Ion channels in postnatal neurogenesis
Potential targets for brain repair

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Abbreviations: NSC/NPCs, neural stem and progenitor cells; SGZ, subgranular zone; VZ, ventricular zone; EGF, epidermal growth factor; \( V_{\text{mem}} \), membrane potential; mV, millivolts; TEA, tetraethylammonium; 4-AP, 4-aminopyridine; GFAP, glial fibrillary acidic protein; \( K_\text{ir} \), inwardly-rectifying \( K^+ \) channel; \( K_\text{Ca} \), \( Ca^{2+} \) sensitive \( K^+ \) channel; \( K_{\text{2p}} \), two pore \( K^+ \) channel

Neural stem and progenitor cells (NSC/NPCs) are unspecialized cells found in the adult peri-ventricular and sub-granular zones that are capable of self-renewal, migration and differentiation into new neurons through the remarkable process of postnatal neurogenesis. We are now beginning to understand that the concerted action of ion channels, multi-pass transmembrane proteins that allow passage of ions across otherwise impermeable cellular membranes tightly regulate this process. Specific ion channels control proliferation, differentiation and survival. Furthermore, they have the potential to be highly selective drug targets due to their complex structures. As such, these proteins represent intriguing prospects for control and optimization of postnatal neurogenesis for neural regeneration following brain injury or disease. Here, we concentrate on ion channels identified in adult ventricular zone NSC/NPCs that have been found to influence the stages of neurogenesis. Finally, we outline the potential of these channels to elicit repair, and highlight the outstanding challenges.

Introduction

Accumulating evidence demonstrates that ion channels are dynamic modulators of all aspects of NSC/NPC biology. More specifically, the sequence diversity of ion channels, even within channel families, as well as their often multi-subunit complex three-dimensional structures provide the potential for the development of drugs that are highly selective for specific channel isoforms expressed at discrete stages of neurogenesis. This approach may be advantageous over infusion of growth factors or other bioactive peptides that are likely to have more widespread, pleiotropic effects across neuronal development. Described in detail below, different ion channels have been identified that control several of these steps. Thus, the identification and the elucidation of the functional roles of specific ion channels present at each stage of neurogenesis could be exploited to develop targeted therapeutic strategies for brain repair. Here we highlight ion channels involved in the regulation of NSC/NPCs and neuroblasts of the VZ, for it is these newly-born cells that have the migratory capacity to reach damaged areas of the brain. We also discuss the obstacles and challenges that need to be addressed for this to become an effective therapeutic strategy.

What is the Relationship between Neurogenesis and Neurodegenerative Disease or Brain Injuries?

Neurons are post-mitotic, complicating brain repair in contrast to many peripheral tissues, in which repair processes are easily mediated by endogenous cell replacement. Excitingly, we now know that new neurons are produced from NSC/NPCs in the subgranular zone (SGZ) of the dentate gyrus and the ventricular zone (VZ) of the lateral ventricles throughout life (recently reviewed in ref. 14). This is a remarkable postnatal developmental process that entails several cell types characterized by specific marker proteins and morphologies (Fig. 1). Furthermore, postnatal neurogenesis is sensitive to external factors, including brain disease and injury, which cause decreases, increases or aberrancies in differentiation or migration. In neurodegenerative diseases like Alzheimer disease, Parkinson disease and Huntington’s disease, aberrancies in the SGZ and VZ precede or parallel the early or premotor symptoms, such as depression, anxiety or olfactory dysfunction. Brain injury and ischemia stimulate NSC/NPCs to undergo marked proliferation in the VZ and SGZ, both in rodents and in humans, that contributes to stroke outcome. Therefore, the ability to modify the neurogenesis response to injury and disease could be used both to mitigate the effects of disease and injury as well as to promote repair. Although major advances have been made in understanding the biology of these special, undifferentiated cells, realizing their repair potential of NSC/NPCs has proven more enigmatic.
Why Look at Ion Channels for Brain Repair?

