Раздел I

КЛИНИЧЕСКИЕ АСПЕКТЫ ЗДРАВООХРАНЕНИЯ

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THEORIES BEHIND PARKINSON DISEASE

SUMMARY

The last century has seen a significant rise in life expectancy at birth among developed countries as people, on average, are living longer compared to prior generations. Longer life has also led to corresponding increases in chronic, neurological impairments such as Parkinson disease (PD). PD has been identified as the second most prevalent age-related neurodegenerative disease in the world. There are over 5 million people estimated to have the PD world-wide, constituting 1 % of the world's population of those 60 years and older. Global prevalence of PD is 60-187 cases for 100,000. The majority of people develop the clinical symptoms of PD over 60 years of age, with those over 80 accounting for 95 % of all cases. With an expected increase of 2.1 billion people over the age of 60 world-wide by 2050 and thus there will come a corresponding increase of people with PD and an ever-growing challenge to more effectively diagnosis, treat and manage symptoms while maintaining an optimal quality of life of those affected. Despite the great amount of research, the pathological mechanisms behind PD-associated selective dopaminergic neurodegeneration still remain largely unknown. Therefore, this article aims to review the current theories of P

Introduction. The last centuru has seen a significant rise in life expectancy at birth among developed countries as people, on average, are living longer compared to prior generations. Longer life has also led to corresponding increases in chronic, neurological impairments such as Parkinson disease (PD). PD has been identified as the second most prevalent age-related neurodegenerative disease in the world [61].There are over 5 million people estimated to have the PD world-wide, constituting 1 % of the world's population of those 60 years and older [64]. Global prevalence of PD is 60-187 cases for 100,000 [39]. The majority of people develop the clinical symptoms of PD over 60 years of age, with those over 80 accounting for 95 % of all cases [39]. With an expected increase of 2.1 billion people over the age of 60 world-wide by 2050 [16]and thus there will come a corresponding increase of people with PD and an ever-growing challenge to more effectively diagnosis, treat and manage symptoms while maintaining an optimal quality of life of those affected. Despite technological progress, the exact molecular trigger that induces selective dopaminergic degeneration is not known. Huge amount of research suggests that oxidative stress, genetic predisposition, environmental toxins and ageing appear to be main players that underlie the pathological mechanisms. Therefore, this article, will describe shortly the biochemistry of oxidative stress, some sources of ROS such as dopamine, ageing and neuroinflammation, a-synculein as well as some genetics and in the oxidative theory of PD.

The biochemistry of ROS generation in dopaminergic neurons.Oxygen is essential for life, but damaging oxidative processes are the dark side of the Moon, as an activation of molecular

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oxygen underlies the chemical origin for the generation of free radicals therefore every living organism should be able to balance between the production of free radicals and detoxification of the reactive intermediate species in order to prevent further cellular damage [57]. Reactive oxygen species (ROS) such as the superoxide anion radical ($O2^{2-}$), hydroxyl radical (·OH) and hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) represent some examples of toxic free radicals produced as by-products of essential chemical reactions [41]. Superoxide anion ($O2^{2-}$) is constantly generated by mitochondrial electron transport chain complexes I and III as well as by peroxisomes, containing catalase; moreover, it easily crosses the inner mitochondrial membrane where it can be reduced into hydrogen peroxide (H_2O_2) [24]. Hydrogen peroxide is further reduced to water (H_2O), but when the catalases within the peroxisomes are not functioning properly, chemically reactive H_2O_2 leaks into the cytosol where it can be interact with highly reactive reduced metal ions such asferrous iron (Fe^{2+}) and beconverted to highly reactive ·OH, in so-called Fenton reactionwhich interferes and damages the cellular physiology [57].

