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# POSSIBLE ROLE OF RESIDENT CONDITIONAL PATHOGENIC MICROORGANISMS AND HELICOBACTER PYLORI IN THE GENESIS OF PARKINSON'S DISEASE

*Avagyan S.A.[1]*, Zilfyan A.V. [1], Ghazarayan H.V. [2]*

[1] Scientific Research Center, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia
[2] Arpimed LLC Pharmaceutical Company, Abovyan, Armenia

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Abstract

*The present paper delivers informative data on impaired metabolism in the sections the brain, representative of Parkinson's disease. It's considered to be an established fact, that at all the stage of Parkinson's disease the level of aliphatic polyamines - putrescine, spermidine and spermine - the highest concentrations of which are known to be of cytotoxic spectrum activity, increases in dopaminergic neurons. The role of* **α***-synuclein in the development of dystrophic processes in dopaminergic neurons of the brain is also presented in the article. According the introduced in the paper the newest literature data, the association between the incidence of neurodegenerative disorder symptomocomplex occurrence in Parkinson's disease and Helicobacter pylori long-term persistence in the organs of gastrointestinal tract disease can be precisely traced. In this regard, the subject under wide discussion is the current hypothesis, according to which as a result of Helicobacter pylori persistence in neuritis, localized in the organs of gastrointestinal tract,* **α***-synucleins begin to cumulate and undergo aggregation. The main postulate of the hypothesis is based on the fact, that namely similar aggregates of* **α***-synucleins enter the sections of the brain by means of perineural penetration or/and through hematoencephalic barrier, causing neurodegenerative disorders, characteristic of Parkinson's disease. This hypothesis is considered by the authors from a critical point of view. Thus, more acceptable is the assumption, that it's not* **α***-synucleins but* **α***-synuclein autoantibodies produced in the organs of immunogenesis that penetrate through hematoencephalic barrier. In this regard, the role of the resident conditional pathogenic microorganisms, produced in the gastrointestinal tract, in the genesis of Parkinson's disease, in our opinion, should be observed from qualitatively new viewpoints. In this aspect, a special attention of the researchers should be paid particularly to the processes of E. coly bacterial translocation, the products of secretion and decomposition (putrescine, lipopolysaccharide) of which can induce the symptomocomplex, characteristic of Parkinson's disease by entering the brain through hematoencephalic barrier.*

**Keywords:** *Parkinson's disease, polyamines,* **α***-synuclein, Helicobacter pylori, E. coli, bacterial translocation.*

***The role of polyamines and α-synuclein in the induction of neurodegenerative disorders in Parkinson's disease.*** The role of aliphatic polyamines (putrescine, spermidine and spermine) and α-synucleins in the genesis of the nervous system diseases, such as Parkinson's disease and epilepsy, is nowadays a subject under discussion. Parkinson's disease is more obviously clinically manifested at the age of 60. Clinical picture is characterized by an increased movement slowness (bradykinesia), muscle rigidity, poor postural control, intermittent gait, insufficiency and limitations of direct movements, sudden loss of ability to move (akinesis). Motor impairments at the initial stages of Parkinson's disease are, as a rule, manifested on one half of the body, then somewhat later a decrease in motor activity with characteristic clinical symptoms affects the symmetrical half of the body. At the same time, it should be noted that the first symptoms of Parkinson's disease appear much earlier, 20-30 days after the onset of the disease, i.e. precisely at the time when a significant part of the dopaminergic neurons degenerate. Degeneration

*Address for Correspondence:*
***Stepan A. Avagyan*** PhD
Research centre, Yerevan State Medical University
2 Koryun Street, Yerevan 0025, Armenia
Tel.: (+374 10) 58-08-40
E-mail: namj.ysmu@gmail.com

of dopaminergic neurons, localized primarily in the substantia nigra leads to deafferentation of the corpus striatum. The resulting structural and functional changes in the above-mentioned areas of the brain are considered to be the key factors contributing to the pathogenesis of Parkinson's disease. At the initial stages, this process proceeds without marked clinical manifestations. The first symptoms appear in the patients only after the degeneration of 50-60% of dopaminergic neurons, localized in the substantia nigra and the decrease of dopaminergic neurons in the corpus striatum.

