

Chapter 2

Adult Neurogenesis in Parkinson's Disease

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Abstract Parkinson's disease (PD) is one of the most common neurodegenerative diseases. Its pathogenesis is based on diminution of neurons in the substantia nigra (SN) that under normal conditions acts as the source of dopamine in the nigrostriatal circuit. Although the etiology of PD remains poorly understood, recent understanding of the mechanisms of neurogenesis may reveal insights into the pathogenesis of PD and provide useful tools to treat PD. This review will focus on adult neurogenesis in SN, subventricular zone, striatum and olfactory bulb of PD and PD models. We also focus on adult neurogenesis in genetic PD models. The enhancement of progenitor cells may represent a potential new source of cells for replacement therapy in PD. In this review, possible treatments to enhance neurogenesis in PD models are also described.

2.1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting approximately 1% of people over the age of 65. Clinical symptoms of PD are resting tremor, rigidity, akinesia, and postural instability. Two major pathological hallmarks are noted: the selective loss of dopaminergic (DA) neurons in the substantia nigra (SN) and the formation of intraneuronal protein inclusions, termed Lewy bodies, in the remaining DA neurons. The current standard PD treatment is oral administration of L-dopa, a precursor of dopamine biosynthesis, to complement decreased dopamine levels in the striatum, with or without co-administration of dopamine agonists. However, it is symptomatic treatment not retarding nor halting the progression of the disease. A new treatment to inhibit or slow the progress of this disease is required.

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On the other hand, increasing evidence points to the presence of adult neural stem cells (NSCs) in many areas of the mammalian brain (Doetsch et al. 1997; Eriksson et al. 1998). In the adult mammalian brain, the main areas of neurogenesis are the hippocampus and subventricular zone (SVZ) near the lateral ventricle. NSCs in the SVZ migrate into the olfactory bulb (OB) via the rostral migratory stream. Adult NSCs represent an attractive source for the production of specific types of neurons in neurodegenerative disorders and for the development of new regenerative gene therapies.

This article will review adult neurogenesis in SN, SVZ, striatum (ST) and OB of PD and PD models that exemplify how adult neurogenesis responds to PD.

2.2 Adult Neurogenesis of SN in PD and PD Models

2.2.1 Adult Neurogenesis of SN in PD

To identify proliferating cells in the adult brain, retroviral labeling or BrdU methods have been used, especially in animal models. On the other hand, intrinsic molecules unique to young neurons, such as nestin, polysialylated neural cell adhesion molecule (PSA-NCAM) and doublecortin, can also be used to detect neurogenesis (Seki and Arai 1993; Fukuda et al. 2003). This is especially important in human subjects, where experimental markers like 5-bromodeoxyuridine (BrdU) or retroviral vectors are not applicable. However, these antibodies only provide adequate staining of high quality, free-floating sections fixed in buffered 4% formaldehyde solution rather than paraffin-embedded sections. Using these methods, we described a detailed examination of neurogenesis in the midbrains of PD autopsy cases (Yoshimi et al. 2005). In our manuscript, staining for intrinsic markers of neurogenesis was attempted, but doublecortin was not very clear in the SN. Nestin gave intense staining of blood vessels but no staining of neural progenitors in the SN, which was evident in the hippocampus. There were no proliferating cells in SN of PD patients.

On the other hand, a large number of PSA-NCAM-positive cells were detected in the SN pars reticulata (SNr) of some patients with PD compared to normal subjects (Fig. 2.1). In rats and a macaque monkey, the dopamine-depleted hemispheres showed more PSA-NCAM staining than the intact side. Furthermore, a small number of tyrosine hydroxylase (TH)-positive cells were PSA-NCAM-positive in these models. We speculate that the PSA-NCAM/TH double-positive cells identified in our study represent newly differentiated dopaminergic neurons in the adult SN. However, no PSA-NCAM and TH double-positive cells in PD patients were detected. The staining patterns of the SNr in humans suggested increases of PSA-NCAM-positive cells in some PD patients, but the results were not conclusive. Further studies and new technical developments to detect newborn cells are warranted to examine adult neurogenesis in the midbrain of PD subjects.

