Journal Club

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Stroke Primes New Hippocampal Neurons for Hyperexcitability

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Review of Ceanga et al.

New neurons are produced in the hippocampal dentate gyrus throughout adulthood in rodents (for review, see Gonçalves et al., 2016; Toda et al., 2019) and likely in humans (Boldrini et al., 2018; cf. Sorrells et al., 2018). Although the total number of adult-born granule cells in the rodent dentate is small relative to the number born during nervous system development, nascent neurons have unique properties that might allow them to disproportionately influence hippocampal function. For example, newborn neurons are highly excitable and exceptionally plastic in structure and synaptic function (Ming and Song, 2011). These features likely underlie the ability of new granule cells to preferentially become incorporated into behaviorally relevant circuits relative to older neurons (Ramirez-Amaya et al., 2006). In addition, young neurons can modulate overall activity of the dentate gyrus by inhibiting mature granule cells via inhibitory interneurons (Ikrar et al., 2013; Drew et al., 2016). Given the unique attributes of new neurons, it may be unsurprising that neurogenesis has been im-

plicated in learning and memory, mood, and neurologic disease (Toda et al., 2019).

Newborn granule cells progress through a stereotyped pattern of development characterized by changes in morphology, physiology, and gene expression. They are generated by neural stem cells in the subgranular zone (SGZ) and then migrate into the nearby granule cell layer. Over subsequent weeks, immature granule cells extend neurites, form synapses, and integrate into existing circuitry. These developmental processes are sculpted by many factors. For example, environmental enrichment and wheel running enhance the rate of hippocampal neurogenesis, modify the morphology and connectivity of newborn neurons, and are associated with improved spatial learning (Kempermann et al., 1997; Gonçalves et al., 2016; Toda et al., 2019). In contrast, aging diminishes neurogenesis, contributing to impaired cognition (van Praag et al., 2005; Toda et al., 2019). Neurologic diseases such as stroke and seizures dramatically increase the production of new neurons in the SGZ, but how the hippocampal neurogenic response influences disease outcome, positively or negatively, is incompletely understood.

A recent study by Ceanga et al. (2019) examined how ischemic stroke influences the electrophysiological development of newborn dentate neurons using double-cortin-dsRed mice in which a fluorescent protein labels immature neurons. The electrophysiological properties of imma-

ture (dsRed⁺) and mature (dsRed[−]) granule cells were assessed using whole-cell patch-clamp recordings in slices taken 2 weeks after sham or transient middle cerebral artery occlusion procedures. This stroke model, reflecting most strokes in humans, damages cortex and striatum, but does not directly affect the hippocampus. By birth-dating new cells with bromodeoxyuridine (a thymidine analog), the authors estimated that ~60% of recorded dsRed⁺ cells were born after experimental stroke.

Maturation of granule cells is characterized by changes in passive membrane properties. A comparison of intrinsic physiological parameters between new and mature granule cells in sham-operated animals revealed several correlates of maturation: relative to mature neurons, immature neurons had higher input resistance, greater capacitance, a more depolarized resting potential, and a longer membrane time constant. Remarkably, experimental stroke altered intrinsic properties in a subset (~25%) of immature neurons, such that they resembled mature granule cells. This suggests that stroke accelerates maturation of intrinsic physiological properties in some newborn granule cells.

Excitability of new neurons also changes considerably with maturation. Synaptic input, as measured by the amplitude of EPSCs, is typically lower in immature granule cells than in mature granule cells. Surprisingly, experimental stroke increased the

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amplitude, but not frequency, of spontaneous and miniature EPSCs in immature neurons. Excitatory input to mature granule cells was not affected. Thus, immature granule cells receive unusually large excitatory input after stroke, perhaps because of an increase in the number of postsynaptic receptors.

Intrinsic properties of immature dentate granule cells make them hyperexcitable relative to their mature counterparts, in part to compensate for typically low excitatory drive (Ming and Song, 2011; Toni and Schinder, 2015). Normally, intrinsic and synaptic excitability of new neurons change in coordination. Specifically, high intrinsic excitability offsets low synaptic drive early in development, but as synaptic drive increases with maturation, intrinsic excitability reciprocally decreases. However, Ceanga et al. (2019) found that experimental stroke uncouples this process. Despite receiving large excitatory inputs after stroke, young granule cells continued to exhibit features of hyperexcitability, such as low rheobase (the minimum current needed to evoke an action potential). Thus, stroke results in the accelerated development of intrinsically hyperexcitable new granule cells that receive unusually large excitatory inputs; a recipe for hyperexcitability within hippocampal circuits.

