# 19 Mechanism of Recovery After Stroke

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**Abstract**

Stroke is one of the biggest health problems in the world, especially considering the aging global population**.** Stroke causes diverse neurological sequelae, for which there is still no cure. In the clinic, it is not rare to see patients showing improvement in their neurological sequelae several weeks or months after stroke compared with their status in the early post-stroke stages. These phenomena are thought to be associated with the natural recovery process after stroke. The exact mechanisms underlying this recovery process are not yet known, but several plausible mechanisms have been suggested. The first is synaptic plasticity, which occurs through the processes of axonal sprouting and synaptogenesis. These processes occur in the peri-infarct area of the brain, but can sometimes be seen in the contralateral hemisphere. The second mechanism is neurogenesis, which arises from endogenous neural stem cells in the subventricular zone and the dentate gyrus in the hippocampus. In this chapter, the suggested plausible mechanisms underlying the natural recovery process that occurs after stroke will be discussed.

Stroke is one of the most common diseases leading to long-term disability worldwide. As such, many patients suffer from the sequelae of stroke, which are a result of the damage done to a large portion of the brain by stroke. Although uncountable clinical trials have been performed with the aim of enhancing recovery of neurological functions after stroke, almost all of them have failed. As a result, there is currently no definitive treatment for the sequelae associated with stroke. Therefore, we can only prescribe medicine as a secondary prevention after the occurrence of a stroke, but not for the treatment of its sequelae. In many cases, however, patients with stroke show substantial spontaneous improvement in neurological functions at discharge or months after the stroke compared with their functions at admission or days after the stroke (Fig. 19.1). If we can elucidate the exact mechanism of recovery after stroke, it might be possible to design new therapeutic strategies for stroke and its sequelae. In the present chapter, the plausible mechanisms involved in recovery after stroke will be reviewed based on published reports. The two most important mechanisms of recovery after stroke are thought to be plasticity and neurogenesis in the brain (Fig. 19.2).

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## 19.1 Plasticity of the Brain After Stroke

Plasticity of the brain is considered to be one of the most important mechanisms involved in the recovery process after focal brain injury. The concept of "plasticity" in the brain was initially suggested more than 50 years ago based on the finding that repeated learning led to behavioral adaptation through an increase in synaptic efficacy in animals [1]. Many researchers have confirmed that enriched environments and skill learning enhance synaptogenesis via growth of dendrites and increase in the number of dendritic spines, and that long-term potentiation and long-term depression are directly associated with changing synaptic efficacy [2]. Therefore, plasticity indicates changes in neural networks that often result in behavioral consequences.

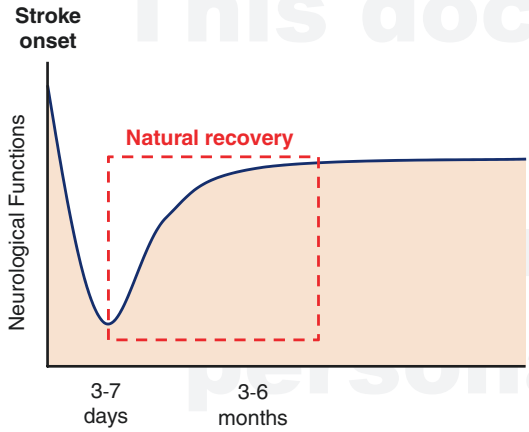


**Fig. 19.1** Natural recovery after stroke. Neurological functions usually deteriorate after stroke, and this deterioration is typically maximized within 7 days after stroke. However, neurological functions often improve with time. This phenomenon is called natural recovery

It has been shown that plasticity can occur in the human brain during the recovery period after focal brain injury, as well as during the motor learning process [3]. In detail, recruitment of secondary motor areas was increased after projections from the primary motor cortex to spinal cord motor neurons were damaged by focal brain injury, and a higher level of recruitment was associated with better functional outcome in patients with chronic stroke [4, 5]. It has also been reported that some secondary motor areas can take on new functions during the recovery process after focal brain injury [6]. Especially, the ipsilesional dorsolateral premotor cortex was proposed to behave as an "executive" motor region similar to the primary motor area [6]. Another suggested mechanism to explain the recovery process after stroke is that the injured brain could use other surviving structures and networks that can generate motor signals, other than secondary motor areas, through plasticity [6].

