate as rapidly as Kv3 channels (compare Figs. 6 and 7). Thus, the AHP produced by closing of these channels should not delay the following AP. However, in contrast to Kv3 channels, Kv1 channels can open before an AP is generated, and as in the case of the HH delayed rectifier current, the increase in the amplitude of the fast, low threshold Kv1 current decreases the excitability of a neuron [123]. Figure 7 shows that the biophysical properties of fast Kv1 channels and the HH delayed rectifier current are very similar, and the HH delayed rectifier current block produces the same effects (Fig. 5b) as DTX application in auditory neurons [120, 123]. In addition, both currents suppressed all APs except for the first one. These observations indicate that the classical delayed rectifier current is in fact a fast, low threshold Kv1 current. Indeed, the Shaker (the old name of the Kv1 family) genes are believed to be responsible for a large fraction of delayed rectifier currents in the squid giant axon [124, 125].

The ability of fast Kv1 currents to suppress any AP that is not synchronized with the start of a stimulus means that these currents strongly enhance coincidence detection [123, 126]. In addition, fast Kv1 currents increase signal to noise ratio by effectively suppressing any small fluctuations caused by noise in the signal [126]. These two properties explain why fast Kv1 currents are detected in almost all auditory neurons [120, 123, 126, 127].

Meanwhile, the effects of slow Kv1 currents on neuronal excitability are subtler. Usually, these currents increase slightly the inter-spike interval and the accommodation of AP firing frequency [113, 114]. Both slow deactivation and low threshold of activation contribute to these effects of slow Kv1 currents. The kinetics of slow Kv1 currents is similar to Kv2 currents, and the analysis of the biophysical role of Kv2 currents presented in the previous section is also applicable for slow Kv1 currents.

In this paper, one important comment should be added. At low membrane potentials, few currents are operating, and even a small additional current may have a big impact on the time-course of the membrane potential. For instance, simulations show that, compared to the low threshold DTX-sensitive current, the Kv3-like current density has to be approximately 1,000 times higher to have a comparable effect on the AP firing frequency [91]. Therefore, although Kv1 currents frequently comprise a small (less than 20%) fraction of the total delayed rectifier current [113, 114], their impact on the firing rates can be even more significant than of the rest of the delayed rectifier current. In fact, simulations show that, in ventral cochlear nucleus, if the fraction of the DTX-sensitive current surpasses 25% of the total outward current, a single AP is generated by a current step because the amplitude of the DTX-sensitive current is sufficient to suppress all subsequent APs [123].

The most profound effect of large variability in the activation rates can be seen in the different ability of Kv1 currents to repolarize APs. Simulations show that only the fast Kv1 channels are able to participate efficiently in AP repolarization. For instance, in ventral cochlear nucleus neurons, over 40% of low threshold fast DTX-sensitive channels will open during an AP. In contrast, less than 10% of slow DTX-sensitive channels will open during an AP in striatal medium spiny neurons (see, for instance, Fig. 6a). Thus, I_D channels that contribute significantly to AP repolarization [24, 108, 114] are fast Kv1 channels according to this classification. There are no direct data on activation time constants for I_D from hippocampal pyramidal neurons, but in visual cortex projection cells, a similar current activates extremely quickly (Fig. 7, [117]).

One may think that, for slow Kv1 currents, lowering the threshold of current activation may be sufficient to attain an efficient channel opening during the AP. However, because the AP width does not decrease dramatically above −40 mV, the lower activation threshold does not increase much the fraction of channels activated during the AP (Fig. 6a). In contrast, even a small shift in $V_{1/2}$ will increase the amplitude of current present below AP threshold and may easily prevent an AP generation. Therefore, in spite of large variability in $V_{1/2}$, slow Kv1 currents (activation $\tau>5$ ms, Fig. 7) never contribute significantly to AP repolarization: large amplitude currents or too negative $V_{1/2}$ can abolish all APs. In fact, when slow, but not fast, Kv1 channels are present in neurons, the application of DTX does not change the AP width [113, 114, 120].

