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Evaluation of Exercise Protocols in MPTP-induced Parkinson Disease Models

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Abstract

Parkinson's Disease is a neurodegenerative disease that impacts the activities of daily life. Exercise has been determined to be beneficial for individuals diagnosed with Parkinson's disease. In studying the mechanisms at play, animal models are frequently used. One such model involves administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce neurodegeneration in mice. Many studies have investigated how exercise in MPTP-induced mouse models provide a protective and restorative effect. Often these studies lack strong reasoning for the exercise protocol used. This review analyzed many of these studies on the basis of exercise duration, intensity, and methodology of MPTP induction to examine their effect on various biomarkers associated with Parkinson's disease in an attempt to determine the exercise protocol that could most optimally reduce and provide relief from the diseased state.

Keywords

Parkinson's, MPTP, Exercise, PD, Tyrosine hydroxylase, protocol

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, following Alzheimer's disease. Between two and three percent of adults over 65 are affected by PD. This disease is characterized by a decrease in dopamine resulting from neuronal loss in the substantia nigra (SN), reductions in nerve terminals that lead from the SN to the striatum (STR), changes in striatal dopaminergic uptake and signaling, and also the accumulation of intracellular alpha-synuclein. (Hood et al., 2016; Poewe et al., 2017). The pathogenesis of PD is complicated and involves many pathways and mechanisms overall. Primarily, this includes alpha-synuclein proteostasis, mitochondrial dysfunction, oxidative stress, calcium homeostasis, and neuroinflammation (Poewe et al., 2017). Often diagnoses of PD do not occur until a reduction of nearly 70% of dopaminergic neurons of the SN has occurred, at which point PD symptoms become increasingly evident (Gerecke et al., 2010; Harrington et al., 1996). Currently no therapeutic options exist to prevent PD or slow its progression; current treatments only apply to the management of associated symptoms. Exercise, however, is strongly recommended to help reduce the symptoms experienced by PD patients. This review will examine the potential neuroprotective and neurorestorative benefits that exercise might provide in the context of PD.

Background of Literature

Animal models of PD are of great importance as they allow for an increased understanding of underlying mechanisms and potential therapeutic options. There are four primary models used for PD induction in animals. The 6-hydroxydopamine (6-OHDA) model is commonly used in rats, and produces a biochemical destruction of the nigrostriatal pathway (Crowley et al., 2019). Another model and relatively new, AAV alpha-synuclein, replicates PD by overexpression of the alpha-synuclein protein. Further models include the Rotenone and the 1-

methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). These are utilized for their similarities to the progressive neurodegeneration seen in PD via the use of neurotoxins, with the MPTP commonly used to model the motor symptoms associated with PD. This review will focus largely on the MPTP model. Focusing specifically on this one model allows for greater distinction regarding the changes to associated biomarkers since differences associated with varying toxins is not present. In addition, the range of animals used with the MPTP model is limited as this model is primarily used with studies involving mice. MPTP induces its effect via its neurotoxin metabolite, 1-methyl-4-phenylpyridine (MPP+). MPP+ is taken into dopaminergic neurons of the SN via the dopamine transporter (DAT), where it acts by blocking and inhibiting mitochondrial activity and therefore causing neuronal degeneration and resultant motor dysfunction (Crowley et al 2019). The studies reviewed used MPTP administration to model PD. Three different methodologies were used: acute, progressive, and chronic. In the acute model MPTP was administered at a dosage typically around 20 mg per kg body weight 4-5 times over the course of a few days. The progressive model used a dosage that increased from start to finish and overlapped with the start of the exercise protocol. Dosing in this method typical increased from about 8 mg/kg to 32 mg/kg and was given 5 times per week for 4 about weeks. Chronic administration was the third and final model used. In this MPTP model, probenecid was used as an adjuvant. Probenecid inhibits clearance of the MPTP neurotoxin and therefore causes a rapid loss of dopaminergic neurons. This effect is responsible for more long-term neurological and behavioral deficiencies that are not as easily restored months after treatment, contrasting acute models that exhibit restoration following excretion of the toxin (Koo et al., 2017; Lau et al., 2011).

Evidence has indicated that physical exercise corresponds with neurodegenerative improvements. Multiple human studies have shown that regular exercise as a young adult yields a reduced risk of the development of PD decades later. In addition to reducing the risk of a PD diagnosis, recent studies have shown that exercise plays a role in the restoration of motor function as well as the reduction of non-motor symptoms in individuals affected by PD. Human studies have observed improved physical performance in regard to increased speed, gait initiation, stride length, muscle strength, balance, and a reduction of falls. These improvements observed in human studies are suggested to be associated with increased gray matter volume, improved cortico-motor excitability, increased striatal dopamine receptor density, and enhanced dopamine levels as a product of exercise. Non-motor symptoms that show improvement through exercise include increases in attention and working memory that are associated with a rise in cognitive function, enhanced executive function, language, and mood. Human studies have provided evidence that exercise not only increases longevity but also results in establishing a higher quality of life in individuals confronted with PD. The use of animal models, especially rodents, provides a deeper, more mechanistic evaluation of this disease, something human studies often lack. Animal studies have provided support for the neuroprotective and neurorestorative benefits of exercise, which focus on mechanisms involving neurogenesis, neurotrophic factors, neuroinflammation, and oxidative stress (Crowley

