



Developmental origins of Parkinson disease: Improving the rodent models

Irene Jiménez-Salvador^{a,b,1}, Patricia Meade^{a,b,c,d,1}, Eldris Iglesias^{a,b,e},
Pilar Bayona-Bafaluy^{a,b,c,d,*}, Eduardo Ruiz-Pesini^{a,b,c,*}

^a Departamento de Bioquímica, Biología Molecular y Celular, Universidad de Zaragoza, 50009- and 50013 Zaragoza, Spain

^b Instituto de Investigación Sanitaria (IIS) de Aragón, 50009 Zaragoza, Spain

^c Centro de Investigaciones Biomédicas en Red de Enfermedades Raras (CIBERER), 28029 Madrid, Spain

^d Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Universidad de Zaragoza, 50018 Zaragoza, Spain

^e Facultad de Ciencias de la Salud, Universidad San Jorge, 50830 Villanueva de Gállego, Zaragoza, Spain

ARTICLE INFO

Keywords:

Parkinson disease
Developmental origins
Pesticide
Oxidative phosphorylation
Rodent model

ABSTRACT

Numerous pesticides are inhibitors of the oxidative phosphorylation system. Oxidative phosphorylation dysfunction adversely affects neurogenesis and often accompanies Parkinson disease. Since brain development occurs mainly in the prenatal period, early exposure to pesticides could alter the development of the nervous system and increase the risk of Parkinson disease. Different rodent models have been used to confirm this hypothesis. However, more precise considerations of the selected strain, the xenobiotic, its mode of administration, and the timing of animal analysis, are necessary to resemble the model to the human clinical condition and obtain more reliable results.

1. Introduction

1.1. Developmental origins of Parkinson disease

The “developmental origins of health and disease (DOHaD)” hypothesis posits that environmental factors to which one is exposed during prenatal, neonatal, and early childhood development act as risk factors for disease in adulthood and old age (Fukunaga, 2021; Gluckman and Hanson, 2004). At the 2003 Mount Sinai Conference on “Early environmental origins of neurodegenerative disease in later life: research and risk assessment” this hypothesis was extended to encompass brain development and explore the impact of toxic substances on this process (Landrigan et al., 2005).

Prenatal and early postnatal periods are vital time spans for brain development, in which the elementary structure of the brain is being built. Disturbances during these periods may adversely impact the establishment of basic neuronal circuits, weakening the fundamental structure of the brain. Exposure to a toxicant during brain cell proliferation, migration, or differentiation can result in hypoplasia (reduced neuronal population), ectopia (neuronal mislocalization), or dysplasia (abnormally configured dendritic arbors), respectively (Bayer et al.,

1993). Such modifications may be responsible for permanent deficiencies.

One of the diseases that could be related to the DOHaD is Parkinson disease (PD). PD is a chronic, progressive, multisystemic, multifactorial, and multi-etiologic neurodegenerative disease that affects people mainly in the last years of life. The incidence of PD increases with age, reaching a peak between 70 and 79 years of age (Hirsch et al., 2016). Degeneration of nigrostriatal dopaminergic (DA) neurons is held to be the primary neuropathological correlate of motor injury in PD. Up to 70 % of DA cells in the nigrostriatal system are lost before the cardinal motor features of PD appear (Giguère et al., 2018). Gastrointestinal disturbances and anosmia often occur years before motor dysfunction. Both the gut and the olfactory system contain dopaminergic neurons and their numbers appear to be reduced in patients with PD (Chalazonitis et al., 2022; Paß et al., 2020).

Neurogenesis occurs mainly during the development of the nervous system, early in life. In humans, DA neurons in the *substantia nigra* (SN) are generated between weeks 5 and 7 after fertilization (Bayer et al., 1993). The development of the enteric and olfactory nervous system also occurs during this time (Goldstein et al., 2013; Müller and O’Rahilly, 2004). The involvement of DOHaD in PD would denote the existence of

* Corresponding authors at: Departamento de Bioquímica, Biología Molecular y Celular, Universidad de Zaragoza, 50009- and 50013 Zaragoza, Spain
E-mail addresses: jimsal@unizar.es (I. Jiménez-Salvador), pmeade@unizar.es (P. Meade), eaiglesias@usj.es (E. Iglesias), pbayona@unizar.es (P. Bayona-Bafaluy), eduruiz@unizar.es (E. Ruiz-Pesini).

¹ These authors have contributed equally.

<https://doi.org/10.1016/j.arr.2023.101880>

Received 20 October 2022; Received in revised form 24 January 2023; Accepted 7 February 2023

Available online 10 February 2023

1568-1637/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

early factors that damage DA neurons or alter the differentiation of their precursors. These early factors could acutely reduce the number of DA neurons. Consequently, neuronal attrition associated with advanced age would drive the number of neurons to levels below those necessary to maintain proper function (von Linstow et al., 2020). Alternatively, a prenatal factor could interfere with the developmental program, accelerate the loss of neurons throughout life, and induce subclinical alterations. In the last case, some type of permanent cellular modification would occur. This “developmental origins of Parkinson disease” (DOPD) hypothesis has already been proposed by several authors (Barlow et al., 2007; Charlton, 2013; Cory-Slechta et al., 2005a; Grova et al., 2019; Iglesias et al., 2018; Landrigan et al., 2005; Liang et al., 2013; Logroscino, 2005; Schaefer and Teuchert-Noodt, 2016; Schwamborn, 2018; Tartaglione et al., 2016).

1.2. Neurogenesis, oxidative phosphorylation, and Parkinson disease

Mitochondrial function plays an obligatory role in brain development (Gyllenhammer et al., 2022). Neurogenesis is the generation of new neurons from stem cells and the oxidative phosphorylation (OXPHOS) function is important for this process (Brunetti et al., 2021; Coelho et al., 2022; Iwata and Vanderhaeghen, 2021). Neurons derived from neural stem cells predominantly use OXPHOS. Therefore, OXPHOS-related mutant genes reduce neuronal differentiation (Iglesias et al., 2019). Some xenobiotics, by binding to mitochondrial DNA (mtDNA)-encoded proteins or RNAs, also negatively affect OXPHOS function and, thus, neurogenesis (Iglesias et al., 2019; Pesini et al., 2019).

Although PD is a multitietologic disease, an OXPHOS dysfunction may be a pathogenic event in many cases of PD (López-Gallardo et al., 2011). Thus, OXPHOS respiratory complex I (CI) activity in SN, CI subunits levels in *striata*, and the percentage of nigral neurons with CI immunohistochemical staining were found to be decreased in PD patients. The CI impairment is systemic, because decreased CI activity has also been demonstrated in muscle and blood cells from PD patients. Moreover, other OXPHOS complexes have also been reported to be reduced in many PD patients (López-Gallardo et al., 2011).

Since OXPHOS function is important for neurogenesis, neurogenesis occurs mainly in the early stages of nervous system development, and a decrease in developmental neurogenesis may be associated with PD, early OXPHOS dysfunction could be considered a risk factor for PD (Iglesias et al., 2018).

1.3. OXPHOS xenobiotics and Parkinson disease

Environmental chemical exposures *in utero* may contribute to PD susceptibility and early postnatal oral exposure to mitochondrial toxins might trigger PD-related pathology in enteric neurons with retrograde progression to the brain via the vagus nerve. Most of these chemicals enter through contaminants in the air we breathe, the water we drink, and the food we eat. Unfortunately, the OXPHOS system is particularly susceptible to many of these toxics, including some pesticides. Thus, environmental exposure to OXPHOS toxins could favor the development of PD. Binding of an OXPHOS inhibitor has been defined as the molecular initiating event that triggers mitochondrial dysfunction, which then causes degeneration of DA neurons, resulting in motor deficit symptoms typical for PD. These causatively linked cellular key events describe an adverse outcome pathway (Delp et al., 2021).

In 1982, some drug addicts developed severe parkinsonism after intravenous injection of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), a by-product in the synthesis of a new synthetic heroin. MPTP is metabolized to 1-methyl-4-phenylpyridinium ion (MPP⁺), which inhibits CI. MPTP is commonly used to model PD (Langston, 2017), though it is not generally found as an environmental toxicant. Rotenone, a CI inhibitor pesticide, is also used to model PD (Betarbet et al., 2000). Epidemiological studies showed an association between PD and

rotenone exposure (Pouchieu et al., 2018; Tanner et al., 2011). However, the risk of human exposure to rotenone is limited because it breaks down readily in the environment (Bové et al., 2005). Many other pesticides are CI inhibitors, such as aldrin, benzimidazole, deguelin, fenazaquin, fenpyroximate, paraquat (PQ), pyrethroids, pyridaben, pyrimidifen, and tebufenpyrad (Agrawal et al., 2015; Czerniczyniec et al., 2015; Degli Esposti, 1998; Delp et al., 2021; Falcioni et al., 2010; Fukushima et al., 1994; Gassner et al., 1997; Liang et al., 2013; Pardini et al., 1971; Tanner et al., 2011; Tawara et al., 1996; Yang and Tiffany-Castiglioni, 2008). A good number of pesticides are respiratory complex III inhibitors, such as atrazine, azoxystrobin, chlordane, dieldrin, fenamidone, heptachlor, kresoxim-methyl, maneb, pycoxystrobin, pyraclostrobin, toxaphene, and trifloxystrobin (Bergen, 1971; Delp et al., 2021; Hong et al., 2013; Lim et al., 2009; Pardini et al., 1971; Zhang et al., 2003). Many of these pesticides reduce the striatal dopamine content and the number of DA neurons, increase the α -synuclein aggregated form, and impair motor coordination (Agrawal et al., 2015; Domico et al., 2006; Fedeli et al., 2014; Li et al., 2014; Nasuti et al., 2017, 2013; Rodríguez et al., 2013; Singh et al., 2012). Some of them have also been associated with an increased risk of PD (James and Hall, 2015).

