Chapter 17

Animal Model of Parkinson Disease: Neuroinflammation and Apoptosis in the 6-Hydroxydopamine-Induced Model

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http://dx.doi.org/10.5772/intechopen.71271

Abstract

6-Hydroxydopamine (6-OHDA), a synthetic neurotoxin, has been used to generate animal models of Parkinson's disease (PD). Even though 6-OHDA induced neurodegenerative model in rat, it does not reproduce all the symptoms of the disease, but it does replicate most of the cellular processes such as oxidative stress, neurodegeneration, neuroinflammation and apoptotic neuronal death. The knowledge of the mechanisms involved in neurodegeneration is relevant to define possible therapeutic targets for PD.

Keywords: neurodegeneration, *substantia nigra pars compacta*, cellular stress, Parkinson's disease, therapy

1. Introduction

Parkinson's disease (PD) is a chronic-neurodegenerative disorder that presents motor and non-motor symptoms. The bradykinesia, resting tremor, rigidity and postural instability are caused by neurobiological defects [1]. PD affects a wide variety of nuclei in the central nervous system (CNS), including the dorsal motor nucleus of the vagus, nuclei of the Rafe, locus coeruleus, pontine peduncle nucleus, retrorubral nucleus, parabrachial nucleus, ventral tegmental area (VTA) and the *substantia nigra pars compacta* (SNpc) [2]. PD could be sporadic or due to genetic alterations (alpha-synuclein, parkin, PINK1, dardarin, and oxDJ-1). Despite the fact that PD is multifactorial; an indisputable sign of the disease is the

progressive degeneration of the dopaminergic neurons of the nigrostriatal pathway, neuroinflammation, the presence of Lewy bodies and generalized damage of the neuronal circuits that control the movement [3].

2. Animal models for PD

Cellular processes associated with PD such as oxidative stress, neurodegeneration, neuroinflammation and cell death, has been successfully evaluated in rat and mice. Till date, there exist two general types of experimental murine models: genetically manipulated and chemically induced.

2.1. Genetically manipulated

The induction of gene mutations, alterations in protein functionality and sub- or overexpression of proteins have generated models for PD. These innovative genetic engineering strategies have been developing for PARK2, alpha-synuclein, PINK1, and oxDJ-1. The results are diverse. For example, the genetic deletion of exon 3 of PARK2 in mice increases extracellular striatal dopamine contents but the DAT levels are decreased [4, 5]. These facts do not alter the nigrostriatal pathway because the number of dopaminergic neurons remains normal. A key factor for Parkinson's disease progression is the formation of Lewy bodies [6], due to which, α-synuclein has been incorporated as a gene or peptide to produce amyloid-like composed fibrils. Other strategy involves the incorporation of drugs to modify alpha synuclein aggregation in mice and in *in vitro* models [7, 8]. In mice, it causes dopaminergic neuronal death [2]. But the deleterious effect is dependent on the site of administration, type of particle (gene, peptides, and oligomers), dose, and molecular vector used.

2.2. Chemically induced

The most commonly used neurotoxins are: (a) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [9], which is converted to 1-methyl-4-phenylpyridinium (MPP+) by monoamine oxidase (MAO-B), (b) 6-hydroxydopamine (6-OHDA) [6, 10], (c) herbicides such as paraquat or rotenone [11] and (d) metals (manganese, iron) [12]. MPTP crosses the blood-brain barrier (BBB) [13], which in addition to cause damage to the nigrostriatal pathway, causes neuronal loss of the GABAergic neurons [14], catecholaminergic neurons (VTA, *locus coeruleus*, retrorubral nuclei) [15], reduction of serotonine receptor in the cortical and subcortical regions and reactive gliosis [16]. The toxicity of herbicides and metals is characterized by mitochondrial dysfunction due to peripheral and brain cellular stress [6, 17]. The neurotoxin 6-hydroxydopamine is more selective for the dopaminergic neurons of the SNpc [18, 19] because it causes specific degeneration of dopaminergic neurons in the SNpc [19–21] and does not cross the BBB. The advantages and limitations of 6-hydroxydopamine model are showed in **Table 1**.

