

Polyamines in Parkinson's Disease: Their Role in Oxidative Stress Induction and Protein Aggregation

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Abstract

Parkinson's disease (PD) is a systemic neurodegenerative disease characterized by tremor, rigidity, bradykinesia, and stooping posture. When more than 60% of dopaminergic neurons in the substantia nigra of the brain have died, motor symptoms manifest in PD. Currently, oxidative stress (OS) is considered to be one of the leading factors provoking death of dopaminergic neurons in PD. This review is concerned with the role of polyamines in PD, especially focusing on their role in OS induction. Polyamines (putrescine, cadaverine, spermidine and spermine) are involved in many molecular mechanisms, including cell proliferation and differentiation, gene transcription and translation, modulation of the functional activity of ion channels and receptors, and other vital processes. It is worth noting that under physiological conditions polyamines are antioxidants. It has been shown that spermine oxidase (SMOX) is up-regulated in PD, activating polyamine breakdown, which leads to excessive formation of toxic aldehydes (such as acrolein), H₂O₂ (a strong cytostatic) and ammonia (a toxic substance). Polyamines are also involved in the pathogenetic mechanism of α -synuclein modification resulting in the formation of Lewy bodies. This review provides data on the changes in polyamine levels at later stages of the disease. The review also examines the role of polyamines, as gliotransmitters, in regulating neural function and vice versa. The mechanisms of polyamine "pumping" from neurons to glia can be considered factors of OS regulation in neurons. Prolonged accumulation of polyamines in glia can lead to oxidation of polyamines and therefore potentially to gliosis in PD. The exact mechanisms of this process are, however, not clear. Answering the questions regarding the role of polyamines in gliosis development and pathogenesis of PD is necessary for treating cognitive impairment in patients with PD, which is particularly important.

Keywords: Parkinson's disease; Spermine; Spermidine; Putrescine;

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Introduction

The year 2017 marked the 200-year anniversary of the description of "paralysis agitans" by the English physician James Parkinson. The condition was subsequently named after him and is now called Parkinson's disease (PD) [1, 2]. PD is a progressive neurodegenerative disorder affecting more than six million people over the age of 60 [1]. Taking into consideration the increase in life expectancy, many neurologists reasonably predict that by 2030, PD incidence will double [3].

The clinical presentation of PD is characterized by movement disorders such as bradykinesia, muscle stiffness, resting tremor, and postural instability [3-5]. The main cause of PD is the death of nigrostriatal dopamine-synthesizing neurons, which leads to dopamine deficiency in the striatum [3]. Moreover, the nigrostriatal degeneration with motion dysfunction is not the only manifestation observed in PD. A significant proportion of patients with PD also suffer from non-motor symptoms, including constipation, depression and cognitive dysfunction.

At present, about 20 genes associated with PD have been identified, but the percentage of hereditary PD forms is only 5-10%, while 90% are idiopathic forms [6]. In both idiopathic and genetic cases of PD, oxidative stress (OS) is the common basic molecular mechanism that causes a cascade of molecular reactions leading to selective death of neurons in the substantia nigra and their terminals in the striatum. OS inductors are reactive oxygen and nitrogen species, aldehydes, dopamine (when not bound within vesicles and only under specific conditions), defects of mitochondrial DNA and iron deficiency. An imbalance between formation and elimination of reactive oxygen species (ROS) and reduction of antioxidant defense contribute to the pathogenesis of PD. It has been shown that OS is closely related to other aspects of the degenerative process, such as mitochondrial dysfunction, inflammation, atypical protein formation (α -synuclein breakdown, etc.) [4, 5, 7-11].

Pathogenetic mechanisms of OS, pathological modification of α -synuclein and other proteins, inflammation and gliosis are the central elements in PD pathogenesis. Investigating them is an important challenge for contemporary neuroscience [12-14]. This review is concerned with the involvement of polyamines in these mechanisms.

Polyamines

Polyamines play an important role in numerous molecular mechanisms, including cellular proliferation and differentiation, gene transcription and translation, posttranscriptional modifications [15-17], modulation of ion channel function, cellular signals [18-20], macromolecular synthesis regulation, etc. [21-31]. Their cellular roles include the modulation of ion channels that participate in the excitability of neuronal networks [18-20].

The antioxidant effect of polyamines

A very significant function of polyamines is their antioxidant action: 1) Spermine, spermidine and putrescine act as free radical scavengers [32-34], and the ability of polyamines to bind toxic aldehydes has been shown [35]; 2) Polyamines have a chelating ability towards metal ions, thereby adjusting the triggering mechanisms of OS [36-39]; and 3) Spermine and spermidine can influence the activity of antioxidant enzymes, interacting with their corresponding DNA [40, 41].

