CellPress

Neuron

Previews

GABAergic Interneurons Control Adult Neurogenesis but Astrocytes Have the Last Word

Mariela F. Trinchero[1] and Alejandro F. Schinder[1,*]
[1]Laboratorio de Plasticidad Neuronal, Fundación Instituto Leloir–Instituto de Investigaciones Bioquímicas de Buenos Aires–Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Av. Patricias Argentinas 435, Buenos Aires C1405BWE, Argentina
*Correspondence: aschinder@leloir.org.ar
https://doi.org/10.1016/j.neuron.2020.09.041

Adult neurogenesis depends on the decision of neural stem cells to leave quiescence and become neurons. In this issue, Asrican et al. show that the neuropeptide cholecystokinin released by interneurons promotes the neuronal fate through astrocytic signaling.

The dentate gyrus of the hippocampus contains radial-glia-like neural stem cells (rNSCs) that give rise to functional neurons throughout the entire lifespan. Host circuits continuously integrate new dentate granule cells (GCs) that impose substantial remodeling involving synapse formation and elimination, activity-dependent competition, and modifications in the balance between excitation and inhibition (Sailor et al., 2017). Thus, neurogenesis changes the manner in which information is processed because the remodeled network may provide new solution outputs to a given input. This remarkable type of plasticity was shown to influence several functions that rely on the hippocampus, including the discrimination of spatial contexts associated with positive or negative rewards, detection of novel features in a familiar environment, resilience to stress and depression, and the ability to forget old memories (Toda et al., 2019). The transformation of rNSCs into neurons is sensitive to regulatory factors that may respond to behavior, aging, or pathological conditions. Regulation may occur at the decision to leave quiescence, the rate at which progenitor cells multiply, or at later points along the pathway that ends with a fully integrated neuron. In general, an increase in physical or cognitive activity and social interaction drives neurogenesis forward, whereas isolation, stress, or aging tend to put the brakes on the process (Kempermann, 2015). All of these variables ultimately converge into different forms of local circuit activity that will impinge on the mechanisms involved in the neurogenic pathway.

Neurogenesis starts with rNSCs leaving quiescence. Once active, they may self-renew to replenish the population or become progenitor cells to produce neuroblasts. Why don't they leave quiescence all at once? What keeps them dormant, and what triggers their activation? There are different components in the hippocampal neurogenic niche that might act as sensors of circuit activity and deliver local cues. Neurons, glia, the vasculature, and axons from long-range projections might release neurotransmitters, modulators, or other factors that transduce information from the niche to rNSCs (Vicidomini et al., 2020). For instance, activation of parvalbumin-expressing GABAergic interneurons (PV-INs) in the dentate gyrus promotes quiescence of rNSCs by tonic GABA spillover from nearby synapses formed between the interneuron and neighboring GCs (Song et al., 2012). This finding indicates that increased circuit activity, in this case carried by GABAergic interneurons, will put the brakes on neurogenesis (Figure 1). This microcircuit is also controlled by long-range projections from the medial septum, which sends GABAergic afferents to contact PV-INs and modulate their firing rate (Bao et al., 2017). Interestingly, PV-INs are depolarized rather than inhibited by these GABAergic inputs. Therefore, activity in the medial septum promotes quiescence of rNSCs via GABA spillover, mediated by local PV-INs in the dentate gyrus.

The rNSC status is also controlled by glutamate. Excitatory hilar mossy cells contact local GABAergic interneurons and GCs and regulate rNSC state in a bimodal fashion. When moderately active, they elicit spiking of PV-INs and, consequently, promote rNSC quiescence via GABA. However, strong activity of mossy cells evokes direct release of glutamate onto rNSCs, which in turn exerts a proneurogenic effect (Yeh et al., 2018). One could then conclude that rNSCs sense glutamate and GABA levels as "go/no-go" signals.

