# Neurogenesis and Stroke

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**Abstract:** Stroke stimulates neurogenesis in select regions of the adult brain, and the newborn neurons that result can migrate to areas of ischemic injury, where they may have the capacity to enhance brain recovery. These observations suggest that stroke-induced neurogenesis may contribute to endogenous brain repair after stroke, and that the mechanisms that underlie neurogenesis may represent potential therapeutic targets. Alternatively, transplantation of exogenously derived neural cells might also be an approach to the treatment of stroke.

**Keywords:** Stroke, ischemia, neurogenesis, proliferation, migration, differentiation.

## INTRODUCTION

Acute brain disorders, including those due to ischemia, trauma or infection, present special difficulties for research on treatment. Unlike chronic, neurodegenerative disorders, these acute conditions progress rapidly from onset to maximal impairment, providing little or no time to institute therapy that will prevent progression. This means that efforts to intervene after brain damage has been inflicted become increasingly important. In the case of ischemia, the brain is affected in two clinical settings. One is cardiac arrest and other hypoperfusion states, which produce global brain ischemia leading to death of selectively vulnerable neuronal populations, such as those in the CA1 sector of the hippocampus. The other is stroke, which results from occlusion of a cerebral blood artery or, less commonly, vein, causing pancellular death in a restricted region of the brain and corresponding focal symptoms and signs.

Current treatment for stroke is focused on preventive measures and, in a relatively small proportion of cases, acute interventions to limit the size of the infarct [1] (Fig. **1**). Preventive measures like treatment of underlying hypertension have reduced the incidence of stroke over the past half-century, and other therapies, such as administration of antiplatelet drugs and statins, have also been beneficial. Depending on the nature and location of vascular occlusion, i.e., whether it is cardioembolic in origin or affects the extracranial carotid circulation, anticoagulants or carotid endarterectomy can be helpful. Thrombolytic drugs have been the principal new advance in treatment, but their use may be complicated by hemorrhage, and the therapeutic window of opportunity is only a few hours after the onset of symptoms.

Notwithstanding the successes enumerated above and increased reliance on technologically advanced stroke care units, a substantial number of patients are left with persistent neurological deficits after stroke, such as hemiparesis, hemisensory deficits, language disturbances and visual field defects. The resulting functional impairments account for the fact that many survivors of stroke end up in nursing homes or otherwise fail to maintain their independence. This is a major human and economic problem.

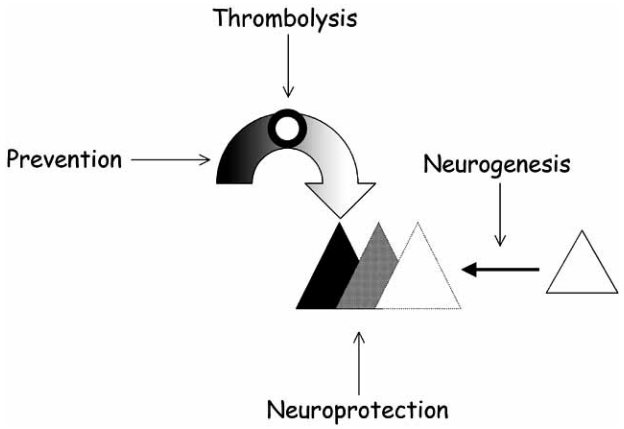


**Fig. (1).** Potential therapeutic targets in stroke.

In this regard, it is encouraging that there is evidence for a capacity of the brain to achieve some degree of self-repair and for endogenous mechanisms that may be involved in this process. The natural history of stroke is associated with spontaneous improvement over the weeks to months following stroke in most patients, although the ultimate extent of improvement is variable, and often incomplete [2]. Nevertheless, the fact that it occurs at all tells us that brain dysfunction manifested in the early post-stroke period is not fixed, and this suggests that it may respond to therapeutic interventions.

Stroke patients are likely to improve through a range of processes that begin at the onset of ischemia and continue for extended periods. Most of what we know about these processes comes from studies of experimental stroke in rodents and, less commonly, in nonhuman primates [3]. Ischemic brain cells (and these include all cell types—neurons, astrocytes, oligodendrocytes, endothelial cells, and others—although neurons have been studied most exhaustively) activate genetic programs that promote their survival, involving, for example, the synthesis of antiapoptotic proteins. Inflammatory cells are mobilized, and endothelial cells are stimulated to proliferate as part of an angiogenic response that helps to restore blood flow. Neurogenesis, which produces new neurons that may have

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the potential to restore brain function, is triggered. Surviving neurons sprout new processes, or neurites, elaborate new synapses, and make new interneuronal connections. Physical therapy and other rehabilitative strategies may operate through these processes, and drugs like amphetamine appear to act in a like manner after completed stroke, but there has been comparatively little research focused on stroke treatment in the chronic phase of the disease.

