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Potassium channel modulation and auditory processing

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ABSTRACT

For accurate processing of auditory information, neurons in auditory brainstem nuclei have to fire at high rates with high temporal accuracy. These two requirements can only be fulfilled when the intrinsic electrical properties of these neurons are matched to the pattern of incoming synaptic stimulation. This review article focuses on three families of potassium channels that are critical to shaping the firing pattern and accuracy of neurons. Changes in the auditory environment can trigger very rapid changes in the phosphorylation state of potassium channels in auditory brainstem nuclei. Longer lasting changes in the auditory environment produce changes in the rates of translation and transcription of genes encoding these channels. A key protein that plays a role in setting the overall sensitivity of the auditory system to sound stimuli is FMRP (Fragile X Mental Retardation Protein), which binds channels directly and also regulates the translation of mRNAs for the channels.

1. Introduction

The central auditory system in mammals discriminates among numerous stimuli in the auditory environment. Appropriate processing of auditory inputs, including the decoding of timbre, pitch and spatial locations of sounds, allows one to identify specific features of a sound in a noisy environment, such as one particular voice, and to ignore other sounds located at a slightly different location. To carry out this task, many neurons in the auditory brainstem nuclei are capable of firing at high rates (up to ~800 Hz) with very high temporal precision (Banks and Smith, 1992; Taschenberger and von Gersdorff, 2000, 2002; Trussell, 1999; Wu and Kelly, 1993). In low-frequency hearing animals, phase locking brainstem neurons accurately lock their action potentials to the phase of incoming auditory stimuli with frequencies up to 2 kHz. At higher frequencies, and in high frequency hearing animals, such neurons lock their action potentials to the envelope of sounds that are amplitude-modulated at these lower frequencies (Joris, 1996; Joris and Yin, 1995). The ability of such neurons to follow auditory stimuli relies in major part on their intrinsic electrical properties, which allow them to generate the appropriate firing rate with the needed precision of timing, and on their ability to change their electrical properties in response to changes in the auditory environment.

2. Auditory brainstem circuits for sound localization

The basic neural circuitry required for discrimination of the spatial location of sounds is located in the auditory brainstem, within the cochlear nuclei and superior olivary complex. Phase locking bushy cells in the anteroventral cochlear nucleus (AVCN) relay information on the timing and intensity of sounds presented to the ipsilateral cochlea to the lateral superior olivary (LSO) nuclei and the medial superior olivary (MSO) nuclei. The nervous system makes a comparison of intensity and time of arrival of sounds at the two ears in the LSO and MSO. A key component of this circuit is the medial nucleus of the trapezoid body (MNTB). The principal neurons of this nucleus receive excitatory inputs from the AVCN globular bushy cells and relay this information via glycinergic inputs to both the LSO and MSO nuclei. (Banks and Smith, 1992; Brand et al., 2002; Brownell, 1975; Kopp-Scheinpflug et al., 2003a; Smith et al., 1998; Taschenberger and von Gersdorff, 2000; Wu and Kelly, 1993). This inhibitory input is required for the processing of both intensity and time differences (Brand et al., 2002; Moore and Caspary, 1983). Excitation of MNTB neurons by globular bushy cells occurs at the giant calyx of Held synapse where glutamatergic excitatory input from the AVCN surrounds the somata of the MNTB neurons (Morest, 1968), and this synaptic contact has proved to be a model system for answering a number of basic questions in neurobiology. For example, rigorous investigations of the mechanisms of neurotransmitter release are possible at

Abbreviations: FMRP, Fragile X mental retardation protein; AVCN, Anteroventral cochlear nucleus; LSO, Lateral superior olive; MSO, Medial superior olive; MNTB, Medial nuclei of the trapezoid body; Kv, Voltage-gated potassium channel family; PKC, Protein kinase C; CRE, Cyclic AMP/calcium response element; CREB, CRE-binding protein; K_{Na}, Sodium-activated potassium channels; Slack, K_{Na} channel subunit; Slick, K_{Na} channel subunit.

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this synaptic terminal because patch clamp electrodes can be used to gain direct chemical and electrical entry into the interior of the presynaptic terminal (Borst and Sakmann, 1996, 1995; Forsythe, 1994; Schneggenburger and Forsythe, 2006; Taschenberger et al., 2002; Trussell, 1999; Wang and Kaczmarek, 1998a). The majority of studies investigating the regulation of intrinsic excitability of auditory neurons have also been carried out in the MNTB, and these are the focus of this review.

3. Classes of potassium channels

The last few decades have seen an enormous growth in the molecular basis of ionic conductances, and it is now believed that the genes encoding most plasma membrane channels have been identified. Without question, channels selective for potassium form the most diverse class of ion channels. Over a hundred genes encode subunits of potassium channels compared to nine genes described for voltage-dependent sodium channels and ten genes for voltage-dependent calcium channels (Hille, 2001). Genetic and pharmacologic manipulation of the levels of various ion channel subunits has allowed investigators to test the role of specific subunits in the generation of different types of firing patterns. The existence of a wide variety of potassium channels, coupled with the fact that the properties of many of these channels can be rapidly modified by intracellular biochemical events such as activation of protein kinases and second messenger pathways, provides the possibility of fine-tuning the excitability of a neuron to an exquisite degree. Because their biological function is linked to their ability to fire at high rates with high temporal precision, auditory brainstem neurons have proved invaluable for probing the role of specific ion channels in control of synaptic transmission and neuronal firing patterns (Joris, 1996; Kaczmarek et al., 2005; Oertel, 1999; Schneggenburger and Forsythe, 2006; Trussell, 1999).

