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The interplay of excitatory and inhibitory coupling modes is crucial for the regulation of neuronal electrical activities by L-type calcium channels

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Background

Neuronal L-type voltage-gated calcium channels (LTCCs) have long been implicated in the regulation of excitability. This function appears to be related to the coupling of LTCC-mediated Ca^{2+} influx to Ca^{2+}-dependent conductances, such as K_{Ca} channels, e.g. $K_V2.x$ (SK), and nonspecific cation (CAN) channels. However, despite numerous data related to the molecular functioning of LTCCs, little is known about the actual role of these channels in cellular electrical excitation. In this study, we examined how activation of LTCCs affects neuronal depolarizations and analyzed the contribution of Ca^{2+}-dependent potassium and cation conductances.

Methods

Using hippocampal neurons in primary culture, pulsed current injections were applied in the presence of TTX for stepwise depolarization, and the availability of LTCCs was modulated by Bay K8644 and isradipine.

Results

Varying pulse length and current strength, we found that weak depolarizing stimuli tend to be enhanced by LTCC activation, whereas in the course of stronger depolarizations LTCCs counteract excitation. Both effect modes appear to involve the same channels that mediate afterdepolarizations (ADPs) and afterhyperpolarizations (AHPs), respectively. Indeed, ADPs were activated at lower stimulation levels than AHPs. In the absence of TTX, activation of LTCCs prolonged or shortened burst firing, depending on the initial burst duration, and invariably augmented brief unprovoked (such as excitatory postsynaptic potentials) and provoked electrical events.

Conclusions

Hence, instantaneous regulation of membrane excitability by LTCCs involves activity of both excitatory and inhibitory Ca^{2+}-activated ion channels. The overall enhancing or damping effect of LTCC stimulation on excitability does not only depend on the presence of the respective coupling partner, but also on the stimulus intensity. These findings might have important implications for the usability of LTCC inhibitors in the treatment of various forms of abnormal neuronal electrical activities.

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