Dissecting the functional role of different isoforms of the L-type Ca\(^{2+}\) channel

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Commentary

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There currently exist a great number of different mouse lines in which the activity of a particular gene of interest has been inactivated or enhanced. However, it is also possible to insert specific mutations in a gene so that the pharmacological sensitivity of the gene product is altered. An example of such an approach shows how the abolition of the sensitivity of an L-type Ca2+ channel isoform to dihydropyridines allows the investigation of the physiological role of these channels in different tissues (see the related article beginning on page 1430).

Nonstandard abbreviations used: dihydropyridine (DHP); L-type Ca2+ channel (LTCC).
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almost ubiquitously expressed in excitable cells, the model provides a very elegant and promising approach for investigating the physiological role of the other DHP-sensitive LTCC isoforms (Ca\textsubscript{1.1}, Ca\textsubscript{1.3}, and Ca\textsubscript{1.4}). This model is particularly useful for the exploration of the function of Ca\textsubscript{1.3} channels, which are coexpressed with Ca\textsubscript{1.2} but at a much lower level in most cell types investigated so far. The Ca\textsubscript{1.1} subunit is responsible for excitation-contraction coupling in skeletal muscle (3), while Ca\textsubscript{1.4} expression appears to be restricted to the retina and T lymphocytes (4–6). In contrast to the tissue-specific expression of Ca\textsubscript{1.1} and Ca\textsubscript{1.4}, both Ca\textsubscript{1.2} and Ca\textsubscript{1.3} are widely expressed and distributed in the brain, the cardiovascular system, and neuroendocrine cells.

**Ca\textsubscript{1.2} versus Ca\textsubscript{1.3} in insulin secretion**

Using the Ca\textsubscript{1.2}\textsuperscript{DHP–/–} mice that exhibit a normal phenotype in spite of their DHP-insensitive Ca\textsubscript{1.2} channels, the authors have been able to differentiate, both in vivo and in vitro, the roles of the Ca\textsubscript{1.2} and Ca\textsubscript{1.3} channels in insulin secretion, cardiac performance, and mood behavior (2). In particular, the finding that insulin secretion in these mice was completely insensitive to DHP agonists and antagonists provides strong evidence in the long-standing debate about the insulin secretagogue role of the Ca\textsubscript{1.2} and Ca\textsubscript{1.3} channels. Opposite conclusions about the importance of the Ca\textsubscript{1.3} LTCC in this secretion process have been drawn by two previous studies using different mouse strains lacking the Ca\textsubscript{1.3} LTCC (7, 8) and a β-cell–specific knockout of the Ca\textsubscript{1.2} LTCC (9). The complete resistance of the insulin secretory process to DHPs in the Ca\textsubscript{1.2}\textsuperscript{DHP–/–} mice strongly supports the minor role of Ca\textsubscript{1.3} in this process.

**LTCC isoforms in mood behavior**

Another important aspect of the study concerns the role of the Ca\textsubscript{1.3} LTCC in integrated neuronal functions. While the expression of the Ca\textsubscript{1.2} LTCC isoform accounts for about 80% of the overall DHP-binding sites in the brain, the remaining 20% of binding can be attributed to Ca\textsubscript{1.3} LTCCs, and little was known about the function of these channels. Indeed, DHP agonists such as BayK8644 cannot be used in vivo because of potent neurotoxic effects mediated by Ca\textsubscript{1.2} channels. Abolition of the sensitivity of the Ca\textsubscript{1.2} channel to DHPs allowed unmasking of a depression-like behavioral effect mediated by Ca\textsubscript{1.3} channels (2). From a molecular point of view, these effects may rely on the recently identified specific interactions of the Ca\textsubscript{1.3} channel with synaptic proteins (10), with possible consequences related to the control of neurotransmitter release classically implicated in depression (as shown by Sinnegger-Brauns et al. in the case of dopamine). Therefore, an attractive prospective application of these findings is in the development of new classes of antidepressant drugs that act selectively on Ca\textsubscript{1.3} channels.

**Relevance of the Ca\textsubscript{1.2}\textsuperscript{DHP–/–} mouse in the study of heart physiology**

The Ca\textsubscript{1.2}\textsuperscript{DHP–/–} mouse model can also help to reveal the functional role of LTCCs in the physiology of the heart. It is widely accepted that the Ca\textsubscript{1.2} subunit constitutes the most abundant LTCC subunit in the heart, where it plays an important role in excitation-contraction coupling in the working myocardium. In addition, a growing body of evidence indicates that the functional roles of Ca\textsubscript{1.2} and Ca\textsubscript{1.3} channels are distinct in the heart, with Ca\textsubscript{1.3} channels playing a major role in pacemaker activity. Indeed, the fact that mice in which the gene encoding the Ca\textsubscript{1.3} subunit has been inactivated show prominent dysfunctions in pacemaker activity in...
The amyloid β-peptide (Aβ peptide) is assumed to play a crucial and early role in the pathogenesis of Alzheimer disease. Thus, strategies for a pharmacotherapy aim at reducing Aβ peptide generation, which proteolytically derives from the amyloid precursor protein (APP). The main targets so far have been β- and γ-secretase, the two proteases that cleave APP at the N- and C-terminus of the Aβ peptide and are thus directly responsible for Aβ peptide generation. A different strategy, namely the activation of α-secretase, has been barely investigated for its therapeutic potential. α-Secretase cleaves within the Aβ peptide domain and thus precludes Aβ peptide generation. Now, new results demonstrate that activation of α-secretase indeed reduces Aβ peptide generation and toxicity in vivo (see the related article beginning on page 1456).

Numerous laboratories are currently investigating β- and γ-secretase, the two amyloidogenic proteases that cleave the Aβ-peptide out of the amyloid precursor protein (APP). The reason is obvious. If we prevent these proteases from working, we will stop the progression of Alzheimer disease (AD). However, a rather old and almost forgotten idea, namely the activation of α-secretase, which cuts the amyloid β-peptide (Aβ peptide) into two nonamyloidogenic pieces, has now been reinvestigated. Compelling evidence that this strategy may work is now presented in a study by researchers in Germany and Belgium led by Falk Fahrenholz at the University of Mainz (1).

AD is the most prevalent neurodegenerative disease, affecting about 20 million people worldwide (for an overview see ref. 2). The amyloid hypothesis of AD, which is now widely accepted, describes the pathogenesis of this disease as a cascade of several steps, from the initial generation of the Aβ peptide to cognitive impairment and neuronal loss (for overviews see refs. 3, 4). Whereas drugs are currently available that may slightly...