Feature	Advantages	Limitations
Animal(s) used [6, 22]	The injection of 6-OHDA can be performed in rats (most common), mice, cats, guinea pigs, dogs and monkeys (uncommon)	None
Usage of the model [1, 20, 23, 24]	Unilateral (standardized and most common) or bilateral (uncommon) injection into the nigrostriatal pathway	None
Mode of administration [20, 25]	As the 6-OHDA does not cross BBB, intracranial injection by stereotaxis needs precise administrations on nigrostriatal pathway	Stereotaxis procedure needs special equipment
Type of lesion [20, 26]	Reproducible; retrograde; relatively progressive. Dose and site dependent	Cannot reproduce complete pathophysiology
Transporter mediated entry [13, 27]	Selective entry into the target using Dopamine transporter (DAT), can cause selective destruction of brain dopaminergic neurons	Noradrenaline transporter (NAT) mediated entry causes damage and destruction of brain noradrenergic neurons
Dopaminergic neuronal loss [6, 28]	More in SNpc, nucleus specific to dopaminergic neuronal population, than in VTA, nucleus containing glutamatergic neuronal populations, representing a good model for PD	Toxic for other catecholaminergic neurons
Progressive and age-dependent effects of PD [6, 22]	None	Absent due to acute neurodegenerative property of 6-OHDA injection
Circling motor behavior [12, 20]	Quantifiable depending on the dosage of methamphetamine or apomorphine injected and severity of the lesion; correlates with the magnitude of nigrostriatal lesions	None
Non-motor behavioral phenotypes [3, 6]	None	Causes cognitive, psychiatric and gastrointestinal disorders
Survival rate [27]	High survival	5 in 100 die due to lack of proper post-surgery recovery
Cellular process associated to the cytotoxicity [3, 13, 29–31]	Oxidative/nitrosative stress, apoptosis, autophagy, necrosis, neuroinflammation	No Lewy body formation

Table 1. Characteristics of 6-OHDA model.

3. Vulnerability of dopaminergic neurons to 6-OHDA

6-Hydroxydopamine (6-OHDA) is a highly oxidizable dopamine analog, which can be captured through the dopamine transporter (DAT) [25]. Till date, three mechanisms have been proposed to explain the cytotoxic effect of 6-OHDA: (1) intra- or extracellular auto-oxidation,

which favors the production of hydrogen peroxide, superoxide and hydroxyl radicals [13]; (2) formation of hydrogen peroxide by the effect of monoamine oxidase [32]; and (3) direct inhibition of the mitochondrial respiratory chain I complex [33].

These mechanisms can act independently or in combination to generate reactive oxygen species (ROS) [30]. Injection of 6-OHDA increases iron levels in the SNpc, which further induces the generation of ROS and cytochrome c release [13]. ROS and quinones derived from 6-OHDA diminishes the antioxidant capacity of the cell, resulting in oxidative damage to proteins, lipids and DNA [34]. Miyama and colleagues observed that 6-OHDA treatment decreased cellular glutathione content in a time-dependent manner before the oxidation of DJ-1 (oxDJ-1), a PD-related endogenous protein [35]. The oxidative stress generated can be amplified by the increase of free calcium in the cytoplasm, which is the product of glutamate excitotoxicity or by the loss of mitochondrial membrane permeability [36].

The dopaminergic neurons of the SNpc are vulnerable to oxidative stress induced by 6-OHDA, because they have increased basal levels of ROS, as well as low levels of glutathione peroxidase, an enzyme that reduces hydrogen peroxide to water [37]. The dopamine neurotransmitter has a high susceptibility to auto-oxidize and to become neuromelanin, which promotes the formation of hydroxyl radicals. This when combined with iron accumulated normally at high concentrations in dopaminergic neurons [3, 38], affects its elimination capacity. Also, during the oxidation of dopamine, several transient metabolites are formed such as dopamine o-quinone, aminochrome and 5,6-indolequinone [39]. These metabolites induce the formation of superoxide and adducts with several proteins like parkin [40, 41], tyrosine hydroxylase (TH) [42], glutathione peroxidase 4 [43] and several others. Indeed, it has been proposed that 5,6-indolequinone is the most reactive species that could form adducts with alpha-synuclein generating neurotoxic oligomers [7].