But there is more to GABAergic inhibitory cells than PV-INs. Cholecystokinin (CCK)-expressing interneurons (CCK-INs) co-release GABA and the neuropeptide CCK, and even though there is a high density of CCK receptors in the dentate gyrus, its putative role in the regulation of adult neurogenesis has remained unclear. Asrican and colleagues decided to investigate whether CCK-INs make an additional contribution to the machinery that senses hippocampal activity to influence fate decisions of rNSCs (Asrican et al., 2020). In their work, a number of genetically modified mice and associated adenoviral vectors (AAVs) were combined to manipulate the activity of restricted cell types in the adult dentate gyrus and determine their impact on rNSC fate. Initially, a CCK-cre::Nestin-GFP mouse was used to deliver the floxed excitatory synthetic receptor hM3Dq to CCK-INs using an AAV. Whole-cell recordings were performed in nestin^{+} rNSCs to monitor changes in their membrane potential when CCK-INs were acutely activated by the synthetic ligand clozapine-N-oxide (CNO) in hippocampal slices. Activation of CCK-INs triggered a depolarizing signal in rNSCs that was blocked by an

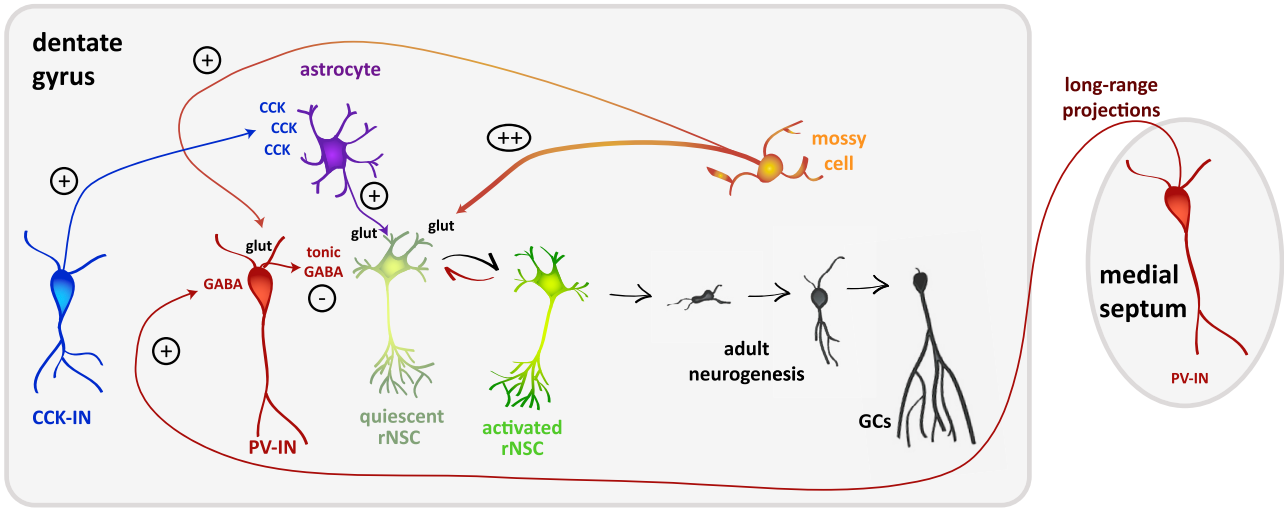

Figure 1. Roadmap to rNSC Activation

Local PV-INs (red) in the dentate gyrus promote quiescence of rNSCs (green) by GABA spillover (Song et al., 2012). PV-INs residing in the medial septum depolarize local PV-INs in the dentate gyrus, also maintaining the quiescent status in an indirect manner (Bao et al., 2017). Activation of ipsi- or contralateral mossy cells (orange) in a moderate manner (+) converges in the same indirect pathway mediated by PV-INs, while strong activation (++) of mossy cells triggers proliferation through the action of glutamate (Yeh et al., 2018). CCK-INs (blue) shift the balance toward the neurogenic pathway by their action on local astrocytes that also release glutamate onto rNSCs (Asrican et al., 2020). (–) denotes a signal promoting quiescence; (+) indicates activation.

antagonist of CCK2 receptors and was mimicked by local perfusion of the neuropeptide CCK8.

