Title: *In vivo*, *In vitro* and Pharmacologic Models of Parkinson's Disease

Sajjad Salari[1,2]**, Maryam Bagheri**[1,2]*

1 Department of Physiology, Faculty of Health Sciences, Ilam University of Medical Sciences, Ilam, Iran.

2 Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran.

*Corresponding author: Maryam Bagheri, Psychosocial injuries research center, Ilam University of Medical Sciences, Ilam, Iran.

Contact information; Email: maryam.bagheri@medilam.ac.ir , cell phone: +98 9124112694

Short title: Representative Models of Parkinson's Disease

Summery

Parkinson's disease (PD), which is the second most common neurodegenerative disorder after Alzheimer's disease, is firstly defined after James Parkinson's report. It carries motor symptoms such as resting tremor, bradykinesia and rigidity of skeletal muscle and freezing of gait. Furthermore, non-motor symptoms such as cognitive and behavioral problems, besides sensory impairments are seen in the patients. However, they may also suffer from sleep disorders or autonomic dysfunction. Although there are some medications in order to symptomatic management, but unfortunately, scientist could not have found exact approaches to cure this disease. Hence, producing a model which can express the most pathophysiologic and behavioral aspects of the disease is a desire. In this paper, we aimed to describe the different models of Parkinson's disease in brief.

Main text

Parkinson's disease

James Parkinson revealed a detailed description of six patients with shaking palsy in 1817 and after his death, the mentioned description known as Parkinson disease which is now the most common neurodegenerative disorder after Alzheimer's disease (Parkinson 2002). Motor symptoms including resting tremor, bradykinesia and rigidity of skeletal muscle, postural instability, stooped posture, and freezing of gait are clinical symptoms in PD. Furthermore, non-motor symptoms such as cognitive and behavioral problems, besides sensory impairments are seen in the patients. However, they may also suffer from sleep disorders or autonomic dysfunction (Chaudhuri & Schapira 2009). The prevalence of PD is approximately 0.3% in the general population in developed countries and affects about 1% of those older than 60 and it is unusual to occur before the age of 50 (de Lau & Breteler 2006). Notably, men are at higher risk than women. In Europe, PD affected 1.2 million people in 2010, resulting in costs per patient of EUR 5,626 for direct health care and EUR 4,417 for non-medical care (de Lau & Breteler 2006). Unfortunately, the exact cost of PD is not clear in Middle East.

Hallmarks of Parkinson's disease

Pathophysiologically, there are some clear hallmarks in the affected patients such as, severe loss of dopaminergic neurons in the substantia nigra pars compacta (SNC) of the basal ganglia. Moreover, the presence of intraneuronal inclusions called Lewy bodies are proved in the brain of PD, which are composed of N-synuclein, a protein that is present basically in presynaptic terminals and has a pivotal role in vesicular release of neurotransmitters, axonal transport, and mechanisms of autophagy (Perez *et al.* 2002, Ben Gedalya *et al.* 2009, Koprich *et al.* 2011). The occurrence of Lewy bodies is one of the basic criteria, which used to diagnose PD.

Degeneration of different parts of the brain including noradrenergic, cholinergic, or serotonergic neurons is the main cause of the non-motor symptoms.

Genetic factors, a positive family history of PD can lead to higher risk of incidence of the disorder, and 5–10% of patients with PD diagnosis carry mutations in the associated genes. The gene encoding N-synuclein was the first gene-related mechanism that was suggested to trigger the initiation of PD. Today, 16 loci designated PARK1 to PARK16 and 11 genes on different chromosomes are known to be associated with a higher risk of PD (Corti *et al.*

2011). Mutations in the mentioned loci affect the expression of some proteins. Ubiquitin ligase, UCHL-1, DJ-1, PTEN-induced kinase and nuclear receptor, which are involved in protection against oxidative stress, mitochondrial dysfunction, and survival of dopaminergic cells are the most important ones which are studied during last years (Thomas & Cookson 2009, Devine *et al.* 2011).