In addition to the aberrant electrophysiological development of new dentate granule cells described by Ceanga et al. (2019), stroke can alter the morphology of new neurons. Previous studies of newborn granule cells after focal ischemia induced by cortical photothrombosis or transient middle cerebral artery occlusion (Niv et al., 2012; Woitke et al., 2017) found that up to 10% of new neurons had abnormal morphology 6–7 weeks post-ischemia. These abnormalities included dendritic arbors extending toward the hilus and, after larger middle cerebral artery-induced lesions, ~3% of new neurons ectopically positioned within the hilus, indicating an abnormal migratory path. Furthermore, experimental stroke increased spine density on new granule cells compared with developmentally- and adult-born granule cells in sham-operated controls. Along with Ceanga et al. (2019), these studies demonstrate that experimental stroke causes abnormalities in some new neurons. Still, the functional implications of these abnormalities are unclear.

Studies of aberrant hippocampal neurogenesis after seizures might provide insight on the consequences of stroke-induced alterations of new granule cells.

In animal models of seizures and epilepsy, SGZ cell proliferation is drastically increased, but new neurons are frequently ectopically positioned, overly excitable, and have abnormal patterns of connectivity that potentiate excessive circuit excitability (Parent et al., 1997; Jessberger and Parent, 2015). There is evidence for similar abnormalities in human epilepsy (Parent et al., 2006). Importantly, inhibiting neurogenesis in a rodent model of epilepsy reduces chronic recurrent seizures and ameliorates epilepsy-associated cognitive deficits (Cho et al., 2015). Together, these data indicate that seizure-induced alterations of neurogenesis are pathological, and provide evidence that the effects of stroke on new hippocampal neurons may be also be harmful.

Augmented hippocampal neurogenesis after stroke might be a compensatory response, but the pathological environment could cause abnormalities. An important function of young granule cells is the inhibition of mature dentate granule cells (Ikhar et al., 2013; Drew et al., 2016). Because epilepsy and stroke can cause hyperactivity within hippocampal circuits, increased neurogenesis after these events might help to reduce this hyperactivity by increasing the number of neurons capable of driving local inhibition. However, because development of new neurons is shaped—sometimes aberrantly—by local activity, the very pathological activity that stimulated the birth of new neurons might cause them to become primed to perpetuate circuit hyperexcitability.

Does the hippocampal neurogenic response affect stroke outcome? Whereas the arrest of neurogenesis before experimentally induced epilepsy impedes the development of chronic seizures (Cho et al., 2015), a similar manipulation before stroke exacerbates cognitive deficits (Sun et al., 2013). One interpretation of these data is that continued or enhanced hippocampal neurogenesis supports some aspects of hippocampal function, but aberrant morphological and electrophysiological development of new granule cells detracts from the benefits of neurogenesis, potentiates the development of new pathologies (e.g., poststroke seizures), or exacerbates circuit hyperexcitability. Therefore, specifically blocking the abnormal development of new granule cells might be a therapeutic avenue.

The mechanisms underlying stroke-induced alterations of neurogenesis likely involve changes in molecular cascades and activity-dependent systems. The Shh, Notch, bone morphogenetic protein, and

Wnt pathways are key regulators of neurogenesis (Ming and Song, 2011; Gonçalves et al., 2016). Ischemia activates gene expression programs involving these signaling systems and can preferentially affect these pathways within neurogenic regions (Liu et al., 2007). For example, experimental stroke upregulates a circulating isoform of vascular endothelial growth factor that permeates the unusually leaky blood–brain barrier characteristic of neurogenic regions (Lin et al., 2019). This leads local endothelial cells to increase Notch signaling that stimulates neurogenesis (Lin et al., 2019). In addition, granule cell development is regulated by activity-dependent mechanisms, especially NMDA receptor-mediated input. For instance, NMDA receptor knock-out in immature granule cells dramatically reduces their survival and causes morphological abnormalities, such as reduced spine density (Tashiro et al., 2006; Mu et al., 2015). Increased spine density on new granule cells after stroke (Niv et al., 2012) might reflect unusually high NMDA receptor activation due to circuit hyperactivity. Excessive NMDA receptor activation may also contribute to the increased EPSCs observed in new neurons after experimental stroke due to postsynaptic receptor insertion (Ceanga et al., 2019).

The study by Ceanga et al. (2019) describes the production of new, abnormally hyperexcitable granule cells after experimental stroke. The next crucial question to be answered is whether aberrant poststroke neurogenesis affects hippocampal function, such as by contributing to stroke-induced cognitive deficits or seizures. Another uncertainty concerns whether neurogenesis is altered permanently by stroke, or if the generation of abnormal granule cells is temporally restricted to a cohort of neurons born near the time of stroke. The availability of techniques that allow for imaging or temporally controllable tagging and manipulation of adult-born neurons (Anacker et al., 2018; Huckleberry et al., 2018) provides a way to answer these questions.

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