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Structural changes for adult-born dentate granule cells after status epilepticus

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SUMMARY

Status epilepticus (SE) not only results in an increased number of newly generated neurons in the dentate gyrus but also leads to structural alterations of many of these newborn granule cells. One of the structural changes involving newly generated dentate granule cells is the formation of hilar basal dendrites that persist on mature granule cells and integrate into synaptic circuitry. SE also causes other newborn granule cells to migrate ectopically into the hilus, and these cells also integrate into synaptic circuitry. This article will describe these structural alterations of granule cells found in the dentate gyrus after SE and will also discuss the time course of these events and possible underlying causes.

KEY WORDS: Temporal lobe epilepsy, Dentate gyrus, Hippocampus, Hilar basal dendrites, Ectopic granule cells.

The maturation and integration of newborn granule cells can be divided into a series of distinct developmental stages (e.g., Kempermann et al., 2004). Based on the work of several studies using BrdU-labeling, endogenous markers, transgenic animals, or retroviral labeling, we now have a sound picture of the morphological and functional maturation of newborn neurons (Overstreet et al., 2004; Overstreet Wadiche et al., 2005; Shapiro et al., 2007). In normal adult rodents (rats and mice), newborn granule cells are initially found in the subgranular zone with no dendritic processes. At this stage, a fraction of newborn cells already express the microtubule-associated protein, doublecortin (DCX), which labels immature neuronal cells for approximately the first 3 weeks after birth (Brandt et al., 2003; Couillard-Despres et al., 2005; Shapiro et al., 2005a; Plumpe et al., 2006). At early stages, in the subgranular zone, DCX-expressing cells appear to be individually cradled by the nonradial processes of astrocytic cells that were identified as radial glial cells (Shapiro et al., 2005a). This one-to-one relationship is altered in the dentate gyrus of epileptic animals (Shapiro & Ribak, 2006; Shapiro et al., 2007). At later time points after their birth, DCX-labeled newborn neurons are located at the hilar border of the granule cell layer and extend an apical dendritic process along the radial process of a radial glial cell (Shapiro et al., 2005a). This apical dendrite later extends into the molecular layer without any apparent glial scaffold for guidance (Shapiro et al., 2007). It should be noted that the exact relationship between an astrocytic scaffold and immature neurons appears to depend on the maturational stage of the newly generated neurons (Shapiro et al., 2005a; Plumpe et al., 2006). Nevertheless, the current data on newborn granule cells support the idea that the radial glial-like astrocytes that cradle the newly generated granule cells immediately after their birth might also provide guidance for the normal apical dendritic growth, migration, and differentiation of these newborn neurons. Approximately16 days after the birth of newborn granule cells, dendritic spines are observed on the apical dendrites in the molecular layer (Zhao et al., 2006).

In addition to an apical dendrite, it seems that many newly generated granule cells in the adult dentate gyrus have a transient basal dendrite, at least in rats (Rao & Shetty, 2004; Ribak et al., 2004). However, in epileptic rodents, the basal dendrite is a persistent feature and it appears to be incorporated into the existing hippocampal circuitry (Jessberger et al., 2007a), with stubby spines and immature synapses appearing as early as 4–5 days after seizures (Shapiro et al., 2007). Another interesting

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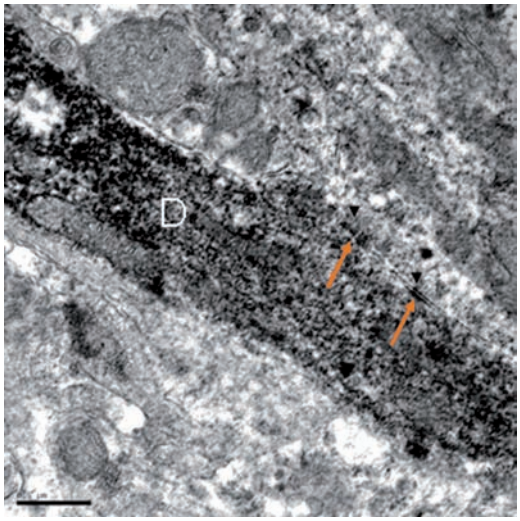

Figure 1.
Electron micrograph of a DCX-labeled basal dendrite (D) at 5 days after pilocarpine-induced seizures. Two synapses (arrows) are formed with this dendrite by a presynaptic terminal that contains synaptic vesicles (arrowheads). Scale bar = 0.5 μm.
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aspect of newly generated neurons in the dentate gyrus from epileptic animals is that they migrate away from the granule cell layer in large numbers to enter the hilus. Thus, these newly generated granule cells that are located in an ectopic location are referred to as hilar ectopic granule cells. The remaining parts of this chapter will focus on these seizure-induced changes to newly generated granule cells and their processes.

