# This Week in The Journal

## Interneurons from Medial Ganglionic Eminence Drive Hippocampal Giant Depolarizing Potentials

Jason C. Wester and Chris J. McBain

(see pages 2646–2662)

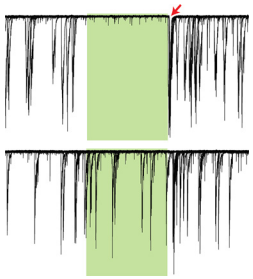
Spontaneous neural activity occurs during periods of peak synaptogenesis in many parts of the developing nervous system. In the rodent hippocampus, for example, spontaneous waves of locally synchronous activity, called giant depolarizing potentials (GDPs), occur during the first 2 postnatal weeks. These waves propagate across the hippocampus and are thought to shape emerging neural circuits.

GDP generation depends largely on GABA-mediated depolarization, and GDPs disappear as GABA becomes hyperpolarizing later in development. Cholecystokinin-expressing neurons are thought to be especially important for GDP generation, because inhibiting GABA release from these neurons suppresses GDPs. But the extent to which other classes of GABAergic interneurons contribute to GDP generation is unclear.

To address this question, Wester and McBain took advantage of the fact that the medial and caudal ganglionic eminences give rise to different classes of hippocampal interneurons. Using optogenetics, they inhibited interneurons derived from either the medial or caudal ganglionic eminence in mouse hippocampal slices and examined the effect on GDP generation. Unexpectedly, inhibiting caudally derived interneurons—which include cholecystokinin-expressing neurons—had a relatively small effect on GDP generation. Although GDP frequency sometimes decreased when neurons from the caudal ganglionic eminence were inhibited, the frequency sometimes increased or was unchanged. In contrast, inhibiting medially derived interneurons—which include parvalbumin- and somatostatin-expressing interneurons—consistently reduced GDP frequency.

While these results are surprising based on previous findings, they make sense given results from paired recordings. Specifically, medially derived interneurons were far more likely than caudally derived neurons to form synapses with pyramidal neurons. In addition, most interneurons from the medial ganglionic eminence appeared to innervate pyramidal cell bodies and have a high release probability, suggesting they provide strong recurrent excitation.

These results suggest that interneurons from the medial ganglionic eminence play a more prominent role in GDP generation than those from the caudal ganglionic eminence, including those that express cholecystokinin. The innervation pattern of the medially derived interneurons suggests that they are primarily fast-spiking, parvalbumin-expressing basket cells. Therefore, these neurons are likely to play an important role in shaping neural circuits in the developing hippocampus.



Optically inhibiting (during time indicated by green shading) hippocampal interneurons born in the medial ganglionic eminence (top) greatly reduced the frequency of GDPs. In contrast, optically inhibiting neurons from the caudal ganglionic eminence (bottom) had little effect. See Wester and McBain for details.

## Upregulating Synaptotagmin 10 Protects Neurons

Anne M.H. Woitecki, Johannes Alexander Müller, Karen M.J. van Loo, Ramona F. Sowade, Albert J. Becker, et al.

(see pages 2561–2570)

Activation of synaptic NMDA receptors leads to calcium influx and downstream activation of various kinases, phosphatases, and transcription factors. These molecules not only drive synaptic plasticity, but also promote neuronal survival. In fact, several "activity-regulated inhibitor of death" (AID) genes are induced by activity-associated calcium influx. The proteins encoded by these genes increase survival of neurons exposed to various insults, including kainic-acid-induced excitotoxicity (Zhang et al., 2009, PLoS Genet 5:e1000604).

How AID proteins protect neurons from insults is largely unknown, but Woitecki, Müller, et al. report that one of the proteins, the transcription factor NPAS4, promotes survival at least in part by increasing expression of synaptotagmin 10 (Syt10), a vesicular calcium sensor. The *Syt10* promoter has an NPAS4 binding sequence and NPAS4 drove expression of a luciferase reporter from that promoter. In addition, overexpressing *Npas4* increased *Syt10* expression in rat hippocampal cultures, whereas knocking down *Npas4* decreased levels of *Syt10* mRNA.

Like *Npas4*, *Syt10* mRNA was upregulated in hippocampal cultures treated with kainic acid. Notably, kainic acid caused more neuronal death in hippocampal cultures from *Syt10*-null mice than in control cultures. Furthermore, *Npas4* overexpression failed to protect neurons lacking Syt10 from excitotoxic death, although it protected wild-type neurons. Nevertheless, survival of Syt10-deficient neurons increased when they were co-cultured with wild-type neurons, suggesting that wild-type neurons secreted a factor that protected neurons lacking Syt-10.

These results strongly suggest that NPAS4 protects neurons from excitotoxic death at least in part by upregulating Syt10, which in turn promotes secretion of neuroprotective factors. Although the identity of these factors is unknown, one candidate is brain-derived neurotrophic factor, which has well known neuroprotective functions and is also regulated by NPAS4 (Lin et al., 2008, Nature 455: 1198). Elucidating the role of Syt10 in neuroprotection may lead to new therapies for reducing excitotoxic neuronal death after stroke and seizures, as well as in neurodegenerative diseases.

*This Week in The Journal is written by Teresa Esch, Ph.D.*