Biomedical Reviews 2003; 14: 121-125.
Founded and printed in Varna, Bulgaria
ISSN 1310-392X

DANCE ROUND

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

ARE THERE FUNCTIONAL PROGENITOR CELLS IN THE ADULT BRAIN PARENCHYMA?

Anton B. Tonchev
Division of Cell Biology, Department of Forensic Medicine, Medical University, Varna, Bulgaria

The subventricular zone (SVZ) of the anterior horn of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus are the only regions of the adult brain that are widely recognized to contain neural progenitor cells – precursors capable of producing both neurons and glia. However, recent evidence suggests that such cells may exist also outside SVZ and SGZ, in the parenchyma of neocortex and striatum. This opens new possibilities for progenitor cell manipulation in situ with consequent development of novel progenitor-based strategies for the treatment of human neurological disease.
Biomed Rev 2003; 14: 121-125.

The adult brain retains progenitor cells in two well-recognized regions (Fig. 1): the subventricular zone (SVZ) of the anterior horn of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus (1). The SVZ progenitors migrate tangentially at a long distance to become interneurons in the olfactory bulb (2). The SGZ progenitors migrate radially at a short distance to become projection neurons in the dentate granule cell layer, immediately adjacent to SGZ (3). Both types of precursor cells are multipotent, i.e. capable of generating both neurons and glia (2,3), and both types are activated by brain injury or by external application of growth factors (Table 1).

Extensively studied in rodents, *in vivo* neurogenesis has been demonstrated also in the primate SVZ (23,24) and SGZ (25-27) in healthy subjects, while its existence outside these regions at normal conditions remains controversial (28-32). Recent data indicate of differences between the commonly used rodent models and the primates, related to neurogenesis. Thus, the human SVZ appears incapable of sending its precursors to the olfactory bulb (33). Further, while the phenomenon of postischemic precursor cell increase (see Table 1) is observed also in the monkey brain, the primate response is much smaller than the rodent one, especially regarding the neuronal differentiation of progenitor cells (12). Such results indicate of differential molecular control over the rodent and primate precursor cells, the revealing of which is a key factor for the development of successful strategies for the treatment of human neurological disease by means of neural progenitor cells.

In addition to the SVZ and SGZ progenitors, yet another source of such cells has gradually emerged, that offers an exciting possibility of progenitor cells manipulation *in situ*. Data in rodents implicate that precursor cells for neurons and glia may be present also in the parenchyma of the striatum and neocortex (10,34,35). Parenchymal progenitors were isolated *in vitro* also in primates (36,37), but their *in vivo*

Received 10 October 2003 and accepted 10 December 2003.
Correspondence and reprint requests to Dr Anton B. Tonchev, Division of Cell Biology, Department of Forensic Medicine, Medical University, BG-9002 Varna, Bulgaria. E-mail: atontchev@yahoo.com

