Chapter

Neurodegenerative Diseases and Their Therapeutic Approaches

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Abstract

Alzheimer's disease and Parkinson's disease are characterized as a chronic and progressive neurodegenerative disorder and are manifested by the loss of neurons within the brain and/or spinal cord. In the present chapter, we would like to summarize the molecular mechanism focusing on metabolic modification associated with neurodegenerative diseases or heritable genetic disorders. The identification of the exact molecular mechanisms involved in these diseases would facilitate the discovery of earlier pathophysiological markers along with substantial therapies, which may consist (of) mitochondria-targeted antioxidant therapy, mitochondrial dynamics modulators, epigenetic modulators, and neural stem cell therapy. Therefore, all these therapies may hold particular assurance as influential neuroprotective therapies in the treatment of neurodegenerative diseases.

Keywords: neurons, mitochondria-targeted antioxidants, mitochondrial dynamics, epigenetic regulations, stem cell, neurodegenerative diseases

1. Introduction

1.1 What are neurons?

Neurons or nerve cells are the functional unit of the brain and nervous system, and they produce electrical signals known as action potentials. Action potentials permit them to speedily pass on the details over long distances. Their connections define who we are as a person. The creation of new neurons in the brain is known as neurogenesis [1].

1.2 Anatomy of a neuron

Different types of neurons may differ in a number of ways, but they all include three distinct regions with differing functions, that is, the cell body (soma), followed by the dendrites, the axons, and the connected axon terminals (**Figure 1**).

a. Cell body: It is the place of biogenesis of almost all neuronal proteins and membranes. It contains a nucleus.

b. Dendrites: The extensions of neurons that receive signals and conduct them toward the cell body (soma) are known as dendrites.

c. Axon (nerve fiber): The extensions of neurons that conduct the signals away from the cell body to the other nerve cells or neuron are known as axons.

d. Axon terminal (end-plate): The end part or terminal part of axons that makes a synaptic contact with other nerve cells is known as an axon terminal. It is responsible for the initiation of transmission of nerve impulse to another nerve cell [2].

1.3 Functions of neurons

a. Conduction and transmission of nerve impulses

b. Initiation and conduction of action potential

c. Synaptic transmission [3]

1.4 How neurons transmit information throughout the body?

Neurons converse with other neurons through axons and dendrites. When a neuron receives information from another neuron, it transmits an electrical signal along the length of the respective axon, known as action potential. At the axon terminal, the electrical signal is changed into chemical signal. The axon releases chemical messengers called neurotransmitters. The neurotransmitters are released into the gap between the axon terminal and the tip of a dendrite (receptor site) of a further neuron. The space between the axon terminal and the tip of a dendrite is called a synapse. The neurotransmitters travel along the short distance through the synaptic gap to the dendrite. The dendrite receives the neurotransmitters and translates the chemical signal into electrical signal. This electrical signal travels all the way through the neuron, to be converted back into a chemical signal when it gets to adjoining neurons [4].

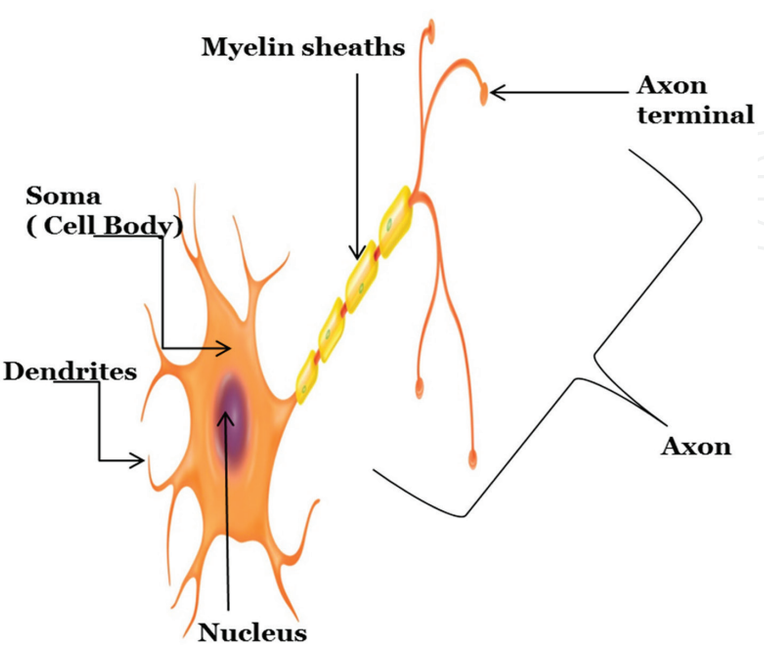

Figure 1.
Anatomy of neuron.