There is a need to better explain the place of I_D among Kv1 currents. All pharmacological properties of I_D are similar to the rest of Kv1 currents. Although many Kv1 currents inactivate incompletely or do not inactivate, the

inactivation τ of I_D, hundreds of milliseconds, is well within the range of inactivating Kv1 currents [114]. The voltage dependence of I_D corresponds well to a typical fast Kv1 current [123]. Probably, the only unique property of I_D that makes it distinct from the other Kv1 currents is its very slow recovery from inactivation (τ >1 s, [18]). None of the reported DTX-sensitive currents did have deinactivation τ of more than 1 s. It is possible that, in contrast to the originally used intracellular recordings by Storm 1989, the cell wash-out during whole cell recordings is changing the recovery process of Kv1 currents. Other than that, I_D is no different from other fast Kv1 currents.

The strongest evidence that Kv1 currents are mediated by channels composed of Kv1 subunits is the pharmacological properties of these currents. In addition, the biophysical properties of Kv1 channels are in good agreement with the expression data of Kv1 subunits. For instance, all currents attained following expression of Kv1 genes in the heterologous expression systems have low threshold of activation [15]. Although, in expression systems, the activation/deactivation time constants of Kv1 channels are slower compared to Kv3 channels, they are usually faster than the time constants of Kv2 channels. With exception of Kv1.4 channels, all homomeric Kv1 channels inactivate slowly or do not inactivate. However, the presence of β subunits may confer inactivation [128].

In the majority of cases, the DTX-I toxin blocks all or a large fraction of DTX sensitive currents [113, 115], and as DTX-I has high affinity only to Kv1.2 subunit [82], it seems that this subunit is the most ubiquitously expressed among all Kv1 family subunits. Immunoprecipitation data confirm that Kv1.2 subunit is the most abundant Kv1 subunit in the brain, but almost all channels are heteromultimers [84]. Kv1.2 subunit is heavily expressed in Ranvier nodes of peripheral myelinated axons [129] and modestly expressed in soma and dendrites of many central neurons [113, 130–132]. In cortical supragranular pyramidal neurons, the amplitudes of DTX-sensitive current did not correlate with the soma size, whereas the amplitude of the DTX-insensitive current did correlate with the soma size, suggesting that these DTX-sensitive channels were largely dendritic [106]. More direct biophysical tests support the hypothesis that a large fraction of DTX-sensitive currents is generated in proximal dendrites [113, 133].

A-Type Potassium Current

Originally, the A-type potassium current was defined as a current that both inactivated and recovered from inactivation rapidly, which is in less than 100 ms [6, 8]. Thus, this current can be distinguished from I_D that inactivates with τ > 300 ms and recovers from inactivation with τ >1 s.

In the very first paper, it has been shown that A-type channels slowed down the AP firing rate and delayed the appearance of the first AP [25, 26]. To do that, at least a fraction of channels have to open below AP threshold that is < −45 mV. Thus, the rapidly inactivating high threshold (> −40 mV) potassium current found in some neurons is functionally different from the classical A-type current [6, 134]. To recognize this fact, the subthreshold rapidly inactivating potassium current is frequently termed I_{SA} [8, 135], and this name will be used here. In addition to slowing AP firing rate, in some neurons, A-type channels contribute significantly to AP repolarization [18, 108]. Although this review is limited to somatic currents, it is worthwhile to remind that A-type channels exert a powerful control of dendritic excitability including, but not limited to, AP back-propagation, thus these channels participate in synaptic integration and plasticity [136, 137].

Studies in *Drosophila* have determined that, in insects, a single Shal gene is responsible for the I_{SA}-like current [138]. Thus, there was little doubt that the mammalian Shal genes [121, 139, 140] encode I_{SA} in neurons [135]. Small discrepancies between the kinetics of I_{SA} in neurons and Kv4 currents expressed in heterologous systems were explained by a number of auxiliary subunits such as KChiP1–4, frequenin, DPPX, and DPP10 [8, 141–143]. Subsequent studies employing quantitative single cell RT-PCR, the negative dominant Kv4 subunit expression, and the gene suppression in neuronal cultures confirmed that I_{SA} is indeed encoded by the Kv4 family genes [144–146].

