

Commentary

On the move to stimulate cell plasticity in the substantia nigra in Parkinson's disease

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Background. Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting over 1% of individuals over 50 years of age. A major neuropathological feature to PD is the progressive degeneration of dopaminergic neurons in substantia nigra leading to a dramatic reduction of dopamine levels in the striatum. The study by Steiner and coworkers published in this issue of *Experimental Neurology* (Steiner et al., this issue) examined functional and morphological effects of housing rats with unilateral neurotoxin-induced lesions of the nigrostriatal pathway in an enriched environment involving physical activity. Enriched environment typically involves housing rodents in large groups with access to appealing "toys", e.g., ladders, tubes and boxes. The additional physical activity consisted of the rats walking on a rotarod for 10–20 min once daily (Steiner et al., this issue). In the unilateral rat model of PD, a combination of altered housing conditions and daily physical activity induced an increase in the number of bromodeoxyuridine (BrdU)-labeled, newborn cells in the substantia nigra. The lesion itself, induced by intrastriatal injections of the neurotoxin 6-hydroxydopamine, did not affect the rate of cell proliferation in the substantia nigra, which is at variance with some earlier studies that have reported increases following nigral lesions (Kay and Blum, 2000; Mohapel et al., 2005; Shan et al., 2006; Zhao et al., 2003). The majority of the BrdU-positive, newborn cells were also positive for NG2, glial fibrillary acid protein (GFAP) or the microglial marker Iba1. The chondroitin sulfate proteoglycan NG2 is expressed on the surface of neural cells whose role in the brain is not fully established. The NG2 positive cells have been called "poly-

dendrocytes" (Nishiyama et al., 2002) and have also been suggested to be oligodendrocyte precursors. In contrast, none of the newborn, BrdU-stained cells in the substantia nigra expressed the markers for neuroblasts and neurons that were studied, i.e., doublecortin, NeuN and tyrosine hydroxylase. Around one third of the BrdU-labeled cells were not labeled by any of the phenotype-specific markers that were examined. Earlier studies have reported the occurrence of angiogenesis in the substantia nigra following dopamine-denervating lesions (Barcia et al., 2005; Carvey et al., 2005). It is therefore possible that newborn cells with an unidentified phenotype were of vascular origin, although endothelial markers were not examined in this study. Steiner and collaborators also report that enriched environment combined with physical activity improves recovery of motor function in one of the studied groups. Their conclusion is based on that there was a significant reduction in amphetamine-induced rotation in rats studied after 7 weeks compared to a similar group tested at 4 weeks after lesion, and that the difference was only significant in rats subjected to exercise in combination with enriched environment. This behavioral recovery was not, however, striking. Also the rats housed under normal conditions exhibited a trend for spontaneous normalization of rotational asymmetry between 4 and 7 weeks post-lesion (see Fig. 2 in (Steiner et al., this issue)). Therefore, despite the clearly significant changes in cellular plasticity in the substantia nigra, there was not a clearly significant impact of the housing conditions and physical activity on functional recovery of the lesion-induced deficits as assessed by rotational behavior. Further studies using behavioral tests that do not involve drug treatment (e.g., spontaneous rotation, forelimb use for stepping or reaching) may help to determine whether the enriched environmental conditions employed by

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Steiner and colleagues can improve function in the nigrostriatal system in this rat model of PD.