2. Neurodegenerative diseases

Etymologically, the word neurodegeneration comprises of "neuro," which refers to neurons, and "degeneration," which refers to the process of losing structure and/or function of either tissues or organs [5]. A neurodegenerative disease is considered as a slow, progressive failure of nerve cells within the central nervous system (CNS). This leads to deficits in particular brain functions like learning, movement, and cognition generally performed by the CNS (brain and spinal cord).

2.1 Factors associated with neurodegenerative diseases

a. Aberrant protein dynamics with aggregation and degradation of defective protein [6]

b. Oxidative stress and reactive oxygen species (ROS) formation

c. Impaired bioenergetics and mitochondrial dysfunction

d. Excessive exposure to metals and pesticides (**Figure 2**)

2.2 Classification based on molecular defects

a. Trinucleotide repeat diseases: HD, spinal cerebellar atrophy, and myotonic dystrophy [7].

b. Prion diseases: Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and fetal familial insomnia [8].

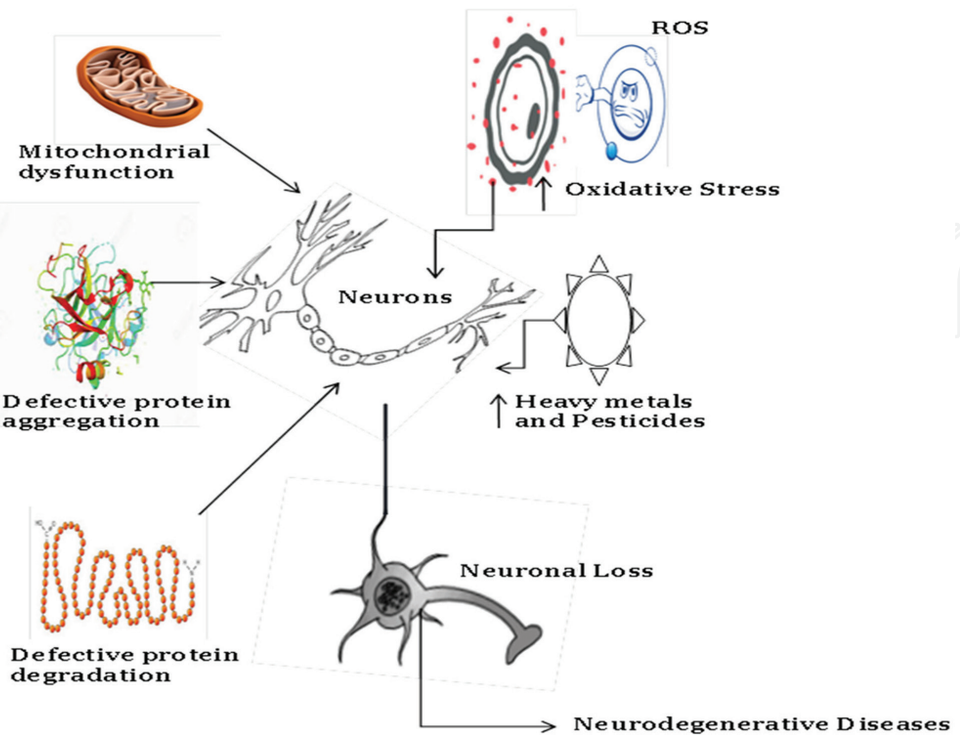

Figure 2.
Factors associated with neurodegenerative diseases.

c. Synucleinopathies: PD, progressive supranuclear palsy and diffuse Lewy body dementia [9].

d. Tauopathies: Corticobasal degeneration, frontotemporal dementia with parkinsonism linked to chromosome 1\(FTDP-17), and pick disease [10].

