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SUPPLEMENT - NEUROGENESIS

Mechanisms and functional significance of aberrant seizure-induced hippocampal neurogenesis

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SUMMARY

Studies of experimental mesial temporal lobe epilepsy (mTLE) indicate that prolonged seizures in the adult not only damage the hippocampal formation but also dramatically stimulate neurogenesis. Endogenous neural progenitor cells (NPCs) located in the adult rodent dentate gyrus and striatal subventricular zone are stimulated by experimental status epilepticus (SE) to generate increased numbers of dentate granule cells (DGCs) and olfactory interneurons, respectively (Bengzon et al., 1997; Parent et al., 1997, 2002; Scott et al., 1998). In this review, we discuss current knowledge regarding the consequences of seizure activity on NPC proliferation, focusing on the hippocampus, and on the migration and integration of adult-born hippocampal neurons. We also describe the effects of seizure-induced neurogenesis on hippocampal network function and the potential relevance of aberrant neurogenesis to human mTLE.

KEY WORDS: Adult, Dentate gyrus, Epileptic network, Hilar ectopic granule cells, Neural progenitor cells, Mesial temporal lobe epilepsy, Status epilepticus.

PROLONGED SEIZURES STIMULATE NPC PROLIFERATION

After a latent period of several days, prolonged seizure activity leads to a dramatic increase in mitotic activity in the hippocampal dentate gyrus (Parent et al., 1997; Gray & Sundstrom, 1998; Jessberger et al., 2005) and striatal subventricular zone (Parent et al., 2002). In the dentate, the early proliferative response appears to be mediated by radial glia-like neural progenitor cells (NPCs) (Huttmann et al., 2003) followed by an increased accumulation of neuroblasts that express doublecortin, polysialylated neural cell adhesion molecule, and similar markers of immature neurons (Parent et al., 1997, 1999; Huttmann et al., 2003; Jessberger et al., 2005). Cell proliferation returns to baseline levels within 3–4 weeks after status epilepticus (SE) (Parent et al., 1997). The mechanisms responsible for seizures increasing neurogenesis are unclear, but in the case of dentate granule cells (DGCs) neurogenesis, some work suggests certain neuropeptides may play a role (Mazarati et al., 2004; Howell et al., 2007), and other data point to the involvement of epigenetic modification altering gene expression in NPCs (Jessberger et al., 2007a).

Recent evidence suggests that at later stages following SE adult neurogenesis decreases markedly (Hattiangady et al., 2004). Potential factors leading to decreased neurogenesis in chronically epileptic animals include exhaustion of the NPC pool, loss of necessary growth/trophic factors, or altered cellular interactions in the neurogenic niche (see review by Hattiangady & Shetty, 2008). Although the senescence-related decline in DGC neurogenesis is reversible in the intact aged rodent (Cameron & McKay, 1999), the potential for reversibility in chronically epileptic animals is unknown.

MATURATION, SURVIVAL, AND INTEGRATION OF DGCS GENERATED AFTER SE

The accelerated NPC proliferation after SE leads to a marked increase in neurogenesis. As in the intact adult rodent dentate gyrus, approximately 75–90% of newly generated cells express markers characteristic of DGCs 4 weeks after mitotic labeling with BrdU or retroviral

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reporters (Parent et al., 1997; Jessberger et al., 2005, 2007b). The survival of DGCs generated after SE, at least in certain experimental paradigms, decreases as seizure severity rises (Mohapel et al., 2004), an effect that may relate to the degree of persistent inflammation (Ekdahl et al., 2003).

What is the fate of the newborn granule cells that do survive after prolonged seizure activity? Interestingly, SE appears to accelerate the functional maturation and integration of adult-born DGCs that appear to otherwise develop normally in the DGC layer (Overstreet-Wadiche et al., 2006). The consequences of this accelerated differentiation on hippocampal network function are unknown (see Zhao & Overstreet-Wadiche, 2008). Sprouting of mossy fibers following seizures does not depend on newborn granule cells (Parent et al., 1999), and DGCs located in the cell layer that were generated after SE do not send axonal sprouts to the supragranular molecular layer (Jessberger et al., 2007b). However, recent work suggests that adult-generated neurons born at least 4 weeks prior to seizure induction do contribute to mossy fiber sprouting (Jessberger et al., 2007b), suggesting an age-dependent influence of SE on axonal remodeling/aberrant outgrowth. Although DGCs born after SE probably do not contribute to mossy fiber sprouting in the dentate molecular layer, they do often show severe morphological abnormalities that implicate them in altering dentate connectivity during epileptogenesis. The two major abnormalities of DGC neurogenesis in experimental mesial temporal lobe epilepsy (mTLE) include the formation of hilar basal dendrites and the ectopic migration of newborn granule cells into the polymorphic cell layer. Hilar basal dendrite formation is discussed in detail in the review by Shapiro et al. (this issue), and we will focus here on the ectopic migration of adult-born DGCs.

