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Review

Prenatal exposure to oxidative phosphorylation xenobiotics and late-onset Parkinson disease

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ABSTRACT

Late-onset Parkinson disease is a multifactorial and multietiological disorder, age being one of the factors implicated. Genetic and/or environmental factors, such as pesticides, can also be involved.

Up to 80% of dopaminergic neurons of the substantia nigra are lost before motor features of the disorder begin to appear. In humans, these neurons are only formed a few weeks after fertilization. Therefore, prenatal exposure to pesticides or industrial chemicals during crucial steps of brain development might also alter their proliferation and differentiation.

Oxidative phosphorylation is one of the metabolic pathways sensitive to environmental toxicants and it is crucial for neuronal differentiation. Many inhibitors of this biochemical pathway, frequently found as persistent organic pollutants, affect dopaminergic neurogenesis, promote the degeneration of these neurons and increase the risk of suffering late-onset Parkinson disease.

Here, we discuss how an early, prenatal, exposure to these oxidative phosphorylation xenobiotics might trigger a late-onset, old age, Parkinson disease.

1. Introduction

1.1. Oxidative phosphorylation

The oxidative phosphorylation system (OXPHOS) processes environmental information. This biochemical pathway, located in the mitochondrial inner membrane, includes the electron transport chain (ETC), containing respiratory complexes I (CI) to IV (CIV), and the adenosine triphosphate (ATP) synthase (complex V, CV) (Fig. 1). Most of uptaken nutrients are finally oxidized in cells. Their electrons are extracted and passed on to the ETC through reduced adenine coenzymes, nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). Coenzyme Q (CoQ), also participates in this electron transport. Most of inhaled oxygen collects these electrons. Therefore, we eat and we breathe mainly to acquire ETC electron donors and acceptors. ETC electron flow is accompanied by proton pumping from mitochondrial matrix to intermembrane space. This activity generates an electrochemical gradient used for energy production and many other purposes. Among them, adjusting the levels of signaling molecules such as ATP, calcium (Ca^{2+}), NAD^+ and reactive oxygen species (ROS), thus, modulating many cell pathways. OXPHOS also regulates apoptosis and cell differentiation. Then, a proper OXPHOS function is important for cellular homeostasis, tissue dynamics and the health status of individuals (Martínez-Romero et al., 2011).

Most OXPHOS subunits are coded in the nuclear chromosomes. However, 13 essential polypeptides are encoded in mitochondrial DNA (mtDNA): 7 CI subunits (p.MT-ND1, 2, 3, 4, 4L, 5 and 6), 1 (p.MT-CYB) for complex III (CIII), 3 CIV subunits (p.MT-CO1, 2 and 3) and 2 CV subunits (p.MT-ATP6 and 8). Subunits p.MT-ND1 and 3 frame the CoQ access route to the enzyme active center (Q site) and accommodate the highly hydrophobic isoprenoid tail (Hirst, 2013). p.MT-CYB contains 2 CoQ binding sites, the outer (Qo) and the inner (Qi) sites (Iwata et al., 1998). p.MT-CO1 contains the oxygen-reduction site (Yoshikawa and Shimada, 2015). p.MT-ATP6 is part of the CV proton channel (Hahn et al., 2016).

Besides reduced adenine coenzymes, CoQ and oxygen, OXPHOS can also interact with many other chemicals that are foreign to human beings, *i.e.* xenobiotics.

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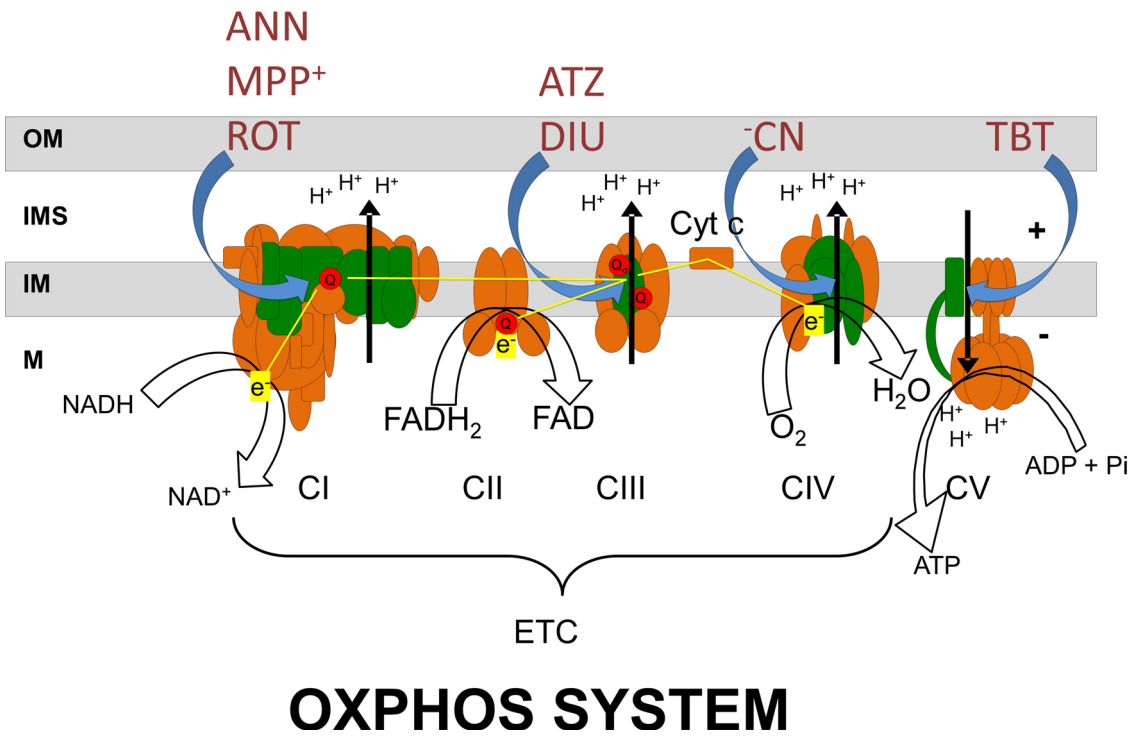