3. Alzheimer's disease

Alzheimer's disease (AD) is an irreparable, progressive neurodegenerative disease that affects normal brain functioning [11]. It is mainly the general cause of dementia [12]. Dementia is a syndrome associated with memory loss and loss of abilities like thinking, reasoning, and language skills along with other mental illness [12].

3.1 History

This disease is named after Dr. Alois Alzheimer. He observed some brain tissue abnormalities in an old woman who died due to some unusual mental illness. Later, he examined her brain and found many abnormal tangled bundles of fibers (called as tau tangles, neurofibrillary) and clumps (called as amyloid plaques). That is how he found the cause of AD [13].

3.2 Causes

The cause of AD is not clearly understood.

a. Genetic: Nearly, 70% of the cases are related to genetic factors with the involvement of many specific genes [14].

1. Autosomal dominant inheritance: Also known as early-onset familial AD [15], it occurs due to the mutation in one of the three genes: Presenilin 1, presenilin 2, or amyloid precursor protein (APP) [16].

   Aβ42: A protein that is the main component of senile plaques, and the levels are increased due to mutation in APP and presenilin genes [17].

2. Sporadic Alzheimer's disease: In this type of AD, genetic and environmental factors play a major role.

   Example: Inheritance of the epsilon 4 allele of the apolipoprotein E (APOE) [18, 19].

b. Cholinergic hypothesis: The cholinergic hypothesis states that AD is caused by the reduced synthesis of neurotransmitter acetylcholine [20].

c. Amyloid hypothesis: The amyloid hypothesis states that AD is caused by the deposits of extracellular amyloid beta (Aβ) [21].

d. Tau hypothesis: The tau hypothesis states that AD is caused due to abnormalities in tau protein, leading to the disintegration of microtubules in nerve cells [22, 23].

3.3 Molecular mechanism

(a) Proteopathy: AD has been recognized by plaque formation occurring due to abnormal folding of amyloid beta (Aβ) protein and tau protein in the nerve cells

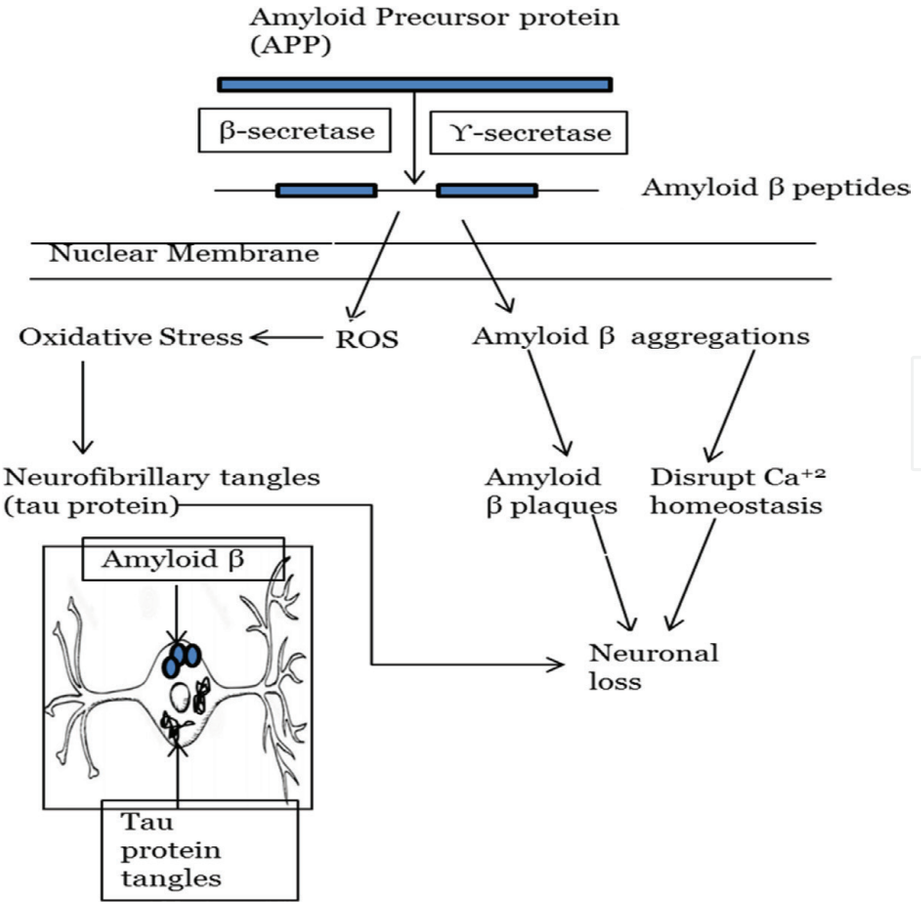

Figure 3.
Molecular mechanism of AD.

