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Exercise: Is it a neuroprotective and if so, how does it work?

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SUMMARY

There is clinical evidence that the symptoms of Parkinson's disease can be ameliorated by physical exercise, and we have been using animal models to explore the hypothesis that such exercise can also be neuroprotective. To do so we have focused on models of the dopamine deficiency associated with motor symptoms of parkinsonism, including mice treated systemically with MPTP and rats treated with 6-hydroxydopamine. Our focus on exercise derives in part from the extensive literature on the ability of exercise to increase mitochondrial respiration and antioxidant defenses, and to stimulate neuroplasticity. Beginning with constraint therapy and then employing wheel running and environmental enrichment, we have shown that increased limb use can reduce the behavioral effects of dopamine-directed neurotoxins and reduce the loss of dopamine neurons that would otherwise occur. While the mechanism of these effects is not yet known, we suspect a central role for neurotrophic factors whose expression can be stimulated by exercise and which can act on dopamine neurons to reduce their vulnerability to toxins. We believe these data, together with observations from several other laboratories, suggest that exercise, as well as neurotrophic factors, is likely to be an effective neuroprotective strategy in the treatment of Parkinson's disease.

1. Parkinson's disease

Parkinson's disease (PD) is an inexorable neurodegenerative disorder involving problems of movement, emotions, and cognition, affecting some 10 million people worldwide. At the time of clinical diagnosis, substantial neurodegeneration has already occurred. Although there are drugs available that can forestall the disease symptoms in most patients for up to a decade, no treatments yet significantly retard its progression or reverse damage that has occurred by the time of diagnosis. There are many obstacles to finding such a neuroprotective or neurorestorative intervention. A first step, however, is likely to be the identification of the causes of the disease, as this should provide insights regarding the development of disease-modifying treatments.

Despite our ignorance regarding the ultimate causes of PD, the considerable literature on this issue indicates that certain assumptions can be made that allow for the establishment of rational models for the development of neuroprotective strategies. We have made several such assumptions, five of which are of particular importance to the approach we will describe in this brief review. (1) Although PD is associated with complex neuropathology involving many brain regions, the loss of dopamine (DA) neurons in the substantia nigra (SN) is responsible for most of the characteristic motor dysfunctions, and there is reason to believe that the loss of DA contributes to other aspects of the disorder, as well. (2) Environmental toxins are major risk factors. (3) Mitochondrial dysfunction is central to the pathophysiology of PD. (4) Oxidative stress – which can result from mitochondrial dysfunction, reduced antioxidant capacity, and reactive oxygen species that occur due to DA metabolism – also plays a significant role in the etiology of the disease. (5) There is a significant inflammatory component to the disease. Each of these assumptions has been reviewed in some detail by others (e.g., see [1,2]). Of course, these are not the only salient characteristics of the disease; a full list would incorporate advanced age, protein aggregations, progressive degeneration that includes the loss of neurons other than those that utilize DA, and, of course, being human! However, it is a start.

2. Models of PD – the value of neurotoxins

The five assumptions we have listed above provide the basis for a model that involves the administration of one of two relatively selective neurotoxins that we have used in many of our studies over the years. One such toxin is 6-hydroxydopamine (6-OHDA), an electroactive analogue of DA first utilized by Urban Ungerstedt in 1968 to produce an animal model of parkinsonism. Upon uptake from the extracellular space by the high affinity

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DA transporter (DAT), 6-OHDA is concentrated in DA nerve terminals, where it produces reactive oxygen species that lead to the death of these neurons. The other agent in common use is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), whose toxicity was identified by Irwin Kopin, William Langston, and their colleagues in the early 1980s. MPTP also causes a relatively selective loss of DA neurons in the SN through its active metabolite, 1-methyl-4-phenylpyridinium (MPP^+) that, like 6-OHDA, is concentrated in DA neurons. MPP^+ emulates several environmental toxins, and acts to inhibit mitochondrial respiration. There are a number of reviews on the use of neurotoxins to mimic key aspects of PD, including those by Gerlach and Riederer [3] and Bove and Perier [4].

"Model bashing" has recently become fashionable in the field of PD, as it is in other areas of neuroscience. This is unfortunate, even destructive. Whereas one must always be alert to the limitations of one's models, the use of neurotoxins in studies of PD has led to many important observations. For example, before the discovery of MPTP-induced parkinsonism there were just a handful of reports on the role that environmental toxins might play in the condition; since then there have been more than 250 such reports cited in PubMed. Before the demonstration that glial cell-line neurotrophic factor (GDNF) was neuroprotective in 6-OHDA and MPTP models, there were no papers on GDNF and PD; now there are almost 500. And before the development of 6-OHDA as a model for parkinsonism, there were five reports of the reduction of PD symptoms by DA agonists; since the advent of 6-OHDA models, there have been more than 4,500! Of course, one cannot draw a straight line from toxin models to each of these reports; some certainly resulted independently. Yet, there can be no question that toxin models have had, and continue to have, a very important positive influence on the field. Recently, the discovery of genetic mutations in patients that either cause PD or serve as risk factors for the disease has led to a number of genetic animal models, and these have already begun to add insight into disease pathology and to suggest possible interventions that would not have emerged with the older toxin models. However, as the authors of the present review begin to make use of models in which the genome is manipulated, we will also retain toxin models as valuable tools in our research.