The structural changes occurring in dopaminergic neurons in Parkinson's disease, are currently the point at issue, as they play a considerable role in the development of neurodegenerative processes in the substantia nigra and corpus striatum. Dystrophic changes of progressive nature occur in dopaminergic neurons both in familial and sporadic forms of Parkinson's disease and ultimately result in the death of a large group of neurons. It is considered to be an established fact that aliphatic polyamines (putrescine, spermidine and spermine) play significant role in biochemical processes, selectively directed towards the activation of the neuronal function of various brain regions. At the same time, several highly informative publications, pointing to the role of polyamines in the pathogenesis of Parkinson's disease have appeared over the recent years (*1, 2, 3, 4*). As a rule, in all the studies aimed to identify the role of polyamines in the pathogenesis of Parkinson's disease, there is one important common fact, i.e. in all the biological objects under investigation, relatively high polyamine (putrescine, spermidine, and spermine) values were recorded in this disease. Moreover, some authors assume that even physiological concentrations of above-named aliphatic polyamines might be involved in the degenerative process induction mechanisms in Parkinson's disease (*2*).

In our opinion, the high levels of all three aliphatic polyamines (putrescine, spermidine and spermine) in complex do not still fully reflect their role in the induction of intracerebral disorders in Parkinson's disease, since each of the three above-named polyamines, in addition to common biologic effects have "individual" biological activity, typical only of each of them, depending on their application point as well. Moreover, while interpreting the obtained results, the "scope" of clinical studies characterizing the motor manifestations of Parkinson's disease was not fully taken into account. Thus, several scales for the quantitative analysis of motor manifestations in Parkinson's disease have been developed. Unified Parkinson's disease rating scale (UPDRS) appeared to be the most informative (*5, 6, 7*). However, in only a few reports on the role of polyamines in the pathogenesis of Parkinson's disease, the researchers used the most informative UPDRS which includes four sub-scales. The fact, in our opinion, undoubtedly had an extremely negative effect on the integration of the obtained paraclinical results.

Intracellular α-synuclein is currently associated with a wide range of neurodegenerative diseases such as dementia with Lewy bodies, multiple system dystrophy, pantothenate kinase-associated neurodegeneration, Pick's disease, diffuse Lewy body disease, amyotrophic lateral sclerosis, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, Krabbe disease, Alzheimer's disease, Parkinson's disease. All of the above-mentioned neurodegenerative diseases are considered under the general name "synucleinopathy". In Alzheimer's disease, α-synuclein was identified as a non-amyloid B-component (NAC), localized in amyloid plaques, while in Parkinson's disease, α-synuclein is nearly permanently present in Lewy bodies as oligomers and aggregate complexes (*8*).

The role of β and γ-synucleins in the genesis of neurodegenerative diseases is far less investigated. β and γ-Synucleins are not detected in Lewy bodies. In such diseases as Parkinson's disease, Lewy body dementia, diffuse Lewy body disease, frontotemporal dementia, Alzheimer's disease, Gaucher disease both synucleins are basically characterized by their typical localization in sphere-like neuronal inclusions (*8*).

Unlike the norm, in Parkinson's disease α-synucleins undergo significant structural changes in the bodies of neurons, in which N-terminally acetylated forms of α-synuclein begin to predominate, due to which its tendency to spiral folding dramatically increases. According to the information provided in the review article by *Burre J.*, the helical folding of α-synuclein in Parkinson's disease is accompanied by the conformation change of the latter, resulting in its aggregation and fibril formation with accumulation in Lewy bodies (*8*). Moreover, according to *Krasnoslobodtsev A. et al.*, (2012) oligomeric α-synuclein compositions turned out to be the most "neurotoxic".