However, not all dopaminergic neurons of SNpc are vulnerable to 6-OHDA toxicity because there are subpopulations of dopaminergic neurons in SNpc expressing calcium-binding proteins such as calretinin and calbindin-D28k, which prevent the accumulation of intracellular calcium, avoiding the consequent excitotoxicity due to glutamate, and the cytotoxic action of 6-OHDA [44, 45]. The redox system plays an important role in protecting the dopaminergic neurons against oxidative stress. The thioredoxin and glutaredoxin systems directly mediate reduction of the 6-OHDA-quinone *in vitro* and protect neurons against dopamine-induced cell death [46].

4. 6-OHDA model

Ungerstedt and colleagues demonstrated that intracerebral stereotaxic injection of 6-OHDA causes degeneration of the nigrostriatal pathway [10]. To evaluate the 6-OHDA toxicity *in vivo*, three models of injury have been developed: (1) the medial forebrain bundle injection [47, 48], (2) the intranigral lesion [21, 49] and (3) the intra-striatal injury [20, 50–52]. Although injury to the medial forebrain bundle and the intranigral lesion is useful to demonstrate the immediate neurotoxic effects, it has the disadvantage of causing rapid and generalized degeneration of the injured nucleus [53], being unfavorable models to study the cell death type generated by long-term oxidative stress. However, the unilateral or bilateral intra-striatal model does cause

the progressive loss of dopaminergic neurons of the SNpc, emulating the nigrostriatal damage observed in PD (**Figure 1**) [23, 24, 54–56].

4.1. Intra-striatal model

Kirik and colleagues [20] described that the ventrolateral region of striatum in the rat that receives afferents from the motor and the sensorimotor areas of the cortex and exclusive innervations of the SNpc. The dorsomedial region of the striatum has a mixture of innervations of the SNpc, the VTA, the frontal cortical area and the limbic system. Therefore, 6-OHDA lesions involving the dorsomedial region have general effects on locomotion and drug-induced (such as amphetamine and apomorphine) rotational behavior, while lesions affecting the ventrolateral region show effects pronounced at the beginning of the movement, sensorimotor orientation and fine motor behavior [20]. In addition, they observed that a single dose given at one striatal site causes 80% reduction in striatal innervation, and a loss of about 90% of the nigral dopaminergic population; while the dose administered at several sites of the striatum generates damage in extra-striatal innervation [20]. The effect of intrastriatal injection depends on the site of injury and dose.