Thus far, attempts to enhance neurogenesis following ischemia, injury or disease have focused mainly on infusion of trophic factors or cytokines (recently reviewed in refs. 30 and 31). These have shown promise in animal models, but are not without major caveats. Erythropoietin, for example, is a cytokine that is made locally in response to injury as a protective factor in the brain, stimulates both angiogenesis and neurogenesis, and exogenously applied improves stroke outcome in animal models. Despite this, large prospective randomized studies have failed to demonstrate a benefit for brain protection and exogenously applied improves stroke outcome in animal models. 30 Despite this, large prospective randomized studies have failed to demonstrate a benefit for brain protection and exogenously applied improves stroke outcome in animal models.

Figure 1. Primer on postnatal neurogenesis in the ventricular zone and the ion channels involved. (A) Postnatal neurogenesis is broadly defined as the process of generating mature, functional neurons from postnatal NSCs, present even in the adult human brain. 30 NSCs continually undergo proliferation, differentiation, apoptosis/survival, migration and functional integration into neuronal circuitry in the ventricular zone (VZ) and the subgranular zone (SGZ) of the dentate gyri of the hippocampus. (B) Different cell types mark the developmental stages of neurogenesis, beginning with the relatively quiescent NSC (red) and progressing to NPCs (bright orange) and migratory neuroblasts (yellow-orange). These distinct cell types are characterized by their morphology and expression of lineage markers, such as the intermediate filaments nestin, glial fibrillary acidic protein (GFAP), the microtubule-binding protein doublecortin (DCX) and class III β tubulin (TuJ-1). The expression of selected ion channels involved in regulating the properties of these cell types are indicated. UN, unknown molecular identity; delayed-rectifier-type K+, Kdr; Panx2, Pannexin 2.

Changes in the K+ Channel Repertoire Associated with Regulating VZ NSC/NPC Proliferation and Differentiation

K+ channels have been implicated in the regulation of three critical steps of neurogenesis: cell proliferation, differentiation and migration. 45-48 The large K+ channel super-family is the most studied in the context of neurogenesis. K+ channel properties are often influenced by factors known to regulate the distinct steps of neurogenesis, such as cytokines and growth factors. 49-51 K+ channel expression has been studied in a number of NSC/NPC models including various embryonic and postnatal cultures from both the VZ and hippocampus, as well as NSC models derived from other types of stem cells. As mentioned above, this review will focus primarily on studies of the postnatal VZ. Both in situ and in vitro studies have revealed a progression of K+ channel over the course of neuronal differentiation in the post-natal VZ. Changes in K+ channels expression (and possibly activity) appear to play a critical role in fine tuning progression from relative quiescent to proliferative phenotypes.

NSCs in the postnatal VZ display a unique glial phenotype intermediate between radial glia and astrocytes. They exhibit a hyperpolarized membrane potential ($V_{m}$ ~ -85 mV), and a low input resistance (~30 MΩ). These properties are conserved in NSCs cultured as neurospheres, which are in vitro cultures of NSC/NPCs similar to embryoid bodies, with a $V_{m}$ of ~82 mV and a relatively low input resistance of ~167 MΩ. The hyperpolarized $V_{m}$ and low input resistance are attributed to a high resting K+ conductance.
Which K⁺ channels are responsible for the high resting conductance (and negative regulation of proliferation)? The high resting K⁺ conductance is likely set by a combination of K⁺ channels that are open at resting \( V_{\text{mem}} \). Using mice that express GFP under the control of the glial fibrillary acidic protein (GFAP) promoter, Liu and colleagues determined the electrophysiological profiles of VZ NSCs, uncovering delayed-rectifier-type K⁺ currents, and 1 mM Ba²⁺-sensitive K⁺ currents (but not 100 μM Ba²⁺-sensitive currents) and an absence of A-type K⁺ currents. While low (1 mM) Ba²⁺ sensitivity is not entirely consistent with inwardly-rectifying K⁺ channels (Kᵢ, channels; sensitive to 100 μM Ba²⁺), VZ NSCs are immunoreactive for Kᵢ,4.1 and Kᵢ,2.1, suggesting that, in these cells, \( K_{\text{ir}} \) may somehow be modified to have low Ba²⁺ sensitivity. Lai et al. also using GFAP fluorescent reporter mice described two distinct electrophysiological profiles for VZ NSCs. One group of cells expressed large, slowly activating sustained outward currents without a fast inactivation component. These currents were only partially blocked by tetraethylammonium (TEA) and 4-aminopyridine (4-AP) and their molecular identity (and ion selectivity) is uncertain. The remainder exhibited a fast inactivating current with a small steady-state component sensitive to TEA and 4-AP, suggesting they are generated by one or more voltage-dependent K⁺ channel isoforms. Studies performed on NSCs in vitro also observed expression of 0.1 mM Ba²⁺-sensitive Kᵢ, In vitro, block of Kᵢ, channels with 0.1 mM Ba²⁺ or 1 mM Ba²⁺ increased cell proliferation. These and other researchers have confirmed the in vitro and in vivo expression of Kᵢ,1.1, Kᵢ,4.1, Kᵢ,5.1, and Kᵢ,3.1. These results are in agreement with a role of Kᵢ, channels in maintaining a hyperpolarized \( V_{\text{mem}} \) and thus limiting cell proliferation. A recent broad microarray analysis of K⁺ channel expression in VZ neurosphere cultures also identified several two pore K⁺ channel (Kᵢ,p) family members present in the VZ, like Kᵢ,p,2.1 (also known as TREK-1) and Kᵢ,p,3.1 (TASK-1), which would be expected to play a similar role in maintaining a hyperpolarized \( V_{\text{mem}} \).

