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The Importance of Rotenone in Generating Neurological and Psychiatric Features in Zebrafish - Relevance for a Parkinson's Disease Model

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Abstract. The predisposition of people to contact or manifest certain diseases is growing. Chemical resistance mixed with other harmful sources could represent one of the causes for the disease appearance. Environmental toxins like rotenone are frequently used in agriculture or in fish extermination to control the soil or water fauna population. Despite the beneficial effects in these cases, acute or chronic exposure to rotenone can be dangerous for non-target organisms and humans. Analyzing different poisoning rotenone stages, it was concluded that rotenone can be an inhibitor mitochondrial complex I, which is a cause of Parkinson's disease (PD). Trying to identify the most important facts about PD, animal models were used in experiments. This review is focused on rotenone description, its effects on organisms and its ability to induce the specific symptoms in people affected by PD.

Abbreviations: PD - Parkinson's disease, ROS - oxygen reactive species, YOPD - young-onset Parkinson's disease, MPTP - 1-methyl-4-phenyl-1,2,3,6-tetrahidropyridine, 6-OHDA - 6-hydroxydopamine

Keywords: rotenone, Parkinson's disease, dopaminergic neurons, zebrafish, model organism

Introduction

A wide range of organic chemicals are used in the world to control a variety of unwanted organisms from soil, water, plant pests or even other organisms. The majority of chemicals often are dangerous due to active substance which is mixed with other substances. The negative consequences are influenced by the abiotic factors such as: light, temperature, humidity and water (Speight, 2017). Also, the persistence of the compound in the environment (Webster et al., 1998). Trying to create new compounds specialized in prevention or eradication of some disturbing organisms, the equilibrium of biocoenosis is disrupted. Beside affecting non-target organisms, even humans are exposed to negative impact of organic chemicals. These compounds can be classificated in natural and synthetic compounds.

Rotenone is a natural organic compound derived from plant species of genus *Derris* and *Lonchocarpus* (Melo et al., 2015). It is used, mostly, as insecticide, pesticide or piscicide (Ott, 2006; Saybasili & Akkentli, 2011). The first utilisation of rotenone as piscicide was in 1975 in a lake from Tasmania, where people tried to eradicate the invasive European carp (Rayner & Creese, 2006). Since then, rotenone was used for insect, pest and fish control, most of the cases (Ling, 2003; Gupta, 2012). In addition, due to the action it exerts on the nervous system, it has been used as a determinant of PD in order to create animal models (Bretaud et al., 2004; Martel et al., 2015; Wang et al., 2017). An animal model must satisfy three conditions: it must possess a similarity of causes of disease occurrence like humans, similarity of disease-specific symptoms, and the third condition is to present adequate responses to active treatments indicated for human diseases (Crawley, 2004). Zebrafish (*Danio rerio*) is one model organism proposed for modeling PD due to advantages it proved to have and to be taken into consideration (Best & Alderton, 2008; Pienaar et al., 2010; Makhija & Jagtap, 2014; Martín-Jiménez et al., 2015).

Parkinson's disease basic features

PD is a well-known disease which affects about 1% of old people population and it is a progressive, neurodegenerative disease (Sherer et al., 2003; Bretaud et al., 2004; Kaur et al., 2011; Goldman, 2014). Tremors, bradykinesia, rigidity, speech abnormalities, depression, dementia are some of specific symptoms of PD, thanks to degeneration of dopaminergic neurons from substance nigra and α-synuclein inclusion (Gelb et al., 1999; Sherer et al., 2003; Nass & Przedborski, 2008; Pienaar et al., 2010; Sanders & Greenamyre, 2013; Goldman, 2014). There are two hypotheses which are proposed to validate the appearance of PD such as: genetic and environmental hypothesis (Goldman, 2014). The environmental hypothesis is often used in experimental studies, where the scientists try to generate this disease at different laboratory animals through administration of a series of specific substances which acts on dopaminergic neurons, like: 1-methyl-4-phenyl-1,2,3,6-tetrahidropyridine (MPTP), 6-hydroxydopamine (6-OHDA) or rotenone (Sherer et al., 2003; Factor & Weiner, 2007; Flinn et al., 2008; Miller et al., 2009; Blandini & Armentero, 2011; Panula et al., 2010; Goldman, 2014; Niedzielska et al., 2015). These neurotoxins are known to be harmful on dopaminergic neurons after systemic or local administration, and the main action is inhibition of mitochondrial complex I (Blandini & Armentero, 2011, Goldman, 2014). Previous studies demonstrate that exposure to rotenone can reproduce some of the features of PD (Alam & Schmidt, 2002; Sherer et al., 2002; Xiong et al., 2012; Sanders & Greenamyre; 2013).

