

A SECOND MESSENGER POTENTIAL LINK TO EPILEPTOGENESIS?

Diacylglycerol Kinase ϵ Regulates Seizure Susceptibility and Long-Term Potentiation Through Arachidonoyl-Inositol Lipid Signaling.

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Arachidonoyldiacylglycerol (20:4-DAG) is a second messenger derived from phosphatidylinositol 4,5-bisphosphate and generated by stimulation of glutamate metabotropic receptors linked to G proteins and activation of phospholipase C. 20:4-DAG signaling is terminated by its phosphorylation to phosphatidic acid, catalyzed by diacylglycerol kinase (DGK). We have cloned the murine DGK ϵ gene that showed, when expressed in COS-7 cells, selectivity for 20:4-DAG. The significance of DGK ϵ in synaptic function was investigated in mice with targeted disruption of the DGKepsilon. DGK $\epsilon^{-/-}$ mice showed a higher resistance to electroconvulsive shock with shorter tonic seizures and faster recovery than DGK $\epsilon^{+/+}$ mice. The phosphatidylinositol 4,5-bisphosphate-signaling pathway in cerebral cortex was greatly affected, leading to lower accumulation of 20:4-DAG and free 20:4. Also, long-term potentiation was attenuated in perforant path-dentate granular cell synapses. We propose that DGK ϵ contributes to modulate neuronal signaling pathways linked to synaptic activity, neuronal plasticity, and epileptogenesis.

COMMENTARY

Arachidonoyldiacylglycerol (ADAG) and other bioactive lipids have been implicated in neuronal plasticity, ischemic brain injury, and epilepsy. ADAG is generated by glutamate through activation of phospholipase A₂ and phospholipase C signaling pathways, and ADAG in turn activates protein kinase C. The absence of the enzyme which phosphorylates ADAG, should lead to increased ADAG, and the authors have postulated some effect on seizure responses (i.e., electroconvulsive shock) and long-term potentiation, when such activity is lost.

The investigators found that ADAG changes were of much lower magnitude in mice lacking the gene coding for diacylglycerol kinase epsilon than they anticipated, presumably due to lower production via the phospholipase A₂ and phospholipase C pathways. Nonetheless, these animals displayed resistance to seizures and impaired long-term potentiation.

This work shows the potential of genetic approaches to explore signaling pathways involved in modulating cellular excitability. The messengers utilized by these paths may contribute to generating excitability or may be involved in the processes leading to the downstream damage that may result. By such exploration critical elements involved in physiologic cell signaling may be discovered, and new classes of therapeutic agents acting as anticonvulsants and neuroprotectants could be developed.

However limitations to this general approach and some specific aspects of the study should be noted. Conclusions of this observational study are based on indirect evidence, and would benefit from a refined mechanistic approach that would more directly probe the pathways involved and corroborate the present findings. Curiously, almost half of the knockouts failed to show the expected changes (in ADAG and free fatty acids) following electroconvulsive shock. No explanation for this unexpected result was given, and these data were not included in the analysis.

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