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Review Article

Neuroprotection and neurorestoration as experimental therapeutics for Parkinson's disease

Veronica Francardo[a,*], Yvonne Schmitz[b], David Sulzer[b], M. Angela Cenci[a,*]

[a] Basal Ganglia Pathophysiology Unit, Department of Experimental Medical Science, Lund University, Lund, Sweden
[b] Departments Neurology, Psychiatry, Pharmacology, Columbia University Medical Center: Division of Molecular Therapeutics, New York State Psychiatric Institute, New York 10032, NY, USA

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ABSTRACT

Disease-modifying treatments remain an unmet medical need in Parkinson's disease (PD). Such treatments can be operationally defined as interventions that slow down the clinical evolution to advanced disease milestones. A treatment may achieve this outcome by either inhibiting primary neurodegenerative events ("neuroprotection") or boosting compensatory and regenerative mechanisms in the brain ("neurorestoration"). Here we review experimental paradigms that are currently used to assess the neuroprotective and neurorestorative potential of candidate treatments in animal models of PD. We review some key molecular mediators of neuroprotection and neurorestoration in the nigrostriatal dopamine pathway that are likely to exert beneficial effects on multiple neural systems affected in PD. We further review past and current strategies to therapeutically stimulate these mediators, and discuss the preclinical evidence that exercise training can have neuroprotective and neurorestorative effects. A future translational task will be to combine behavioral and pharmacological interventions to exploit endogenous mechanisms of neuroprotection and neurorestoration for therapeutic purposes. This type of approach is likely to provide benefit to many PD patients, despite the clinical, etiological, and genetic heterogeneity of the disease.

1. Introduction: plasticity in the parkinsonian brain

The mammalian central nervous system (CNS) is endowed with a remarkable potential for plasticity, as it can functionally and structurally reorganize in response to challenges. This capacity provides the basis for both learning and compensatory processes following brain damage or neurodegeneration.

Human imaging studies have indicated that plasticity and functional compensation are prominent in Parkinson's disease (PD) (Adams et al., 2005; Carbon et al., 2010; Lee et al., 2000). Presynaptic compensation in the nigrostriatal dopamine (DA) pathway may account for the observation that parkinsonian motor symptoms become apparent only when more than 30% of nigral DA neurons or 50% of striatal DA contents are lost (Bernheimer et al., 1973; Cheng et al., 2010; Fearnley and Lees, 1991).

Studies performed in monkeys intoxicated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have revealed structural plasticity of tyrosine hydroxylase (TH)-positive axons, including increased branching and thickness (Song and Haber, 2000). Structural plasticity and bona fide sprouting of dopaminergic axon terminals are well documented in rodent models of nigrostriatal degeneration, as detailed below. Although evidence of dopaminergic axon sprouting in PD is inconclusive (Porritt et al., 2005), positron emission tomography studies (PET) in both MPTP-treated monkeys and early-stage PD patients have demonstrated compensatory changes at the biochemical level, involving decreased DA transporter binding, increased activity of L-amino acid decarboxylase (AADC), and up-regulation of DA turnover (Barrio et al., 1990; Calne and Zigmond, 1991; Doudet et al., 1998; Lee et al., 2000; Sossi et al., 2002; Sossi et al., 2004). Furthermore, electrophysiological studies performed in rodent models report that the damaged DA system is able to recruit a reserve of normally quiescent DA neurons in an attempt to preserve the proportion of active neurons, and thus maintain basal DA output (Bunney and Grace, 1978; Grace, 2002, 2008; Grace and Bunney, 1984, 1986; Hollerman and Grace, 1990).

The nigrostriatal pathway is not the only system that responds to the loss of DA with compensatory adaptations. Other monoaminergic systems affected in PD, such as noradrenergic and serotonergic projections, are capable of similar plastic responses (Bezard et al., 2003; Brotchie and Fitzer-Attas, 2009; Mattson et al., 2004). Moreover, studies

* Corresponding authors.
E-mail addresses: Veronica.Francardo@med.lu.se (V. Francardo), Angela.Cenci_Nilsson@med.lu.se (M.A. Cenci).

