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NICOTINE-DEPENDENT RISK OF DEVELOPING PARKINSON'S DISEASE

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Abstract

For the past twenty years, information concerning the relationship between Parkinson's disease and the use of tobacco products has appeared in highly respected scientific publications. As a whole, these studies were epidemiological. As a rule, these studies showed that individuals who abused tobacco products for many years and quit smoking only in old age had a significantly increased risk of developing Parkinson's disease.

Only a few studies have attempted to identify the structural-functional relationship between the effects of nicotine on the representative brain areas responsible for the onset of Parkinson's disease. During prolonged tobacco use, nicotine that enters the brain tissue activates the nicotine-dependent acetylcholine receptors localized in dopaminergic neurons, resulting in the release of dopamine.

In this study, we attempted to investigate the mechanisms underlying the onset of Parkinson's disease in individuals who have quit smoking, i.e. under conditions of nicotine withdrawal in the brain."

In our opinion, the "preventive effect" of nicotine on dopaminergic neurons is realized through four interdependent mechanisms:

1. By the receptor mechanism, due to the nicotine-dependent acetylcholine receptors located on dopaminergic neurons,
2. Due to the balanced release and reuptake of dopamine to dopaminergic neurons,
3. Due to prevention of α-synuclein aggregation and fibrillation process,
4. Due to the inhibitory effect of nicotine on the processes of activating the synthesis of aliphatic polyamines in dopaminergic neurons of the corpus striatum and nucleus caudatum.

In cases of nicotine "deficiency", neurodegenerative disorders pathognomonic for Parkinson's disease can occur in the brain:

1. The exchange of dopamine and aliphatic polyamines in dopaminergic neurons is disturbed,
2. The processes of transforming native α-synuclein into its aggregated and fibrillar forms are intensified,
3. Ultimately, the intraneuronal dopamine-synuclein complex with a pronounced neurotoxic action spectrum may appear.
4. *Older adults, in conditions of abrupt smoking cessation, are recommended to use Eflornithine, as well as a polyamine-free and polyamine-deficient diet.*

Keywords: *Parkinson's disease, tobacco products, nicotine, dopamine, dopaminergic neurons, abrupt smoking cessation.*

Introduction

As paradoxical as it may sound, the well-known medical admonition since ancient times – "The same remedy can be harmful in some cases and healing in others".

A similar expression is most vividly manifested in relation to nicotine. Thus, long-term tobacco consumption has a very harmful effect on the state of patients suffering from malignant oncological

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diseases, cardiovascular and respiratory diseases, immunodeficiency and endocrine disorders.

Several studies have established a correlation between disrupted polyamine metabolism in tobacco users and the incidence of strokes [*Okonkwo U et al., 2021; Alruzayhi I, 2023*]. At the same time, as numerous studies have shown, the risk of developing Parkinson's disease is significantly reduced in older adults who have been using tobacco products for many decades [*Benedetti M et al., 2000; Kelton M et al., 2000; Hernan M et al., 2001; O'Reilly E et al., 2005; Ritz B et al., 2007; Li X et al., 2015; Veljkovic E et al., 2018; Kesoyan A et al., 2022*].

Our article may be strange and "dangerous" for some neuropathologists, therapists, hygienists and public health organizers, who have been legitimately and reasonably fighting against smoking for many years.

The authors of this publication in no way aim to dispute the harmful effects of smoking on our body. The problem is developed in a completely different context.

Thus, in recent years, prestigious medical publications have revealed a hidden link between "chronic" smokers who quit smoking in old age and the risk of developing neurological symptoms typical of Parkinson's disease.

Population studies by a number of authors have shown that in 40-50% of cases, the risk of developing Parkinson's disease is reduced in individuals who use tobacco products for a long time [*Hernan M et al., 2002; Ritz B et al., 2007; Kesoyan A et al., 2022*]. Noteworthy are the studies of a number of authors, as they have shown based on meta-analysis that the risk of developing Parkinson's disease was 58% lower in current smokers and 24% lower in former smokers [*Thacker E et al., 2007*]. An inverse relationship has been established, according to which tobacco use is inversely associated with the risk of developing Parkinson's disease [*Liu Z et al., 2017; Kesoyan A et al., 2022*].

Based on the available literature data on the relationship between tobacco use and the risk of developing Parkinson's disease, several authors [*Kesoyan A et al., 2022*] rightfully claim that "the inverse relationship between Parkinson's disease and smoking correlates with an increase in the intensity and duration of smoking. This relationship is more pronounced in current smokers compared to former smokers and decreases with years after quitting smoking".