In addition to the role of the ipsilateral hemisphere after stroke, a number of imaging studies

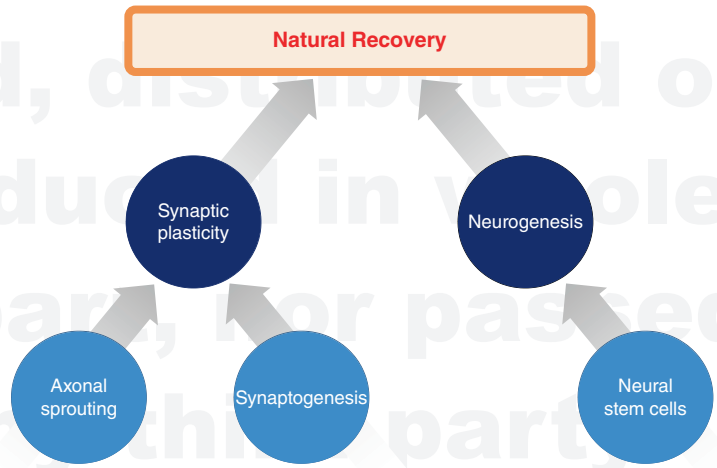


**Fig. 19.2** Plausible mechanisms of natural recovery. Natural recovery is thought to occur due to synaptic plasticity and neurogenesis after stroke. Synaptic plasticity is achieved by axonal sprouting and synaptogenesis. Endogenous neural stem cells are thought to contribute to neurogenesis

have demonstrated that bilateral networks are more activated in recovering patients than in healthy controls [7, 8]. This finding suggests that the unaffected hemisphere can help patient recovery after stroke through plasticity, albeit to a limited extent. This suggestion is also supported by longitudinal studies confirming that both hemispheres are involved in recovery from stroke affecting motor and language functions: one study was about strokes that affected motor functioning [9], and the other investigated aphasia associated with subcortical stroke [10]. The studies revealed that increasing performance after stroke is correlated with an increase in activation in the respective networks. For example, chronic aphasic patients with increased activation in Wernicke's homologue showed improved language performance [11]; stronger activation in language-related areas in both hemispheres was correlated with improvement of acute aphasia [10]; and simultaneous electromyography and functional magnetic resonance imaging (fMRI) revealed that bilateral recruitment of premotor and motor areas is related to recovery after acute stroke affecting motor functions [12]. Considering these findings, it seems reasonable to conclude that the unaffected hemisphere positively affects the recovery process after stroke.

On the contrary, however, there are findings against this hypothesis. Some studies have shown that poorer recovery after stroke was markedly correlated with stronger involvement of the unaffected hemisphere [6, 13, 14]. Two explanations for this phenomenon can be proposed. First, patients with lesions to areas of the brain more essential for motor and language might have to depend more highly on contralesional areas to effectively compensate for damaged areas. Second, even if contralesional areas initially positively contribute to the recovery process after stroke, their lasting activation might result in a maladaptive process due to interhemispheric inhibition and could impair more complete recovery. The existence of this negative impact caused by recruitment of the unaffected hemisphere has been supported by several studies using repetitive transcranial magnetic stimulation (rTMS), which can suppress activity in the brain. These studies suggested that suppression of the unaffected hemisphere by rTMS resulted in an improvement in language and motor tasks during the recovery period after stroke [15, 16].

Although there is still some disagreement about the role of the unaffected hemisphere in the recovery process, it seems likely that involvement of the contralesional hemisphere occurs during the recovery process. It has also been reported that the affected and unaffected hemispheres have different recovery time courses. The unaffected hemisphere showed a relatively early upregulation in activity, while the activity of the affected hemisphere was upregulated after the unaffected hemisphere had already normalized [17, 18]. In detail, the entire neural network is depressed just after stroke, and then the activity of the unaffected hemisphere is upregulated and overactivated. Bilateral normalization of activation in most task-related areas follows these phases. During this normalization phase, new network balances in the remaining, non-lesioned portions of the brain seem to be established to recover functions after stroke [17, 18]. However, the precise timing of the events that occur during the recovery period after stroke should be addressed.

Although the exact mechanisms underlying plasticity in the human brain after stroke have not yet been fully elucidated, many studies have suggested that an increase in synaptic efficacy and synaptogenesis could contribute to plasticity and then to recovery after stroke [19]. Here, we outline a diverse number of possible mechanisms thought to underlie plasticity based on numerous studies on the subject.