Non-genetic factors, occupational exposure to toxins and heavy metals can increase the risk of PD (Caudle 2015). It is proved that exposure to agricultural chemicals such as pesticide rotenone and the herbicide paraquat due to harmful effects on dopaminergic neurons (Betarbet *et al.* 2000, de Lau & Breteler 2006) and exposure to some heavy metals, including iron, manganese, zinc, and copper due to inducing oxidative stress, which causes dopaminergic neuronal depletion in the SNC (Lai *et al.* 2002, Tanaka *et al.* 2011) can increase the developing PD.

Homocysteine is the essential amino acid that may have a toxic effect on neurons, which accelerate cell death in general. Recent investigations on this substance have examined the development of PD and higher intake of vitamin B, a substance that is associated with lower plasma levels of homocysteine (de Lau & Breteler 2006). Some of these studies expressed that high consumption of vitamin B6 can lead to a decreased risk of PD (Murakami *et al.* 2010).

Mitochondrial dysfunction and increased oxidative stress may also play a pivotal role in the pathogenesis and development of PD (Henchcliffe & Beal 2008, Aroso *et al.* 2016). Byproduct of lipids, proteins, and DNA oxidative damage, and reduced levels of the antioxidant glutathione have been proved in the brain samples from individuals with PD (Voshavar *et al.* 2015, Yuan *et al.* 2015). Antioxidants such as vitamins E and C can protect dopaminergic cells against free radicals although, during the very early stages of the disease (Devore *et al.* 2010).

Intracellular ionic channels may play roles in the pathogenesis of PD. Ion channels have been found in the intracellular organelles membrane including mitochondria (Bednarczyk 2009, Fahanik-Babaei *et al.* 2011) and endoplasmic reticulum (ER) (Salari *et al.* 2011, Salari *et al.* 2015). ER potassium channel plays important role in ER calcium homeostasis (Kuum *et al.* 2012, Ghasemi *et al.* 2014), and interruption in ER calcium homeostasis can lead to ER stress which is prominent pathway in neurodegenerative disease pathogenesis (Magi *et al.* 2016, Xiang *et al.* 2017). Mitochondrial potassium channels are involved in oxidative stress and cell survival.

Activation of mitochondrial ATP sensitive potassium channels enhances angiotensin-induced oxidative damage and promotes dopaminergic neuron degeneration (Rodriguez-Pallares *et al.* 2012).

In order to investigate the mechanisms underlying the disease and to evaluate new treatments different models have been developed based on the hallmarks of Parkinson's disease. Here, we try to describe diverse models of PD including *in vitro*, *in vivo* and transgenic ones with brief introduction to advantages and disadvantages of the models.

In vivo models of Parkinson's disease

Animal models, which are used broadly in the experiments, represent potential tools in our attempts to understand the mechanisms underlying the PD, and have an important role in the development of new treatment strategies.

Pharmacologic animal models of selective damage of dopaminergic neurons have been used for many years in PD research.

6-OHDA

The known toxins including 6-hydroxy dopamine (6-OHDA), 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP), rotenone, paraquat, lipopolysaccharide, and manganese are the toxins that have been applied most widely in rats, mice, cats and monkeys (Klivenyi & Vecsei 2011, Blesa *et al.* 2012). However, 6-OHDA is more often used in rats (Roeling *et al.* 1995, Valette *et al.* 1995, Annett *et al.* 1997, Ruffy & Leonard 1997). It is usually injected unilaterally to the medial forebrain bundle. Injection of 6-OHDA to the SNC may kill up to 60% of tyrosine-hydroxylase containing neurons. These toxins produce the PD (Penttinen *et al.* 2016) models by inducing mitochondrial dysfunction and increased oxidative stress that in return lead to neuronal degeneration in specific parts of the brain. 6-OHDA cannot mimic all aspects of the disease but seemingly, it is a replicate of PD in human. 6-OHDA is structurally similar to dopamine and norepinephrine. Consequently, it binds to the plasma membrane transporters of catecholamines. However, 6-OHDA does not cross the blood brain barrier, but, it kills neurons containing dopamine and norepinephrine by producing hydrogen peroxidase when injected to the brain (Javoy *et al.* 1976). The 6-OHDA animal model is useful when researchers wish to evaluate the effects of new drugs on motor skills. Depends on the animal species, the concentration of toxins, the type of vehicle, and the methods of administration employed may vary. A typical behavioral symptom after unilateral injection of this toxin is rotational behavior after apomorphine injection (Baluchnejadmojarad

et al. 2009). Overall, pharmacological animal models are reproducible and have made important contributions to our current knowledge about PD.