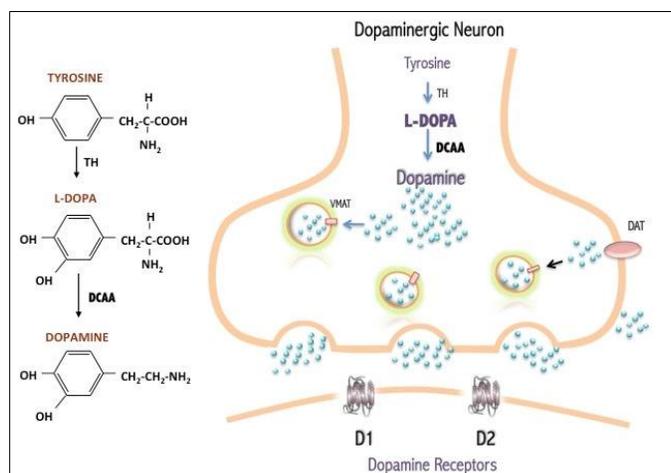


Figure 2. The pathway of dopamine and the role of synaptic molecules, including tyrosine hydroxylase (TH). (From Bravo et al., 2014)

Another important marker is the dopamine transporter (DAT), which is responsible for reuptake of DA into pre-synaptic nerve terminals, thus regulating DA transmission (Harrington et al., 1996). Decreased DAT expression accompanies PD (Hood et al., 2016). Expression of the synaptic vesicle amine transporter (VMAT) is also reduced in PD. VMAT is responsible for repackaging monoamines into synaptic vesicles (Harrington et al., 1996). Additionally, ionized calcium binding adaptor molecule 1 (IBA-1) is involved in facilitating phagocytosis by microglia and therefore IBA-1 expression indicates microglia activation (Ohsawa 2004). Increased IBA-1, associated with increased alpha-synuclein, is observed in PD (Su et al., 2008). Alpha-synuclein is highly involved in PD, although its full function is not quite clear. It has been shown to bind to TH and reduce the phosphorylation of TH, which as a result, reduces the production of dopamine (Daubner et al., 2011). Additionally, alpha-synuclein is suggested to play an early role in PD development through its role in inflammation, especially regarding proinflammatory molecules such as TNF alpha and IL-beta (Su et al., 2008).

The synaptic proteins PSD-95 and synaptophysin exhibit decreased expression in PD and in MPTP models, as well as a related decrease in dendritic spine density. PSD-95 is located post-synaptically and is involved in the regulation of synaptic strength and plasticity. Synaptophysin is an integral membrane protein of presynaptic vesicles and is often used to indicate synaptic density. A decreased level of these two proteins corresponds with decreased synaptic transmissions and decreased plasticity (Shin et al., 2016). A decrease in dendritic spine density is associated with PD and this loss often occurs as a result of a loss of dopaminergic neurons (Toy et al., 2014). Overall, many markers for PD are known, and administration of MPTP in mouse models is able to replicate many of these changes.

Animal studies have indicated that brain neurotrophic factors, especially BDNF and GDNF, play an important role in promoting the survival of adult neurons and facilitate processes involved in neuroprotection from exercise (Lau et al., 2011). BDNF and GDNF are active in the regulation of a signaling cascade that impacts TH transcription, and therefore necessary for

dopamine synthesis. (da Silva et al., 2016). Both BDNF and GDNF have been shown to increase following exercise, particularly in both the substantia nigra and striatum (Lau et al., 2011). Overall, these two neurotrophic factors, upregulated through exercise, are involved in dopaminergic survival and differentiation, inhibition of microglia activation, and neuroplasticity and as a result improve motor function (da Silva et al., 2016). Therefore BDNF and GDNF appear to have a strong role in neuroprotection when it comes to PD.

Studies have detailed the rise of many other markers through exercise. Animal models have shown that exercise improves mitochondrial respiration, improves ATP function, and maintains antioxidant SOD levels (Lau et al., 2011). Additionally, exercise leads to an upregulation of antioxidant enzymes and increased activity of mitochondrial enzymes while decreases oxidative stress markers (Marques-Alexio et al., 2012). Anti-inflammatory effects have also been observed with exercise in animal models, suggesting a role for exercise to attenuate neuroinflammation (Crowley et al., 2019). A benefit such as this would help reduce oxidative stress and other negative deficits associated with inflammatory processes, which can be especially harmful for cognition. Suppressed inflammation can be seen by a reduction in TNF-alpha and IL-1beta following exercise (Jang et al., 2017). Furthermore, exercise is suggested to lower reactive oxygen species and improve mitochondrial function (Lau et al., 2011), which is necessary to help prevent the accumulation of alpha-synuclein via reactive oxygen species, which leads to dopaminergic neuron death. In the context of PD, evidence has shown that exercise has a neurorestorative effect in the way it restores motor recovery (Jang et al., 2017).

Methods for Literature Analysis

An initial search involved exercise protocols in rodent models of PD. This soon was narrowed down to specifically focus on MPTP models of PD, and therefore mice models.