It should be noted that they play an antioxidant role in the brain. Spermine and spermidine enhance antioxidant protection of excitable tissues by modulating glutamate receptors [42], and polyamines are involved in the biosynthesis of other antioxidants. Thus, putrescine is the predominant precursor in the synthesis of homocarnosine in cerebral tissue [43, 44], and spermine can influence dopamine binding in synaptic vesicles. Those seem to be the most important effect of polyamines, considering their role in OS induction in PD, as formation of dopamine quinones is currently considered as one of the trigger mechanisms for selective OS [45-47].

For these reasons, there is currently a special emphasis on antioxidating polyamines in nutrition science, preferably those that prevent harmful environmental and dietary effects [34, 41].

Polyamines and aging

Polyamine levels decrease with aging [23, 31, 23, 48-50], which leads to age-related impairment of cognitive and other behavioral reactions [51].

We have previously shown in experiments with senescence-accelerated mice prone (SAMP) and senescence-accelerated mice resistant (SAMR) 1 mice that, polyamine levels were much lower in mice with accelerated type of aging characterized by low antioxidant protective activity than in controls [48].

Polyamines and PD

PD is generally associated with aging and causes progressive decline of cognitive function [2]. Physical activity (PA) levels have been implicated in cognitive reduction in Parkinson patients via N-methyl-D-aspartate receptor (NMDAR) pathway [52].

Polyamine levels in PD

At present, several studies on polyamines in brain tissue, cerebrospinal fluid (CSF) and blood of PD patients have been published. Early studies using high-performance liquid chromatography (HPLC) showed an increase in spermidine and spermine in erythrocytes of patients with PD [53]. A study of polyamine contents in the basal ganglia of the human brain showed age-related conditions, but no significant changes in PD patients [54]. Paik et al studied polyamine concentrations in CSF of PD patients using gas chromatography and mass spectrometry in ion monitoring mode with N-ethoxycarbonyl/N-pentafluoropropionyl derivatives. CSF polyamine concentrations were significantly different in patients with PD compared with those in the control group [55]. In the PD group, concentrations of putrescine, N1-acetylspermidine and the N1-putrescine/spermidine ratio were significantly higher, while concentration of spermidine was reduced [55]. The authors conclude that polyamine contents may serve as a metabolic marker for the diagnosis of PD.

PD progression is a typical problem, and the differences between slow and rapid forms of progression can provide valuable information for improving early diagnosis. In particular, it was found that N8-acetylspermidine was significantly elevated in fast progressive patients compared to control subjects and slowly progressive patients [56]. Balashova et al recently used mass spectrometry of plasma to diagnose early PD stages (Hoehn and Yahr stages 1, 1.5 and 2). They found an increase in the levels of polyamine metabolites such as 4-aminobutyraldehyde, N-acetylputrescine and asymmetric dimethylarginine. It is important to emphasize that lysine breakdown activates at early stages, with an increased formation of L-lysine 1,6-lactam or fragments of lysine such as diaminohexanoate [57]. Increased lysine breakdown indicates disturbances in the cadaverine metabolism [57].

We have also investigated blood spermidine level in PD patients at both early and late stages (Hoehn and Yahr stages 1 through 4). At stage 1, spermidine level was 3.5 times higher than that in healthy individuals. At stage 2 PD, spermidine level was also significantly higher than that in controls. At stage 3, a 63% decrease in spermidine compared to controls was registered. PD patients in this group typically manifested cognitive impairments (Min-Mental State Examination (MMSE) = 12). Stage 4 showed a further decrease in spermidine content compared to controls [58].

The cited study showed that polyamine levels first increase and subsequently decrease at different stages of the disease. Therefore, it is not advisable to associate specific changes in polyamine levels with PD without knowing the stage of the condition.

The role of polyamines in OS induction in PD

A review by Hussain et al covered the general molecular mechanisms for spermine and spermidine involvement in OS induction in various pathologies, as well as possible therapies for OS correction involving these polyamines [59]. In the pre-

sent review, we attempt to determine the role of polyamines in OS induction in the pathogenesis of PD, taking into account their selectivity in the substantia nigra.