2. Discussion

2.1. Rodent models to study the effect of prenatal exposure to OXPHOS xenobiotics on Parkinson disease

Human epidemiological studies have suggested that the risk of developing PD may be related to pesticide exposures (Brown et al., 2006; Goldman, 2014). One of the disadvantages of this type of study is the lack of homogeneity among participants. Although animal models allow strong control over confounding factors, according to one estimate, as much as \$28 billion is wasted annually in the United States alone in pre-clinical experiments involving laboratory animals due to the lack of repeatability of these studies (Freedman et al., 2015). Improving the experimental design to reflect as closely as possible the human situation is key to improving the predictive nature of animal studies (Jackson et al., 2017). Therefore, in the following sections, we will go deeper into how to achieve models much closer to human conditions.

2.1.1. Selection of the rodent strain

Animal studies in DOHaD research have been performed in a range of species (Dickinson et al., 2016). However, many characteristics of rodents make them interesting models to test the DOPD hypothesis. In fact, the vast majority of animals used for neurotoxin models are rodents (Kin et al., 2019; Konnova and Swanberg, 2018). Neurotoxin-induced rodent models of PD produce data that underpin biomedical research, but translation from animals into successful clinical outcomes is often lacking (El-Gamal et al., 2021).

Inbred rodent strains are isogenic, each exhibiting a unique set of phenotypic characteristics and providing absolute control over genetic variability. Thus, diverse rodent strains will provide different characteristics that make them more or less interesting for these studies. For example, mouse strain-specific differences in the relative expression of electron transport chain (ETC) proteins have been shown (Singh et al., 2021). Some of these differences are due to the particular mtDNA of the strain. In the liver of 2-year-old BL/6^{NZB} conplastic mouse (C57BL/6 nuclear and NZB/OlaHsd mitochondrial genome), the relative abundance of CI and respiratory complex IV subunits is significantly higher than that of BL/6^{C57} mouse (C57BL/6 nuclear and C57BL/6 mitochondrial genome). Moreover, respiration of liver mitochondria steadily declines in BL/6^{C57} mouse but remains constant between days 20 and 300 in BL/6^{NZB} mouse (Latorre-Pellicer et al., 2016). On the other hand, a large body of evidence suggests that C57BL/6 J mice have a much higher sensitivity to neurotoxic agents, such as MPTP (Hamre et al., 1999; Sedelis et al., 2003, 2000; Vidyadhara et al., 2021, 2019). A single

dose of MPTP in C57BL/6 mice had a more profound effect on the activity of ETC complexes, mitochondrial inner membrane potential (MIMP), striatal dopamine levels, and locomotor activity than in BALB/c mice (Pathania et al., 2021). Interestingly, C57BL mice have a lower SN tyrosine hydroxylase (TH)-positive neuron number than those from other strains (Muthane et al., 1994; Vadasz et al., 2007; Vidyadhara et al., 2021, 2017). Regarding the ATP content, in embryonic fibroblasts from C57BL/6 J mice growing in galactose medium, rotenone had a lower half maximal inhibitory concentration (IC50) than in other mouse strains (Pereira et al., 2012). Importantly, phenotypic and genetic differences among mouse substrains (Mekada and Yoshiki, 2021) and differences in the responsiveness of rat strains to chemicals have also been reported (Kacew, 2001). The C57BL/6 J mouse strain and the Sprague Dawley rat have been the most commonly used in DOPD studies (Table 1). In humans, mtDNA genetic variation, which codes for OXPHOS-related proteins and RNAs, affects sensitivity to rotenone (Strobbe et al., 2018). In conclusion, it is important to choose the most appropriate rodent strain for the studies to be carried out. Inbred strains

have greater phenotypic uniformity, and any observed difference among strains would suggest genetic variation in response to the xenobiotic, providing key data transferable to humans (Festing, 2016; Gómez-Durán et al., 2011; López-Gallardo et al., 2011).

2.1.2. Selection of xenobiotic and administration protocol

An essential part of cell models, in addition to the cell type, is the culture medium and conditions (Bayona-Bafaluy et al., 2019). Similarly, in addition to the selected species, the xenobiotic and the administration protocol are crucial components of neurotoxic animal models.

It is often not easy to know whether or not someone has been exposed to a xenobiotic, when, how, for how long, and how much. The prenatal environmental exposome can include many man-made chemicals, such as pesticides, and global analytical approaches to characterize environmental chemicals relevant to prenatal exposures are required (Vermeulen et al., 2020). These chemicals have been shown to reach placenta tissues and cross into cord blood (Rager et al., 2020). Fortunately, it is possible to reproduce these conditions in a rodent model.

Table 1

Studies that have assessed the effect of prenatal exposure to oxidative phosphorylation xenobiotics/pesticides. DA, dopaminergic; DAT, dopamine active transport; DMSO, dimethylsulfoxide; GD, gestational day; MPTP, 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; OXPHOS, oxidative phosphorylation; PBS, phosphate buffered saline; PND, postnatal day; SD, Sprague-Dawley; SN, substantia nigra; TH, tyrosine hydroxylase; V, reduction; A, increment.

OXPHOS xenobiotics	Species (Strain)	Administration	Offspring analysis	Reference
Atrazine (corn oil)	Mouse (CD-1)	GD14-PND21. Drinking water, 100 µg/kg/day.	PND16. No effect on locomotor activity.	(Belloni et al., 2011)
Atrazine (absolute ethanol and deionized water)	Mouse (C57BL/6)	GD6-PND23. Drinking water, 3 mg/l (estimated intake 1.4 mg/kg/day).	PND35. A striatal dopamine and traveled distance. V (males) time spent swimming and A time spent immobile. PND70. No effect on striatal dopamine and locomotor activity.	(Lin et al., 2014)
Atrazine (corn starch)	Rat (SD)	GD0-PND1. Oral gavage, 25 or 50 mg/kg/day.	6- and 12-month-old females. V midbrain mRNA and protein levels for DA markers. 12-month-old females. V striatal dopamine concentration.	(Li et al., 2014)
Atrazine (starch solution)	Rat (SD)	GD5-PND22. Oral gavage, 25 or 50 mg/kg/day.	12-month-old offspring. V striatal dopamine concentration and SN mRNA levels for DA markers.	(Sun et al., 2014)
Atrazine (corn oil)	Rat (SD)	GD1-PND21. Oral gavage, 100 µg/kg/day or 10 mg/kg/day. Upon weaning, male offspring continued daily for 6 months.	6-month-old males. V motor functioning (10 mg/kg/day). 7-month-old males. V striatal dopamine concentration (both doses).	(Walters et al., 2015)
Cypermethrin (DMSO, Tween 80, and NaCl)	Mouse (CBA/J)	GD6-PND15. Intranasal, 5 or 20 mg/kg three times a week.	PND15 males. Disturbed neuromotor development.	(Laugeray et al., 2017)
MPTP (ethanol and saline)	Mouse (C57BL/6J)	GD9–17. Subcutaneous, 2.8 mg/kg/day.	1- and 6-week-old offspring. V caudoputamen dopamine immunoreactivity.	(Furune et al., 1989)
MPTP (distilled water)	Mouse (C57BL)	GD17. Single subcutaneous, 25 mg/kg.	GD18; PND1; and 2- and 4-week-old offspring. No effect on brain and striatal dopamine.	(Melamed et al., 1990)
MPTP (distilled water)	Mouse (C57BL/6N)	GD18. Single intramuscular, 30 mg/kg.	GD18 + 3, 6, 12, 24 h. V brain dopamine content.	(Ohya et al., 1990)
MPTP (distilled water)	Mouse (C57BL/BYA)	GD12–18. Intramuscular, 5 mg/kg/day.	4- and 12-week-old offspring. V brain TH activities and striatal dopamine.	(Ochi et al., 1991)
MPTP (PBS)	Mouse (C57BL/6J)	GD8–12. Intraperitoneal, 10 mg/kg/day.	12-week-old offspring. V striatal dopamine and TH levels.	(Muthian et al., 2012, 2010)
MPTP (saline)	Mouse (C57BL/6J)	GD12. Single intraperitoneal, 25 mg/kg.	12 h after treatment. V DAT and TH mRNA and TH protein levels and marked SN TH-positive cell loss.	(Sai et al., 2013a, 2013b)
MPTP (saline)	Rat (SD)	GD13-birth. Intraperitoneal, 10 mg/kg/day.	PND21 and PND50. V hypoactivity. Striatal dopamine not affected.	(Weissman et al., 1989)
Paraquat (liquid commercial form)	Mouse (Swiss)	GD6–21. Oral gavage, 20 mg/kg/day.	PND60. V locomotor activity and SN TH-immunoreactivity.	(Ait-Bali et al., 2016)
Paraquat (ultrapure water)	Mouse (C57BL/6J)	GD6–18. Aerosols, 0.1 mg/m ³ , 1.5 h, 6 days/week.	PND14. Changes in the gene expression of <i>striatum</i> . V OXPHOS genes and neuronal maturation.	(Hamdaoui et al., 2022)
Paraquat (saline)	Mouse (NMRI)	GD12-GD20. Intraperitoneal, 10 mg/kg, every 48 h.	PND30. V locomotor activity.	(Miranda-Contreras et al., 2005)
Maneb/ Paraquat (saline)	Mouse (C57BL/6J)	GD10–17. Subcutaneous, 1 mg/kg/day (Maneb) or PQ (0.3 mg/kg/day). PND48–55. Intraperitoneal, 30 mg/kg/day (Maneb) or 5 mg/kg/day (PQ).	PND45–55. No effect. PND62–64. Prenatal Maneb and adulthood Paraquat V (males) locomotor activity, striatal dopamine, and SN dopaminergic-neuron loss.	(Barlow et al., 2004; Cory-Slechta et al., 2005a, 2005b)

