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Is neurogenesis reparative after status epilepticus?

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Neurogenesis persists in the hippocampal dentate gyrus of mammals, including human and nonhuman primates, throughout life (Altman and Das, 1965; Cameron et al., 1993; Kuhn et al., 1996; Eriksson et al., 1998; Gould et al., 1999; Kornack and Rakic, 2001). Neural stem-like cells reside in the subgranular zone (SGZ) at the border of the hilus and DGC layer (Seri et al., 2001; Filippov et al., 2003), where they generate neuroblasts that migrate into the layer and differentiate into granule neurons (Cameron et al., 1993; Kuhn et al., 1996). Adult-born dentate granule cells (DGCs) send axonal projections to appropriate targets (Stanfield and Trice, 1988; Markakis and Gage, 1999; van Praag et al., 2002) and acquire electrophysiological characteristics of mature DGCs (van Praag et al., 2002; Wadiche et al., 2005; Ge et al., 2006). Although the precise function is unknown, evidence implicates DGC neurogenesis in certain forms of hippocampus-dependent learning and memory (reviewed in Doetsch and Hen [2005]).

DGC Neurogenesis Is Altered After SE Or Kindling

Studies in adult rodent models of mesial temporal lobe epilepsy (mTLE) indicate that status epilepticus (SE) potently stimulates DGC neurogenesis (Parent et al., 1997; Gray and Sundstrom, 1998; Parent et al., 1998). Kainate- or pilocarpine-induced SE increases dentate gyrus cell proliferation approximately 5- to 10-fold within 3 days (Parent et al., 1997; Gray and Sundstrom, 1998), and over 80% of the cells become DGCs. Electrical kindling of amygdala (Parent et al., 1998; Scott et al., 1998), hippocampus (Bengzon et al., 1997), or perforant path (Nakagawa et al., 2000) also stimulates DGC neurogenesis. SE-induced neurogenesis may be short-lived, however, as chronically epileptic rats show decreased DGC production 5 months after SE (Hattiangady et al., 2004).

In addition to increased production, adult rodent DGCs generated after SE show abnormalities of structure and location. Basal dendrites persist on adult-born DGCs much more frequently after SE (Scharfman et al., 2000; Dashtipour et al., 2001), and cells with basal dendrites appear both in the inner DGC layer and hilus after SE. Interestingly, new DGCs with abnormal basal dendrites continue to form many months after SE (Jessberger et al., 2007a), suggesting that the responsible cues persist well after the initial insult. Another abnormality involves dispersion of the DGC layer and abnormal locations of DGCs outside the layer. The dentate gyrus in human mTLE often shows excessive DGC dispersion and ectopic granule-like neurons in the hilus and molecular layer (Houser, 1990; Parent et al., 2006). DGC layer dispersion and hilar-ectopic DGCs appear in rodent mTLE models and persist chronically (Parent et al., 1997; Scharfman et al., 2000; Dashtipour et al., 2001; Jessberger et al., 2005; Parent et al., 2006). Ectopic cells in human and experimental mTLE are similar in terms of their morphology and expression of DGC-specific markers (Scharfman et al., 2000; Dashtipour et al., 2001; Parent et al., 2006).

Mechanisms Underlying SE-Induced Neurogenesis

The mechanisms by which SE stimulates neurogenesis are unknown. Huttmann et al. (2003) used a neural stem cell reporter mouse to show that kainate-induced SE influences proliferation of the SGZ radial glia-like progenitors. SE may increase neurogenesis indirectly through the stimulation of astrocytosis, as astrocytes stimulate hippocampal neurogenesis via wnt signaling and perhaps other mechanisms (Song et al., 2002; Lie et al., 2005). SE also increases the expression of growth factor and other molecules with the potential to influence neurogenesis.

The formation of ectopic DGCs after SE likely involves developmental cues that persist in the adult. The migration guidance cue reelin, for example, is expressed in the adult human and rodent dentate gyrus and is implicated in DGC layer dispersion in human mTLE (Haas et al., 2002). Recent work shows that hilar-ectopic DGCs in experimental mTLE arise from aberrantly migrating DGC progenitors (Parent et al., 2006). This altered migration is associated with loss of reelin signaling that may disrupt the migratory behavior of DGC progenitors (Gong et al., 2007).