Characterization of rotenone

Even if rotenone has been used since 1848 as insecticide, the first registration of its high properties was in 1947 by Federal Insecticide Fungicide Rodenticide Act (Gupta, 2007). Rotenoids, especially rotenone, are extracted from the roots of the *Derris* or *Lonchocarpus* plants, and it is native in Asia and South-

Central America (Gupta, 2012). In 2012, Peru was the main source for rotenone extracts (Gupta, 2012). Depending on the state of formulas in which it is found (dust, emulsifiable solutions or crystalline preparations), rotenone has different toxicity grades (Ling, 2003; Gupta, 2012). Regarding its physical and chemical properties, rotenone is found as brown or white crystals, odorless, soluble in ethanol, acetone, chloroform (NCBI, 2018).

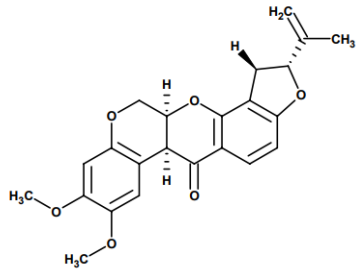

Figure 1 – Structure of rotenone (after Ling, 2003)

The molecular and chemical structure of rotenone is similar to those seen in the isoflavones group and it is degraded by air, water and light (Figure 1) (NCBI, 2018; Ott, 2006). Currently, rotenone is used as insecticide to combate different insects from house and grain stores, stables or to treat pests the in agricultural crops (Ling, 2003). As an piscicide, it is useful to control undesirable fish from certain areas, but its excessive use leads to another big problem (Ling, 2003). Due to high absorption capacity by fish, rotenone is toxic in small quantities, considering that fish has no enzymes able to degrade the compound (Ling, 2003; Ott, 2006).

The tentative to balance the unwanted fish in lakes or other spaces, can be finished by killing non-target organisms such as invertebrates, amphibians or other organisms (Ling, 2003; Ott, 2006; Gupta, 2012). For mammals and humans, the consumption of high quantities of rotenone is toxic (Ling, 2003; Ott, 2006; Gupta, 2012). When rotenone is in a high quantity in body, it determines the appearance of some symptoms specific to people with PD and, for that, rotenone reached be used in experiments to generate animal models for this disease (Miller et al., 2009; Johnson & Bobrovskaya, 2015).

What is the mechanism of action for rotenone in the organisms?

Rotenone is easy absorbed in organism due to lipophilic state and it accumulates, predominant in mitochondria, center of production of ATP (Nass & Przedborski, 2008). At insects, rotenone inhibits the transformation of NADH in energy (Gupta, 2012). The same mechanism can be observed in other organisms: fish, amphibians or mammals (Gupta, 2012). It inhibits the mitochondrial respiratory chain complex I, a fact which leads at a low production of ATP, increase quantity of oxygen reactive species (ROS) due to the presence of oxidative stress (Saybasili & Akkentli, 2011; Gupta, 2012; Melo et al., 2015).

Oxidative stress is defined as an imbalance between antioxidants and oxidants which leads to DNA, proteins and lipids degradation and formation of ROS (Sherer et al., 2003; Emerit et al., 2004; Niedzielska et al., 2015). Also, rotenone is able to reduce the activity of glutathione which is one antioxidant warrior against ROS (Miller et al., 2009).

