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Voluntary exercise delays progressive deterioration of markers of metabolism and behavior in a mouse model of Parkinson's disease

Jing-Huei Lai[a,b], **Kai-Yun Chen**[b,c], **John Chung-Che Wu**[b,d,e], **Lars Olson**[f], **Stefan Brené**[f], **Chi-Zong Huang**[b,c], **Yen-Hua Chen**[b,d], **Shuo-Jhen Kang**[b,d], **Kuo-Hsing Ma**[g], **Barry J. Hoffer**[h], **Tsung-Hsun Hsieh**[i], **Yung-Hsiao Chiang**[a,b,d,e,*]

[a]Core Laboratory of Neuroscience, Office of R&D, Taipei Medical University, Taipei, Taiwan,

[b]Center for Neurotrauma and Neuroregeneration, Taipei Medical University, Taipei, Taiwan,

[c]Graduate Institute of Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan,

[d]Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan,

[e]Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan,

[f]Department of Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden,

[g]Department of Biology and Anatomy, National Defense Medical Center, Taipei, Taiwan,

[h]Department of Neurosurgery, Case Western Reserve University, School of Medicine, Cleveland, OH, USA,

[i]Department of Physical Therapy and Graduate Institute of Rehabilitation Science, College of Medicine, Chang Gung University, Taoyuan, Taiwan

Abstract

* Corresponding author: Yung-Hsiao Chiang, MD, Department of Surgery, School of Medicine, College of Medicine Taipei Medical University 250 Wu-Hsing Street, Taipei 11031, Taiwan. ychiang@tmu.edu.tw.

Author Contributions

JHL, KYC, SB, CZH, YHChen, SJK took part in the collection and analysis of the results; JHL, KYC, JCW, SB, KHM, BJH, THH, YHChiang designed and conducted the study. JHL, JCW, SB, LO, KHM, BJH, YHChiang contributed to data interpretation and drafting the original article. JHL, KYC, BJH, LO, YHChiang revised the final manuscript.

(JHL: Jing-Huei Lai, m105095006@tmu.edu.tw, Tel: 886-2-2736-1661 ext.7650; KYC: Kai-Yun Chen, kychen08@tmu.edu.tw, Tel: 886-2-2736-1661 ext.7650; JCW: John Chung-Che Wu, dr.jcwu@gmail.com, Tel: 886-2-2736-1661 ext.7650; LO: Lars Olson, Lars.Olson@ki.se, 46852487050; SB: Stefan Brené, stefan.brene@gmail.com; CZH: Chi-Zong Huang, manyluckymoney@gmail.com, Tel: 886-2-2736-1661 ext.7650; YHChen: Yen-Hua Chen, swallows3366@gmail.com, Tel: 886-2-2736-1661 ext.7650; SJK: Shuo-Jhen Kang, terbiun@gmail.com, Tel: 886-2-2736-1661 ext.7650; KHM: Kuo-Hsing Ma, kuohsing91@yahoo.com.tw, Tel: 886-2-8792-3100 ext.18728; BJH: Barry J. Hoffer, bjh82@case.edu, Tel:+216-368-4169; THH: Tsung-Hsun Hsieh, hsiehth@mail.cgu.edu.tw, ;YHChiang, Yung-Hsiao Chiang, ychiang@tmu.edu.tw, Tel: 886-2-2736-1661 ext. 76500)

Conflict of Interest and Author Disclosure Statement

LO is a co-owner of a company that owns commercial rights to the MitoPark mouse. The other authors have no conflict of interest.

Although a good deal is known about the genetics and pathophysiology of Parkinson's disease (PD), and information is emerging about its cause, there are no pharmacological treatments shown to have a significant, sustained capacity to prevent or attenuate the ongoing neurodegenerative processes. However, there is accumulating clinical results to suggest that physical exercise is such a treatment, and studies of animal models of the dopamine (DA) deficiency associated with the motor symptoms of PD further support this hypothesis. Exercise is a non-pharmacological, economically practical, and sustainable intervention with little or no risk and with significant additional health benefits. In this study, we investigated the long-term effects of voluntary exercise on motor behavior and brain biochemistry in the transgenic MitoPark mouse PD model with progressive degeneration of the DA systems caused by DAT- driven deletion of the mitochondrial transcription factor TFAM in DA neurons. We found that voluntary exercise markedly improved behavioral function, including overall motor activity, narrow beam walking, and rotarod performance. There was also improvement of biochemical markers of nigrostriatal DA input. This was manifested by increased levels of DA measured by HPLC, and of the DA membrane transporter measured by PET. Moreover, exercise increased oxygen consumption and, by inference, ATP production via oxidative phosphorylation. Thus, exercise augmented aerobic mitochondrial oxidative metabolism vs glycolysis in the nigrostriatal system. We conclude that there are clear-cut physiological mechanisms for beneficial effects of exercise in PD.