Data from selected articles was obtained and entered into an Excel document. When available, raw data was used and the percent change compared to the control group (C) was determined for the MPTP induced non-exercised group (M) and the MPTP plus exercise group (ME). In cases when numerical data was not given, approximations were made from published graphical results. For purposes of this review, the control group used to compare M and ME was that of a sedentary, non-MPTP induced model group. This data was used to design the graphs. Studies that measured similar biomarkers, such as TH and synaptic proteins, were used for comparisons. Furthermore, studies were compared that were at the two extremes based on treadmill intensity. Data was also used graph was constructed using data that compared results when eight weeks of additional exercise was conducted. The biomarkers most common to the largest amount of studies, TH and synaptic protein expression, were used to compare results. (See Appendix for additional biomarker data and complete table).

Ten studies from the 20 total were selected for more direction comparison. This was based on characteristic intensities and duration of the exercise protocols used in the study. Also, these studies measured similar biomarkers, which allowed for closer comparisons to be made based on the type of exercise protocol used.

Neuroprotective effects were categorized by basis of MPTP administration at the conclusion of exercise protocols. Administration following exercise is indicative of how exercise primes the body against toxin-induced neurodegeneration. Neurorestorative effects were categorized as MPTP administration that occurred prior to the start of exercise. Studies such as these, of which were more predominant, observed how exercise while under the influence of the diseased state can allow for improved function overall. The data from these studies was then used to determine the type of exercise protocols that provided the most benefit in counteracting the diseased state.

| Source | Mice | Exercise pre or post MPTP admin | Exercise Type | Intensity | Duration | Length of protocol |
|-----------------------|----------|---|---------------|--|----------|--------------------|
| Gerecke 2010 | Adult; F | Pre | Voluntary WR | 2.4 km/day 4.8 km/day 7.5 km/day | - | 90d |
| Gerecke 2012 | Adult; F | Pre | Voluntary WR | - | - | 90d |
| Sconce 2015 | Adult; M | Pre; 2wk | Voluntary WR | - | - | 14d |
| Churchill 2017 | Adult; M | Post; 4wk | Forced TM | 10.8 m/min | 60 min | 5d/wk for 4 wk |
| Jang 2018 | Adult; M | Post; 4 wk | Forced TM | 12 m/min | 60 min | 5d/wk for 6 wk |
| Koo 2017 | Adult; M | Post; immedietly | Forced TM | 12 m/min | 60 min | 5d/wk for 8 wk |
| Lau 2011 | Adult; M | 5d/wk for 1 wk pre; 5wk during; 12wk post | Forced TM | 15m/min | 40 min | 5d/wk for 18 wk |
| Shin 2016 | Adult; M | Post; 1d | Forced TM | 8 m/min | 30 min | 5d/wk for 28d |
| Smith 2011 | Adult; M | Post; 1d | Forced TM | 10.8 m/min | 60 min | 5d/wk for 19d |
| Toy 2014 | Adult; M | Post; 5d | Forced TM | 24 m/min | 30x2 min | 5d/wk for 6wk |

Table 1. Summary table of s10 selected studies. These studies were used most directly in the graphical analysis described in this review. They were based on their time of MPTP administration, intensity, length of protocol, and biomarkers measured.

Results

Neuroprotection

Voluntary wheel running before MPTP administration protected dopaminergic neurons from MPTP induced cell death (Figure 3). This protective effect was observed to the greatest extent when mice exercised for 3 months prior to MPTP administration. No protection occurred when mice only exercised for one-month prior. Additionally, mice that were allowed to voluntarily run the greatest set distance at 7.5 km per day were protected the most from neuronal loss. In the case where the running wheel was locked once a specified distance was hit (2.4 and 4.8 km per day), mice in these groups received less protective benefits and therefore were more vulnerable to neuronal loss when MPTP was administered using an acute model.

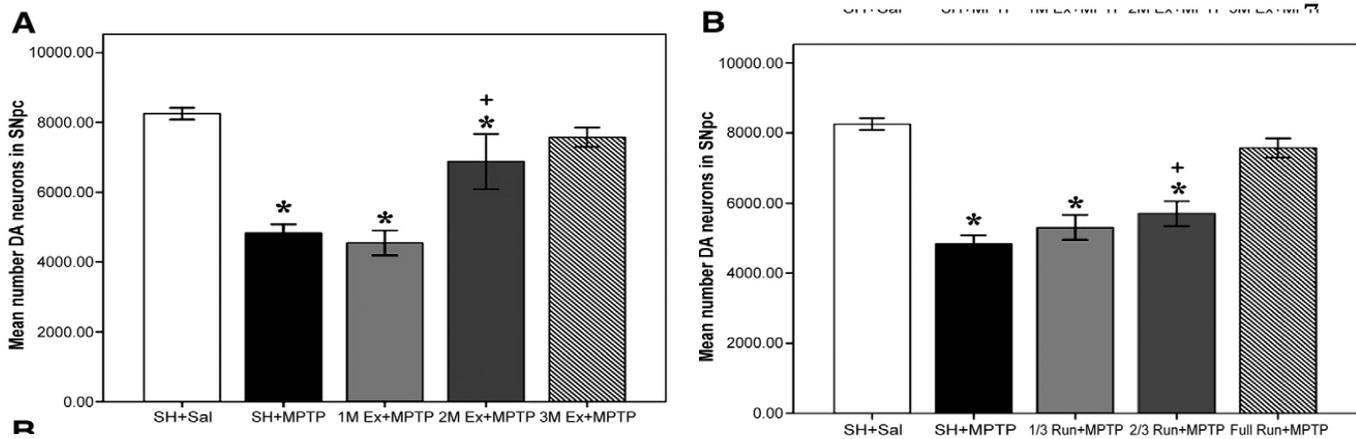


Figure 3.