Correlation between rotenone and Parkinson's disease

Environmental risk-factors for PD are known since various decades. Butterfield and collaborators in 1993 conducted an exploratory study of young-onset Parkinson's disease (YOPD) with the goal to investigate occupational and environmental factors associated with disease risk. In this research a link between some pesticide agents (e.g. insecticide and herbicide) and YOPD was found (Butterfield et al., 1993). After a few years, another study confirmed this hypothesis. In a research conducted in 1998 (Gorell et al., 1998), PD was associated with an occupational exposure to insecticide and herbicide. Farming, as an occupation, was positive correlated with PD oneset but there was no increased risk of the disease with farm or rural residence. No relation between PD and fungicide exposure was found.

The rotenone-PD model has become of scientific interest following experiments conducted in 2000 by Betarbet and collaborators (Betarbet et al., 2000). This research showed for the first time that rotenone was able to reproduce the two pathological hallmarks of PD, as well as some parkinsonian motor dysfunctions. Since 2000, in many research labs the rotenone-PD model has been used worldwide (Alam & Schmidt, 2002; Sherer et al., 2003; Xiong et al., 2009; Pan-Montojo et al., 2010; Johnson & Bobrovskaya, 2015).

Zebrafish as experimental model in psychiatric disorders

Although many human brain disorders and disease were modeling, with certain success, using traditional laboratory species (e.g., rats and mice), zebrafish appears to have an excellent future as animal model species in research. Zebrafish (*Danio rerio*, Hamilton, 1822) is a very popular freshwater tropical fish, used as animal model organism in biomedical and neuropharmacology research. Behavioural tests in different experiments showed that it is possible to modeled various psychiatric disorders in zebrafish (Kalueff et al., 2014).

This species offers a potential tool to study various human brain diseases associated with abnormal social behaviour (e.g., schizophrenia and autism). Also some neuropsychiatric conditions correlated with impaired social behaviour, like depression and anxiety disorders, can be studied in laboratory with zebrafish. Since it has complex sociality, shoaling (tendency to stay in group for social reasons) is perhaps the main feature studied in artificial environment. Shoaling can be quantified and analysed in many different ways (Wright et al., 2006; Miller et al., 2007) and can be an excellent indicator of psychiatric disorders in fish species.

In research, many behavioral tests have been used on zebrafish and other fish species. Simple behavioral tests based on habitat preference, phototactic responses and escape behaviour, have been experimented with success on both larval and adult *Danio rerio* (Li & Dowling, 2000). But, also more complex behavioral tests, such as mazes (learning, memory and exploratory behaviour) and sociality tests, were performed with success in different experiments with this species (Peitsaro et al., 2003; Anichtchik et al., 2004).

Moreover, zebrafish genome is well sequenced and danios possess rapid development, relative long lifespan, quite simple laboratory keeping and easy genetic manipulation. The availability of different species strains is another very important aspect, enabling studies of strain differences in behaviour, brain physiology and drug responses. For this, zebrafish appears a valuable animal model for studying psychiatric and neurodegenerative human diseases (Martín-Jiménez et al., 2015).

How rotenone acts in fish?

There are several studies which highlights the negative impact of rotenone on fish. Exposure of fish at rotenone determines decreased swimming performance, metabolic rate, oxygen consumption disturbances, increase free radical formation and presence of oxidative stress, effects which, in many cases, lead to cellular dead (Melo et al., 2015). In animal models, rotenone is responsible for the occurrence of Parkinson-specific symptoms such as: mitochondrial disorder, ROS generation, microglial activation and reduction of ATP production (Goldman, 2014). In some experiments, zebrafish, as new animal model, was exposed to different concentrations of rotenone to generate PD.

Lately there is a current interest for zebrafish which has become a popular organism and it is a perfect organism for PD because: it has high gene homology with human genome, easy genetic manipulation and similar neuroanatomy with other vertebrates (Flinn et al., 2008; Nass & Przedborski, 2008; Kalueff et al., 2014; Martín-Jiménez et al., 2015). So, the results obtained after exposure of zebrafish at rotenone were observed visually and microscopically. According to Melo and his collaborators (2015), acute exposure of zebrafish embryos for 96 h at different concentrations of rotenone (5, 10, 20, 40 and 80 µg/L) has determined: abnormal pigmentation of the body, deformation of the spine and tail, appearance of edema in heart. The absence of specific enzymes responsible with the degradation of rotenone, justify the decreased activity of antioxidant enzymes (catalase and glutathione peroxidase). Also, at 40 and 80 µg/L of rotenone a high level of mortality was found.