Keywords

Parkinson's Disease; Exercis; PET; Mitochondria; Dopamine

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition in the central nervous system, characterized by dopamine (DA) neuron loss in the nigrostriatal system and other neurodegenerative processes that may differ between different types of PD. Clinical symptoms include resting tremor, rigidity, akinesia, and disturbances of postural reflexes, and affect some 10 million people worldwide (Sethi, 2002).

Exercise is currently often used as an important part of the treatment for PD (Lauze et al., 2016; Shen et al., 2016). Although both motor and non-motor symptoms may affect PD patients' ability to participate in, and/or impact the outcomes of exercise, most PD patients can respond to exercise interventions similarly to subjects of matching age who do not suffer from PD. Increasing evidence also indicates that exercise improves specific PD motor symptoms and reduces DA neuron loss in PD animal models (Shi et al., 2017; Tillerson et al., 2001). This may involve several mechanisms, including angiogenesis (Pereira et al., 2007; Pianta et al, 2019), increased mitochondrial function, neurogenesis (Watson et al, 2015; Yasuhara et al, 2007) and enhanced neuronal plasticity (Cho et al., 2013; Svensson et al., 2015). In addition, neurotrophic factors that play a crucial role in changes in brain plasticity and neurogenesis are induced by exercise (McAllister, 1999; Zigmond et al., 2012; Zigmond and Smeyne, 2014).

Here we use the MitoPark mouse PD model in which DA neurons are targeted for respiratory chain dysfunction. This is accomplished by dopamine transporter (DAT) promoter-driven removal of the crucial mitochondrial transcription factor TFAM (Ekstrand et al., 2007). Such mice develop progressive Parkinsonian symptoms over several months and exhibit neuropathology similar to idiopathic PD. Intraneuronal inclusions develop sequentially within substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) DA neurons, followed by progressive degeneration of the mesencephalic DA projections to the forebrain with subsequent loss of DA in the striatum (Ekstrand et al 2007). As in PD, DA neurons in SNc in this mouse model degenerate before, and more completely than, those in VTA, even though both neuronal types are targeted for mitochondrial disruption. As in PD, L-DOPA medications in the mouse model have profound normalizing effects on phenotypes dependent on DA neurotransmission at 20-weeks and even at 30 weeks, albeit lesser in the latter “post- honeymoon” phase of L-DOPA treatment. Furthermore, even the “wearing off” of L-DOPA is apparent in this slowly progressing model (Galter et al 2010, Shan et al 2015, Gellhaar et al 2015). Using the MitoPark mouse model we now describe the long-term effects of voluntary exercise on motor behavior and brain biochemistry.

Results

Behavioral Studies.

The behavioral studies detailed below are from two series of mice, studied in Sweden and in Taiwan, respectively (see Experimental Procedures). We have previously reported that by 10–12 weeks of age MitoPark animals already show a significant reduction in overall motor activity and rotarod performance (Ekstrand et al., 2007). Importantly, as shown in Fig. 1, given access to a running wheel, MitoPark animals actually run more than wild type mice during the first 10–11 weeks of life if the exercise is started early (5–6 weeks of age) (Series 1). Given the severe phenotype of these animals, however, there is soon a progressive reduction in running wheel activity (Fig. 2). Behavioral recordings were carried out weekly with mice from 6 to 20 weeks of age, after which animals were sacrificed for biochemical measurements. Behavioral measurements showed that exercise improved motor performance in MitoPark animals as evidenced by beam walking (Fig. 3) and rotarod performance (Fig. 4A-C). When normalized to wild type animals (normalized to 100%, data not shown), sedentary MitoPark mice performed significantly worse on the rotarod than wild type mice, whereas exercising MitoPark mice did not (Fig. 4D).

PET study of DAT.

The behavioral data were complemented by PET imaging at weeks 6, 10, and 20 (Fig. 5). There was a transient but significant increase in striatal DAT binding at 10 weeks. Again, because of the severity of the phenotype, this was no longer apparent at 20 weeks.

Postmortem respiratory assay. Biochemical observations after sacrifice of 20 weeks old animals support the effects of exercise in the MitoPark PD model. As shown in Fig 6 (top) there is more oxidative phosphorylation (OCR) for ATP generation and less use of glycolysis (ECAR) for ATP generation in exercised, compared to sedentary MitoPark mice.

Levels of DA and its metabolites.

HPLC showed that there were small but significant increases in the levels of DA and its metabolites in the exercised compared to sedentary MitoPark mice (Fig. 6 bottom).

