S 11-4

ACTIVITY-DEPENDENT PLASTICITY OF METABOTROPIC GLUTAMATE RECEPTOR

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Glutamate is the major excitatory neurotransmitter in brain and it produces both fast excitation through the activation of ionotropic receptors and slower actions through metabotropic receptors (mGluRs). Burst stimulation of parallel fibers releases glutamate which activates perisynaptic mGluR1 in the dendritic spines of cerebellar Purkinje cells (PC). mGluR1-stimulated signaling is G-protein-dependent and diverges into two limbs: 1) activation of phospholipase C (PLC), resulting in production of diacylglycerol and IP3 and mobilization of Ca from internal stores, and 2) activation of a slow EPSC mediated by the plasma membrane cation channel TRPC1. We observed that activity of PC by a short membrane potential depolarization (50~100 ms to 0 mV) potentiated mGluR-evoked slow EPSC in PC. This potentiation of mGluR signal was transient and the duration of this potentiation was indistinguishable to the potentiation of mGluR-evoked synaptic potential following climbing fiber stimulation. The short depolarization of PC increased IP3-induced Ca release (IICR) which was evoked by uncaged-IP3. The potentiation of IICR was transient with a decay tau which was not different from that of mGluR-evoked slow EPSC. This similar decay kinetics of depolarization-induced potentiation of mGluR-evoked signal and IICR prompted us to test whether the depolarization filled the Ca store and the subsequent increase in IICR underlies the depolarization-induced potentiation of mGluR-evoked EPSC. Combination of whole-cell recording and confocal Ca imaging revealed that the depolarization of PC potentiated both mGluR-evoked slow EPSC and Ca transient. To discharge the filled Ca store, uncaging of IP3 was given between depolarization and subsequent synaptic activation of mGluR. This maneuver prevented the depolarization evoked potentiation of mGluR-evoked slow EPSC and Ca transient. On the other hand, simultaneous uncaging of IP3 and synaptic mGluR-stimulation increased the amplitude of the potentiation of slow EPSC. Intracellular heparin, which blocks IP3 receptors, inhibited the depolarization evoked potentiation of slow EPSC. From these results, we suggest that the transient filling of Ca store underlies the activity-dependent short-term potentiation of mGluR-evoked slow EPSC.

S 12-1

MITOCHONDRIAL ION CHANNELS AS KEY ARBITERS OF CELL LIFE AND DEATH

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Mitochondria are involved in oxidative phosphorylation, thermogenesis, reactive oxygen species production, and intracellular Ca^{2+} homeostasis. Mitochondrial dysfunction during metabolic inhibition causes energy depletion and loss of cellular function and integrity, leading to cell death. Mitochondria possess a highly permeable outer membrane and an inner membrane that was originally thought to be relatively impermeable to ions to prevent dissipation of the electrochemical gradient for protons. Ion channels on the mitochondrial inner membrane influence membrane potential ($\Delta\Psi_m$) and cell function in specific ways that can be detrimental to cell survival. Mitochondrial K^+ channels ($mitoK_{Ca}$ and $mitoK_{ATP}$) are important determinants of resistance to ischemic damage and apoptosis, and may be clinically recruitable to prevent cardiac ischemic injury. In contrast, inner membrane anion channel (IMAC) initiates oscillations of mitochondrial redox and membrane potential, and thus might influence the overall function of the cell. In this study we recorded IMAC in cardiac mitochondrial inner membrane using nano patch-clamp techniques, and we tested whether IMAC confers protection against ischemic-reperfusion injury or not. We demonstrated that metabolic inhibition can trigger synchronized oscillations in $\Delta\Psi_m$, ROS production, and mitochondrial redox potential. In the open-channel current-voltage curve, single channel currents with a full unitary conductance of 107 pS were often observed. DIDS, 4'-chlorodiazepham and PK11195 decreased the channel activity and prevented metabolic inhibition-induced $\Delta\Psi_m$ loss. They also protected cardiac myocytes against ischemic-reperfusion injury. We are now trying to confirm the nature and molecular identity of the channel components. Our results suggest that IMAC is present in cardiac mitochondria and plays a role as key arbiters of cell life and death. Our studies may contribute to understanding the close relationship between mitochondrial ion channels, membrane potential, and the overall function of the cell. The ion channels should be present in all cell types containing mitochondria and the implications for normal as well as for pathophysiological cell function are universal.