Basal Dendrites on Newly Generated Granule Cells

As mentioned above, newly generated granule cells in the normal adult hippocampus often have a transient basal dendrite. The appearance of this basal dendrite during the migration from the newly generated neuron's origin in the subgranular zone to its destination in the granule cell layer suggests that the basal dendrite is involved in migration. The fact that no synapses have been observed on the basal dendrite (Shapiro & Ribak, 2006) is consistent with the notion that it is a transient structure (Seress & Pokorny, 1981; Seress & Ribak, 1990; Ribak et al., 2004). Following seizures, the basal dendrites from the newly generated neurons persist and are postsynaptic to axon terminals (Shapiro & Ribak, 2006). Both immature and developing synapses (Fig. 1) were observed as early as 4 days after seizures on DCX-labeled basal dendrites (Shapiro et al., 2007). These hilar basal dendrites (Figs 2 and 3A) have been shown to grow along an ectopic glial scaffold (Fig. 2; Shapiro et al., 2005b) supporting the notion that glial hypertrophy might play a role in epileptogenesis (Vessal et al., 2005; Binder & Steinhäuser, 2006; Kang et al., 2006). Following status epilepticus (SE), newly generated granule cells display a significantly greater percentage of hilar basal dendrites as compared to mature granule cells (Walter et al., 2007). The fact that these basal dendrites

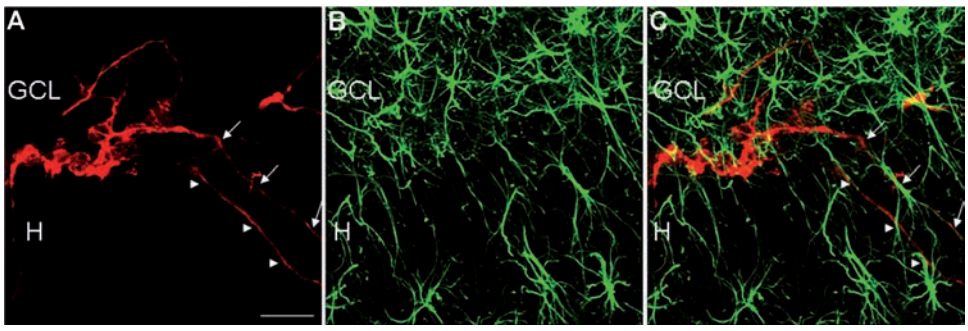

Figure 2.
Confocal images of DCX (red) and GFAP (green) immunolabeling at 5 days after pilocarpine-induced seizures. In (**A**), a cluster of DCX-labeled cells in the granule cell layer (GCL) is shown, and one of these cells has a hilar basal dendrite (arrows) extending into the hilus (H). Also note that there is another hilar basal dendrite (arrowheads) but it could not be traced back to its cell body of origin. In (**B**), GFAP-labeled astrocytes show hypertrophy of their processes. In (**C**), the images were merged to show the relationship between the hilar basal dendrites and the hypertrophied astrocytic processes. Note that the DCX-labeled basal dendrite (arrows) that was continuous with its cells body aligns along a GFAP-labeled cell and its processes. The other hilar basal dendrite (arrowheads) also apposes glial processes. Scale bar in **A** = 20 μm and also applies to **B** and **C**.
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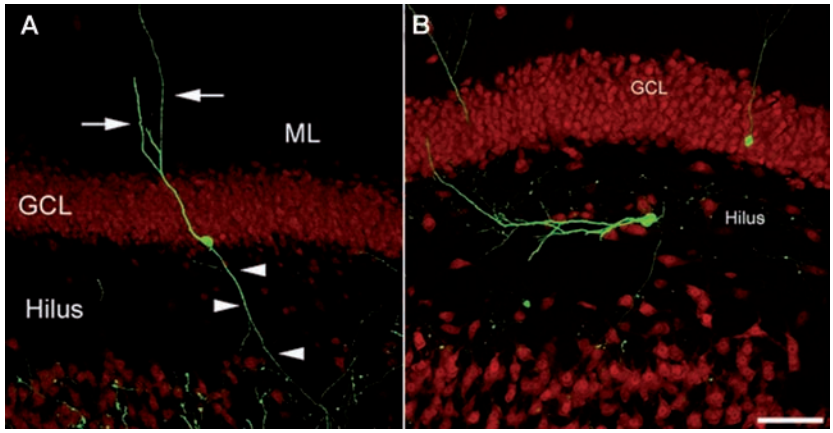