It seemed that there was a nearly perfect match between the original description of I_{SA} and our current knowledge about the properties of potassium channel proteins. However, a discovery that one of the auxiliary subunits, KChiP4a, was capable to eliminate both the rapid inactivation, and fast recovery from inactivation of Kv4 currents [147] demonstrated that the same gene can be responsible for an entirely different current. Indeed, the earlier study employing quantitative single cell RT-PCR suggested that some slowly inactivating currents are encoded by the Kv4.2 gene [144]. These observations were further supported by detection of a perfect correlation between the expression of KChiP4a mRNA and the presence of slowly inactivating component in I_{SA} [148]. It has been known from the earlier studies that, in I_{SA}, a slow component of recovery from inactivation can be found in some neurons [135]. The new feature of I_{SA} in globus pallidus neurons was that, in a fraction of cells, no fast component (τ<90 ms) of either inactivation or deinactivation was present [144, 148]. Although there is evidence that Kv1.4 gene is likely to be responsible for the slowly recovering I_{to} current in left ventricle heart cells [149], these results show that, in neurons, the slowly recovering current can be encoded by Kv4 genes.

In addition, these data [135] demonstrated that the original distinction between I_{SA} and I_D based on the differences in current kinetics is confusing when the molecular basis of the current is sought. In this case, pharmacological properties of the current are more indicative of the composition of the channels underlying the current. The slowly inactivating current that correlated with Kv4.2 mRNA expression [144] had pharmacological profile of a typical I_{SA}: insensitive to TEA and DTX (50 mM of TEA reduced the current amplitude by <20%) and moderately sensitive to 4-AP (IC_{50}>1 mM, [144, 148], Baranauskas, unpublished observations). In addition, the voltage dependence of these currents was shifted by divalent cations in the same fashion as of I_{SA} and Kv4 currents [150–152].

Furthermore, several distinct biophysical features of Kv4 currents could be identified even in slow I_{SA}. First, the activation and deactivation kinetics of I_{SA} is extremely rapid [144, 148]. In fact, although, in slow I_{SA}, the activation/deactivation time constants are two- to threefold slower than in a typical fast I_{SA} [144, 148], these time constants never exceeded 5 ms at room temperature. Second, the activation threshold of slow I_{SA} was very low (approximately −50 mV), and the voltage dependence of the current amplitude was shallow. One can note that biophysical properties of such slow I_{SA} are very similar to the fast Kv1 currents (see previous section). Simulations confirm that the functional role of slow I_{SA} is the same as of the fast Kv1 currents, namely, to exert a powerful control over excitability and participate in AP repolarization. Because slow I_{SA} are found in neurons that are prone to long-lasting bursting behavior, it is likely that they shape the duration of these bursts [153].

Finally, recent studies indicated that, in contrast to Kv1.4 and Kv3.4 channels [154], Kv4 channels could rapidly inactivate without opening in heterologous expression systems [155, 156]. More accurate study on Kv4.3 currents expressed in *Xenopus* oocytes showed that, to explain all experimental data, it is necessary to consider both inactivation pathways, with and without channel opening [157]. According to the Connors and Stevens [25] model of I_{SA}, a balance between current activation and inactivation processes below AP threshold determines how much the AP is delayed by I_{SA}. If I_{SA} channels can inactivate without opening, it will result in less delay. However, it is not clear whether the native A-type channels with a large number of modifying subunits can inactivate without opening.

Classification of Outward Potassium Currents

This review of the three types of outward potassium currents suggests a modified version of their classification [6, 18]. The new version is based on the presumed family of genes that encodes a current. The idea to group currents according to the families but not single genes is based on two observations. First, a number of studies have shown that native potassium channels are heteromultimers [20, 84, 90, 158]. Second, so far, with a notable exception of Kv2 proteins forming functional channels with Kv5–9 subunits, all data indicate that no heteromultimers containing subunits from different families are formed [159–161]. Third, many highly specific pharmacological tools such as MgTX and DTX-I will block current in the presence of a single subunit sensitive to the agent. Thus, as of today, it is difficult to identify the exact composition of the channels responsible for the recorded current. Nevertheless, by exclusion, one can be almost certain that a DTX-sensitive current is a result of the channels formed by the Kv1 family subunits because, at low nM concentrations, DTX binds only Kv1 subunits and, if a channel contains one Kv1 subunit, the pore of this channel should not include any subunit from other families. In conclusion, usually, it is possible to identify a family of potassium channel genes that is likely to be responsible for a native current but no good means exist to identify the precise composition of the channels that mediate this current.