As will be described in this review, the intrinsic excitability of these neurons is dynamic and can rapidly change to adapt to different acoustic environments. Although most of the work examining regulation of ion channels in auditory brainstem has used rodents, the ion channels and signaling pathways that underlie rapid changes in neuronal excitability are highly conserved between rodent and humans. Thus it would not be surprising to find that such plasticity of intrinsic excitability also occurs in humans and may contribute to, for example, improvements in auditory discrimination tasks following training.

This review article will focus on three types of potassium channels that are known to shape the intrinsic excitability of MNTB neurons: “high-threshold” voltage-dependent Kv3 family potassium channels, “low-threshold” voltage-dependent Kv1 family channels, and the Slack/Slick sodium-activated channels. Neurons can rapidly respond to various patterns of stimulation using biochemical mechanisms to modulate the properties of potassium channels.

4. Rapid firing requires Kv3.1 channels

First defined in the squid giant axon, delayed rectifier channels provide current for the repolarization of action potentials (Hodgkin and Huxley, 1952). Kv3.1 channels are voltage-dependent potassium channels belonging to the delayed rectifier channel family (Swanson et al., 1990) located on presynaptic terminals as well as immediately adjacent to subsynaptic membranes of MNTB neurons (Wang et al., 1998c). However, the properties of Kv3.1 diverge substantially from most channels in this classification. Kv3.1 currents recorded using patch clamp techniques on heterologous cell lines expressing the *Kv3.1* gene, activate and deactivate very rapidly in response to voltage changes (Kanemasa et al., 1995) (Fig. 1A). Kv3.1 currents become activated when a cell depolarizes to potentials more positive than −10 mV. Because of its rapid deactivation, however, very few Kv3.1 channels remain open after the end of an action potential. For most other delayed rectifier channels, their slow rate of deactivation after an action potential results in the relative refractory period. In numerical simulations, neurons with Kv3.1 currents have narrow action potentials and can fire at high rates because of the lack of a relative refractory period (Kanemasa et al., 1995).

MNTB and AVCN neurons express high levels of Kv3.1 channels (Li et al., 2001a; Perney and Kaczmarek, 1997; Wang et al., 1998c) and are capable of generating action potentials at high rates (Martina et al., 1998; Massengill et al., 1997; McDonald and Mascagni, 2006; Perney et al., 1992; Weiser et al., 1995). A potassium current matching Kv3.1 in its kinetic and pharmacological characteristics has been demonstrated in patch clamp recordings from MNTB neurons (Wang et al., 1998b) and this component of potassium current is lacking in mice in which the *Kv3.1* gene has been deleted (*Kv3.1*$^{-/-}$) (Fig. 1C) (Macica et al., 2003). The firing pattern of MNTB neurons from *Kv3.1*$^{-/-}$ mice does not differ from wild type cells when stimulated with intracellular current pulses at frequencies less than ~200 Hz. But at stimulus rates above 200 Hz, MNTB neurons from *Kv3.1*$^{-/-}$ mice become incapable of sustaining action potential firing beyond the first or second stimulus (Fig. 1C). These experiments on *Kv3.1*$^{-/-}$ mice, coupled with a variety of pharmacological approaches, have demonstrated that Kv3.1 is essential for MNTB neurons to fire at high rates (Kaczmarek et al., 2005). Moreover, increasing the level of Kv3.1 current either in real neurons or in numerical simulations of MNTB neurons (Fig. 2) further increases the rate at which a neuron can be stimulated and still maintain sustained firing of action potentials (Kaczmarek et al., 2005; Song et al., 2005).

5. MNTB neurons expressing high levels of Kv3.1 channels make mistakes in timing

In addition to allowing cells to fire at rapid rates, high levels of Kv3.1 can promote the occurrence of the irregular firing patterns that degrade timing information. Fig. 2A illustrates the response of an MNTB neuron in a brain slice to current pulses applied at frequencies from 100 Hz to 600 Hz (Wang et al., 1998b). This neuron precisely locks an action potential in response to every stimulus at stimulation rates below 400 Hz. At 400 Hz, however, the response pattern becomes irregular. Different action potentials evoked during the train have different latencies to the onset of the stimulus pulses and some of the stimuli fail to trigger action potentials. Once the stimulation rate is raised to 600 Hz, there is a restoration of the regular firing pattern, although now only every other stimulus pulse evokes an action potential. Accuracy of timing is restored at this higher stimulus rate because, in fact, the neurons fire at a lower rate (300 Hz) in response to the 600 Hz stimulus than in response to the 400 Hz stimulus. Clearly, however, information is lost when cells only respond to a subset of stimuli.

A firing pattern such as that observed for 400 Hz stimulation in Fig. 2B poses a problem for the processing of auditory information. While higher levels of Kv3.1 current in a neuron are required for firing at high rates, they also promote such irregular firing responses to regular patterns of input. The loss of accuracy with high levels of Kv3.1 can be attributed to the fact that, at higher current amplitudes, even the rapidly-deactivating Kv3.1 channels begins to contribute to the relative refractory period, producing a progressive delay in the timing of successive action potentials evoked by a regular stimulus. This can readily be quantified in real neurons and in numerical simulations by calculating the strength of a phase vector that measures the temporal relation between a stimulus and its evoked action potential. The value of this phase