Treated versus control animals would solve the question of exposure to a xenobiotic and to which one.

If the aim is to study the effect of xenobiotic exposure during early development on the appearance of PD, the timing of exposure would also be very well defined, mainly during pregnancy. However, a limitation of rodent models is that they are altricial species and are relatively immature at birth compared to humans, who are precocial. Mice and rats are born with poorly-developed brains, and their development continues into postnatal life. The interventions directed at the same stage of gestation cannot be considered comparable (McMullen and Mostyn, 2009). Similar to humans, specification and differentiation of SN DA neurons in rodents occurs prenatally, between embryonic days (E) 7 and E15 in mice (Bayer et al., 1995; Farzanehfar, 2018; Islam et al., 2021; Luo and Huang, 2016; Veenliet and Smidt, 2014), and between E13 and E15 in rats (Bayer et al., 1993). Perhaps this explains why a single exposure to MPTP in the gestational day (GD) 17 mouse did not affect brain dopamine levels (Melamed et al., 1990) (Table 1). It is important to realize that pregnancy affects various physiological processes. These changes can affect the toxicokinetics of xenobiotics (van Donge et al., 2020), and should therefore be considered in the neurotoxic animal model to study the DOPD, because these physiological processes are different at the beginning (weeks 5–7 in humans) or in the middle (E7-E15 in mice, E13-E15 in rats) of the pregnancy.

It is important to consider the vehicle used to administer the pesticide (Table 1). Some pesticides are degraded in water, and light and temperature also affect degradation (Innos and Hickey, 2021). Moreover, toxicokinetics influences model development. Thus, the administration route will affect the pesticide bioavailability. Gut mucosa and liver first-pass metabolism will reduce bioavailability. Intravenously, subcutaneously, or dermally administered pesticides are protected from much of the metabolism because they enter the general circulation before passing through the gut mucosa and liver (Innos and Hickey, 2021) (Table 1). The xenobiotic under study should be administered by the route most relevant to potential human exposure (De Miranda et al., 2022). Exposures to pesticides are most likely to occur orally, through the consumption of food or drinking water (Rager et al., 2020). Other routes, such as dermal penetration and inhalation of airborne aerosols, may be used depending on the known human exposure route.

It is also important to differentiate between acute and continuous exposures. This can be modeled through single or sequential treatments (Table 1). The acute nature of some xenobiotic models fails to effectively represent the progressive, age-dependent changes seen in humans with PD. As an example, GD18 + 3 h mice from dams treated in GD18 with a single intramuscular MPTP dose showed reduced brain dopamine content (Ohya et al., 1990); and GD12 + 12 h mice from dams treated in GD12 with a single intraperitoneal MPTP dose showed a reduction in dopamine active transporter (DAT) and TH mRNA and TH protein levels and marked SN TH-positive cell loss (Sai et al., 2013a, 2013b). These results suggest that the doses of xenobiotics administered in these models are extremely high and cause overt toxicity rather than PD phenotypes, and that low-concentration protocols are more likely to mimic PD.

It is difficult to know the amounts of a specific OXPHOS xenobiotic to which one has been exposed, and, therefore, it is not easy to determine what doses should be administered to animal models. However, continued studies of these xenobiotics in drinking water, food, or human blood would help to get a more general idea of exposure to these compounds (López-Pacheco et al., 2019). Moreover, the OXPHOS xenobiotic equivalent dose for rodents should not be extrapolated from a human dose by simple conversion based on body weight. For a more appropriate conversion, the allometric approach seems to work best (Janhavi et al., 2022; Phillips, 2017). Furthermore, toxicokinetic aspects significantly complicate estimations of the amount of xenobiotic that should be administered to the animal model (Innos and Hickey, 2021).

2.1.3. Selecting the time of analysis

Some pesticides have been considered potential mutagens. Thus, multiple exposures to pesticides in fruit growers caused mtDNA somatic point mutations in lung tissue (Wang and Zhao, 2012); the leukocyte mtDNA deletion ratio increased in individuals who experienced long-term pesticide exposure (Choi et al., 2020); and rotenone increased the percentage of mtDNA deletions in rat pheochromocytoma PC12 cells (Xiao et al., 2021). Clonal expansion could cause those low-level heteroplasmic mtDNA mutations during the prenatal stage to reach significant percentages when they are old. Supporting this fact, humans show a progressive accumulation of multiple mtDNA deletions in SN DA neurons (Manini et al., 2022). Therefore, ageing greatly affects OXPHOS function (Amorim et al., 2022; Lesnefsky and Hoppel, 2006; Miwa et al., 2022). PD patients suffer from increased heteroplasmic mtDNA mutations in the SN (Bender et al., 2006; Buneeva et al., 2020; Coxhead et al., 2016). The prevalence of PD increases after the age of 60 years (Elbaz et al., 2016), but despite the fact that PD affects aged populations, pre-clinical DOPD studies never use old animals (Sun et al., 2020). The average lifespan of laboratory mice and rats is about 24 months (Carter et al., 2020; Dutta and Sengupta, 2016), but none of these studies in mice has been done with individuals older than 12 weeks, which can hardly be considered sexually mature (Table 1). To be considered old individuals, mice should be older than 18 months (Dutta and Sengupta, 2016; Flurke y et al., 2007; Wang et al., 2020). Several studies on rats analyzed 12-month-old individuals (Table 1). However, 12-month-old rats are equivalent to 30-year-old humans (Andreollo et al., 2012; Sengupta, 2013). Aging is a central feature of PD (Reeve et al., 2014), and this disease would therefore not be appropriately modeled in young adults (Sun et al., 2020). Thus, using non-elderly individuals eliminates the model's most significant risk factor for PD.

2.1.4. Do we study male or female rodents?

There are gender differences in susceptibility to environmental neurotoxicants (Barlow et al., 2004; Cory-Slechta et al., 2005a; Dluzen and McDermott, 2000; Lin et al., 2014). Male sex is a risk factor for PD, but women also suffer from this disease (Meoni et al., 2020). Moreover, there are sex-related differences in the clinical features of the disease, therefore, the effect of xenobiotics should be studied in male and female rodents (Cerri et al., 2019). Estrogen has potent neuroprotective properties (Lee et al., 2019), and has been shown to increase ETC activity, stabilize the MIMP, prevent reactive oxygen species production, and ameliorate the basal respiration and the production of ATP levels (Lejri et al., 2018). Perhaps these facts explain the partial protection of women from PD. However, women can live an important part of their lives in a postmenopausal state (Brooks et al., 2016). Female rodents do not undergo menopause (Lu et al., 2022). To adapt the animal model to human reality, some modification would be required. The average age of menopause in humans is 51 years (Brooks et al., 2016). This age would be equivalent to 15 months in female mice (Dutta and Sengupta, 2016; Flurke y et al., 2007; Wang et al., 2020). 4-vinylcyclohexene diepoxide (VCD) causes loss of primordial and primary ovarian follicles in female mice and has been used to simulate human menopause in these animals, since it closely approximates the natural human progression, including periods of perimenopause and postmenopause. VCD administration to 11-month-old female mice would cause menopause at 15 months of age, simulating the mean age of onset in women (Brooks et al., 2016).