The most attractive target for pharmacological treatment of stroke has been the intra- or immediate post-ischemic period, partly because of the relative ease with which this period can be studied in the laboratory. Some candidate treatments identified in this manner have proved useful (e.g., thrombolytics), whereas others (e.g., excitatory amino acid antagonists) have not. In the latter case, though, the reasons for this disparity may have more to do with the manner in which clinical translation was attempted than in the soundness of the underlying basic research. This issue is still disputed. Another approach that may prove beneficial in acute stroke is induced hypothermia.

## ADULT NEUROGENESIS AND STROKE

It is now well known that new neurons, glia and endothelial cells continue to be produced in the adult brain, well beyond the primary developmental period. This phenomenon has potential implications for neurological disease in general, because it suggests that mechanisms are in place that, if made to function optimally, might assist in recovery. In addition, many but not all brain disorders appear to further stimulate adult neurogenesis, which has been interpreted as an endogenous mechanism for brain repair. Of course, spontaneously occurring, injury-induced neurogenesis is insufficient to fully reverse disease pathophysiology, as is evidenced by the persistence (as in stroke) or even progression (as in Alzheimer's disease) of symptoms, but this does not mean that injury-induced neurogenesis has no function. One question we might ask is whether the ultimate severity or rate of progression in these disorders might be greater in the absence of constitutive neurogenesis, and some studies suggest that it might. Another question is whether it might be possible to harness and improve upon this endogenous repair process as a therapeutic strategy.

Certain features of adult neurogenesis may be especially important in the context of stroke. The first is that neurogenesis declines with advancing age [4], which suggests that disorders which tend to affect the elderly, including stroke, may be relatively refractory to whatever beneficial effects neurogenesis might confer. However, at least in experimental animals, the aged brain retains the capacity to respond to physiological regulators (such as growth factors) and disease processes (such as stroke) with increased neurogenesis. In fact, in some cases, this response may be greater (relative to basal levels of neurogenesis) than is observed in the young brain.

Another property of adult neurogenesis that may be crucial to consider vis-à-vis stroke is its facality. Because stroke, by definition, is also focal, it follows that sites of injury may be remote from sites at which new neurons are manufactured. This means that the injury signal transmitted from ischemic to neuroproliferative regions of the brain must be conveyable over substantial distances, and that new neurons produced in response to this signal must be capable of long-range migration within the brain. There is evidence that both are the case. First, even small infarcts that clearly spare the canonical adult neuroproliferative zones (hippocampal dentate gyrus and rostral subventricular zone) stimulate neurogenesis, especially in the subventricular zone [5]. Second, young neurons can be seen in the region surrounding cortical strokes in both experimental rodents [6] and human stroke patients [7]. Therefore, distance alone does not seem to be an insurmountable obstacle to neurogenesis-based repair of ischemic lesions.

A third issue that bears on the potential of neurogenesis to improve outcome after stroke relates to the quantity and diversity of neuronal (and other cellular) loss in this disease. Strokes can affect substantial fractions of the total brain volume, and involve many billions of neurons. Moreover, these neurons are not all alike. They include both local interneurons and projection neurons that provide connectivity at a distance, as well as neurons with a variety of neurotransmitter phenotypes. Thus, one obvious challenge in stroke, as opposed to disorders (e.g., Parkinson's disease) that affect more restricted neuronal populations and spare non-neuronal cells, is whether a broad enough range of new cell types can be generated post-injury to restore function, even partially. It may not be necessary to achieve quantitative neuronal replacement, since we know that some patients return to almost normal function after stroke despite large, permanent lesions seen by imaging or at autopsy, and because in degenerative neurological disorders like Parkinson's disease, symptoms do not appear until the great majority of susceptible neurons are lost. In addition, it may be possible to restore function to some extent by bypassing premorbid neuronal circuitry with less complex interconnections.