OS activation in the substantia nigra in PD has been confirmed in biochemical studies of autopsy and biopsy samples from these brain areas. Despite the large number of studies are devoted to the molecular mechanism of OS activation in PD, this process is not currently clear [4, 5, 7, 9-11]. A sharp activation of lipid peroxidation, a decrease in glutathione and other antioxidants, as well as iron accumulation in the above-mentioned structures of the brain have been established. As most dying substantia nigra neurons are dopaminergic, a theory of PD pathogenesis based on dopamine autoxidation and quinone formation was proposed and experimentally confirmed [60].

Dopamine is an antioxidant in physiological concentrations, but with a significant increase in its content within the cell and in the presence of other inducers of the OS, dopamine exhibits prooxidant properties [60]. As mentioned above, spermine regulates the binding of dopamine to vesicles in dopaminergic neurons [46, 47]. Under certain pathological conditions that cause a disturbance in the metabolism of spermine, one can assume the formation of an imbalance in the binding of dopamine to the vesicles, as well as the subsequent accumulation of high concentrations of dopamine and their subsequent autoxidation leading to induction of the OS. Oxidation of the polyamines plays a key role in the metabolism of polyamines, and later catabolites develop, but the mechanism is formed through which the polyamines are converted into molecules that show tremendous activity [61]. The impartment enzyme of polyamines catabolism is spermine oxydase (SMOX) [62-65]. SMOX is included in the dopamine receptor signaling pathway. SMOX gene expression was intensified in PD which can lead to excessive formation of toxic aldehydes (acrolein), H_2O_2 (strong cytostatic) and ammonia (toxic substance) [66, 67].

Acrolein concentration was significantly increased in the substantia nigra of PD [68]. Acrolein acts as a parkinsonian neurotoxin in substantia nigra of rat brain. That was shown by acrolein local infusion in nigrostriatal dopaminergic system [69].

The reduction in the spermidine/spermine N1-acetyltransferase activity of another polyamine breakdown enzyme in PD was shown earlier [52].

It should be noted that the oxidized form of monoamine oxidase (MAO) plays a special role in the molecular mechanisms of OS startup in PD [70]. It is known that the "oxidized" form of MAO is able to change its substrate specificity and use polyamines, in particular putrescine and its metabolite-homocarnosine as a substrate [71-73].

The role of polyamines in synucleinopathy, protein aggregation and fibrillation

Antony et al were among the first researchers to find that the cellular polyamines putrescine, spermidine and spermine promote aggregation and fibrillation of α -synuclein [74]. For a long time α -synuclein was considered the main protein to

be involved in the formation of Lewy bodies [75-81]. Therefore, the formation of its aggregates with spermine was suggested as one of the leading factors of PD. Through circular dichroism and fluorometric thioflavin T kinetic studies, it was found that the spermine-protein interaction leads to transition of α -synuclein from non-aggregated to aggregated state. Spermine and spermidine affect the timing of this transition so that the transition period in the presence of polyamines is significantly shorter. Due to their chemical structure, polyamines can easily accelerate aggregation and fibrillation of proteins other than α -synuclein, including amyloid-beta and tau protein [75]. In the presence of polyamines, protein fibrils form large networks, resulting in isolated condensed aggregates [75-81].

The mechanism of polyamine aggregate formation for α -synuclein has been studied in detail. It has been established that spermine, spermidine and putrescine drastically accelerate the aggregation and fibrillation of α -synuclein [9] by binding to the N-terminal region of the amyloid beta peptide (binding site of metal ions such as Cu^{2+} and Zn^{2+}). Obviously, polyamines can compete with metal ions for binding to proteins. Accordingly, a hypothesis has been proposed that decreasing polyamine content in PD can contribute to correction of neurodegenerative processes in the brain [9]. The authors conclude that lower polyamine levels can be viewed as a potential therapeutic goal for the treatment of PD and that lower values can be reached by administration of compounds that either enhance the catalytic activity of the polyamine in question or inhibit polyamine synthesis. However, these conclusions do not show promise [9].

Another molecular mechanism by which polyamines affect the structure of brain proteins is their interaction with glutamyl residues of proteins, such as neuronal tubulin and transglutaminase, which form an irreversible post-translational modification of γ -glutamylamine [82]. Transglutaminase activation boosts formation of protein aggregates with polyamines [82]. On the other hand, increased polyamine content leads to cytotoxic effects by promoting formation of toxic metabolites, including aldehydes and H_2O_2 . This begs the question, whether polyamine-related protein aggregation is in fact neuroprotective or neurotoxic [28].

The role of glia polyamines in gliosis and OS induction in PD

Recently numerous studies have been carried out with advanced imaging technologies (e.g. functional MRI), which demonstrated that PD is a disorder of the nervous network affecting various parts of the motor and sensory systems in the brain [14].