Despite the fact that many types of neurons are involved in the pathological process in Parkinson's disease, the "loss" of dopaminergic neurons local-

ized in specific areas of the brain such as black substance, thalamus, hypothalamus, hippocampus, cerebellum, eye bulb is considered to be the underlying cause of the disease. In this aspect, the studies carried out by *Illes -Toth E. et al.,* (2013) on the binding mechanisms of dopamine to α-synuclein, in our opinion, are of considerable interest.

What particularly stands out is the assertion of *Jellinger K.A.,* (2011) according to which the selective loss of dopaminergic neurons and sedimentation of Lewy bodies, in the formation of which fibrillar α-synuclein takes an active part, acts as the main signs of Parkinson's disease. In the mechanism of damage to neuronal ultrastructure in Parkinson's disease, significant importance is given to intracellularly localized α-synuclein, as in the disease, the oxidative processes in nerve cells are activated, making dopaminergic neurons very vulnerable and often leading to the cell death. α-Synuclein plays an equally important role in the initiation of the "intraneuronal oxidative burst" process, due to mitochondrial damage, as a result of the association of α-synuclein with oxidative ligands (*11, 12, 13, 14*).

For this particular reason, α-synuclein should be given a more important part in the processes of the indicated neurotransmitter α-dopamine cumulation and release, since α-synuclein plays a crucial role in the "modulation of synaptic vesicle recycling" (*9*). In cases of impaired vesicle integrity, high concentrations of dopamine may be accompanied by destructive processes in dopaminergic neurons, due to the formation of the dopamine structural complex α-synuclein, which is endowed with a marked cytotoxic spectrum of action, i.e. in the induction of neurodegenerative disorders in Parkinson's disease (9, *15, 16*).

The conformational state of α-synuclein significantly affects the exchange of dopamine in the brain neurons. Normally, α-synuclein regulates the monoamine homeostasis in neurons (particularly, dopamine metabolism). At the same time, it was found, that overexpression of α-synuclein in Parkinson's disease is accompanied by dopamine synthesis inhibition in dopaminergic neurons. Simultaneously, under the conditions of α-synuclein overexpression and intraneuronal dopamine deficiency, dopamine reuptake by neuron is significantly suppressed, which allowed *Burre J.,* (2015) to conclude that dopaminergic neurons are characterized by a high dependence on α-synuclein function, and in pathological conditions they begin to display higher susceptibility to α-synuclein dysfunction. According to *Hansson O. et al.,* (2014), the oligomeric structures of α-synuclein turned out to be the most "toxic" in terms of the neurodegenerative disorder induction in Parkinson's disease. Along with the discovery of the fact, the authors recommend considering the levels of oligomeric α-synuclein in the cerebrospinal fluid, as an informative laboratory criterion for the differential diagnosis of Parkinson's and Alzheimer's diseases (clinical manifestations of dementia in Parkinson's and Alzheimer's diseases compared to dementia with the presence of Lewy bodies in neurons of the brain). According to *Sharon R. et al.,* (2003), *Paleologou E.E. et al.,* (2009) high levels of soluble α-synucleine oligomer in the cerebrospinal fluid in Parkinson's disease with evidence of dementia and dementia with the presence of Lewy bodies are the result of their intake from brain structures, since they are determined in relatively high concentrations in particular areas of the CNS.

Pursuant to some authors, *Hampel H. et al.,* (2010) the biomarker sometimes occurs to be more informative than the clinical symptoms of Parkinson's and Alzheimer's diseases. Therefore, certain α-synucleins in the form of oligomers, according to the authors, should be assumed an informative diagnostic and prognosis criterion for Parkinson's disease.

As mentioned above, α-synucleins localized in Lewy bodies of dopaminergic neurons have a significant part in the pathogenesis of Parkinson's disease. With the progress of the disease, the oligomeric structures of α-synucleins undergo fibrillation and aggregation. Unlike Parkinson's disease, the Tau proteins which are involved in "amyloid fibrillation" play an important role in Alzheimer's disease (*21*).