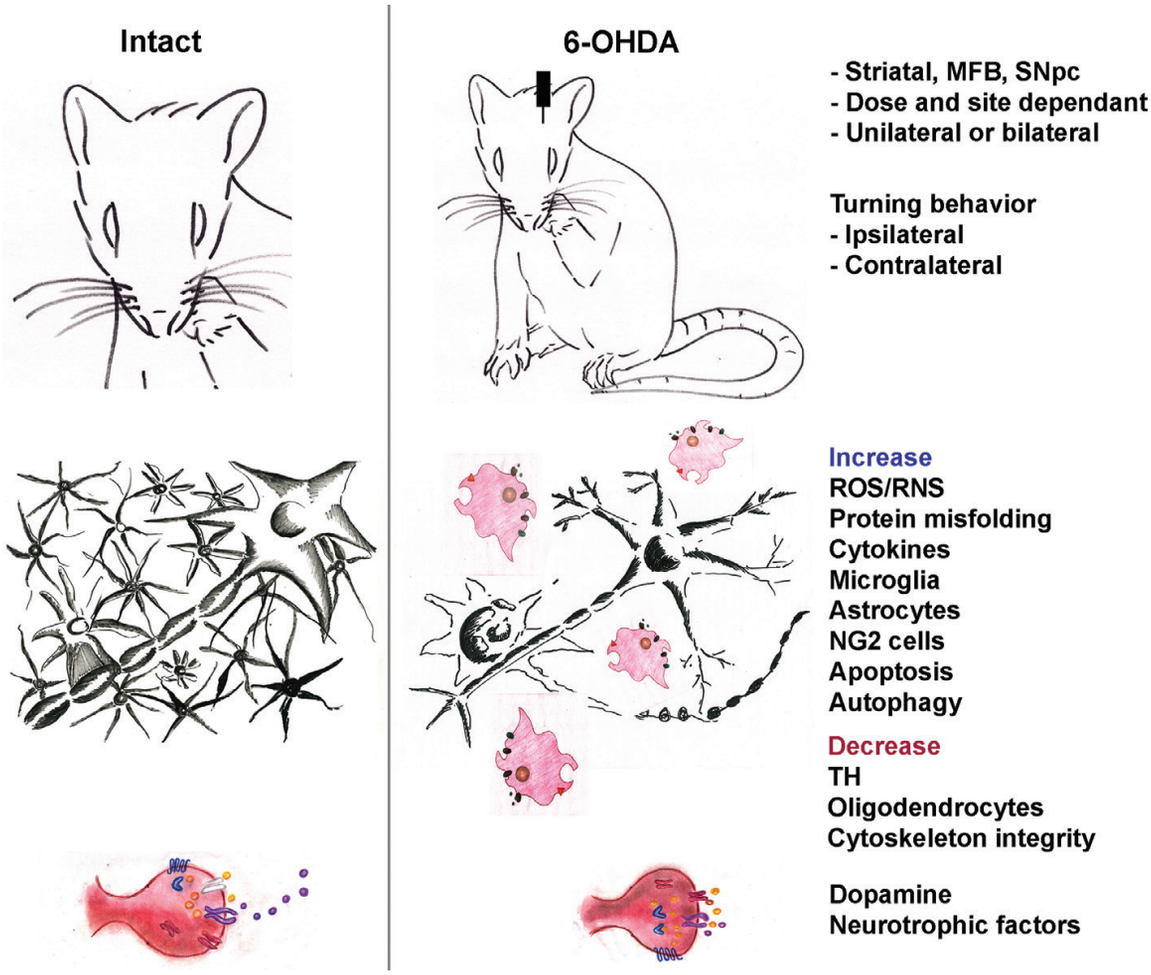

Figure 1. Overview of cellular processes promoted by 6-OHDA in rat.

The intra-striatal injection of 6-OHDA mainly affects dopaminergic neurons of the SNpc, and it also generates a reduction of dopaminergic neurons in the VTA, which form the mesolimbic pathway and innervate to the nucleus accumbens [28, 57]. The loss of dopaminergic neurons in the VTA does not exceed 20% of the population, and the damage does not progress over time, as observed in the SNpc. The 6-OHDA model does not replicate the presence of Lewy bodies [8], and for this reason, murine models with alpha-synuclein have been established. These approaches are based on gene knockout models [58], or gene overexpression [59] and intracerebral injection of alpha-synuclein [60]. These approaches might be the relevant in understanding the degeneration of the nigrostriatal pathway and its impact on other brain nuclei, but further research is still needed.

5. Neuroinflammation

Neuroinflammation in PD is characterized by microgliosis and astrogliosis increased around the dopaminergic neurons in SNpc [61]. These cellular process promotes high levels of expression of major histocompatibility complex type II (MHC-II) [62], chemokine receptors, integrins, neurotrophins and several other markers [63]. Elevated levels of pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), nitric oxide and reactive oxygen or nitrogen species (ROS/RNS) by NADPH oxidase system or by mitochondria are also observed in PD patients [31, 64]. Recently it has been demonstrated that copper-zinc superoxide dismutase (SOD1) released by microglial cells, or a TNF receptor 2 selective agonist, could confer neuroprotection against 6-OHDA toxicity *in vivo* [65, 66].

Injury of CNS leads to cell death, cellular swelling, excitotoxicity and the release of free radicals and nitric oxide, which triggers a strong glial response [67, 68] referred as reactive gliosis, involving the activation of microglia, astrocytes, oligodendrocytes and Neuron/glial 2 (NG2) cells [69, 70]. After injury, mature astrocytes proliferate and acquire stem cell properties suggesting their capacity to promote regeneration [71]. Depending on the stimulus and intensity of the lesion, all the three types of glia directs the cell either toward the neuroprotection by producing neurotrophic factors or toward the neurodegeneration by producing apoptotic mediators and ROS/RNS. However, NG2 cells, with their neurogenic [72], oligodendrogenic [73], astrogenic [74] and microgliogenic properties play indirect role in directing the cell toward apoptosis or protection. The presence of NG2-positive cells has been identified in SNpc but not in the striatum of the rat [75]. A recent study in a murine paradigm showed that conversion of NG2 cells to astrocytes to produce cerebral dopamine neurotrophic factor (CDNF) is anti-inflammatory in 6-OHDA-induced rat PD model [76]. However, studying the role, mode of activation and conversion of NG2 cells could give further clues to the field of neuroinflammation.