Dopamine as a source of oxidative stress. The symptoms of PD are mainly associated with selective dopaminergic neurodegeneration in the basal ganglia leading to the dopamine deficiency in the brain. Dopamine is synthesized by tyrosine hydroxylase, monoamine oxidase-A and B (MAO-A and MAO-B respectively) as well as catechol O-methyl transferase (COMT). Dopamine is sequestered in storage vesicles via vesicular monoamine transporter 2 (VMAT 2) and it is re-uptaken back from synaptic clefts by dopamine transporters (DAT) [40]. Thus, some research showed that when VMAT2 or DAT is not functioning properly, there is greater amount of free dopamine and thus higher amount of free radicals species [17]. The excessive amount of dopamine is catalyzed in cytosol by deamination as well as MAO-A in catecholaminergic neurons regulates the dopamine levels through oxidative metabolism [44]. However, under the pathological conditions, MAO-B becomes a predominant enzyme to metabolize dopamine into 3,4-dihydroxyphenyl-acetaldehyde, an ammonium molecule and H_2O_2 [46] which in turn lead to a progressive neurodegeneration of dopaminergic neurons [42]. Dopamine quinones can cyclize leading to a highly reactive aminochrome generation resulting in depletion of cellular NADPH and $O2^{2-}$ generation [27]. Furthermore, aminochrome can interfere with α-synuclein and trigger neuroinflammation[48]. Moreover, an increasing amount of evidence shows that oxidative stress and mitochondrial dysfunction ultimately can lead to the cell death. Particularly, an immunohistochemical study of postmortem brain tissue of PD patients showed an increased amount of 4-hydroxynonenal protein (HNE, a by-product of lipid peroxidation), which in turn suggests that oxidative stress contribute to the dopaminergic cell death in these patients [57,67]. Moreover, it was also shown that other by-products of oxidative processes such as carbonyl modifications of soluble proteins, DNA and RNA oxidation products 8-hydroxy-deoxyguanosine and 8-hydroxy-guanosine were also elevated in the PD patients compared to the healthy age-matched control groups [17]. Moreover, animal-based studies with modeling motor aspects of PD also show that there might be a link between amount of oxidative stress and dopaminergic neurons degeneration. For instance, environmental toxins such as 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) [51], rotenone [60], 1, 1'- dimethyl-4, 4'-bipyridinium dichloride (paraquat) [20], and 6-hydroxydopamine (6-OHDA) [7] were shown to induce motor-aspects of PD in animals-based studies of the disease. These substances can interfere with neuronal physiology and thereby lead to mitochondrial dysfunction, disruptions in the dopamine metabolism and neuroinflammation, which in turn can result in the neuronal cell death.

Neuroin flammation as a source of ROS. Microglia is a brain innate immunological system. Microglia arephaogocytic cells that under the physiological conditions are resting, but become immediately activated after the injury or the presence of pathological agents [29]. Activated microglia produce NO and $O2^{2-}$ which in turn helps to eliminate pathological agents. Increased amount of activated microglia, T lymphocytesand pro-inflammatory mediators were detected in the brain and cerebrospinal fluid of PD patients [50]. Nevertheless, microglia represents a double-sided sword as from one hand it is neuroprotective as it has high levels of glutathione peroxidase that protects from oxidative stress. On the other hand, microglia is a source of free radicals that can induce and promote neurodegeneration [29]. Quite

interestingly, environmental factors such as MPTP and rotenone, 6-OHD also induced microglial activation in SN [30]. Degenerating dopaminergic neurons also activate microglia by releasing oxidized proteins, lipids and fragmented DNA. The midbrain contains more microglial cells comparedto other brain regions, thus activation of microglia leads to selective damage of dopaminergic neurons [52]. Therefore there exists a vicious cycle that not only induces but also promotes further degeneration of cells.Several studies have suggested alink between the innate inflammatory response of the central nervous system and theperipheral immune system, particularly, increased concentrations of neuroinflammatory markers,such as IL-2, IL-6, TNF-alpha, osterpontin and RANTES/chemokine (C-C motif) ligand 5has even been detected in the serum of PD patients [21]. However, there are no in-vivo studies to show oxidative stress being a key trigger in the neurodegeneration. Nevertheless, these preliminary results raise the hypothesis that the loss ofdopaminergic neurons induced by a genetic insult or environmental toxin can be exacerbated.