(brain) leading to the degeneration of nerve cells [24]. The amyloid precursor protein (APP) leads to the formation of Aβ. APP plays an important role in neuron-like developments and post-injury repair mechanism and survival [25, 26]. In AD, secreting enzymes like β-secretase and γ-secretase together will break down APP into small fragments that penetrate through the neuron membrane [27]. This leads to the formation of Aβ fibrils that later cluster together to form senile plaques and deposits in the outer side of neurons [28, 29]. Aggregated amyloid fibrils accumulation leads to the disruption of cell's calcium ion homeostasis, which results in apoptosis [30] (**Figure 3**).

(b) Tauopathy: In AD, there is an abnormal accumulation of tau protein. Upon phosphorylation, tau protein stabilizes the microtubules, and it is known as microtubule-associated protein. Tau protein undergoes certain chemical changes, and becomes hyperphosphorylated. This leads to the formation of neurofibrillary tangles upon aggregation with other threads, which results in decaying the neurotransport system [31].

3.4 Therapeutic approaches

3.4.1 Mitochondrial-directed therapies

Decline of N-acetyl aspartate and creatine is associated with dementia [32]. Supplementation of creatine was found to protect neurons in AD [33]. In hippocampal neurons, administration of creatine defends against glutamate and Aβ toxicity in rats [34].

In AD patients, administration of lipoic acid (600 mg/day) [LA - an antioxidant; coenzyme for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase]

stabilizes the cognitive measures [35, 36]. Decreased oxidative stress of mitochondria in fibroblasts was found in AD patients due to LA and/or N-acetyl cysteine (antioxidant and glutathione precursor) administration [37].

CoQ10 (an antioxidant and cofactor of the electron transport chain) blocks apoptosis by inhibiting the permeability transition pore (PTP) of mitochondria [38]. Treatment of CoQ10 neutralizes the brain mitochondrial alterations made by amyloid-β1–40 [39]. CoQ10 was shown to protect paraquat and rotenone-induced mitochondrial dysfunction and neuronal death in SHSY-5Y cells (human neuroblastoma cells) and primary rat mesencephalic neurons, [40, 41]. In R6/2 mice, combined treatment of CoQ10 and minocycline reduces HTT accumulation, brain atrophy, and striatal neuron atrophy [42].

MitoQ (mitochondrial coenzyme Q) reduces oxidative stress and prevents mitochondrial dysfunction [43]. Oral administration of MitoQ (1 mg/kg body weight) showed better pharmacokinetics behavior with plasma (Cmax = 33.15 ng/ml and Tmax = 1 hr.) in Phase I trial (Antipodean Pharmaceuticals Inc., San Francisco, CA).

3.4.2 Stem cell therapy

Neural stem cell therapy provides a potential to neurons derived from stem cells to integrate with existing neuronal network of the host brain [44]. In animal models, stem cell transplantation elevates the level of acetylcholine, resulting in an improved cognitive and memory function. Stem cells secrete neurotrophic factors, which modulate neuroplasticity and neurogenesis [45, 46].

Embryonic stem cells (ESCs)-derived neuron progenitor cells (NPCs) when transplanted into an amyloid-β injured in vitro model, after 2 weeks of amyloid-β injection, showed an increased escape latency when compared with phosphate-buffered saline-treated controls [47]. It has been reported that ESCs-derived NPCs improve memory impairment in AD models [48].

Human induced pluripotent stem cell (iPSC) therapy delivers a possible strategy for drug development against AD [49]. Neurons differentiated from iPSCs increase the secretion of amyloid-β42 as it is affected by γ-secretase inhibitors [50].