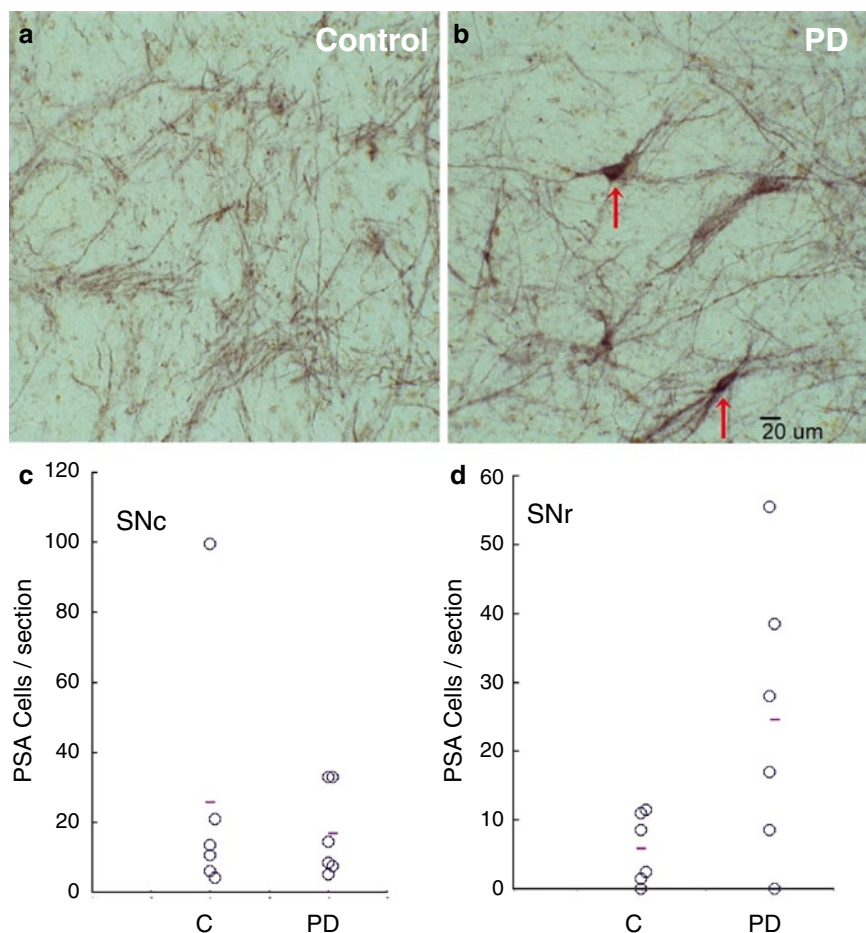


Fig. 2.1 Polysialic acid (PSA)-positive cells in the substantia nigra. Sections of humans are immunostained with monoclonal anti-PSA. **(a, b)** PSA-positive cells in human substantia nigra (arrows). SNr of a control **(a)** and Parkinson's disease **(b)** brain. **(c, d)** Number of PSA-positive cells in the SNc **(c)** and SNr **(d)** of human hemisphere sections. The average of duplicated counting of each sample by blinded observer is shown. Some nigral samples of Parkinson's disease showed the presence of large numbers of PSA-positive cells especially in the SNr

2.2.2 Adult Neurogenesis of SN in PD Models

Whether dopaminergic neurogenesis occurs in the adult SN in PD brains or in PD animal models is still a matter of debate. The potential of neurogenesis in the SN has been studied by labeling proliferative neural precursor cells with BrdU (Kay and Blum 2000; Lie et al. 2002; Zhao et al. 2003; Frielingsdorf et al. 2004). Expecting compensatory recovery (Nakatomi et al. 2002; Zhu et al. 2004; Kawai et al. 2004), neurogenesis after dopaminergic cell deprivation has been examined

as well as in intact brains. Kay and Blum (2000) reported the presence of BrdU-positive proliferative cells in the SN: some of these cells were microglia, but none of them differentiated into dopaminergic neurons. In another study, neuronal progenitor cells isolated from the SN of rats could differentiate into neurons in the hippocampus but not in the midbrain (Lie et al. 2002). Dopaminergic neurons with BrdU-positive nuclei were found in the SN, which were considered to have migrated from the midbrain aqueduct (Zhao et al. 2003), although a different conclusion was reported in another study (Frielingsdorf et al. 2004). The discrepancy between the two studies (Zhao et al. 2003; Frielingsdorf et al. 2004) was due to technical uncertainty in confocal microscopy to locate the BrdU-positive nuclei within the cytoplasm. On the other hand, it was reported recently that mature neurons become immunopositive for proliferative cell markers in some neurodegenerative conditions (Hoglinger et al. 2007). It is important to distinguish such cell death cascades from cell proliferation and neurogenesis in the adult brain.

To identify living proliferating cells, retroviral labeling is more selective than BrdU (Lie et al. 2002; Gould and Gross 2002) because retroviral integration into DNA requires new DNA synthesis (Fig. 2.2). We have already shown efficient labeling of NSCs by retroviral infection, both in vitro and in vivo (Kaneko et al. 2001; Suzuki et al. 2002; Yamada et al. 2004; Tanaka et al. 2004). Enhanced green fluorescent protein (GFP) filled the cytoplasm of the cells and expressed a clear Golgi-like morphology of infected cells. Moreover, local injection in the brain tissue allowed a clear mapping of the migration route (Yamada et al. 2004; Suzuki and Goldman 2003) (Fig. 2.3). First, proliferating cells in SN were labeled efficiently with retroviral infection of GFP. Subsequent differentiation of labeled cells was examined, and many infected cells became microglia but none had differentiated into TH-positive neurons at 4 weeks postinfection, in both intact and MPTP-treated rodents. Second, PSA-NCAM-like immunoreactivity, indicative of newly differentiated neurons, was detected in the SN of rodents and primates. In rats and a macaque monkey, the dopamine-depleted hemispheres showed more PSA-NCAM staining than the intact side. A small number of TH-positive cells were

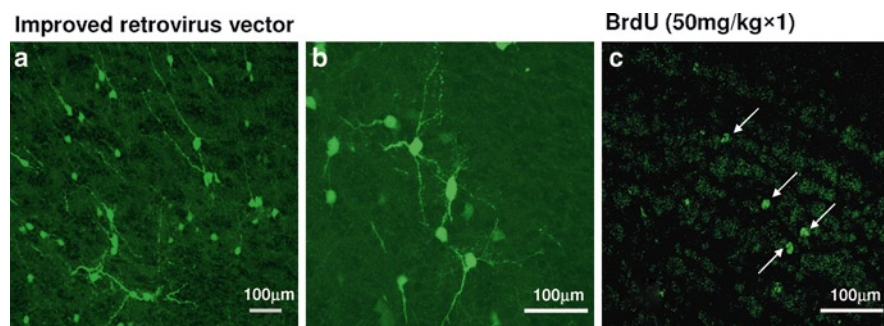


Fig. 2.2 Improved retrovirus vector versus BrdU as a marker for neurogenesis: (a, b) differentiated cells by retrovirus injection; (c) BrdU positive cells by immunohistochemistry. It is easy to detect the detailed cell morphology by the retrovirus vector marking