Tau proteins and α-synucleins in mammals are characterized by different localization in neurons, which, under normal conditions, largely reflects their functional purpose. So, Tau-protein stabilizes and stimulates the process of polymerization of microtubules (13, *22*), while α-synuclein is localized mainly in the terminal sections of axons, taking an active part in the synaptic function of dopaminergic neurons (*23*). Under the conditions of pathology, both proteins are polymerized into fibrils, which accumulate in the form of intraneuronal aggregates in a number of neurodegenerative diseases, referred to as "taupathy and synucleinopathy", respectively (*13, 23, 24, 25*). Thus, particularly neurofibrillary glomeruli formed from Tau proteins are considered pathognomonic for Alzheimer's disease, and Lewy bodies are the "pathological signature inclusions" of Parkinson's dis-

ease, consisting of α-synucleins (*21*). In the research by *Giasson B. et al.*, (2003) the modulating effect of Tau protein on α-synuclein fibrillation and vice versa was studied *in vitro* and *in vivo*. α -Synuclein was found to cause Tau protein fibrillation. It is noteworthy that co-incubation of the Tau protein and α-synuclein contributes to the fibrillation of both proteins. The authors come to a highly significant, in our opinion, conclusion that in a number of neurodegenerative diseases structural and functional remodeling of neurons in representative areas of the brain is largely due to the interaction between α-synuclein and Tau-protein by their fibrillation.

The results obtained by the authors deserve special attention as, in our opinion, the common Tau- and α-synuclein-dependent mechanisms are involved in Parkinson's and Alzheimer's diseases. These mechanisms apparently contribute to the target differentiated activation of intraneuronal fibrillation of Tau-protein in Alzheimer's disease and α-synuclein in Parkinson's disease. It is possible that at the initial stages of neurodegenerative disorder development in the CNS, a single-vector process occurs ensuring the simultaneous synthesis of Tau protein and α-synuclein. Subsequently, more intimate neuroendocrine neuromodulator mechanisms are involved in the pathological process, ensuring the formation of clinico-morphological symptoms, which determine its belonging to Parkinson's or Alzheimer's diseases.

According to the authors (*2*), polyamines (putrescine, spermidine, and spermine) even in physiological concentrations have a modeling effect on α-synuclein, which is expressed in the formation of fibrillar structures. The authors come to a highly significant, in our opinion, conclusion, that the aforementioned polyamines play an important role in the pathogenesis of neurological diseases, in which "cytolytic α-synuclein aggregates" act as a morphological substrate. The influence of polyamines on the structural organization of synucleins was also studied under experimental conditions by a number of researchers (*3*), who, when making experiments, adhered to a quite justified scientific and methodological approach that allowed the authors to extrapolate the results of an experiment on symptomatology of neurological diseases. Thus, in accelerated rats, the level of cellular polyamines was determined by aggregated α-synuclein. According to the authors, increasing the level of spermidine (and possibly other polyamines) initiates a number of neurological diseases associated with the aggregation of α-synuclein (Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis). The opinion was expressed that, in Alzheimer's disease polyamines indirectly (through α-synuclein) cause the formation and, subsequently, aggregation of the amyloid substance (*26*).

It should be particularly noted, that among the endogenous factors affecting the structural and functional characteristics of synucleins, over the past 25 years, special attention has been paid to polyamines - putrescine, spermidine, and spermine. At present, we are only at the initial stages of studying this issue. Some highly informative data concerning the causal relationship between polyamines and synucleins is presented to the reader. Thus, aliphatic polyamines (putrescine, spermidine, and spermine) accelerate the aggregation and fibrillation of α-synuclein, a large protein component of Lewy's bodies associated with Parkinson's disease (*27*). All three polyamines accelerate α-synuclein aggregation and fibrillation, depending on the total charge, the length in the common chain of specific polyamines and concentration. The method of electron and scanning microscopy to determine the substrate revealed the presence of aggregated particles of protofibrils and small fibrils. So, after the transient phase completion, α-synuclein forms long fibrils with minor morphological variations. In the presence of polyamines, fibrils begin to form long network-like formations, leading ultimately to thickening of the aggregates. In the absence of polyamines, fibrils look more isolated.