MPTP

In 1983, many people exhibited typical signs of PD after taking an opioid that was contaminated with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) during processing. This important finding led to the theory that MPTP selectively damages dopaminergic neurons in the SNC, which in turn revealed the hypothesis that some environmental toxins can raise the risk of PD. Since then, numerous studies have been achieved to examine the role of other environmental factors in the pathogenesis of the disease. Notably, MPTP is the gold standard for researchers in order to induce all aspects of PD hallmarks in animal model of the disease. It should be mentioned that via this model, Lewy body inclusions can be developed in the brain of affected animals (Kowall *et al.* 2000, Fornai *et al.* 2005). Unlike the 6-OHDA, MPTP can cross the blood-brain-barrier immediately and metabolizes in to active form. The active form, MPP$^+$ is stored in neurons via dopamine transporter (DTA), and through this, interferes with the mitochondrial electron transport chain that leads to energy depletion. PMTP is used in dogs, cats but more often in nonhuman primates and mice. Motor impairments can be seen in behavioral test after toxin administration but less detectable in acute injection in rodents (Blesa *et al.* 2012).

Paraquat

Paraquat or N, N_-dimethyl-4-4-4_-bypiridinium is an agricultural herbicide, which is similar to MPP+ structurally that due to this similarity, researchers expect to have similar pathological changes after injection of this toxin (Day *et al.* 1999, Berry *et al.* 2010). It affects the redox cycle in mitochondria and can increase the production of oxidative stress that in return can cause protein, lipid, DNA and RNA damage. The nigrostriatal damage after Paraquat injection is dose dependent in mice while some investigations revealed no damages in the mentioned area (Kozuch & Mayer 1975, Thiffault *et al.* 2000, Thiruchelvam *et al.* 2000, McCormack *et al.* 2002). Notably, Rappoled et al. in 2011 reported the toxicity of paraquat to the dopaminergic neurons through dopaminergic transporter at high doses (Rappold *et al.* 2011). No clear motor deficits have been found after paraquat administration (Blesa *et al.* 2012).

Rotenone

Rotenone that is a natural occurring in tropical plants is a neurotoxic agent and used as an herbicide and pesticide (Inden *et al.* 2007). Since it is a lipophilic agent, it can cross the blood brain barrier. It has been reported that Lewis rats are more sensitive to Rotenone rather than other species (Betarbet *et al.* 2000). Dopaminergic neuronal damage as well as α-synoclein aggregation and Lewy body inclusion are seen after intravenous injection (Sherer *et al.* 2003). The most pathologies, which are induced after paraquat inject, can be seen with the administration of Rotenone (Sherer *et al.* 2003), but the side effects do not restricted to the dopaminergic systems. Other brain areas such as serotonergic, noradrenergic and cholinergic systems are affected as well (Hoglinger *et al.* 2003).The positive issue regarding rotenone is that oral administration of these chemicals employs in researches (Pan-Montojo *et al.* 2010). Decreased motor activity has been reported in this model (Blesa *et al.* 2012).

Manganese

Manganese (Mn) is naturally exist in the environment; air, water, soil and food (Aschner *et al.* 2007). It has several important roles in the synthesis and metabolism of neurotransmitters as a co-factor (Bowman *et al.* 2011). However, excessive accumulation of Mn in the brain can lead to manganism, which shows extrapyramidal motor dysfunction comparable to Parkinsonism (Sadeghi *et al.* 2018). Mn can accumulate in globus pallidus and subthalamic nucleus that are involved in the control of motor and non-motor function (Bouabid *et al.* 2016). Intraperitoneal injection of 10 mg of $MnCl_2$ for 5 weeks can deteriorate locomotors function (Bouabid *et al.* 2014). Decreased levels of serotonergic and norepinephrine system parallel with changes in firing rate and pattern of basal ganglia neurons are present after Mn-induced toxicity (Bouabid *et al.* 2014). Rout of administration and dosage of Mn can affect the dopaminergic neurons in the brain. In a drinking water, Mn can significantly increase the dopamine content while it is decreased after intrathecal administration.