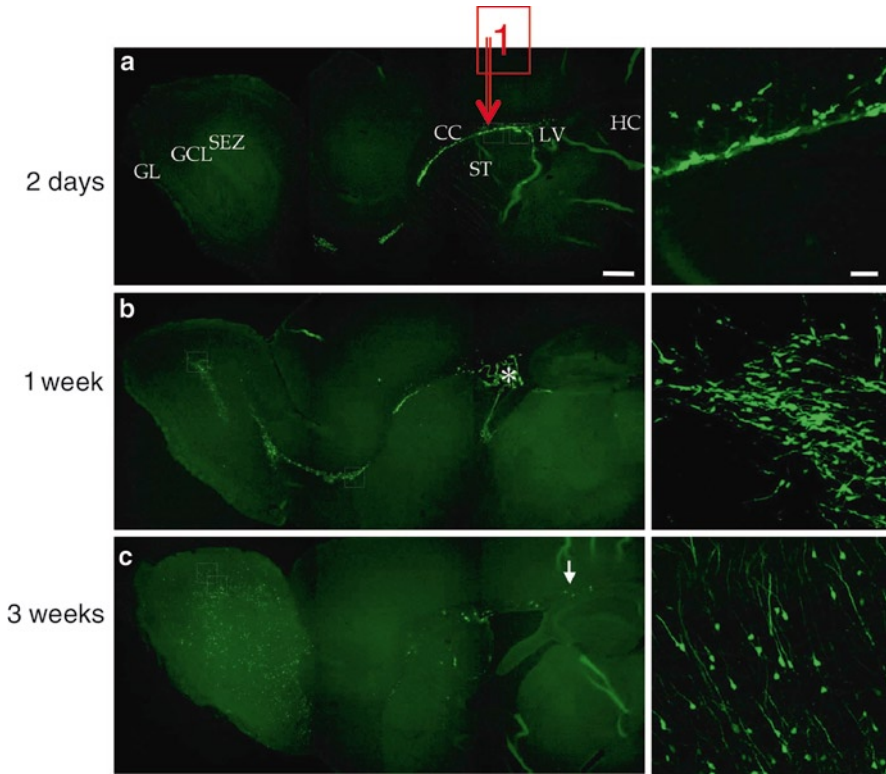


Fig. 2.3 Migration from SVZ to OB in rat retrovirus vector encoded green fluorescent protein are microinjected into the subventricular zone (*red arrow*). The proliferating cells in the subventricular zone are detected as GFP positive cells: 1 week after infection, the GFP positive cells are present in the rostral migratory stream; 3 weeks after infection, the GFP positive cells are present in the olfactory bulb. Some GFP positive cells are also positive for MAP2 as a neuronal marker

PSA-NCAM-positive (Yoshimi et al. 2005). We speculate that the PSA-NCAM/TH double-positive cells identified in our study represent newly differentiated dopaminergic neurons in the adult SN of PD models. In addition, Parish et al. describe the creation of a salamander 6-hydroxydopamine model of PD to examine midbrain DA regeneration (Parish et al. 2007). They demonstrate a robust and complete regeneration of the mesencephalic and diencephalic DA system after elimination of DA neurons.

2.3 Adult Neurogenesis of SVZ in PD and PD Models

In the mammalian brain, the main areas of neurogenesis are the hippocampus and SVZ near the lateral ventricle. The NSCs in the SVZ migrate into the OB via the rostral migratory stream. It is well known that changes occurring in the SVZ

depend upon the pathological condition. Postmortem analysis of human brains suggested that stroke (Macas et al. 2006), Huntington's disease (Curtis et al. 2003) and multiple sclerosis (Nait-Oumesmar et al. 2007) lead to an increase in precursor cell proliferation in the adult human SVZ. In this section, I focus on changes of adult SVZ neurogenesis in PD and PD models.

2.3.1 Adult Neurogenesis of SVZ in PD

Using postmortem brains of PD patients, Hoglinger et al. reported changes in the SVZ of PD patients by immunohistochemistry (Hoglinger et al. 2004). The numbers of proliferating cells in the SVZ are reduced in postmortem brains of individuals with PD. They also found that dopaminergic fibers contact epidermal growth factor receptor (EGFR)-labeled cells in the normal human SVZ. They concluded that the generation of neural precursor cells is impaired in PD as a consequence of dopaminergic denervation.

2.3.2 Adult Neurogenesis of SVZ in PD Models

The neurogenetic potential of SVZ in PD models is a highly debated topic. Several groups have reported that experimental depletion of dopamine in rodents decreased precursor cell proliferation in the SVZ (Hoglinger et al. 2004; Baker et al. 2004). These results mainly rely on PCNA staining using immunohistochemistry. Hoglinger et al. has also shown that there are dopaminergic afferents in the adult mammalian SVZ (Baker et al. 2004). D1L receptors were present in the cytoplasm of type C (transit amplifying) cells and in the plasma membranes of type A (neuroblast) cells. D2L receptors were most abundant in C-cells. They concluded that there was dopaminergic regulation of neural precursor cell proliferation in the adult brain, and that dopaminergic denervation may be responsible for the reduction in neural precursors.

