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Seizure-Induced Neurogenesis: 1 Out of 3 Ain't Bad

Commentary on: Parent J. When newborn neurons stray. *Epilepsy Currents* 5(6):231-3. doi:10.1111/j.1535-7511.2005.00072.x

Over half a century of work has cemented the idea that neurogenesis, the generation of new neurons, persists in specific regions of the adult mammalian brain and is altered by brain insults. Similarly, adult neurogenesis is now firmly entrenched as one of many forms of seizure-induced brain plasticity. As a postdoctoral fellow in Daniel Lowenstein's laboratory many years ago before adult neurogenesis had gained widespread notoriety, I naively expected to quickly prove my first serious scientific hypothesis, namely that seizure-induced mossy fiber sprouting (MFS) arises specifically from adult-generated dentate granule cells (DGCs). Over 2 decades from conceiving that hypothesis and my initial description of seizure-induced aberrant neurogenesis,[1] and 15 years after writing an *Epilepsy Currents* commentary on the topic,[2] I have been asked to reflect on my sense of how the field has progressed over this time. I liken this current commentary to the old Meatloaf song, "Two Out of Three Ain't Bad," except with a slightly lower bar. Rather than "want," "need," and "love," 3 of the main questions the field initially set out to test had been the following: (1) Are the new neurons solely responsible for seizure-induced MFS?; (2) Does seizure-induced DGC neurogenesis, particularly aberrant neurogenesis, lead to seizure initiation or progression in medial temporal lobe epilepsy (mTLE)?; and (3) Is seizure-induced adult DGC neurogenesis relevant to human mTLE? Let us delve into each question in turn.

Our laboratory and others were very interested in MFS in the late 1990s due to its potential role in epileptogenesis via the establishment of new recurrent excitatory circuitry in the hippocampal formation (reviewed by Scharfman[3]). To my mind, the hypothesis that adult neurogenesis is solely responsible for seizure-induced supragranular MFS was a compelling one. MFS is a developmental process, with growth of an axon collateral to a target to form a new synapse. Thus, why would reactivation of a developmental process in a preexisting neuron be necessary when newly generated neurons are available to achieve this outcome? Nonetheless, the initial work showing seizure-induced stimulation of adult DGC neurogenesis did not provide compelling evidence of MFS arising from newly generated DGCs.[1] A subsequent finding that MFS sprouting persisted even after neurogenesis was completely depleted by irradiating rats before and after pilocarpine-induced status epilepticus provided strong evidence against the hypothesis.[4] More recent studies using retroviral reporter labeling alone or combined with rabies virus retrograde trans-synaptic tracing confirmed that both neonatally and adult-generated DGCs contribute to MFS in the rat pilocarpine mTLE model.[5-7] Importantly, some of these reports have shown intriguing sprouting from or onto both adult-generated and preexisting DGCs and area CA3, CA2, and even CA1 pyramidal cells, as well as interneurons.[6,7] The latter findings, including CA3 back projections onto adult-generated DGCs and new CA1 projections onto preexisting DGCs, are likely much more relevant to epileptogenic mechanisms than supragranular MFS. Moreover, sprouting specifically onto adult-generated DGCs that are ectopically located in the hilus or onto hilar basal dendrites (HBDs) has yet to be explored in depth.

A second major area of study involves the question of whether seizure-induced neurogenesis is epileptogenic. Initial approaches using irradiation or pharmacologic ablation strategies had shown mixed results (recently reviewed by Danzer[8]). Moreover, an early in vitro electrophysiological study making recordings from retroviral reporter-labeled, adult-generated DGCs in an electrical stimulation-induced status epilepticus model suggested that the new neurons are preferentially inhibited and may counteract network excitability.[9] However, these new neurons appeared to be normally integrated, that is, they were positioned normally in the granule cell layer with dendrites appropriately targeting the molecular layer. Yet the field early on recognized that epileptogenic insults lead to some new neurons that migrate ectopically and are hyperexcitable,[1,2,5,10] while others have persistent HBDs or apical dendritic

abnormalities.[5,11-13] These early findings raised the possibility of different subpopulations of DGCs generated after insults that had differing implications for epileptogenic processes.