Genetic engineered models of Parkinson's disease
Transgenic animals

Transgenic animals are being used widely in different investigations since it is believed that the genetic and the sporadic forms of the disease express some common features of the

diseases (Devine *et al.* 2011). Mice that are genetically engineered to develop loss of dopaminergic neurons in the SN are used mostly.

Inducing some restriction in the enzymes PstI or mito-PstI which targets the mitochondrial oxidative phosphorylation can induce a mouse model that carries a double –stranded mitochondrial DNA breakage (Pickrell *et al.* 2011).

This model has the most of PD features i.e. motor dysfunction and degeneration of dopaminergic neurons in the SN. Furthermore, this model carries the potential to evaluate the role of mitochondria in the pathophysiology of the disease.

Two genetically engineered mice models that generate progressive neuronal loss in the SNC have been proposed as well. The former is Pitx3 -/- mice with a spontaneous mutation in the homeobox transcription factor Pitx3, and the latter is engrailed knockout mice with SNC neuronal loss accompanied 17 by cerebellar pathology (Meredith *et al.* 2008).

The familial forms of PD can be developed by mutations in genes encoding N-synuclein (Kay *et al.* 2008), parkin (Miklya *et al.* 2014), DJ1, and LRRK2 (Tan & Skipper 2007, Wider *et al.* 2010). However, animals with N-synuclein mutation display the symptoms of the disease while they do not exhibit neuronal loss. Hence, they are not very useful for investigating PD pathophysiology or treatment approaches.

On the other hand, early onset of familial PD model can be produced by mutations in the gene encoding parkin, which in return can cause proteasomal dysfunction (Meredith *et al.* 2008).

Interestingly, mice and flies are being used for mutations in genes for DJ1 which can lead to decreased cell resistance to oxidative stress but not loss of cells. However, these models have some limitations due to not having cell loss.

In addition, late onset of familial form of PD can be developed through mutations in LRRK2 and a transgenic mouse model caries these aberrations is currently being developed (Meredith *et al.* 2008).

In vitro models of Parkinson's disease
Viral-based animal models

Viral-based animal models can be developed by acute delivery of virally expressed genes such as recombinant adeno-associated virus (rAAV) into the SN, that exhibit neuronal loss so often. For example, animals with over expression of N-synuclein show neuronal loss as well as behavioral deficits. Thus, these models are more useful than other engineered mouse

models, if the goal is to acquire animals with the hallmarks of PD (Meredith *et al.* 2008, Dehay & Bezard 2011).

The nematode *Caenorhabditis elegans* (Alexander *et al.* 2014) and the fruit fly *Drosophila melanogaster* have also been employed in the investigation of cellular and molecular pathways involved in different forms of familial PD (Bayersdorfer *et al.* 2010).

Drosophila melanogaster can show duplication or triplication of the N-synuclein gene, which makes these flies a good model for investigating synucleinopathies. The weakness of these two invertebrate species which are not desired to researchers is that they do not produce Lewy body inclusions, which are the chief feature of PD in humans (Meredith *et al.* 2008). It can be mentioned that none of the animal models pronounced above express the genotype and/or phenotype observed exactly in humans. For example, most genetically engineered mice do not exhibit the nigrastriatal degeneration that is the main hallmark of PD in human. However, the models based on delivery of virally-expressed genes into the SN can affect the SN and induce local degeneration. However, they do not develop the neuronal depletion or pathology to the other area in the brain, which is seen during progression of the disease in humans. Furthermore, absence of Lewy bodies is the characteristics of many of these models.

Conclusion

Here, we aimed to describe different genetic and pharmacologic models of Parkinson disease. Each model has its advantages and disadvantages. While pathophysiologic pathways can be studied in the pharmacologic models, pivotal roles of genes can be investigated in the genetic forms of the disease. It can be mentioned that the pathologic disturbances induced in the pharmacologic models mostly express the late stages of the disease while, with the genetic form, investigators may face the disease with the early onset. Depends on the question researchers wish to answer, evaluating a therapeutic approaches or investigating the detailed of underlying mechanisms, different type of animals can be selected. However, economical aspect and reproducibility of the models seem to be important in experiments. Overall, employing a genetic model in combination with pharmacologic agents may be an ideal model for future studies, while perfect model of Parkinson's disease remains beyond doubt yet.