The depolarizing action of CCK8 was prevented by glutamate but not GABA receptor antagonists, suggesting that CCK does not signal directly, but it may require glutamate release onto rNSCs by other players in the circuit. The authors hypothesized that mossy cells or GCs might be responsible for this signal. They performed calcium imaging to study how their activity responded to the activation of CCK-INs using hM3Dq. Mossy cells showed decreased levels of activity that were mediated by both CCKRs and $GABA_A$Rs. Similar inhibitory signals were found in GCs, demonstrating that neither of these neuron types were involved in the rNSC depolarization by CCK-INs. They reasoned that reducing the level of inhibition might be an alternative pathway to enhance glutamate signaling in the dentate gyrus. However, the firing rate in PV-INs was increased upon activation of CCK interneurons, which would eventually reduce, rather than enhance, glutamate release from excitatory neurons.

Because astrocytes secrete glutamate, they could also be putative candidates for the glutamate-mediated depolarization observed in rNSCs. Using calcium imaging, Asrican and colleagues found that CCK increased the frequency of calcium spikes in astrocytes in a manner that required CCKRs and was mimicked by local perfusion of CCK8. Moreover, direct activation of astrocytes by the synthetic receptor hM3Dq elicited depolarization of rNSCs that was blocked by GluR antagonists. In accordance with these observations, loading astrocytes with the calcium chelator BAPTA or with fluorocitric acid, a metabolic inhibitor, prevented CCK-mediated depolarization of rNSCs, implicating them as mediators of the CCK signal (Figure 1).

After thoroughly dissecting the circuits that connect CCK-INs with rNSCs, the authors showed that CCK release recruits the ERK pathway in rNSCs, which promotes their activation. Conversely, reducing CCK levels in the dentate gyrus using short hairpin RNAs (shRNAs) also decreases rNSC activation and proliferation, ultimately impinging on the number of new GCs. Finally, they show that downregulating CCK is associated with the induction of reactive astrocytes and expression of several transcripts related to neuroinflammation and neuropathological conditions. This change in the gene expression profile might lead to decreased proliferation of rNSCs and an overall reduction in the rate of adult neurogenesis.

GABAergic interneurons as a whole seem to play antagonistic roles in the regulation of rNSCs. Activation of PV-INs decreases the rate of neurogenesis by imposing a strong GABA tone and keeping rNSCs in their quiescent stage. In contrast, CCK-INs promote the neurogenic pathway by release of CCK, acting indirectly on local astrocytes. Intriguingly, the CCK neuropeptide also increases firing rate of PV-INs, which would cause a negative feedback loop on its own effect, putting the brakes on neurogenesis. This apparent contradiction might be reconciled by viewing it as a parallel to excitation and inhibition, which converge in most neurons and elicit an outcome (spiking or not) determined by the balance and timing of these antagonistic signals. This balance rules the function of each neuron in a network.

The decision of rNSCs to remain quiescent or move toward the neuronal fate depends on the integration of multiple intrinsic and extrinsic cues. Electrical activity with distinct features encoded in the frequency and duration of spike trains, origin of the inputs (type of neuron), or metabolic state might result in different decisions over rNSC fate. For example, both physical exercise and exploration of an enriched environment boost the electrical activity in the dentate gyrus,

yet only exercise increases proliferation of rNSCs (Kempermann, 2015). The complexity of this regulation seems to be overridden under conditions of pathological activity such as epileptic seizures, which result in massive proliferation of progenitor cells and ectopic neuronal migration (Jessberger and Parent, 2015). Conversely, aging reduces overall neurogenesis by altering the niche at the level of cell-cell interactions, neurotrophic signaling, and overall activity and also by affecting intrinsic cell properties like oxidative stress and metabolism (Fan et al., 2017). Understanding the mechanisms underlying the transitions from dormant rNSCs to mature GCs is critical to harness neurogenesis as a strategy to enhance circuit plasticity in the senescent brain and to promote repair in neurological disorders.

REFERENCES

Asrican, B., Wooten, J., Li, Y.-D., Quintanilla, L., Zhang, F., Wander, C., Bao, H., Yeh, C.-Y., Luo, Y.-J., Olsen, R., et al. (2020). Neuropeptides Modulate Local Astrocytes to Regulate Adult Hippocampal Neural Stem Cells. Neuron *108*, 1–18.

Bao, H., Asrican, B., Li, W., Gu, B., Wen, Z., Lim, S.A., Haniff, I., Ramakrishnan, C., Deisseroth, K., Philpot, B., and Song, J. (2017). Long-Range GABAergic Inputs Regulate Neural Stem Cell Quiescence and Control Adult Hippocampal Neurogenesis. Cell Stem Cell *21*, 604–617.