Why is it interesting to study the effects of environmental stimuli on functional recovery in Parkinson's disease? The study by Steiner and colleagues contributes novel evidence supporting an important concept, namely that functional and structural plasticity after brain damage can be promoted by an enriched environmental conditions, involving also increased physical activity. As mentioned earlier, in experimental work with rodents, housing in an enriched environment typically involves keeping several animals together in one cage and exposing them to various objects and toys which they can explore and climb on (Will et al., 2004). The experimentally enriched environment can be viewed as an attempt to partially mimic some of the living conditions that rodents normally experience in the wild. Thus, animals are exposed to more sensory stimuli than are present in the “impoverished environment” represented by standard housing conditions. Exposure to enriched environment can improve the performance of normal rodents in, e.g., learning and memory tests (Will et al., 2004). Importantly, numerous earlier studies have shown that an enriched environment increases functional recovery from different forms of experimental brain damage or neurodegenerative disease in rodents (Will et al., 2004). For example, rodents subjected to experimental stroke and brain trauma exhibit enhanced recovery in a variety of functional tests if they are housed under enriched environment conditions (Belayev et al., 2003; Johansson, 2004; Passineau et al., 2001; Puurunen and Sivenius, 2002) (Biemaskie and Corbett, 2001; Nygren and Wieloch, 2005). Similarly, in transgenic mouse models of slowly progressing neurodegenerative disorders, such as Huntington's disease and Alzheimer's disease, exposure to an enriched environment can retard development of behavioral deficits, brain pathology and in some cases even prolong survival of the animals (Glass et al., 2004; Hockly et al., 2002; Jankowsky et al., 2005; Lazarov et al., 2005; Schilling et al., 2004; Spires et al., 2004a,b; van Dellen et al., 2000). In the field of PD research, housing of mice in an enriched environment for 2 months has been found to confer partial resistance to the toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which targets nigrostriatal dopamine neurons (Bezard et al., 2003). A particular form of enriched environment involving a combination of exercise, social interactions and learning was tested by Faherty and coworkers (Faherty et al., 2005). Mice exposed to such an environment for 10 days were protected from a subsequent MPTP-induced insult to the nigrostriatal dopamine system (Faherty et al., 2005). The mechanisms underlying improved brain function upon treatment of experimental brain disorders with enriched environment are not fully understood. As described in more detail below, exposure to enriched environment has been found to increase the genesis of newborn cells, including neurons, in the adult brain (Brown et al., 2003; Kempermann et al., 1997, 1998; Komitova et al., 2002, 2005a,b, in press; Matsumori et al., 2005; Nilsson et al., 1999; van Praag et al., 1999, 2000). Other effects of enriched environment that may support enhanced functional recovery are increases in the production of neurotrophic factors (e.g., brain derived neurotrophic

factor, BDNF, and glial cell line-derived neurotrophic factor, GDNF) (Cohen et al., 2003; Tillerson et al., 2003) and improved synaptic transmission due to the induction of higher dendritic spine density on affected neurons (Bezard et al., 2003; Glass et al., 2004; Spires et al., 2004a,b; Young et al., 1999). Studies have reported a regulation of genes associated with metabolism and neuronal plasticity following exposure to enriched environment (Dahlqvist et al., 1999; Keyvani et al., 2004; Zhao et al., 2000).

In addition to a stimulating environment, there is increasing evidence that regular physical training alone can promote functional recovery. Studies employing a variety of animal models of brain injury have shown that exercise can boost behavioral performance and neuroplasticity in the hippocampus, cortex and spinal cord (Kempermann et al., 2000). Following experimental stroke, however, results are conflicting and the effects of exercise appear to be intensity-dependent, possibly due to a negative stress component (Komitova et al., 2005b; Marin et al., 2003; Ploughman et al., 2005). Recent studies have examined the effects of physical training also in animal models of PD. Tillerson and coworkers showed that motorized treadmill running improves the neurochemical and behavioral outcomes in two rodent models of PD: the unilateral 6-hydroxydopamine rat model and a bilateral MPTP lesion model in aged mice (Tillerson et al., 2003). When animals with lesions were exposed to the treadmill task twice daily for the first 10 days post-lesion, they did not display significant behavioral deficits. Compared to sedentary animals with lesions, animals subjected to physical exercise also exhibited significant sparing concerning striatal levels of dopamine, dopamine metabolites, tyrosine hydroxylase, vesicular monoamine transporter and dopamine transporter. These results demonstrated that exercise following nigrostriatal damage ameliorates motor disability, and suggested that the motor improvement was related to a restorative effect on the damaged nigrostriatal dopamine system. Using a similar experimental approach, Fisher and collaborators showed that 30 days of regular exercise on a motorized treadmill improved motor performance in young mice that had been exposed to a MPTP lesion (Fisher et al., 2004). These authors did not observe sparing of dopamine neurons (as assessed by measurements of tyrosine hydroxylase levels in the striatum). Nevertheless, the treadmill exercise was found to modulate the expression of several proteins and genes involved in basal ganglia function (i.e., striatal levels of the dopamine transporter, dopamine D2 receptors and glutamate). The results of Steiner et al. (this issue) are in keeping with the report of Fisher et al. (2004), since the environmental enrichment/physical exercise paradigm used in their study did not significantly affect the number of tyrosine hydroxylase-immunopositive neurons in the substantia nigra.