Discussion

Physical exercise is an economical, practical, and relatively safe approach to achieve neuroprotective and neurorestorative effects in PD. There are robust clinical data supporting positive effects of aerobic exercise in PD (Fang et al., 2018; Fiorelli et al., 2019; Oliveira de Carvalho et al., 2018; Park et al., 2014). Similarly, there are well-documented positive effects of aerobic exercise in genetic and toxin-induced PD models in rodents using both behavioral and cellular indices of nigrostriatal DA activity. Animal models show that exercise promotes mitochondrial efficiency, upregulates antioxidant mechanisms, reduces inflammation, triggers angiogenesis, and neurogenesis, increases neurotrophic factors and produces synaptogenesis (Choe et al., 2012; da Costa et al., 2017; Hsueh et al., 2018; Jang et al., 2018; Koo et al., 2017; Real et al., 2017; Tajiri et al., 2010; Wi et al., 2018; Zigmond et al., 2012).

Our present results are compatible with previous data showing that physical exercise constitutes an effective intervention also in other neurodegenerative diseases and attenuates disease progression (Ahlskog, 2011; Alonso-Frech et al., 2011; Sutoo and Akiyama, 2003). The mechanisms contributing to these phenomena may not only derive from peripheral effects of acute exercise, including increasing cardiac output and cerebral blood flow (Paillard et al., 2015), but may also derive directly from CNS effects on neurobiological mechanisms, including increases in angiogenesis (Pianta et al, 2019), neurogenesis, synaptogenesis, and neurotransmitter synthesis in cerebral areas involved in cognition and mobility in PD (Radak et al., 2010; Zigmond et al., 2012).

Neurogenesis specifically is enhanced by exercise as evidenced by increased cell proliferation in known brain neurogenic niches, which coincides with neuronal gene expression (Watson et al, 2015; Yasuhara et al, 2007). Such exercise-induced neurogenesis and behavioral function stands as a potent therapy for many brain disorders characterized by impaired neurogenesis in motor and cognitive abnormalities.

Physical exercise activates antioxidant enzymes and reduces chronic oxidative stress. Exercise also stimulates mitochondrial biogenesis, and there is up-regulation of mitophagy in PD patients (Monteiro-Junior et al., 2015). However, while exercise may lead to improved mitochondrial quality control through autophagy, as well as mitochondrial renewal through biogenesis that would be beneficial in prematurely ageing mice with pathologically enhanced mtDNA mutation rates (Safdar et al., 2011), exercise is less likely to exert similar positive effects long-term at the mitochondrial level in MitoPark mice, due to the lack of the mitochondrial transcription factor TFAM in the DA neurons. It follows that the demonstration of positive effects in our specific PD model, in which mitochondria in DA neurons cannot be rescued, may also be achieved by mechanisms other than direct support of the DA system.

Exercise also stimulates trophic factor synthesis (BDNF, GDNF, FGF-2, IGF-1, among others), which promotes neuroplasticity, decreases neural apoptosis (Monteiro-Junior et al., 2015), and alters dopaminergic neurotransmission (Petzinger et al., 2007; Tillerson et al., 2003). Exercise may exert neuroprotective effects or enhance neuronal survival by increasing neurotrophic factor availability (Gerecke et al., 2012; Gerecke et al., 2010; Hsueh et al., 2018; Tuon et al., 2012). Physical training also elevates intracellular defenses against ROS. This in turn increases the capacity of DA neurons to deliver transmitter (Tajiri et al., 2010; Zigmond et al., 2009).

Mitochondrial dysfunction and energy failure are implicated as the cause of death of DA neurons in PD (Dauer and Przedborski, 2003; Dawson and Dawson, 2003; Ellis et al., 2005; Mizuno et al., 1989; Shen and Cookson, 2004; Ved et al., 2005). Toxins used to model PD, such as MPTP and rotenone, impair respiratory chain function by inhibiting complex I (Betarbet et al., 2000; Langston et al., 1983; Mizuno et al., 1987; Sherer et al., 2003; Smeyne and Jackson-Lewis, 2005). In further support for a “mitochondrial hypothesis” for PD pathophysiology, Bender et al (2006) reported higher levels of mitochondrial DNA deletions in nigral neurons from PD patients. Moreover, both Bender et al (2006) and Kraytsberg et al (2006) reported higher levels of mitochondrial DNA deletions in nigral neurons in aged humans with sharp elevations starting shortly before age 70. This correlates with age being a known risk factor for PD.