Figure 3.
Structural changes of granule cells born after SE. Newborn cells were labeled with a retrovirus expressing GFP 1 week after KA-induced SE and killed 4 weeks later. (**A**) Shows a newborn neuron (GFP, green) within the granule cell layer (NeuN in red) extending an apical dendrite in the molecular layer (arrows) and a basal dendrite into the hilus (arrowheads). In addition to the aberrant extension of hilar basal dendrites, seizure-generated granule cells often ectopically migrate into the hilus as depicted in (**B**). GCL, granule cell layer; ML, molecular layer. Scale bar in **B** = 100 μm for **A** and **B**.

persist for long durations after seizures (Ribak et al., 2000; Walter et al., 2007) and develop mature synapses on dendritic spines (Jessberger et al., 2007a) is consistent with the hypothesis that newly born granule cells are involved in a recurrent excitatory circuit. Electrophysiological studies of this aberrant circuitry have shown that it results in a hyperexcitable state in the hippocampus (Austin & Buckmaster, 2004; Patel et al., 2004). Thus, seizure-induced basal dendrites are involved in the incorporation of newly generated neurons into an aberrant hyperexcitable circuitry that may facilitate seizures.

Ectopic Granule Cells

The abnormal extension of basal dendrites towards the hilus is not the only altered feature for newly generated granule cells from adult animals that had experienced SE. The vast majority of granule cells are located in the dentate gyrus granule cell layer even though a very small fraction of neurons with typical features of granule cells can also be found in the hilus in healthy rodents (approximately 0.1% out of the whole granule cell population, McCloskey et al., 2005). Interestingly, the very first reports on seizure-induced neurogenesis noticed a substantial fraction of BrdU-labeled cells in the hilus following SE (Parent et al., 1997). Later studies used immunohistochemical, ultrastructural, and electrophysiological approaches to show that seizure-induced ectopic cells in the hilus (Fig. 3B) had distinct characteristics that identified them as dentate granule cells (Scharfman et al., 2000; Dashtipour et al., 2001; Scharfman et al., 2002, 2003). Why do granule cells ectopically migrate into the hilus and what are the functional consequences of hilar granule cells in the context of epilepsy?

Several different rodent models of SE display this ectopic migration of granule cells (Jung et al., 2004; Mohapel et al., 2004; Jessberger et al., 2007a). It appears that there is a positive correlation of ectopic migration with excitotoxic cell death. For example, a single electroconvulsive shock upregulates the number of newborn neurons in the granule cell layer but does not induce ectopic granule cell migration (Scott et al., 2000). Thus, surplus activity does not seem to be a sufficient stimulus, as potentially long-lasting structural or molecular alterations are required to lead to ectopic granule cell migration. Cajal-Retzius cells that produce the secreted glycoprotein reelin, which is a critical neuronal guidance molecule during development (Rice & Curran, 2001), are especially vulnerable to excitotoxicity which results in decreased levels of reelin following SE (Haas et al., 2002). Indeed, a recent study suggested that reelin likely contributes to seizure-associated ectopic migration (Gong et al., 2007; Parent & Murphy, 2008), a hypothesis that is also supported by the finding that a mutant in the reelin gene called *reeler* has increased numbers of ectopic granule cells (Stanfield et al., 1979). However, other pathways (e.g., cdk5/p35 signaling; Wenzel et al., 2001; Patel et al., 2004) and growth factors (e.g., VEGF and BDNF signaling; Jin et al., 2002) might also be involved.

Electrophysiological studies showed that the basic membrane properties of hilar ectopic granule cells are

remarkably similar to granule neurons within the granule cell layer (Scharfman et al., 2000). However, ectopic granule cells showed epileptic burst discharges synchronized with CA3 pyramidal neurons, with a time signature that suggested monosynaptic connections between CA3 pyramidal cells and ectopic granule cells. Thus, ectopic granule cells might be a critical component in establishing a recurrent excitatory circuitry eventually leading to heightened excitability in the epileptic hippocampus.

Synaptic Integration of Seizure-Generated Granule Cells

Following a distinct maturation process, newborn granule cells become synaptically integrated into the adult hippocampus (van Praag et al., 2002; Schmidt-Hieber et al., 2004). Under normal conditions the first input onto newborn neurons appears to be a depolarizing tonic GABAergic input. In contrast, excitatory, glutamatergic synaptic connections are formed approximately 14 days after the birth of neurons which is just prior to the time when dendritic spines first appear (Esposito et al., 2005; Ge et al., 2006; Zhao et al., 2006). New neurons that are born shortly before or after SE also form dendritic spines and form synapses on preexisting structures (Scharfman et al., 2000; Jakubs et al., 2006; Jessberger et al., 2007a). Experiments using the pro-opiomelanocortin (POMC) reporter mouse indicated that seizure activity accelerated the maturation process of newborn granule cells after SE (Overstreet-Wadiche et al., 2006; Zhao & Overstreet-Wadiche, 2008). Importantly, the effects on dendritic and synaptic architecture were persistent because 3-month-old seizure-generated granule cells had relatively more mature mushroom spines compared to cells born under control conditions (Jessberger et al., 2007a).