The relationship between focal motor therapy and nigrostriatal dopamine sparing has been systematically addressed in an elegant series of experiments performed in rats with unilateral 6-hydroxydopamine lesions. In these experiments, animals were forced to use either the impaired or the non-impaired limb by restraining one limb at a time with a cast. In one seminal paper, Tillerson and collaborators reported that forced use of the limb contralateral to the nigrostriatal lesion prevented lesion-induced motor asymmetries in long-term assessments (Tillerson et al.,

2001). Behavioral sparing was evident when forced limb use started during or soon after exposure to 6-hydroxydopamine. If started 3 days after the lesion, this experimental motor therapy had only a minor beneficial effect (Tillerson et al., 2001). Conversely, a later study showed that restraining the use of the limb contralateral to the lesion exacerbated the degree of functional motor deficit as assessed at later time points (Tillerson et al., 2002). Importantly, the studies by Tillerson and colleagues provided evidence that forced activation of the affected limb resulted in a neuroprotective effect. Thus, neurochemical indices of nigrostriatal damage (e.g., reductions in vesicular monoamine transporter, dopamine and its metabolites) were mitigated by the forced use of the affected limb (Tillerson et al., 2001). On the other hand, restraining the use of the impaired limb post-lesion exacerbated neurochemical signs of nigrostriatal dopamine damage (Tillerson et al., 2002).

Despite some discrepancies regarding neurochemical sparing effects, the studies reviewed above concur to suggest that enriched environment, including physical exercise, can promote functional recovery in rodents models of PD. Importantly, environmental enrichment and exercise might induce changes outside the nigrostriatal dopamine system, in other brain regions involved in the control of motor functions. Thus, while we often focus our attention on the basal ganglia in animal models of PD, it is conceivable that, for example, plasticity in neocortical or cerebellar circuitry contribute to improved motor function. In some of the rodent models of PD, the observed behavioral improvement was clearly associated with a neuroprotective effect against neurotoxin-induced damage, possibly through increased expression of neurotrophic factors. None of these earlier studies, however, have examined whether the environmental stimuli affected the migration and survival of newborn cells in the substantia nigra. Moreover, it is important to appreciate differences in training paradigms between studies on the effect of exercise and directed physical therapy. Some forms of strenuous exercise (e.g., sustained wheel-running) may easily become a compulsive behavior with a significant stress component, which may have detrimental effects on plasticity processes and, in particular, cell genesis.

The effects of enriched environment and physical exercise on newborn cells in the adult brain. Exposing rats and mice to enriched environment has been shown to increase neurogenesis in the dentate gyrus of the adult hippocampus (Brown et al., 2003; Kempermann et al., 1997, 1998, 2000; van Praag et al., 2000). Moreover, letting rodents conduct physical activity, e.g., by running in a wheel, can also significantly increase the number of newborn neurons in the adult hippocampus, but not in the olfactory bulb (Brown et al., 2003; van Praag et al., 1999). In these cases, the observed effects in the hippocampus are believed to be due to both increasing the birth of new cells from precursors and to an improved survival of the newborn cells. Possibly the positive effect of increased physical activity on neurogenesis in the normal intact brain is exclusive to the hippocampus. The present study by Steiner et al. (this issue) provides no evidence for increased numbers of newborn neurons in the midbrain, and as mentioned above earlier work did not reveal increased numbers of newborn neurons in the subventricular zone or olfactory bulb following exposure to a running wheel (Brown et al., 2003).