The proposed scheme is presented in Table 1. Most of the data were discussed in the previous sections of this review, and only general remarks are provided in this section.

This is not the first attempt to assign particular genes to native currents [15, 162]. Although, frequently, these assignments are rather tentative, there is compelling evidence that two types of outward potassium current are encoded by a particular gene family. First, channels of the transient low threshold current (I_{SA}) are usually composed of Kv4 subunits [135, 144–146]. Second, Kv3/Shaw subunits are responsible for the fast delayed rectifier currents [17].

Although it has been suggested that a fraction of I_{SA} is encoded by the Kv1 family genes [163], it seems unlikely that Kv1 currents may be responsible for the rapidly recovering I_{SA} (<100 ms). In some basal ganglia neurons, only the slow component of inactivation and deinactivation of Kv4 currents (τ =100–700 ms) was detected [8, 135, 144]. Hence, the slow recovery from inactivation alone cannot be used to identify Kv1 currents such as I_D. The most consistent feature of I_{SA} is the low threshold of activation (< −45 mV). Besides, Kv4 currents activate and deactivate very rapidly; activation/deactivation time constants are less than 5 ms. However, one should note that many divalent cations such as Cd^{2+} and Zn^{2+} (100–400 μM) slow down dramatically the activation/deactivation rates of I_{SA} [144]. There are several pharmacological features that are very useful for Kv4 current identification.

Table 1 Proposed scheme

Current type	Main distinct characteristics	Activation threshold	Inactivation τ if any at 0 mV (at 20–25°C)	Activation/ deactivation τ (at 20–25°C)	Pharmacology
Kv1 slow	DTX sensitive (100 nM), activation τ >10 ms at 0 mV	Usually < −30 mV	50–1,000 ms or none	τ(act)=7–30 ms at 0 mV τ(deact)=5 20 ms at −70 mV	DTX blocks at 100 nM, TEA>10 mM, usually 4-AP blocks with IC_{50}<100 μM; Insensitive to BDS.
Kv1 fast	DTX sensitive (100 nM), activation τ <10 at 0 mV	Usually < −40 mV	50–1,000 ms or none	τ(act)=1–3 ms at 0 mV τ(deact)=3–7 ms at −70 mV	DTX blocks at 100 nM; TEA>10 mM; usually 4-AP blocks with IC_{50}<100 μM; insensitive to BDS.
Kv2	Slow activation rates (τ>10 ms at 0 mV), 10 mM TEA blocks most of the current, insensitive to 1 mM of 4-AP	Approximately −30 mV	3–6 s at 0 mV	τ(act)=15–30 ms at 0 mV τ(deact)=15–40 ms at −70 mV	TEA IC_{50} ~1 mM; 4-AP>3 mM; insensitive to BDS, DTX, MgTX, ChTX (>100 nM); hanatoxin blocks at 100 nM.
Kv3	TEA and 4-AP sensitive (IC_{50}<0.5 mM), fast deactivation kinetics (τ<3 ms at −80 mV), insensitive to DTX	Approximately −15 mV	Usually >100 ms. In few cell types, a Kv3.4-like current is present for which τ ~10 ms	τ(act)=3–10 ms at 0 mV τ(deact)=1–5 ms at −70 mV	TEA (IC_{50} ~0.3 mM); 4-AP (IC_{50} ~0.3 mM); BDS-I and BDS-II (voltage dependent block at 0.2–2 μM); insensitive to DTX, MgTX, ChTX (>100 nM).
Kv4	TEA insensitive (IC_{50}>50 mM), low threshold (<−45 mV), rapidly activating (τ<3 ms at 0 mV), 100 μM of Cd^{+} or Zn^{+} shifts voltage dependence of both activation and inactivation >20 mV	< −45 mV	Fast τ<90 ms, slow τ>90 ms	τ(act)=0.5–3 ms at 0 mV τ(deact)=0.5–3 ms at −70 mV	4-AP (IC_{50} ~1–5 mM, use dependent block); Arachidonic acid (IC_{50} ~2 μM); Heteropotodatoxin (IC_{50} ~100 nM); insensitive to BDS (>10 μM); insensitive to TEA (IC_{50}>50 mM); 100 μM of Cd^{+} or Zn^{+} shifts voltage dependence of both activation and inactivation by >20 mV.