Cortical plasticity has been observed in many experiments for decades. For a better understanding of cortical plasticity, the development of the brain needs to be further studied. Behavioral experience is the most well-known potent modulator of cortical structure and function [20]. Namely, repetitive behavior and temporal coincidence for skilled motor activities are thought to induce cortical plasticity through axonal sprouting. Repetition of certain behaviors provokes the maturation of thalamocortical connections via two distinct phases. The first phase occurs when

the spontaneous neural activity generated by repetitive behavior increases the expression of axonal guidance molecules, including brain-derived neurotrophic factor (BDNF), so that thalamocortical axons are directed to their cortical targets. The second phase involves continuous cortical activity that causes axonal sprouting within the cerebral cortex [21]. In the past, long-range axonal sprouting was not thought to occur in the adult brain; however, it was recently discovered that injury to the brain can induce axonal sprouting even in adults. For example, axonal sprouting was confirmed to occur after focal cerebral infarction [22]. Now, it is well accepted that the adult brain has a notable capacity to recover following injury through a phenomenon called spontaneous recovery. While spontaneous recovery occurs after injury, behavioral compensation might contribute significantly to the recovery process [23]. For example, when patients have hemiparesis, they use compensatory movements of the trunk during reaching movements [24]. These compensatory movements could change the topography of the brain. For example, the increased use of a proximal limb with impaired digits induces a redistribution of forelimb representation: digit representations are reduced while proximal representations are enlarged [25]. Neural plasticity in the adjacent and intact cortex plays an important role in these processes and in spontaneous recovery after focal stroke. There is a plethora of evidence suggesting that adjacent regions of the cortex compensate for the damaged area. Nudo and Milliken induced focal brain injury to the area of thumb representation in monkeys. After a certain period of spontaneous recovery, it was confirmed that the brains were remapped, and the thumb area reappeared in the adjacent and undamaged cortex [26]. Similar findings have been suggested in humans: the intact, peri-infarct cortex is thought to play a critical role in the recovery process after focal brain injury [27]. Moreover, motor representations in the damaged hemisphere are enlarged after several weeks of rehabilitation [28].

Neuroanatomical alterations are also found in the peri-infarct cortex. In vivo studies using animals with cerebral infarction showed increased GAP-43 immunoreactivity between 3 and 14 days post-infarct [29], and local sprouting and synaptogenesis were elevated between 14 and 60 days post-infarct [30]. With regard to blood supply, arteriolar collateral growth and the number of new capillaries also increased in the peri-infarct area [31]. To date, there have been many suggested mechanisms of axonal sprouting and synaptogenesis. Axonal sprouting and synaptogenesis can occur to help compensate for neuronal loss after stroke. Understanding the mechanisms of synaptic plasticity in the entorhinal/dentate circuit in normal conditions could make it easier to explain the mechanisms regulating axonal sprouting and synaptogenesis in the brain after stroke. Synaptogenesis can naturally occur in the fiber systems of neural circuits through the spatial arrangement of inputs. CA4 synapses extend distally to the granule cell dendritic tree, and septal cholinergic synapses decrease their domain to the entorhinal zone. This synaptogenesis is followed by a sequence of events: [1] CA4 fibers invade the regions controlled by entorhinal inputs, and then [2] the dendritic tree grows outward from the cell body, which causes the migration of CA4 fibers toward the outer molecular layer [32]. When stroke occurs in the mature brain, this growth process starts in a damaged system. The old system is coordinated with the initiation of growth and the formation of new synapses. Neuronal growth requires at least four extrinsic conditions. The normal process underlying neuronal growth occurs as follows: the first step is glial involvement in clearing degenerated tissue; the next step involves an increase in the expression of neurite outgrowth-promoting factors; the third step is establishment of the new composition of the extracellular matrix and expression of cell-adhesion molecules; and the last step is targeting and synapse formation and the expression of molecular systems regulating neurotransmitter release and proper postsynaptic receptors. During this process, the proper expression of neurotrophic factors and cell-adhesion molecules plays critical roles in axon sprouting and regeneration. These diffusible factors are synthesized either by target neurons or by the surrounding glia and

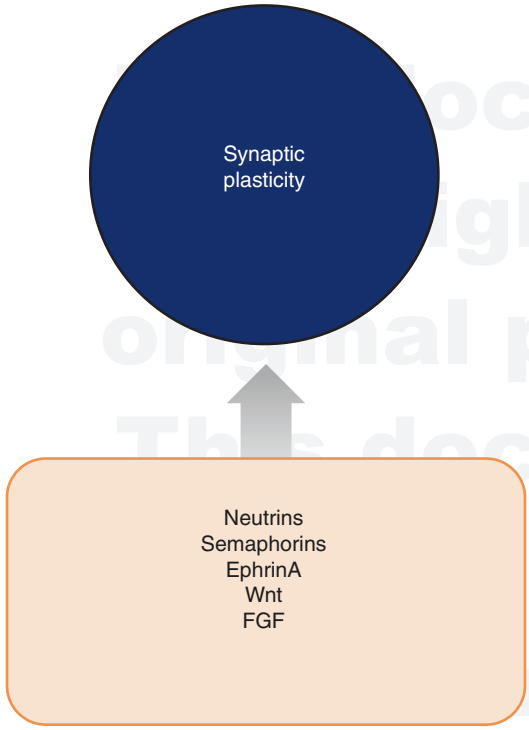


**Fig. 19.3** Factors contributing synaptic plasticity. Neutrins, semaphorins, ephrinA, Wnt, and fibroblast growth factor (FGF) are well-known contributors to synaptic plasticity