In neurodegenerative conditions, the functional deficiency of glioneurovascular units is determined by an imbalance in the glia/neuron ratio and the glial cell ratio between astrocytes and microglia [83-85]. In their experiments on rat brain glial cell cultures, Takano et al showed that, in the presence of fetal serum, spermidine and spermine kill microglia to a larger extent than astrocytes [83]. It was shown that polyamine-induced glial cell death was associated with OS induced by acrolein.

Introducing antioxidants, such as reduced glutathione, cysteine and N-acetylcysteine, into the incubation medium prevented cell death [83]. These differences in polyamine toxicity against the two types of glial cells may regulate the balance of glial activation in PD. The fact that polyamines are produced in neurons but accumulated in glia allowed Skatchkov et al [85] to propose a hypothesis that polyamines act as gliotransmitters with a neuroregulatory function. Moreover, in specific cases glial polyamines reach neurons through endothelium and brain capillaries. Investigating the role of polyamines as gliotransmitters in PD is especially important.

It is vital for brain function to maintain homeostasis between polyamine levels in glia and neurons. An imbalance in polyamine exchange can be caused by inflammation [86-88]. Niranjana showed that chronic inflammation is typical for PD [12].

Stress is an important factor affecting polyamine exchange [29, 89, 90]. Two forms of stress reactions associated with polyamine metabolism alterations have been described: 1) General or non-specific reaction; and 2) The reaction due to central neural system (CNS) stress. Thus, inflammation and stress can be seen as factors stimulating polyamine accumulation in glia, elevating their levels as well as increasing the concentration of their breakdown products. It must be noted that in PD, gliosis of the substantia nigra is present that manifests as an increase in overall glia and astrocytes [12]. It is now clear that the solution to the problem of underlying molecular mechanisms of gliosis in PD and approaches to its management lie in regulation of polyamine metabolism in the brain.

Neuroprotective Effect of Spermidine

A study using the rotenone-induced rat model of PD showed that spermidine had neuroprotective action [91]. It was established that spermidine administration concurrently with rotenone prevented loss of dopaminergic neurons, attenuated OS and neuroinflammation, and restored monoamine levels [91-93].

Nematode model studies have demonstrated that spermidine has a neuroprotective action towards α -synuclein. The studies suggest that this cytoprotective action (autophagy) accounts for the beneficial effects of spermidine administration [91-93].

Conclusions

The purpose of this review was to suggest possible answers to the question how polyamines are involved in OS induction in PD. Polyamines are ubiquitous and important components of all mammalian cells. They have numerous functions, including critical roles in nucleic acid and protein synthesis, gene expression, protein function, gene expression, protection against oxidative damage, ion channel regulation and maintenance of cellular macromolecule structures. At the early stages of PD, polyamine levels are elevated [52, 53, 58]. In PD in general, SMOX is upregulated, which leads to excessive formation of

toxic aldehydes, such as acrolein, H_2O_2 and ammonia [61, 83]. This is accompanied by formation of various derivatives reflecting the dysfunction of polyamine metabolism in PD. These metabolites, especially from spermine, can cause significant toxicity damaging proteins, DNA and other cellular components [62, 64, 68].

Especially promising is the study of spermidine metabolism in PD. For example, animal model studies have shown the neuroprotective effect of spermidine associated with autophagy activation [93].

At advanced stages, blood spermidine level decreased in PD patients who manifested declining cognitive functions [58]. It can be suggested that falling blood spermidine level is due to lower concentrations in tissues and a decrease in autophagy [93].

Polyamines' ability to alter protein structure, such as α -synuclein, is of great importance for PD pathogenesis [74, 81, 82, 94]. Glial polyamines have a regulatory effect on neurons and vice versa. The mechanism of this action has not been thoroughly studied [85].

Identifying the role of polyamines in PD pathogenesis is necessary in order to manage dysfunctions in their metabolism, which would allow more efficient treatments for cognitive disorders.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

Abbreviations

PD: Parkinson's disease; OS: oxidative stress; SMOX: spermine oxidase; ROS: reactive oxygen species; HPLC: high-performance liquid chromatography; SAMP: senescence-accelerated mice prone; SAMR: senescence-accelerated mice resistant; PA: physical activity; NMDAR: N-methyl-D-aspartate receptor; CNS: central neural system; CSF: cerebrospinal fluid; MAO: monoamine oxidase; MMSE: Mini-Mental State Examination

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