In this publication, we first analyze possible mechanisms underlying the pathogenesis of Parkinson's disease. According to modern concepts and hypotheses, an important role in the mechanism of Parkinson's disease induction is given to the disrupted metabolism of aliphatic polyamines – putrescine, spermidine, spermine, and α-synuclein, which are mainly localized in dopaminergic neurons of the corpus striatum and nucleus caudatum.

At the second stage, we will present our own analysis of the available data regarding the nicotine receptor function, metabolic disorder of aliphatic polyamines and α-synuclein in dopaminergic neurons, under conditions of nicotine cessation in the representative areas specific to Parkinson's disease – the nucleus caudatum and corpus striatum.

1. The Role of Polyamines in the Integrative Activity of Vertebrate Mammals

Polyamines are essential polycations found in all cells. One of the aliphatic polyamines – spermine, was discovered by Anthony van Leeuwenhoek as early as 1678. The structure of putrescine and spermine was deciphered only in the early 20th century [*Wallace H et al., 2003*].

Levels of aliphatic polyamines (putrescine, spermidine and spermine) in mammalian organisms are maintained through their *de novo* synthesis [*Schipper R et al., 2000; Pegg A, 2009; 2016*], including under conditions of resident microorganism persistence [*Gerner E, Meyskens F, 2009; Hullar M, 2013*], as well as by food intake [*Zoumas-Morse C, 2007; Ali A, 2011*].

The classical way of *de novo* polyamine synthesis starts with ornithine. The initial stage of polyamine synthesis is carried out by ornithine decarboxylase (ODC), which decarboxylates ornithine to putrescine. Further transformation of polyamines within its three representatives is also carried out due to the enzymatic mechanism, by adding two aminochronyl groups, to form spermidine from putrescine and enable the formation of spermine from spermidine.

It should be noted that in case of normal functioning of the mammalian organism, aliphatic

polyamines act as powerful intracellular modulators providing multifaceted functions that support the life cycle of all cell populations of the body.

Polyamines participate in the cell proliferation process by synthesizing and stabilizing DNA, regulating gene transcription and translation, modifying proteins after translation, stabilizing membranes, ensuring the function of ion channels, maintaining their balanced flow within the same cell [*Gerner E, Meyskens F, 2004; Pegg A, 2009; Wallace H, 2009; Igarashi K, Kashiwagi K, 2010; Lee S, 2011*]. A more detailed description of the aliphatic polyamine function is presented in our book – "Polyamines and synucleins in the diagnosis and pathogenesis of neurological and oncological diseases" [*Avagyan S, Zilfyan A, 2020*].

2. The role of aliphatic polyamines in the pathogenesis of Parkinson's Disease

Currently, there is a wide discussion on the aspects related to the role of aliphatic polyamines (putrescine, spermidine, and spermine) in the pathogenesis of Parkinson's disease.

Parkinson's disease is a progressive disorder that most visibly manifests clinically from the age of 60. Clinical symptoms are characterized by such manifestations as slow movements (bradykinesia), muscle immobility (rigidity), poor postural ability, intermittent gait, insufficient and limited direct movements, sudden cessation of movements (akinesis). It should be especially noted that the first symptoms of Parkinson's disease appear much earlier, i.e. during the degeneration of dopaminergic neurons. Degeneration of dopaminergic neurons, predominantly localized in the substantia nigra, leads to deafferentation of the corpus striatum. The resulting structural and functional changes in the above brain areas are considered as key factors in the pathogenesis of Parkinson's disease. At the initial stages, this process proceeds without pronounced clinical manifestations. The first symptoms appear in patients only after degeneration of 50-60% of dopaminergic neurons localized in the substantia nigra and striatum.

In recent years, informative publications have appeared discussing the role of aliphatic polyamines in the pathogenesis of Parkinson's disease [*Gomes-Trolin C et al., 2002; Kaplan B et al., 2003; Krasnosobodtseva A et al., 2012; Koehler N et al., 2015; Avagyan S, Zilfyan A, 2020*]. As a rule, in all studies aimed at elucidating the role of polyamines in the pathogenesis of Parkinson's disease, in our opinion, one important fact is indicated: high levels of aliphatic polyamines - putrescine, spermidine, and spermine - were consistently detected in dopaminergic neurons of the substantia nigra, corpus striatum, and nucleus caudatum [*Avagyan S, Zilfyan A, 2020*].