Finally, although stroke affecting the cerebral cortex or striatum triggers neurogenesis in rodents and humans, the neurogenesis response to stroke in other locations has not been characterized. Stroke affecting the brainstem or cerebellum, for example, is even more distant from the subventricular zone than is striatum or cortex, and it is possible that the greater distance involved exceeds that over which the necessary signaling mechanisms can operate.

## PRINCIPLES OF STROKE-INDUCED NEUROGENESIS

### Stroke and Neuroproliferation

The idea that stroke might induce neurogenesis arose from previous studies demonstrating injury-induced neurogenesis in other settings. These include excitotoxic damage to the dentate gyrus [8], epilepsy [9], and targeted ablation of corticothalamic neurons [10]. Later, Liu and colleagues [11] showed that global forebrain ischemia, which affects preferentially the CA1 region of hippocampus, enhances dentate neurogenesis. Each of these examples, except corticothalamic neuronal injury, involves a pathological process that also affects the neuroproliferative zone that responds to the injury, specifically the dentate gyrus. This raises a question as to whether injury at a site distant from the proliferative zones can also trigger neurogenesis. Middle cerebral artery occlusion in the mouse or rat produces cortical and striatal ischemia, but spares both

the dentate gyrus and subventricular zone, providing a system in which to address this issue. Gu and colleagues [12] first showed that focal cerebral ischemia, which they produced by photocoagulation of small cortical vessels, increased neurogenesis, as evidenced by the appearance of cells that incorporated bromodeoxyuridine (indicating that they were the product of recent cell division) and NeuN (indicating neuronal lineage). Jin and colleagues [12] showed subsequently that middle cerebral artery occlusion increases neurogenesis in both the dentate gyrus and subventricular zone, and that this affects not only the hemisphere ipsilateral to ischemia, but also the contralateral hemisphere, albeit to a lesser extent. Several groups have reported similar findings, although not all have observed a bilateral effect. A massive infarct is not necessary to stimulate neurogenesis, as smaller infarcts, such as those produced by intracerebal injection of endothelin-1, are also effective [5]. In fact, even ischemic preconditioning following transient middle cerebral artery occlusion of insufficient duration to cause a stroke also enhances subventricular zone neurogenesis [13]. From all of these studies we can conclude that cerebral ischemia, even at distant and perhaps contralateral locations, provides a stimulus to neurogenesis, and that sublethal ischemia is sufficient to do so. Possible mediators of stroke-induced neuroproliferation (Fig. **2**) include a variety of growth factors that can stimulate neurogenesis when administered *in vivo* (reviewed in [14]), such as epidermal growth factor, erythropoietin, fibroblast growth factor-2, granulocyte colony-stimulating factor, stem-cell factor, heparin-binding epidermal growth factor and vascular endothelial growth factor. These factors could be released from ischemic brain tissue and reach the subventricular zone by entry into the cerebrospinal fluid, but such a route is speculative. Interruption of neuronal pathways by stroke might also provide a trigger to neurogenesis, as has been shown to occur when the perforant path from entorhinal cortex to dentate gyrus is lesioned.

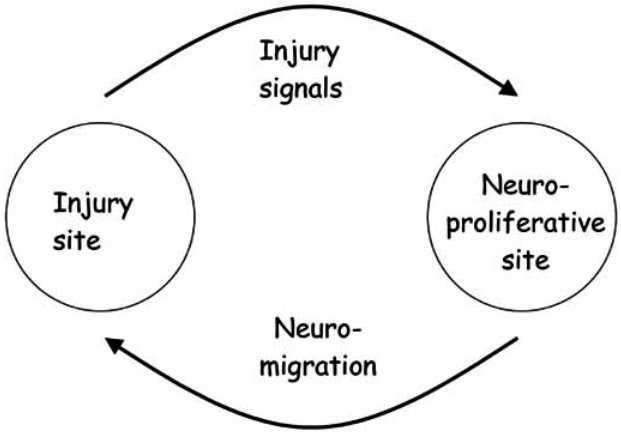


**Fig. (2).** Simplified scheme for injury- (including stroke-) induced neurogenesis. Brain injury triggers signals that stimulate neurogenesis in distant, neuroproliferative sites. Neurons arising at these sites, in turn, migrate to the site of injury.