References

ALEXANDER AG, MARFIL V & LI C: Use of Caenorhabditis elegans as a model to study Alzheimer's disease and other neurodegenerative diseases. *Front Genet* **5:** 279, 2014.

ANNETT LE, TORRES EM, CLARKE DJ, ISHIDA Y, BARKER RA, RIDLEY RM, BAKER HF & DUNNETT SB: Survival of nigral grafts within the striatum of marmosets with 6-OHDA lesions depends critically on donor embryo age. *Cell Transplant* **6:** 557-569, 1997.

AROSO M, FERREIRA R, FREITAS A, VITORINO R & GOMEZ-LAZARO M: New insights on the mitochondrial proteome plasticity in Parkinson's disease. *Proteomics Clin Appl* 2016.

ASCHNER M, GUILARTE TR, SCHNEIDER JS & ZHENG W: Manganese: recent advances in understanding its transport and neurotoxicity. *Toxicol Appl Pharmacol* **221:** 131-147, 2007.

BALUCHNEJADMOJARAD T, ROGHANI M, NADOUSHAN MR & BAGHERI M: Neuroprotective effect of genistein in 6-hydroxydopamine hemi-parkinsonian rat model. *Phytother Res* **23:** 132-135, 2009.

BAYERSDORFER F, VOIGT A, SCHNEUWLY S & BOTELLA JA: Dopamine-dependent neurodegeneration in Drosophila models of familial and sporadic Parkinson's disease. *Neurobiol Dis* **40:** 113-119, 2010.

BEDNARCZYK P: Potassium channels in brain mitochondria. *Acta Biochim Pol* **56:** 385-392, 2009.

BEN GEDALYA T, LOEB V, ISRAELI E, ALTSCHULER Y, SELKOE DJ & SHARON R: Alpha-synuclein and polyunsaturated fatty acids promote clathrin-mediated endocytosis and synaptic vesicle recycling. *Traffic* **10:** 218-234, 2009.

BERRY C, LA VECCHIA C & NICOTERA P: Paraquat and Parkinson's disease. *Cell Death Differ* **17:** 1115-1125, 2010.

BETARBET R, SHERER TB, MACKENZIE G, GARCIA-OSUNA M, PANOV AV & GREENAMYRE JT: Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* **3:** 1301-1306, 2000.

BLESA J, PHANI S, JACKSON-LEWIS V & PRZEDBORSKI S: Classic and new animal models of Parkinson's disease. *J Biomed Biotechnol* **2012:** 845618, 2012.

BOUABID S, DELAVILLE C, DE DEURWAERDERE P, LAKHDAR-GHAZAL N & BENAZZOUZ A: Manganese-induced atypical parkinsonism is associated with altered Basal Ganglia activity and changes in tissue levels of monoamines in the rat. *PLoS One* **9:** e98952, 2014.

BOUABID S, TINAKOUA A, LAKHDAR-GHAZAL N & BENAZZOUZ A: Manganese neurotoxicity: behavioral disorders associated with dysfunctions in the basal ganglia and neurochemical transmission. *Journal of neurochemistry* **136:** 677-691, 2016.

BOWMAN AB, KWAKYE GF, HERRERO HERNANDEZ E & ASCHNER M: Role of manganese in neurodegenerative diseases. *J Trace Elem Med Biol* **25:** 191-203, 2011.

CAUDLE WM: Occupational exposures and parkinsonism. *Handb Clin Neurol* **131:** 225-239, 2015.

CHAUDHURI KR & SCHAPIRA AH: Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* **8:** 464-474, 2009.

CORTI O, LESAGE S & BRICE A: What genetics tells us about the causes and mechanisms of Parkinson's disease. *Physiol Rev* **91:** 1161-1218, 2011.

DAY BJ, PATEL M, CALAVETTA L, CHANG LY & STAMLER JS: A mechanism of paraquat toxicity involving nitric oxide synthase. *Proc Natl Acad Sci U S A* **96:** 12760-12765, 1999.