These currents are very little sensitive to TEA (IC_{50}> 50 Mm), and many divalent cations such as Cd^{2+} and Zn^{2+} (100–400 μM) shift the voltage dependence of activation and inactivation by as much as 40 mV [150–152]. The recently introduced spider toxins are highly specific to Kv4 currents [164], but they produce a voltage-dependent block that complicates interpretation of the results. Similarly, although arachidonic acid inhibits well Kv4 channels [165], two factors should be considered while using this compound. First, the effect is heavily dependent on auxiliary subunits that can differ from cell to cell [166]. Second, arachidonic acid is involved in major second messenger cascades and the modulatory effects of the compound can be difficult to predict (see, for instance, [167]).

The following three groups are subtypes of the delayed rectifier-like currents.

First, Kv3 currents are highly sensitive to TEA and 4-AP (IC_{50}<0.5 mM) and insensitive to DTX [17, 162]. In addition, many Kv3 currents are sensitive to blood depressing substance (BDS) toxins [90, 168], although the complexity of the block may render the interpretation of BDS effects very complicated [169]. At −80 mV, these currents deactivated in less than 3 ms, and activation time constants are less than 3 ms above +20 mV [88, 90, 93] (Fig. 4). The threshold of current activation is above −30 mV, and the voltage dependence of current activation is steep [88, 89, 93]. It should be stressed that the Kv3 currents activate without the HH-type delay and the first order kinetics adequately describe the activation time-course of the current [93].

In the soma of most central neurons, Kv3 currents are slowly inactivating outward, high threshold, delayed rectifier-like currents. Although found mainly in the fast spiking interneurons, Kv3 currents are also detected in hippocampal pyramidal neurons [88], Purkinje cells [170, 171] and magnocellular neurosecretory neurons [172]. In hippocampal granule cells, a high threshold A-type current sensitive to BDS was detected [134], and a similar TEA-sensitive transient current was observed in some cortical pyramidal neurons [173]. It is likely that homomeric Kv3.4 channels are responsible for these currents.

The second group of the delayed rectifier-like currents is Kv1 currents. They are largely distinguished by pharmacological properties. These currents are highly sensitive to DTX, and I_D belongs to this group of currents. Not all Kv1 subunits are sensitive to DTX-Kv1.4 and Kv1.5, and Kv1.7 are insensitive to 100 nM DTX. Nevertheless, Kv1 channels are predominantly heteromultimers [84], and Kv1.2 subunit is found in the majority of Kv1 channel complexes [84] warranting the DTX-sensitivity to the majority of Kv1 currents in neurons.

The key feature of all Kv1 currents is their low threshold of activation. Although a large variability exists, in almost all types of neurons tested, the DTX-sensitive current had consistently the lowest threshold of activation among all delayed rectifier-like currents found in that neuron. Because of such a low threshold of activation, DTX-sensitive currents invariably reduced the number of generated APs and prolonged the delay to the first AP. For the same reason, these currents can have very strong influence on AP generation in spite of small current amplitude. Such a strong influence should be well controlled, and the evidence from squid confirms that elaborate mechanisms are used to tune the properties of Kv1 currents [174]. It is likely that heteromultimer formation is one of such fine-tuning mechanisms.

There is a remarkable diversity in the time constants of activation/deactivation of Kv1 currents. Only fast Kv1 currents that include I_D and the classical delayed rectifier current contribute significantly to AP repolarization [117, 122]. Slow Kv1 currents are 5–20 times slower [113, 114], and they are in part responsible for medium (10–100 ms) AHP [113]. Similar to the classical delayed rectifier current, fast Kv1 currents activate with a clear delay, and the fourth order kinetics fit well the current activation time-course [123].

Finally, the fourth group of outward potassium currents is Kv2 currents. These delayed rectifier-like currents inactivate slowly (τ >3 s, in some cases, a faster component is detected with τ ~0.5 s [94]). The activation/deactivation time constants are relatively slow and, for physiological membrane potentials, range from 20 to 120 ms. In fact, it is likely that the so-called slow delayed rectifier is usually encoded by Kv2 subunits. The voltage dependence of Kv2 currents is intermediate between Kv1 and Kv3 currents with $V_{1/2}$ falling between −30 and −10 mV. The activation time-course can be often well described by the first order kinetics [94].