3. Conclusions

Rodents have been the predominant model organisms for mammalian biology. However, recent studies in rodents and humans have revealed that the gaps between the two species are larger than previously understood. Genetic, physiological, and environmental differences among rodents and humans can affect prenatal exposure and/or the response to OXPHOS xenobiotics. To test the DOPD hypothesis in a reliable way, many aspects of species, strain, neurotoxicant, and

administration protocol should be considered before choosing a particular model, although no model can capture the full complexity of conditions encountered in the human body. This fact effectively defines the term “model”. The combination of animal and non-animal models would enable capturing a greater proportion of human complexity (Aerts et al., 2022). All models have advantages and disadvantages, and the model that is most appropriate for any particular study is hypotheses-dependent (McMullen and Mostyn, 2009).

Declaration of Competing Interest

None.

Acknowledgements

This work was supported by grants from Instituto de Salud Carlos III (ISCIII-FIS-PI21/00229) and European Regional Development Fund (FEDER); Gobierno de Aragón (LMP22_21; Grupos Consolidados B33_20R) and FEDER 2014–2020 ‘Construyendo Europa desde Aragón’. The CIBERER is an initiative of the ISCIII. Sponsors have not had any role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article to publication.

References

- Aerts, L., Miccoli, B., Delahanty, A., Witters, H., Verstraelen, S., De Strooper, B., Braeken, D., Verstreken, P., 2022. Do we still need animals? Surveying the role of animal-free models in Alzheimer’s and Parkinson’s disease research. *EMBO J.* 41, e110002 <https://doi.org/10.15252/emj.2021110002>.
- Agrawal, S., Singh, A., Tripathi, P., Mishra, M., Singh, P.K., Singh, M.P., 2015. Cypemethrin-induced nigrostriatal dopaminergic neurodegeneration alters the mitochondrial function: a proteomics study. *Mol. Neurobiol.* 51, 448–465. <https://doi.org/10.1007/s12035-014-8696-7>.
- Ait-Bali, Y., Ba-M’hamed, S., Bennis, M., 2016. Prenatal paraquat exposure induces neurobehavioral and cognitive changes in mice offspring. *Env. Toxicol. Pharm.* 48, 53–62. <https://doi.org/10.1016/j.etap.2016.10.008>.
- Amorim, J.A., Coppotelli, G., Rolo, A.P., Palmeira, C.M., Ross, J.M., Sinclair, D.A., 2022. Mitochondrial and metabolic dysfunction in ageing and age-related diseases. *Nat. Rev. Endocrinol.* 18, 243–258. <https://doi.org/10.1038/s41574-021-00626-7>.
- Andreollo, N.A., Santos, E.F., Araújo, M.R., Lopes, L.R., 2012. Rat’s age versus human’s age: what is the relationship? *Arq. Bras. Cir. Dig.* 25, 49–51. <https://doi.org/10.1590/s0102-67202012000100011>.
- Barlow, B.K., Richfield, E.K., Cory-Slechta, D.A., Thiruchelvam, M., 2004. A fetal risk factor for Parkinson’s disease. *Dev. Neurosci.* 26, 11–23. <https://doi.org/10.1159/000080707>.
- Barlow, B.K., Cory-Slechta, D.A., Richfield, E.K., Thiruchelvam, M., 2007. The gestational environment and Parkinson’s disease: evidence for neurodevelopmental origins of a neurodegenerative disorder. *Reprod. Toxicol.* 23, 457–470. <https://doi.org/10.1016/j.reprotox.2007.01.007>.
- Bayer, S.A., Altman, J., Russo, R.J., Zhang, X., 1993. Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. *Neurotoxicology* 14, 83–144.
- Bayer, S.A., Wills, K.V., Triarhou, L.C., Ghetti, B., 1995. Time of neuron origin and gradients of neurogenesis in midbrain dopaminergic neurons in the mouse. *Exp. Brain Res* 105, 191–199. <https://doi.org/10.1007/BF00240955>.
- Bayona-Bafaluy, M.P., Esteban, O., Ascaso, J., Montoya, J., Ruiz-Pesini, E., 2019. Oxidative phosphorylation inducers fight pathological angiogenesis. *Drug Discov. Today* 24, 1731–1734. <https://doi.org/10.1016/j.drudis.2019.03.014>.
- Belloni, V., Dessi-Fulgheri, F., Zaccaroni, M., Di Consiglio, E., De Angelis, G., Testai, E., Santochirico, M., Alleva, E., Santucci, D., 2011. Early exposure to low doses of atrazine affects behavior in juvenile and adult CD1 mice. *Toxicology* 279, 19–26. <https://doi.org/10.1016/j.tox.2010.07.002>.
- Bender, A., Krishnan, K.J., Morris, C.M., Taylor, G.A., Reeve, A.K., Perry, R.H., Jaros, E., Hersheson, J.S., Betts, J., Klopstock, T., Taylor, R.W., Turnbull, D.M., 2006. High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat. Genet.* 38, 515–517. <https://doi.org/10.1038/ng1769>.
- Bergen, W.G., 1971. The in vitro effect of dieldrin on respiration of rat liver mitochondria. *Proc. Soc. Exp. Biol. Med.* 136, 732–735. <https://doi.org/10.3181/00379727-136-35352>.
- Betarbet, R., Sherer, T.B., MacKenzie, G., Garcia-Osuna, M., Panov, A.V., Greenamyre, J. T., 2000. Chronic systemic pesticide exposure reproduces features of Parkinson’s disease. *Nat. Neurosci.* 3, 1301–1306. <https://doi.org/10.1038/81834>.
- Bové, J., Prou, D., Perier, C., Przedborski, S., 2005. Toxin-induced models of Parkinson’s disease. *NeuroRx* 2, 484–494. <https://doi.org/10.1602/neurorx.2.3.484>.
- Brooks, H.L., Pollow, D.P., Hoyer, P.B., 2016. The VCD mouse model of menopause and perimenopause for the study of sex differences in cardiovascular disease and the metabolic syndrome. *Physiol.* 31, 250–257. <https://doi.org/10.1152/physiol.00057.2014>.
- Brown, T.P., Rumsby, P.C., Capleton, A.C., Rushton, L., Levy, L.S., 2006. Pesticides and Parkinson’s disease—is there a link? *Environ. Health Perspect.* 114, 156–164. <https://doi.org/10.1289/ehp.8095>.
- Brunetti, D., Dykstra, W., Le, S., Zink, A., Prigione, A., 2021. Mitochondria in neurogenesis: implications for mitochondrial diseases. *Stem Cells* 39, 1289–1297. <https://doi.org/10.1002/stem.3425>.
- Buneeva, O., Fedchenko, V., Kopylov, A., Medvedev, A., 2020. Mitochondrial dysfunction in Parkinson’s disease: focus on mitochondrial DNA. *Biomedicines* 8. <https://doi.org/10.3390/biomedicines8120591>.
- Carter, C.S., Richardson, A., Huffman, D.M., Austad, S., 2020. Bring back the rat. *J. Gerontol. A Biol. Sci. Med. Sci.* 75, 405–415. <https://doi.org/10.1093/gerona/glz298>.
- Cerri, S., Mus, L., Blandini, F., 2019. Parkinson’s disease in women and men: what’s the difference? *J. Parkinson’s Dis.* 9, 501–515. <https://doi.org/10.3233/JPD-191683>.
- Chalazonitis, A., Rao, M., Sulzer, D., 2022. Similarities and differences between nigral and enteric dopaminergic neurons unravel distinctive involvement in Parkinson’s disease. *npj Parkinson’s Dis.* 8, 50. <https://doi.org/10.1038/s41531-022-00308-9>.
- Charlton, C.G., 2013. Fetal and Environmental Basis for the Cause of Parkinson’s Disease. In: Barrios, F.A., C.B. (Eds.), *Basal Ganglia - An Integrative View*. IntechOpen, pp. 31–64. <https://doi.org/10.5772/52680>.
- Choi, J.R., Park, S., Kim, S.K., Kim, J.Y., Lee, K., Oh, S.S., Koh, S.B., 2020. Mitochondrial DNA content and deletion ratio are associated with metabolic syndrome in a general population exposed to pesticide. *Molecular Cell. Toxicol.* 16, 347–354. <https://doi.org/10.1007/s13273-020-00079-5>.
- Coelho, P., Fão, L., Mota, S., Rego, A.C., 2022. Mitochondrial function and dynamics in neural stem cells and neurogenesis: Implications for neurodegenerative diseases. *Ageing Res Rev.* 80, 101667 <https://doi.org/10.1016/j.arr.2022.101667>.
- Cory-Slechta, D.A., Thiruchelvam, M., Barlow, B.K., Richfield, E.K., 2005a. Developmental pesticide models of the Parkinson disease phenotype. *Environ. Health Perspect.* 113, 1263–1270. <https://doi.org/10.1289/ehp.7570>.
- Cory-Slechta, D.A., Thiruchelvam, M., Richfield, E.K., Barlow, B.K., Brooks, A.I., 2005b. Developmental pesticide exposures and the Parkinson’s disease phenotype. *Birth Defects Res. A Clin. Mol. Teratol.* 73, 136–139. <https://doi.org/10.1002/bdra.20118>.
- Coxhead, J., Kurzawa-Akanbi, M., Hussain, R., Pyle, A., Chinnery, P., Hudson, G., 2016. Somatic mtDNA variation is an important component of Parkinson’s disease, 217.e1–217.e6. *Neurobiol. Aging* 38 <https://doi.org/10.1016/j.neurobiolaging.2015.10.036>.
- Czerniczyniec, A., Lanza, E.M., Karadayian, A.G., Bustamante, J., Lores-Arnaiz, S., 2015. Impairment of striatal mitochondrial function by acute paraquat poisoning. *J. Bioenerg. Biomembr.* 47, 395–408. <https://doi.org/10.1007/s10863-015-9624-x>.
- De Miranda, B.R., Goldman, S.M., Miller, G.W., Greenamyre, J.T., Dorsey, E.R., 2022. Prev. Parkinson’s Dis.: *Environ. Agenda J. Park. Dis.* 12, 45–68. <https://doi.org/10.3233/JPD-212922>.
- Degli Esposti, M., 1998. Inhibitors of NADH-ubiquinone reductase: an overview. *Biochim Biophys. Acta* 1364, 222–235. [https://doi.org/10.1016/s0005-2728\(98\)00029-2](https://doi.org/10.1016/s0005-2728(98)00029-2).
- Delp, J., Cediel-Ulloa, A., Suciu, I., Kranaster, P., van Vugt-Lussenburg, B.M., Muncic, V., van der Stel, W., Carta, G., Bennekou, S.H., Jennings, P., van de Water, B., Forsby, A., Leist, M., 2021. Neurotoxicity and underlying cellular changes of 21 mitochondrial respiratory chain inhibitors. *Arch. Toxicol.* 95, 591–615. <https://doi.org/10.1007/s00204-020-02970-5>.
- Dickinson, H., Moss, T.J., Gatford, K.L., Moritz, K.M., Akison, L., Fullston, T., Hryciw, D. H., Maloney, C.A., Morris, M.J., Wooldridge, A.L., Schjenken, J.E., Robertson, S.A., Waddell, B.J., Mark, P.J., Wyrwoll, C.S., Ellery, S.J., Thornburg, K.L., Muhlhauser, B.S., Morrison, J.L., 2016. A review of fundamental principles for animal models of DOHaD research: an Australian perspective. *J. Dev. Orig. Heal. Dis.* 7, 449–472. <https://doi.org/10.1017/S2040174416000477>.
- Bluzen, D.E., McDermott, J.L., 2000. Gender differences in neurotoxicity of the nigrostriatal dopaminergic system: implications for Parkinson’s disease. *J. Gen. Specif. Med.* 3, 36–42.
- Domico, L.M., Zeevalk, G.D., Bernard, L.P., Cooper, K.R., 2006. Acute neurotoxic effects of mancozeb and maneb in mesencephalic neuronal cultures are associated with mitochondrial dysfunction. *Neurotoxicology* 27, 816–825. <https://doi.org/10.1016/j.neuro.2006.07.009>.
- Dutta, S., Sengupta, P., 2016. Men and mice: Relating their ages. *Life Sci.* 152, 244–248. <https://doi.org/10.1016/j.lfs.2015.10.025>.
- Elbaz, A., Carcaillon, L., Kab, S., Moisan, F., 2016. Epidemiology of Parkinson’s disease. *Rev. Neurol.* 172, 14–26. <https://doi.org/10.1016/j.neuro.2015.09.012>.
- El-Gamal, M., Salama, M., Collins-Praino, L.E., Baetu, I., Fathalla, A.M., Soliman, A.M., Mohamed, W., Moustafa, A.A., 2021. Neurotoxin-induced rodent models of Parkinson’s disease: benefits and drawbacks. *Neurotox. Res.* 39, 897–923. <https://doi.org/10.1007/s12640-021-00356-8>.
- Falcioni, M.L., Nasuti, C., Bergamini, C., Fato, R., Lenaz, G., Gabbianelli, R., 2010. The primary role of glutathione against nuclear DNA damage of striatum induced by permethrin in rats. *Neuroscience* 168, 2–10. <https://doi.org/10.1016/j.neuroscience.2010.03.053>.
- Farzanehfar, P., 2018. Comparative review of adult midbrain and striatum neurogenesis with classical neurogenesis. *Neurosci. Res.* 134, 1–9. <https://doi.org/10.1016/j.neures.2018.01.002>.
- Fedeli, D., Montani, M.C., Nasuti, C., Gabbianelli, R., 2014. Early life permethrin treatment induces in striatum of older rats changes in synuclein content. *J. Nutr.* 17, 75–93. <https://doi.org/10.1159/000365938>.
- Festing, M.F., 2016. Genetically defined strains in drug development and toxicity testing. *Methods Mol. Biol.* 1438, 1–17. https://doi.org/10.1007/978-1-4939-3661-8_1.