On the other hand, some groups have reported increased proliferation of neural precursors in the SVZ of PD models. Liu et al. (2006) unilaterally lesioned the nigrostriatal pathway by injection of 6-hydroxydopamine (6-OHDA), and then BrdU was injected (ip). They showed that the BrdU-positive cells increased significantly in the SVZ ipsilateral to the lesion. The differences in these results in each group could be from differences in the toxin treatment to create the PD models or differences in the methods to detect proliferating cells. We found alterations of the differentiation-related molecular expression in SVZ after acute or chronic MPTP treatment (Oizumi et al. 2008). We examined the relationship between proliferation and differentiation of NSCs in SVZ of both acute and chronic PD models. Only acute MPTP treatment significantly increased the areas of glial fibrillary acidic protein (GFAP)-expressing cells and decreased the areas of PSA-NCAM-expressing

cells in the SVZ. In the case of caspase-11 knockout mice, MPTP did not induce alterations in the areas of GFAP-expressing cells and PSA-NCAM-expressing cells. Our results suggest that neuroinflammation related to the caspase-11 cascade in the striatum also regulates differentiation of NSCs in the SVZ of a mouse model of PD.

Regarding SVZ cell death in PD models, He et al. reported the details of the changes in the SVZ after exposure of MPTP in mice (He et al. 2006). They detected apoptotic cells in the SVZ that peaked 24 h after MPTP treatment. In this study, the majority of cells undergoing apoptosis in the SVZ were identified as migrating neuroblast (type A cells). MPTP may also directly interact with cells in the SVZ in addition to regulation by the dopaminergic fibers from SN.

Problems of evaluating SVZ changes include difficulties in identifying and counting cell numbers, because these cells are very dense in a narrow space. New methods are needed for detecting significant changes of cell densities over the entire area of immunostained sections.

2.4 Adult Neurogenesis of OB in PD and PD Models

Olfactory deficits are an early and common symptom in PD (Ponsen et al. 2004). In the OB, TH-positive cells are present in the glomerular layer (GL), which is the most superficial layer in the OB. As most newborn SVZ cells migrate to the OB to form new neurons, the changes of neurogenesis in OB could be important for the pathogenesis of olfactory deficits as PD symptoms.

2.4.1 Adult Neurogenesis of OB in PD

Olfactory stimulation clearly established the presence of olfactory impairment in PD (Ponsen et al. 2004; Barz et al. 1997). This olfactory deficit is so reliable that it is used in the diagnosis of idiopathic PD (Hawkes and Shephard 1998). On an anatomical level, work by Hawkes and colleagues (Pearce et al. 1995; Hawkes et al. 1997) indicated significant neuronal loss in the anterior olfactory nucleus (AON) obtained from postmortem of patients with IPD. In addition, recent data suggest that neurodegeneration at early PD stages involves the olfactory system, including the OB (Del Tredici et al. 2002; Braak et al. 2003).

2.4.2 Adult Neurogenesis of OB in PD Models

Several groups have created PD models and examined neurogenesis in the OB. Hoglinger et al. examined newborn neurons in the OB of mice with four intraperitoneal injections of 10 mg/kg of MPTP by BrdU treatment (Hoglinger et al. 2004). They reported that fewer BrdU positive cells had migrated to the OB in MPTP-lesioned

than in control mice, and fewer newborn neurons had integrated into the OB, as assessed by the colocalization of BrdU with the neuronal marker neuronal nuclear antigen (NeuN) by confocal microscopy. They suggested that chronic impairment of neural (neuronal or glial) regeneration might also contribute to olfactory impairment in PD.

In 6-OHDA models, Winner et al. also examined the details of OB neurogenesis after treating animals with BrdU (Winner et al. 2006). They found that transient decreases in the granule cell layer contrasted with a sustained increase of newly generated neurons in the GL. They concluded that the loss of dopaminergic input to the SVZ led to a distinct cell fate decision towards stimulation of dopaminergic neurogenesis in the OB GL.

We also reported enhanced neurogenesis in the OB after dopaminergic neuron loss by MPTP (Yamada et al. 2004) (Fig. 2.3). Neurogenesis was confirmed mainly by the uptake of BrdU, a marker of proliferating cells, but methodological problems related to BrdU labeling might result in inaccurate findings with respect to specificity, toxicity and incorporation into normal/lesioned brain. For a better identification of neurogenesis, we used a modified retroviral vector reported previously. First, we investigated the population dynamics of newly generated neurons in different regions of OB including the GL, the most superficial layer of OB. Quantification of neurogenesis in OB revealed by our retroviral vector was substantially similar to that found by BrdU-based methods. Next, we investigated the influence of dopaminergic neuron loss induced by MPTP, a selective toxin for dopaminergic neurons, on dopaminergic neurogenesis in the OB. One week after MPTP intoxication, neurogenesis of dopaminergic neurons in the OB increased by threefold while there was minimal influence on nondopaminergic neurogenesis. These results indicate profiles of selective neurogenesis in OB in response to various lesions.

In addition, adult neurogenesis may be enhanced as a repair system in the TH-positive cells of the OB after MPTP administration in PD models (Hayakawa et al. 2007). The isolation of NSCs from the OB after MPTP administration has helped to establish the cellular basis of neurogenesis and supports a role for the transplant-mediated treatment of PD.

