RIM2 α /RBP2/ β -subunit co-expression stabilizes slow Cav1.3 channel inactivation to improve auditory perception

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Introduction

Cav1.3 channels are voltage-gated L-type Ca²⁺ channels that are highly expressed in cochlear inner hair cells (IHCs) [1]. The channels are localized predominantly in the active zones of presynaptic ribbons of IHCs and carry most of the Ca²⁺ currents (>90%) required for transforming sound-evoked depolarization into graded Ca²⁺-dependent glutamate release at the IHC-auditory nerve synapse [3]. Cav1.3 channels activate at relatively negative potentials and exhibit fast activation and very slow inactivation kinetics [5, 7, 12]. In this way, they allow fast and sustained Ca²⁺ signals in a broad range of voltages, making them suitable to transform sound-evoked IHC receptor potential into glutamate release at the postsynaptic ending of auditory nerves. While fast activation and a negative activation voltage range are typical hallmarks of Cav1.3 channels in a variety of excitable cells [3, 7, 8], their slow inactivation kinetics is unique to IHCs. As other voltage-gated Ca²⁺ channels, Cav1.3 channel inactivation is both Ca²⁺ (CDI)- and voltage (VDI)-dependent [2]. CDI is fast and calmodulin (CaM)-dependent. CaM, activated by Ca²⁺, binds to the N- and C-terminal motifs of the pore-forming α 1-subunit and inactivates the open channel. VDI of Cav1.3 channels is the predominant inactivation mechanism and is measured by replacing Ca²⁺ with Ba²⁺ to prevent Ca²⁺-dependent CaM activation [2]. In IHCs, VDI is ultra-slow while CDI is nearly absent since mediated by CaBP2, a CaM-like Ca²⁺-binding protein abundantly expressed in IHCs that prevents CaM-mediated CDI [11].

Although it is known that accessory β -subunits and other intracellular proteins can modify Cav1.3 channel inactivation [9], the underlying molecular components regulating the slow VDI in IHCs are not yet fully identified. For instance, the major β -isoforms expressed in IHCs (β 2a and β 2e) are known to slow VDI to a greater degree than β 3, which has been consistently detected in IHCs [9]. Proteins of the presynaptic active zone, such as bassoon, RIM, and RIM-binding proteins (RBPs) [6] are also able to slow VDI of Cav1.3 in IHC. These proteins favor Cav1.3 channels positioning close to the readily releasable synaptic vesicles at the IHC ribbon synapse and can therefore tightly regulate Cav1.3 channel inactivation kinetics. This hypothesis is supported by previous observation by Joerg Striessnig laboratory [4] that RIM2 α binding to the β 3-subunit stabilizes slow Cav1.3 VDI but not to the extent as observed in IHCs.

In this issue, the Joerg Striessnig group (Ortner et al., 2020) shows with impressive details that co-expression of RBP2 together with RIM2 α in heterologous tsA-201 cells dramatically slows the VDI of the Cav1.3L/ β 3 channel complex, mimicking the ultra-slow Ca²⁺ current inactivation kinetics existing in IHCs [10]. Figure 1 (left) summarizes how VDI inactivation of Cav1.3L currents become progressively slower by co-expressing β 3 or β 2a with RIM2a and RBP2a to mimic closely the slow VDI in adult mouse IHC. This occurs due to the unique properties of RBP2a that can bind through distinct SH3 domains simultaneously to the β -subunits associated to RIM2 α and to the C terminus of long Cav1.3 splice variants (Fig. 1, right). This effect requires the presence of the Cav1.3 long C terminus splice variant, which contains the RBP2 interaction site and occurs both in the presence β 2a (β 2e) or β 3 subunits. In conclusion, Ortner et al. 2020 show clearly that the slow VDI of Cav1.3 channels, mimicking the ultra-slow inactivation in IHC, is effectively controlled by interactions with proteins of the presynaptic active zone (RIM2 α and RBP2) in association with β 2 or β 3-subunits in a Cav1.3 splice variant-dependent manner.

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Fig. 1 Progressively slower I_{Ba} inactivation of Cav1.3L co-expressed in tsA-201 cells with $\beta 3$ and $\beta 2a$ -subunits and RIM2 α /RBP2 proteins. (Left) Normalized mean Ba^{2+} currents (15 mM Ba^{2+}) of Cav1.3L/ $\alpha 2\delta 1$ with $\beta 3$ (black), $\beta 3$ /RIM2 α /RBP2 (dark red), or $\beta 2a$ /RIM2 α /RBP2 (red) recorded during the first 2 s of a depolarization to reach

maximal current amplitude. For comparison is shown the mean Ba^{2+} current recorded in mature mouse IHCs (gray). (Right) Schematic illustration of the molecular components ($\beta 3$, RIM, RBP) co-expressed with Cav1.3L (modified from Figs. 8 and 13 of ref. 10; Ortner et al. 2020)

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