A) Voluntary wheel running and its protective effect on dopaminergic neurons at durations of 1, 2, and 3 months prior to MPTP administration. B) The protective effect of voluntary wheel running when daily distance ran was controlled. Mice were allowed to run for 2.5, 4.8, or 7.5 km per day for three months prior to MPTP administration. (From Gerecke et al., 2010)

Neurorestoration

Comparisons of a low intensity, 8 m/min (Shin et al., 2016) with a high intensity, 24 m/min (Toy et al., 2014) exercise protocol provided a distinct advantage for higher intensity exercise (Figure 4). The average amount of recovery from the high intensity exercise protocol was almost twice that of the less intense protocol, with an average of 16% more recovery across the three markers measured.

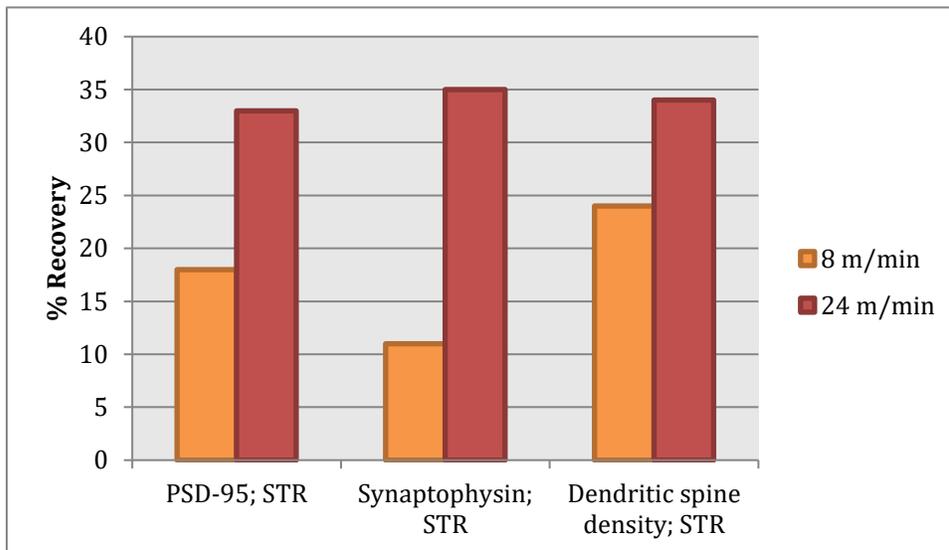


Figure 4. Summary of comparison of acute high intensity to low intensity exercise on biomarker recovery.

Measurement of SN and STR TH expression by way of optical density was a common technique used in multiple studies. Mice models showed a fair amount of variability in TH expression recovery when exercised (Figure 5). The majority of these studies displayed a recovery effect that was near 20%. However, two studies did show that exercise reduced the potential for TH recovery. On average, a recovery of 20.5% of TH in the SN was observed, while striatal TH recovery averaged 19% compared to the non-exercised MPTP models.

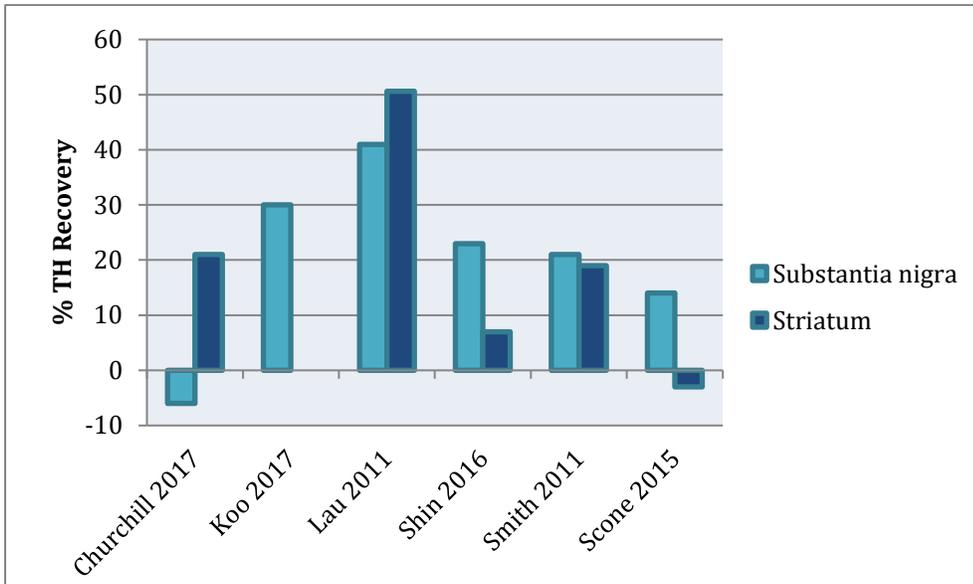


Figure 5. Summary of TH recovery. TH was determined via optical density and compared in the SN and STR.

In a chronic MPTP model, the duration of the exercise protocol had a large impact on the associated benefits (Figure 6). In both 10 week at 18 week studies conducted by Lau et al. (2011) exercise provided recovery in multiple parameters. Recovery as a result of exercise following MPTP administration was substantially greater in mice that exercised for a total of 18 weeks versus 10 weeks when both were compared to MPTP non-exercised group. The mice exposed to 18 weeks of exercise showed nearly a 4-fold increase in recovery when compared to the mice that exercised for 8 weeks less. In this study the intensity remained the same, which provides support for importance of exercise of an extended period of time.