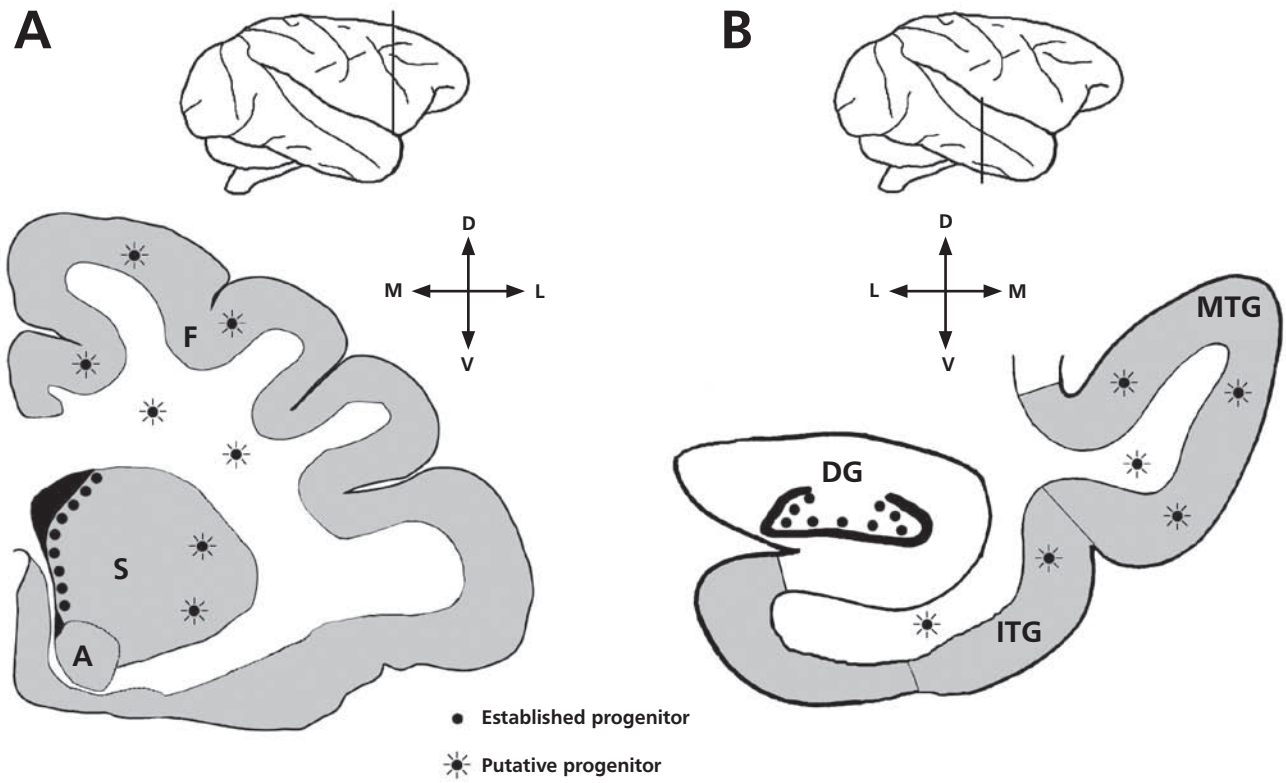

Figure 1. *Schematic maps of the adult monkey brain.* ***(A)*** *Coronal section through the frontal lobe (lower image) at the level depicted on the whole-brain map (upper image). The SVZ progenitors are located around the walls of the anterior horn of the lateral ventricle (V). Putative progenitors may be present in the frontal neocortex (F) or the striatum (S). A, accumbens nucleus.* ***(B)*** *Coronal section through the temporal lobe (lower image) at the level depicted on the whole-brain map (upper image). The SGZ progenitors are located in the hippocampal dentate gyrus (DG). Putative progenitors may be present in the temporal neocortex, including the middle (MTG) and inferior (ITG) temporal gyri. Directions: D, dorsal; V, ventral; M, medial; L, lateral.*

capabilities remain elusive. If parenchymal (e.g. in neocortex or striatum, see Fig. 1) progenitors really exist in the adult brain and are functional, i.e. capable of neuronal replacement *in vivo*, they offer a great clinical potential because of their spatial proximity to sites of injury in the brain parenchyma. The spatial proximity is of a particular importance in the case of the large primate brain, in which it may take weeks or months for the SVZ progenitors to travel from their site of origin to a distant portion of the brain parenchyma in order to replace lost cells.

A significant step toward the understanding that parenchymal progenitors may exist *in vivo* was made by a recent study of Ourednik *et al* (38). The authors implanted human neural stem cells in the lateral ventricles of embryonic monkey brains, and investigated the fate of these cells 4 weeks later. While most of the implanted cells had adopted a differentiated cell fate – either neuronal or glial – in the prefrontal neocortex, Ourednik *et al* also observed a few cells with features of undifferentiated progenitors in the brain parenchyma (38). While it is unclear whether this phenomenon is applicable also to the adult monkey brain, the results of Ourednik *et al* suggest that the adult primate brain might retain some kind of progenitors in the parenchyma.

Our recent data in adult monkeys represent additional evidence in this direction. We used a model of global cerebral ischemia in adult macaques (39) that completely but transiently blocks all blood flow to the brain structures, causing a major neuronal injury to the hippocampus, and a lesser injury to the striatum and neocortex (40,41). We found increased progenitor cell proliferation in the hippocampal dentate gy-

Table 1. *Selected pathological conditions and growth factors that increase the proliferation of SVZ and/or SGZ progenitors.*

Conditions	References
Ischemia	4-12
Seizures	13-16
Growth factors	
EGF	8
bFGF	8,17
BDNF	18,19
TGFα	20
IGF-I	21
VEGF	22

Abbreviations: EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; BDNF, brain-derived neurotrophic factor; TGFα, transforming growth factor-α; IGF-I, insulin-like growth factor-I; VEGF, vascular endothelial growth factor.

rus within the second postischemic week (12), similarly to the rodent brain after ischemia (4,5,7,8). However, the proliferation and neuronal differentiation of progenitor cells were much smaller in the monkey than in the rodent dentate gyrus (12). Further, in the same monkey model, we showed *in vivo* evidence of actively proliferating precursor cells in the core white matter of the olfactory bulb (42), in coherence with previous *in vitro* results in humans (43) and rodents (44). The finding of multipotent progenitors residing in the olfactory bulb is important, because it shows that such cells may exist outside SVZ and SGZ, the two established germinal zones of the adult brain. Our yet unpublished observations (Tonchev and Yamashima, in preparation) suggest that the striatal and neocortical parenchyma is another location containing neural progenitor cells. We found *in vivo* evidence of actively proliferating cells with progenitor immunophenotype in the adult monkey parenchyma, in combination with data for a limited neuronal replacement in these regions after ischemia. Importantly, we found no evidence of progenitor cell migration from SVZ to these areas, suggesting that the new neocortical and striatal neurons are derived from a local pool of precursors.