The effects of enriched environment on cell genesis following stroke have also been studied in a recent series of papers. Placing rats in an enriched environment following experimental stroke has differential effects on the two main neurogenic regions in the adult brain. In the subgranular zone of the hippocampal dentate gyrus, the increased cell genesis and the increased neurogenic response stimulated by ischemia was not influenced by enriched environment (Komitova et al., 2002). However, the number of newborn astrocytes was increased in the enriched animals. In the subventricular zone, both neurogenesis and astrocytogenesis were enhanced by stroke, but there was no additional effect of enriched environment (Komitova et al., 2005a). However, enriched environment did not stimulate the progenitors to adopt a mature neuronal phenotype in the areas close to the lesion (Komitova et al., 2005a; Matsumori et al., 2005). Instead, the reactive astrocytes increased in number at the rim of the infarct and the numbers of NG2-immunopositive polydendrocytes were increased close to the lesion and in the homotopic contralateral cortex (Komitova et al., in press). In summary, from experiments in rat models of stroke it appears that enriched environment does not increase formation of new neurons, but enhances gliogenesis that may promote plasticity in surviving neurons and assist in the remodeling of existing neuronal networks.

Lack of newborn neurons in the substantia nigra. In the study by Steiner and coworkers there were no newborn neurons observed in the substantia nigra (Steiner et al., this issue). The existence of neurogenesis in the adult substantia nigra is an area of controversy. A study by Zhao and coworkers suggested that in adult mice there is a constant turnover of dopamine neurons, with both apoptosis and neurogenesis occurring in parallel (Zhao et al., 2003). They reported that new dopaminergic neurons cells were derived from cells lining ventricular space in adult mice, migrated to the substantia nigra and then grew axons to the striatum. Furthermore, their data suggested that the process was enhanced by when the mice were exposed to a partial lesion of the substantia nigra by systemic injections of MPTP (Zhao et al., 2003). How is it then possible that Steiner and collaborators fail to observe any newborn dopaminergic neurons in their rats? In fact, several other recent papers have also failed to see newborn dopamine neurons in adult rats and mice (Chen et al., 2005b; Cooper and Isacson, 2004; Frielingsdorf et al., 2004; Kay and Blum, 2000; Lie et al., 2002; Mohapel et al., 2005). We have previously suggested that the initial claims from Zhao and coworkers (Zhao et al., 2003) are based on a misinterpretation of labeled cells and that there is no evidence for neurogenesis occurring in the adult substantia nigra in rodents (Frielingsdorf et al., 2004; Mohapel and Brundin, 2004). Of course, it is always difficult to definitely prove that a rare event never occurs, and it is possible to that completely novel treatments can stimulate newborn cells in the nigra to differentiate into dopaminergic neurons in the future. A study headed by Lie suggested that NG2-positive cells found in the nigra are capable of differentiating into neurons under special conditions (Lie et al., 2002). Indeed, they reported that the NG2-positive cells develop into neurons when transplanted into the dentate gyrus, which is a neurogenic niche in the adult brain. A very recent study reports that new dopaminergic

neurons can develop in the adult mouse substantia nigra (Shan et al., 2006). The facts that very low numbers of newborn dopamine neurons (less than 5 in each mouse) were observed, and that the paper did not present three dimensional reconstruction confocal images to support claims of double labeled cells (Shan et al., 2006) calls for caution. Nevertheless, the concept that adult neurogenesis in the substantia nigra could one day become the foundation of a treatment for PD continues to excite scientists and remains an area of intense speculation (Shan et al., 2006; van Kampen and Robertson, 2005; Yoshimi et al., 2005). Recent developmental studies have shed light on molecular signaling that control the maturation of progenitors into dopamine neurons in the normal, immature midbrain. For example, the homeodomain transcription factors *lmx1a* and *msx1* are key determinants that trigger development into dopamine neurons (Andersson et al., 2006b). Neurogenin2 and *Pitx3* are other transcription factors that have been found to be essential for the normal migration, maturation and survival of nigral dopamine neurons during development (Andersson et al., 2006a; Kele et al., 2006; Smidt et al., 2004). Signaling triggered by the extracellular Wnt family of glycoproteins also plays a key role in the normal development of mesencephalic dopamine neurons (Prakash et al., 2006; Rawal et al., 2006). In the future, it may be possible to deliver crucial signaling proteins or overexpress an specific cascades of transcription factors in newborn cells located in the midbrain of PD patients. Thereby it could be possible to coax them to switch fates and develop into dopamine neurons that can replace those lost to disease. Because the signaling molecules probably need to be expressed under a strict temporal control, the task of generating new dopamine neurons in the adult substantia nigra is unlikely to be trivial.

