EPILEPSY CURRENTS

Current Literature
In Basic Science

Neurogenesis in Epilepsy: Better to Burn Out or Fade Away?

Neuronal Hyperactivity Accelerates Depletion of Neural Stem Cells and Impairs Hippocampal Neurogenesis.

Sierra A, Martin-Suárez S, Valcárcel-Martin R, Pascual-Brazo J, Aelvoet SJ, Abiega O, Deudero JJ, Brewster AL, Bernales I, Anderson AE, Baekelandt V, Maletić-Savatić M, Encinas JM. *Cell Stem Cell* 2015;16:488–503.

Adult hippocampal neurogenesis is believed to maintain a range of cognitive functions, many of which decline with age. We recently reported that radial neural stem cells (rNSCs) in the hippocampus undergo activation-dependent conversion into astrocytes, a mechanism that over time contributes to a reduction in the rNSC population. Here, we injected low and high levels of kainic acid (KA) in the dentate gyrus to assess whether neuronal hyperexcitation, a hallmark of epileptic disorders, could accelerate this conversion. At low levels of KA, generating epileptiform activity without seizures, we indeed found increased rNSC activation and conversion into astrocytes. At high levels, generating sustained epileptic seizures, however, we find that rNSCs divide symmetrically and that both mother and daughter cells convert into reactive astrocytes. Our results demonstrate that a threshold response for neuronal hyperexcitation provokes a dramatic shift in rNSC function, which impairs adult hippocampal neurogenesis in the long term.

Commentary

The generation of hippocampal dentate granule cells continues throughout life in almost all mammalian species. The function of these new neurons remains a topic of intense scientific scrutiny; however, the general consensus from studies in rodents indicates that these neurons have roles in both spatial memory and affective behavior, with dorsal hippocampus mediating the former and ventral the latter (1).

During the development of epilepsy, generation of these new neurons is profoundly disrupted. Animal models reveal a complex temporal dynamic: increased neurogenesis occurs during the days and weeks after an epileptogenic insult, but decreased neurogenesis manifests during chronic phases (2). Disrupted neurogenesis may produce both loss- and gain-of-function defects (1). Loss-of-function deficits could result from reduced neurogenesis during chronic epilepsy and might contribute to epilepsy comorbidities such as cognitive impairment or depression (1, 3). Gain-of-function deficits, however, can be mediated by new neurons generated during epileptogenesis. These neurons contribute to the aberrant rewiring of the hippocampus and are hypothesized to promote epileptogenesis. Indeed, genetically ablating adult-generated neurons before an epileptogenic injury in rodents has been shown to mitigate epileptogenesis (4).

The work by Sierra and colleagues provides new insights into the complex dynamics of disrupted neurogenesis in epilepsy. They developed a clever approach using different doses of kainic acid to generate either chronic epileptiform activity without overt seizures, or full-blown status epilepticus followed by the development of recurrent seizures. Proliferative activity was tracked using a transgenic mouse line that expresses green fluorescent protein in granule cell progenitors and all of their daughter cells. Both epileptiform activity and status epilepticus increased neurogenesis acutely, followed by chronic reductions in proliferation. The treatments differed, however, both quantitatively and qualitatively. While epileptiform activity decreased the number of progenitor cells by 40% within 50 days of kainic acid treatment, status epilepticus decreased the progenitor pool by greater than 90% over the same period. Exacerbating the decline, cell proliferation in mice that underwent status epilepticus switched from neuron generation to reactive astrocyte generation. Paradoxically, the transient increase in neuron production induced by epileptiform activity and seizures may drive the chronic reductions. While increased neurogenesis in itself is not necessarily harmful, granule cell progenitors are not a limitless resource. Although they are capable of self-renewal, they eventually terminally differentiate, leading to reductions in new neuron generation with age (1). Increasing neurogenesis in the short term, therefore, appears to accelerate the eventual depletion of progenitors, either slowly with modest epileptiform activity, or rapidly with a severe insult.

Both treatments also have the potential to produce gain-of-function deficits by promoting the production of aberrant neurons; although whether kainic acid–induced epileptiform activity is sufficient to promote aberrant integration has yet to be assessed. The rapid elimination of neurogenesis with more severe insults might have the beneficial effect of limiting the accumulation of abnormal granule cells; however, the switch from neuron production to reactive astrocyte production likely produces its own damaging effects on hippocampal function and excitability (5).