3. Physical exercise and PD

At a purely logical level, physical exercise is a rational approach to developing neuroprotective and neurorestorative treatments for PD: it increases mitochondrial energy production, stimulates antioxidant defenses, reduces inflammation, causes angiogenesis, and produces synaptogenesis. The use of exercise is also consistent with an enormous body of data testifying to the value of physical therapy in treating motor impairments and improving cognition and emotional status.

For many years, there has been the notion that an altered environment can have an impact on neuronal structure and function. One of the earliest mentions of this idea was by the Italian neuroanatomist Michele Vicenzo Malacarne, who reported in 1793 that dogs and birds that had undergone "training" had larger and more complex cerebellar structures than unattended littermates. In the early 1800s, Johann Spurzheim suggested that the brain was capable of increasing in size due to exercise and proposed that this idea be tested by a rigorous application of the scientific method. The idea that the size of the brain could be altered in response to changes in the environment, however, stayed within the purview of phrenologists for over 100 years.

In 1947, Donald Hebb described superior maze performance of rats reared as domestic pets compared with their relatively impoverished laboratory-reared counterparts. Then, in the 1960s, Krech, Bennett, and Rosenzweig brought this concept into the lab for more controlled testing. The team housed groups of rats in a large cage that provided many opportunities to explore the space and the objects it contained, some of which were frequently changed. They found that this led to increased social interaction, physical exercise, and opportunities to learn that were associated with changes in the structure, neurochemistry, and function of the rodent brain [5]. This research has been continued by a number of investigators, including William Greenough and Fred Gage, and we now know that exposure to this type of environment, usually termed environmental complexity or environmental enrichment, can increase neurogenesis, learning behavior, and synaptic density [6,7].

As we have learned from our own studies and will discuss below, increased physical exercise is an important component of the impact of enriched environment. And for more than half a century, the belief that physical exercise can help to forestall the onset of PD and slow its progression has prompted many clinicians to recommend exercise to their patients. Indeed, there is now a considerable body of research to show that exercise does benefit PD patients, just as it benefits those with other conditions involving CNS damage, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, spinal cord injury, and stroke. The literature indicates, for example, that there is a negative correlation between the incidence of PD and lifetime level of physical activity, and that physical exercise improves movement initiation [8–10].

These clinical data are encouraging; however, they exhibit several shortcomings. The few epidemiological studies that have been performed cannot distinguish between a beneficial impact of exercise on PD and the converse – that patients with PD tend to exercise less. Furthermore, prospective studies have generally been brief, underpowered, lacking proper controls, and/or unable to differentiate between symptomatic improvement and reduction in disease progression. A large clinical trial with the capacity to differentiate between symptomatic relief and disease modification must await the funding that such a trial would require. In fact, we hope to assist in the mounting of just such a trial in the near future. But in the meantime, we have turned to animal studies. As we have noted above, we are mindful of the fact that our models do not replicate either the cause or the pathophysiology of PD. Nonetheless, we believe that they provide important insights into the possibility that exercise can reduce the vulnerability of DA neurons to stressors of many kinds and, if so, by what mechanism.

We began our studies on exercise the late 1990s in collaboration with Tim Schallert and his students. We used unilateral 6-OHDA injections to deplete DA on one side of the rat brain and to examine the effects of "constraint therapy" in which the normal, ipsilateral limb was restrained to force over-use of the normally affected, contralateral limb. We found that this intervention led to a reduction in the behavioral and pathological effects of the toxin [11]. Constraint therapy has been proposed as a potential approach to the treatment of stroke, where the insult is acute and typically unilateral as in our 6-OHDA model. However, this intervention can at best have only proof-of-principle value for PD. This is because, in contrast to the 6-OHDA model, PD is a progressive and typically bilateral condition. Moreover, in our hands the effects of constraint therapy on the response to 6-OHDA were not always predictable. Thus, several years ago we turned to the use of running in a wheel or on a treadmill as our intervention, and have generated a great deal of evidence that such exercise also reduces the behavioral consequences of 6-OHDA or MPTP in the rat, mouse, and monkey. This is supported by many other studies in the 6-OHDA-rat [12–15] and the MPTP mouse [16].

In one of our studies, mice (2–4 months old) were given access to a running wheel attached to their cages for 3 months and then