3. The structure and function of intracerebral α-synuclein

The structure of α-synuclein includes two amino acid sequences: N-terminal and C-terminal. The N-terminus of α-synuclein forms associative bonds with neuronal lipid membranes; while the C-terminal sequence of α-synuclein is unstructured and is considered responsible for interactions with proteins, ionic and polycationic polyamine binding, modification of membrane binding, protection of α-synuclein from aggregation [*Burre J et al., 2015*].

As a rule, α-synuclein is mainly detected in the presynaptic terminals of dopaminergic neurons, while associated with synaptic vesicles.

Under physiological conditions, folding of α-synuclein proteins has a stabilizing effect on neuronal membrane structures; in turn, membrane binding of α-synuclein prevents their transition into an aggregated state [*Burre J et al., 2015*]. The presynaptic localization of α-synuclein on membranes indicates its participation in the implementation of pluripotent synaptic functions, such as synaptic activity and plasticity, neurotransmitter release, vesicular transport and dopamine metabolism. The action of α-synuclein on dopamine and dopamine receptors is realized as follows: α-synuclein inhibits the dopamine synthesis by inhibiting the expression and activity of tyrosine hydroxylase.

4. Possible polyamine and α-synuclein associative mechanisms in Parkinson's disease induction

In Parkinson's disease, the spiral folding of α-synuclein is accompanied by a conformational change, leading to its aggregation and the formation of fibrils with accumulation in Lewy bodies. Moreover, oligomeric compositions of α-synuclein turned out to be the most "neurotoxic" [*Krasnoslobodtsev A et al., 2012*].

In this aspect, the studies ivestigating the mechanisms of dopamine binding to α-synuclein are of significant interest [*Illes-Toth E et al., 2013*].

Currently, α-synuclein is believed to play an important role in the processes of accumulation and release of this neurotransmitter dopamine, since α-synuclein is crucial in "modulating secondary processing of synaptic vesicles" [*Illes-Toth E et al., 2013*]. In cases of impaired vesicle integrity, high concentrations of dopamine can lead to destructive processes in dopaminergic neurons due to the formation of a structural complex of dopamine-α-synuclein, which has a pronounced cytotoxic spectrum of action [*Rochet J et al., 2004; LiH et al., 2005; Illes-Toth E et al., 2013*]. Normally, α-synuclein in neurons regulates the homeostasis of monoamines, including dopamine. In Parkinson's disease, overexpression of α-synuclein is accompanied by inhibition of dopamine synthesis in dopaminergic neurons. Simultaneously, in case of α-synuclein overexpression and intraneuronal dopamine deficiency, dopamine reuptake by neurons is significantly suppressed.

It should be particularly noted that aliphatic polyamines (putrescine, spermidine, and spermine) at high concentrations have a modeling effect on α-synuclein, which is expressed in the formation of fibrillar structures [*Kaplan B et al., 2003]*.

The authors come to a very important conclusion, in our opinion, according to which the above polyamines play an important role in the pathogenesis of Parkinson's disease, as a morphological substrate – cytolytic α-synuclein aggregates and their fibrillation [*Antony T et al., 2003*].

5. Possible intracerebral mechanisms underlying the induction of Parkinson's disease in the older adults, who quitted smoking at this age

Unfortunately, the mechanisms underlying the symptom complex of neurodegenerative disorders characteristic of Parkinson's disease in older adults, who quit smoking abruptly are poorly understood.

There are only limited data related to dopamine metabolism in corpus striatum neurons. Thus, it is established that nicotine plays an important role in the corpus striatum regulation, by activating nicotine-dependent acetylcholine receptors on dopaminergic terminals, mainly providing the release of dopamine into the interneuronal space [*Quik M, 2004; Grady S et al., 2007; Quik M, Wannacot S, 2011*].

It appears that in individuals who quit smoking, due to a deficit of nicotine intake in the central nervous system, nicotinic-dependent receptor mechanisms in the striatum are noticeably inhibited, leading to a disruption of dopamine release from dopaminergic neurons, resulting in its excessive intraneuronal accumulation and damage to the structure of nerve cells.