Growing evidence suggests that some adult-born granule cells migrate normally and integrate into the granule cell layer, while others fail to do so and instead migrate aberrantly into the hilus (Figs 1A–D and 2A) (Parent et al., 1997, 2006a; Scharfman et al., 2000). Importantly,

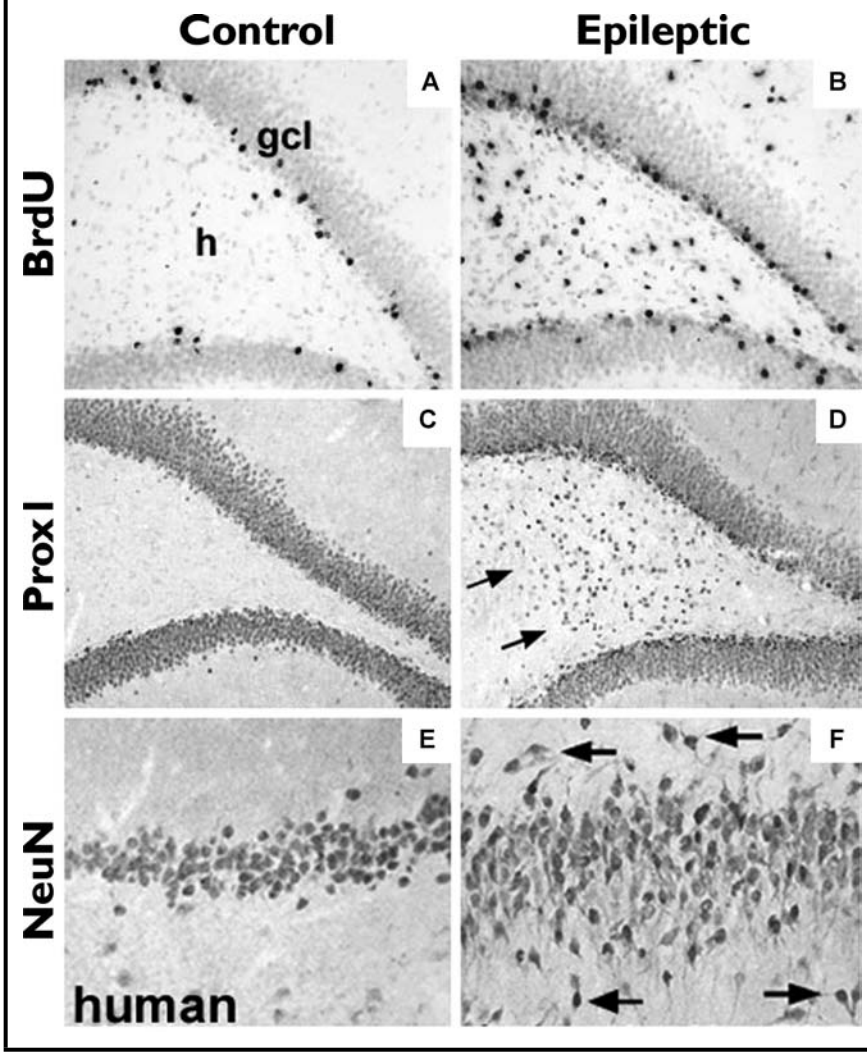

Figure 1.
Hilar ectopic granule cells (HEGCs) in experimental and human mTLE. Bromodeoxyuridine (BrdU; **A, B**) and Prox1 (**B, C**) immunolabeled sections through the adult rat dentate gyrus show marked increases in recently born ($BrdU^+$) cells that express the DGC-specific marker Prox1 in the hilus (h) of animals 35 days after pilocarpine-induced status epilepticus (**B, D**) compared to controls (**A, C**). BrdU was given 7 days after seizure induction. (**E, F**) Surgically resected hippocampal tissue from a patient with intractable mTLE immunostained for NeuN also shows hilar and molecular layer (ml) ectopic granule-like neurons (arrows in **F**) not seen in an autopsy control (**E**). gcl, granule cell layer. Scale bar: 50 μm for **A, B**; 150 μm for **C, D**; 30 μm for **E, F**. Modified with permission from Parent et al. (2006a).
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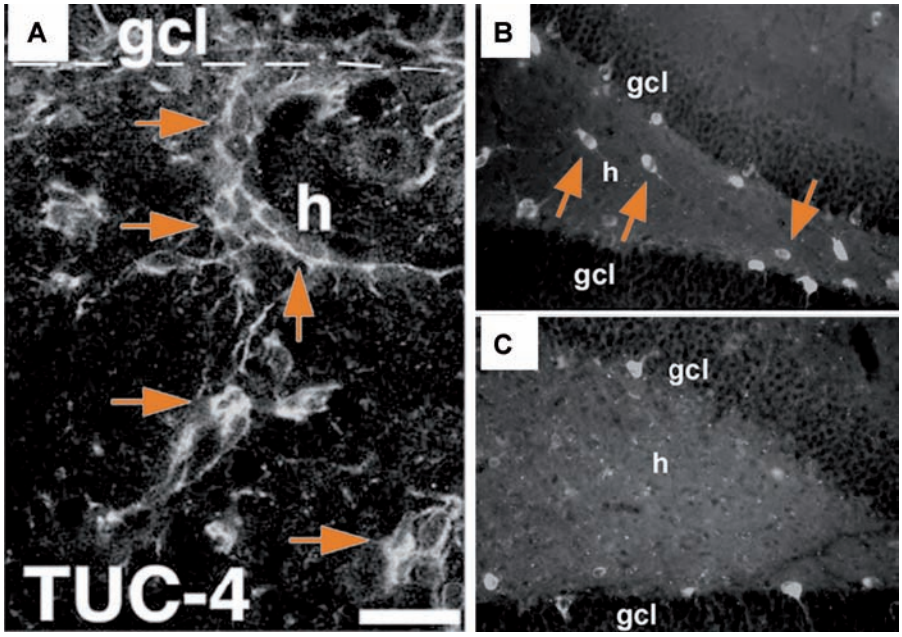

Figure 2.
Chain migration of DGC progenitors and loss of reelin in the epileptic dentate gyrus. Two weeks after pilocarpine-induced status epilepticus (SE), immunostaining for the neuroblast-specific marker TUC-4 shows immunoreactive DGC progenitors migrating aberrantly from the granule cell layer (gcl) into