- Flurke y, K., Curren, J.M., Harrison, D.E., 2007. Mouse Models in Aging Research. In: Press, A. (Ed.), *The Mouse in Biomedical Research. History, Wild Mice, and Genetics*. American College of Laboratory Animal Medicine, pp. 637–672. <https://doi.org/10.1016/B978-012369454-6/50074-1>.
- Freedman, L.P., Cockburn, I.M., Simcoe, T.S., 2015. The economics of reproducibility in preclinical research. *PLoS Biol.* 13, e1002165. <https://doi.org/10.1371/journal.pbio.1002165>.
- Fukunaga, H., 2021. Mitochondrial DNA copy number and developmental origins of health and disease (DOHAD). *Int J. Mol. Sci.* 22. <https://doi.org/10.3390/ijms22126634>.
- Fukushima, T., Yamada, K., Hojo, N., Isobe, A., Shiwaku, K., Yamane, Y., 1994. Mechanism of cytotoxicity of paraquat. III. The effects of acute paraquat exposure on the electron transport system in rat mitochondria. *Exp. Toxicol. Pathol.* 46, 437–441. [https://doi.org/10.1016/S0940-2993\(11\)80056-4](https://doi.org/10.1016/S0940-2993(11)80056-4).
- Furune, S., Miura, K., Watanabe, K., Nagao, S., Takahashi, H., Sakai, M., Spatz, M., Nagatsu, I., 1989. Transplacental effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on brain dopaminergic neurons in the mouse. An immunohistochemical study. *Acta Neuropathol.* 79, 279–285. <https://doi.org/10.1007/BF00294662>.
- Gassner, B., Wüthrich, A., Scholtysik, G., Solioz, M., 1997. The pyrethroids permethrin and cyhalothrin are potent inhibitors of the mitochondrial complex I. *J. Pharm. Exp. Ther.* 281, 855–860.
- Giguère, N., Burke Nanni, S., Trudeau, L.E., 2018. On cell loss and selective vulnerability of neuronal populations in Parkinson's disease. *Front Neurol.* 9, 455. <https://doi.org/10.3389/fneur.2018.00455>.
- Gluckman, P.D., Hanson, M.A., 2004. Living with the past: evolution, development, and patterns of disease. *Science (80-)* 305, 1733–1736. <https://doi.org/10.1126/science.1095292>.
- Goldman, S.M., 2014. Environmental toxins and Parkinson's disease. *Annu Rev. Pharm. Toxicol.* 54, 141–164. <https://doi.org/10.1146/annurev-pharmtox-011613-135937>.
- Goldstein, A., Hofstra, R., Burns, A., 2013. Building a brain in the gut: development of the enteric nervous system. *Clin. Genet.* 83, 307–316. <https://doi.org/10.1111/cge.12054>.
- Gómez-Durán, A., Pacheu-Grau, D., López-Pérez, M.J., Montoya, J., Ruiz-Pesini, E., 2011. Mitochondrial pharma-Q-genomics: targeting the OXPHOS cytochrome b. *Drug Disco Today* 16, 176–180. <https://doi.org/10.1016/j.drudis.2010.11.010>.
- Grova, N., Schroeder, H., Olivier, J.L., Turner, J.D., 2019. Epigenetic and neurological impairments associated with early life exposure to persistent organic pollutants. *Int J. Genom.* 2019, 2085496. <https://doi.org/10.1155/2019/2085496>.
- Gyllenhammer, L.E., Rasmussen, J.M., Bertele, N., Halbing, A., Entringer, S., Wadhwa, P. D., Buss, C., 2022. Maternal inflammation during pregnancy and offspring brain development: the role of mitochondria. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 7, 498–509. <https://doi.org/10.1016/j.bpsc.2021.11.003>.
- Hamdaoui, Q., Zekri, Y., Richard, S., Aubert, D., Guyot, R., Markossian, S., Gauthier, K., Gaie-Levrel, F., Bencsik, A., Flamant, F., 2022. Prenatal exposure to paraquat and nanoscaled TiO₂. *Chemosphere* 287, 132253. <https://doi.org/10.1016/j.chemosphere.2021.132253>.
- Hamre, K., Tharp, R., Poon, K., Xiong, X., Smeyne, R.J., 1999. Differential strain susceptibility following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration acts in an autosomal dominant fashion: quantitative analysis in seven strains of *Mus musculus*. *Brain Res.* 828, 91–103. [https://doi.org/10.1016/S0006-8993\(99\)01273-1](https://doi.org/10.1016/S0006-8993(99)01273-1).
- Hirsch, L., Jette, N., Frolkis, A., Steeves, T., Pringsheim, T., 2016. The incidence of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology* 46, 292–300. <https://doi.org/10.1159/000445751>.
- Hong, S., Kim, J.Y., Hwang, J., Shin, K.S., Kang, S.J., 2013. Heptachlor induced mitochondria-mediated cell death via impairing electron transport chain complex III. *Biochem Biophys. Res Commun.* 437, 632–636. <https://doi.org/10.1016/j.bbrc.2013.07.018>.
- Iglesias, E., Pesini, A., Garrido-Pérez, N., Meade, P., Bayona-Bafaluy, M.P., Montoya, J., Ruiz-Pesini, E., 2018. Prenatal exposure to oxidative phosphorylation xenobiotics and late-onset Parkinson disease. *Ageing Res Rev.* 45, 24–32. <https://doi.org/10.1016/j.arr.2018.04.006>.
- Iglesias, E., Bayona-Bafaluy, M.P., Pesini, A., Garrido-Pérez, N., Meade, P., Gaudó, P., Jiménez-Salvador, I., Montoya, J., Ruiz-Pesini, E., 2019. Uridine prevents negative effects of OXPHOS xenobiotics on dopaminergic neuronal differentiation. *Cells* 8. <https://doi.org/10.3390/cells8111407>.
- Innos, J., Hickey, M.A., 2021. Using rotenone to model Parkinson's disease in mice: a review of the role of pharmacokinetics. *Chem. Res Toxicol.* 34, 1223–1239. <https://doi.org/10.1021/acs.chemrestox.0c00522>.
- Islam, K.U.S., Meli, N., Blaess, S., 2021. The development of the mesoprefrontal dopaminergic system in health and disease. *Front Neural Circuits* 15, 746582. <https://doi.org/10.3389/fncir.2021.746582>.
- Iwata, R., Vanderhaeghen, P., 2021. Regulatory roles of mitochondria and metabolism in neurogenesis. *Curr. Opin. Neurobiol.* 69, 231–240. <https://doi.org/10.1016/j.conb.2021.05.003>.
- Jackson, S.J., Andrews, N., Ball, D., Bellantuono, I., Gray, J., Hachoumi, L., Holmes, A., Latcham, J., Petrie, A., Potter, P., Rice, A., Ritchie, A., Stewart, M., Strepka, C., Yeoman, M., Chapman, K., 2017. Does age matter? The impact of rodent age on study outcomes. *Lab Anim.* 51, 160–169. <https://doi.org/10.1177/0023677216653984>.
- James, K.A., Hall, D.A., 2015. Groundwater pesticide levels and the association with Parkinson disease. *Int J. Toxicol.* 34, 266–273. <https://doi.org/10.1177/1091581815583561>.
- Janhavi, P., Divyashree, S., Sanjailal, K.P., Muthukumar, S.P., 2022. DoseCal: a virtual calculator for dosage conversion between human and different animal species. *Arch. Physiol. Biochem* 128, 426–430. <https://doi.org/10.1080/13813455.2019.1687523>.