Aging as a source of ROS. According to the research, the etiology of PD is largely sporadic (80-85 %), whereas only 10-15 % are genetically linked [26] so the age can be considered as one of the main risk factors for PD, where the chance of developing PD increases exponentially above the age of 65 [16]. It is assumed that aging is associated with an accumulation of toxic substances, misfolded proteins, mitochondrial dysfunction and DNA damage until the critical threshold [67]. Particularly, high levels of mitochondrial DNA (mtDNA) deletions were detected in the brain of aged PD patients [3,36]. Thereby, these lead to the impairment of mitochondrial functioning and their numerical reduction as well as morphological changes, accumulation of toxic substances and thus the death of neurons [1]. Besides that decades needed for misfolding ofpathogenic proteins to reach a critical threshold to induce neuronal death, age associatedimpairment of mitochondrial function and consequent increased ROS production seem tobe important aspects of neurodegenerative disorders that can develop later in life course [36]. ROS-mediateddamage can result in mutations in the mitochondrial genome [Bender et al., 2006) resulting in theexpression of mutant forms of the electron transport chain subunits and mitochondrialtransfer RNAs essential for the translation processes collectively exacerbating ROS production [3]. All these in turn create a vicious cycle of further injury to mtDNA and othermitochondrial components causing to neurodegeneration [58].

Environmental toxins as a source of ROS. Many epidemiological studies showed that exposure to some environmental pesticides can trigger the pathogenesis of PD. PD patients had increased amount of pesticides in their serum [54,60]. In addition, IHC showed that the substantianigraof the PD patients showed higher amount of organochlorine insecticides [51]. These pesticides are even more dangerous when they accumulate altogether in the brain [32]. These substances increase the ROS and free radicals amount thereby leading to cell death, particularly the herbicide paraquat undergoes redox cycling followed by the reduction by NADPH into $O2^{2-}$ [63]. The role of different environmental factors such as MPTP in PD pathology was shown in the MPTP-induced PD patients among drug users, particularly these patients developed quick PD-like motor fluctuations associated with significant loss of dopaminergic neurons in their SN [54]. MPTP crosses the blood-brain barrier followed by the uptake by astrocytes. In the astrocytes MPTP is converted into 1-methyl-4-phenylpyridinuim (MPP^+) NY MAO-B and released into the extracellular space. MPP^+ is taken by dopamine transporter thereby it is selectively deposits in dopaminergic neurons. In the dopaminergic neurons MPP^+ interferes with mitochondrial Complex I [54]. Table 1 shortly summarizes some of the well-studied toxins that can induce neurodegeneration.

Mitochondria as a source of free radicals. Mitochondria are organelles, so-called, energy factories of the cell that are also very multifunctional, for instance, they regulate calcium homeostasis, cell programmed death programs such as apoptosis and necrosis [67]. Mitochondria have 2 membranes, the outer and the inner ones. The electron transport chain is based on the proton gradient across the inner mitochondrial membrane thatdrives the synthesis of ATP through ATP synthase (complex V). Complexes I, II, III andsome dehydrogenases of the tricarboxylic acid (TCA) cycle may also generate superoxideanion [67]. The electron transport chain represents a main source of ROS as during the reduction of Oxygen, small amount of $O2^{2-}$ leaks outside [67].

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The major environmental pesticides and PD

Toxin	Motor symptoms	Damage location	Mechanism of action	Ref.
6-OHDA	Unilateral rotation after apomorphine. Bilateral akinesia	Decreased striatal TH-IHC; degeneration of TH-immunoreactive neurons in SN	Oxidative stress	[7]
MPTP	Akinesia, rigidity, tremor in some species	Decreased striatal TH-immunreactivity; degeneration of TH-immunoreactive neurons in SN , some loss of locus coeruleus neurons, α-sunyclein aggregation	Oxidative Stress, inhibition of mitochondrial complex I.	[54]
Rotenone	Akinesia, rigidity, tremor, piloerection, flexed posture	Decreased striatal immunoreactivity	Chronic oxidative stress, chronic inhibition of mitochondrial Complex I.	[32]
Paraquat	Decreased locomotor activity	striatal TH-immunreactivity; degeneration of TH-immunoreactive neurons in SN , some loss of locus coeruleus neurons, inclusions reminiscent Lewy Bodies.	Oxidative stress	[60]

