PERSPECTIVES

C-terminal tailoring of L-type calcium channel function

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Voltage-gated L-type (Ca_v1) Ca^{2+} channels are the well-known pharmacotherapeutic targets of Ca^{2+} channel blockers, such as dihydropyridines. Unlike what is expected from the selective effects of these drugs in heart and (vascular) smooth muscle L-type Ca^{2+} channels (LTCCs) are also expressed in skeletal muscle, endocrine tissues, sensory cells and neurons. Thus they serve as key signalling molecules for excitation–contraction coupling in skeletal muscle, stimulus–secretion coupling in endocrine tissues, sensory cell signalling, pacemaking in neurons and sinoatrial node and for neuronal plasticity. To adapt channel function to these different physiological needs, four pore-forming LTCC α1-subunits ($Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, $Ca_v1.4$) with unique functional properties evolved. Tight conformational coupling to ryanodine receptors makes $Ca_v1.1$ channels perfect voltage sensors for intracellular Ca^{2+} release in skeletal muscle; activation at relatively low voltages enables $Ca_v1.3$ Ca^{2+} currents (I_{Ca}) to support pacemaking activity in sinoatrial node (SAN) and some neurons, and very slow inactivation of $Ca_v1.4$ currents strengthens synaptic efficacy in retinal ribbon synapses.

However, this structural diversity is still not sufficient to fine-tune LTCC function to specific cellular functions. A well documented example exists for $Ca_v1.3$ channels: $Ca_v1.3$ I_{Ca} inactivates rapidly in SAN cells (Mangoni *et al.* 2003) where the transient inward current is suitable to support diastolic depolarization between two action potentials. In contrast, almost no inactivation occurs in cochlear inner hair cells (IHCs) (Platzer *et al.* 2000) where sound stimuli induce graded and tonic presynaptic depolarization and make neurotransmitter release dependent on sustained activation of presynaptic $Ca_v1.3$ channels.

The article by Cui *et al.* (2007) in this issue of *The Journal of Physiology* adds valuable information to a series of recent reports illustrating that sustained LTCC currents, as required in IHCs ($Ca_v1.3$) and retinal neurons ($Ca_v1.4$), are generated by switching off so-called Ca^{2+}-dependent inactivation (CDI), an important negative feedback mechanism also found in other voltage-gated Ca^{2+} channel families. Ca^{2+} ions entering through $Ca_v1.3$ (or $Ca_v1.2$) channels can activate calmodulin (CaM), which is prebound to cytoplasmic regions (particularly an 'IQ-domain', Fig. 1) within the proximal C-terminal tail of α1-subunits. Upon activation CaM introduces conformational changes which promote inactivation of the channels.

In analogy to previous observations with $Ca_v1.2$ (Zhou *et al.* 2004), Yang *et al.* (2006) were the first to show that the CaM-like Ca^{2+} binding proteins (CaBPs) CaBP1 and CaBP4 can eliminate CDI of $Ca_v1.3$ channels by competing for C-terminal CaM binding when coexpressed in HEK-293 cells. This resulted in currents resembling those recorded in native IHCs. They found CaBP4, but not CaBP1, to be expressed in adult IHCs and therefore speculated that CaBP4 modulation of $Ca_v1.3$ is required for normal auditory function. However, their hypothesis was challenged by the observation that human mutations in CaBP4 result in visual disturbances (Zeitz *et al.* 2006) but no obvious auditory dysfunction. The present article by Cui *et al.* (2007) now provides further and more direct evidence that CaBP4 modulation is not required for normal cochlear function. They found that CaBP4-deficient mice hear normally and detected only a minimal increase of $Ca_v1.3$ current CDI in their IHCs when compared to wild-type cells. In contrast to Yang *et al.* (2006), their biochemical, immunohistochemical and functional data strongly suggest that CaBP1, rather than CaBP4, is responsible for the hearing-relevant moderation of CDI in IHCs (Fig. 1).

The relevance of CDI as a modulatory target is evident from the fact that CaBP-mediated control of LTCC inactivation represents only one of several different molecular mechanisms (Fig. 1) known to switch off CDI. Outer hair cells (OHCs) express a short $Ca_v1.3$ α1-subunit splice variant that lacks the IQ domain as major CaM interaction site and therefore also CDI (Ihara *et al.* 1995; Shen *et al.* 2006). An even more complex mechanism was discovered for retinal $Ca_v1.4$ α1. Although these subunits are principally capable of CaM-dependent CDI, it is completely prevented by a modulatory domain located within the distal C-terminus through its binding to upstream CaM interaction domains (Singh *et al.* 2006; Wahl-Schott *et al.* 2006).

Given this multitude of mechanisms moderating CDI, the paper by Cui *et al.* leaves us with an important question: Does CaBP1 account for most of the inhibition of CDI in IHCs or are multiple mechanisms involved? This question can only be addressed by targeted CaBP1 knockdown or knockout in future experiments.

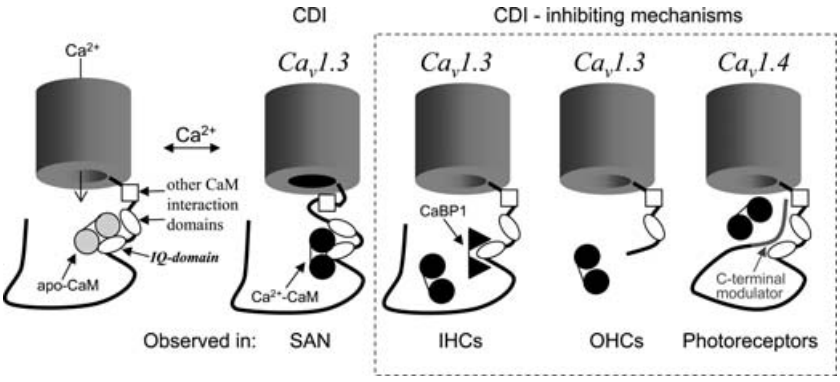

Figure 1. CDI-inhibiting mechanisms in $Ca_v1.3$ and $Ca_v1.4$ L-type Ca^{2+} channels

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