the hilus (h) in chains (**A**, arrows). These chains are not seen in controls (not shown). At the same time point after SE (14 day postseizure; **C**), CR-50 antibody labeling of reelin shows decreased hilar reelin expression compared to a control (arrows in **B**). Scale bar, 40 μm in **A**; 100 μm in **B, C**. Modified with permission from Parent et al. (2006a) and Gong et al. (2007).

in both cases the intrinsic neuronal properties of the neurons appear to be unaltered despite their different locations (Scharfman et al., 2000, 2003; Jakubs et al., 2006). The hilar ectopic granule cells (HEGCs) also receive synaptic input from the perforant path similar to DGCs located normally in the cell layer (Scharfman et al., 2002, 2003); however, other synaptic inputs onto these newly generated neurons are significantly different than the synaptic connectivity normally observed within the granule cell body layer. In addition to aberrant structural integration (see review by Shapiro et al, 2008), recent work indicates that HEGCs also functionally integrate into existing circuitry within the dentate gyrus. It is of course speculated that the functional integration of these neurons is critical to any potential involvement they may have in epileptogenesis, as it seems unlikely that isolated neurons (by themselves) could drive the spontaneous synchronized activity that is the hallmark of mTLE. As described in detail below, it is the aberrant integration of HEGCs that implicates them as key contributors to abnormal network function in the epileptic hippocampal formation.