However, protective enzymes such as manganese superoxide dismutase (MnSOD) convert $O2^{2-}$ into H_2 O_2 [24]. Complex I (NADH:ubiquinone oxidoreductase) catalyses the first step in the mitochondrialelectron transport chain. It extracts energy from the oxidation of NADH and transfers it toubiquinone, generating ubiquinol, which is a membrane-soluble electron carrier that releases apair of electrons to Complex III [53]. Complex II (succinate-coenzyme Q reductase) makesthe link between the TCA cycle and the electron transport chain, releasing electrons to Complex III through ubiquinol [45]. Complex III (ubiquinone-cytochrome c oxidase) contributes to the proton gradient through the reduction of cytochrome C by oxidation ofubisemiquinone and the pumping of protons from the mitochondrial matrix into the intermembranespace [45]. When there is a decrease in electron transfer, molecular oxygen cancapture electrons from Complex III, resulting in superoxide anion formation [45]. Growing amount of research suggests thatmitochondrial function is impaired in PD at different levels from organellebiogenesis, mitochondrial fusion/fission, mitochondrial functioning andmitophagy [3, 53].

Ubiquitin-Proteasome system (UPS). During evolution, all living organism evolved a free radicals protecting shield such as antioxidants, defensive enzymes and chaperones [41].The ubiquitin-proteasome system (UPS) is the main protective pathway for cellular removal and degradation of damaged or excessive amount of proteins such as α-synuclein [5]. Degraded or damaged proteins by itself can be a source ofROS, thereby their removal prevents oxidative stress. On the other hand, some amino acids from the degraded proteins can scavenge ROS products thereby reducing the amount of oxidative stress [25]. Leaking electrons and/or free radicals from damaged/ defective mitochondria are also removed by the UPS system [4]. Quite interestingly, there are several mutations detected in the PD-associated genes, such as parkin and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) which are a part of the UPS system [49]. Furthermore, a key-component of Lewy Bodies such as α-sunyclein is also removed by the UPS system, and many studies shows that the UPS system is impaired in the PD patients [43]. The oxidative stress leads to an inhibition of mitochondrialComplex I as well as

impairment of the proteasomal activity through oxidative modification of proteasomecomponents [9]. McNaught and colleagues showed that SNpc of the PD patients had impaired UPS with structuralproteasome alterations including loss of the alpha-subunit, the component that regulates andstabilizes the proteasome complex [43]. Moreover, in vitro experiments showed that protesome inhibition by oxidative stress can induce cellular death [5]. Thus, increased oxidative stress can lead to the impairment of the UPS as well as the genetic mutations in the UPS proteins can promote and exacerbates the vulnerability of dopaminergic neurons to the toxic substances. Moreover, an accumulation of excessive proteins can also inducesproteosomal inhibition, thereby leading to the oxidative stress and vice versa [41]. Moreover, the research shows that there exists a linked vicious cycle between different mechanisms that not only induce but also promote the generation of ROS. The plenty of animal-based studies demonstrated that several molecular pathways are involved in the ROS-induced neurodegeneration but clinical trials failed to show the ROS by itself being a significant trigger in the disease progression [11,35].

The role of PD associated genes in the oxidative stress. Increasing amount of research showed that although the etiology of PD is complex and largely unknown, there are several genes that can cause autosomal dominant and recessive forms of the disease. Although there are huge amount of mutations claimed every year, there are only a few genes were proved by Genome Wide Association to be linked with PD. The discovery of genes that are associated with familial forms of PD, such as alpha-synuclein, parkin, PINK-1,Leucine-rich repeat kinase 2 (LRRK2) and α-synucleinhas provided significant insights to the molecular pathwaysby which oxidative stress contributes to the disease. Therefore, some of the genes that were identified to be associated with PD are described below.