- Kacew, S., 2001. Confounding factors in toxicity testing. *Toxicology* 160, 87–96. [https://doi.org/10.1016/S0300-483X\(00\)00440-6](https://doi.org/10.1016/S0300-483X(00)00440-6).
- Kin, K., Yasuhara, T., Kameda, M., Date, I., 2019. Animal Models for Parkinson's Disease Research: Trends in the 2000s. *Int J. Mol. Sci.* 20. <https://doi.org/10.3390/ijms20215402>.
- Konnova, E.A., Swanberg, M., 2018. Animal Models of Parkinson's Disease, in: *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Codon Publications @font-face {font-family:"Cambria Math"; panose-1:2 4 5 3 4 6 3 2 4; mso-font-charset:0; mso-generic-font-family:roman; mso-font-pitch:variable; mso-font-signature:536870145 1107305727 0 0 415 0;}@font-face {font-family:Calibri; panos, Brisbane (AU). <https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch5>.
- Landrigan, P.J., Sonawane, B., Butler, R.N., Trasande, L., Callan, R., Droller, D., 2005. Early environmental origins of neurodegenerative disease in later life. *Environ. Health Perspect.* 113, 1230–1233. <https://doi.org/10.1289/ehp.7571>.
- Langston, J.W., 2017. The MPTP story. *J. Park. Dis.* 7, S11–S19. <https://doi.org/10.3233/JPD-179006>.
- Latorre-Pellicer, A., Moreno-Loshuertos, R., Lechuga-Vieco, A.V., Sánchez-Cabo, F., Torroja, C., Acín-Pérez, R., Calvo, E., Aix, E., González-Guerra, A., Logan, A., Bernad-Miana, M.L., Romanos, E., Cruz, R., Cogliati, S., Sobrino, B., Carracedo, A., Pérez-Martos, A., Fernández-Silva, P., Ruiz-Cabello, J., Murphy, M.P., Flores, I., Vázquez, J., Enríquez, J.A., 2016. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. *Nature* 535, 561–565. <https://doi.org/10.1038/nature18618>.
- Laugeray, A., Herzine, A., Perche, O., Richard, O., Montecot-Dubourg, C., Menuet, A., Mazaud-Guitot, S., Lesné, L., Jegou, B., Mortaud, S., 2017. In utero and lactational exposure to low-doses of the pyrethroid insecticide cypermethrin leads to neurodevelopmental defects in male mice—An ethological and transcriptomic study. *PLoS One* 12, e0184475. <https://doi.org/10.1371/journal.pone.0184475>.
- Lee, Y.H., Cha, J., Chung, S.J., Yoo, H.S., Sohn, Y.H., Ye, B.S., Lee, P.H., 2019. Beneficial effect of estrogen on nigrostriatal dopaminergic neurons in drug-naïve postmenopausal Parkinson's disease. *Sci. Rep.* 9, 10531. <https://doi.org/10.1038/s41598-019-47026-6>.
- Lejri, I., Grimm, A., Eckert, A., 2018. Mitochondria, Estrogen and Female Brain Aging. *Front Aging Neurosci.* 10, 124. <https://doi.org/10.3389/fnagi.2018.00124>.
- Lesnefsky, E.J., Hoppel, C.L., 2006. Oxidative phosphorylation and aging. *Ageing Res Rev.* 5, 402–433. <https://doi.org/10.1016/j.arr.2006.04.001>.
- Li, Y., Sun, Y., Yang, J., Wu, Y., Yu, J., Li, B., 2014. Age-dependent dopaminergic dysfunction following fetal exposure to atrazine in SD rats. *Env. Toxicol. Pharm.* 37, 1275–1282. <https://doi.org/10.1016/j.etap.2014.04.023>.
- Liang, L.P., Kavanagh, T.J., Patel, M., 2013. Glutathione deficiency in *Gclm* null mice results in complex I inhibition and dopamine depletion following paraquat administration. *Toxicol. Sci.* 134, 366–373. <https://doi.org/10.1093/toxsci/kft112>.
- Lim, S., Ahn, S.Y., Song, I.C., Chung, M.H., Jang, H.C., Park, K.S., Lee, K.U., Pak, Y.K., Lee, H.K., 2009. Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. *PLoS One* 4, e5186. <https://doi.org/10.1371/journal.pone.0005186>.
- Lin, Z., Dodd, C.A., Xiao, S., Krishna, S., Ye, X., Filipov, N.M., 2014. Gestational and lactational exposure to atrazine via the drinking water causes specific behavioral deficits and selectively alters monoaminergic systems in C57BL/6 mouse dams, juvenile and adult offspring. *Toxicol. Sci.* 141, 90–102. <https://doi.org/10.1093/toxsci/kfu107>.
- von Linstow, C.U., DeLano-Taylor, M., Kordower, J.H., Brundin, P., 2020. Does developmental variability in the number of midbrain dopamine neurons affect individual risk for sporadic Parkinson's disease? *J. Parkinson's Dis.* 10, 405–411. <https://doi.org/10.3233/JPD-191877>.
- Logroscino, G., 2005. The role of early life environmental risk factors in Parkinson disease: what is the evidence? *Environ. Health Perspect.* 113, 1234–1238. <https://doi.org/10.1289/ehp.7573>.
- López-Gallardo, E., Iceta, R., Iglesias, E., Montoya, J., Ruiz-Pesini, E., 2011. OXPHOS toxicogenomics and Parkinson's disease. *Mutat. Res* 728, 98–106. <https://doi.org/10.1016/j.mrrev.2011.06.004>.
- López-Pacheco, I.Y., Silva-Núñez, A., Salinas-Salazar, C., Arévalo-Gallegos, A., Lizarazo-Holguin, L.A., Barceló, D., Iqbal, H.M.N., Parra-Saldívar, R., 2019. Anthropogenic contaminants of high concern: existence in water resources and their adverse effects. *Sci. Total Env.* 690, 1068–1088. <https://doi.org/10.1016/j.scitotenv.2019.07.052>.
- Lu, H., Ma, L., Zhang, Y., Feng, Y., Zhang, J., Wang, S., 2022. Current animal model systems for ovarian aging research. *Ageing Dis.* 13, 1183–1195. <https://doi.org/10.14336/AD.2021.1209>.
- Luo, S.X., Huang, E.J., 2016. Dopaminergic neurons and brain reward pathways: from neurogenesis to circuit assembly. *Am. J. Pathol.* 186, 478–488. <https://doi.org/10.1016/j.ajpath.2015.09.023>.
- Manini, A., Abati, E., Comi, G.P., Corti, S., Ronchi, D., 2022. Mitochondrial DNA homeostasis impairment and dopaminergic dysfunction: A trembling balance. *Ageing Res Rev.* 76, 101578. <https://doi.org/10.1016/j.arr.2022.101578>.
- McMullen, S., Mostyn, A., 2009. Animal models for the developmental origins of health and disease. *Proc. Nutr. Soc.* 68, 306–320. <https://doi.org/10.1017/S0029665109001396>.
- Mekada, K., Yoshiki, A., 2021. Substrains matter in phenotyping of C57BL/6 mice. *Exp. Anim.* 70, 145–160. <https://doi.org/10.1538/expanim.20-0158>.
- Melamed, E., Rosenthal, J., Youdim, M.B., 1990. Immunity of fetal mice to prenatal administration of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *J. Neurochem* 55, 1427–1431. <https://doi.org/10.1111/j.1471-4159.1990.tb03156.x>.