have a wide range of activities, including the ability to guide axonal projections to their correct targets, promoting neuronal differentiation and maturation, and helping the formation of functional synaptic junctions (Fig. 19.3) [33]. Neutrins, semaphorins, and ephrinA are well-known molecules that can induce axonal sprouting, but their direct functions have not yet been fully established [33]. The Wnt and fibroblast growth factor (FGF) families, which are secreted by neurons and other neuronal cells, are also involved in axonal sprouting and synaptogenesis [33]. Neurotrophins, such as BDNF, can also cause neuronal maturation. BDNF is known to directly control synaptogenesis, so it is considered to be a synaptogenic priming molecule [33]. Other glial cell-derived factors have also been shown to increase axonal sprouting and synaptogenesis. Cell-adhesion molecules (CAMs) are important in guiding synapse specificity. Several classes of CAMs play crucial roles in the formation of synapses via target recognition. Cadherins and protocadherins are the most famous examples: cadherin-6, cadherin-8, and N-cadherin guide subclasses of axons to their targets. In addition, neuronal activity-regulated pentraxin (Narp), Ephrin B1, Syn CAM, and neuroligin can trigger synaptogenesis. All of these molecules enhance axonal sprouting and synaptogenesis through diverse and complicated signaling pathways.

Axonal sprouting occurs through many complex steps. Briefly, two distinct steps have been fully elucidated. First, stroke induces dendritic changes. After stroke, it is well established that dendritic spines undergo remodeling in the peri-infarct area. Both the number of dendritic spines and the spine turnover rate increase within the first 2 weeks after stroke in the peri-infarct area, and these changes are known to contribute to rapid synaptogenesis. Second, neurons located in the peri-infarct area extend branches and form new connections after stroke. Sometimes, this axonal sprouting can occur in long descending pathways and give rise to the formation of new local circuits, long-distance intracortical connections, and long, descending projections to the spinal cord [34]. Synaptogenesis occurs at the same time as axonal sprouting, but does not occur separately from this process. The mechanisms underlying synaptogenesis after stroke are as follows: membrane trafficking associated with presynaptic assembly starts in the presynaptic neurons in the peri-infarct area after stroke; membrane trafficking associated with postsynaptic assembly follows; and the new synapses mature [33].

## 19.2 Regeneration of the Brain After Stroke

Another possible mechanism for functional recovery after stroke is regeneration of the damaged brain by endogenous neural stem cells, although this contribution might be small. The regeneration of the brain by neural stem cells is a process that was only recently confirmed. As

recently as several decades ago, regeneration of the brain was not considered to be possible. Since it was discovered that there are multipotent, self-renewing progenitor cells and stem cells in the brain [35], many studies have confirmed the existence of neural stem cells in various areas of the brain and of endogenous neurogenesis in the adult brain [36].

Endogenous neural stem cells located in the subventricular zone and the subgranular zone of the hippocampus can be activated by diverse stimuli. Stroke is one of the well-known stimuli that can activate neural stem cells. When stroke occurs in the brain, several types of cytokines are released from damaged neurons and glial cells and induce regeneration of the brain by endogenous neural stem cells. For example, stromal cell-derived factor 1-alpha is a strong activator of stem cells, including neural stem cells. Activated neural stem cells can proliferate and differentiate into various neuronal cells, such as neurons, ependymal cells, astrocytes, and oligodendrocytes, to replace damaged cells. However, neural stem cells can be damaged depending on the severity, size, and location of stroke [37]. In addition, hypoxia and ischemia can result in a change in the differentiation of neural stem cells so that they differentiate into glial cells rather than neurons [38, 39]. This so-called gliosis definitely inhibits functional recovery after stroke, especially at the chronic stage. Damage to neural stem cells might explain the lower functional recovery sometimes seen in patients who experienced a large stroke or damage to the brain that includes the subventricular zone where neural stem cells exist [40]. Therefore, regeneration of the brain by neural stem cells could contribute to the recovery process after stroke if the stroke does not affect the areas where neural stem cells are located.