Several genes (Parkin, Pink-1, DJ-1, LRRK2) implicated in PD are considered important for mitochondrial function (Shen and Cookson, 2004; Valente et al., 2004; West et al., 2005). To further study the role of such genes, transgenic mouse models are used to knockout normal alleles or overexpress mutant alleles. However, such models in mice tend to fail to recapitulate the full behavioral and pathological features of PD, and some models have produced conflicting or inconclusive data. Despite these shortcomings, studies of transgenic mice have identified mitochondrial dysfunction as possibly underlying the slow degeneration in PD.

Interpretation of results from more traditional experiments with neurotoxins are complicated by additional pharmacological effects in DA neurons, effects on non-DA cell types, or both. Targeting mitochondrial respiratory chain function as used in the current study leads to a strikingly PD-like phenotype, with respect to both behavior and progressive neuropathology. Because the MitoPark mouse model is purely genetic, the degenerative events are inevitable when there is no intervention such as exercise. However, the symptoms occur only after reaching adulthood, as in the vast majority of cases of PD, which provides a long window of opportunity for studies of pathophysiology and tests of treatment strategies. Because the genetic defect and its consequences are controlled from the outset, intervention can begin at any time, even presymptomatically. Those properties are becoming more relevant for clinical interventions as genetic risk factors are further unraveled.

Summary

In this study, we investigated the long-term effects of voluntary exercise on motor behavior and biochemistry in the MitoPark mouse PD model with progressive degeneration of the DA

systems. We found that voluntary exercise markedly improved overall motor activity, narrow beam walking, and rotarod performance. There was also improvement of biochemical markers of nigrostriatal DA input. This was manifested by increased levels of DA measured by HPLC and of the DA membrane transporter measured by PET. Moreover, exercise increased oxygen consumption and, by inference, ATP production via oxidative phosphorylation. Thus, exercise augmented aerobic mitochondrial oxidative metabolism vs glycolysis in striatum. We conclude that exercise activates physiological mechanisms with beneficial effects in PD.

Experimental Procedures

Animals.

The breeding scheme for generating MitoPark mice has been described previously (Ekstrand et al., 2007; Galter et al., 2010; Good et al., 2011). Briefly, animals on a C57BL6 background, in which the DAT promoter was used to drive cre-recombinase expression, were crossed with mice in which the TFAM gene had been loxP-flanked. MitoPark mice used in these experiments were heterozygous for DAT-cre expression (DAT/DATcre) and homozygous for the loxP-flanked Tfam gene (TfamloxP/TfamloxP), ensuring complete removal of TFAM. Two sets of studies on exercise were carried out. In one series, MitoPark mice were compared with an equal number of wild type littermates with both groups housed individually in cages equipped with running wheels. These animals were subsequently studied on the rotarod to evaluate motor coordination and motor learning. In a second series, MitoPark mice were individually housed in cages with or without running wheels to compare exercising and sedentary animals both with slowly degenerating DA neurons. Behavioral, PET, and biochemical studies were carried out. For this second study, 14 MitoPark mice were randomly assigned to the exercise and non-exercise groups.

All mice were housed with water and standard food ad libitum at 25 °C in a 12 h/12 h light/dark cycle. The first series of animals was maintained and studied at the Department of Neuroscience, Karolinska Institute. All experimental procedures in this study were approved by the Northern Stockholm Animal Ethics Committee. The second series of animals was maintained and studied in the Laboratory Animal Center (LAC) of the National Defense Medical Center (NDMC) in Taipei. This animal study was approved by the Institutional Animal Care and Use Committees (IACUC) of the NDMC and Taipei Medical University (TMU). Animal protocol numbers were IACUC-15–270, 16–269 and 17–298.

Exercise.

Exercising MitoPark mice were housed in open acrylic plastic cages. Each cage contained one stainless steel, hollow running wheel (diameter, 12 cm). The rotation numbers were recorded by magnetic (Series 1) or infrared sensors (Series 2).

Beam walk.

This test was used to determine fine motor coordination and balance. Mice were trained for 3 days to walk along a narrow Plexiglas beam (100 cm long, 0.5 cm wide) towards a home cage located at one end of the beam. The mean time to walk across the beam was used as a

measure of motor coordination. Three trials with 30 min intervals were done at each age that was tested.

Rotarod.

A rotating rod instrument (Rotarod, Ugo Basile, Washington D.C, US) was used to further validate motor coordination. The accelerating protocol started at a speed of 5 rpm and reached 40 rpm within 300 seconds. Three measures of performance were taken: 1) time to fall, 2) rotarod rotation velocity at falling, and 3) distance travelled on the rotarod before falling. Three trials were given at each age with a 15 minute interval between trials.

Catecholamine measurements.