Because of slow kinetics, usually, these currents contribute very little to AP repolarization. However, Kv2 currents can exert strong influence on the intrinsic excitability (see above), and their expression is controlled by activity [106]. Hence, they may be these unidentified potassium currents that are thought to contribute to the homeostatic regulation of intrinsic excitability [33, 175].

Kv2 currents are characterized by modest sensitivity to TEA (IC_{50} between 1 and 10 mM) and low sensitivity to 4-AP (IC_{50}>5 mM). Hanatoxin, a peptide from the Chilean tarantula, is highly selective to Kv2.1 subunits [176] but the voltage dependence of the block and a limited availability of the toxin severely limits the usefulness of this pharmacological agent.

Interestingly, among four groups of currents discussed here, Kv1 currents turn out to be the most heterogenous and, probably, the least investigated group of potassium currents in central mammalian neurons. The most striking differences seem to be found in the activation/deactivation kinetics of the Kv1 currents, and these properties are rarely reported. Computer simulations show that such neglect can limit our ability to understand the function of a current.

As a final note, this brief summary shows that the operationally defined delayed rectifier current ('outward potassium current that is not I_D and I_{SA}') may include more than three components, Kv3, Kv2 currents, a number of Kv1 currents, and M-current. It is a challenging task to identify the properties of these components especially in the view that small amplitude does not necessary mean small impact on the neuron behavior. Many earlier studies underestimated the number of components of the delayed rectifier-like currents. Today, a combination of pharmacological and biophysical methods is likely to provide the most reliable data on these multiple components of outward potassium currents [88, 89, 118, 122].

Appendix

Hodgkin and Huxley have established that, during an AP, there are changes in the membrane permeability to certain ions. These changes in permeability could be conveniently described in the terms of separate sodium and potassium conductances as driving forces seemed to remain constant. In the case of sodium conductance, the current amplitude is expressed as

$$I_{\mathrm{Na}} = g_{\mathrm{Na}} \times (V - V_{\mathrm{Na}})$$

where I_{Na} is sodium current, g_{Na} is the sodium conductance that is a function of membrane potential and time, V is the membrane potential, V_{Na} is the reversal potential for sodium ions.

According to Hodgkin and Huxley, the sodium conductance is described by the following equation:

$$g_{\mathrm{Na}} = g_{\mathrm{Na}M} \times m^3 \times h \tag{1}$$

where $g_{\mathrm{Na}M}$ is a constant, m represents the probability that an activation gate will be in an open position, and h represents the probability that an inactivation gate will be in an open position. This equation simply states that a current can pass the channel then all gates are open. Three activation gates were employed to describe current increase at the start of the test pulse ("activation"), and one inactivation gate was dedicated to describe the decay of current while the membrane potential was held constant ("inactivation", see Fig. 2).

A separate set of first order differential equations determined the kinetics of m and h parameters:

$$\begin{aligned} \mathrm{d}h/\mathrm{d}t &= \alpha_h \times (1 - h) - \beta_h \times h \\ \mathrm{d}m/\mathrm{d}t &= \alpha_m \times (1 - m) - \beta_m \times m \end{aligned} \tag{2}$$

where α_h, β_h, α_m, and β_m are the voltage dependent rate constants.

A general solution for such equations is

$$A + B \times \exp(-t/\tau_m) \tag{3}$$

where τ_m is the time constant equal to

$$\tau = 1/(\beta + \alpha) \tag{4}$$

It is usually assumed that the rate constants follow the Boltzman equation that can be presented in the following simplest form:

$$\begin{aligned} \alpha &= \alpha_o \times \exp\left[-\left(V - V_{\alpha 1/2}\right)/V_{\alpha s}\right] \\ \beta &= \beta_o \times \exp\left[\left(V - V_{\beta 1/2}\right)/V_{\beta s}\right] \end{aligned} \tag{5}$$

where α_{o}, β_{o} are constants, V is the membrane voltage, $V_{1/2}$ is a voltage constant and V_{s} is a slope factor.