There is now ample evidence that granule cells born after SE synaptically integrate into the dentate circuitry. As outlined above, ectopic granule cells in the hilar region become synchronized with CA3 pyramidal cells and might thus contribute to seizure-associated recurrent excitation (Scharfman et al., 2000, 2002). The functional connectivity following synaptic integration of seizure-generated granule cells that are located within the boundaries of the granule cell layer is less clear. A recent study showed that 4-week-old granule cells in the epileptic dentate gyrus did not substantially differ from cells born in running animals regarding their intrinsic cell properties, but showed a connectivity that suggested overall less excitability (Jakubs et al., 2006). However, it remains unclear if these differences remain stable over time or might just differ between running and SE animals but not between control and SE animals. Furthermore, the model of epilepsy used might be an important factor influencing the network connectivity of granule cells born after SE.

Conclusion

SE induces robust structural and functional changes throughout the adult brain. The recent finding that seizure activity also dramatically increases the number of newborn neurons in the hippocampal dentate gyrus adds an additional level of seizure-associated neuronal plasticity. As outlined in this review, not only is the number of new neurons altered, but the morphology and location of seizure-generated granule cells are drastically changed as compared to control conditions. What are the reasons and what might be the functional consequences of seizure-induced neurogenesis?

The knowledge regarding the molecular and synaptic maturation processes of newborn neurons in the adult hippocampus under normal conditions is constantly growing (Piatti et al., 2006). The developmental steps and their alteration in the context of seizure-induced neurogenesis are less clear but SE clearly affects the speed of maturation (Overstreet-Wadiche et al., 2006), dendritic morphology (Shapiro et al., 2005b; Jessberger et al., 2007a; Walter et al., 2007), and cell body location within the dentate gyrus (Parent et al., 1997; Scharfman et al., 2000). SE also affects the structural integrity of the hippocampus by causing neuronal death. In addition, there is evidence that SE changes the molecular composition of dividing cells and/or newborn neurons themselves that might result in altered cellular behavior. The relative contributions of intrinsic cell alterations of precursor cells or immature neurons versus changes in external cues generated in the dentate neurogenic niche are only poorly understood. First steps toward understanding the molecular mechanisms of SE-induced, aberrant neurogenesis are being made (e.g., Gong et al., 2007), but further cell-type specific genetic tools only affecting newborn cells such as cellular manipulation using retroviral vectors and/or transplantation experiments are required in the future.

What remains is one key question: Is seizure-induced neurogenesis an attempt of the injured brain to repair itself or are aberrant newborn neurons contributing to epileptogenesis? The structural alterations of newborn neurons that might represent a circuit for recurrent excitation, which is typical for the epileptic hippocampus, might favor a "negative" role of seizure-induced neurogenesis. In the same line, several studies showed behavioral and electrophysiological normalization when seizure-induced neurogenesis was blocked (Jung et al., 2004; Jessberger et al., 2007b; but see also Raedt et al., 2007). However, there are also data that suggest seizure-induced neurogenesis as a compensatory attempt of the adult brain. In fact, Jakubs et al. found that newborn granule cells in the epileptic dentate gyrus

appear to be less excitable than control cells (Jakubs et al., 2006). Given this broad spectrum of findings that is even more complicated by the use of different seizure models, the answer to the question whether SE-induced neurogenesis is "good" or "bad" remains far from being answered. Rather, it seems plausible that some aspects of seizure-induced neurogenesis might be beneficial for the epileptic brain while other aspects and consequences might be harmful. In any case adult neurogenesis associated with SE leads to dramatic alterations in dentate connectivity simply by the fact that (1) many more cells are born compared to control conditions, (2) a substantial number of newborn granule cells display abnormal features such as persistent basal dendrites forming aberrant synapses, and (3) a dramatic increase in hilar ectopic granule cells occurs. Nevertheless, the molecular mechanisms and functional consequences of seizure-induced neurogenesis remain largely unknown but future studies will try to gain further insights into this exciting new aspect of seizure-associated plasticity in the adult brain.

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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 of this paper declare no conflicts of interest.

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