Why some seizure-generated granule cells migrate to ectopic locations is not entirely clear. Recent work indicates that prolonged seizures stimulate abnormal chain migration of granule cell progenitors into the hilus (Fig. 2A) (Parent et al., 2006b), suggesting that the migratory behavior of the progenitor cells is altered in the injury environment. In terms of potential molecular mechanisms underlying this effect, migration guidance cues that influence neuronal migration during development are strong candidates. Reelin is one such factor that is expressed in the adult rodent and human hippocampal dentate gyrus and has been implicated in DGC layer dispersion in human mTLE (Haas et al., 2002). Reelin is expressed in the adult dentate gyrus by specific subsets of hilar interneurons known to be vulnerable to SE-induced injury; as one might predict, therefore, dentate gyrus reelin expression decreases markedly after pilocarpine-induced SE in the adult rat (Fig. 2B, C) (Gong et al., 2007). Moreover, adult rat DGC progenitors express the molecular machinery for activation by reelin and altering reelin signaling in vitro leads to changes in DGC progenitor migration similar to those seen after SE (Gong et al., 2007). Together, these findings suggest that SE-induced loss of reelin-expressing, GABAergic hilar interneurons plays a part in the abnormal integration of adult-born DGCs during epileptogenesis.

Other potential mechanisms exist for inducing HEGCs. One is loss of GABA itself. GABA stimulates DGC differentiation (see review by Zhao & Overstreet-Wadiche, 2008) and also decreases neuroblast migration in the other adult neurogenic region, the subventricular zone (SVZ)-olfactory bulb pathway (Liu et al., 2005). Brain-derived neurotrophic factor (BDNF) is another molecular candidate for stimulating HEGC formation after SE. BDNF expression is increased by seizures (Isackson et al., 1991), and BDNF infusions into the intact adult rat brain stimulate DGC neurogenesis and lead to the appearance of ectopic DGCs (Scharfman et al., 2005). None of these potential mechanisms are mutually exclusive and thus they may all contribute to the aberrant integration of adult-born neurons after seizure-induced injury.

Function of Adult-born DGCs in the Cell Layer

Whereas abnormal features such as basal dendrites and ectopic migration led to the hypothesis that seizure-induced neurogenesis contributes to the epileptic disease process (Parent & Lowenstein, 2002), recent evidence sheds new light on a potential compensatory role seizure-generated neurons might play. In contrast to SE induced by kainic acid or pilocarpine, many adult-born DGCs appear to develop normally after electrically induced SE. Jakubs et al. (2006) used intrahippocampal injections of a retroviral vector carrying the gene for green fluorescent protein (GFP) to label newborn DGCs that were generated after voluntary running or self-sustained electrical SE. This method allowed them to visualize GFP-labeled, newborn DGCs and perform in vitro whole-cell patch clamp recordings in hippocampal slices. They found that the excitatory synaptic drive to newborn DGCs was reduced in SE animals as compared with animals that voluntarily ran, as measured by a reduction in the mean frequency of recorded spontaneous excitatory postsynaptic currents. In addition, DGCs newly generated after SE appeared to receive an enhanced inhibitory input: the observed frequency of spontaneous inhibitory postsynaptic currents was significantly higher in the newborn DGCs. HEGCs were not commented upon in this work. In addition, although Jakubs et al. (2006) observed a small proportion of DGCs with hilar basal dendrites, the overwhelming majority of cells recorded in this study appeared to be morphologically normal.

Thus, newborn DGCs that integrate into the granule cell layer under pathological conditions (i.e., SE) may form atypical synaptic connections that minimize excitation and maximize inhibition. Although it is presently unclear how this synaptic weighting is achieved, it offers a target that may be exploited therapeutically. The finding of a potential compensatory role for seizure-induced neurogenesis also raises the question of whether the net influence of adult-born DGCs is pathophysiological or reparative.

Functional Significance of HEGCs

HEGCs show many similarities to the newborn granule cells described above that migrate into the cell body layer of the dentate gyrus. For example, DGCs that are found in abundance within the dentate hilus after SE appear to exhibit intrinsic neuronal properties (resting membrane potential, input resistances, etc.) that are quite similar to preexisting, mature granule cells (Scharfman et al., 2000, 2003), and these neurons functionally integrate into the local circuitry of the dentate gyrus. However, several lines of evidence indicate that HEGCs integrate in an aberrant fashion. Using in vitro hippocampal slice preparations, Scharfman et al. have demonstrated that seizure-generated HEGCs, like granule cells found in the cell layer, exhibit excitatory postsynaptic potential (EPSP)s in response to extracellular stimulation of the outer molecular of the dentate gyrus (Scharfman et al., 2003). Despite this similar innervation, the latency to EPSP onset was always greater for HEGCs, with the greatest latencies observed in HEGCs that lacked dendritic representation in the molecular layer. This finding suggests that these neurons likely receive perforant path excitation through polysynaptic innervation. The exact nature of the polysynaptic input onto the HEGCs is presently unknown (see also Zhang & Overstreet-Wadiche, 2008). Identifying their presynaptic partners would be an important step in definitively determining if HEGCs play a role in seizure generation.

