CURRENT LITERATURE

METABOTROPIC GLUTAMATE RECEPTORS, PLCBETA 1 SIGNALING AND HIPPOCAMPAL EPILEPTIFORM DISCHARGES

Group I Metabotropic Glutamate Receptors Elicit Epileptiform Discharges in the Hippocampus Through PLCbeta1 Signaling

Chuang SC, Bianchi R, Kim D, Shin HS, Wong RK

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Activation of metabotropic glutamate receptors (mGluRs) produces multiple effects in cortical neurons, resulting in the emergence of network activities including epileptiform discharges. The cellular mechanisms underlying such network responses are largely unknown. We examined the properties of group I mGluR-mediated cellular responses in CA3 neurons and attempted to determine their role in the generation of the network activities. Group I mGluR stimulation causes depolarization of hippocampal neurons. This depolarization is primarily mediated by two sets of conductance change: the opening of a voltage-dependent cationic conductance (mediating I(mGluR(V))) and the closing of a voltage-independent (background) K(+) conductance. I(mGluR(V)) was no longer elicited by group I mGluR agonists in the presence of U73122, a phospholipase C (PLC) blocker. Also, the current could not be activated in hippocampal CA3 neurons from PLCbeta1 knock-out mice. In contrast, suppression of PLC signaling did not affect the group I mGluR-mediated suppression of background K(+) conductance. Thus, the suppression of the background K(+) conductance occurred upstream to PLC activation, whereas the generation of I(mGluR(V)) occurred downstream to PLC activation. Group I mGluR agonists normally elicited rhythmic single cell and population burst responses in the CA3 neurons. In the absence of an I(mGluR(V)) response, CA3 neurons in slices prepared from PLCbeta1–/– mutant mice could no longer generate these responses. The results suggest that I(mGluR(V)) expression in CA3 hippocampal neuron is PLCbeta1-dependent and that I(mGluR(V)) plays a necessary role in the generation of rhythmic single cell bursts and synchronized epileptiform discharges in the CA3 region of the hippocampus.

COMMENTARY

Stimulation of group I metabotropic glutamate receptors (mGluRs) elicits synchronized rhythmic firing in the hippocampus. The oscillatory behavior is maintained by cycles of R, S-alpha-Amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)-mediated phasic depolarizations of pyramidal cells mediated by mGluRs. This is a fascinating line of research that has been diligently pursued by this, as well as other, laboratory groups. In this study, the hypothesis tested is that each episode of oscillations is initiated and sustained by a group I mGluR-mediated depolarization, which in turn drives recurrent synapses to bring about the synchronized discharge. Group I mGluRs can modulate a large number of intrinsic conductances in hippocampal neurons. Here the investigators show convincingly that at membrane potentials subthreshold to most intrinsic depolarization-activated persistent conductances (approximately –70 mV), group I mGluR agonists produced two major effects in hippocampal CA3 pyramidal cells: the generation of a voltage-dependent inward (cationic) current and the suppression of a background current that is most likely carried by potassium. Furthermore, the former (but not the latter) effect was found to be dependent on phospholipase C, probably through the IP3 pathway. Cycles of firing induced by the noninactivating (persistent) inward current generated by mGluR activation could provide the basic pattern for the cycles of synchronized epileptiform discharges that are observed after group I mGluR stimulation in the synaptically intact CA3 population.

What is remarkable about this area of research is that it provides insight into how transmitter or modulator effects mediated on single cells are integrated to give rise to alterations in network behaviors. Group I mGluRs may be recruited when

glutamatergic synapses are strongly activated, as has been demonstrated in certain experimental models of seizures. In a broader context, it may be postulated that this can also occur following neuronal damage from various etiologies, which likewise result in excessive glutamate release. Accordingly, mGluR activation may contribute to epileptogenesis following neuronal insults and perhaps to interictal to ictal transitions through the synchronizing actions revealed in this study.

by Larry S. Benardo, M.D., Ph.D.