A critical modeling study published in 2008 suggested that only a small percentage of abnormally hyperconnected DGCs was necessary for seizure initiation.[14] This "in silico" finding then received biological confirmation via a key proof-of-concept genetic study. By conditionally deleting the phosphatase and tensin homolog in a small subset (about 10%-20%) of postnatally developing murine DGCs, Pun and colleagues demonstrated that DGC morphological abnormalities and spontaneous seizures developed.[15] More recently, in vitro recordings from DGCs birthdated by retroviral reporters injected neonatally or in adulthood in the rat pilocarpine mTLE model indicated that aberrantly integrated new DGCs, particularly the ectopic population in the hilus or molecular layer, exhibit the greatest net excitatory drive compared to normally integrated DGCs generated neonatally or in adulthood in epileptic animals.[16] Together, this work suggests that the aberrantly integrated (ectopic) adult-generated DGC population contributes to seizure initiation or progression in experimental mTLE and potentially represents the so-called "hub" cells predicted by Morgan and Soltesz.

Studies using more advanced pharmacogenomic ablation strategies to suppress adult neurogenesis further support the idea that seizure-induced neurogenesis is pro-epileptogenic. Two different laboratories have found about a 50% reduction in seizure frequency with peri-insult ablation of new neurons in adult mouse mTLE models.[17,18] In addition, a third study reported that suppression of the new neurons after spontaneous seizures had already developed was able to prevent further progression of epilepsy.[19] Interestingly, in other studies, new neurons in adult animals seem to be protective against acute seizures, as ablating them prior to chemoconvulsant treatment worsens the acute seizure episode, at least in 1 model[20] (for a more thorough discussion of this and conflicting studies see the study by Danzer[8]). All of the pharmacogenomic ablation strategies used to date, however, do not specifically target aberrantly integrated new neurons. Thus, further work is needed to unequivocally resolve the outstanding questions in the field as to whether some subpopulations of new neurons restore inhibition after epileptogenic insults while other subsets contribute to epilepsy. Future efforts should be directed at the use of reversible methods to transiently activate or suppress specific subpopulations (ie, aberrantly vs normally integrated DGCs), based upon cell subpopulation-specific promoters that will eventually be gleaned by single-cell transcriptomic techniques.

The last area covered in this commentary, a 2-pronged question, is the issue of relevance to human mTLE. An exciting study from the 1990s by Eriksson and Gage using bromodeoxyuridine labeling suggested that adult DGC neurogenesis persists in humans.[21] This work was later bolstered by carbon dating methods that took advantage of nuclear weapons testing in the mid-20th century to support the idea that substantial hippocampal neurogenesis persists throughout life in humans.[22] However, these findings have recently been called into question by a careful immunohistochemical study indicating that human DGC neurogenesis declines markedly by late childhood to negligible levels in adulthood.[23] The topic remains controversial, with other recent reports coming to opposite conclusions.[24,25] The final verdict no doubt awaits improvements in techniques beyond immunohistochemistry, with the hope that single-cell transcriptomics, proteomics, and other methods will provide more definitive answers in the near future.

Irrespective of the outcome, altered human DGC neurogenesis may still be relevant for the initial epileptogenic changes in mTLE developing during younger ages with a latent period until adolescence or adulthood. And beyond this question lies the issue of translational relevance. Whether or not adult neurogenesis is involved in the proximal or upstream epileptogenic process, by the time mTLE patients present for treatment a neurogenic mechanism may or may not be the optimal target for therapy. Yet we do not know that this is the case, and it remains possible that manipulating neurogenesis might be one part of a combined approach targeting several facets (eg, inhibitory tone, acquired ion channelopathies) of a hyperexcitable network. It seems that more work needs to be done. Perhaps "one out of three ain't bad" after all.

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