In addition to the polysynaptic excitatory input from the perforant path, HEGCs receive strong excitatory input from area CA3. As recently reviewed (Scharfman, 2007), anatomical evidence suggests that the pyramidal neurons in CA3—particularly area CA3c—send axon collaterals into the hilar region of the dentate. These projections are particularly interesting in terms of seizure generation in that hippocampal slices prepared from pilocarpine-treated rats exhibit spontaneous bursts of activity in CA3 which in turn drives synchronized activity in the HEGCs (Scharfman et al., 2000). These observations, together with the fact that pyramidal neurons in CA3 make recurrent synapses within CA3 and seizure-induced sprouting of recurrent mossy fibers occurs within the dentate (Buckmaster & Dudek, 1997), have led to the hypothesis that HEGCs may contribute to seizure activity by participating in a reverberatory loop. Activity within this loop might eventually exit the hippocampus and propagate seizure activity to the neocortex or other brain regions (Scharfman, 2004).

Do HEGCs Contribute to Epileptogenesis or other Epilepsy-Associated Abnormalities?

Seizure-associated neurogenesis may play a role in two features of TLE that are poorly understood from a mechanistic point of view. First, altered neurogenesis might contribute to epileptogenic network changes. DGCs born after SE have two features that might indicate an epileptogenic role. Those with hilar basal dendrites receive excitatory input from mossy fibers and could thus form a recurrent excitatory circuit (Thomson et al., 1998). Similarly, HEGCs appear to be abnormally synchronized with spontaneous, rhythmic bursts of CA3 pyramidal neurons (Scharfman et al., 2000). Consistent with these data is the finding that ablating neurogenesis after SE attenuates subsequent epileptogenesis, with a reduction of the frequency and severity of spontaneous recurrent seizures (Jung et al., 2004, 2006). Thus, abnormal networks that develop from altered neurogenesis after brain injury also may support seizure propagation or adversely influence seizure termination mechanisms.

Network abnormalities due to aberrant seizure-induced neurogenesis may also contribute to the learning and memory disturbances associated with mTLE (Helmstaedter, 2002, 2003; Elger et al., 2004). Growing evidence implicates adult neurogenesis in certain forms of hippocampus-dependent learning and memory under normal conditions (Shors et al., 2001, 2002; Santarelli et al., 2003; Snyder et al., 2005; Meshi et al., 2006; Saxe et al., 2006; Winocur et al., 2006), and altered neurogenesis in the epileptic hippocampus may interfere with this functional plasticity. For example, the "normal" function of adult-generated neurons that might depend on specific plasticity of immature neurons (Schmidt-Hieber et al., 2004) might be disrupted due to an altered integration pattern (Overstreet-Wadiche et al., 2006; Jessberger et al., 2007b) or due to decreased levels of adult neurogenesis at late stages after an epileptogenic insult (Hattiangady et al., 2004). Supporting the former hypothesis is the finding that inhibition of seizure-induced neurogenesis with the histone deacetylase (HDAC)-inhibitor and antiepileptic drug valproic acid protects kainic acid-treated animals from impairment in a hippocampus-dependent object recognition task (Jessberger et al., 2007b).