The neuroinflammatory process has been evaluated through glial cell markers such as glial fibrillary acidic protein (GFAP) for astrocytes [77, 78] and OX-42 or Iba-1 antibodies to microglia [79, 80]. The temporal course of activation of these glial populations has been determined by the neurotoxic effect, from day 3 post-injury [51], and even its activation was observed up to 3 weeks after injury with 6-OHDA [78]. The neuroinflammatory process to that precedes the death of nigral dopaminergic neurons (2 weeks post-injury) is probably a mechanism indicating

cell damage. Another body of evidence suggests that the increase in the activation of glial cells, and the consequent release of pro- and anti-inflammatory cytokines at the site of damage, could increase the cytotoxicity of 6-OHDA [26]. Overexpression of human alpha-synuclein in a mouse model of PD showed enhanced expression of proinflammatory cytokines and microglial activation [81]. Recently, the studies focused on NG2 cells, mitochondrial dysfunction or Lewy body accumulation (trend topic based in alpha-synuclein model) has been relevant to understand neuroinflammatory process and define alternative therapeutic targets for PD.

6. Apoptosis

The majority of studies indicated that apoptosis is the main type of cell death produced by 6-OHDA, but necrosis and autophagy contribute on neurodegenerative process also [29, 82, 83]. Given the variety of experimental models, it is not still possible to determine the proportion of dopaminergic neurons of the SNpc affected by one or other types of cell death. However, the convergence of several types of cell death could explain the time course of degeneration and the activation of the neuroinflammatory process [84].

Cell death has been highlighted as the final effect of 6-OHDA cytotoxicity. Several techniques are used to determine cell death type in dopaminergic neurons in rats (TUNEL, silver staining, and immunostaining to caspase-3, GSK-3β, Bax, Bad) [85–87]. Interestingly TUNEL technique is unspecific to identify apoptosis because on *in vitro* studies the 6-OHDA induces necrosis at same dose used *in vivo* [88, 89]. So the use of other apoptotic markers is recommended to show the loss of cellular integrity or specific chromatin condensation on the dopaminergic neurons of the SNpc [51].

Caspase-3 is the major effector caspase in neurons and its activation has been demonstrated by applying neurotoxins *in vitro* and *in vivo*. This cysteine protease is enrolled both in intrinsic and in extrinsic apoptotic pathway [90–92]. In *in vivo* studies, its presence has been evidenced 1 week after intra-striatal injection of 6-OHDA in rats [78, 93]. Most *in vivo* studies have demonstrated the expression of caspase-3 in different cell death models, suggesting that caspase-3 activation is involved in programmed cell death of the SNpc [92, 94, 95]. However, some recent studies are unable to confirm the presence of active caspase-3 or caspase-9 and, based on this, state that these caspases are not involved in the apoptosis of dopaminergic neurons of the SNpC [96, 97]. This controversy is further exacerbated by recent findings demonstrating the involvement of caspase-3 in non-apoptotic functions, such as the activation of microglia [98, 99]. Although most authors agree with the involvement of caspase-3 in the 6-OHDA-induced neurodegeneration, the doubt still remains if caspase-3 expression only leads to neuronal death. It has therefore been necessary to explore other markers of the apoptotic process and in this regard, scientists have highlighted the study and role of glycogen synthase kinase 3β (GSK-3β).

GSK-3β is involved in the signaling pathway of neuronal apoptosis activated by oxidative stress [100], a central factor in the neuropathological process of PD [101]. GSK-3β is activated by phosphorylation of the tyrosine residue 216 (Y216), located in the kinase domain and inactivated by the phosphorylation of serine 9 (S9) [100]. It was observed that a single dose of 6-OHDA administered in the neostriatum of the rat causes caspase-3 and GSK-3β expression,

loss of cytoskeletal integrity, TH levels decreased and activation of apoptotic process in dopaminergic neurons of SNpc [51, 85, 92].