Levels of DA, DOPAC (3, 4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) in dorsolateral striatal brain samples were determined by treatment with 200 mM KCl followed by several rounds of physical disruption by trituration. The disrupted slices were then freeze-thawed, sonicated, and filtered at 0.2 μm. DA, DOPAC, and HVA contents were analyzed using an HPLC-EC system (ESA, Chelmsford, MA)(Yuan et al., 2002). On the HPLC chromatograms, DA, DOPAC, and HVA were separate peaks that were quantified by comparing their heights to those of DA, DOPAC, and HVA standard curves using linear regression analysis.

Mitochondrial Oxygen Consumption.

A respiratory assay (Seahorse XF Analyzer, Agilent) was used to measure oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) according to previously published methods (Fried et al., 2014). Nigrostriatal tissue from MitoPark mice was dissected on ice after anesthesia with 3% isoflurane. The tissue was kept in ice-cold aCSF solution (124 mM NaCl, 2.5 mM KCl, 2.0 mM MgSO4, 1.25 mM KH2PO4, 10 mM glucose, 4 mM sucrose, and 2.5 mM CaCl2 adjusted to pH to 7.4). Before the respiratory assay, we dissected the tissue into approximately $1.5 \times 1.5 \times 0.5$ mm^3 pieces and placed them in the center of meshes. The mesh with tissue was gently loaded into a well filled with 37°C aCSF. A microplate with these wells was then incubated at 37°C for 30 minutes and aCSF was calibrated for temperature and pH equilibration. The assay protocol was executed following a continuous procedure of 3-min mix, 3-min wait, and 2-min measure sequences for 5 cycles. OCR and ECAR values were normalized to protein concentration.

PET Imaging.

We used the DAT radiotracer [18F]-FE-PE2I (Schou et al., 2009) (14.8–18.5 MBq; 0.4–0.5 mCi), to evaluate presence of DA neuron elements in the mice. The radiotracer was synthesized in the Positron Emission Tomography (PET) Center of the Department of Nuclear Medicine of Tri-Service General Hospital. We delivered [18F]-FE-PE2I to MitoPark mice by tail vein injections at 6, 10, and 20 weeks of age. The mice were anesthetized by passive inhalation of isoflurane/oxygen (5% isoflurane for induction and 2% for maintenance) (Abbott Laboratories Ltd., Maidenhead, UK). PET imaging (PET R4 scanner, Concorde MicroSystems, Knoxville, TN, USA) was performed for 30 minutes after [18F]-

FE-PE2 injections. Images of striatum were analyzed using appropriate software (ASIPro VM 6.3.3.1 Concorde MicroSystems).

Statistical Analysis

Evaluations were undertaken in an observer blinded manner. Statistical analyses were performed with Student's t-test and one-way or two-way ANOVA. Significance was inferred at $p \leq 0.05$ or less, and is noted within each Figure legend. Data are presented as mean ± SEM values throughout.

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Highlights

- Voluntary exercise markedly improves behavioral function in the MitoPark mouse PD model with progressive degeneration of the DA systems.
- Exercise increased levels of DA and the DA membrane transporter, measured by HPLC and PET, respectively.
- Exercise increases oxygen consumption and, by inference, ATP production via oxidative phosphorylation.
- Exercise augments aerobic mitochondrial oxidative metabolism over glycolysis in the nigrostriatal system.

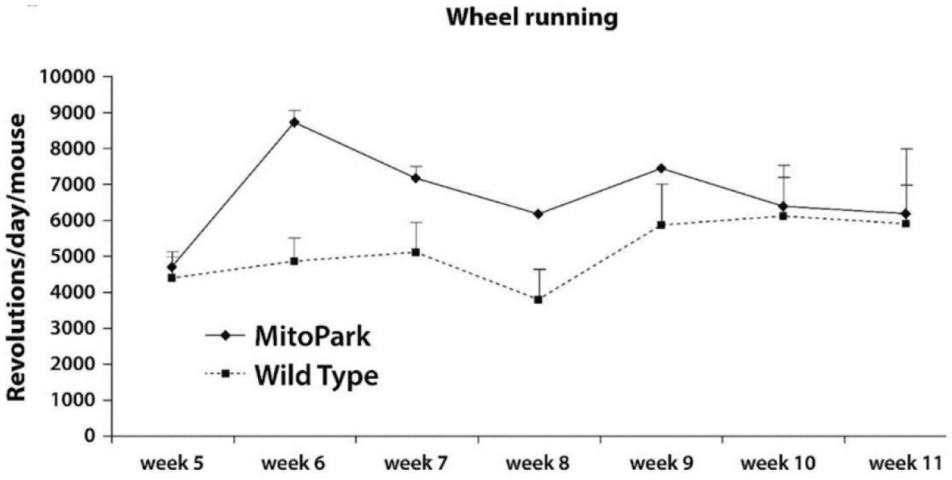

Fig. 1.