Bone marrow (BM)-derived mesenchymal stem cells (MSCs) play an important role in the removal of amyloid-β plaques from the hippocampus [51]. Human MSCs promoted amyloid-β clearance and enhanced autophagy and neuronal survival in an amyloid-β-treated mouse model [46]. Transplantation of adipose-derived MSCs (AMSCs) into AD brain improved the acetylcholine levels along with microglia activation and cognitive functions [52, 53]. In a transgenic mouse model, human umbilical cord-derived MSCs differentiated themselves into neuron-like cells, and these cells when transplanted into an amyloid-β precursor protein (AβPP) and PS1 (AβPP/PS1) resulted in improved cognitive function and decreased amyloid β deposition [54].

3.4.3 Epigenetic modulators

Histone deacetylases have been linked to AD. Treatment with HDACi (histone deacetylase inhibitors) induced dendrite growth, increased the number of synapses, and restored learning and memory deficits in mice with AD [55] (**Table 1**).

3.4.4 Mitochondrial dynamics modulators

Two recent studies have also shown the protective effects mediated by inhibition of mitochondrial fission via Drp1 deficiency on mitochondria and neurons in tau and APP transgenic animal models for AD [60, 61].

HDACi	Function	References
Sodium butyrate	In neuroblastoma cells, it induces phosphorylation of tau protein and programmed cell death resulting in restoring memory.	[56]
Phenylbutyrate (4-PBA)	InTg2576 mouse model, 4-PBA restores fear learning and rescues dendritic spine losses that are associated with memory shortage.	[57]
Suberoylanilide hydroxamic acid	In mutant mice model, systemic treatment restores contextual memory	[58]
Resveratrol (activator of class III HDAC)	In in vivo and in vitro studies, SIRT1 reduces the amyloidogenic processing of APP	[59]

Table 1.
Histone deacetylase inhibitors and their respective functions in AD.

4. Parkinson's disease

Parkinson's disease (PD) is a progressive, long-term neurodegenerative disorder that affects the motor neurons [62]. It is caused by a loss of neurons in the brain part known as substantia nigra leading to a reduction in a neurotransmitter called dopamine [62].

4.1 History

In 1817, James Parkinson (before known as Jean-Martin Charcot) published an essay named "Shaking Palsy" describing six cases of paralysis agitans showing certain characteristics of this disease [63, 64].

In 1865, William Sanders termed this disease as Parkinson's disease [65].

4.2 Causes

The following are the causes of PD:

(a) Environmental factors: Exposure to metals, solvents, and pesticides, or any head injuries are considered to be a factor for the onset of PD [66, 67].

(b) Genetics: Few percent of cases are developing this disease due to mutation in one specific gene out of several genes related to PD (**Table 2**).

4.3 Molecular mechanism

The mechanism involved in the development of PD includes various factors like the aggregations of misfolded proteins, activation of protein degradation

	Name	Gene	References
Autosomal-dominant PD	PARK1/PARK4	SNCA (α-synuclein)	[68, 69, 72]
	PARK2	Parkin	[68, 69, 72]
	PARK5	UCHL	[68, 69, 72]
	PARK8	LRRK2	[68, 69, 72]
Autosomal-recessive PD	PARK6	PINK1	[68, 70–72]
	PARK7	DJ-1	[68, 70–72]

Table 2.
Genes involved in PD.

pathways, mitochondrial damage, and oxidative stress, along with certain gene mutations [73–75].

4.3.1 Aggregation of misfolded proteins

- Accumulation of Lewy bodies in dopamine neurons of the substantia nigra pars compacta [75]
- Hyperphosphorylation of tau protein causes accumulation of neurofibrillary tangles [76]

4.3.2 Protein degradation pathways

- Ubiquitin-proteasome system (UPS): It is responsible for the degradation of misfolded or damaged proteins in the cytosol, nucleus, or endoplasmic reticulum (ER) [77]. Impairment in this system leads to aggregation of misfolded amyloid proteins (Lewy bodies) [78]. Other proteins like UCH-L1 and Parkin are involved in the degradation of misfolded α-synuclein [79]
- Chaperones (heat shock proteins/HSP): Chaperones undergo dysfunctioning in PD, as they play a vital role in cell-defense mechanism involved in protein degradation and folding of proteins. Major HSPs involved are HSP 26, HSP40, HSP 60, HSP 70, HSP 90, and HSP 100 [80]. HSPs aggregate with α-synuclein or tau protein and form insoluble structures resulting in reduced toxicity of α-synuclein or tau protein [81, 82]
- Autophagy-lysosomal pathway (ALP): It serves to clear Lewy bodies in PD acting as an alternative clearance mechanism for proteins [83, 84]. Chaperone-mediated autophagy (CMA) helps in the degradation of α-synuclein by selectively translocating into lysosomes [83]. Therefore, dysfunctioning of CMA decreases the efficiency of α-synuclein, leading to excessive accumulation of this protein. This results in impaired neuronal activity as observed in PD [73, 85]. Failure of formation of autophagosome, its inability to bind with lysosomes due to deficiency of lysozymes, or dysfunction of HSP70 results in dysfunction of ALP in PD [73, 85] (**Figure 4**)