Very informative studies conducted by a number of authors [*Hong D et al., 2009*] deserve attetntion. In *in vitro* experiments, the authors studied the effects of tobacco products on the structural and functional parameters of α-synuclein: specifically, its fibrillation process, in relation to the effects of five ingredients found in tobacco: anabasine, cotinine, hydroquinone, nicotine, and nornicotine. At the same time, the authors used a wide range of modern complementary studies: including Thioflavin T assays, gel electrophoresis, size chromatography - high performance liquid chromatography (SEC-HPLC), and atomic force microscopy (AFM). The authors found that only two out of the five – nicotine and hydroquinone, inhibit α-synuclein fibrillation, with the effect of nicotine being more pronounced. Using SEC-HPLC, both ingredients stabilized the solubility of oligomeric states of α-synuclein. Morphological studies using AFM revealed three stable oligomers with average heights of 16 *nm*, 10nm and 4 *nm*. Based on their findings, the authors came to a reasonable conclusion that two of the ingredients in tobacco – nicotine and hydroquinone, inhibit α-synuclein fibrillation and simultaneously stabilize soluble oligomeric structures of α-synuclein.

During prolonged smoking, nicotine actively participates in the metabolic and neurotransmitter functions of dopaminergic neurons, mainly localized in the nucleus caudatum and corpus striatum. One of the possible mechanisms for regulating the functions of dopaminergic neurons is described as a possible receptor mechanism, which is due to the effect of nicotine on nicotinic acetylcholine receptors. Through the stimulation of dopaminergic neurons, these receptors also provide dopamine release.

Thus, the proposed hypothesis suggests the directed effect of nicotine on the receptor apparatus of neurons, which is responsible for dopamine release

and plays an important role in the metabolism and structural architecture of dopaminergic neurons.

Apparently, in older adults, a similar mechanism (possibly of an adaptive character) appears to become fixed with age, thus providing the initial stages of dopamine metabolism, i.e. its release. Abrupt smoking cessation disrupts the functioning of such a receptor-involved mechanism, resulting in neurodegenerative processes in Parkinson's disease, with a main focus on the disturbed dopamine metabolism in dopaminergic neurons.

In addition, we hypothesize that in case of abrupt smoking cessation, another mechanism may be involved, based on the processes of impaired metabolism of aliphatic polyamines and α-synuclein in dopaminergic neurons.

In our view, long-term use of tobacco products has a very negative effect on metabolic processes in specific brain structures. We are talking about a sharp decrease in the metabolism of aliphatic polyamines in representative cells – dopaminergic neurons and glial cells, mainly localized in the corpus striatum and nucleus caudatum. Paradoxically, long-term nicotine use, prevents the risk of neurodegenerative disorders characteristic of Parkinson's disease.

According to our hypothesis, an abrupt smoking cessation "disinhibits" the course of metabolic processes in functionally activated neurons, resulting in intensified synthesis of aliphatic polyamines and the aggregation and fibrillation of α-synucleins caused by them. There is no direct evidence confirming the validity of our hypothesis. However, there are very informative data indicating that nicotine significantly reduces polyamine synthesis in gastric epithelial cells by inhibiting ornithine decarboxylase [*Shin V et al., 2002*].

According to the authors, the healing processes of stomach wounds are sharply disrupted under conditions of intracellular polyamine deficiency, which may involve nicotine-dependent inhibition of ornithine decarboxylase. Unfortunately, at present, we do not have data on aspects of the nicotine effect on the ODS activity in the neurons of the mature organism, as well as in dopaminergic neurons of the corpus striatum and nucleus caudatum.

There are only indirect data about the nicotine effect in the neonatal and postnatal periods [*Smith I et al., 1991; Slotkin T et al., 1991; 2003*]. The studies were exclusively experimental, where, at various stages of prenatal and postnatal development of laboratory animals, a heterogeneous picture of the functional link was revealed between nicotine entering the brain and ODS activity in the forebrain, midbrain, brainstem and cerebellum. Thus, in particular, it was found that prenatal exposure to nicotine causes activation of nicotinic receptors in the postnatal period, with a disruption of the differentiation processes of nerve cells. In the offspring of female rats exposed to nicotine, there was a significant increase in the ODS activity in response to the postpartum "load" of nicotine in the earliest period. However, in a relatively late period, the "pathological" effects of nicotine were not due to the ODS activity, but to its secondary effects, as a result of systemic hypoxia development.

It is possible that in case of long-term use of tobacco products, secondary nicotine-dependent hypoxic processes in the corresponding brain structures occur in older adults. There is a need to extrapolate the obtained results of all the above authors when interpreting the mechanisms in our hypothesis. However, in our opinion, such studies to determine the effect of nicotine (in conditions of its long-term use) on the ornithine decarboxylase activity in dopaminergic neurons should be the subject of a special study.