Which K⁺ channels are involved in positive regulation of proliferation? Block of Kᵢ, channel isoforms with TEA reduced proliferation of NSC/NPCs cultured as neurospheres in vitro. In that particular study, cell proliferation was not reduced by the selective A-type K⁺ channel blocker dendrotoxin-I, suggesting a minimal contribution of A-type K⁺ channels to proliferation and a strong contribution of delayed-rectifying K⁺ channels. Further experiments identified Kᵢ,3.1 as the specific K⁺ channel isoform. However another study observed predominant A-type K⁺ current (albeit in a slightly different cellular model). In situ, highly proliferating NPCs in the VZ express 4-AP/TEA-sensitive and CdCl₂-sensitive inward currents, suggesting the expression of Kᵢ,p and Ca²⁺-sensitive K⁺ (Kᵢ,C) channels. Thus, which specific Kᵢ isoforms are present in proliferating VZ NPCs is still somewhat of an open question.

L-type Channels in Differentiation and Negative Regulation of Proliferation

Specific to postnatal neurogenesis, an important relationship has been identified between Ca²⁺ influx through Ca₁,1 (also known as L-type) voltage-gated Ca²⁺ channels in the negative regulation of proliferation and the stimulation of differentiation. D’Ascenzo et al. studied the contribution of Ca₁ voltage-gated Ca²⁺ channels to differentiation using cortical neonatal neurosphere cultures. During in vitro differentiation, depolarization-evoked Ca₁ voltage-gated Ca²⁺ channels currents increased in an expanding percentage of NSCs. Furthermore, neuronal differentiation, assessed by lineage marker analysis was strongly inhibited by the Ca₁ blocker, nifedipine, and increased by the Ca₁ activator, Bay K 8644. In the postnatal hippocampus, Ca²⁺ influx through Ca₁ voltage-gated Ca²⁺ channels is essential for expression of the basic helix-loop-helix transcription factor, NeuroD, and inhibition of pro-glial genes HES1 and Id2. SVZ neurogenesis also depends on NeuroD. These studies built upon a large body of work demonstrating the role of Ca₁ channels in activity-dependent gene expression. Recent groundbreaking work by the Dolmetsch group has further demonstrated the powerful impact of the Ca₁ channel in NPCs with drastic consequences for development and developmental disabilities like Timothy syndrome (caused by a missense mutation in Ca₁,2).}

