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Developmental origins of Parkinson disease: Improving the rodent models

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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 multietiologic 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

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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; Schaefers 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 multietiologic 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, dimethysulfoxide; 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, tyroxine hydroxylase; V, reduction; Λ, 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. Λ striatal dopamine and traveled distance. V (males) time spent swimming and Λ 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 *striatum.* 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; Veenvliet 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.

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