### Stroke and Neuromigration

One of the most extensively studied aspects of developmental neurogenesis is the transit of newborn neurons from their birthplace to their final locale, which occurs through a combination of radial and tangential migration. An intriguing feature of injury-induced adult neurogenesis is that it is also associated with neuronal migration, and that in many instances, this migration involves homing of newborn neurons to sites of injury. Arvidsson and colleagues [6] demonstrated migration of newborn neurons from the subventricular zone into the adjacent striatum after middle cerebral artery occlusion, and migration to the ischemic striatum, cortex or both has been confirmed by several groups. Newborn neurons are generally detected in the ischemic penumbra rather than the core, although whether they never reach the core, or enter the core only to die in a toxic environment there, is unclear. Thus, ischemia-induced neurogenesis appears to be coupled to an intrinsic mechanism for targeted migration (Fig. **2**). What that mechanism might be is less clear, but is likely to involve both diffusible guidance molecules such as trophic factors or chemokines, and extracellular matrix components that delineate pathways for migrating cells to follow. For example, one candidate mediator that has been studied at some length is the α-chemokine, stromal cell-derived factor 1α, which interacts with the chemokine receptor, CXCR4 [15].

### Stroke and Neuronal Function

Several studies have demonstrated neuronal function in progeny of adult neurogenesis. In ischemia affecting the striatum [16], new neurons migrating into the striatum differentiate towards a phenotype resembling that of the dead or injured cells. Whether these new neurons integrate into the surviving brain circuitry and function normally is unclear. The contribution of neurogenesis to functional recovery from brain injury is difficult to ascertain, because treatments that stimulate neurogenesis may have additional effects on cell function. However, blocking neurogenesis with cranial x-irradiation in gerbils impairs recovery from global cerebral ischemia [17] and recovery of learning and memory function in rats after global ischemia is temporally associated with the reappearance of hippocampal CA1 neurons [18], which may imply that neurogenesis contributes to recovery. In some cases, injury-induced neurogenesis could have detrimental effects. For example, neurogenesis induced by seizures (and conceivably by other factors) may be associated with epileptogenesis due to the incorporation of newborn cells into aberrant hippocampal networks [9], although homeostatic mechanisms appear to exist which can promote adaptation of neuronal circuits to the presence of new neurons [19].

## NEUROGENESIS FROM EXOGENOUS SOURCES

Another approach to cell replacement for stroke is transplantation from exogenous sources [20]. Advantages include the ability to expand, differentiate and engineer cells, and deliver them to sites of injury. Transplantation of neuronal precursor cells can improve outcome from focal cerebral ischemia in rodents. Neuronally differentiated mouse embryonic stem cells transplanted into ischemic cortex or striatum of adult rat brain proliferate, continue to differentiate, and improve functional recovery [21]. Transplantation of neuronal precursor cells from embryonic day 14 rat hippocampus into ischemic rat striatum also

improves neurological function 8-12 weeks after middle cerebral artery occlusion [22]. Monkey embryonic stem cell-derived neuronal precursor cells transplanted into ischemic mouse striatum express mature neuronal markers and form projections to anterior thalamus and substantia nigra by 28 days [23].

Human neuronal precursor cells have also been transplanted into the brains of adult rodents with strokes. Chu and colleagues [24] used cells from 15-week human embryonic brains, which were given intravenously, 24 hours after transient middle cerebral artery occlusion. Transplanted cells (of which ~20% expressed neuronal markers) were present in the brain, especially in ischemic cortex and striatum, for at least 18 months. Compared to controls, transplant recipients showed decreased brain atrophy and improved performance on sensorimotor tests by about 3 weeks. Kelly and colleagues [25] performed 1-hour middle cerebral artery occlusions in rats who, 7 days later, received intracerebral injections of cells cultured from 16-20 week fetal human brain. Four weeks post-transplant, about one third of perilesional transplanted cells had survived. Roughly 50% of these expressed neuronal markers, and many migrated preferentially toward the ischemic lesion. Ishibashi *et al.* [26] administered neuronal precursor cells derived from human fetal brain into the caudate nucleus of Mongolian gerbils, 4 days after two 10-minute episodes of ischemia, separated by 5 hours, and induced by clip occlusion of the common carotid artery. By 4 weeks, about 7% of transplanted human cells had survived, most in the ischemic hemisphere. Of these, about one-third stained for the neuronal marker, NeuN. Infarct volume was reduced by about 25% in transplant recipients compared to controls. Transplant recipients also performed better on sensorimotor and cognitive tests. Finally, Chu and colleagues [27] gave human neuronal precursor cells cultured from 15-week embryonic brains to rats, 24 hours after 90-minutes of middle cerebral artery occlusion. In some cases, vascular endothelial growth factor was infused intravenously 24 hours later. Behavioral testing at 2-4 weeks showed improvement after cell administration, and more so when vascular endothelial growth factor was given as well. The same pattern was observed when brain atrophy was measured at 5 weeks.