Taken together with previous *in vitro* data in primates (36,37), our results argue that the parenchymal progenitors of the adult primate brain exist and are functional, i.e. capable of neuronal replacement *in vivo*. Instruction of proliferation and neuronal differentiation to these cells by genetic manipulations such as pro-neuronal transcription factor overexpression (45) might further improve their ability to replace dead neurons *in situ*. Over 4 decades after Joseph Altman, the pioneer of the adult neurogenesis research, asked "Are new neurons formed in the brains of adult mammals?" (46), we ask ourselves whether neurogenesis may also take place by parenchymal progenitors at sites of injury in the adult brain. The clinical implications of such cells in the treatment of human neurological disease could be enormous.

ACKNOWLEDGEMENTS

The author would like to thank Dr. Tetsumori Yamashima for critically reading the manuscript. Research was supported by a grant from the Japanese Ministry of Education, Science and Technologies to T.Y. A.B.T. is supported by a grant (#L1311/03) of the National Science Fund of Bulgaria.

REFERENCES

1. Gage FH. Mammalian neural stem cells. *Science* 2000; 287: 1433–1438.
2. Garcia-Verdugo, JM, Doetsch F, Wichterle H, Lim DA, Alvarez-Buylla A. Architecture and cell types of the adult subventricular zone: in search of the stem cells. *J Neurobiol* 1998; 36: 234-248.
3. Gage FH, Kempermann G, Palmer TD, Peterson DA, Ray J. Multipotent progenitor cells in the adult dentate gyrus. *J Neurobiol* 1998; 36: 249-266.
4. Liu J, Solway K, Messing RO, Sharp FR. Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J Neurosci* 1998; 18: 7768–7778.
5. Kee NJ, Preston E, Wojtowicz JM. Enhanced neurogenesis after transient global ischemia in the dentate gyrus of the rat. *Exp Brain Res* 2001; 136: 313–320.
6. Jin K, Minami M, Lan JQ, Mao XO, Batteur S, Simon RP, *et al*. Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat. *Proc Natl Acad Sci USA* 2001; 98: 4710-4715.
7. Yagita Y, Kitagawa K, Ohtsuki T, Takasawa K-I, Miyata T, Okano H, *et al*. Neurogenesis by progenitor cells in the ischemic adult rat hippocampus. *Stroke* 2001; 32: 1890-1896.
8. Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Kawahara N, *et al*. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 2002; 110: 429-441.
9. Zhang, RL, Zhang ZG, Zhang L, Chopp M. Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia. *Neuroscience* 2001; 105: 33–41.