Apart from the brain neurons, α-synuclein expression was also revealed on the "periphery", i.e. in the hematopoietic cells (*28*), in the serum and red blood cells of elderly and senile patients. A number of authors (*4*) consider the presence of α-synuclein in plasma and erythrocytes to be risk markers of neurodegenerative diseases (Alzheimer's and Parkinson's diseases above all) in these groups of people.

Based on the aforesaid, it is very relevant, in our opinion, to conduct studies of theoretical and paraclinical orientation in neuralgia in the nearest future, aimed at clarifying the role of specific representatives of aliphatic polyamines - putrescine, spermidine and spermine in the processes of hypersecretion, fibrillation and aggregation of α-synuclein which plays an important role in the pathogenesis of Parkinson's and Alzheimer's diseases.

That is why the "simultaneous" determination of polyamines by high performance liquid chromatography and the determination of α-synuclein in

serum and erythrocytes in blood is extremely necessary in Parkinson's disease.

The subsequent stage in the planned studies should mandatorily be a multi-factor correlation analysis between specific clinical manifestations of Parkinson's disease on the one hand, and an intersystem correlation between the level of polyamines and α-synuclein in erythrocytes and plasma on the other.

Determination of polyamines and α-synucleins precisely at the periphery i.e. in plasma, urine, and erythrocytes occurs to be quite valid since, as indicated above by *Shin E. et al.,* (2000), high levels of α-synuclein and polyamines (putrescine, spermidine and spermine) in the above bioassays are considered to be informative criteria to diagnose the severity of Parkinson's disease. *Koehler N. et al.,* (2015) also regards the shifts in the content of polyamines and α-synuclein in the above-mentioned biological objects in the elderly and senile people as objective markers of the risk degree of Parkinson's disease.

***The possible role of α-synuclein produced in the gastrointestinal tract in the pathogenesis of Parkinson's disease in Helicobacter pylori.*** As noted earlier, many aspects of the Parkinson's disease pathogenesis are yet unsolved. Besides the local factors that contribute to the induction mechanisms of neurodegenerative disorders, the aspects regarding the role of infection are now under consideration, taking into account the taxonomic potency of specific pathogens.

Another aspect which currently deserves a special attention is the contribution of *Helicobacter Pylori* infection to the pathogenesis of Parkinson's disease. There have been highly informative reports on this issue published over the last 12 years (*29, 30, 31, 32, 33,* 46, *47*). The readers are highly recommended to get acquainted with the research of *Mc Gee D.J. et al.,* (2018), as many of the issues related to the role of *Helicobacter Pylori* infection in the induction mechanisms of Parkinson's disease are analyzed from the point of view presented in this review article. First of all, in our opinion, the epidemiological research turned out to be highly informative. Thus, in their research *Charlett A. et al.,* (1999) discovered that those suffering from Parkinson's disease had a threefold increased risk in terms of the seropositive response to *Helicobacter Pylori,* as compared to the control. A similar pattern was also revealed by a number of researchers (*37, 38, 39, 40, 41*) in the statistical analysis of significant number of cases, i.e. patients suffering from "idiopathic" Parkinson's disease. As noted by *Mc Gee J. et al.,* (2018), the associative links between Parkinson's disease and the persistence of *Helicobacter Pylori* in the gastrointestinal tract are not studied. According to the authors, there are many concerned factors in this case. There is an assumption, that a number of substances with a toxic spectrum of activity, being the products of the *Helicobacter Pylori* synthesis are "concerned" in the pathogenesis of Parkinson's disease. Thus, *Helicobacter Pylori* particularly produces a compound which is considered to be one of the factors of toxic effect on the brain tissue in Parkinson's disease. This compound is similar in structure to methyl 4-phenyl-1,2,3,6-tetrahydropyridine (*42*). It's this compound that is used to obtain a model of Parkinson's disease in laboratory animals. In addition, *Helicobacter Pylori* produces a number of other toxins (vacuolating cytotoxin, Vac A and the gene associated with the cytotoxin encoding Cag A) (*38*). The "vitality" of *Helicobacter Pylori* and its long persistence in the gastrointestinal tract, is largely due to the microorganism entrance into the cytoplasm. According to *Bjorkhem J. et al.,* (2013), cholesterol glucosides formed in *Helicobacter Pylori,* can penetrate from the gastrointestinal tract through the blood-brain barrier into the brain tissue, causing neurodegenerative changes in the brain neurons, pathognomonic for Parkinson's disease.