Other authors demonstrated atrophy and progressive death of dopaminergic neurons dependent on translocation to the nucleus of the inducing factor of Apoptosis-inducing factor (AIF), in which there was no activation of caspase-3 or release of cytochrome C or signs of apoptosis. These researchers further demonstrate that death induced by 6-OHDA in dopaminergic neurons is mediated by activation of AIF-dependent Bax [97]. In this work, AIF activation suggests the involvement of regulated necrosis. The controversy between dependent or independent death of caspase-3 could be explained by the dose, study model and site of injury employed. However, since most evidence includes the involvement of caspase-3 in the 6-OHDA-induced apoptotic process, studies that contradict this fact suggest that 6-OHDA could also lead to neuronal death by apoptosis (independent of caspase-3) or other cell death processes (necrosis and autophagy) *in vivo*.

All the toxin-induced PD models had scant attention when it comes to the neuroprotective or regenerative strategies. Neuropathology and studies related to the correlation between inflammation and immune cells need to pay much more attention. It is of great interest to know the stimulus by which glial cells respond to the microenvironment and how do they decide whether to release neuroprotective or apoptotic mediators. It would be of interest to know if all the activated glial cells arise from a limited number of precursor cells or if all glia have equal potential to proliferate. It is also most important to study in detail about the types of receptors which are present on glial cells that play a major role in the field of neuroinflammation.

7. Relevance of 6-OHDA model in gene therapy

The 6-OHDA injury model has been used to demonstrate the benefits of neurotrophic therapy (NT) [102]. NT consists of directed delivery of genes encoding neurotrophic factors such as brain derived neurotrophic factor (BDNF) [103], glial cell line-derived neurotrophic factor (GDNF) [104–109], cerebral dopamine neurotrophic factor (CDNF) [76, 110], mesencephalic astrocyte-derived neurotrophic factor (MANF) [111], vascular endothelial growth factor (VEGF) [112] through nanoparticles [113, 114], or through viral or non-viral gene vectors [76, 104–107, 115]. The purpose of NT assessed in the 6-OHDA model is to prevent the progression of neurodegeneration and to stimulate the functional regeneration of the nigrostriatal system [116, 117]. The recovery of dopaminergic populations could improve motor function. It is therefore important to identify further underlying mechanisms of oxidative stress, neuroinflammation, neurodegeneration and neuronal death caused by 6-OHDA. This knowledge is the key to discovery novel therapies to treat PD.

8. Conclusion

The 6-OHDA model reproduces several cellular processes identified in the PD, therefore it is a key model to explore the molecular bases of cytotoxicity, as well as to study the cellular

processes activated by oxidative stress (neuroinflammation and neuronal death), and consequently a useful model to understand the mechanisms of novel therapies for PD.

Acknowledgements

This work was supported by Consejo Nacional de Ciencia y Tecnología (Cátedra CONACyT # 1840 for DHB) and the Instituto de Neuroetología from Universidad Veracruzana (DGI-174332015137 to MJRH). Special thanks to Nancy Gabriela Vazquez Ixtepan, Cesar Augusto Sandoval Vargas and Erick Hernandez Baltazar for the illustration resources.

Abbreviations

6-OHDA	6-hydroxydopamine
AIF	apoptosis-inducing factor
BBB	blood–brain barrier
BDNF	brain derived neurotrophic factor
CDNF	cerebral dopamine neurotrophic factor
CNS	central nervous system
COX2	cyclooxygenase 2
DAT	dopamine transporter
GDNF	glial cell line-derived neurotrophic factor
GFAP	glial fibrillary acidic protein
GSK-3	glycogen synthase kinase-3
Iba-1	ionized calcium binding adaptor molecule 1
iNOS	inducible nitric oxide synthase
MANF	mesencephalic astrocyte-derived neurotrophic factor
MHC-II	major histocompatibility complex type II
MPP+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
NADPH	nicotinamide adenine dinucleotide phosphate
NAT	noradrenaline transporter
NG2	neuron/glial 2

NT	neurotrophic therapy
OX-42	CD11b antibody (integrin, alpha M)
oxDJ-1	oxidized DJ-1 protein
PD	Parkinson's disease
PINK1	PTEN-induced putative kinase 1
ROS	reactive oxygen species
ROS/RNS	reactive oxygen or nitrogen species
S9	serine 9
SN	*substantia nigra*
SNpc	*substantia nigra pars compacta*
SOD1	superoxide dismutase 1
TNF	tumor necrosis factor
TUNEL	terminal deoxynucleotidyl transferase mediated X-dUTP nick end labeling
VEGF	vascular endothelial growth factor
VTA	ventral tegmental area
Y216	tyrosine residue 216

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