DE LAU LM & BRETELER MM: Epidemiology of Parkinson's disease. *Lancet Neurol* **5:** 525-535, 2006.

DEHAY B & BEZARD E: New animal models of Parkinson's disease. *Mov Disord* **26:** 1198-1205, 2011.

DEVINE MJ, PLUN-FAVREAU H & WOOD NW: Parkinson's disease and cancer: two wars, one front. *Nat Rev Cancer* **11:** 812-823, 2011.

DEVORE EE, GRODSTEIN F, VAN ROOIJ FJ, HOFMAN A, STAMPFER MJ, WITTEMAN JC & BRETELER MM: Dietary antioxidants and long-term risk of dementia. *Arch Neurol* **67:** 819-825, 2010.

FAHANIK-BABAEI J, ELIASSI A, JAFARI A, SAUVE R, SALARI S & SAGHIRI R: Electro-pharmacological profile of a mitochondrial inner membrane big-potassium channel from rat brain. *Biochim Biophys Acta* **1808:** 454-460, 2011.

FORNAI F, SCHLUTER OM, LENZI P, GESI M, RUFFOLI R, FERRUCCI M, LAZZERI G, BUSCETI CL, PONTARELLI F, BATTAGLIA G, PELLEGRINI A, NICOLETTI F, RUGGIERI S, PAPARELLI A & SUDHOF TC: Parkinson-like syndrome induced by continuous MPTP infusion: convergent roles of the ubiquitin-proteasome system and alpha-synuclein. *Proc Natl Acad Sci U S A* **102:** 3413-3418, 2005.

GHASEMI M, KHODAEI N, SALARI S, ELIASSI A & SAGHIRI R: Gating behavior of endoplasmic reticulum potassium channels of rat hepatocytes in diabetes. *Iran Biomed J* **18:** 165-172, 2014.

HENCHCLIFFE C & BEAL MF: Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clin Pract Neurol* **4:** 600-609, 2008.

HOGLINGER GU, FEGER J, PRIGENT A, MICHEL PP, PARAIN K, CHAMPY P, RUBERG M, OERTEL WH & HIRSCH EC: Chronic systemic complex I inhibition induces a hypokinetic multisystem degeneration in rats. *J Neurochem* **84:** 491-502, 2003.

INDEN M, KITAMURA Y, TAKEUCHI H, YANAGIDA T, TAKATA K, KOBAYASHI Y, TANIGUCHI T, YOSHIMOTO K, KANEKO M, OKUMA Y, TAIRA T, ARIGA H & SHIMOHAMA S: Neurodegeneration of mouse nigrostriatal dopaminergic system induced by repeated oral administration of rotenone is prevented by 4-phenylbutyrate, a chemical chaperone. *J Neurochem* **101:** 1491-1504, 2007.

JAVOY F, SOTELO C, HERBET A & AGID Y: Specificity of dopaminergic neuronal degeneration induced by intracerebral injection of 6-hydroxydopamine in the nigrostriatal dopamine system. *Brain Res* **102:** 201-215, 1976.

KAY DM, FACTOR SA, SAMII A, HIGGINS DS, GRIFFITH A, ROBERTS JW, LEIS BC, NUTT JG, MONTIMURRO JS, KEEFE RG, ATKINS AJ, YEAROUT D, ZABETIAN CP & PAYAMI H: Genetic association between alpha-synuclein and idiopathic Parkinson's disease. *Am J Med Genet B Neuropsychiatr Genet* **147B:** 1222-1230, 2008.

KLIVENYI P & VECSEI L: Pharmacological models of Parkinson's disease in rodents. *Methods Mol Biol* **793:** 211-227, 2011.

KOPRICH JB, JOHNSTON TH, HUOT P, REYES MG, ESPINOSA M & BROTCHIE JM: Progressive neurodegeneration or endogenous compensation in an animal model of Parkinson's disease produced by decreasing doses of alpha-synuclein. *PLoS One* **6:** e17698, 2011.

KOWALL NW, HANTRAYE P, BROUILLET E, BEAL MF, MCKEE AC & FERRANTE RJ: MPTP induces alpha-synuclein aggregation in the substantia nigra of baboons. *Neuroreport* **11:** 211-213, 2000.