Involvement of Other Types of Channels

Connexins, mammalian gap-junction forming proteins, play an important developmental role in neurogenesis and particularly in neuroblast migration and also in proliferation. Recent work also detected expression of a member of the recently discovered pannexin family, Pannexin 2 in postnatal hippocampal neural stem cells with a role in modulating neuronal development. Aquaporin-4, responsible for water and ion homeostasis in the central nervous system, is also expressed in NSCs and plays important roles in the proliferation, survival, migration and neuronal differentiation of adult VZ NSCs via modulation of intracellular Ca²⁺ dynamics. Highly selective pharmacological tools are still lacking for these particular large pore-type channels. Their usefulness as therapeutic targets must therefore be put on hold until such tools are discovered. The study of ion channel control of neurogenesis is really only in its infancy. The growth of systems biology approaches like proteomics, will continue to expand our knowledge of the ion channel repertoire in neuronal development in healthy animals and also in the context of disease. This may eventually enable the development of finely tuned treatment paradigms that can specifically target endogenous neurogenesis-based brain repair mechanisms.

What About Age-related Declines in Neurogenesis and/or Changes in NSC/NPC Ion Channels in Aged Brain?

For ion channels to be useful targets for brain repair, the aging brain must still maintain its regenerative potential. Recent work demonstrates that VZ neurogenesis in humans drops precipitously with increasing age. However, several lines of evidence suggests age-related changes in the microenvironment are responsible for the decrease in numbers rather than changes in number...
the proliferative potential of the NSC/NPCs themselves. Basal levels of corticosteroids increase with age, while several cytokines and growth factors decline with age. Both of these changes are associated with a decrease in neurogenesis and reversal of these processes mitigates age-related declines. Furthermore, proliferating and differentiating NSC/NPCs from each of these groups exhibited similar input resistance and resting \( V_{\text{mem}} \) suggesting similar types and levels of ion channel expression in aged brain. Focal cerebral ischemia following experimental stroke, induces similar magnitudes of neurogenesis in young (3 mo) and old (15 mo) rats. Furthermore, activation of neurogenesis occurs in the human brain following cerebral ischemia in patients up to 84 y old, despite a mere trickle of neurogenesis in aged healthy brain. These data highlight the continued validity of ion channels as targets for repair in the aged brain.

What are Other “Logistical” Issues to Overcome?

There are several major challenges to be addressed in order to optimally develop stimulation of endogenous neurogenesis as a safe and effective restorative brain therapy following injury or disease. Generally speaking, more data on the mechanisms modulating endogenous neurogenesis in functional recovery are needed. For instance, what are the signals triggering (as in ischemia) or hampering proliferation (as in Parkinson disease)? And, can these be adjusted without risking further problems, i.e., tumorigenesis? Work by the Stühmer group and others has demonstrated an important role of abnormal expression of certain K channels and other ion channels in the genesis of several cancer types—reinforcing the connection between stem cells and brain cancer and the notion that the selectivity and safety of ion channel modulating agents targeting VZ NSC/NPC ion channels will need to be closely and carefully monitored. Finally, following cerebral injury, VZ neuroblasts migrate to the injured penumbra for many months, and the mechanism controlling migration and can we fine-tune these to optimize ‘useful neuronal integration’ and prevent ectopic neuronal integration, akin to what is seen in epilepsy?

Summary—Targeting Specific Channels for Brain Repair

Clearly, the most well-studied ion channels in the context of postnatal neurogenesis are the K+ channel superfamilies. According to the expression profiles described above, blocking K+ channels with high resting conductance (e.g., specific K\(_{\text{ir}}\) 53,55,57 and K\(_{\text{ir}}\) 2P isoforms) could be used to enhance or stimulate proliferation. This strategy could be useful in scenarios where proliferation itself has been reduced by the particular disease, like Parkinson disease. In many diseases and injury, maturation and/or survival are also impaired. For differentiation, Ca\(_{\text{1a}}\) voltage-gated Ca\(_{\text{2+}}\) channels as well as other yet to be identified channels involved in maturation could be stimulated (e.g., Bay K8644) to enhance differentiation. It should be noted, however, that broadly-acting agonists or antagonists of widely-expressed channels, like Ca\(_{\text{1a}}\) voltage-gated Ca\(_{\text{2+}}\) channels are less attractive therapeutic options due to their expression in multiple cell types involved in multiple cellular processes including cell death. However, if NPC-specific regulators of Ca\(_{\text{1a}}\) could be targeted, such as interacting proteins, then Ca\(_{\text{1a}}\) could be a useful target. Using systems biology approaches to identify cell-type specific channel isoforms, to develop drugs highly selective for specific channel isoforms and to identify cell-type specific protein-protein interactions will be important for the development of cell-type selective therapeutic agents used to promote brain repair by fine-tuning neurogenesis.