2.5 Adult Neurogenesis in Genetic PD Models

Mutation or duplication in the α -synuclein gene is a cause of familial PD. Transgenic mice expressing wild-type (WT) mouse and mutant (mut) human α -synuclein serves as a good model of PD. Using these mice, Winner et al. have shown that accumulation of WT and mut- α -synuclein in the CNS of tg mice results in reduced neurogenesis in the OB and hippocampus (Winner et al. 2004, 2008).

The studies in α -synuclein-overexpressing mouse embryonic stem (ES) cells and in young-adult α -synuclein tg mice by Crews et al. offer a clue suggesting that accumulation of α -synuclein might impair neurogenesis by reducing NPC survival via downregulation of Notch-1 expression (Crews et al. 2008). A recent report also

suggests that Notch activity supports the survival of both progenitors and newly differentiating cells in the developing nervous system (Mason et al. 2006). These results suggest that accumulation of α -synuclein might impair survival of NPCs by interfering with the Notch signaling pathway.

We investigated neurosphere formation *in vitro* and migration of NSCs *in vivo* after transduction of an α -synuclein-encoding retroviral vector (alpha-syn) to characterize the function of α -synuclein in NSCs. Overexpression of alpha-syn caused less effective formation of neurospheres and induced morphological changes. Fluorescence-activated cell sorting showed diminished NSC cell cycle progression induced by overexpression of α -synuclein. Intriguingly, suppression of NSC migration along the rostral migratory stream was observed when the α -synuclein-encoding vector was directly injected into the SVZ of mice *in vivo*. These results indicate that the accumulation of α -synuclein in NSCs led to a cell-autonomous influence on the generation of neural progenitors, suggesting that effective elimination of toxic species of α -synuclein could pave the way to halt and possibly reverse the clinical symptoms of patients with α -synucleinopathy (Tani et al. 2010).

2.6 Therapeutic Window for Adult Neurogenesis in PD

The enhancement of progenitor cells may represent a potential new source of cells for replacement therapy in PD. The possible treatment to enhance neurogenesis in PD models is discussed below.

Dopamine D2L (D2, D3 and D4 receptors) agonists were reported to enhance the damaged SVZ in PD models (Hoglinger et al. 2004). Especially, Van kampen and colleagues reported that D3 receptor stimulation promoted proliferation in the SVZ (Van Kampen et al. 2004) and SN (Van Kampen and Robertson 2005) in adult rat. The same group examined the cell proliferative, neurogenic, and behavioral effects of a dopamine D3 receptor agonist in a 6-hydroxydopamine model of PD (Van Kampen and Eckman 2006). They observed a significant induction of cell proliferation in the SNc with a time-dependent adoption of a neuronal dopaminergic phenotype in many of these cells. The dopamine D(3) receptor may play a key role in SVZ neurogenesis, as a particularly strong expression of D(3) receptor mRNA occurs in the proliferative SVZ during prenatal and early postnatal ontogeny.

Winner et al. reported that treatment with the oral dopamine receptor agonist pramipexole (PPX) selectively increases adult neurogenesis in the SVZ-OB system by increasing proliferation and cell survival of newly generated neurons. They also demonstrated that D2 and D3 receptors are present on adult rat SVZ-derived neural progenitors *in vitro*, and PPX specifically increased mRNA levels of EGFR and paired box gene 6 (Pax6) (Winner et al. 2009). However, several researchers have reported that dopamine antagonist antipsychotic drugs also enhance neurogenesis (Kippin et al. 2005; Dawirs et al. 1998). In addition, Milosevic J et al. reported that Dopamine D2/D3 receptor stimulation fails to promote dopaminergic neurogenesis

of murine and human midbrain-derived neural precursor cells by microarray data analysis and quantitative RT-PCR (Milosevic et al. 2007). In this area, the function of specific dopamine receptor agonists in neurogenesis is still debated.

2.6.1 Neurotrophic Factors

Neural progenitor cells respond to several neurotrophic factors that affect cell proliferation, migration and maturation. In PD models, Copper et al. found that intrastriatal transforming growth factor alpha delivery induced proliferation and migration of endogenous adult neural progenitor cells without differentiation into dopaminergic neurons (Cooper and Isacson 2004). Platelet-derived growth factor (PDGF-BB) and brain-derived neurotrophic factor (BDNF) also induce striatal neurogenesis in PD models (Mohapel et al. 2005). The effects of i.c.v. infused PDGF-BB and BDNF on cell genesis, as assessed with BrdU incorporation, were studied in adult rats with unilateral 6-hydroxydopamine lesions. It is well known that the most potent neurotrophic factor for dopamine neurons described so far is the glial-cell-line-derived neurotrophic factor (GDNF) (Gash et al. 1996). Although Chen et al. (2005) indicated a GDNF-mediated increase in cell proliferation, providing further evidence for the restorative actions of this growth factor, they failed to demonstrate that the TH-positive cells were newly generated.

Fibroblast growth factor 2 also enhances striatal and nigral neurogenesis in the acute MPTP model of PD as examined by incorporation of BrdU in cells expressing an immature neuronal marker (Peng et al. 2008).