4.3.3 Damage to mitochondria and oxidative stress

- Abnormality of complex-I in mitochondria directly interferes with ATP production in the cell, resulting in cell death [86]. Monoamines such as dopamine are cleaved by monoamine oxidase-B (MAO-B) and combined with oxygen-forming reactive oxygen species (ROS) [87]. Increased oxidative stress was observed in PD.

4.3.4 Genetic mutations

The most common genes related to PD are α-synuclein, DJ-1, PINK1, and Parkin [88] (**Table 3**).

4.4 Therapeutic approaches

4.4.1 Mitochondria-directed therapies

Administration of creatine increases tyrosine hydroxylase immunoreactive fiber density and soma size of dopaminergic neurons in mesencephalic cultures by protecting against neurotoxic insults induced by serum and glucose deprivation, MPP+, and 6-hydroxydopamine [33, 92]. It has been reported that dopamine loss was prevented by administration of creatine. In substantia nigra, creatine also

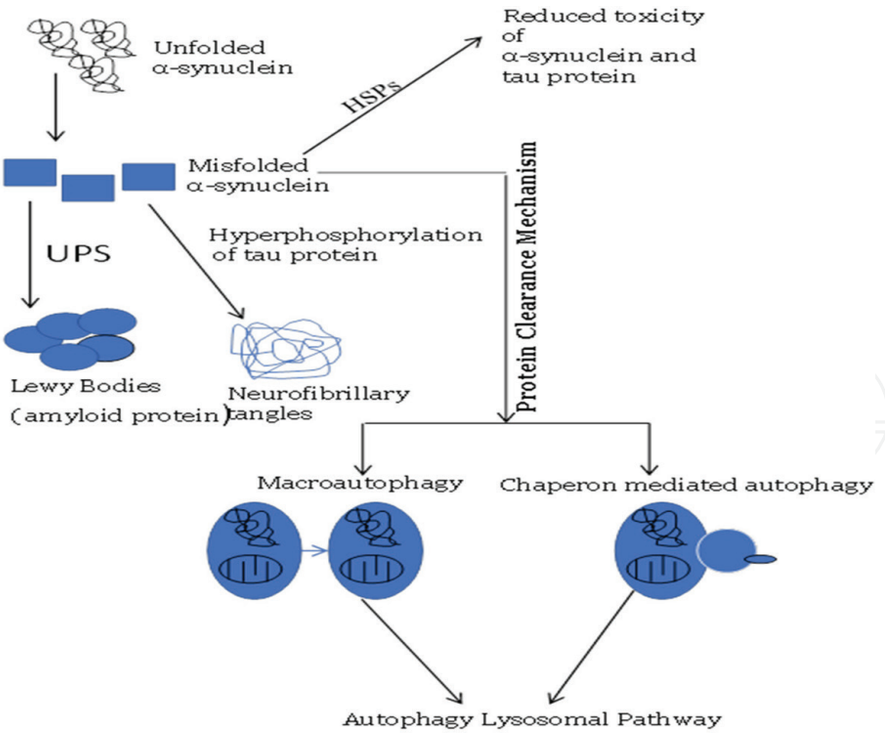

Figure 4.
Molecular mechanism of PD.

Genes	Dysfunction	References
α-synuclein	Aggregation of misfolded amyloid proteins	[89]
Parkin	Aggregation of misfolded amyloid proteins within SNpc	[89]
DJ-1 (PARK7)	Activities like transcriptional regulation, antioxidants, chaperone, and protease are dysregulated	[90]
PINK1 (PARK6)	Mitochondrial dysfunctioning Degeneration of substantia nigra neuron	[91]

Table 3.
Specific gene mutations and their dysfunction involved in the development of PD.

reduces loss of neuron in the mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [93].