Wheel running in MitoPark mice and wild type littermates. After 12 weeks, and at later stages, MitoPark mice run progressively less than WT animals (see also Ekstrand et al 2007) $p<0.05$ weeks 6–9.

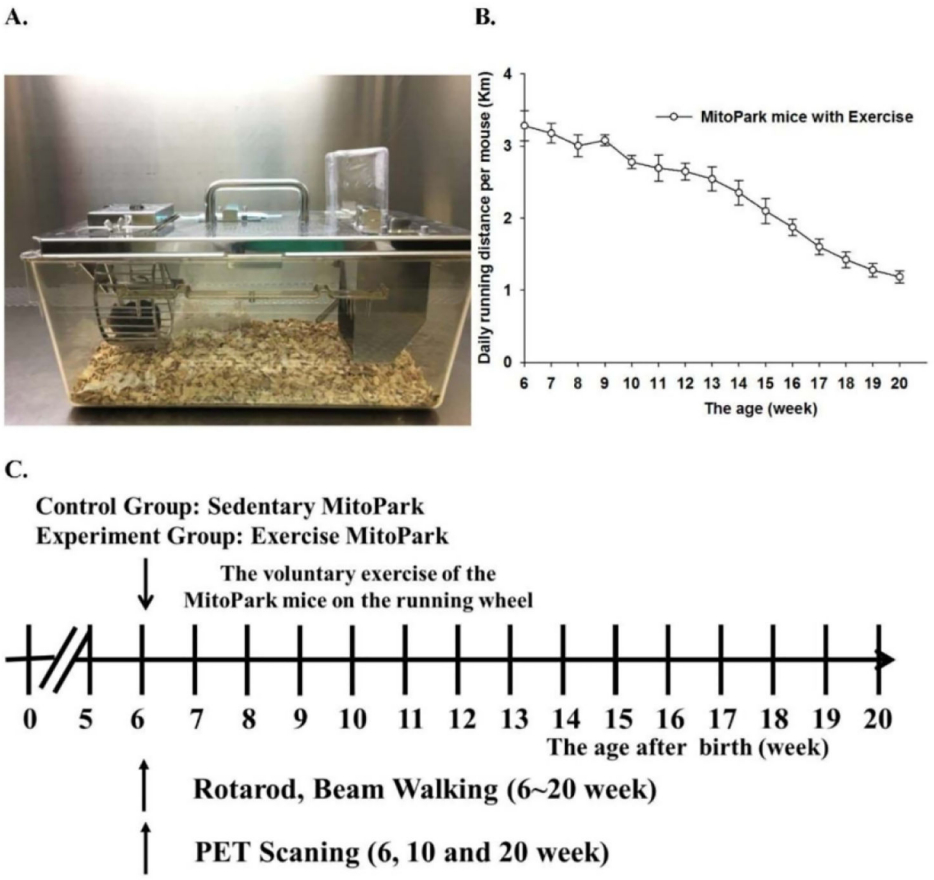

Fig. 2.

A. Exercising MitoPark mice were fed in the home cage which also contained the running wheel. B. Running wheel rotations per day of MitoPark mice (N = 7). C. A schematic graph of behavioral tests for MitoPark mice with and without access to running wheel exercise. We investigated DA neuron activity by PET scanning and behavior at the indicated times (7 MitoPark mice in each group)

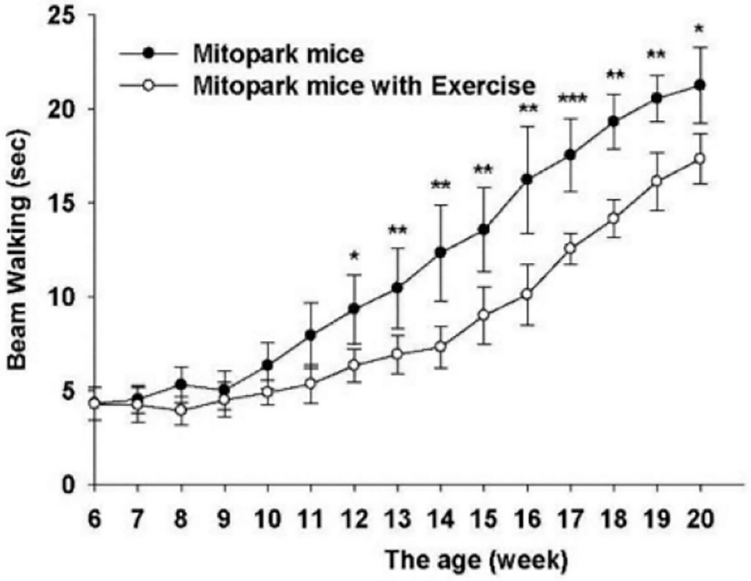

Fig 3.

