UC Irvine

UC Irvine Previously Published Works

Title

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

Permalink

<https://escholarship.org/uc/item/0g12r5qx>

Journal

Epilepsia, 49 Suppl 5(SUPPL 5)

ISSN

0013-9580

Authors

Shapiro, Lee A
Ribak, Charles E
Jessberger, Sebastian

Publication Date

2008-06-01

DOI

10.1111/j.1528-1167.2008.01633.x

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

SUPPLEMENT - NEUROGENESIS

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

*Lee A. Shapiro, *Charles E. Ribak, and †‡Sebastian Jessberger

*Department of Anatomy and Neurobiology, University of California, Irvine, California, U.S.A; and †Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, California, U.S.A

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 ec-

topically 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. Approximately 16 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

‡Current address: Institute of Cell Biology, Swiss Federal Institute of Technology (ETH) Zurich, 8093 Zurich, Switzerland.

Address correspondence to Dr. Charles E. Ribak, Department of Anatomy and Neurobiology, School of Medicine, University of California at Irvine, Irvine, CA 92697-1275, U.S.A. E-mail: ribak@uci.edu

Blackwell Publishing, Inc.

© 2008 International League Against Epilepsy

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 .

Epilepsia © ILAE

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

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

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 cell 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.

Epilepsia © ILAE

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 μ m for **A** and **B**.

Epilepsia © ILAE

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.

ACKNOWLEDGMENTS

The authors would like to acknowledge support from NIH grant R01-NS38331 (to CER) and a grant from the American Epilepsy Society (to SJ). We would also like to thank Fred H. Gage for conceptually important comments on the studies described in this paper.

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.