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Brain-derived neurotrophic factor (BDNF) is another candidate, as hippocampal BDNF infusion in adult rat increases DGC neurogenesis and induces ectopic DGCs (Scharfman et al., 2005). The combined action of multiple factors likely are involved, each potentially acting on different steps in the neurogenic cascade.

Consequences of SE-Induced Neurogenesis

Recent evidence suggests that DGCs generated after SE integrate abnormally into existing networks (Scharfman et al., 2000; Dashtipour et al., 2001; Jessberger et al, 2007a). Intracellular recordings from hilar-ectopic DGCs in hippocampal slices from epileptic rats show that they are hyperexcitable and burst synchronously with CA3 pyramidal cells (Scharfman et al., 2000). This increased excitability may relate to excessive excitatory input onto basal dendrites of ectopic DGCs (Dashtipour et al., 2001). Moreover, granule cells that extend hilar basal dendrites stably integrate into the dentate circuitry (Jessberger et al., 2007a), leading to lasting changes in connectivity that may contribute to epileptogenesis. Further support for the epileptogenicity of SE-induced neurogenesis comes from the work of Jung et al. (2004). They inhibited DGC neurogenesis after pilocarpine treatment by antimitotic agent infusion and found that rats developed fewer and shorter spontaneous recurrent seizures than controls. These data suggest that DGCs integrate abnormally after SE, are hyperexcitable, and may contribute to seizure generation or propagation (Fig. 1).

Other work suggests a more complex influence of adult-born DGCs on hippocampal excitability after SE. In contrast to chemoconvulsant SE models, the morphology of developing DGCs after electrically-induced SE appears unaltered, at least in the DGC layer (Jakubs et al., 2006). In this model, newborn DGCs receive increased inhibitory input resulting in less excitability than newborn cells generated after exercise (Jakubs et al., 2006). Some DGCs generated after SE therefore could have compensatory antiepileptogenic effects.

As mentioned above, adult hippocampal neurogenesis likely underlies specific learning and memory functions, raising the possibility that defective neurogenesis may contribute to the progressive memory dysfunction seen in mTLE (Fig. 1; Helmstaedter, 2002). This idea is supported by recent findings of Jessberger et al.. They suppressed neurogenesis after kainic acid-induced SE with the histone deacetylases inhibitor and anticonvulsant valproic acid and found that decreased neurogenesis was associated with better performance in a hippocampus-dependent object recognition task than in SE controls (Jessberger et al., 2007b). These data may be reconciled with the decline in neurogenesis chronically after the experimental SE described above (Hattiangady et al, 2004), if one considers that memory function may be impaired both by aberrant neurogenesis or a reduction of normal DGC neurogenesis. However, further progress in understanding the functional consequences of SE-induced neurogenesis for epileptogenesis or cognitive impairment awaits more specific and selective experimental strategies to manipulate adult neurogenesis.

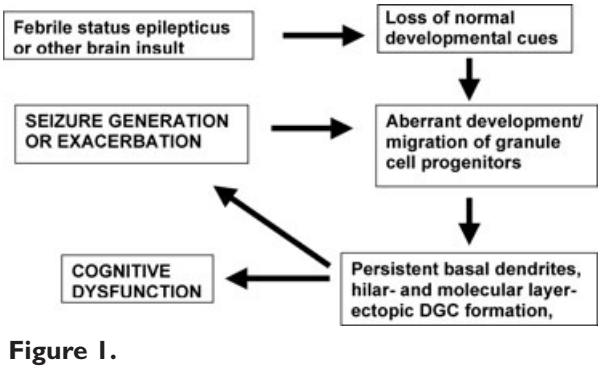

Figure 1.
Aberrant neurogenesis hypothesis of mTLE pathophysiology.
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References

Altman J, Das GD. (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol* 124:319–335.

Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O. (1997) Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc Natl Acad Sci USA* 94:10432–10437.

Cameron HA, Woolley CS, McEwen BS, Gould E. (1993) Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. *Neuroscience* 56:337–344.

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.

Doetsch F, Hen R. (2005) Young and excitable: the function of new neurons in the adult mammalian brain. *Curr Opin Neurobiol* 15:121–128.

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA. (1998) Neurogenesis in the adult human hippocampus. *Nat Med* 4:1313–1317.

Filippov V, Kronenberg G, Pivneva T, Reuter K, Steiner B, Wang LP. (2003) Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. *Mol Cell Neurosci* 23:373–382.