KOZUCH O & MAYER V: Pig kidney epithelial (PS) cells: a perfect tool for the study of flaviviruses and some other arboviruses. *Acta Virol* **19:** 498, 1975.

KUUM M, VEKSLER V, LIIV J, VENTURA-CLAPIER R & KAASIK A: Endoplasmic reticulum potassium–hydrogen exchanger and small conductance calcium-activated potassium channel activities are essential for ER calcium uptake in neurons and cardiomyocytes. *J Cell Sci* **125:** 625-633, 2012.

LAI BC, MARION SA, TESCHKE K & TSUI JK: Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism Relat Disord* **8:** 297-309, 2002.

MAGI S, CASTALDO P, MACRI ML, MAIOLINO M, MATTEUCCI A, BASTIOLI G, GRATTERI S, AMOROSO S & LARICCIA V: Intracellular Calcium Dysregulation: Implications for Alzheimer's Disease. *Biomed Res Int* **2016:** 6701324, 2016.

MCCORMACK AL, THIRUCHELVAM M, MANNING-BOG AB, THIFFAULT C, LANGSTON JW, CORY-SLECHTA DA & DI MONTE DA: Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol Dis* **10:** 119-127, 2002.

MEREDITH GE, SONSALLA PK & CHESSELET MF: Animal models of Parkinson's disease progression. *Acta Neuropathol* **115:** 385-398, 2008.

MIKLYA I, GOLTL P, HAFENSCHER F & PENCZ N: [The role of parkin in Parkinson's disease]. *Neuropsychopharmacol Hung* **16:** 67-76, 2014.

MURAKAMI K, MIYAKE Y, SASAKI S, TANAKA K, FUKUSHIMA W, KIYOHARA C, TSUBOI Y, YAMADA T, OEDA T, MIKI T, KAWAMURA N, SAKAE N, FUKUYAMA H, HIROTA Y, NAGAI M & FUKUOKA KINKI PARKINSON'S DISEASE STUDY G: Dietary intake of folate, vitamin B6, vitamin B12 and riboflavin and risk of Parkinson's disease: a case-control study in Japan. *Br J Nutr* **104:** 757-764, 2010.

PAN-MONTOJO F, ANICHTCHIK O, DENING Y, KNELS L, PURSCHE S, JUNG R, JACKSON S, GILLE G, SPILLANTINI MG, REICHMANN H & FUNK RH: Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. *PLoS One* **5:** e8762, 2010.

PARKINSON J: An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci* **14:** 223-236; discussion 222, 2002.

PENTTINEN AM, SULEYMANOVA I, ALBERT K, ANTTILA J, VOUTILAINEN MH & AIRAVAARA M: Characterization of a new low-dose 6-hydroxydopamine model of Parkinson's disease in rat. *J Neurosci Res*2016.

PEREZ RG, WAYMIRE JC, LIN E, LIU JJ, GUO F & ZIGMOND MJ: A role for alpha-synuclein in the regulation of dopamine biosynthesis. *J Neurosci* **22:** 3090-3099, 2002.

PICKRELL AM, PINTO M, HIDA A & MORAES CT: Striatal dysfunctions associated with mitochondrial DNA damage in dopaminergic neurons in a mouse model of Parkinson's disease. *J Neurosci* **31:** 17649-17658, 2011.

RAPPOLD PM, CUI M, CHESSER AS, TIBBETT J, GRIMA JC, DUAN L, SEN N, JAVITCH JA & TIEU K: Paraquat neurotoxicity is mediated by the dopamine transporter and organic cation transporter-3. *Proc Natl Acad Sci U S A* **108:** 20766-20771, 2011.

RODRIGUEZ-PALLARES J, PARGA JA, JOGLAR B, GUERRA MJ & LABANDEIRA-GARCIA JL: Mitochondrial ATP-sensitive potassium channels enhance angiotensin-induced oxidative damage and dopaminergic neuron degeneration. Relevance for aging-associated susceptibility to Parkinson's disease. *Age (Dordr)* **34:** 863-880, 2012.