Yang et al. investigated the potential role of ciliary neurotrophic factor (CNTF), because it is predominantly produced in the nervous system and is an endogenous regulator of neurogenesis (Yang et al. 2008). They reported that nigrostriatal denervation did not affect SVZ proliferation in CNTF^{-/-} mice, suggesting that the dopaminergic innervation normally regulates neurogenesis through CNTF.

2.6.2 G-CSF

Granulocyte colony-stimulating factor (G-CSF) is a member of the cytokine family of growth factors and is clinically used for the treatment of neutropenia. G-CSF stimulates the proliferation, survival, and maturation of cells committed to the neutrophilic granulocyte (NG) lineage by binding to a specific G-CSF receptor (G-CSFR) (Hartung 1998). In addition to its use for the treatment of different types of neutropenia in humans, G-CSF also has trophic effects on neuronal cells; several recent reports have described the neuroprotective effects of G-CSF in stroke (Schabitz et al. 2003; Komine-Kobayashi et al. 2006). One of the main mechanisms of action for this effect is activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway through intracellular signaling from G-CSF-G-CSFR binding in cerebral ischemia (Komine-Kobayashi et al. 2006;

Jung et al. 2006). Furthermore, recent studies suggest that G-CSF triggers neurogenesis in an animal model of neurological disorders (Sehara et al. 2007; Tsai et al. 2007). G-CSF could induce the differentiation of NSCs in vitro, and this effect paralleled the in vivo finding that G-CSF also induced neurogenesis and subsequently enhanced functional recovery after cortical cerebral ischemia (Schneider et al. 2005). In PD models, several reports indicate that G-CSF rescues dopaminergic cell loss (Meuer et al. 2006; Cao et al. 2006; Huang et al. 2007). In our experiment, we examined whether G-CSF can protect dopaminergic neurons against MPTP-induced cell death in a mouse model of PD. G-CSF significantly prevented MPTP-induced loss of TH-positive neurons ($p < 0.05$), increased Bcl-2 protein and decreased Bax protein expression. We now plan to examine the relationship between G-CSF treatment and changes in neurogenesis in PD models.

2.7 Conclusion

Dopamine is an important molecule in neurogenesis. Therefore, many investigators now focus on neurogenesis in PD. However, controversy persists regarding neurogenesis in SN and/or in PD models. These problems should be resolved by progress in techniques to identify neurogenesis in vivo. Another goal is to identify new treatments or drugs to upregulate or enhance neurogenesis of SVZ, ST or SN in PD. We are now assaying for several drugs which possess such effects to rescue the degeneration in PD as a replacement therapy. Another concern is potential side effects of drugs to enhance neurogenesis in PD models. Excessive enhancement of neurogenesis could cause the problems of tumor formation after exposure to such drugs. Newborn neurons need to migrate and differentiate and need to work functionally at the appropriate areas. Some papers have indicated functional recovery in PD models but this may not indicate the function of new neurons. Cell numbers are controlled by an intricate balance of cell death and cell proliferation (Hipfner and Cohen 2004). Deregulation of the apoptotic/proliferative balance leads to impaired development and many diseases including neurodegenerative disorders, viral infections, and tumors. Newborn neurons may help to keep the balance, but they also need appropriate cell death signals. To be or not to be? It could be an eternal theme in human beings.

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References

- Baker SA, Baker KA, Hagg T. Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone. *Eur J Neurosci* 2004;20:575–579.
- Barz S, Hummel T, Pauli E, Majer M, Lang CJ, Kobal G. Chemosensory event-related potentials in response to trigeminal and olfactory stimulation in idiopathic Parkinson's disease. *Neurology* 1997;49:1424–1431.

- Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.
- Cao XQ, Arai H, Ren YR, et al. Recombinant human granulocyte colony-stimulating factor protects against MPTP-induced dopaminergic cell death in mice by altering Bcl-2/Bax expression levels. *J Neurochem* 2006;99:861–867.
- Chen Y, Ai Y, Slevin JR, Maley BE, Gash DM. Progenitor proliferation in the adult hippocampus and substantia nigra induced by glial cell line-derived neurotrophic factor. *Exp Neurol* 2005;196:87–95.
- Cooper O, Isacson O. Intrastratial transforming growth factor alpha delivery to a model of Parkinson's disease induces proliferation and migration of endogenous adult neural progenitor cells without differentiation into dopaminergic neurons. *J Neurosci* 2004;24:8924–8931.
- Crews L, Mizuno H, Desplats P, et al. Alpha-synuclein alters Notch-1 expression and neurogenesis in mouse embryonic stem cells and in the hippocampus of transgenic mice. *J Neurosci* 2008;28:4250–4260.
- Curtis MA, Penney EB, Pearson AG, et al. Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc Natl Acad Sci USA* 2003;100:9023–9027.
- Dawirs RR, Hildebrandt K, Teuchert-Noodt G. Adult treatment with haloperidol increases dentate granule cell proliferation in the gerbil hippocampus. *J Neural Transm* 1998;105:317–327.
- Del Tredici K, Rub U, De Vos RA, Bohl JR, Braak H. Where does Parkinson disease pathology begin in the brain? *J Neuropathol Exp Neurol* 2002;61:413–426.
- Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J Neurosci* 1997;17:5046–5061.
- Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;4:1313–1317.
- Frielingsdorf H, Schwarz K, Brundin P, Mohapel P. No evidence for new dopaminergic neurons in the adult mammalian substantia nigra. *Proc Natl Acad Sci USA* 2004;101:10177–10182.
- Fukuda S, Kato F, Tozuka Y, Yamaguchi M, Miyamoto Y, Hisatsune T. Two distinct subpopulations of nestin-positive cells in adult mouse dentate gyrus. *J Neurosci* 2003;23:9357–9366.
- Gash DM, Zhang Z, Ovadia A, et al. Functional recovery in Parkinsonian monkeys treated with GDNF. *Nature* 1996;380:252–255.
- Gould E, Gross CG. Neurogenesis in adult mammals: some progress and problems. *J Neurosci* 2002;22:619–623.
- Hartung T. Anti-inflammatory effects of granulocyte colony-stimulating factor. *Curr Opin Hematol* 1998;5:221–225.
- Hawkes CH, Shephard BC. Olfactory evoked responses and identification tests in neurological disease. *Ann N Y Acad Sci* 1998;855:608–615.
- Hawkes CH, Shephard BC, Daniel SE. Olfactory dysfunction in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;62:436–446.
- Hayakawa H, Hayashita-Kinoh H, Nihira T, Seki T, Mizuno Y, Mochizuki H. The isolation of neural stem cells from the olfactory bulb of Parkinson's disease model. *Neurosci Res* 2007;57:393–398.
- He XJ, Nakayama H, Dong M, et al. Evidence of apoptosis in the subventricular zone and rostral migratory stream in the MPTP mouse model of Parkinson disease. *J Neuropathol Exp Neurol* 2006;65:873–882.
- Hipfner DR, Cohen SM. Connecting proliferation and apoptosis in development and disease. *Nat Rev Mol Cell Biol* 2004;5:805–815.
- Hoglinger GU, Rizk P, Muriel MP, et al. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. *Nat Neurosci* 2004;7:726–735.
- Hoglinger GU, Breunig JJ, Depboylu C, et al. The pRb/E2F cell-cycle pathway mediates cell death in Parkinson's disease. *Proc Natl Acad Sci USA* 2007;104:3585–3590.
- Huang HY, Lin SZ, Kuo JS, Chen WF, Wang MJ. G-CSF protects dopaminergic neurons from 6-OHDA-induced toxicity via the ERK pathway. *Neurobiol Aging* 2007;28:1258–1269.

- Jung KH, Chu K, Lee ST, et al. Granulocyte colony-stimulating factor stimulates neurogenesis via vascular endothelial growth factor with STAT activation. *Brain Res* 2006;1073–1074:190–201.
- Kaneko S, Onodera M, Fujiki Y, Nagasawa T, Nakauchi H. Simplified retroviral vector gcsap with murine stem cell virus long terminal repeat allows high and continued expression of enhanced green fluorescent protein by human hematopoietic progenitors engrafted in nonobese diabetic/severe combined immunodeficient mice. *Hum Gene Ther* 2001;12:35–44.
- Kawai T, Takagi N, Miyake-Takagi K, Okuyama N, Mochizuki N, Takeo S. Characterization of BrdU-positive neurons induced by transient global ischemia in adult hippocampus. *J Cereb Blood Flow Metab* 2004;24:548–555.
- Kay JN, Blum M. Differential response of ventral midbrain and striatal progenitor cells to lesions of the nigrostriatal dopaminergic projection. *Dev Neurosci* 2000;22:56–67.
- Kippin TE, Kapur S, van der Kooy D. Dopamine specifically inhibits forebrain neural stem cell proliferation, suggesting a novel effect of antipsychotic drugs. *J Neurosci* 2005;25:5815–5823.
- Komine-Kobayashi M, Zhang N, Liu M, et al. Neuroprotective effect of recombinant human granulocyte colony-stimulating factor in transient focal ischemia of mice. *J Cereb Blood Flow Metab* 2006;26:402–413.
- Lie DC, Dziewczapolski G, Willhoite AR, Kaspar BK, Shults CW, Gage FH. The adult substantia nigra contains progenitor cells with neurogenic potential. *J Neurosci* 2002;22:6639–6649.
- Liu BF, Gao EJ, Zeng XZ, et al. Proliferation of neural precursors in the subventricular zone after chemical lesions of the nigrostriatal pathway in rat brain. *Brain Res* 2006;1106:30–39.
- Macas J, Nern C, Plate KH, Momma S. Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. *J Neurosci* 2006;26:13114–13119.
- Mason HA, Rakowiecki SM, Gridley T, Fishell G. Loss of notch activity in the developing central nervous system leads to increased cell death. *Dev Neurosci* 2006;28:49–57.
- Meuer K, Pitzer C, Teismann P, et al. Granulocyte-colony stimulating factor is neuroprotective in a model of Parkinson's disease. *J Neurochem* 2006;97:675–686.
- Milosevic J, Schwarz SC, Maisel M, et al. Dopamine D2/D3 receptor stimulation fails to promote dopaminergic neurogenesis of murine and human midbrain-derived neural precursor cells in vitro. *Stem Cells Dev* 2007;16:625–635.
- Mohapel P, Frielingsdorf H, Haggblad J, Zachrisson O, Brundin P. Platelet-derived growth factor (PDGF-BB) and brain-derived neurotrophic factor (BDNF) induce striatal neurogenesis in adult rats with 6-hydroxydopamine lesions. *Neuroscience* 2005;132:767–776.
- Nait-Oumesmar B, Picard-Riera N, Kerninon C, et al. Activation of the subventricular zone in multiple sclerosis: evidence for early glial progenitors. *Proc Natl Acad Sci USA* 2007;104:4694–4699.
- Nakatomi H, Kuriu T, Okabe S, et al. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 2002;110:429–441.
- Oizumi H, Hayashita-Kinoh H, Hayakawa H, et al. Alteration in the differentiation-related molecular expression in the subventricular zone in a mouse model of Parkinson's disease. *Neurosci Res* 2008;60:15–21.
- Parish CL, Beljajeva A, Arenas E, Simon A. Midbrain dopaminergic neurogenesis and behavioural recovery in a salamander lesion-induced regeneration model. *Development* 2007;134:2881–2887.
- Pearce RK, Hawkes CH, Daniel SE. The anterior olfactory nucleus in Parkinson's disease. *Mov Disord* 1995;10:283–287.
- Peng J, Xie L, Jin K, Greenberg DA, Andersen JK. Fibroblast growth factor 2 enhances striatal and nigral neurogenesis in the acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *Neuroscience* 2008;153:664–670.
- Ponsen MM, Stoffers D, Booi J, van Eck-Smit BL, Wolters E, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol* 2004;56:173–181.
- Schabitz WR, Kollmar R, Schwaninger M, et al. Neuroprotective effect of granulocyte colony-stimulating factor after focal cerebral ischemia. *Stroke* 2003;34:745–751.
- Schneider A, Kruger C, Steigleder T, et al. The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. *J Clin Invest* 2005;115:2083–2098.

