BMC Pharmacology

Meeting abstract

L-type voltage-gated calcium channels in hippocampal neurons and their potential as anti-epilept(ogen)ic drug targets

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from 15th Scientific Symposium of the Austrian Pharmacological Society (APHAR) Joint meeting with the Hungarian Society of Experimental and Clinical Pharmacology (MFT) and the Slovenian Pharmacological Society (SDF)
Graz, Austria. 19-21 November 2009

Published: 12 November 2009

BMC Pharmacology 2009, **9**(Suppl 2):A20 doi:10.1186/1471-2210-9-S2-A20

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S2/A20

Background

Neuronal L-type voltage-gated calcium channels (LTCCs) were shown to be involved in the control of neuronal excitability, synaptic plasticity and gene expression. These mechanisms are altered in epileptic tissue and are thought to contribute to epileptogenesis. Hence, LTCCs are interesting targets for epileptic and anti-epileptic therapy. However, their role in epilepsy, whether LTCCs enhance or reduce epileptiform/epileptogenic activity, remained unclear. The aim of this study was to identify in which manner LTCCs contribute and/or modulate electrical excitation.

Methods

Current-clamp experiments were performed on hippocampal neurons in culture using the perforated patch-clamp method to record membrane voltage. The neurons were continuously superfused and LTCC activity was modulated by application of the dihydropyridines BayK 8644 (LTCC agonist) and isradipine (LTCC antagonist), all in the presence of TTX. Electrical excitation was evoked by incremental current injections, whereby the neurons were depolarised experimentally beyond the LTCC activation threshold.

Results

With 8 s long depolarisations LTCC-mediated effects appeared as bumps, oscillatory activity or hyperpolarising sags. Using ion channel blockers and ion-exchange experiments we provide evidence that LTCCs couple to both SK(K_{Ca}2.x) and CAN (probably TRPM) channels, that these couplings underlie the various LTCC-mediated effects and show up as after-depolarisations (ADPs) or after-hyperpolarisations (AHPs) following the current pulse. These coupling modes operate in parallel, because blocking one type of afterpotential uncovered the other. Varying pulse length and current strength we obtained evidence that ADPs are activated at a lower LTCC activity than AHPs. Most notably, irrespective of the predominant coupling mode leading to a depolarising or hyperpolarising modulation of the voltage responses, the initial effect of LTCC activation (e.g. the one occurring within the first second) was, in all cells, an enhancement of the depolarisations.

Conclusion

Varied predominance of LTCC coupling may explain the controversy surrounding LTCC blockers as antiepileptic drug targets. However, short excitatory signals were always subject to LTCC-mediated augmentation. Brief (≤1 s), excessive depolarisations (so-called paroxysmal depolarisation shifts or PDS) were recently implied as important elements in epileptogenesis, appearing prior to actual seizures, probably altering neuronal circuits by causing repetitive, synchronised pulsative cytosolic Ca^{2+} rises. In the framework of this hypothesis our data point to a potential use of LTCC inhibitors to counteract PDS, and hence epileptogenesis.

Acknowledgements
Supported by FWF grant P19710.