- Meoni, S., Macerollo, A., Moro, E., 2020. Sex differences in movement disorders. *Nat. Rev. Neurol.* 16, 84–96. <https://doi.org/10.1038/s41582-019-0294-x>.
- Miranda-Contreras, L., Dávila-Ovalles, R., Benítez-Díaz, P., Peña-Contreras, Z., Palacios-Prü, E., 2005. Effects of prenatal paraquat and mancozeb exposure on amino acid synaptic transmission in developing mouse cerebellar cortex. *Brain Res Dev. Brain Res* 160, 19–27. <https://doi.org/10.1016/j.devbrainres.2005.08.001>.
- Miwa, S., Kashyap, S., Chini, E., von Zglinicki, T., 2022. Mitochondrial dysfunction in cell senescence and aging. *J. Clin. Invest.* 132. <https://doi.org/10.1172/JCI158447>.
- Müller, F., O'Rahilly, R., 2004. Olfactory structures in staged human embryos. *Cells Tissues Organs* 178, 93–116. <https://doi.org/10.1159/000081720>.
- Muthane, U., Ramsay, K.A., Jiang, H., Jackson-Lewis, V., Donaldson, D., Fernando, S., Ferreira, M., Przedborski, S., 1994. Differences in nigral neuron number and sensitivity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in C57/Bl and CD-1 mice. *Exp. Neurol.* 126, 195–204. <https://doi.org/10.1006/exnr.1994.1058>.
- Muthian, G., Mackey, V., King, J., Charlton, C.G., 2010. Modeling a sensitization stage and a precipitation stage for Parkinson's disease using prenatal and postnatal 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration. *Neuroscience* 169, 1085–1093. <https://doi.org/10.1016/j.neuroscience.2010.04.080>.
- Muthian, G., King, J., Dent, L., Smith, M., Mackey, V., Charlton, C., 2012. Prenatal and postnatal exposures to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) impaired mouse midbrain dopamine system and may produce a predisposing and inducing model for Parkinson's disease. *J. Behav. Brain Sci.* 2, 485–494. <https://doi.org/10.4236/jbbs.2012.24057>.
- Nasuti, C., Carloni, M., Fedeli, D., Gabbianelli, R., Di Stefano, A., Serafina, C.L., Silva, I., Domingues, V., Ciccocioppo, R., 2013. Effects of early life permethrin exposure on spatial working memory and on monoamine levels in different brain areas of pre-nescent rats. *Toxicology* 303, 162–168. <https://doi.org/10.1016/j.tox.2012.09.016>.
- Nasuti, C., Brunori, G., Eusepi, P., Marinelli, L., Ciccocioppo, R., Gabbianelli, R., 2017. Early life exposure to permethrin: a progressive animal model of Parkinson's disease. *J. Pharm. Toxicol. Methods* 83, 80–86. <https://doi.org/10.1016/j.vascn.2016.10.003>.
- Ochi, N., Naoi, M., Mogi, M., Ohya, Y., Mizutani, N., Watanabe, K., Harada, M., Nagatsu, T., 1991. Effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration in prenatal stage on the dopamine system in the postnatal mouse brain. *Life Sci.* 48, 217–223. [https://doi.org/10.1016/0024-3205\(91\)90348-f](https://doi.org/10.1016/0024-3205(91)90348-f).
- Ohya, Y., Naoi, M., Ochi, N., Mizutani, N., Watanabe, K., Nagatsu, T., 1990. Transplacentally-transported 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) affects the catecholamine and indoleamine levels in the fetal mouse brain. *J. Neural Transm. Park Dis. Dement Sect.* 2, 277–283. <https://doi.org/10.1007/BF02252922>.
- Pardini, R.S., Heidker, J.C., Payne, B., 1971. The effect of some cyclodiene pesticides, benzenehexachloride and toxaphene on mitochondrial electron transport. *Bull. Environ. Contam. Toxicol.* 6, 436–444. <https://doi.org/10.1007/BF01684365>.
- Paš, T., Abfal, M., Tolve, M., Blaess, S., Rothermel, M., Wiesner, R.J., Ricke, K.M., 2020. The Impact of Mitochondrial Dysfunction on Dopaminergic Neurons in the Olfactory Bulb and Odor Detection. *Mol. Neurobiol.* 57, 3646–3657. <https://doi.org/10.1007/s12035-020-01947-w>.
- Pathania, A., Garg, P., Sandhir, R., 2021. Impaired mitochondrial functions and energy metabolism in MPTP-induced Parkinson's disease: comparison of mice strains and dose regimens. *Metab. Brain Dis.* 36, 2343–2357. <https://doi.org/10.1007/s11011-021-00840-2>.
- Pereira, C.V., Oliveira, P.J., Will, Y., Nadanaciva, S., 2012. Mitochondrial bioenergetics and drug-induced toxicity in a panel of mouse embryonic fibroblasts with mitochondrial DNA single nucleotide polymorphisms. *Toxicol. Appl. Pharm.* 264, 167–181. <https://doi.org/10.1016/j.taap.2012.07.030>.
- Pesini, A., Iglesias, E., Bayona-Bafaluy, M.P., Garrido-Pérez, N., Meade, P., Gaudó, P., Jiménez-Salvador, I., Andrés-Benito, P., Montoya, J., Ferrer, I., Pesini, P., Ruiz-Pesini, E., 2019. Brain pyrimidine nucleotide synthesis and Alzheimer disease. *Aging (Albany NY)* 11, 8433–8462. <https://doi.org/10.18632/aging.102328>.
- Phillips, J.E., 2017. Inhaled efficacious dose translation from rodent to human: a retrospective analysis of clinical standards for respiratory diseases. *Pharm. Ther.* 178, 141–147. <https://doi.org/10.1016/j.pharmthera.2017.04.003>.
- Pouchieu, C., Piel, C., Carles, C., Gruber, A., Helmer, C., Tual, S., Marcotullio, E., Lebaill, P., Baldi, I., 2018. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study. *Int. J. Epidemiol.* 47, 299–310. <https://doi.org/10.1093/ije/dyx225>.
- Rager, J.E., Bangma, J., Carberry, C., Chao, A., Grossman, J., Lu, K., Manuck, T.A., Sobus, J.R., Szilagyi, J., Fry, R.C., 2020. Review of the environmental prenatal exposure and its relationship to maternal and fetal health. *Reprod. Toxicol.* 98, 1–12. <https://doi.org/10.1016/j.reprotox.2020.02.004>.
- Reeve, A., Simcox, E., Turnbull, D., 2014. Ageing and Parkinson's disease: why is advancing age the biggest risk factor. *Ageing Res Rev.* 14, 19–30. <https://doi.org/10.1016/j.arr.2014.01.004>.
- Rodríguez, V.M., Limón-Pacheco, J.H., Mendoza-Trejo, M.S., González-Gallardo, A., Hernández-Plata, I., Giordano, M., 2013. Repeated exposure to the herbicide atrazine alters locomotor activity and the nigrostriatal dopaminergic system of the albino rat. *Neurotoxicology* 34, 82–94. <https://doi.org/10.1016/j.neuro.2012.10.012>.
- Sai, T., Uchida, K., Nakayama, H., 2013a. Acute toxicity of MPTP and MPP(+) in the brain of embryo and newborn mice. *Exp. Toxicol. Pathol.* 65, 113–119. <https://doi.org/10.1016/j.etp.2011.06.008>.
- Sai, T., Uchida, K., Nakayama, H., 2013b. Biochemical evaluation of the neurotoxicity of MPTP and MPP⁺ in embryonic and newborn mice. *J. Toxicol. Sci.* 38, 445–458. <https://doi.org/10.2131/jts.38.445>.
- Schaefer, A.T., Teuchert-Noodt, G., 2016. Developmental neuroplasticity and the origin of neurodegenerative diseases. *World J. Biol. Psychiatry* 17, 587–599. <https://doi.org/10.3109/15622975.2013.797104>.
- Schwamborn, J.C., 2018. Is Parkinson's disease a neurodevelopmental disorder and will brain organoids help us to understand it. *Stem Cells Dev.* 27, 968–975. <https://doi.org/10.1089/scd.2017.0289>.