In cases caused by polyamines and intracellular aggregation of α-synucleins, with the formation of Lewy bodies, synaptic activity and plasticity, vesicular transport and release of neurotransmitters are disturbed in dopaminergic neurons [*Avagyan S, Zilfyan A, 2020*].

In our opinion, it is also possible that the dopamine metabolism in dopaminergic neurons is disturbed in older adults who quit smoking. There should be two, presumably independent, factors involved in this mechanism. The first factor is implemented through a receptor mechanism – the effect of nicotine on the receptor apparatus of dopaminergic neurons, which significantly disrupts dopamine release. The second factor is due to a different metabolic mechanism that disrupts dopamine metabolism, resulting in increased levels of polyamines and the subsequent formation of aggregated and fibrillar states of α-synuclein, their involvement in the formation of Lewy bodies, and a sharp disruption of dopamine reuptake into dopaminergic neurons.

Recent studies have established that the activation processes of nicotine-dependent acetylcholine receptors are also modulated by polyamines [*Dhara M et al., 2020*]. The authors obtained very informative data showing that spermidine-spermine-acetyltransferase selectively controls the biogenesis of the nicotinic acetylcholine receptor. Thus, it was found that decreased level of polyamines enhances the expression of the nicotinic acetylcholine receptor in cortical neurons and, thereby, enhancing nicotine-mediated neuroprotection.

In our opinion, neuroprotection may also affect the processes of dopamine metabolism regulation, i.e. its release by dopaminergic neurons. According to our assumption, long-term use of tobacco products significantly reduces the level of polyamines in dopaminergic neurons and, thus, in individuals who have been using tobacco products for many years, a similar (presumably adaptive) mechanism is activated, aimed at normalizing dopamine metabolism through receptor mechanisms. At the same time, in the absence of nicotine entering the brain, in individuals who quit smoking, the processes of polyamine synthesis are activated by spermidine/spermine N (1) - acetyltransferase (SPD/SPM acetyltransferase) fermentation with simultaneous activation of acetylcholine nicotinic receptors. It is possible that this polyamine-dependent receptor mechanism of dopamine metabolic disorder in dopaminergic neurons is also activated in older adults who have quit smoking.

Undoubtedly, our assumption needs special studies to confirm or exclude the involvement of this polyamine-dependent receptor mechanism in case of nicotine deficiency in the brain of older adults who abruptly quit smoking.

We also consider it appropriate to discuss another aspect related to the activation of autoimmune mechanisms, in which an important role is given to aggregated α-synucleins. In this regard, according to some authors, immunopathological disorders also occur in the representative areas of the brain during the development of neurodegenerative disorders in Parkinson's disease [*Papachroni K et al., 2007*]. According to the authors, specific autoantibodies directed against α-synuclein play an important role in the mechanism of the development of these disorders. Moreover, such antibodies are directed not against native α-synuclein, but against α-synuclein that has undergone the process of destruction, i.e., is in a state of aggregation and fibrillation. Glial cells may be a possible source of such antibodies. It is also noted that antibodies against β-synuclein and γ-synuclein are not associated with Parkinson's disease. The authors state that the autoimmune mechanism, which involves the production of specific antibodies against aggregated and fibrillar α-synuclein, is specifically associated with inherited Parkinson's disease.

In our view, antibodies to aggregated α-synuclein, which are produced peripherally, may also serve as a source of autoantibodies in brain tissue.

As a rule, elderly people, especially those of advanced age, suffer from many chronic diseases of various etiologies, which often involve peripheral nervous system damage.

We state that in a number of the internal organ lesions in older adults, peripheral nerve endings experience aggregation of α-synuclein. We believe that it is the aggregated α-synuclein that causes directed humoral activation of the immune system organs, accompanied by the production of specific autoantibodies against the aggregated α-synuclein. We do not exclude the possibility of an autoimmune mechanism of damage to dopaminergic neurons and glial cells in the corresponding areas of the brain by autoantibodies to α-synuclein produced by immune competent cells in the periphery. The penetration of specific autoantibodies into the brain is possible due to the increased selective permeability of the blood-brain barrier. Penetrating into the brain, specific autoantibodies will undoubtedly undergo selective expression precisely on dopaminergic neurons, whose cytoplasm is "saturated" with α-synucleins in the form of their fibrillar aggregates in Parkinson's disease.