However, we still do not understand the mechanisms contributing to the regeneration of the brain by neural stem cells after stroke, and only hypothetical suggestions have been proposed (Fig. 19.4). One of the most well-known proposed mechanisms is the phosphatidyl-inositol 3 kinase (PI3K) pathway. The PI3K pathway plays critical roles in cell proliferation, growth, differentiation, motility, survival, and intracellular trafficking. The PI3K family includes three different classes based on the primary structure, role, and in vitro lipid substrate specificity of the molecules. The Class I PI3Ks are the most well-characterized to date and are further divided into two types: Class IA (p110α, p110β, and p110δ) and Class IB (p110γ). The PI3K pathway interacts with the insulin receptor substrate (IRS) and is associated with the tumor suppressor phosphatase and tensin homolog (PTEN), which can inhibit members of the PI3K family. When PI3Ks are activated, they phosphorylate the hydroxyl group in the third position of the inositol ring of phosphatidylinositol (Ptdlns), so that Ptdlns [4, 5] $P_2$ becomes Ptdlns [3–5] $P_3$. Ptdlns [3–5] $P_3$ in

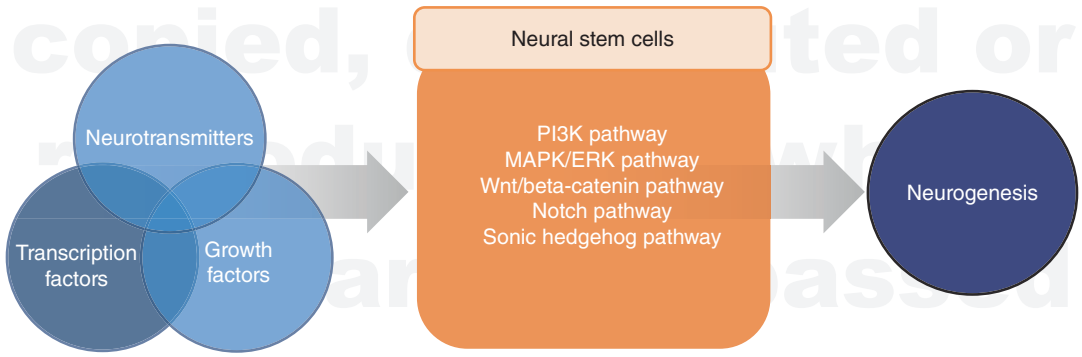


**Fig. 19.4** Neurogenesis from neural stem cells. Neural stem cells are activated after stroke, and this activation is affected by diverse growth factors, neurotransmitters, and transcription factors. These molecules induce neurogenesis through the activation of various pathways, such as the PI3K pathway, the MAPK/ERK pathway, the Wnt/beta-catenin pathway, the Notch pathway, and the Sonic hedgehog pathway

turn phosphorylates many downstream effectors, including Akt. Phosphorylated (activated) Akt controls glycogen synthase kinase (GSK)-3β and mammalian target of rapamycin (mTOR), nuclear factor kappa–light-chain-enhancer of activated B cells (NF-kB), endothelial nitric oxide synthase (eNOS), S6 kinase, forkhead box O (FOXO)s, and BAD. These downstream effectors are involved in cell growth, DNA translation, cell-cycle regulation, glucose metabolism, DNA repair, and inhibition of apoptosis [41]. Because of the importance of the PI3K pathway, chemicals affecting this pathway are under a high amount of scrutiny. IRS-1 substrate and platelet-derived growth factor receptor$^{740}$Y-P (PDGFR$^{740}$Y-P) activate this pathway and enhance neuronal cell survival and differentiation of NSCs. The role of the PI3K pathway in cerebral infarction has been well established. Ischemia can affect this pathway depending on its duration. The PI3K pathway is activated just after ischemia, but becomes inhibited as the duration of ischemia increases [41]. As described above, the inhibition of the PI3K pathway means PI3Ks cannot control critical signaling proteins that contribute to cell survival, proliferation, differentiation, and so on. Therefore, there has been much effort to develop PI3K activators for the treatment of stroke [41]. The role of the PI3K pathway in the regulation of NSCs is important. The PI3K pathway directly controls the proliferation, differentiation, and migration of endogenous NSCs. BDNF, FGF, SDF-1a, and many other neurotrophic factors can activate the PI3K pathway in NSCs. The activated PI3Ks strongly increase the survival, proliferation, and migration of NSCs. It is well known that many neurotrophic factors are released in the infarct and peri-infarct areas. Therefore, it is likely that the neurotrophic factors released after stroke activate NSCs, and the activated NSCs can contribute to the regeneration of the brain and the recovery process after stroke.

