Presentation Abstract

Program#/Poster#:	686.10/B3
Presentation Title:	Activation of inositol trisphosphate receptors is sufficient for inducing graded intrinsic plasticity in hippocampal pyramidal neurons
Location:	WCC Hall A-C
Presentation time:	Wednesday, Nov 19, 2014, 8:00 AM -12:00 PM
Presenter at Poster:	Wed, Nov. 19, 2014, 9:00 AM - 10:00 AM
Topic:	++B.04.f. HCN and non-selective cation channels
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Abstract:	A class of studies that endeavors to understand the role of store Ca^{2+} in neuronal plasticity employs pharmacological activation of metabotropic glutamate (mGluR) or acetylcholine receptors to mobilize cytosolic inositol trisphosphate ($InsP_3$). However, due to the intracellular presence of mGluRs, the diversity of signaling mechanisms downstream of these receptors, and the non-specificities associated with their pharmacological activation, the precise roles for Ca^{2+} released through $InsP_3$ receptors ($InsP_3R$) in neuronal plasticity has remained ambiguous. To overcome these limitations, we intracellularly injected D-myo-$InsP_3$ through whole-cell patch pipettes into rat (4[[unable to display character: –]]10 weeks male Sprague Dawley) hippocampal pyramidal neurons, and recorded several intrinsic properties for a 45-min period (at ~34 °C). We found that the injection of $InsP_3$ was sufficient to induce persistent plasticity of intrinsic response dynamics (IRD). Specifically, incorporation of 10 μM D-myo-$InsP_3$ in the recording pipette induced a reduction in input resistance (34.9 ± 6.8%) accompanied by an increase in the optimal response frequency (34.0 ± 5.7%) of

these neurons. This plasticity in IRD also reflected as an increase in sag ratio, a reduction in temporal summation and an increase in the impedance phase lead. Strikingly, the magnitude of plasticity in all these measurements was dependent upon [$InsP_3$], emphasizing the graded dependence of such plasticity on the activation of $InsP_3R$. Assessing the mechanistic basis for this $InsP_3$-induced plasticity, we found that changes in all intrinsic response properties were abolished in the presence of ZD7288 (20 μM, pipette), establishing that this form of plasticity depended on hyperpolarization-activated cyclic-nucleotide gated (HCN) channels. Moreover, this Ca^{2+}-dependent (20 mM BAPTA, pipette) form of plasticity was critically contingent on the release of Ca^{2+} through $InsP_3Rs$ (1 mg/mL Heparin, pipette) and was modulated by the influx of Ca^{2+} through NMDA receptors (50 μM D,L-AP5, bath) and *T*-type Ca^{2+} channels (50 μM $NiCl_2$, bath). Finally, this form of $InsP_3$-dependent plasticity was reliant on the activation of the protein kinase A (PKA) pathway, evidenced by the blockade of plasticity by a PKA inhibitory peptide (20 μM, pipette) or KT5720 (500 nM, bath). Our results suggest a critical role for the intracellular Ca^{2+} stores in regulating intrinsic properties under physiological conditions, thereby emerging as a pivotal cog in neuronal information encoding and homeostasis.

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PATCH CLAMP

ENDOPLASMIC RETICULUM

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