Epilepsy Currents, Vol. 16, No. 4 (July/August) 2016 pp. 268–269

These findings add to a developing story that predicts a complex sequela of changes during epileptogenesis. Acute seizures in healthy animals consistently increase neurogenesis rates. More severe seizures (status epilepticus) also increase neurogenesis over the near term (days to weeks). Many of these new cells integrate abnormally, potentially contributing to epileptogenesis (6). Chronically, however, persistent epileptiform activity and seizures deplete the progenitor cell pool, leading to reduced neurogenesis and increased gliosis. The very different responses to distinct levels of epileptiform activity in animals predict significant variability among patients with epilepsy, dependent on their disease history. Patients with mild epilepsy would be predicted to show increased neurogenesis following seizures early in the disease, with slow depletion over time. This depletion can be viewed as premature aging of the hippocampus, potentially contributing to loss of cognitive ability. These patients might also exhibit greater accumulation of abnormal granule cells since neurogenesis is not immediately disrupted. Patients with frequent seizures, a history of status epilepticus, or both, on the other hand, could show rapid loss of neurogenic potential and a shift from aberrant neurogenesis toward hippocampal gliosis.

Additional work is needed to elucidate the role of adult neurogenesis in human epilepsy, but a number of findings have been confirmed. Recent work examining hippocampal C^{14} accumulation from Cold War–era nuclear tests has established that neurogenesis continues throughout life in humans (7). Studies examining tissue resected from temporal lobe epilepsy patients also paint a relatively consistent picture showing impaired neurogenesis in chronic epilepsy (8), although it is much more difficult to assay for persistent neurogenesis in human tissue specimens than in animal models. Robust studies to determine whether neurogenesis is increased in newly diagnosed epilepsy will need to await the development of noninvasive approaches to measure cell proliferation, because tissue (fortunately) is typically not available. Also consistent with the idea that epileptiform activity depletes progenitors, Paradisi and colleagues found a negative correlation between disease duration and proliferation rates in neurospheres generated from resected patient tissue (9). Moreover, reduced proliferative capacity in resected hippocampi is correlated with cognitive dysfunction (10). Nonetheless, the key observation that epileptiform activity is sufficient to deplete granule cell progenitors has yet to be established in humans. Indeed, it is not clear how well kainic acid-induced epileptiform activity in rodents models spontaneous epileptiform activity in humans. If depletion does occur in humans, it would have important implications for whether and how aggressively to treat nonictal events, such as very frequent spikes. Controlling these events could provide long-term benefits for the cognitive function of the patient.

In summary, the study by Sierra and colleagues advances our understanding of neurogenesis in epilepsy by clearly demonstrating that the severity of epileptiform activity impacts cell differentiation in the dentate, and the rate of progenitor cell burnout. The findings also imply that seizure history and duration in epilepsy patients are critical variables impacting the state of the neurogenic niche, which is likely to manifest as phenotypic differences among patients.

by Steven C. Danzer, PhD

References

1. Christian KM, Song H, Ming GL. Functions and dysfunctions of adult hippocampal neurogenesis. *Annu Rev Neurosci* 2014;7:243–262.
2. Hattiangady B, Shetty AK. Decreased neuronal differentiation of newly generated cells underlies reduced hippocampal neurogenesis in chronic temporal lobe epilepsy. *Hippocampus* 2010;20:97–112.
3. Eisch AJ, Petrik D. Depression and hippocampal neurogenesis: A road to remission? *Science* 2012;338:72–75.
4. Cho KO, Lybrand ZR, Ito N, Brulet R, Tafacory F, Zhang L, Good L, Ure K, Kernie SG, Birnbaum SG, Scharfman HE, Eisch AJ, Hsieh J. Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline. *Nat Commun* 2015;6:6606. doi: 10.1038/ncomms7606.
5. Robel S, Sontheimer H. Glia as drivers of abnormal neuronal activity. *Nat Neurosci* 2015;19:28–33.
6. Singh SP, LaSarge CL, An A, McAuliffe JJ, Danzer SC. Clonal analysis of newborn hippocampal dentate granule cell proliferation and development in temporal lobe epilepsy. *eNeuro* 2016;2. doi: 10.1523/ENEURO.0087-15.2015.
7. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Boström E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisén J. Dynamics of hippocampal neurogenesis in adult humans. *Cell* 2013;153:1219–1227.
8. Fahrner A, Kann G, Flubacher A, Heinrich C, Freiman TM, Zentner J, Frotscher M, Haas CA. Granule cell dispersion is not accompanied by enhanced neurogenesis in temporal lobe epilepsy patients. *Exp Neurol* 2007;203:320–332.
9. Paradisi M, Fernández M, Del Vecchio G, Lizzo G, Marucci G, Giulioni M, Pozzati E, Antonelli T, Lanzoni G, Bagnara GP, Giardino L, Calzà L. Ex vivo study of dentate gyrus neurogenesis in human pharmacoresistant temporal lobe epilepsy. *Neuropathol Appl Neurobiol* 2010;36:535–550.
10. Coras R, Siebzehnrubl FA, Pauli E, Huttner HB, Njunting M, Kobow K, Villmann C, Hahnen E, Neuhuber W, Weigel D, Buchfelder M, Stefan H, Beck H, Steindler DA, Blümcke I. Low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction in humans. *Brain* 2010;133:3359–3372.