Two specific solutions of the differential Eq. 2 are useful for further analysis. For depolarizing voltage steps from hyperpolarized membrane potentials, the time-course of sodium currents can be described by the following equation (Eq. 19 in Hodgkin and Huxley [2]):

$$\begin{aligned} I_{\mathrm{Na}} &= g_{\mathrm{Namax}} \times (V - V_{\mathrm{Na}}) \times [1 - \exp(-t/\tau_m)]^3 \times \exp(-t/\tau_h) \\ &= \mathrm{I}_{\mathrm{Namax}} \times [1 - \exp(-t/\tau_m)]^3 \times \exp(-t/\tau_{\mathrm{h}}) \end{aligned} \tag{6}$$

where I_{Na} is the amplitude of the sodium current, g_{Namax} is the maximal sodium conductance at the test potential, I_{Namax} for the maximal amplitude of the sodium current at the test potential, t for the time from the start of the voltage step, τ_m for the activation time constant at the test voltage, and t_h for the inactivation time constant at the test voltage. As, for sodium currents, $\tau_h >> \tau_m$, for $t << \tau_h$, Eq. 6 can be rewritten as

$$I_{\mathrm{Na}} \sim [1 - \exp(-t/\tau_m)]^3 \tag{7}$$

By expanding this equation, one can obtain:

$$\begin{aligned} I_{\mathrm{Na}} \sim\ & 1 - 3 \times \exp(-t/\tau_{\mathrm{m}}) + 3 \times [\exp(-t/\tau_m)]^2 \\ & - [\exp(-t/\tau_{\mathrm{m}})]^3 \end{aligned} \tag{8}$$

Since $[\exp(-t/\tau_m)]^2$ and $[\exp(-\mathrm{t}/\tau_{\mathrm{m}})]^3$ decay faster than $\exp(-\mathrm{t}/\tau_{\mathrm{m}})$, for $\tau_{\mathrm{h}} >> t >> \tau_{\mathrm{m}}$

$$I_{\mathrm{Na}} \sim 1 - 3 \times \exp(-t/\tau_m) \tag{9}$$

Although, in practice, the condition $\tau_{\mathrm{h}} >> t >> \tau_{\mathrm{m}}$ can be achieved only for depolarizing steps of less than −40 mV, the Eq. 3 provides a good estimate of the expected delay for the currents described by the functions like $[1-\exp(-t/\tau_m)]^n$, $n>1$. The estimate of the delay is found by following Eqs. 6–9 for the function

$$I_{\mathrm{Na}} = I_{\mathrm{Namax}} \times [1 - \exp(-t/\tau_m)] \times \exp(-t/\tau_h) \tag{10}$$

that describes the time-course of the current governed by the first order kinetics (a single gate model). In this case, Eq. 9 becomes:

$$I_{\mathrm{Na}} \sim 1 - \exp(-t/\tau_m) \tag{11}$$

For comparison with Eq. 11, Eq. 9 can be rewritten as

$$\begin{aligned} I_{\mathrm{Na}} &\sim 1 - \exp(\ln[3]) \times \exp(-t/\tau_m) \\ &= 1 - \exp(-[t - \ln(3) \times \tau_m]/\tau_m) \\ &= 1 - \exp(-[t - \delta]/\tau_m) \text{ here } \delta = \ln(3) \times \tau_m \end{aligned}$$

Thus, for $\tau_h >> t >> \tau_m$, the difference between two functions is a shift in time (delay) of $\delta = \ln(3) \times \tau_m$. In the case of the m^2 kinetics, this difference is $\ln(2) \times \tau_{\mathrm{m}}$. This

result shows that, in the HH model, the delay is always proportional to the τ_m and it is voltage dependent in the same way as τ_m.

The second solution of differential Eq. 2 describes the time-course of currents obtained during hyperpolarizing voltage steps from the depolarized membrane potentials, when most of the channels are open and no inactivation has yet occurred:

$$I_{\mathrm{Na}} = I_{\mathrm{Namax}} \times [\exp(-t/\tau_m)]^3 = I_{\mathrm{Namax}} \times \exp(-t/\{\tau_m/3\}) \quad (12)$$

This equation describes the so-called tail currents that are indicative of channel closure kinetics. By comparing to Eq. 9, one can see that, in the HH model, tail currents decay three times faster than the current rises during the activation process. It is easy to see that, in the case of a single gate (Eq. 10), tail currents decay with the same time constant as the current activates.

