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INTRINSIC ACTIVITY

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MEETING ABSTRACT

A3.29

Reconsidering the neuropathogenic role of paroxysmal depolarization shifts in epilepsy, epileptogenesis and beyond

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Background: Paroxysmal depolarization shifts (PDS) have first been described by epileptologists in the 1960s. However, today controversy still exists regarding their actual role in neuropathogenesis. Seemingly contrary hypotheses on epileptogenic and anti-ictogenic effects of PDS have meanwhile emerged, in addition to the initial view of a lack of a crucial role in epileptic mechanisms. Evidence for the roles of PDS has primarily arisen from investigations of the multi-unit correlate of PDS: an electrographic spike termed "interictal" because of its continuance during seizure-free periods of epilepsy patients. However, interictal spikes have meanwhile been linked with neuronal diseases other than epilepsy, for example Alzheimer's disease, which may indicate a broader implication of PDS in neuropathogenesis. Notably, PDS come with perturbation of neuronal membrane voltage and of intracellular Ca^{2+}. Hence, there are various conceivable pathomechanisms by which PDS may lead to neuronal dysfunction.
Methods: We performed electrophysiological (perforated patch-clamp) recordings and confocal imaging of various fluorescent dyes and genetically-encoded indicators on rat hippocampal neurons in primary culture to study the effect of PDS on several cellular and intraorganelle parameters. PDS were elicited by application of bicuculline (10 µM) together with the L-type calcium channel agonist Bay K8644 (3 µM).
Results: We have recently demonstrated that PDS can acutely inhibit neuronal discharge activity, for example seizure-like discharge activity elicited by low-Mg^{2+} solution. In addition we obtained compelling evidence that Ca^{2+} influx via L-type calcium channels (which is a crucial component of PDS) affects mitochondrial functions—including ATP synthase reversal—in a semi-acute fashion, with presumably neuroprotective consequences (***e.g.*** maintenance of mitochondrial membrane potential). However, we observed that the continuous occurrence of PDS leads to alterations in dendritic arborization. Hence, in the long term, PDS appear to impact on neuronal morphology.
Discussion: Our results suggest that PDS can exert both beneficial as well as detrimental effects. Hence, if, how and at which time point of therapy PDS discharge should be targeted, needs to be carefully reconsidered.
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Keywords: epilepsy – hippocampus – mitochondria – L-type calcium channels – paroxysmal depolarization shift – neuropathogenesis

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