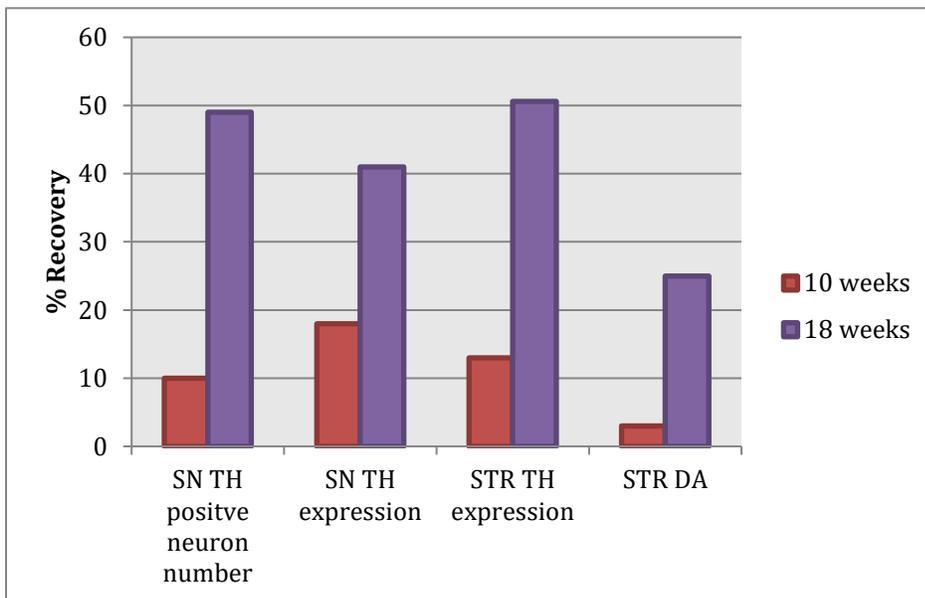


Figure 6. Comparison of exercise durations upon PD biomarker recovery at constant intensity. (Lau et al., 2011)

The method of MPTP administration used played a role in the amount of recovery that was possible with exercise. While recovery from MPTP administration occurred in all models, the acute and chronic PD models allowed for a greater extent of recovery compared to the progressive models. The average percent of recovery of SN TH and STR TH for studies involving each model was compared (Figure 7). The acute model averaged a 22% recovery of TH combined between the SN and STR, and the chronic averaged a 29.5% recovery. The progressive model showed the least amount of possible restoration, with an average TH recovery of 8.5%.

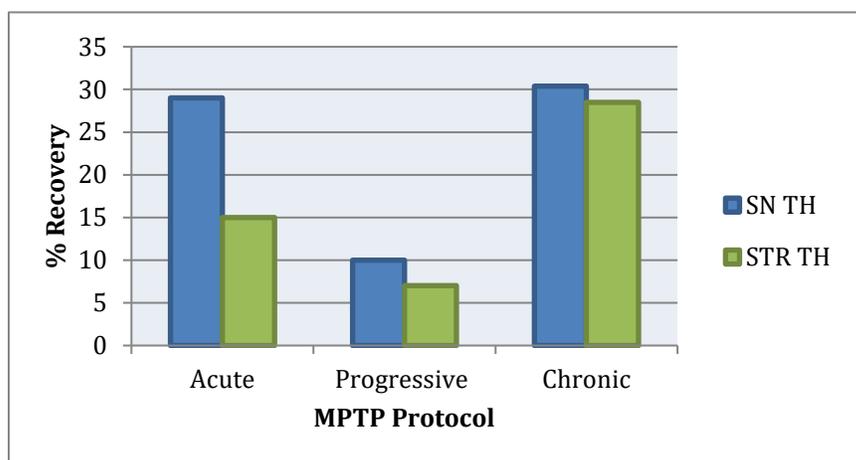


Figure 7. Comparisons of MPTP administration methods related to TH recovery from exercise.

Discussion

The protective effects of exercise prior to MPTP administration were most noticeable when mice were allowed to run for a full 3 months prior combined with the greatest total daily distance of 7.5 km. Protocols that were shortened by one or two months provide less protection. Similarly protocols that limited the mice to 2.4 km or 4.8 km per day maximum saw less protection from the loss of dopaminergic neurons. This highlights the combined importance of both intensity and length of exercise for most optimal results, and indicates that in an acute model of PD, exercise exhibits preventative measures. Showing that exercise exerts a protective results suggests that exercise has the potential to minimize neuronal loss in individual who may be susceptible to PD.

Of the selected forced treadmill studies, Shin et al. (2016) was the least intensive at 8 m/min, while Toy et al. (2014) was the most intensive, with an intensity that started at 10 m/min and increased to 24 m/min as the exercised mice became more conditioned. These studies both focused on measurements that involved dendritic spine density and the synaptic protein markers PSD-95 and synaptophysin. Mice in the more intensive exercise study however had 10 additional days of exercise compared to the low intensity study. Both studies showed that exercise was successful in attenuating biomarker changes that followed MPTP administration, although the more intensive study, Toy et al. (2014) provided a noticeably greater amount of biomarker recovery in each of the three categories. This provides support for

higher intensity exercise having an increased restorative effect following MPTP administration. As evident with these studies, the restorative effect was seen with recovered levels of synaptic proteins and dendritic spine densities. An increase in these markers close to the control level of expression is associated with improved synaptic transmission and synaptic plasticity (Shin et al., 2016).