Another important signaling pathway is the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway. ERKs are involved in the regulation of meiosis, mitosis, and postmitotic functions in NSCs. The ERK pathway can be activated by many growth factors, cytokines, and other molecules. Ras, c-Raf, mitogen-activated protein kinase, and MAPK are upstream signaling proteins involved in the activation of ERKs. Activated ERKs increase the expression of many different transcription factors. These alterations affect the cell cycle and proliferation of NSCs. Focusing on the effect of the ERK pathway in stem cells, it has been shown that Erk signaling induces cell differentiation. Specifically, FGF activates ERKs, and the activation of ERKs provokes the differentiation of stem cells. This finding was confirmed in previous studies showing that inhibition of either the FGF receptor or ERKs eliminates neuronal differentiation of stem cells [42]. As described earlier, the release of FGF increases in the brain after stroke, which in turn enhances the neurogenesis caused by neural stem cells.

The Wnt/beta-catenin pathway is also involved in adult neurogenesis. Wnt3 is highly expressed in dentate gyrus hilar cells, and Wnt is reported to mediate neuroblast proliferation and neuronal differentiation via the beta-catenin pathway. This finding was confirmed by a study suggesting that inhibition of Wnt resulted in a marked decrease in neurogenesis [43]. NeuroD1, a pro-neurogenic basic helix-loop-helix (bHLH) transcription factor, is a downstream mediator of Wnt-induced neurogenesis. A study of NeuroD1 conditional knock-out mice showed that NeuroD1 is necessary for neurogenesis in the brain [44].

The Notch pathway is one of the most important signaling pathways in cell proliferation, differentiation, and apoptosis. Activation of the pathway begins with the binding of ligands to Notch receptors, which are single-pass transmembrane heterodimers. When ligands bind to the receptor, gamma-secretase mediates cleavage of the transmembrane domain, and the notch intracellular domain (NICD) is released into the cytosol. NICD forms a complex with the DNA-binding protein RBPj by translocating to the nucleus. The NICD–RBPj complex induces neurogenesis. It has been confirmed that the Notch pathway also plays vital roles in adult neurogenesis. Notch controls NSCs by promoting cell cycle exit and decreasing the adult neural

progenitor pool [44]. Notch 1 is also known to be important in dendritic arborization of immature neurons in the adult brain.

The Sonic hedgehog (Shh) pathway was discovered to participate in cell differentiation during the development period of the brain. Shh is a soluble extracellular signaling protein, and it activates the Shh pathway via a receptor complex consisting of the transmembrane receptor protein patched (Ptc) and its G protein-coupled co-receptor smoothened (Smo). Shh is now considered to be involved in neuronal differentiation in many different areas during development of the nervous system. Shh also regulates cellular migration in the adult brain, as well as self-renewal and proliferation of NSCs [44]. Defects in the Shh pathway in mice resulted in defective hippocampal neurogenesis.

Various growth factors and neurotrophic factors contribute to neurogenesis in the adult brain. For example, nerve growth factor (NGF), BDNF, neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5) are famous neurotrophic factors. These factors bind to three different Trk receptors: NGF binds to TrkA; BDNF and NT-4/5 to TrkB; and NT-3 to TrkC. The binding of these factors to their respective receptors leads to activation of a diverse range of signal transduction cascades, which then induces neurogenesis in the hippocampus and enhances the survival of neurons [44]. The term growth factors refer to extracellular proteins that promote cell growth and maintenance. To date, fibroblast growth factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) are the most well-known. These growth factors provoke neurogenesis through activation of the PI3K pathway and the Ras/Raf/Mek/Erk pathway as described above.

Neurotransmitters are small diffusible molecules that play a role in the chemical communication between neurons. Neurotransmitters are also known to be associated with proliferation, differentiation, and synaptic integration of adult neural progenitor cells. In addition, they aid neurogenesis. Glutamate, GABA, and dopamine are known to take part in neurogenesis in the adult brain. Glutamate is an excitatory neurotransmitter that can bind to NMDA, AMPA, kainic acid, and metabotropic glutamate receptors. Through binding to the NMDA receptor, glutamate induces the survival, proliferation, migration, differentiation, and appropriate functional integration of neuroblasts. AMPA and kainic acid receptors are also known to be involved in neural progenitor cell proliferation and neurogenesis [44]. GABA, the main inhibitory neurotransmitter, is necessary for neurogenesis. Especially, reactions with the $GABA_A$ receptor enhance neurogenesis by controlling neural stem cell proliferation. Dopamine is a catecholamine neurotransmitter and is critical in modulating movement. Recently, it was suggested that dopamine increases the proliferation of neural stem cells in the adult subventricular zone.

