A silver lining to stroke: does ischemia generate new cortical interneurons?

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New work identifies a latent population of neuronal progenitor cells in neocortical layer 1 of adult rats. These cells proliferate in response to forebrain ischemia, then integrate into the cortical network as interneurons.

The search for neurogenesis in the central nervous systems (CNS) of adult mammals has been long and controversial. Despite enormous efforts to detect it, in the normal CNS, there is little evidence for robust neurogenesis outside of the hippocampal subgranular zone (SGZ) and the forebrain subventricular zone (SVZ). In fact, although SVZ neurogenesis is present in rodents, it likely does not result in productive neurogenesis in the human brain[1]. Thus, it would seem that, except for a few notable exceptions, neurogenesis is not central to mammalian brain homeostasis. However, accumulating data suggest that brain damage can both enhance ongoing neurogenesis in known regions, such as the SGZ and SVZ, and activate latent neurogenesis elsewhere. For instance, under hypoxic/ischemic conditions in rats, the SVZ can redirect newborn neurons to sites of injury within the striatum[2]. Similarly, increased numbers of new hippocampal neurons are generated after seizures[3]. Even more tantalizing evidence comes from nonproliferative regions of the brain, as the neocortex appears to initiate a degree of reparative neurogenesis in response to the selective ablation of specific projection neurons[4].

Ohira *et al.*[5] in this issue now report another potential source of cortical neurons in the adult rodent brain. Surprisingly, these cortical progenitors seem to comprise a population that, during normal development, is largely if not completely generated in the subpallium. The authors found in the subpial zone of the adult rat neocortex a small number of dividing cells that until now have been largely overlooked. These cells have some characteristics of interneurons but not of glia (they express the GABA-synthetic enzyme GAD67 but not other neuronal markers). Tracing the fates of these cells with retroviruses injected into the subpial zone, the authors conclude that the cells do not generate new neurons in the brain under physiological conditions. However, after animals were subjected to a mild ischemic insult resulting from a 10-minute occlusion of both common carotid arteries, the dividing cells in the subpial zone accumulated through accelerated division and then migrated radially into deeper cortical layers (**Fig. 1**). On the basis of their morphology and marker expression, they seemed to differentiate into some form of GABAergic interneuron.

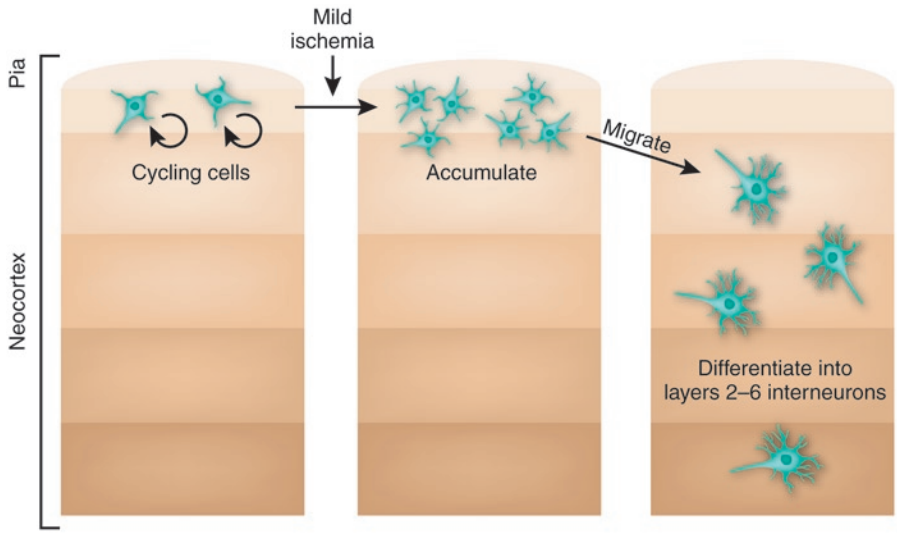

Figure 1 Transient ischemia stimulates proliferation and migration of interneuron precursors in the subpial region of the neocortex. Cycling cells reside in the subpial zone of the adult rat neocortex (left). Some of these express GAD67. After a transient episode of global forebrain ischemia, these cells are stimulated to proliferate and migrate into the lower layers of the cortex (middle). Finally, these precursors differentiate into GABAergic interneurons in layers 2–6 (right).

The authors speculate that these subpial interneuron precursors enter the cortex during the wave of interneuron migration from the ganglionic eminences into the embryonic neocortex and then do not fully differentiate. This inference is based on the expression of both Nkx2 and MafB in 80% of the cells they identified. These markers are associated with development of progenitors in the medial ganglionic eminence (MGE)[6,7], a region of the subpallium. (During normal development, the MGE produces the bulk of cortical interneurons.) Previous data have indeed hinted that such a population exists in human subpial cortex, at least during development[8]. Determining whether these GAD67$^+$ cells actually originate in the ventral forebrain awaits further study. Nonetheless, the mature populations resulting from these progenitors express markers associated with the MGE, consistent with their having some relationship with cells generated embryonically in the subpallium. Transplanted MGE cells show a greater propensity for robust migration in the postnatal brain than do progenitors from the lateral ganglionic eminence or neocortex[9], supporting the observations and speculations of Ohira *et al.*[5].