Six of the selected studies were graphed according to the percent of TH loss that was attenuated when exercise was applied to the MPTP model. Two of the studies saw a lack of TH recovery; one with a lack of SN TH recovery and the other involving a lack of STR TH recovery. Apart from these two results, the majority of the studies indicated varying degrees of recovery in both the substantia nigra and striatum (Koo et al., 2016 did not measure STR TH). This provides evidence for exercise's restorative effects, although a range of variation exists.

The study conducted by Lau et al., (2011) was unique among those selected based on how exercise and MPTP administration were applied. In this protocol, forced treadmill exercise began 1 week prior to MPTP administration. MPTP was administered every 3.5 days for 5 weeks, during which treadmill exercise continued. Following the completion of MPTP administration, 12 additional weeks of exercise was completed, for a total of 18 weeks. A much-reduced impairment was observed in the extended, 18 weeks of exercise compared to 10 weeks. Reduced impairments involving the number of SN TH positive neurons, SN and STR TH optical densities, and STR dopamine contents were all observed in the longer exercised mice. This helps clarify the importance of exercise duration. A more prolonged period of exercise was noticeably more beneficial in this case, and provides support frequent, regular exercise for patients with PD.

Overall, exercise was beneficial in counteracting the negative effects of MPTP administration. The degree of effectiveness and the types of improvements that were made varied. Most studies did see behavioral improvements following exercise such as increased Rotarod and Beam test performance. More variability existed in regard to the biological markers. In many instances exercise had a beneficial effect, although the extent of this effect was not always clearly evident, and a few showed worsening of biomarkers. Following analysis of these studies, the importance of the MPTP administration protocol plays a serious role in the amount of benefit that can be seen with exercise, particularly regarding the measurement of biological markers, which is likely due to the amount of overall dopaminergic cell death caused. Acute, progressive and chronic models of PD were used in these studies based on the MPTP administration process. Different types of administration were used to for the study of specific characterizations of this disease, although clarity regarding the amount of neurodegeneration desired in the models was often vague. Based on the data from exercised groups from each of these studies, it appears that there becomes a point when the benefits of exercise decrease. In the progressive model, which increased dosage of toxin on a weekly basis, only a minimal amount of recovery, on average, was observed. This could highlight the potential for there to be a most optimal window corresponding to a percentage of remaining dopaminergic neurons. Once too much loss has occurred, the benefits of exercise may cease. Such a possibility

provides even more reason for exercise to be an important aspect of daily life for both non-PD individuals and those with the disease.

Overall, exercise protocols that maintained relative similarity showed that longer-term exercises were more beneficial to shorter exercise protocols. This was particularly clear regarding the potential neuroprotective effects of exercise prior to MPTP administration, as seen in Gerecke et al. (2010). Improvements were also observed related to increased exercise longevity when exercise was initiated following the loss of dopaminergic neurons as seen in Lau et al. (2011) when more benefits arose when the exercise protocol was extended by 8 weeks. When considering intensity, the more intense protocols, determined by treadmill speed, resulted in greater beneficial effects compared to lower intensity exercise, although benefits existed in both scenarios.

Moving forward, exercise protocols in MPTP studies must take into serious consideration the process and amount of MPTP administration used. This appears to be the influential factor in determining the type of benefits that exercise can provide in counteracting the diseased state. This does correspond to the pathogenesis of PD; as individuals with PD age, their ability for exercise will be reduced, and from the analysis of these studies it would suggest that as PD progresses the benefits associated with exercise decrease as well. This would support evidence that shows that regular exercise in early adulthood helps reduce the occurrence of PD later in life, as this is a time period when exercise could be most optimally effective in individuals. In regard to mouse models, protocols should attempt to reach a reasonably high intensity. One way to accomplish this is through weekly increases in treadmill speed, similar to what was employed by Toy et al. (2014). Here, researchers increased treadmill speed so that mice were in a forward position on the treadmill for 75% of the daily exercise period. Because of this standard, treadmill intensities were able to increase weekly as the level of performance increased. For mouse models that want the greatest possible recovery from MPTP toxicity, protocols that focus on high intensity for several months are most applicable. Further research focusing on animal models should strongly consider the utilization of newer PD models that more closely replicate the symptoms and pathogenesis of this disease. Such models would allow for a more applicable comparison that would provide more useful insight overall, in addition to looking at exercise related benefits. The analysis of mouse model MPTP studies in this review has supported existing evidence that not only is exercise critical for health overall, but that it can alleviate some of the negative consequences that arise with Parkinson's disease, and therefore lead to an overall increased quality of life for individuals faced with this challenging disease.

High intensity, long duration exercise protocols were found to be the most effective in this review. High intensity and longer duration exercise showed the greatest recovery in the biomarkers examined in this review. This finding, however, raises an issue with the viability of such exercise in PD patients. When decreased motor function is present, the ability to participate in a high intensity workout is likely to be heavily impaired. Based on the data collected in this review, if an individual is unable to reach an ideal intensity during exercise, the duration of the exercise could be increased in order to maximize the potential health benefits.