REFERENCES

- Austin JE, Buckmaster PS. (2004) Recurrent excitation of granule cells with basal dendrites and low interneuron density and inhibitory post-synaptic current frequency in the dentate gyrus of macaque monkeys. *J Comp Neurol* 476:205–218.
- Binder DK, Steinhäuser C. (2006) Functional changes in astroglial cells in epilepsy. *Glia* 54:358–368.
- Brandt MD, Jessberger S, Steiner B, Kronenberg G, Reuter K, Bick-Sander A, von der Behrens W, Kempermann G. (2003) Transient calretinin expression defines early postmitotic step of neuronal differentiation in adult hippocampal neurogenesis of mice. *Mol Cell Neurosci* 24:603–613.
- Couillard-Despres S, Winner B, Schaubeck S, Aigner R, Vroemen M, Weidner N, Bogdahn U, Winkler J, Kuhn HG, Aigner L. (2005) Doublecortin expression levels in adult brain reflect neurogenesis. *Eur J Neurosci* 21:1–14.
- Dashtipour K, Tran PH, Okazaki MM, Nadler JV, Ribak CE. (2001) Ultrastructural features and synaptic connections of hilar ectopic granule cells in the rat dentate gyrus are different from those of granule cells in the granule cell layer. *Brain Res* 890:261–271.
- Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, Schinder AF. (2005) Neuronal differentiation in the adult hippocampus recapitulates embryonic development. *J Neurosci* 25:10074–10086.
- Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H. (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature* 439:589–593.
- Gong C, Wang TW, Huang HS, Parent JM. (2007) Reelin regulates neuronal progenitor migration in intact and epileptic hippocampus. *J Neurosci* 27:1803–1811.
- Haas CA, Dudeck O, Kirsch M, Huszka C, Kann G, Pollak S, Zentner J, Frotscher M. (2002) Role for reelin in the development of granule cell dispersion in temporal lobe epilepsy. *J Neurosci* 22:5797–5802.
- Jakubs K, Nanobashvili A, Bonde S, Ekdahl CT, Kokaia Z, Kokaia M, Lindvall O. (2006) Environment matters: synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. *Neuron* 52:1047–1059.
- Jessberger S, Zhao C, Toni N, Clemenson GD Jr., Li Y, Gage FH. (2007a) Seizure-associated, aberrant neurogenesis in adult rats characterized with retrovirus-mediated cell labeling. *J Neurosci* 27:9400–9407.
- Jessberger S, Nakashima K, Clemenson GD Jr, Mejia E, Mathews E, Ure K, Ogawa S, Sinton CM, Gage FH, Hsieh J. (2007b) Epigenetic modulation of seizure-induced neurogenesis and cognitive decline. *J Neurosci* 27:5967–5975.
- Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. (2002) Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci U S A* 99:11946–11950.
- Jung KH, Chu K, Kim M, Jeong SW, Song YM, Lee ST, Kim JY, Lee SK, Roh JK. (2004) Continuous cytosine-b-D-arabinofuranoside infusion reduces ectopic granule cells in adult rat hippocampus with attenuation of spontaneous recurrent seizures following pilocarpine-induced status epilepticus. *Eur J Neurosci* 19:3219–3226.
- Kang TC, Kim DS, Kwak SE, Kim JE, Won MH, Kim DW, Choi SY, Kwon OS. (2006) Epileptogenic roles of astroglial death and regeneration in the dentate gyrus of experimental temporal lobe epilepsy. *Glia* 54:258–271.
- Kempermann G, Jessberger S, Steiner B, Kronenberg G. (2004) Milestones of neuronal development in the adult hippocampus. *Trends Neurosci* 27:447–452.
- McCloskey DP, Croll SD, Scharfman HE. (2005) Depression of synaptic transmission by vascular endothelial growth factor in adult rat hippocampus and evidence for increased efficacy after chronic seizures. *J Neurosci* 25:8889–8897.
- Mohapel P, Ekdahl CT, Lindvall O. (2004) Status epilepticus severity influences the long-term outcome of neurogenesis in the adult dentate gyrus. *Neurobiol Dis* 15:196–205.
- Overstreet LS, Hentges ST, Bumashchy VF, de Souza FS, Smart JL, Santangelo AM, Low MJ, Westbrook GL, Rubinstein M. (2004) A transgenic marker for newly born granule cells in dentate gyrus. *J Neurosci* 24:3251–3259.
- Overstreet Wadiche L, Bromberg DA, Bensen AL, Westbrook GL. (2005) GABAergic signaling to newborn neurons in dentate gyrus. *J Neurophysiol* 94:4528–4532.
- Overstreet-Wadiche LS, Bromberg DA, Bensen AL, Westbrook GL. (2006) Seizures accelerate functional integration of adult-generated granule cells. *J Neurosci* 26:4095–4103.
- Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. (1997) Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 17:3727–3738.
- Parent JM, Murphy GG. (2008) Mechanisms and functional significance of aberrant seizure-induced hippocampal neurogenesis. *Epilepsia* 49(Suppl. 5):19–25.
- Patel LS, Wenzel HJ, Schwartzkroin PA. (2004) Physiological and morphological characterization of dentate granule cells in the p35 knockout mouse hippocampus: evidence for an epileptic circuit. *J Neurosci* 24:9005–9014.
- Piatti VC, Esposito MS, Schinder AF. (2006) The timing of neuronal development in adult hippocampal neurogenesis. *Neuroscientist* 12:463–468.
- Plumpe T, Ehninger D, Steiner B, Klempin F, Jessberger S, Brandt M, Romer B, Rodriguez GR, Kronenberg G, Kempermann G. (2006) Variability of doublecortin-associated dendrite maturation in adult hippocampal neurogenesis is independent of the regulation of precursor cell proliferation. *BMC Neurosci* 7:77.
- Raedt R, Boon P, Persson A, Alborn AM, Botterberg T, Van Dycke A, Linder B, De Smedt T, Wadman WJ, Ben-Menachem E, Eriksson PS. (2007) Radiation of the rat brain suppresses seizure-induced neurogenesis and transiently enhances excitability during kindling acquisition. *Epilepsia* 48:1952–1963.
- Rao MS, Shetty AK. (2004) Efficacy of doublecortin as a marker to analyse the absolute number and dendritic growth of newly generated neurons in the adult dentate gyrus. *Eur J Neurosci* 19:234–246.