It is probably significant that Ohira *et al.*[5] used a far less destructive ischemic insult than many stroke models that result in tissue necrosis and eventual cavitation and scarring. The short period of ischemia apparently did not even result in any neuronal death, although it did cause

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increased and widespread proliferation of glia, including microglia and cells that express the NG2 proteoglycan and the Olig2 transcription factor, markers of glial precursor cells that can generate oligodendrocytes and some astrocytes after injury[10,11]. Identifying the signal(s) for subpial cell proliferation, migration and differentiation may ultimately be a rewarding project, and could inform potential therapeutic strategies designed to stimulate neurogenesis after hypoxia/ischemia. The activated microglial and astrocyte populations are likely sources of such factors, including monocyte chemoattractant protein-1, which is expressed by these cells after an ischemic insult, and which promotes neuroblast migration, interacting with its receptor, CCR2, on immature neurons[12].

All of these observations beg the question of whether the observed neurogenesis represents pathology itself or a reparative process initiated to compensate for ischemic damage. Indeed, is the generation of new interneurons beneficial, and if so, how? Of the various cortical neuronal populations, the large projection neurons are more sensitive to hypoxic/ischemic damage than are the interneurons. And yet, though the large projection neurons seem to be the population most in need of replacement, neurogenesis seemingly produces more interneurons. New interneurons might serve several purposes. First, they may protect projection neurons from further damage by hypoxic/ischemic events, either by secreting substances such as NPY and somatostatin that promote neuronal survival or by dampening excessive excitatory input that may cause neuronal death or seizures. Second, they may act to reroute information from projection neurons in damaged areas to neighboring areas that may have sustained less damage. That is, they might be able to reconfigure cortical circuits in beneficial ways. Whereas the authors provide some evidence that the ischemia-induced interneuron populations integrate into cortical circuits by demonstrating their expression of the immediate early gene product c-Fos, future studies should attempt more direct physiological measures of their function and should provide a more precise picture of their contributions to cortical networks. Assessment of their synaptic inputs and intrinsic physiological properties, as well as paired recordings with efferent synaptic partners[13], should all clarify whether these neurons functionally integrate into cortical networks. Until then, we can only speculate whether these new neurons have a positive effect on mild ischemic damage and contribute to the generally favorable clinical outcomes of patients enduring minor vascular accidents.

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A 'sustain pedal' in the hippocampus?

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A study reveals that a largely ignored cell type in the dentate gyrus, semilunar granule cells, are persistently depolarized after a transient input and recruit interneurons to regulate the gating of information into the hippocampus.

In our day-to-day lives, we rely on numerous temporary memory stores, often lasting seconds, for a wide variety of functions, such as performing mental calculations, remembering to turn the gas off and keeping track of which article in this journal we are reading. These memories need to be transient in comparison with longer-term memories such as memorizing the essential message of this article. This large capacity, but transient, store of accessible information has been likened to the "blackboard of the brain" and is termed working memory[1].

That working memory has a neural substrate has been established in experiments in which primates are trained to delay the execution of a movement until some time after a sensory cue[1]. A typical task consists of the animal observing food being placed into one of several wells (stimulus) that it subsequently has to retrieve. These delayed response trials are associated with sustained neuronal firing during the interval period and this has been proposed to be the correlate of working memory[2]. The ability of a network to maintain short-term increases in activity following an input is a common feature of sensory processing not only in the cortex, but also in the cerebellum[3].

The hippocampus and related structures of the medial temporal lobe have long been recognized as being critical for encoding long-term memory; more recent evidence, however, indicates that the medial temporal lobe is also necessary for the maintenance of working memory for novel items and associations[4]. But how do the medial temporal lobe and hippocampus sustain neuronal activity? The article by Larimer and Strowbridge[5] in this issue describes the behavior of a set of neurons in the dentate gyrus that can be likened to a 'sample and hold' circuit, providing an unexpected substrate for working memory.

Initial attempts to explain persistent activity following a stimulus centered on recurrent, reinforcing excitatory connections and both computational and experimental support for this exists in some systems[6]. However, there is growing evidence that persistent firing can also be maintained by the intrinsic properties of neurons themselves. In particular, certain neurons are intrinsically bistable and have, in effect, two resting membrane potentials (a relatively negative potential at around –70 mV and a potential around –50 mV close to firing threshold). Notably, a change of state in a few neurons (from down- to up-state) can drive other neurons in the network into an up-state; thus, bistable neurons can result in bistable networks[7]. Some neurons even have multiple stable states; layer V entorhinal cortex pyramidal cells can respond to consecutive transient stimuli with stable, graded changes in firing rates[8]. Bistable neurons are found in many cortical and subcortical structures, but are relatively rare overall in the mammalian CNS.

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