Cycling on a stationary bike would be optimal for this scenario. Intensity and duration could be manipulated, and the balance issues associated with PD would negate. Research has shown cycling to be beneficial in PD patients, specifically when done in an instructor led group. In such a group an instructor is partly responsible for the overall intensity, and individuals who exercised in the group were able to maintain a greater intensity than those who exercised individually (McGough et al., 2016). For individuals who found difficulty in reaching a specified intensity, increasing the duration could be an alternative method for optimal benefits, as suggested by the data collected here in this review. Future considerations should look at additional exercise types, focusing both on intensity and duration. Additionally, investigating the effects of intensity and duration directly on exercises such as cycling, boxing, and swimming could provide beneficial feedback for individuals who want to incorporate this as part of their PD treatment. Having a scientifically backed approach for substituting intensity for duration and vice-versa could provide encouraging and necessary motivation for PD patients to pursue regular exercise. Incorporating frequent exercise is an important aspect for improving the lives of individuals living with PD and should be of serious focus for treatment plans.

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Appendix

| Source | Exercise Type | Dose | Mice | Exercise occur pre or post administration | Max Intensity | Time per session | Total days | Results |
|----------------|---------------|--|----------|---|---------------|------------------|------------|---|
| Faherty 2005 | Voluntary WR | 20mg/kg every 2h x4 | Aged; F | Pre | - | - | 7d | SN TH positive neurons: ME attenuated loss by 38% SN BDNF mRNA expression: ME attenuated loss by 28% SN GDNF mRNA expression: ME attenuated loss by 46% SN DAT mRNA expression: ME attenuated loss by 17% SN VMAT2 mRNA expression: ME attenuated loss by 20% |
| Gerecke 2010 | Voluntary WR | 20mg/kg x4 every 2h | Adult; F | Pre | - | - | 90d | 1 mo unrestricted exercise: ↓ 41.5% TH positive neurons in SN 2 mo unrestricted exercise: ↓ 16.6% vs. M 3 mo unrestricted exercise: ↓ 9.2% vs. M 3 mo at 2.4 km/day: ↓ 35.6% in TH positive neurons in SN 3 mo at 4.8 km/day: ↓ 30.7% vs. M 3 mo at 7.5 km/day: fully protected vs. M STR DA: ME attenuated loss by 18% |
| Gerecke 2012 | Voluntary WR | 20mg/kg x4 every 2h | Adult; F | Pre | - | - | 90d | SN TH positive number: ME attenuated loss by 35% SN TH positive number: ME (+/-BDNF) attenuated loss by only 11% |
| Klein 2016 | Voluntary WR | 20mg/kg for 3 days | Adult; F | Post; 7d | - | - | 10d 20d | STR DA: 10day: ME attenuated loss by 10% STR DA: 28day: ME attenuated loss by 10% |
| Sconce 2015 | Voluntary WR | 8mg/kg incr. to 32mg/kg 5d/wk for 4wk | Adult; M | Pre; 2wk before start of exercise. | - | - | 14d | STR TH (OD): ME attenuated loss by -3% SN TH (OD): ME attenuated loss by 14% SN VMAT2: ME fully attenuated loss by 41% SN DAT (ratio): ME fully attenuated the increased ratio by 71% SN VGLUT1: ME attenuated increase by 66% SN GLT-1: ME fully attenuated loss by 89% |
| Churchill 2017 | Forced TM | 8mg/kg incr. to 32mg/kg 5d/wk for 4wk | Adult; M | Post; 4wk | 10.8 m/min | 60 min | 20d | SN TH protein expression (OD): ME attenuated loss by 6% STR TH protein expression (OD): ME attenuated loss by 21% SN DAT protein expression(OD) ME fully attenuated increase by 170% STR DAT protein expression (OD):ME attenuated loss by 45% STR BDNF and TRKB: No change STR GLT-1 levels: Me increased by 100% IBA-1 protein levels in the STR: ME attenuated increase by 200% |
| Hood 2016 | Forced TM | 6mg/kg incr. to 24 mg/kg 5d/wk for 4wk | Aged; M | Post; 2 wk | 10.8 m/min | 60 min | 20d | ME increased spontaneous locomotion STR TH (OD): ME attenuated loss by -2% STR TH: ME attenuated loss by 0% STR DAT: ME attenuated loss by 0% STR DA: ME attenuated loss by 0% Mctx TH expression: ME attenuated loss by 106% |
| Jang 2017 | Forced TM | 25mg/kg every 3.5d for 5wk | Adult; M | Post; immediately | 10 m/min | 60 min | 40d | Alpha-synuclein: ME attenuated increase by 18% STR TLR2 ME attenuated increase by 55% STR TNFalpha: ME fully attenuated increase by 30% STR IL-1beta: ME attenuated increase by 50% STR apoptotic cell death: ME fully attenuated increased by 200% STR TH protein: ME attenuated loss by 25% SN TH protein: ME attenuated loss by 20% SN TH positive neurons: ME attenuated loss by 50% |
| Koo 2017 | Forced TM | 25mg/kg every 3.5d for 5wk | Adult; M | Post; immediately | 12 m/min | 60 min | 40d | ME: ↑ in retention time on Rotarod TH protein in SN: ME attenuated loss by 30% DAT protein in the SN: ME attenuated loss by 30% SN number of TH positive cells: ME attenuated loss by 30% Alpha-syn expression in SN: ME attenuated increase by 70% Alpha-syn expression in STR: ME attenuated increase by 55% Bcl-2 protein in SN: ME attenuated loss by 25% Bax protein in SN: ME attenuated loss by 120% cleaved capase 3 protein in SN: ME attenuated increase by 55% SN MIM proteins TOM-40 (ME attenuated loss by 50%) TOM-20 (ME attenuated loss by 45%) TIM-23 (ME attenuated loss by 20%) SN COX-1 protein (ME attenuated loss by 35%) COX-IV protein (ME attenuated loss by 35%) mHSP70 protein (ME attenuated loss by 20%) |