Finally, it is important to note that, in the HH model, the voltage dependence of τ_m and the current amplitude can be related in the following way. It can be shown that, for the depolarizing voltage steps from hyperpolarized membrane potentials at which all channels stay closed and not inactivated (Eq. 6),

$$g_{\mathrm{Namax}} = g_{\mathrm{NaM}} \times m_{\mathrm{o}}^3, \quad (13)$$

where g_{NaM} is the maximal sodium conductance (all channels open), m_{o} is the steady state value at voltage V. The expression for m_{o} can be obtained assuming $\mathrm{d}m/\mathrm{d}t=0$ in Eq. 2:

$$\begin{aligned} 0 &= \alpha_m \times (1 - m_o) - \beta_m \times m_o \\ m_o &= \alpha_m/(\alpha_m + \beta_m) = 1/(1 + \alpha_m/\beta_m) \end{aligned} \quad (14)$$

By inserting the expressions for α_m and β_m from Eq. 5, one obtains:

$$m_o = 1/\left(1 + \alpha_o/\beta_o \times \exp\left[-\left(V - V_{\alpha 1/2}\right)/V_{\alpha s} - \left(V - V_{\beta 1/2}\right)/V_{\beta s}\right]\right) \quad (15)$$

Thus, for such voltage command, the voltage dependence of the g_{Namax} can be expressed as

$$g_{\mathrm{Namax}}(V) = g_{\mathrm{NaM}} \times \left\{1/\left(1 + \exp\left[-(V - V1/2)/V_{\mathrm{mslope}}\right]\right)\right\}^3 \quad (16)$$

where $V_{1/2}$, a half voltage, and V_{mslope}, a slope factor, can be expressed in the following way:

$$\begin{aligned} &V_{\mathrm{mslope}} = \left(V_{\alpha s} \times V_{\beta s}\right)/\left(V_{\alpha s} + V_{\beta s}\right) \\ &V_{1/2} = \left(V_{\alpha 1/2} \times V_{\beta s} + V_{\alpha s} \times V_{\beta 1/2}\right)/\left(V_{\alpha s} + V_{\beta s}\right) \\ &\text{If } V_{\alpha s} = V_{\beta s}, = V_{os}, \\ &V_{\mathrm{mslope}} = V_{os}/2 \end{aligned} \quad (17)$$

$$V_{1/2} = \left(V_{\alpha 1/2} + V_{\beta 1/2}\right)/2 \quad (18)$$

For $V \gg V_{1/2}$, the exponential term in Eq. 16 becomes very large, and this equation can be rewritten in the following way:

$$\begin{aligned} g_{\mathrm{Namax}}(V) &\sim g_{\mathrm{NaM}} \times \left\{\exp\left[\left(V - V_{1/2}\right)/V_{\mathrm{mslope}}\right]\right\}^3 \\ &= g_{\mathrm{NaM}} \times \exp\left[\left(V - V_{1/2}\right)/\left(V_{\mathrm{mslope}}/3\right)\right] \\ &= g_{\mathrm{NaM}} \times \exp\left[\left(V - V_{1/2}\right)/\left(V_{\mathrm{os}}/6\right)\right] \end{aligned} \quad (19)$$

Thus, in the HH model, for $V_{h\alpha}=V_{h\beta}$, the voltage dependence of current amplitude is six times steeper than the voltage dependence of activation/deactivation time constant.

In summary, in the HH model, the activation time constant is equal to τ_m, whereas the deactivation time constant is three times faster. That is, for the same voltage, the deactivation time constant is three times faster than the activation time constant. The delay is approximately equal to τ_m. In the HH m^3 model, for $V_{\alpha s}=V_{\beta s}$, the voltage dependence of current amplitude is six times steeper than the voltage dependence of activation/deactivation time constant. In contrast, in a single gate model, for $V_{\alpha s}=V_{\beta s}$, this difference in steepness is 2. Consequently, for the same voltage dependence of the current amplitude, the time constants of currents are more strongly dependent on voltage in a single gate model than in the traditional HH m^3 model.

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