Parkin. Parkin is a cytoplasmic and nuclear protein that functions as an E3 ubiquitin ligase. Several point mutations of Park-2 gene products were found to be associated with autosomal recessive early-onset form of PD [33]. Parkin plays a role in neuroprotection against several insults, including α-synuclein toxicity, oxidative and nitrosative stress as well as being an essential component for dopaminergic neurons survival [19]. Several research suggest that parkin is a neuroprotective protein, particularly, SH-SY5Y cells over-expressing wild-type parkin demonstrated increased oxidative stress resistance, particularly, these cells were resistant to excessive dopamine and 6-OHDA- induced apoptosis [56]. One of the potential neuroprotective mechanisms are that parkin can induce clearance of damaged/dysfunctioning mitochondria by inducing translocation of depolarized mitochondria and their autophagy [47]; in addition to, parkin ubiquities multiple mitochondrial substrates leading to their degradation by UPS and mitophagy [12]. Some research suggests that in genetically modified mice, they lack parkin and over-express α-synuclein, the dopaminergic degeneration is much more accelerated [31].

PINK1. A parkin partner in neuroprotection. PTEN-induced putative kinase 1 (PINK1) is a serine-threoninekinase located in mitochondria, whose mutations are linked to PARK-6 gene that is associated with autosomal recessiveform of PD [14]. PINK1 mutations are associated with loss of its kinase activity [26]. Increasing amount of data showed that PINK1 as a key regulator of mitochondrial quality control, supporting preservation of mitochondrial respiration through cristae stabilization, phosphorylation of chaperones and possibly regulation of mitochondrial transport or mitophagy [14]. PINK1 also modulates mitochondrial function and oxidative stress response through its functionalinteractions with other PD-associated proteins such as parkin through the PINK1/parkin pathway. Genetic studies demonstrated that PINK-1lacking mutants are similar to parkin lacking animals [37]. Moreover, in vivo studies showed that parkin protects PINK1 lacking mice from MPTP toxicity [28,65]. Therefore, it was suggested that PINK1/parkin are partners for the mitochondrial monitoring and the mitochondrial clearance.

LRRK2. LRRK2 (Leucine-rich repeat kinase-2) is a large multi-domain protein linked to autosomal dominant form of the disease. PD- associated mutations are identified in almost all domains but are most frequent in its kinasedomain leading to increased kinase activity [8,15]. As kinase activity is required for cell-death, it is suggested that LRRK2 enzymatic activity plays an important role in thepathogenesis of PD [55]. LRRK2 is mainly a cytoplasmic protein but

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it can also be associated with the outer mitochondrial membrane, raising the possibility that the increased kinase activity ofmutant LRRK2 might directly affect mitochondrial function [18]. In agreement withthis hypothesis, increased LRRK2 activity leads to neuronal death via mitochondrialdependentapoptosis, while lack of LRRK2 has a protective effect on mitochondrialdysfunction [68]. Over-expression of wild-type or mutant LRRK2 with enhanced kinaseactivity in various cell lines or primary neurons leads to mitochondrial fragmentation anddysfunction associated with increased ROS generation and increased susceptibility to oxidative stress and toxins [26,28]. A proposed mechanism for the increased vulnerability ofLRRK2 mutant cells to oxidative stress is via the kinase-dependent interaction between LRRK2 and dynamin-like protein (DLP1), which facilitates DLP1 translocation tomitochondria and subsequent mitochondrial fission [15]. Another mechanism isthrough the interaction of LRRK2 with peroxiredoxin 3, which is a mitochondrialmember of the antioxidant family of thioredoxin peroxidases. Mutations in the LRRK2 kinase domain increase phosphorylation of PRDX3 leading to decreased peroxidase activity,increased ROS production, and increased cell death. Indeed, postmortem brains analysis of PD patients carrying the G2019S mutation, commonest mutation in the kinase domain of LRRK2, has shownmarked increase in phosphorylated PRDX3 compared to normal brains [23].