Our hypothesis is also based on an analysis of the available literary data on the role of anti-α-synuclein antibodies in the development of neurodegenerative disorders induced experimentally. For example, experimental studies on the "Parkinson's disease" model have established that autoantibodies to α-synuclein produced by immune competent cells have neurotoxicity, causing selective death of dopaminergic neurons in the substantia nigra [*Huber V et al., 2006*].

We are far from promoting the idea of the expediency of continuing smoking by older adults;

quitting smoking is necessary at any age. However, at the same time, it is necessary to develop strategy for therapeutic and preventive measures among this contingent of people, in order to prevent the development of Parkinson's disease.

In our opinion, it is necessary to recommend to this group of people, immediately after quitting smoking, the use of drugs that block the excess synthesis of aliphatic polyamines – putrescine, spermidine and spermine, during the initial period. As a choice, we can recommend α-difluoromethylornithine (DFMO), or its analogs, such as Eflornithine. The use of medication should be combined, in our view, with a correction of the diet, in which aliphatic polyamines are absent, or they are determined in very low levels. We are talking about polyamine-free and polyamine-deficient diets, which are widely used in some developed countries in the treatment of patients with various diseases (especially oncological patients), who have an increased synthesis of aliphatic polyamines.

CONCLUSION

Thus, nicotine, through a receptor mechanism, provides the release of dopamine in dopaminergic neurons. On the other hand, as shown by several authors [Hong D et al., 2009], nicotine inhibits α-synuclein fibrillation and stabilizes the solubility of fully functional oligomeric structures of α-synuclein.

In case of long-term tobacco use, nicotine maintains the normal structure of α-synuclein in presynaptic terminals. In conditions of abrupt smoking cessation, i.e. when this mechanism is disrupted, α-synuclein aggregation starts. As a result of delayed dopamine release, dopamine-aggregated α-synuclein complexes begin to form in presynaptic neuronal terminals, which have a pronounced cytotoxic spectrum of action and spread during Parkinson's disease to dopaminergic neurons in the corpus striatum and nucleus caudatum.

On the other hand, it is possible that in case of long-term smoking, nicotine has an inhibitory effect on metabolic processes occurring in the brain of the older adults, including the polyamine metabolism.

At the same time, it is established that in Parkinson's disease, there is a significant increase in the content of aliphatic polyamines in dopaminergic neurons, which is considered to be one of the pathogenic factors of the disease. In cases of abrupt smoking cessation, i.e. when nicotine intake to the brain is stopped, we believe that there is an activation of polyamine metabolism in dopaminergic neurons, which as is known, leads to aggregation and fibrillation of α-synuclein *in situ*.

Long-term nicotine intake into brain tissue, in conditions of long-term tobacco use, largely reduces the risk of developing Parkinson's disease.

In our view, the "preventive effect" of nicotine on dopaminergic neurons is implemented through four interdependent mechanisms:

1. Through a receptor mechanism, due to the nicotinic acetylcholine receptors located on dopaminergic neurons,
2. Due to the balanced release and reuptake of dopamine in dopaminergic neurons.
3. By preventing the process of aggregation and fibrillation of α-synuclein.

Due to the inhibitory effect of nicotine on the activation of aliphatic polyamine synthesis in dopaminergic neurons that are mainly localized in the corpus striatum and nucleus caudatum.

In cases of nicotine "deficiency" in brain tissue, due to the abrupt smoking cessation by older adults, neurodegenerative disorders may develop in the central nervous system, pathognomonic for Parkinson's disease, since it is possible that dopamine and aliphatic polyamine metabolism is disturbed in dopaminergic neurons, processes of transforming soluble oligomers of α-synuclein into its aggregated and fibrillar forms are intensified. Ultimately, intraneuronal dopamine-synuclein complexes with a pronounced neurocytotoxic spectrum of action may appear.

In case of abrupt smoking cessation, we propose to the older adults the following "preventive" measures aimed at partial inhibition of polyamine-synthetic processes in dopaminergic neurons of the brain:

Use of α-difluoromethylornithine and its commercial dosage form – Eflornithine. The effect is achieved through the inhibitory effect of DFMO on the ornithine decarboxylase activity, as a result of which the initial stages of aliphatic polyamine synthesis are suppressed.

Use of polyamine-free and polyamine-deficient diets in the general registry of nutritious products. The main recommendations of both diets are given in our previous studies [*Avagyan S et al., 2020; 2022*].

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