Effect of exercise on time to cross a beam. Stars indicate significances between exercised and non-exercised MitoPark mice. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.

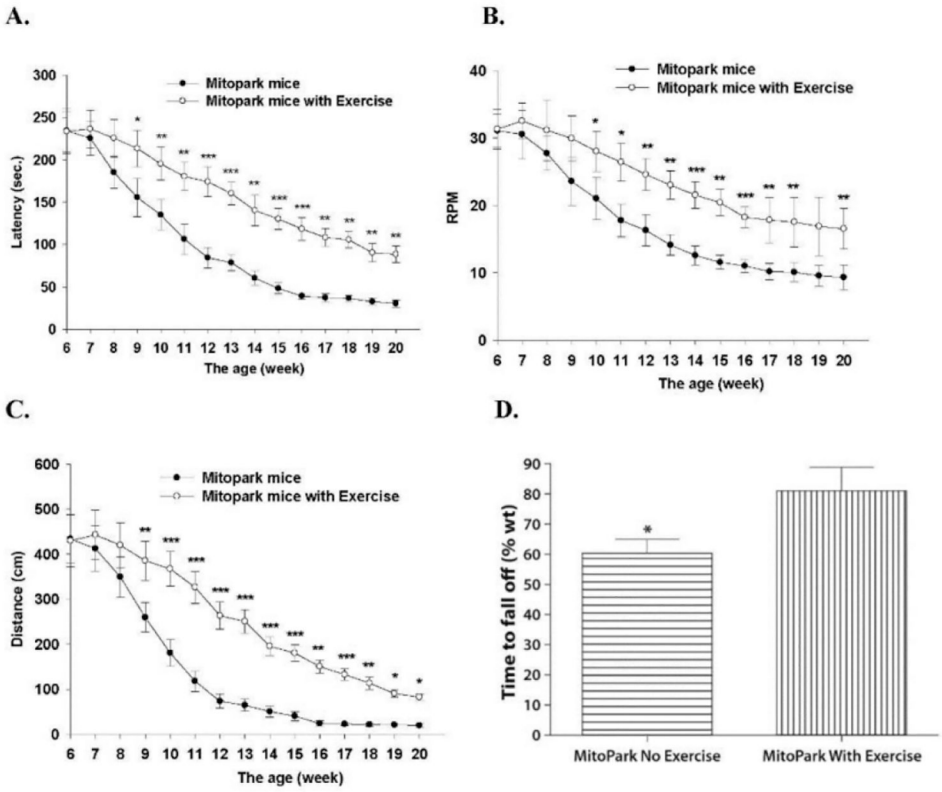

Fig. 4.

Effects of exercise on motor coordination of MitoPark mice determined using the rotarod test. The latency **(A)**, the rotational velocity **(B)** and the distance **(C)** of MitoPark mice compared with MitoPark-Exercise mice. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. **(D)** Rotarod data from MitoPark mice with and without exercise normalized to wild type animals *p<0.05 (7 MitoPark mice in each group).