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performed in non-human primate (NHP) models of PD have indicated that non-monoaminergic systems are involved too. For example, an upregulation of enkephalinergic transmission in the pallidum externum (GPe) has been proposed to compensate for an excessive GABAergic input to this structure originating from the striatal indirect pathway (Maneuf et al., 1994). Compensatory changes in glutamatergic transmission have been described in the subthalamic nucleus and pallidum internum (GPi) in presymptomatic NHP models of PD (Bezard et al., 1999; Vila et al., 2000). Finally, homeostatic postsynaptic plasticity in striatal projection neurons has been proposed to counter the concomitant changes in DA receptor tone and corticostriatal transmission associated with PD. A remarkable example of this plasticity consists of homeostatic reductions in dendritic spine density and glutamatergic synapses in striatal neurons forming the indirect pathway (Day et al., 2006; Deutch et al., 2007; Fieblinger et al., 2014). DA depletion moreover leads to a loss of GABergic presynaptic inhibition on direct pathway neurons, which effectively enhances the activity of striatonigral synapses (Borgkvist et al., 2015). Together, the latter changes may underlie both compensatory and maladaptive responses eventually leading to L-DOPA-induced dyskinesia (Borgkvist et al., 2015; Schuster et al., 2009) (Fig. 1).

A key question is whether the plastic and regenerative potential of neural systems affected in PD can be harnessed for therapeutic purposes. An even more intriguing question is whether enhancing neuroplasticity may not only improve function but also protect against primary pathogenic events associated with PD. The latter issue is warranted and timely. Contemporary research has established that adaptive neuroplasticity and neuronal survival depend on similar molecular mediators. For example, activity-dependent stimulation of synaptic NMDA receptors and neutrotrophin-induced activation of extracellular signal-regulated kinases 1/2 (ERK1/2) promote both synaptic plasticity and neuronal survival (discussed below). Conversely, activation of extrasynaptic NMDA receptors and neuroinflammation are detrimental to neuroplasticity and neuronal survival (Bartlett and Wang, 2013; Knafo and Esteban, 2012; Nistico et al., 2017). Against this background, we will discuss therapeutic strategies that may achieve disease-modifying effects by enhancing adaptive plasticity in PD. Several promising approaches have been identified and are currently being evaluated in both animal models of PD and clinical trials.

2. Animal models to detect neuroprotective and neurorestorative effects of interventions

PD has never been reported to occur in animals, and there is wide consensus that no single animal model can recapitulate the complexity of the disorder. Nevertheless, studies in animal models of PD can yield an integrated view of a treatment's mechanisms of action, linking functional improvements with changes that occur in specific molecular pathways, categories of cells, and brain networks. Animal models of PD therefore continue to provide fundamental tools in experimental therapeutic research.

Here we focus on the utility of animal models to determine if a particular intervention acts by reducing the neurodegenerative process (neuroprotection) or by boosting adaptive plasticity and regeneration (neurorestoration). These two mechanisms of action can be distinguished in animal models where the neurodegenerative process occurs within a restricted time window, in contrast to PD where neurodegeneration and compensation/plasticity proceed hand-in-hand. For the sake of studying regenerative processes in nigrostriatal DA neurons, it is advantageous to use models where residual neurons have a well-documented capacity for axonal sprouting. Both of the above requirements are fulfilled by neurotoxin-based models of PD, more specifically, rodents lesioned with 6-hydroxydopamine (6-OHDA) and mice or NHPs lesioned with MPTP. In both types of models, nigrostriatal DA degeneration is complete within days or weeks following toxin administration. In both models, moreover, sprouting of nigrostriatal dopaminergic fibers can be induced by neuroplasticity-enhancing treatments (see below).