Conclusions

VZ NSCs possess tremendous potential for injury repair in the brain. In order to harness this potential we need to understand why they respond to injury and disease and how we can safely potentiate, or reverse, this response. Elucidating the cascade of ion channel activity that ensues, may allow us to fine-tune this complex process.
32. Kolb B, Morshead C, Gonzalez C, Kim M, Gregg C, Shingo T, et al. Growth-factor-stimulated generation of new cortical tissue and functional recovery after stroke damage to the motor cortex of rats. J Cereb Blood Flow Metab 2007; 27:983-97; PMID:16985595.

33. Nolte J, Uhl G, Guiller B, Bruder N, Pianko P. Erithrophycin 2nd cerebral protection after acute injuries: a double-edged sword? Pharmacol Ther 2010; 128:445-59; PMID:20732352; http://dx.doi.org/10.1016/j.pharmthera.2010.08.002.

34. Gonzaquez-Perez O, Romano-Rodriguez R, Soriano-Navauro M, Garcia-Verdugo JM, Alvarez-Buylla A. Epidermal growth factor induces the progeny of subventricular zone type B cells to migrate and differentiate into oligodendrocyttes. Stem Cells 2009; 27:2032-43; PMID:19544429; http://dx.doi.org/10.1002/stem.119.

35. Doetsch F, Peteateau L, Caillé I, Garcia-Verdugo JM, Alvarez-Buylla A. EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. Neuron 2002; 36:1021-34; PMID:11849617; http://dx.doi.org/10.1016/S0896-6273(02)01133-9.

36. Clare JJ. Targeting ion channels for drug discovery. Discov Med 2010; 9:253-60; PMID:2050493.

37. Hille B. Ion channels of excitable membranes. Sunderland, Massachusetts: Sinauer Associates, Inc. 1992.

38. Parent JM, Vekly ZS, Gong G, Derugin N, Ferriero DM. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. Ann Neurol 2002; 52:802-13; PMID:12447935; http://dx.doi.org/10.1002/ana.10853.

39. Enikolopov G, Muñoz-Orozco OB, Priest BT, Garcia ML. Ion channels as drug targets: the next GPCRs. J Gen Physiol 2008; 131:399-405; PMID:18413313; http://dx.doi.org/10.1085/jgp.200709946.

40. Overington JP, Al-Lazikani B, Hopkins AL. How many drug targets are there? Nat Rev Drug Discov 2006; 5:993-6; PMID:17139284; http://dx.doi.org/10.1038/nrd2199.

41. Spitler NC. Electrical activity in early neuronal development. Nature 2006; 444:707-12; PMID:17151658; http://dx.doi.org/10.1038/nature05300.

42. Cone JD. Electromosotic interactions accompanying mitosis initiation in somatic cells in vitro. Trans NY Acad Sci 1969; 31:404-27; PMID:5257510.

43. Cone JD, Tongier M Jr. Control of somatic cell mitosis by simulated changes in the transmembrane potential level. Oncology 1971; 25:168-82; PMID:5148061; http://dx.doi.org/10.1159/000224567.

44. Stillwell EE, Cone CM, Cone JD Jr. Stimulation of DNA synthesis in CIN neurons by sustained depolarization. Nat New Biol 1973; 246:110-3; PMID:4518395.

45. Puro DG, Roberge F, Chan CC. Retinal glil cell proliferation and ion channels: a possible link. Invest Ophthalmol Vis Sci 1989; 30:521-9; PMID:2466809.

46. Dubois JM, Prée M, Derlet C, Fernández-Klett F. Yeh RW. Potassium channel expression in adult rat brain. J Biol Chem 2002; 277:1974-80; PMID:1196120; http://dx.doi.org/10.1016/j.mcn.2007.10.003.