Fig. 1. Inhibitors of the oxidative phosphorylation system. Orange and green oxidative phosphorylation system subunits are nuclear DNA and mitochondrial DNA-encoded, respectively. OM, IMS, IM and M indicate mitochondrial outer membrane, intermembrane space, inner membrane and matrix, respectively. CI-CV, cytc, ETC, Q, Qi and Qo code for complexes I–V, cytochrome c, electron transport chain, coenzyme Q binding site, inner and outer coenzyme Q binding sites, respectively. ANN, MPP^+, ROT, ATZ, DIU, ^-CN and TBT designate annonacin, 1-methyl-4-phenylpidinium ion, rotenone, atrazine, diuron, cyanide and tributyltin, respectively.

1.2. OXPHOS xenobiotics

Many xenobiotics bind OXPHOS proteins and affect their function. The number of known CI inhibitors is increasing and the exposure to CI inhibitors of natural origin is difficult to avoid (Degli Esposti, 1998). For example, annonaceous plants produce CI inhibitors acetogenins (Fig. 1). The acetogenins quantity in annonaceous fruits is such that a cumulative dose sufficient to cause disorders in rats can be attained in humans by regular consumption within a year (Hollerhage et al., 2009). Cyanide is a well-known CIV inhibitor. Cyanide is present in fruit seeds such as those in peaches and apricots, in lima beans, and in cassava plants. Acute cyanide intoxications may be observed in children after the ingestion of cyanide-containing plants and food contaminated with cyanogenic products (Akil et al., 2013).

The slow rate of environmental degradation gives some chemicals the potential for bioaccumulation in upper trophic species of the food chain. The organotin tributyltin (TBT) was used in marine antifouling ship paints. Widespread environmental contamination of marine ecosystems with organotins began in the 1960s and a global ban against them was created from 2003 onward (Grun, 2014). However, environmental contamination by organotins goes beyond aquatic ecosystems because they are also used in industrial and agricultural activities (Grun, 2014). Several studies have found TBT concentrations in human blood (Kannan et al., 1999; Whalen et al., 1999). Previous reports suggested that ATP synthase proton channel, particularly p.MT-ATP6 subunit, was the target of TBT (von Ballmoos et al., 2004). Supporting this suggestion, we have recently observed that a p.MT-ATP6 mutation was responsible for the phenotypic differences in several OXPHOS parameters in response to TBT (Lopez-Gallardo et al., 2016).

The high mutation rate of mtDNA favors the generation of polypeptide variants, which could interact differently with certain substances (Lopez-Gallardo et al., 2011; Lopez-Gallardo et al., 2016). Diuron is a herbicide derived from urea and can interact with ETC CIII p.MT-CYB (Proctor et al., 2002). In yeast, a p.MT-CYB:I17F mutation causes diuron-resistance. 80% of mammals, including humans, contain phenylalanine at the equivalent position (position 18 in humans) and are naturally resistant to diuron (di Rago et al., 1986). However, humans with mtDNA genetic backgrounds, or haplogroups, J1c and K have a p.MT-CYB:F18L mutation (Gomez-Duran et al., 2011; Ruiz-Pesini et al., 2004). The CI inhibitor rotenone can be obtained from Leguminosae plants and is also used as pesticide. It has been also found that cybrids with mtDNA haplogroup B5, harboring a p.MT-ND3 polymorphism, show higher resistance to rotenone than those from haplogroup B4 (Liou et al., 2016). Thus, nuclear DNA (nDNA) and mtDNA genetic variants might affect OXPHOS susceptibility to xenobiotics (Lopez-Gallardo et al., 2011).

Although brain represents only about 2% of body weight, it consumes 20% of body's energy supply. OXPHOS is the main energy provider to power neuronal activity (Hall et al., 2012). Therefore, any OXPHOS xenobiotics might affect the nervous system function.

1.3. OXPHOS xenobiotics and neural dysfunction

A number of OXPHOS environmental toxicants have been associated with neural dysfunction and neurodegenerative disorders, such as parkinsonism (Lopez-Gallardo et al., 2011). For example, 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 (Langston et al., 1983; Langston et al., 1999). MPTP is metabolized to its toxic form 1-methyl-4-phenylpyridinium ion (MPP +), which is taken up into nigral neurons and inhibits ETC CI (Ramsay et al., 1986). Although MPTP is not generally found as an environmental toxic, it is commonly used to model late-onset Parkinson disease (LOPD).

Rotenone is also used to model LOPD. Rats which were chronically and systemically exposed to rotenone showed highly selective nigrostriatal dopaminergic degeneration, hypokinesia and rigidity. Nigral neurons accumulated fibrillar cytoplasmic inclusions that contain

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