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 TS, Huang HS, Parent J. (2007) Reelin regulates neuronal progenitor migration in intact and epileptic hippocampus. *J Neurosci* 27:1803–1811.

Gould E, Reeves AJ, Graziano MS, Gross CG. (1999) Neurogenesis in the neocortex of adult primates. *Science* 286:548–552.

Gray WP, Sundstrom LE. (1998) Kainic acid increases the proliferation of granule cell progenitors in the dentate gyrus of the adult rat. *Brain Res* 790:52–59.

Haas CA, Dudeck O, Kirsch M, Huszka C, Kann G, Pollak S. (2002) Role for reelin in the development of granule cell dispersion in temporal lobe epilepsy. *J Neurosci* 22:5797–5802.

Hattiangady B, Rao MS, Shetty AK. (2004) Chronic temporal lobe epilepsy is associated with severely declined dentate neurogenesis in the adult hippocampus. *Neurobiol Dis* 17:473–490.

Helmstaedter C. (2002) Effects of chronic epilepsy on declarative memory systems. *Prog Brain Res* 135:439–453.

Houser CR. (1990) Granule cell dispersion in the dentate gyrus of humans with temporal lobe epilepsy. *Brain Res* 535:195–204.

Huttmann K, Sadgrove M, Wallraff A, Hinterkeuser S, Kirchhoff F, Steinhauser C. (2003) Seizures preferentially stimulate proliferation of radial glia-like astrocytes in the adult dentate gyrus: functional and immunocytochemical analysis. *Eur J Neurosci* 18:2769–2778.

Jakubs K, Nanobashvili A, Bonde S, Ekdahl CT, Kokaia Z, Kokaia M. (2006) Environment matters: synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. *Neuron* 52:1047–1059.

Jessberger S, Romer B, Babu H, Kempermann G. (2005) Seizures induce proliferation and dispersion of doublecortin-positive hippocampal progenitor cells. *Exp Neurol* 196:342–351.

Jessberger S, Zhao C, Toni N, Clemenson GDJ, Li Y, Gage FH. (2007a) Seizure-associated, aberrant neurogenesis in adult rats characterized with retrovirus-mediated cell labeling. *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. *Neurosci* 27:5067–5075.

Jung KH, Chu K, Kim M, Jeong SW, Song YM, Lee ST. (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.

Kornack DR, Rakic P. (2001) The generation, migration, and differentiation of olfactory neurons in the adult primate brain. *Proc Natl Acad Sci U S A* 98:4752–4757.

Kuhn HG, Dickinson-Anson H, Gage FH. (1996) Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci* 16:2027–2033.

Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A. (2005) Wnt signalling regulates adult hippocampal neurogenesis. *Nature* 437:1370–1375.

Markakis EA, Gage FH. (1999) Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. *J Comp Neurol* 406:449–460.

Nakagawa E, Aimi Y, Yasuhara O, Tooyama I, Shimada M, McGeer PL. (2000) Enhancement of progenitor cell division in the dentate gyrus triggered by initial limbic seizures in rat models of epilepsy. *Epilepsia* 41:10–18.

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, Janumpalli S, McNamara JO, Lowenstein DH. (1998) Increased dentate granule cell neurogenesis following amygdala kindling in the adult rat. *Neurosci Lett* 247:9–12.

Parent JM, Elliott RC, Pleasure SJ, Barbaro NM, Lowenstein DH. (2006) Aberrant seizure-induced neurogenesis in experimental temporal lobe epilepsy. *Ann Neurol* 59:81–91.

Scott BW, Wang S, Burnham WM, De Boni U, Wojtowicz JM. (1998) Kindling-induced neurogenesis in the dentate gyrus of the rat. *Neurosci Lett* 248:73–76.

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 H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. (2005) Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. *Exp Neurol* 192:348–356.

Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A. (2001) Astrocytes give rise to new neurons in the adult mammalian hippocampus. *J Neurosci* 21:7153–7160.

Song H, Stevens CF, Gage FH. (2002) Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417:39–44.

Stanfield BB, Trice JE. (1988) Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. *Exp Brain Res* 72:399–406.

van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. (2002) Functional neurogenesis in the adult hippocampus. *Nature* 415:1030–1034.

Wadiche L, Bromberg DA, Bensen AL, Westbrook GL. (2005) GABAergic signaling to newborn neurons in dentate gyrus. *J Neurophysiol* 94:4528–4532.