Another noteworthy subject of current discussion is the data, according to which, as a result of *Helicobacter Pylori* persistence in the stomach, **α**-synuclein aggregation takes place in the gastric nerve, which penetrating through the blood-brain barrier causes clinico-morphological symptomocomplex. A similar mechanism is symbolically designated as a "double impact hypothesis". There is another opinion which suggests that, as a result of long-term inflammatory process persistence in the stomach, various biologically active substances of cytokine, pro-inflammatory and toxic spectrum of action penetrate from the stomach through blood-brain barrier into the brain, potentiating the α-synuclein penetration into the glial cells (*44, 45*). According to *Noto J.M., Peek R.M.,* (2007), due to *Helicobacter Pylori* long persistence in the gastrointestinal tract, regional microbial homeostasis is disrupted, leading to the development of dysbacteriosis. As a result, regionally functioning immune cells, and leukocytes first of all, secrete neurotoxic factors that penetrate the blood-brain barrier and contribute to the aggregation of α-synuclein (*37, 33, 47*). Somewhat doubtful, according to *Mc Gee D.J.,* (2018), is the assumption that *Helicobacter Pylori* penetrates the blood-brain barrier in cases where

this microorganism is phagocytosed by monocytes and white blood cells localized in different parts of the gastrointestinal tract.

In general, the possible peripheral mechanisms underlying the induction of neurodegenerative disorders, in which α-synucleins produced in different sections of the gastrointestinal tract are concerned, are thoroughly analyzed and summarized as a hypothesis in a review article by *Mulak A., Bonaz B.* (2015). According to the authors, Parkinson's disease is characterized as α-synucleopathy. Peripheral mechanisms localized in the nervous apparatus of the gastrointestinal tract underlie the induction of the disease.

In the hypothesis, the violation of intestinal bacterial homeostasis, characterized by an excessive growth of gram-negative microflora, is considered to be the initial stage of the Parkinson's disease onset. As a result of dysbacteriosis, the permeability of the micro vessels of the intestinal tract increases markedly, which is accompanied by a regional inflammatory reaction with the development of a number of pro-inflammatory factors, including the ones of the cytotoxic spectrum of action.

At the same time, according to the suggested hypothesis, the authors consider regional processes in glial cells of the nervous apparatus of the gastrointestinal tract associated with the synthesis of **α**-synuclein as a fundamental link in the development of a symptomocomplex, pathognomonic for Parkinson's disease. The concept of the brain-gastrointestinal tract-microbiota axis, which exists in Parkinson's disease, has been put forward. It is based on a hypothesis of chronological sequence of the stage development, as given in the points 1-6 below.

1. The state of dysbacteriosis associated with impaired intestinal bacterial homeostasis, is accompanied by the development of a regional inflammatory process, with the development of anti-inflammatory mediator factors, including the ones of the neurotoxic spectrum of action.
2. Synthesis of α-synuclein in glial cells of the nervous tissue of the gastrointestinal tract, with subsequent production of autoantibodies to α-synuclein by immunocompetent cells.
3. Perineural penetration of α-synuclein (in a retrograde manner) and/or through the blood-brain barrier into the brain tissue of the brain.
4. In the brain tissue, α-synuclein from the periphery "cumulates" mainly in glial cells.
5. As a result of the existing associative link between glial cells and neurons, α-synuclein begins to accumulate in the cytoplasm of neurons, with the formation of Lewy's bodies.
6. The process of α-synuclein cumulation in the nerve cells of the brain, according to the suggested hypothesis, triggers the initial stage of neurodegenerative disorders in Parkinson's disease.

In the light of the analysis of available literature information on this issue, we consider it necessary to share our thoughts with the reader.