Fan, X., Wheatley, E.G., and Villeda, S.A. (2017). Mechanisms of Hippocampal Aging and the Potential for Rejuvenation. Annu. Rev. Neurosci. *40*, 251–272.

Jessberger, S., and Parent, J.M. (2015). Epilepsy and Adult Neurogenesis. Cold Spring Harb. Perspect. Biol. *7*, a020677.

Kempermann, G. (2015). Activity Dependency and Aging in the Regulation of Adult Neurogenesis. Cold Spring Harb. Perspect. Biol. *7*, a018929.

Sailor, K.A., Schinder, A.F., and Lledo, P.M. (2017). Adult neurogenesis beyond the niche: its potential for driving brain plasticity. Curr. Opin. Neurobiol. *42*, 111–117.

Song, J., Zhong, C., Bonaguidi, M.A., Sun, G.J., Hsu, D., Gu, Y., Meletis, K., Huang, Z.J., Ge, S., Enikolopov, G., et al. (2012). Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. Nature *489*, 150–154.

Toda, T., Parylak, S.L., Linker, S.B., and Gage, F.H. (2019). The role of adult hippocampal neurogenesis in brain health and disease. Mol. Psychiatry *24*, 67–87.

Vicidomini, C., Guo, N., and Sahay, A. (2020). Communication, Cross Talk, and Signal Integration in the Adult Hippocampal Neurogenic Niche. Neuron *105*, 220–235.

Yeh, C.Y., Asrican, B., Moss, J., Quintanilla, L.J., He, T., Mao, X., Cassé, F., Gebara, E., Bao, H., Lu, W., et al. (2018). Mossy Cells Control Adult Neural Stem Cell Quiescence and Maintenance through a Dynamic Balance between Direct and Indirect Pathways. Neuron *99*, 493–510.e4.

Probing Olfaction in Space and Time

José Esquivelzeta Rabell[4] and Sebastian Haesler[1,2,3,4,*]
[1]VIB, 3001 Leuven, Belgium
[2]Imec, 3001 Leuven, Belgium
[3]KU Leuven, Department of Neuroscience, Research Group Neurophysiology, 3000 Leuven, Belgium
[4]Neuroelectronics Research Flanders, 3001 Leuven, Belgium
*Correspondence: sebastian.haesler@nerf.be
https://doi.org/10.1016/j.neuron.2020.10.007

In this issue, Gill et al. apply holographic optogenetic stimulation in the olfactory bulb to control select neuronal ensembles in 3D. This approach allows them to dissociate the contribution of temporal spike features and spike rate to stimulus detection.

The ability to detect volatile chemicals in the environment is critical for survival in many animal species. Odorant detection involves the transformation of chemical signals into spatiotemporal patterns of neural activity in olfactory sensory areas. In the first step of this process, inhalation carries airborne odorant molecules into the nasal cavity, where they bind olfactory receptors of the nasal epithelium. The axons from each receptor cell expressing the same olfactory receptor projects to one or two olfactory glomeruli, where they connect to the dendrites of excitatory mitral and tufted (M/T) cells, the major output projections of the olfactory bulb (OB). In rodents, the sense of smell has evolved to be exquisitely sensitive. Mice have been trained in the laboratory to reliably detect one in 1 billion molecules (Williams and Dewan, 2020). How can the nervous system perform such sensitive detection, and what determines perceptual detection thresholds?

M/T cells increase their spike rates in response to olfactory stimulation. Moreover, distinct temporal spike patterns, related to respiration and behavioral performance, have been observed in M/T cells (Cury and Uchida, 2010; Shusterman et al., 2011), suggesting the temporal coordination of spikes is critical for olfactory computations. Dissociating the contribution of spike timing and spike rates in psychophysical paradigms is experimentally challenging. Even precisely timed delivery of odorant stimuli can introduce signal fluctuations, which are difficult to differentiate from noise fluctuations intrinsic to the neural system.

In this issue of *Neuron,* Gill et al. (2020) develop a powerful optical approach to independently control the timing and spatial activation patterns of neurons in