Relevance of HEGCs to Human mTLE

While there is fairly good consensus regarding the existence of seizure-induced HEGCs in animal models of epilepsy, the picture with regard to human mTLE is less clear, with some investigations reporting the existence of HEGCs and others failing to make similar findings (for review see Siebzehnrubl & Blumcke, this issue). This apparent contradiction may arise from the fact that in many cases the human tissue that is available comes from patients who have experienced years of seizure activity, which results in a wide range of neuropathology of varying severity within the hippocampus. Therefore, it seems likely that emerging data from experiments that utilize tissue from younger patients will help shed light on this topic. These controversies notwithstanding, no studies have been published to our knowledge that examine whether HEGCs in the epileptic human dentate gyrus functionally integrate into local circuits. We therefore have begun making intracellular recordings in hippocampal slices prepared from human tissue resected during surgery for intractable mTLE. Although this work is at an early stage, we have indeed been able to make recordings from neurons located in the hilar region of hippocampal slices recovered from mTLE patients. Fig. 3 presents representative traces made from a granule cell located within the granule cell layer as well as a putative HEGC located within the hilus. Our ongoing experiments seek to examine the intrinsic neuronal properties of these neurons as well as their synaptic connectivity.

Conclusions

Within the last decade our understanding of the basic biology of neural stem cells and neurogenesis in the adult brain has dramatically expanded. At present there is good agreement from multiple lines of experimental evidence that the enhanced neurogenesis and aberrant migration of adult-born granule cells are key features of aberrant plasticity in animal models of mTLE. Molecular, structural, and electrophysiological evidence all suggest that ectopic granule cells found within the hilar region of the dentate gyrus form aberrant local circuits which likely drive seizure activity within the hippocampus and may lead to seizure activity that escapes to the neocortex.

In spite of the rapid increase in our knowledge regarding seizure induced neurogenesis and the basic neurobiology of HEGCs, many questions have yet to be answered. What are the relevant changes in molecular signaling that lead to the aberrant localization of these neurons? Once integrated into the local circuitry what is the exact neuronal identity and topology of the presynaptic partners that drive the activity of the HEGCs? To what extent do these HEGCs play a role in either the establishment or maintenance of human mTLE? And finally, does aberrant integration or chronic loss of adult-born DGCs contribute to the memory dysfunction commonly seen in mTLE. These questions seem to be of paramount importance in that their answers might provide us with targets that could be leveraged for therapeutic intervention.

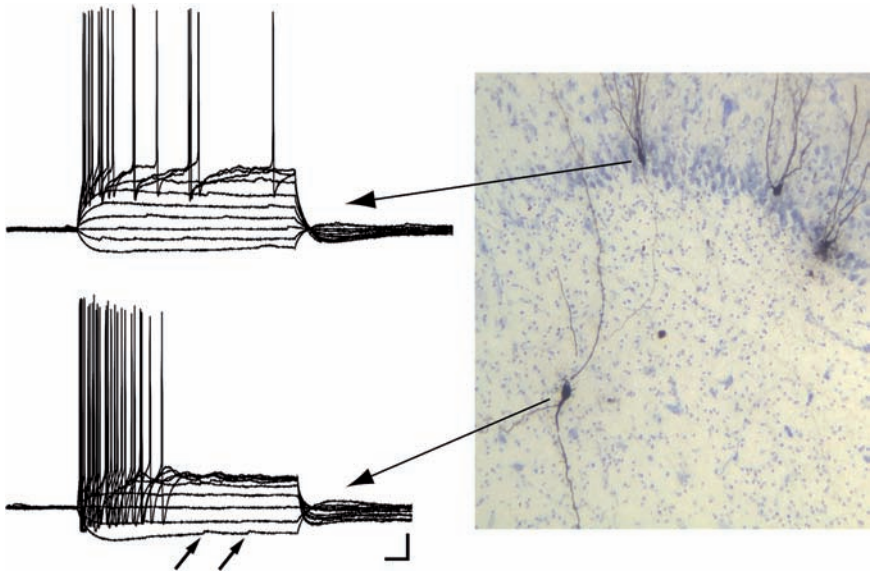

Figure 3.
Representative recordings from human mTLE tissue. Right panel presents a photomicrograph of the dentate gyrus region of an in vitro hippocampal slice preparation prepared from a mTLE patient. Biocytin filled patch pipettes were used to make whole-cell patch recordings from three granule cells within the granule cell layer and one putative granule cell in the hilar region. Representative traces from recordings made from a single granule cell in the granule cell layer (top trace) and within the hilus (bottom trace) in response to a series of current steps. In both cases recordings were made at resting membrane potential. Note the presence of spontaneous EPSPs (small arrows) in the recording made from the putative ectopic granule cell (bottom trace). Scale bar 10 mV/50 ms.

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Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The authors have declared no conflicts of interest.

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