Potential neurorestorative effects of occupational and motor therapies in Parkinson's disease. The treatment of PD is largely based on pharmacological strategies to replace or enhance the failing dopaminergic neurotransmission. Currently, there is no treatment that can clearly mitigate cell loss and retard disease progression. Several clinical studies, however, suggest that patients subjectively feel better and exhibit enhanced motor functions if subjected to stimulation with occupational therapy and / or physical exercise (Gage and Storey, 2004; Sunvisson et al., 1997). In one interesting study, early stage PD patients were subjected to a 10-day training program aimed at specifically improving their ability to walk. Compared to control PD subjects, they significantly improved their gait performance, e.g., stride length, until the end of the study which was 4 weeks after the training had ceased (Lehman et al., 2005). The promising effects of experimental motor therapies in rodent models of PD have prompted a broad interest in the possible benefits associated with general physical exercise in this neurodegenerative condition. The data obtained in animal models of PD seem to have found some support in a recent clinical study. This study prospectively investigated the association between physical activity in early adulthood and the risk for developing PD later in life (Chen et al., 2005a). It reported that men who performed strenuous exercise in early adult life had a 60% lower PD risk compared with men with a more sedentary life style (for unknown reasons, the inverse relationship between

exercise and PD risk was not significant in women). Another intriguing and recent epidemiological study suggests that subjects with some occupations involving marked physical activity have a reduced risk of developing PD, whereas those with higher education stand an increased risk of developing PD compared to the general population (Frigerio et al., 2005).

The mechanisms underlying improved function in PD by occupational and motor activities are not known. A recent open-label pilot study on the effects of infusions of glial cell-line derived neurotrophic factor (GDNF) on five patients suggest that the degenerating dopaminergic neurons in PD are still responsive to trophic stimulation (Gill et al., 2003). Both positron emission tomography (Gill et al., 2003) and post-mortem findings (Love et al., 2005) suggest that the failing nigrostriatal pathway can be boosted in PD. Combined with the findings that exposing adult rodents to enriched environment can increase the production of neurotrophic factors in the brain, this provides hope that occupational therapy and physiotherapy could even promote restorative plasticity in PD.

Concluding remarks. The study of Steiner and colleagues shows that a relatively mild schedule of physical training, combined with housing in an enriched environment, can boost cellular plasticity in the substantia nigra in a rat model of severe nigrostriatal dopamine degeneration (Steiner et al., *this issue*). There was no evidence for either improved survival or increased genesis of nigral dopamine neurons in the animals with lesions that had been exposed to the enriched environment/exercise condition. This study adds fuel to the hope that the debilitating symptoms of PD can eventually be ameliorated by devising appropriate programs of occupational therapy and physical exercise. Differently from current pharmacotherapies, approaches based on “environmental enrichment” have few, if any, adverse effects and long-term complications. Occupational and physical therapies can improve the quality of life for patients in many ways. On one level, physiotherapy and exercise can train the patients to better cope with some aspects of their motor disability (e.g., balance problems) and improve their ability to perform daily tasks. On another level, these therapies can contribute to a general well-being, and improve emotional and motivational problems associated with the disease. On a third and deeper level, these therapies may actually delay PD progression through neuroprotective and restorative effects. Obviously, occupational and motor therapies that can achieve neuroprotection have the highest potential to contribute to a long-lasting benefit. More basic research is therefore required to understand which environmental conditions have the ability to boost neurochemical and structural recovery in the damaged nigrostriatal dopamine system. Eventually, this knowledge will provide ideas for novel restorative strategies that can take advantage of the endogenous plastic potential in the brain.

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