A neurotoxin model widely used in the neuroprotection literature consists in rodents sustaining intrastriatal 6-OHDA lesions, yielding retrograde degeneration of nigral DA neurons (Berger et al., 1991; Bjorklund et al., 1997; Ichitani et al., 1991; Kirik et al., 1998). In this model, the neurodegenerative process exhibits a biphasic pattern, with a first rapid phase of DA cell loss occurring within 1 week post-lesion, followed by a mild additional loss of DA neurons proceeding for approximately 4 weeks (Bjorklund et al., 1997; Kirik et al., 1998; Sauer and Oertel, 1994). This biphasic time course appears to mimic the temporal pattern of nigrostriatal degeneration in human PD, where the loss of dopaminergic axons in the motor part of the striatum is very rapid during the first 5 years from clinical diagnosis, but very slow thereafter (Kordower et al., 2013). Injections of 6-OHDA into the dorsolateral striatum yield an anatomical pattern of DA fiber loss resembling that in PD: the lateral (motor) striatum becomes severely denervated, whereas DA fiber sparing is evident in ventromedial regions (Francardo et al., 2011) (Fig. 2). As demonstrated using retrograde labeling methods (Bjorklund et al., 1997; Sauer and Oertel, 1994), intrastriatal 6-OHDA lesions cause actual death of neuronal cell bodies in the substantia nigra, not simply a downregulation of their phenotypic markers. A downregulation of TH, however, does occur in neurons that become atrophic before undergoing cell death (Sauer and Oertel, 1994).

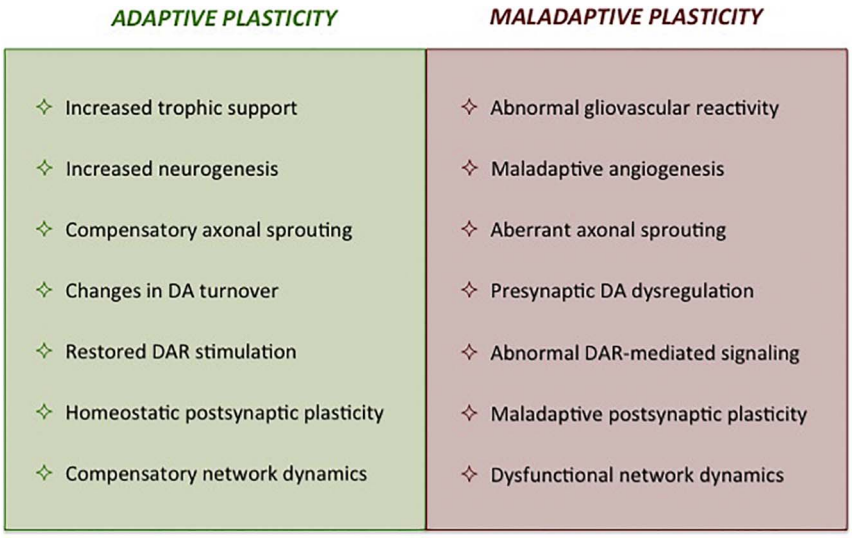

Fig. 1. Adaptive and maladaptive plasticity in the treatment of PD. The green and red compartments highlight plastic changes that have been attributed adaptive and maladaptive effects, respectively. Adaptive plasticity has been mainly studied in animal models with partial nigrostriatal DA lesions, mimicking early or presymptomatic PD. The mechanisms of maladaptive plasticity here reported have been uncovered in animal models of advanced PD affected by L-DOPA-induced dyskinesia. The Table summarizes data and concepts from a vast number of original research reports and review articles, in particular, Carta et al., 2017; Cenci, 2014; Cenci and Konradi, 2010; Cenci et al., 2009; Fieblinger et al., 2014; Jourdain et al., 2016. Abbreviations: DA, dopamine; DAR, dopamine receptors.