CoQ10 protects against iron-induced apoptosis in dopaminergic neurons [94]. In vitro, CoQ10 exerts anti-amyloidogenic effects by disrupting preformed amyloid-β fibrils [95].

SS peptides (Szeto Schiller) act as antioxidants that target mitochondria in an independent manner. In mice, reports showed that SS-20 and SS-31 provide protection against MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) neurotoxicity. SS-31 provides protection against dopamine loss in the striatum. In substantia nigra, SS-31 also provides protection against the loss of tyrosine hydroxylase immunoreactive neurons. In MPTP-treated mice, SS-20 provides potential neuronal protection on dopaminergic neurons in PD [96].

4.4.2 Stem cell therapy

In the first trial of cell-based therapy, post-mitotic dopamine neuroblasts isolated from human embryonic mesencephalic tissue have been successfully grafted in PD patients [97]. It has been confirmed through increase in 18F-dopa intake,

detected through positron emission tomography (PET) [98, 99]. The grafts restore dopamine release. Disadvantages of this therapy are limited tissue availability and grafts standardization.

Recently, researchers have shed light on stem cell therapy. The production of dopamine neuroblasts from stem cells for transplantation in PD patients has been focused on. The aim was to release dopamine in a stable manner and exhibit the electrophysiological, molecular, and morphological properties of substantia nigra neurons [100, 101]. In clinical trials, it has been found that dopaminergic cells derived from embryonic stem cells can survive and reverse behavioral deficits after transplantation in PD animal models [102, 103].

4.4.3 Epigenetic modulators

In sporadic PD patients, there is an increased α-synuclein expression in dopaminergic neurons, which is linked with α-synuclein hypomethylation [104]. In familial PD patients, decreased histone acetylation is linked with increased α-synuclein levels [105]. In vitro model, mutation in α-synuclein leads to increased histone acetylation mediated through HDAC Sirt2. Treatment of Sirt2 siRNA resulted in decreased α-synuclein-mediated toxicity [106]. Administration of levodopa elevated the dopamine level, which partially showed decreased symptoms of PD.
It is correlated with deacetylation of H4K5, K12, and K16 [107].

4.4.4 Mitochondrial dynamics modulators

Recombinant adeno-associated virus expressing the dominant negative Drp1 (dynamin-related protein 1) mutant or Mdivi-1, a small molecular inhibitor of Drp1, has been reported to inhibit mitochondrial fragmentation, restore dopamine release, and prevent dopamine neuron loss in PD animal models [108].

Activation of DRP1-mediated mitochondrial fission is an important contributing factor in the progression of PD. Neurons lacking PINK or Parkin accumulate DRP1, resulting in excessive mitochondrial fission, increased oxidative stress, and reduced ATP production [108, 109]. These defects can be reversed by the inhibition of mitochondrial fission with the use of mdivi-1, an inhibitor of the DRP1 pathway, or by overexpression of MFN2 (Mitofusin 2) or OPA1 (Optic atrophy protein 1) [109, 110].

In vitro models of glutamate-toxicity or OGD (oxygen-glucose deprivation) in mouse hippocampal neurons or in vivo mouse models of transient focal ischemia can be protected from enhanced mitochondrial fission and apoptosis by DRP1 knockdown or mdivi-1 inhibition [111, 112].

5. Conclusion

The recent advancements in the field of neurodegenerative diseases like AD and PD are based on targeting the degenerative progressions that lead to the death of neurons. The death of neurons leads to irreversible neuropathological conditions, making it difficult to be functional in humans. Because of the intricacy involved in respective neurodegenerative diseases, researchers have identified few potential biomarkers. At present, many therapeutic approaches have been suggested to treat the symptoms of both neurodegenerative diseases. Yet there exists a lacuna for the effective therapies. Hence, few therapeutic approaches like mitochondria-targeted antioxidant therapy, mitochondrial dynamics modulators, epigenetic modulators, and neural stem cell therapy may prove to have a potential in treating AD and PD.

Conflict of interest

Authors have no conflict of interest to declare.

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