- Ribak CE, Tran PH, Spigelman I, Okazaki MM, Nadler JV. (2000) Status epilepticus-induced hilar basal dendrites on rodent granule cells contribute to recurrent excitatory circuitry. *J Comp Neurol* 428:240–253.
- Ribak CE, Korn MJ, Shan Z, Obenaus A. (2004) Dendritic growth cones and recurrent basal dendrites are typical features of newly generated dentate granule cells in the adult hippocampus. *Brain Res* 1000:195–199.
- Rice DS, Curran T. (2001) Role of the reelin signaling pathway in central nervous system development. *Annu Rev Neurosci* 24:1005–1039.
- Scharfman HE, Goodman JH, Sollas AL. (2000) Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. *J Neurosci* 20:6144–6158.
- Scharfman HE, Sollas AL, Goodman JH. (2002) Spontaneous recurrent seizures after pilocarpine-induced status epilepticus activate calbindin-immunoreactive hilar cells of the rat dentate gyrus. *Neuroscience* 111:71–81.
- Scharfman HE, Sollas AE, Berger RE, Goodman JH, Pierce JP. (2003) Perforant path activation of ectopic granule cells that are born after pilocarpine-induced seizures. *Neuroscience* 121:1017–1029.
- Schmidt-Hieber C, Jonas P, Bischofberger J. (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429:184–187.
- Scott BW, Wojtowicz JM, Burnham WM. (2000) Neurogenesis in the dentate gyrus of the rat following electroconvulsive shock seizures. *Exp Neurol* 165:231–236.
- Seress L, Pokorny J. (1981) Structure of the granular layer of the rat dentate gyrus. A light microscopic and Golgi study. *J Anat* 133:181–95.
- Seress L, Ribak CE. (1990) Postnatal development of the light and electron microscopic features of basket cells in the hippocampal dentate gyrus of the rat. *Anat Embryol* 181:547–565.
- Shapiro LA, Korn MJ, Shan Z, Ribak CE. (2005a) GFAP-expressing radial glia-like cell bodies are involved in a one-to-one relationship with doublecortin-immunolabeled newborn neurons in the adult dentate gyrus. *Brain Res* 1040:81–91.
- Shapiro LA, Korn MJ, Ribak CE. (2005b) Newly generated dentate granule cells from epileptic rats exhibit elongated hilar basal dendrites that align along GFAP-immunolabeled processes. *Neuroscience* 136:823–831.
- Shapiro LA, Ribak CE. (2006) Newly born dentate granule neurons after pilocarpine-induced epilepsy have hilar basal dendrites with immature synapses. *Epilepsy Res* 69:53–66.
- Shapiro LA, Figueroa-Aragon S, Ribak CE. (2007) Newly generated granule cells show rapid neuroplastic changes in the adult rat dentate gyrus during the first five days following pilocarpine-induced seizures. *Eur J Neurosci* 26:583–592.
- Stanfield BB, Caviness VS Jr., Cowan WM. (1979) The organization of certain afferents to the hippocampus and dentate gyrus in normal and reeler mice. *J Comp Neurol* 185:461–483.
- van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. (2002) Functional neurogenesis in the adult hippocampus. *Nature* 415:1030–1034.
- Vessal M, Dugani CB, Solomon DA, McIntyre Burnham W, Ivy GO. (2005) Might astrocytes play a role in maintaining the seizure-prone state? *Brain Res* 1044:190–196.
- Walter C, Murphy BL, Pun RY, Spieles-Engemann AL, Danzer SC. (2007) Pilocarpine-induced seizures cause selective time-dependent changes to adult-generated hippocampal dentate granule cells. *J Neurosci* 27:7541–7552.
- Wenzel HJ, Robbins CA, Tsai LH, Schwartzkroin PA. (2001) Abnormal morphological and functional organization of the hippocampus in a p35 mutant model of cortical dysplasia associated with spontaneous seizures. *J Neurosci* 21:983–998.
- Zhao C, Teng EM, Summers RG Jr., Ming GL, Gage FH. (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci* 26:3–11.
- Zhao C-S and Overstreet-Wadiche L. (2008) Integration of adult generated neurons during epileptogenesis. *Epilepsia* 49(Suppl. 5):3–12.