The above hypothesis was based mainly on literature data concerning the mechanisms of peripheral synthesis of **α**-synuclein in the nervous system in *Helicobacter Pylori* infection. At the same time, the role of conditionally pathogenic resident microorganisms, persistent in the alimentary tract has not been well covered. Only in single reports (as mentioned above) has the role of E. coli liposaccharide in the directed synthesis of **α**-synuclein antibodies by immunocompetent cells been discussed. In this aspect, the very informative data presented in the publication by *Sergeeva T.N.* and *Sergeev V.G.* (2011) deserves special attention. As a result of the carried-out studies, the authors conclude that with a single intraperitoneal introduction of bacterial endotoxin (commercial LPS E. coli drug) the number of immunocompetent cells (macrophages and lymphocytes) with high **α**-synuclein expression increases significantly in lymph nodes. On *in vitro* E. coli stimulation, introduction of specifically stimulated macrophages to animals is accompanied by the activation of humoral immunity reactions, aimed at selective synthesis of **α**-synuclein antibodies by immunocompetent cells. Under certain favorable condition, such as introduction of high doses of LPS E. coli to laboratory animals, resulting in the blood-brain barrier permeability increase, circulating α-synuclein antibodies penetrate the nervous tissue, subsequently developing degenerative disorders in the dopaminergic neurons.

In our opinion, the perineural and/or hematoencephalic barrier paths of **α**-synuclein entry into the brain from periphery is extremely doubtful, since conditions for local **α**-synuclein synthesis by glial cells of the brain tissue occur in Parkinson's disease. It is also possible that, produced at the periphery, **α**-synucleins in the course of their perineural "migration" and/or blood entry are exposed to various hematogenous factors, phagocytosis and intracellular aggregation, which makes their entry into the brain by perineural path and, moreover, through the hematoencephalic barrier almost unreal.

Hitherto, the mechanisms underlying the directed synthesis of **α**-synuclein in glial cells of the

brain, followed by its accumulation in neurons are not sufficiently studied.

According to the suggested hypothesis, the **α**-synuclein migration to the brain with its subsequent phagocytosis by glial cells is considered as a pathological process that occurs mainly in *Helicobacter Pylori* infection. Moreover, the possible paths of **α**-synuclein "penetration" into the neuronal cytoplasm from glial cells have not been studied. The "peripheral pathway" of the **α**-synuclein entry into the nervous tissue also seems rather doubtful, since in case it is involved, the pathological process would be diffuse, covering all zones of the brain. At the same time, as it is known, in Parkinson's disease, it's mainly dopaminergic neurons, localized in specific areas of the brain, that are affected.

The main thing is, in our opinion, one significant circumstance that has been overlooked by the supporters of the hypothesis. When analyzing modern literature, it becomes obvious that under the normal functioning conditions of the brain dopaminergic neurons, intraneuronal α-synucleins play a very important role, as it is α-synucleins, localized in the region of synaptic neuron terminals, which provide the plastic function of the latter, taking an active part in the spread of the nerve impulses.

In our opinion, dysbacteriosis occurring in the intestinal tract, especially when there is a noticeable activation of the resident gram-negative microflora (primarily E. coli), cannot but affect the morpho-functional state of the brain neurons. I recommend the readers to get acquainted with the fundamentals presented in "System of Intracorporal Resident Association of Microorganisms", the monograph published in 2016 by Professor Zilfyan A.V., the Honored Scientist of the Republic of Armenia, in which the mechanisms associated with the emergence of bacterial translocation of resident intestinal microorganisms, both in normal conditions and pathology, are highlighted from a qualitatively new aspect (54). Thus, according to the author, under the conditions of normal body functioning, endotoxins of resident gram-positive and gram-negative microorganisms participate in the processes of neuroendocrine regulation as evidenced by the facts of selective activation of catecholamine, serotonin and cholerenergic systems, in the certain brain structures. In this case, in our opinion, at least 3 mechanisms are involved. The effect is realized by: 1. stimulation of immunocytes by endotoxin and the subsequent entry of cytokines from the periphery into the central nervous system, through the blood-brain barrier; 2. local synthesis of lymphokine-like factors and other mediators in the central nervous system (by glial cells and neurons) due to endotoxin (LPS) E. coli penetration through the blood-brain barrier.