| | | | | | | | | |
|----------------------|-----------|-----------------------------|----------|---------------------------------------|------------|----------|-----|---|
| Lau 2011 | Forced TM | 15mg/kg every 3.5d for 5 wk | Adult; M | 1 wk prior; 5 wk during; 12 week post | 15m/min | 40 min | 90d | Number of SN TH-positive neurons: ME attenuated loss by 49%SN TH (OD): ME attenuated loss by 41%STR TH (OD): ME attenuated loss by 50.6%STR DA: ME attenuated loss by 25%STR DAT: (OD) ME attenuated loss by 20%Beam Test Performance: ME attenuated slips by 11%STR Carbonylated proteins: ME attenuated increase by 14%Mn SOD (STR antioxidant enzyme): ME attenuated loss by 31%Cu-Zn SOD (STR antioxidant enzyme): ME attenuated loss by 22%BDNF in SN: ME increased by 50%; no change in STRGDNF in STR ME increased by 79%; no change in SN |
| Patki 2011 | Forced TM | 15mg/kg every 3.5d for 5 wk | Adult; M | 1 wk prior; 5 wk during; 12 week post | 15m/min | 40 min | 90d | STR cytochrome C: ME attenuated loss by 20% STR mRNA of p53: ME attenuated increase by 20 STR mRNA of TFAM: ME attenuated increase by 226% STR mRNA of PGC-1alpha: ME attenuated increase by 33% |
| Shin 2016 | Forced TM | 20mg/kg x4 every 2h | Adult; M | Post; 1d | 8 m/min | 30 min | 28d | Rotarod performance: ME attenuated loss by 90% SN TH+ SN: ME attenuated loss by 23% STR TH positive fibers (OD): ME attenuated loss by 7% STR PSD-95 protein: ME attenuated loss by 18% STR synaptophysin protein: ME attenuated loss by 11% STR dendritic spine density: ME attenuated loss by 24% |
| Smith 2011 | Forced TM | 30mg/kg for 7d | Adult; M | Post; 1d | 10.8 m/min | 60 min | 19d | ME: ↑ physical ability and improved gait performance SN TH + cells: ME attenuated loss by 21% SN Thionin stained cells: ME attenuated loss by 15% STR TH (OD): ME attenuated loss by 19% STR DAT (OD): ME attenuated loss by 23% |
| Sung 2015 | Forced TM | 25mg/kg every 3.5d for 5wk | Adult; M | Post; 1d | 10 m/min | 30 min | 20d | ME: ↑ latency in passive avoidance test SN TH protein: ME attenuated loss by 39% SN D2DR protein: ME attenuated loss by 16% SN BDNF: ME attenuated loss by 13% SN Trk B: ME attenuated loss by 19% ME: restored BrdU/DCX positive cells and BrdU/NeuN positive cells in the hippocampus to control levels. |
| Tillerson | Forced TM | 2x 15mg/kg for 1d | Aged; M | Post; 12hours | 5 m/min | 5x2 min | 9d | STR TH: ME attenuated loss by 21% STR VMAT2: ME attenuated loss by 12% STR DAT: ME attenuated loss by 15% |
| Toy 2014 | Forced TM | 20mg/kg x4 every 2h | Adult; M | Post; 5d | 24 m/min | 30x2 min | 30d | ME mice able to achieve running velocity that was not different from that of controls after 5 weeks of treadmill exercise Exercise overall ↑ spine density vs. non exercised; STR DA: No recovery STR dendritic spine density: ME attenuated loss by 34% STR PSD-95 synaptic protein ME attenuated loss by 33% STR synaptophysin synaptic protein: ME attenuated loss by 35% |
| Jang 2018 | Forced TM | 25mg/kg every day for 1 wk | Adult; M | Post; 4 wk | 12 m/min | 60 min | 30d | SN TH positive cell number: ME attenuated loss by 28% SN DAT level: ME attenuated loss by 26% |
| Fisher 2004 | Forced TM | 20mg/kg every 2h x4 | Adult; M | Post; 4 days | 23.0 m/min | 30x2 min | 30d | Velocity m/min after protocol: ME attenuated loss by 90% STR DAT (optical density): ME attenuated loss by -17% STR TH expression (optical density): ME attenuated loss by -27% |
| Pothakos 2009 | Forced TM | 25mg/kg every 3.5 days x10 | Aged; M | 1 wk prior; 5 wk during; 12 week post | 15 m/min | 40 min | 90d | STR DA (ng/mg tissue): ME attenuated loss by 5% SN TH positive neurons: No recovery |
| Sung 2012 | Forced TM | 20mg/kg every 3.5 days x10 | Adult; M | Post; 1d | 12 m/min | 30 min | 20d | SN TH cell number: ME attenuated loss by 22% STR TH fiber density (OD): ME attenuated loss by 10% Rotarod performance: ME attenuated performance loss by 75% |