Transcription factors, such as cAMP response element-binding protein (CREB), paired homeobox transcription factor 6 (Pax6), Ascl1 (Mash1), distal-less homeobox 2 (Dlx2), Tlx, Sox2, Emx2, and Tbr2, have also been linked with neurogenesis. CREB is a fundamental regulator of cellular growth and development. Phosphorylation of CREB by cAMP increases neurogenesis by stimulating neural stem cell proliferation. In addition, CREB is also known to be involved in the survival, migration, and differentiation of NSCs. Pax6 is vital for development of the telencephalon and restricts the differentiation of NSCs in the rostral migratory stream to neuronal cells. Ascl1 is involved in control of NSC fate during embryonic and adult neurogenesis [44]. Ascl1 enhances the differentiation of NSCs into GABAergic interneurons, especially in the olfactory bulb. Overexpression of Ascl1 in vivo increases the production of oligodendrocytes from NSCs. Expression of Dlx2 is associated with migration and proliferation of neuroblasts in the subventricular zone. Tlx is highly expressed in the developing brain and the adult brain and has been reported to regulate adult neurogenesis [44]. Namely, Tlx promotes the proliferation and differentiation of NSCs. Sox2 is associated with NSC proliferation and neurogenesis. Reduced level of Sox2 causes impaired NSC proliferation and decreased adult neurogenesis [44]. Additionally, Sox11 and Sox9 were found to act

as downstream mediators of neuronal differentiation. Emx2 is essential for proper morphogenesis of the CNS. Emx2 negatively controls the proliferation of NSCs by increasing the number of cells that undergo differentiation [44]. Trb2 is expressed in intermediate neuronal progenitors and affects neurogenesis [44].

Epigenetic regulators are also important in the regulation of neurogenesis. Epigenetic mechanisms involved in this process include DNA methylation and histone modification. Epigenetic modifications can result in new cellular phenotypes. Methyl-CpG-binding domain protein 1 (MBD1) is expressed in the adult hippocampus and has been confirmed to promote neuronal differentiation. Methyl-CpG-binding protein 2 (MeCP2) is also involved in neurogenesis in the adult brain. MeCP2 plays crucial roles in neuronal maturation and in NSC proliferation and differentiation. Growth arrest and DNA-damage-inducible protein 45 beta (GADDA45b) mediate NSC proliferation in the hippocampus and dendritic growth of newborn neurons. TET1 is known to regulate activity-induced neurogenesis in the adult hippocampus. The histone methyltransferase mixed-lineage leukemia 1 (Mll1) is closely linked with neuronal differentiation in the adult subventricular zone. Members of the family of fragile Z mental retardation proteins are associated with adult neurogenesis.

## 19.3 Conclusions

Although the exact mechanisms underlying the natural recovery process after stroke still need to be fully elucidated, two important mechanisms are thought to involved. First, synaptic plasticity, including axonal sprouting and synaptogenesis, is considered to be essential for successful recovery after stroke. These processes have been shown to occur around the peri-infarct area and sometimes even in the contralateral hemisphere. Second, neurogenesis caused by NSCs located in the subventricular zone and hippocampus also contributes to the recovery process. As described above, axonal sprouting, synaptogenesis, and neurogenesis occur through extremely complicated mechanisms. To help the recovery process after stroke and lessen the neurological sequelae of stroke patients, ways to increase axonal sprouting, synaptogenesis, and neurogenesis should be established based on the exact mechanisms.

## References


1. Hebb DO. Organization of behavior. New York, NY: Wiley; 1949.
2. Hess G, Donoghue JP. Long-term potentiation and long-term depression of horizontal connections in rat motor cortex. Acta Neurobiol Exp (Wars). 1996;56(1):397–405.
3. Butefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, et al. Mechanisms of use-dependent plasticity in the human motor cortex. Proc Natl Acad Sci U S A. 2000;97(7):3661–5.
4. He SQ, Dum RP, Strick PL. Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. J Neurosci. 1993;13(3):952–80.
5. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of outcome after stroke: a cross-sectional fMRI study. Brain. 2003;126(Pt 6):1430–48.
6. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain. 2003;126(Pt 11):2476–96.
7. Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol. 1991;29(1):63–71.
8. Weiller C, Chollet F, Friston KJ, Wise RJ, Frackowiak RS. Functional reorganization of the brain in recovery from striatocapsular infarction in man. Ann Neurol. 1992;31(5):463–72.
9. Nhan H, Barquist K, Bell K, Esselman P, Odderson IR, Cramer SC. Brain function early after stroke in relation to subsequent recovery. J Cereb Blood Flow Metab. 2004;24(7):756–63.
10. de Boissezon X, Demonet JF, Puel M, Marie N, Raboyeau G, Albucher JF, et al. Subcortical aphasia: a longitudinal PET study. Stroke. 2005;36(7):1467–73.
11. Musso M, Weiller C, Kiebel S, Muller SP, Bulau P, Rijntjes M. Training-induced brain plasticity in aphasia. Brain. 1999;122(Pt 9):1781–90.
12. Butefisch CM. Plasticity in the human cerebral cortex: lessons from the normal brain and from stroke. Neuroscientist. 2004;10(2):163–73.
13. Heiss WD, Kessler J, Thiel A, Ghaemi M, Karbe H. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. Ann Neurol. 1999;45(4):430–8.