Alpha-Synuclein (α-sunyclein) mutations and dopaminergic degeneration. Alpha-synuclein is a natively unfolded protein that participates in synaptic vesicle storage, recycling and compartmentalization of neurotransmitters [60]. Multiplications of the gene dosage of α-synuclein, such as duplication or triplication, are associated with not only autosomal dominant form of PD [2]. It is suggested that increased amount of α-synuclein increases its propensity to aggregate and form Lewy Bodies and thereby produce oxidative and nitrosative stress itself in addition to other oxidative sources [50]. Moreover, oxidative conjugation of α-synucleinwith dopamine leads to the potential the potential accumulation ofcytotoxic soluble protofibrils in dopaminergic neurons. Some research suggests that antioxidants reverse the formation of these adducts underlying that oxidation can contribute to the accumulation of α-synucleinprotofibrils [13]. On the other hand, some in vivo and in vitro research showed that exposure to cytochrome C and H_2O_2 as well as to H_2O_2 and Fe^{2+}, MPP^+ can trigger α-synuclein aggregation [50]. Moreover, resulting from nuclear membrane modification, α-synuclein can translocate into the nucleus [22] where itoligomerize and forms insoluble fibrils with DNA histones [65]. Moreover, in vivo experiment showed that paraquat and rotenone induce α-synuclein aggregation [20]. On the other hand, it should be noted, that overexpression or mutant versions of α-synuclein can by itself induce its aggregation and ROS generation [31]. Moreover, mutant forms of α-synuclein can increase the vulnerability to stress factors. Quite interestingly, mice lacking α-synuclein showed resistance to induced MPTP toxicity [35]. Oxidative stress can induce α-synuclein aggregation as well as excessive amount of α-synuclein can also trigger free radicals generation thereby inducing vicious damaging cycle. There exist several theories on the role of α-synuclein in the selective neurodegeneration.

The first theory is that, α-synuclein has a role in vesicular neurotransmitter storage, therefore when the disruption of vesicular storage takes place the cytosolic catecholamine concentrations can increase leading to exacerbation of the toxicity of oxidized catechol metabolites [6]. A second theory is that α-synuclein participates in synaptic vesicles recycling through phospholipase D2 (PLD2) localized primarily in the plasma membrane [2]; therefore, mutations and thus misfolding in α-synuclein can lead to dysregulation in vesicle recycling which in turn lead to the reduction of number of vesicles available for dopamine storage [40,66]. Moreover, the altered α-synuclein can have higher affinity for dopamine transporters thus leading to greater dopamine reuptake into neurons which in turn can be toxic to the neurons [13,38]. Therefore, α-synuclein can increase intracellular dopamine concentrations and thus induce dopamine auto-toxicity.

A third theory is that, excessive α-synuclein can interfere with the inner mitochondrial membrane and interfere with mitochondrial Complex I thereby leading to mitochondrial dysfunction as well as electrons leakage and further generation of ROS [10,62,63]. Some studies showed that following to A53t α-synuclein binding, mitochondria releases cytochrome C, Ca^{2+} and apoptotic proteins which in turn lead to induced cell death [11].

Furthermore, another studies showed that aberrant α-synuclein can induce mitophagy leading to bio-energetic misbalance leading to the dopaminergic cell death [58]. Alpha-synuclein can also damage mitochondria indirectly by inducing of peroxisome proliferator-activated receptor gamma-coactivator-1 alpha (PGC1?) gene leading to downregulation of PGC1?-target genes and consequently disturbing mitochondrial morphology and function [58].

Another theory is that excessive amount of α-synuclein such as gene duplication and triplication and its mutations such as A53T can induce neuroinflammation because its excessive number is not cleared by the UPS system which in turn can lead to proto-fibrills formation. For instance, in-vitro experiments showed that microlglial BV-2 cells incubated with Ala30Pro, A53T α-synuclein resulted in pro-inflammatory response induction production followed by thesecretion of TNF-alpha, IL6 and IL-1beta [59] and the activation of intracellular pathways such as ERK1/2 and p38 MAPK [34]. The more persistentneuro in flammatory response seen in transgenic mice carrying the human α-synuclein A53T mutation following systemic LPS administration compared with wild-type mice isassociated with the accumulation of nitrated alpha-synuclein and dopamine neurondegeneration [21]. Moreover, in vitro experiments with cultured dopaminergic neurons and isolated lysosomes showed that dopamine can modify aberrant α-synuclein leading to its poor degradation by chaperones and thus accumulation within cells [49]. More interestingly, that α-synucleincan behave as the prion-like transneuronalagent leading to progressive neurodegeneration [50]. Therefore, α-synuclein can not only form Lewy bodies within certain neurons but it can also induce aggregation and proto-fibrills formation in other cells [6]. However, there were no evidence found in vivo but the research is going on the transmissibility of PD.