An another study in which were used embryos, exposure to 30 and 50 µg/L of rotenone conducted to opacification of tissues and body blackening (Xiong et al., 2012). In 2017, Wang and his team exposed adult zebrafish to 2 µg/L rotenone for 4 weeks. Locomotor activity, olfaction, neurotransmitter levels, anxiety and depression were tested at the beginning of the experiment. The same tests were performed in the end of the experiment. Thus, after 4 weeks of rotenone exposure, the locomotory activity and olfaction decreased. Compared with the levels of neurotransmitter of control fish, level of exposed fish decreased up to 40% (Wang et al., 2017). For testing anxiety and depression, researchers used the light-dark box. After the experiment, the exposed fish were tested with the light-dark box and the results confirmed the existence of anxiety and depression due to the time spent in the light compartiment (Wang et al., 2017).

Effects of rotenone on other organisms than fish

Rats are used for decades to study the mechanism, pathology, evolution, treatment of variate diseases. Administration of rotenone to rats induced biochemical, behavioral and neuropathological characteristics of PD. Researchers wanted to know the perfect dose for rats to reproduce the specific symptoms of PD.

According to Zhang and his collaborators (2017), 2 mg/kg of rotenone which is subcutaneous injected is the optim dose to determine the accumulation of α-synuclein and maintain a low mortality of animals. Depending the mode of administration of rotenone, the impact on an organism is different. So, when male rats received intraperitoneally 1,5 mg/kg/day of rotenone for 8 days, the main effects observed were: a decreased activity of glutathione and superoxide dismutase, a high level of acetylcholine and an impaired motor coordination inregistrated after the behavioral tests (Madiha & Haider, 2017).

In another study conducted on rats, rotenone was administered intranasal, 2,5mg/kg every other day for 2 weeks. After that time, microscopically were observed several changes in the structure of olfactory bulbs, reduction of the number of dopaminergic neurons and accumulation of α-synuclein which leaded at formation of well-known body Lewy (Voronkov et al., 2017). The same observation was made when rotenone was administered intranasal to mice for 2 weeks by Sasajima et al., (2017).

The effects of chronic exposure to rotenone was observed in dogs. The 10 mg/kg/day rotenone was the dose administered to dogs for 6 months. After that period, weight lost was the main effect which was observed in dogs (Goldman, 2014).

Rotenone can be absorbed by humans through ingestion or inhalation, and despite the route of administration, it is no lethal because this compound is in a low concentration in formulas (PMEP, 2018). In accidental cases of poisoning, the observed effects were: nausea, vomiting, convulsions, bradycardia or even dermatitis in case of chronic exposure (Patel, 2011; Gupta, 2012).

Conclusions and future directions

1. Rotenone, a natural compound found in several species of the genus *Derris* and *Lonchocarpus* is considered a handy tool in Parkinson's disease appearance. Due to its capacity to inhibit the mitochondrial chain complex I and to determine an imbalance between oxidants and antioxidants, rotenone can be used as determinant of Parkinson's disease in many animal models.
2. In recent years, the researchers started to use a new model organism: zebrafish (*Danio rerio*). Beside the advantages it has, the obtained results are valuable and significant in scientific research. The majority of tests which were performed in rats, another experimental organism, can be used and adapted as alternative tests to measure many parameters in zebrafish.
3. We intend to generate the features of PD in zebrafish after exposure it to rotenone and to succeed in improving old experimental protocols which are found in literature. In the meantime, our goal is to administrate different

concentrations of rotenone to zebrafish and to observe the main changes and validate it after several tests like: light-dark box test, olfactory response to some chemical substances, the Y test to evaluate their memory, the locomotory activity test to determine the swimming performance and, eventually, the general motor impairment.

4. Based on information discovered in different experimental studies and the easy manipulation of zebrafish, it can be concluded that it could represent a good model organism to study Parkinson's disease.

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