14. Serrien DJ, Strens LH, Cassidy MJ, Thompson AJ, Brown P. Functional significance of the ipsilateral hemisphere during movement of the affected hand after stroke. Exp Neurol. 2004;190(2):425–32.
15. Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, et al. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang. 2005;93(1):95–105.
16. Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology. 2005;64(10):1802–4.
17. Carey LM, Abbott DF, Egan GF, Bernhardt J, Donnan GA. Motor impairment and recovery in the upper limb after stroke: behavioral and neuroanatomical correlates. Stroke. 2005;36(3):625–9.
18. Tombari D, Loubinoux I, Pariente J, Gerdelat A, Albucher JF, Tardy J, et al. A longitudinal fMRI study: in recovering and then in clinically stable subcortical stroke patients. NeuroImage. 2004;23(3):827–39.
19. Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. Arch Neurol. 2004;61(12):1844–8.
20. Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M. Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. J Neurosci. 2004;24(3):628–33.
21. Uesaka N, Ruthazer ES, Yamamoto N. The role of neural activity in cortical axon branching. Neuroscientist. 2006;12(2):102–6.
22. Carmichael ST, Chesselet MF. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. J Neurosci. 2002;22(14):6062–70.
23. Whishaw IQ, Pellis SM, Gorny BP, Pellis VC. The impairments in reaching and the movements of compensation in rats with motor cortex lesions: an endpoint, videorecording, and movement notation analysis. Behav Brain Res. 1991;42(1):77–91.
24. Cirstea MC, Levin MF. Compensatory strategies for reaching in stroke. Brain. 2000;123(Pt 5):940–53.
25. Nishibe M, Barbay S, Guggenmos D, Nudo RJ. Reorganization of motor cortex after controlled cortical impact in rats and implications for functional recovery. J Neurotrauma. 2010;27(12):2221–32.
26. Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. J Neurophysiol. 1996;75(5):2144–9.
27. Teasell R, Bayona NA, Bitensky J. Plasticity and reorganization of the brain post stroke. Top Stroke Rehabil. 2005;12(3):11–26.
28. Carey JR, Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey L, Rundquist P, et al. Analysis of fMRI and finger tracking training in subjects with chronic stroke. Brain. 2002;125(Pt 4):773–88.
29. Stroemer RP, Kent TA, Hulsebosch CE. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. Stroke. 1995;26(11):2135–44.
30. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann Neurol. 2006;59(5):735–42.
31. Wei L, Erinjeri JP, Rovainen CM, Woolsey TA. Collateral growth and angiogenesis around cortical stroke. Stroke. 2001;32(9):2179–84.
32. McNeill TH, Brown SA, Hogg E, Cheng HW, Meshul CK. Synapse replacement in the striatum of the adult rat following unilateral cortex ablation. J Comp Neurol. 2003;467(1):32–43.
33. Waites CL, Craig AM, Garner CC. Mechanisms of vertebrate synaptogenesis. Annu Rev Neurosci. 2005;28:251–74.
34. Benowitz LI, Carmichael ST. Promoting axonal rewiring to improve outcome after stroke. Neurobiol Dis. 2010;37(2):259–66.
35. Temple S. Division and differentiation of isolated CNS blast cells in microculture. Nature. 1989;340(6233):471–3.
36. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science. 1992;255(5052):1707–10.
37. Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med. 2002;8(9):963–70.
38. Park J, Park HH, Choi H, Kim YS, Yu HJ, Lee KY, et al. Coenzyme Q10 protects neural stem cells against hypoxia by enhancing survival signals. Brain Res. 2012;1478:64–73.
39. Morrison SJ, Perez SE, Qiao Z, Verdi JM, Hicks C, Weinmaster G, et al. Transient notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells. Cell. 2000;101(5):499–510.
40. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY, et al. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells. 2010;28(6):1099–106.
41. Koh SH, Lo EH. The role of the PI3K pathway in the regeneration of the damaged brain by neural stem cells after cerebral infarction. J Clin Neurol. 2015;11(4):297–304.
42. Lanner F, Rossant J. The role of FGF/Erk signaling in pluripotent cells. Development. 2010;137(20):3351–60.
43. Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A, et al. Wnt signalling regulates adult hippocampal neurogenesis. Nature. 2005;437(7063):1370–5.
44. Faigle R, Song H. Signaling mechanisms regulating adult neural stem cells and neurogenesis. Biochim Biophys Acta. 2013;1830(2):2435–48.