47. Peyron B, Dieberg B, Brandin P, Li YF. Involvement of Ngn2, Trb and NeuroD proteins during postnatal olfactory bulb neurogenesis. Eur J Neurosci 2000; 12:232-43; PMID:10672974; http://dx.doi.org/10.1046/j.1465-2448.2000.01644.x.

48. Lai B, Mao XO, Xie L, Chang SY, Xiong ZG, Jin K, et al. Electrophysiological properties of subventricular zone cells in adult mouse brain. Brain Res 2010; 1360:96-105; PMID:20434486; http://dx.doi.org/10.1016/j.brainres.2010.04.057.

49. Prius H, Dewes M, Derst C, Fernández-Klett F. Veh RW. Priller J. Potassium channel expression in adult marine neuron progenitor cells. Neuroscience 2011; 180:19-29; PMID:21379741; http://dx.doi.org/10.1016/j.neuroscience.2011.02.021.

50. Scheffler B, Wultan NM, Lin DD, Goetz AK, Enikolopov G, Roper SN, et al. Phenotypic and functional characterization of adult brain neuroprogenitors. Proc Natl Acad Sci USA 2005; 102:9353-8; PMID:15951540; http://dx.doi.org/10.1073/pnas.0503956102.

51. Roybon L, Dieberg B, Brandin P, Li YF. Involvement of Ngn2, Trb and NeuroD proteins during postnatal olfactory bulb neurogenesis. Eur J Neurosci 2000; 12:232-43; PMID:10672974; http://dx.doi.org/10.1046/j.1465-2448.2000.01644.x.

52. Luo CX, Zhu XJ, Zhang AX, Wang W, Yang XM, Liu SH, et al. Blockade of L-type voltage-gated Ca channel inhibits ischemia-induced neurogenesis by downregulating iNOS expression in adult mouse neurogenesis. Neurochem Int 2005; 44:1077-86; PMID:16001519; http://dx.doi.org/10.1016/j.neuint.2005.03.062x.

53. Hardingham GE, Arnold FJ, Bading H. Nuclear calcium signaling controls CREB-mediated gene expression triggered by synaptic activity. Nat Neurosci 2001; 4:2617-71; PMID:11224542; http://dx.doi.org/10.1038/85109.

54. Deisseroth K, Heiz EK, Tien RW. Translocation of calmodulin to the nucleus supports CREB phosphorylation in hippocampal neurons. Nature 1998; 392:198-202; PMID:9531967; http://dx.doi.org/10.1038/32448.

55. Dolmetch RE, Pavani U, Fick K, Spors J, Greenberg ME. Signaling to the nucleus by an L-type calcium channel-calmodulin complex through the MAP kinase pathway. Science 2001; 294:339-43; PMID:11389829; http://dx.doi.org/10.1126/science.106395.

56. Gomez-Ospina N, Tsiourta F, Barreto-Chang O, Hu L, Dolmetch R. The C terminus of the L-type voltage-gated calcium channel Ca(V)1.2 encodes a transcription factor. Cell 2006; 125:591-606; PMID:17081980; http://dx.doi.org/10.1016/j.cell.2006.10.017.
Aurousseau C, Le Moal M, et al. Lifelong corticosterone level determines age-related decline in neurogenesis and memory. Neurobiol Aging 2006; 27:645-54; PMID:15958661; http://dx.doi.org/10.1016/j.neurobiolaging.2005.02.014.

Ahlenius H, Visan V, Kokaia M, Lindvall O, Kokaia Z. Neural stem and progenitor cells retain their potential for proliferation and differentiation into functional neurons despite lower number in aged brain. J Neurosci 2009; 29:4408-19.

Darsalia V, Heldmann U, Lindvall O, Kokaia Z. Stroke-induced neurogenesis in aged brain. Stroke 2005; 36:1790-6; PMID:16002766; http://dx.doi.org/10.1161/01.STR.0000173151.36031.be.