10. 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: 963-970.
11. Zhang R, Zhang Z, Wang L, Wang Y, Gousev A, Zhang L, *et al*. Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. *J Cereb Blood Flow Metab* 2004; in press.
12. Tonchev AB, Yamashima T, Zhao L, Okano HJ, Okano H. Proliferation of neural and neuronal progenitors after global brain ischemia in young adult macaque monkeys. *Mol Cell Neurosci* 2003; 23: 292-301.
13. Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 1997; 17: 3727-3738.
14. Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc Natl Acad Sci USA* 1997; 94: 10432-10437.
15. Scharfman HE, Goodman JH, Sollas AL. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. *J Neurosci* 2000; 20: 6144-6158.
16. Parent JM, Valentin VV, Lowenstein DH. Prolonged seizures increase proliferating neuroblasts in the adult rat subventricular zone-olfactory bulb pathway. *J Neurosci* 2002; 22: 3174-3188.
17. Wagner JP, Black IB, DiCicco-Bloom E. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J Neurosci* 1999; 19: 6006-6016.
18. Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. *J Neurosci* 2001; 21: 6706-6717.
19. Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *J Neurosci* 2001; 21: 6718-6731.
20. Fallon J, Reid S, Kinyamu R, Opole I, Opole R, Baratta J, *et al*. In vivo induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain. *Proc Natl Acad Sci USA* 2000; 97: 14686-14691.
21. Aberg MA, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *J Neurosci* 2000; 20: 2896-2903.
22. Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci USA* 2002; 99: 11946-11950.
23. Pencea V, Bingaman KD, Freedman LJ, Luskin MB. Neurogenesis in the subventricular zone and rostral migratory stream of the neonatal and adult primate forebrain. *Exp Neurol* 2001; 172: 1-16.
24. Kornack DR, Rakic P. The generation, migration, and differentiation of olfactory neurons in the adult primate brain. *Proc Natl Acad Sci USA* 2001; 98: 4752-4757.
25. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson, DA, *et al*. Neurogenesis in the adult human hippocampus. *Nat Med* 1998; 4: 1313-1317.
26. Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult Old World primates. *Proc Natl Acad Sci USA* 1999; 96: 5263-5267.
27. Kornack DR, Rakic P. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. *Proc Natl Acad Sci USA* 1999; 96: 5768-5773.
28. Gould E, Reeves AJ, Graziano MS, Gross CG. Neurogenesis in the neocortex of adult primates. *Science* 1999; 286: 548-552.
29. Gould E, Vail N, Wagers M, Gross CG. Adult-generated hippocampal and neocortical neurons in macaques have a transient existence. *Proc Natl Acad Sci USA* 2001; 98: 10910-10917.
30. Bedard A, Cossette M, Levesque M, Parent A. Proliferating cells can differentiate into neurons in the striatum of normal adult monkey. *Neurosci Lett* 2002; 328: 213-216.
31. Kornack DR, Rakic P. Cell proliferation without neurogenesis in adult primate neocortex. *Science* 2001; 294: 2127-2130.
32. Koketsu D, Mikami A, Miyamoto Y, Hisatsune T. Nonrenewal of neurons in the cerebral neocortex of adult macaque monkeys. *J Neurosci* 2003; 23: 937-942.
33. Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, *et al*. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* 2004; in press.
34. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science* 1992; 255: 1707–1017.
35. Magavi SS, Leavitt BR, Macklis JD. Induction of neurogenesis in the neocortex of adult mice. *Nature* 2000; 405: 951-955.
36. Arsenijevic Y, Villemure JG, Brunet JF, Bloch JJ, Deglon N, Kostic C, *et al*. Isolation of multipotent neural precur-

sors residing in the cortex of the adult human brain. *Exp Neurol* 2001; 170: 48-62.
37. Nunes MC, Roy NS, Keyoung HM, Goodman RR, McKhann G 2nd, Jiang L, *et al*. Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. *Nat Med* 2003; 9: 439-447.
38. Ourednik V, Ourednik J, Flax JD, Zawada WM, Hutt C, Yang C, *et al*. Segregation of human neural stem cells in the developing primate forebrain. *Science* 2001; 293: 1820-1824.
39. Yamashima T, Kohda Y, Tsuchiya K, Ueno T, Yamashita J, Yoshioka T, *et al*. Inhibition of ischaemic hippocampal neuronal death in primates with cathepsin B inhibitor CA-074: a novel strategy for neuroprotection based on 'calpain-cathepsin hypothesis'. *Eur J Neurosci* 1998; 10: 1723-1733.
40. Yamashima T. Implication of cysteine proteases calpain, cathepsin and caspase in ischemic neuronal death of primates. *Prog Neurobiol* 2000; 62: 273-295.
41. Yoshida M, Yamashima T, Zhao L, Tsuchiya K, Kohda Y, Tonchev AB, *et al*. Primate neurons show different vulnerability to transient ischemia and response to cathepsin inhibition. *Acta Neuropathol (Berl)* 2002; 104: 267-72.
42. Tonchev AB, Yamashima T, Zhao L, Okano H. Differential proliferative response in the postischemic hippocampus, temporal cortex and olfactory bulb of young adult macaque monkeys. *Glia* 2003; 42: 209-224.
43. Pagano SF, Impagnatiello F, Girelli M, Cova L, Grioni E, Onofri M, *et al*. Isolation and characterization of neural stem cells from the adult human olfactory bulb. *Stem Cells* 2000; 18: 295-300.
44. Gritti A, Bonfanti L, Doetsch F, Caille I, Alvarez-Buylla A, Lim DA, *et al*. Multipotent neural stem cells reside into the rostral extension and olfactory bulb of adult rodents. *J Neurosci* 2002; 22: 437-445.
45. Heins N, Malatesta P, Cecconi F, Nakafuku M, Tucker KL, Hack MA, *et al*. Glial cells generate neurons: the role of the transcription factor Pax6. *Nat Neurosci* 2002; 5: 308-315.
46. Altman J. Are new neurons formed in the brains of adult mammals? *Science* 1962; 135: 1127-1128.