ROELING TA, DOCTER GJ, VOORN P, MELCHERS BP, WOLTERS EC & GROENEWEGEN HJ: Effects of unilateral 6-hydroxydopamine lesions on neuropeptide immunoreactivity in the basal ganglia of the common marmoset, Callithrix jacchus, a quantitative immunohistochemical analysis. *J Chem Neuroanat* **9:** 155-164, 1995.

RUFFY R & LEONARD M: Chemical cardiac sympathetic denervation hampers defibrillation in the dog. *J Cardiovasc Electrophysiol* **8:** 62-67, 1997.

SADEGHI L, BABADI VY & TANWIR F: Manganese dioxide nanoparticle induces Parkinson like neurobehavioral abnormalities in rats. *Bratisl Lek Listy* **119:** 379-384, 2018.

SALARI S, ELIASSI AA & SAGHIRI R: Evidences on the existence of a new potassium channel in the rough endoplasmic reticulum (RER) of rat hepatocytes. *Physiology and Pharmacology* **15:** 16-26, 2011.

SALARI S, GHASEMI M, FAHANIK-BABAEI J, SAGHIRI R, SAUVE R & ELIASSI A:
Evidence for a KATP Channel in Rough Endoplasmic Reticulum (rerKATP Channel)
of Rat Hepatocytes. *PLoS One* **10:** e0125798, 2015.

SHERER TB, KIM JH, BETARBET R & GREENAMYRE JT: Subcutaneous rotenone
exposure causes highly selective dopaminergic degeneration and alpha-synuclein
aggregation. *Exp Neurol* **179:** 9-16, 2003.

TAN EK & SKIPPER LM: Pathogenic mutations in Parkinson disease. *Hum Mutat* **28:** 641-
653, 2007.

TANAKA K, MIYAKE Y, FUKUSHIMA W, SASAKI S, KIYOHARA C, TSUBOI Y,
YAMADA T, OEDA T, MIKI T, KAWAMURA N, SAKAE N, FUKUYAMA H,
HIROTA Y, NAGAI M & FUKUOKA KINKI PARKINSON'S DISEASE STUDY
G: Occupational risk factors for Parkinson's disease: a case-control study in Japan.
BMC Neurol **11:** 83, 2011.

THIFFAULT C, LANGSTON JW & DI MONTE DA: Increased striatal dopamine turnover
following acute administration of rotenone to mice. *Brain Res* **885:** 283-288, 2000.

THIRUCHELVAM M, BROCKEL BJ, RICHFIELD EK, BAGGS RB & CORY-SLECHTA
DA: Potentiated and preferential effects of combined paraquat and maneb on
nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease?
Brain Res **873:** 225-234, 2000.

THOMAS KJ & COOKSON MR: The role of PTEN-induced kinase 1 in mitochondrial
dysfunction and dynamics. *Int J Biochem Cell Biol* **41:** 2025-2035, 2009.

VALETTE H, DELEUZE P, SYROTA A, DELFORGE J, CROUZEL C, FUSEAU C &
LOISANCE D: Canine myocardial beta-adrenergic, muscarinic receptor densities
after denervation: a PET study. *J Nucl Med* **36:** 140-146, 1995.

VOSHAVAR C, SHAH M, XU L & DUTTA AK: Assessment of Protective Role of
Multifunctional Dopamine Agonist D-512 Against Oxidative Stress Produced by
Depletion of Glutathione in PC12 Cells: Implication in Neuroprotective Therapy for
Parkinson's Disease. *Neurotox Res* **28:** 302-318, 2015.

WIDER C, FOROUD T & WSZOLEK ZK: Clinical implications of gene discovery in
Parkinson's disease and parkinsonism. *Mov Disord* **25 Suppl 1:** S15-20, 2010.

XIANG C, WANG Y, ZHANG H & HAN F: The role of endoplasmic reticulum stress in
neurodegenerative disease. *Apoptosis* **22:** 1-26, 2017.

YUAN Y, TONG Q, ZHANG L, JIANG S, ZHOU H, ZHANG R, ZHANG S, XU Q, LI D, ZHOU X, DING J & ZHANG K: Plasma antioxidant status and motor features in de novo Chinese Parkinson's disease patients. *Int J Neurosci*2015.