Pardo LA, Stuhmer W. Eag1: an emerging onco-logical target. Cancer Res 2006; 68:1611-3; PMID:18339837; http://dx.doi.org/10.1158/0008-5472.CAN-07-5710.

Fraser SP, Pardo LA. Ion channels: functional expres-sion and therapeutic potential in cancer. Colloquium on Ion Channels and Cancer. EMBO Rep 2008; 9:512-5; PMID:18451877; http://dx.doi.org/10.1038/embob.2008.75.

Becchetti A. Ion channels and transporters in can-cer. 1. Ion channels and cell proliferation in can-cer. Am J Physiol Cell Physiol 2011; 301:255-65; PMID:21430288; http://dx.doi.org/10.1152/ajpcell.00847.2011.

McFerrin MB, Sontheimer H. A role for ion chan-nels in glioma cell invasion. Neuron Glia Biol 2006; 2:39-49; PMID:16520829; http://dx.doi.org/10.1017/S1740925X06000404.

Westphal M, Lamszus K. The neurobiology of gliomas: from cell biology to the development of therapeu-tic approaches. Nat Rev Neurosci 2011; 12:495-508; PMID:21811295; http://dx.doi.org/10.1038/nrn3060.

Thored P, Arvidsson A, Caeci E, Ahlenius H, Kallur T, Darsalia V, et al. Persistent production of neurons from adult brain stem cells during recovery after stroke. Stem Cells 2006; 24:739-47; PMID:16210404; http://dx.doi.org/10.1634/stemcells.2005-0281.

Leker RR, Soldner F, Velasco I, Gavir DK, Androutellos-Thesuktis A, McKay RD. Long-lasting regeneration after ischemia in the cerebral cortex. Stroke 2007; 38:153-61; PMID:17122419; http://dx.doi.org/10.1161/01.STR.0000252156.65953.a9.

Scharfman HE, McCloskey DP. Postnatal neurogen-eis as a therapeutic target in temporal lobe epilepsy. Epilepsy Res 2009; 85:150-61; PMID:19369038; http://dx.doi.org/10.1016/j.eplepsyres.2009.03.006.

Winner B, Melrose HL, Zhao C, Hinkle KM, Yue M, Kent G, et al. Adult neurogenesis and neurite outgrowth are impaired in LRRK2 G2019S mice. Neurobiol Dis 2011; 41:706-16; PMID:21168496; http://dx.doi.org/10.1016/j.nbd.2010.12.008.

Winner B, Kohl Z, Gage FH. Neurodegenerative disease and adult neurogenesis. Eur J Neurosci 2011; 33:1139-51; PMID:21935858; http://dx.doi.org/10.1111/j.1460-9586.2011.07613.x.

Höglinger GU, Rick P, Muriel MP, Duyckaerts C, Ortel WH, Caillet I, et al. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 2004; 7:276-35; PMID:15195955; http://dx.doi.org/10.1038/nn1265.

O’Keeffe GC, Tyers P, Aarsland D, Dalley JW, Barker RA, Caldwell MA. Dopamine-induced proliferation of adult neural precursor cells in the mammalian subven-tricular zone is mediated through EGF. Proc Natl Acad Sci USA 2009; 106:8754-9; PMID:19433789; http://dx.doi.org/10.1073/pnas.0803955106.

Ming GL, Song H. Adult neurogenesis in the mam-malian central nervous system. Annu Rev Neurosci 2005; 28:223-50; PMID:16022595; http://dx.doi.org/10.1146/annurev.neuro.28.051804.101459.

Duan X, Kang E, Liu CY, Ming GL, Song H. Development of neural stem cell in the adult brain. Curr Opin Neurobiol 2008; 18:108-15; PMID:18514504; http://dx.doi.org/10.1016/j.conb.2008.04.001.

Ma DK, Bonaguidi MA, Ming GL, Song H. Adult neural stem cells in the mammalian central nervous system. Cell Res 2009; 19:672-82; PMID:19346263; http://dx.doi.org/10.1038/cr.2009.56.

Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. Nat Med 1998; 4:1313-7; PMID:9809557; http://dx.doi.org/10.1038/3305.