- Sedelis, M., Hofele, K., Auburger, G.W., Morgan, S., Huston, J.P., Schwarting, R.K., 2000. MPTP susceptibility in the mouse: behavioral, neurochemical, and histological analysis of gender and strain differences. *Behav. Genet* 30, 171–182. <https://doi.org/10.1023/a:1001958023096>.
- Sedelis, M., Hofele, K., Schwarting, R.K., Huston, J.P., Belknap, J.K., 2003. Chromosomal loci influencing the susceptibility to the parkinsonian neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *J. Neurosci.* 23, 8247–8253.
- Sengupta, P., 2013. The laboratory rat: relating its age with human's. *Int. J. Prev. Med* 4, 624–630.
- Singh, A.K., Tiwari, M.N., Upadhyay, G., Patel, D.K., Singh, D., Prakash, O., Singh, M.P., 2012. Long term exposure to cypermethrin induces nigrostriatal dopaminergic neurodegeneration in adult rats: postnatal exposure enhances the susceptibility during adulthood. *Neurobiol. Aging* 33, 404–415. <https://doi.org/10.1016/j.neurobiolaging.2010.02.018>.
- Singh, S., Periasamy, M., Bal, N.C., 2021. Strain-specific differences in muscle Ca. *J. Exp. Biol.* 224. <https://doi.org/10.1242/jeb.238634>.
- Strobbe, D., Caporali, L., Iommarini, L., Maresca, A., Montopoli, M., Martinuzzi, A., Achilli, A., Olivieri, A., Torroni, A., Carelli, V., Ghelli, A., 2018. Haplotype J mitogenomes are the most sensitive to the pesticide rotenone: relevance for human diseases. *Neurobiol. Dis.* 114, 129–139. <https://doi.org/10.1016/j.nbd.2018.02.010>.
- Sun, M., McDonald, S.J., Brady, R.D., Collins-Praino, L., Yamakawa, G.R., Monif, M., O'Brien, T.J., Cloud, G.C., Sobey, C.G., Mychasiuk, R., Loane, D.J., Shultz, S.R., 2020. The need to incorporate aged animals into the preclinical modeling of neurological conditions. *Neurosci. Biobehav. Rev.* 109, 114–128. <https://doi.org/10.1016/j.neubiorev.2019.12.027>.
- Sun, Y., Li, Y.S., Yang, J.W., Yu, J., Wu, Y.P., Li, B.X., 2014. Exposure to atrazine during gestation and lactation periods: toxicity effects on dopaminergic neurons in offspring by downregulation of Nurr1 and VMAT2. *Int. J. Mol. Sci.* 15, 2811–2825. <https://doi.org/10.3390/ijms15022811>.
- Tanner, C.M., Kamel, F., Ross, G.W., Hoppin, J.A., Goldman, S.M., Korell, M., Marras, C., Bhudhikanok, G.S., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Meng, C., Priestley, B., Fernandez, H.H., Cambi, F., Umbach, D.M., Blair, A., Sandler, D.P., Langston, J.W., 2011. Rotenone, paraquat, and Parkinson's disease. *Environ. Health Perspect.* 119, 866–872. <https://doi.org/10.1289/ehp.1002839>.
- Tartaglione, A.M., Venerosi, A., Calamandrei, G., 2016. Early-life toxic insults and onset of sporadic neurodegenerative diseases-an overview of experimental studies. *Curr. Top. Behav. Neurosci.* 29, 231–264. https://doi.org/10.1007/7854_2015_416.
- Tawara, T., Fukushima, T., Hojo, N., Isobe, A., Shiwaku, K., Setogawa, T., Yamane, Y., 1996. Effects of paraquat on mitochondrial electron transport system and catecholamine contents in rat brain. *Arch. Toxicol.* 70, 585–589. <https://doi.org/10.1007/s002040005316>.
- Vadasz, C., Smiley, J.F., Figarsky, K., Saito, M., Toth, R., Gyetvai, B.M., Oros, M., Kovacs, K.K., Mohan, P., Wang, R., 2007. Mesencephalic dopamine neuron number and tyrosine hydroxylase content: Genetic control and candidate genes. *Neuroscience* 149, 561–572. <https://doi.org/10.1016/j.neuroscience.2007.06.049>.
- van Donge, T., Evers, K., Koch, G., van den Anker, J., Pfister, M., 2020. Clinical pharmacology and pharmacometrics to better understand physiological changes during pregnancy and neonatal life. *Handb. Exp. Pharm.* 261, 325–337. https://doi.org/10.1007/164_2019_210.
- Veenvlit, J.V., Smidt, M.P., 2014. Molecular mechanisms of dopaminergic subset specification: fundamental aspects and clinical perspectives. *Cell Mol. Life Sci.* 71, 4703–4727. <https://doi.org/10.1007/s00118-014-1681-5>.
- Vermeulen, R., Schymanski, E.L., Barabási, A.L., Miller, G.W., 2020. The exposome and health: where chemistry meets biology. *Science* 367 (80), 392–396. <https://doi.org/10.1126/science.aay3164>.
- Vidyadhara, D.J., Yarreiphang, H., Raju, T.R., Alladi, P.A., 2017. Admixing of MPTP-resistant and susceptible mice strains augments nigrostriatal neuronal correlates to resist MPTP-induced neurodegeneration. *Mol. Neurobiol.* 54, 6148–6162. <https://doi.org/10.1007/s12035-016-0158-y>.
- Vidyadhara, D.J., Sasidharan, A., Kutty, B.M., Raju, T.R., Alladi, P.A., 2019. Admixing MPTP-resistant and MPTP-vulnerable mice enhances striatal field potentials and calbindin-D28K expression to avert motor behaviour deficits. *Behav. Brain Res* 360, 216–227. <https://doi.org/10.1016/j.bbr.2018.12.015>.
- Vidyadhara, D.J., Yarreiphang, H., Raju, T.R., Alladi, P.A., 2021. Differences in neuronal numbers, morphology, and developmental apoptosis in mice nigra provide experimental evidence of ontogenic origin of vulnerability to Parkinson's disease. *Neurotox. Res* 39, 1892–1907. <https://doi.org/10.1007/s12640-021-00439-6>.
- Walters, J.L., Lansdell, T.A., Lookingland, K.J., Baker, L.E., 2015. The effects of gestational and chronic atrazine exposure on motor behaviors and striatal dopamine in male Sprague-Dawley rats. *Toxicol. Appl. Pharm.* 289, 185–192. <https://doi.org/10.1016/j.taap.2015.09.026>.
- Wang, C.Y., Zhao, Z.B., 2012. Somatic mtDNA mutations in lung tissues of pesticide-exposed fruit growers. *Toxicology* 291, 51–55. <https://doi.org/10.1016/j.tox.2011.10.018>.
- Wang, S., Lai, X., Deng, Y., Song, Y., 2020. Correlation between mouse age and human age in anti-tumor research: Significance and method establishment. *Life Sci.* 242, 117242. <https://doi.org/10.1016/j.lfs.2019.117242>.
- Weissman, E.M., Norman, A.B., Calderon, S.F., Zubrycki, E.M., el-Etri, M.M., Shipley, M. T., Sanberg, P.R., 1989. The effect of prenatal treatment with MPTP or MPP⁺ on the

- development of dopamine-mediated behaviors in rats. *Pharm. Biochem Behav.* 34, 545–551. [https://doi.org/10.1016/0091-3057\(89\)90556-x](https://doi.org/10.1016/0091-3057(89)90556-x).
- Xiao, J., Dong, X., Peng, K., Ye, F., Cheng, J., Dan, G., Zou, Z., Cao, J., Sai, Y., 2021. PGC-1 α mediated-EXOG, a specific repair enzyme for mitochondrial DNA, plays an essential role in the rotenone-induced neurotoxicity of PC12 cells. *J. Mol. Neurosci.* 71, 2336–2352. <https://doi.org/10.1007/s12031-020-01775-6>.
- Yang, W., Tiffany-Castiglioni, E., 2008. Paraquat-induced apoptosis in human neuroblastoma SH-SY5Y cells: involvement of p53 and mitochondria. *J. Toxicol. Environ. Heal. A* 71, 289–299. <https://doi.org/10.1080/15287390701738467>.
- Zhang, J., Fitsanakis, V.A., Gu, G., Jing, D., Ao, M., Amarnath, V., Montine, T.J., 2003. Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. *J. Neurochem* 84, 336–346. <https://doi.org/10.1046/j.1471-4159.2003.01525.x>.