The fact that lipopolysaccharide E. coli and putrescine are determined in the serum of a healthy individuals and intact animals - with great constancy, but in rather low concentrations - also indicates the important role of the products of E. coli synthesis - endotoxin and putrescine in the processes of integrative activity of mammals. So, the concentration of lipopolysaccharide E. coli in the serum of human is 0.076 *ng/ml* (*49*); in the serum of pigs - 0.2 *ng/ml* (*50*). According to *Ikeguchi Y. et al.*, the level of putrescine in the serum of mammals is determined to be within 20 ± 2 *nmol/g* of blood protein (*51*), while according to the data by *Delzenne N. et al.*, it is 8,2 ± 1.2 μmol/l (52).

It is necessary to take into account the fact that under physiological conditions, the blood-brain barrier is bilaterally permeable both for some pro-inflammatory immunocytokines and for LPS E. coli. (53).

Under the conditions of pathology, as a result of the sharp activation of the bacterial translocation process, the migration of conditionally pathological microorganisms (primarily E. coli.) from the intestine, with their hematogenous spread to the new host econiches occurs, which does not exclude the entry of E. coli synthesis and decomposition products (putrescine and endotoxin) into the central nervous system. A number of authors do not exclude the E. coli entry into the brain as a result of the increased permeability of the hemato-synovial barrier.

However, a similar entry mechanism of synthesis and decomposition products of intestinal resident gram-negative microorganisms into the brain tissue undoubtedly should be of a diffuse character, covering glial neurons localized in all sections of the brain. That is particularly why the role of *Helicobacter Pylori* intestinal resident microflora (under conditions of dysbacteriosis) and α-synuclein production in glial cells of the enteric nervous system in Parkinson's disease is very doubtful, especially since in this disease selectively affected are dopaminergic neurons, localized only in specific areas of the brain.

At the same time, the autoimmune damage mechanism of dopaminergic neurons and glial cells in the corresponding brain sections due to **α**-synuclein autoantibodies produced by the immunocompetent cells on the periphery, in our opinion, seems to be

more real and apparently involved in the Parkinson's disease against the background of dysbacteriosis. The penetration of specific autoantibodies by the selective increase in the permeability of the blood-brain barrier we consider to be more real. Such autoantibodies will certainly undergo selective expression precisely on dopaminergic neurons whose cytoplasm, in Parkinson's disease, is "saturated" with **α**-synucleins in the form of their oligomeric configurations and/or in the form of fibrillar aggregation. The assumption seems to be very reasonable, since it is also based on the analysis of the very informative data available in the literature on the role of anti-**α**-synuclein antibodies in the development of neurodegenerative disorders induced under the experimental conditions. Thus, by experimental studies, on the "Parkinson's disease" model, it was found that autoantibodies to **α**-synuclein produced in cells of the phagocytic series have neurotoxicity, causing the selective death of dopaminergic neurons in the substantia nigra (*55*).

All pointed above, from our standpoint, allows to approach the problem from a drastically another position aimed to determine the role of synuclein in physiological activity of mammal organism. Unfortunately, the only available is the information concerning physiological role of **α**- synucleins in the neurons (not even in all the neurons, but only in dopaminergic ones) in which **α**- synuclein plays a plastic role in the nerve impulse transmission. Paradoxically, the physiological purpose of **β** and **γ**-synucleins hasn't been the subject of the special study.

In our opinion, the researches aimed to determine the physiological significance of synucleins in the integrative activity of the organism, performed at least within the framework of the nervous, immune, endocrine and reproductive systems have high perspectives.

The standpoints of the physiological role of erythrocytes also need to be substantially revised, since their function goes far beyond the framework of intracellular oxygen transport and transmembrane transport of endogenous biologically active substances. It's highly likely that mammalian erythrocytes have a multipotent spectrum of action and we consider this demands special investigations to be carried out by the advanced scientists in the fields of molecular biology, biochemistry, biophysics and medicine.

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