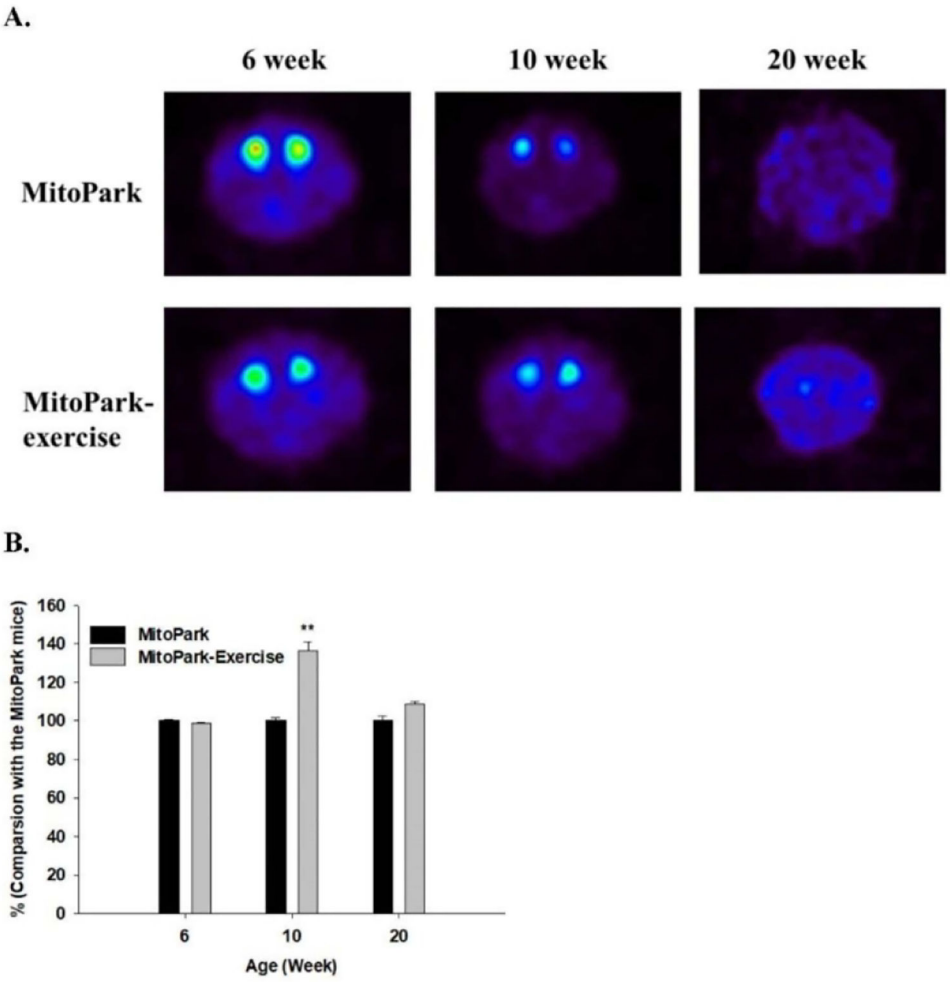

Fig. 5.

Dopamine neuron activity determined by PET using a DAT ligand. **A.** Examples of the distribution of [18F]-FE-PE2 in MitoPark mice without and with exercise 6, 10, and 20 weeks after intravenous administration. **B.** Ligand binding in striatum in MitoPark mice with exercise compared with MitoPark mice without exercise. ** $P < 0.01$(5 MitoPark mice in each group)

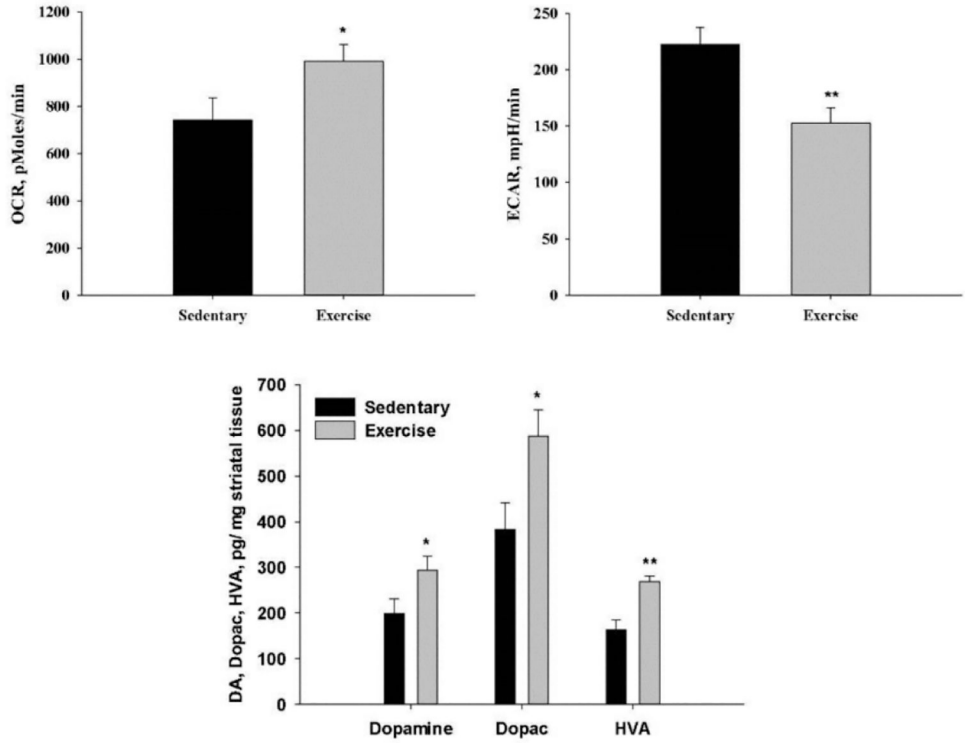

Fig. 6.

Bioenergetics, DA and DA metabolites in striatum from sedentary and exercised MitoPark mice. Top: Seahorse assays (7 MitoPark mice in each group) of mitochondrial respiration rate (oxygen consumption rate, OCR) (left) and glycolytic rate (extracellular acidification rate, ECAR) (right). Bottom: Levels of Dopamine, Dopac and HVA from 5 MitoPark mice in each group. ** $P < 0.01$, * $P < 0.05$.