- Sehara Y, Hayashi T, Deguchi K, et al. Potentiation of neurogenesis and angiogenesis by G-CSF after focal cerebral ischemia in rats. *Brain Res* 2007;1151:142–149.
- Seki T, Arai Y. Highly polysialylated neural cell adhesion molecule (NCAM-H) is expressed by newly generated granule cells in the dentate gyrus of the adult rat. *J Neurosci* 1993;13:2351–2358.
- Suzuki SO, Goldman JE. Multiple cell populations in the early postnatal subventricular zone take distinct migratory pathways: a dynamic study of glial and neuronal progenitor migration. *J Neurosci* 2003;23:4240–4250.
- Suzuki A, Obi K, Urabe T, et al. Feasibility of ex vivo gene therapy for neurological disorders using the new retroviral vector GCDNsap packaged in the vesicular stomatitis virus G protein. *J Neurochem* 2002;82:953–960.
- Tanaka R, Yamashiro K, Mochizuki H, et al. Neurogenesis after transient global ischemia in the adult hippocampus visualized by improved retroviral vector. *Stroke* 2004;35:1454–1459.
- Tani M, Hayakawa H, Yasuda T, Nihira T, Hattori N, Mizuno Y, Mochizuki H. Ectopic expression of alpha-synuclein affects the migration of neural stem cells in mouse subventricular zone. *J Neurochem*. 2010;115:854–863.
- Tsai KJ, Tsai YC, Shen CK. G-CSF rescues the memory impairment of animal models of Alzheimer's disease. *J Exp Med* 2007;204:1273–1280.
- Van Kampen JM, Eckman CB. Dopamine D3 receptor agonist delivery to a model of Parkinson's disease restores the nigrostriatal pathway and improves locomotor behavior. *J Neurosci* 2006;26:7272–7280.
- Van Kampen JM, Robertson HA. A possible role for dopamine D3 receptor stimulation in the induction of neurogenesis in the adult rat substantia nigra. *Neuroscience* 2005;136:381–386.
- Van Kampen JM, Hagg T, Robertson HA. Induction of neurogenesis in the adult rat subventricular zone and neostriatum following dopamine D3 receptor stimulation. *Eur J Neurosci* 2004;19:2377–2387.
- Winner B, Lie DC, Rockenstein E, et al. Human wild-type alpha-synuclein impairs neurogenesis. *J Neuropathol Exp Neurol* 2004;63:1155–1166.
- Winner B, Geyer M, Couillard-Despres S, et al. Striatal deafferentation increases dopaminergic neurogenesis in the adult olfactory bulb. *Exp Neurol* 2006;197:113–121.
- Winner B, Rockenstein E, Lie DC, et al. Mutant alpha-synuclein exacerbates age-related decrease of neurogenesis. *Neurobiol Aging* 2008;29:913–925.
- Winner B, Desplats P, Hagl C, et al. Dopamine receptor activation promotes adult neurogenesis in an acute Parkinson model. *Exp Neurol* 2009;219:543–552.
- Yamada M, Onodera M, Mizuno Y, Mochizuki H. Neurogenesis in olfactory bulb identified by retroviral labeling in normal and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated adult mice. *Neuroscience* 2004;124:173–181.
- Yang P, Arnold SA, Habas A, Hetman M, Hagg T. Ciliary neurotrophic factor mediates dopamine D2 receptor-induced CNS neurogenesis in adult mice. *J Neurosci* 2008;28:2231–2241.
- Yoshimi K, Ren YR, Seki T, et al. Possibility for neurogenesis in substantia nigra of Parkinsonian brain. *Ann Neurol* 2005;58:31–40.
- Zhao M, Momma S, Delfani K, et al. Evidence for neurogenesis in the adult mammalian substantia nigra. *Proc Natl Acad Sci USA* 2003;100:7925–7930.
- Zhu DY, Lau L, Liu SH, Wei JS, Lu YM. Activation of cAMP-response-element-binding protein (CREB) after focal cerebral ischemia stimulates neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* 2004;101:9453–9457.

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Clinical Implications

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