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АННОТАЦИЯ

Благодаря научно-техническому прогрессу, значительно увеличилась средняя продолжительность жизни. Так, в развитых и большинстве развивающихся странах люди живут дольше по сравнению с предыдущими поколениями. Однако увеличение продолжительности жизни привело к увеличению распространённости хронических неврологических заболеваний, таких как болезнь Паркинсона (БП). БП представляет собой второе наиболее распространенное возраст-ассоциированное нейродегенеративное заболевание в мире. По литературным данным, в мире наблюдается более 5 млн. чел., страдающих этим заболеванием, что составляет 1 % населения мира старше 60 лет. По результатам эпидемиологических исследований, глобальная распространенность БП составляет 60-187 случаев на 100 тыс. населения. В большинстве случаев основные клинические симптомы развиваются у людей старше 60 лет. В свою очередь, 95 % всех случаев представляет контингент старше 80 лет. Следует отметить, что в связи с ожидаемым увеличением населения мира до 2,1 млрд. людей старше 60 к 2050 г., ожидается соответствующее увеличение числа людей с болезнью Паркинсона и постоянно растущей проблемой эффективной диагностики, лечения и реабилитации с целью сохранения оптимального качества жизни больных. Несмотря на большое количество исследований, патологические механизмы, лежащие в основе селективной дофаминергической нейродегенерации, до сих пор остаются неизвестными. Таким образом, целью данной статьи является проведение обзора существующих теорий развития БП, таких как роль окислительного стресса и его источников, таких, как сам дофамин, нейроинфламмация, естественное старение,токсины окружающей среды и альфа-синуклеин в качестве ключевых игроков, которые могут быть триггером селективной дофаминергической нейродегенерации.

Ключевые слова: нейродегенерация, болезнь Паркинсона, старение, окислительный стресс, повреждение митохондрий, а-синуклеин.

ТҮЙІН

Ғылыми-техникалық прогресс нәтижесінде, өмір сүру ұзақтығы айтарлықтай өсті, сонымен қатар алдыңғы ұрпақтармен салыстырғанда дамыған және дамушы елдердің көпшілігінде адамдар ұзақ өмір сүреді. Алайда, өмір сүру ұзақтығының артуы Паркинсон ауруы (ПА) сияқты созылмалы неврологиялық аурулардың таралуы ұлғайды. ПА әлемде екінші ең кең тараған жасы-қауымдастырылған нейродегенеративті ауру болып табылады [61]. Әдебиет деректері бойынша, әлемде осы аурумен ауыратын 5 миллионнан аса адам бар, бұл әлемдегі 60 жастан жоғары халықтың 1% құрайдыс [64]. Эпидемиологиялық зерттеулерді бағалауы бойынша ПА жаһандық таралуы 100 мың тұрғынға шаққанда 60-187 оқиғаны құрайды [39]. Көп жағдайларда, негізгі клиникалық симптомдары 60 жастан асқан адамдарда дамиды, өз кезегінде, барлық жағдайлардың 95 % 80 жастан асқан контингентке тиесілі [39]. Айта кету керек, 2050 жылға қарай әлем халқының 2,1 миллиард адамы 60-тан асқан адамдар болады деп күтілуде [16], демек сәйкесінше Паркинсон ауруымен ауыратындар саны артады, ауруға шалдыққан науқастардың оңтайлы өмір сапасын сақтау мақсатында тиімді диагностикалау, емдеу және оңалту мәселесі де көбейеді. Зерттеулердің көптігіне қарамастан, патологиялық механизмдері негізінде жатқан селективті дофаминергиялық нейродегенерация әлі күнге дейін белгісіз болып қалуда. Осылайша, осы мақаланың мақсаты ПА дамуының қолданыстағы теорияларына шолу жүргізу және негізгі ойыншылар, мүмкін болатын триггер таңдамалы дофаминергиялық нейродегенерациясы ретінде дофамин, нейроинфламмация, табиғи қартаю, токсиндер қоршаған орта және альфа-синуклеин сияқты тотығу күйзелісі және оның көздерінің рөлі болып табылады.

Түйінді сөздер: нейродегенерация, Паркинсон ауруы, старение, тотығу күйзелісі, митохондрия зақымдануы, а-синуклеин.

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