## DRUG TARGETS

Current knowledge about physiological and pathological stimuli for neurogenesis suggests a variety of potential therapeutic targets (Fig. **3**). If we conceive of neurogenesis as involving neuroproliferation, neuromigration and neuromaturation, then any of these processes might be subject to manipulation. Many factors have been shown to stimulate neuroproliferation in adult rodent brain, and in some cases these are likely to affect other phases of neurogenesis as well. They include both chemical and environmental factors. For example, a wide range of growth factors [28] and many drugs in current clinical use [29], such as antidepressants, mood stabilizers, and drugs used to treat erectile dysfunction, can increase neurogenesis in the dentate gyrus, subventricular zone or both. These agents have the advantage that their use for other purposes is already approved and their general safety is established. Numerous growth factors also enhance neurogenesis, but their clinical application is less straightforward. In many cases this is because systemic administration is infeasible or potentially hazardous. In addition, the specific population of neuronal stem or progenitor cells affected by any of these agents is unclear. It may be, for example, that a given drug or growth factor targets a subpopulation of cells that is unsuitable for producing the kinds of neurons that need to be replaced after stroke. Environmental influences, such as the extent of environmental enrichment with toys, modify adult neurogenesis in rodents [30]. By analogy, a more stimulating environment could enhance neurogenesis in stroke patients and improve their recovery. Exercise also spurs neurogenesis, and this effect may contribute to the beneficial effects of physical therapy after stroke.

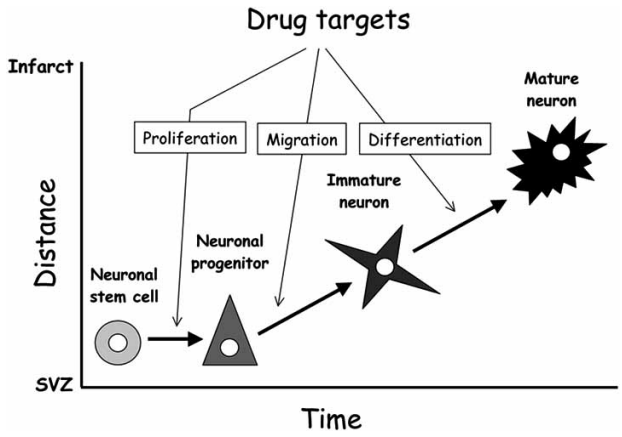


**Fig (3).** Phases of stroke-induced neurogenesis that might provide targets for therapy include neuronal proliferation, migration and differentiation to produce mature, functional neurons.

Targeting neuromigration might also potentiate post-stroke neurogenesis, although endogenous mechanisms appear to be capable of directing the migration of newborn neurons to sites of ischemic injury. Whether this can be improved upon is unclear. Interventions to enhance migration might require establishing a chemoattractive gradient by administration of an attractant substance into the ischemic lesion. Such a strategy might require a surgical approach, although it is possible that systemic administration could lead to preferential delivery of a chemoattractant agent to the ischemic brain because of its defective blood-brain barrier. It is also conceivable that a chemorepellent could be administered into the ventricular system and help to drive newborn neurons away from the adjacent subventricular zone.

Stimulating the maturation of newborn neurons to become fully mature, functional neurons might also be possible. Some of the factors that appear to contribute to this process, such as neuronal activity and neurotransmitters, are subject to modification by environment or drugs. As we learn more about how neuronal maturation, function and integration are regulated in the normal adult brain, this will suggest additional strategies.

## CONCLUSION

Brain injury of various kinds, including ischemic injury, stimulates the adult brain to produce more new neurons than

it normally does. This suggests that injury-induced adult neurogenesis might be a mechanism for endogenous brain repair, and that it might be amplified for therapeutic purposes. Experimental stroke increases neurogenesis, especially in the subventricular zone, and is associated with migration of newborn neurons to sites of ischemic injury. To what extent these new neurons enhance functional recovery from stroke is unclear. However, a long list of drugs, growth factors, hormones and other mediators can stimulate neurogenesis, as can environmental modifications. These findings raise the hope that such interventions might have therapeutic potential for patients who survive stroke but are left with significant neurological deficits in its aftermath. Much additional basic research is required to identify the most promising clinical strategies

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