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ACCUMULATION OF AGGREGATED ALPHA-SYNUCLEIN IN NEURAL TISSUE STRUCTURES IN NEURODEGENERATIVE DISEASES

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ABSTRACT

A critical analysis of the literature on the structure and properties of alpha-synuclein under physiological and pathological conditions is presented, when the conformation of this protein changes, which contributes to its aggregation and changes in localization features in brain structures in such neurodegenerative diseases as Parkinson's disease, dementia with Lewy bodies, multiple systemic atrophy and Alzheimer's disease. It has been shown that the toxic effect of conformationally altered alpha-synuclein can indirectly affect the functions of neurons due to its interaction with neuroglial cells, primarily microglia and astrocytes, and can also modulate the aggregation and expression of other proteins that are functionally important for the development of neurodegeneration.
Further study of the mechanisms of interaction of conformationally altered alpha-synuclein with other proteins and clarification of the relationship between its accumulation in brain structures and neuronal dysfunction remains relevant for modern neurology.
Literature search was carried out in the "PubMed" and "eLIBRARY" databases.

Key words: *conformations of alpha-synuclein, neurons, neuroglia, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Alzheimer's disease*

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НАКОПЛЕНИЕ АГРЕГИРОВАННОГО АЛЬФА-СИНУКЛЕИНА В СТРУКТУРАХ НЕРВНОЙ ТКАНИ ПРИ НЕЙРОДЕГЕНЕРАТИВНЫХ ЗАБОЛЕВАНИЯХ

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РЕЗЮМЕ

Представлен критический анализ литературы о строении и свойствах альфа-синуклеина в физиологических условиях и в условиях патологии, когда изменяется конформация этого белка, что способствует его агрегации и изменению особенностей локализации в структурах головного мозга при таких нейродегенеративных заболеваниях, как болезнь Паркинсона, деменция с тельцами Леви, множественная системная атрофия и болезнь Альцгеймера.
Показано, что токсическое действие конформационно изменённого альфа-синуклеина может опосредованно влиять на функции нейронов вследствие его взаимодействия с клетками нейроглии, в первую очередь с микроглией и астроцитами, а также может модулировать агрегацию и экспрессию других белков, функционально значимых для развития нейродегенерации.
Дальнейшее исследование механизмов взаимодействия конформационно измененного альфа-синуклеина с другими белками и уточнение взаимосвязи между его накоплением в структурах головного мозга и дисфункцией нейронов остаются актуальными для современной неврологии.
Поиск литературы проводился в базах данных «PubMed» и «eLIBRARY».

Ключевые слова: *конформации альфа-синуклеина, нейроны, нейроглия, болезнь Паркинсона, деменция с тельцами Леви, множественная системная атрофия, болезнь Альцгеймера*

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INTRODUCTION

Most neurodegenerative diseases associated with old age are characterised by morphochemical signs of proteinopathies, i.e. impairment accompanied by disturbances in the structure of certain proteins (alpha-synuclein, tau-protein, beta-amyloid, etc.) and their metabolism [1]. The most common diseases in this group are Parkinson's (PD) and Alzheimer's (AD) diseases [2]. At their core are proteinopathies associated with impaired aggregation of alpha-synuclein, a protein that accumulates in brain structures [3]. In experiments on laboratory animals and studies using brain autopsy material in the mentioned nosological forms of alpha-synucleinopathies, the peculiarities of changes in the structure of this protein have been revealed [4], but the peculiarities of its accumulation in nervous tissue in these and other forms of alpha-synucleinopathies have been studied insufficiently.

THE AIM OF THE STUDY

To characterise the peculiarities of aggregated alpha-synuclein accumulation in neural tissue structures in neurodegenerative diseases based on the analysis of literature sources.

GENERAL CHARACTERIZATION OF ALPHA-SYNUCLEIN AND ITS BIOCHEMICAL PROPERTIES

Alpha-synuclein is a small protein (molecular mass not exceeding 40 kilodaltons) that is synthesised mainly in the cytoplasm and presynaptic terminals of neurons of the human and vertebrate central nervous system [5]. The structure of this protein distinguishes between a hydrophobic central domain, known as the non-amyloid component, and two terminal areas: one is the N-terminal, which exhibits amphipathic properties and interacts with cell membranes, and the other area is the negatively charged C-terminal, which contains several phosphorylation sites [6]. The non-amyloid component accumulates in high concentrations in senile plaques during AD [7], the N-terminus has the ability to undergo most of the known mutations associated with PD – A53T, A30P as well as E46K, G51D and H50Q [8], and phosphorylation (by serine) of site-129 of the C-terminus causes impaired polymerisation and aggregation of alpha-synuclein with subsequent formation of intracellular inclusions in brain structures, which is characteristic of both PD and other alpha-synucleinopathies (dementia with Lewy bodies (DLB), multiple system atrophy (MSA), etc.) [9]. Compared to other synucleins with a similar structure to alpha-synuclein, it has a significant level of expression in brain structures (compared to gamma-synuclein) and is capable of aggregation (compared to beta-synuclein, which has no non-amyloid component in its structure) [10].

Alpha-synuclein is characterized by structural diversity. Thus, while in physiological conditions it is located in cells in the state of a monomer (non-toxic low-molecular polypeptide capable of polymerisation reactions), in the above-mentioned neurodegenerative diseases its structure changes, which promotes its self-organisation first into oligomers (dimers, trimers, tetramers), which consist of single monomers, and later, by transforming all or part of the previously unstructured polypeptide into well-defined β-sheet-rich secondary structures (insoluble filaments or fibrils) [11], penetrating into other neurons, "recruiting" endogenous alpha-synuclein into them, and forming new insoluble aggregates [12]. Due to the ability of pathological forms of alpha-synuclein to be transmitted from neuron to neuron, alpha-synucleinopathies are often correlated with prion diseases [13] and it is assumed that, by analogy with prion diseases, which are caused by different strains of prions that differ in their biochemical characteristics (ability to be cleaved by proteinase K, glycosylation capacity, etc.), different alpha-synucleinopathies may also be associated with different "strains" of pathological alpha-synuclein [14]. As evidence, the observation that the pathological process in the limbic cortex, as well as in other areas of the brain, develops much faster in DLB than in PD [15] is provided, and it is suggested that this may be due to the fact that these diseases are caused by different "strains" of alpha-synuclein [6]. Such evidence is not conclusive, however, since to date no biochemical differences have been demonstrated between the types of alpha-synuclein that accumulates in cortical structures during PD and DLB. It would appear that a more significant argument in favour of the "prion hypothesis" is the fact that wild-type alpha-synuclein contains glutamate at amino acid residue 46 and lysine in cases of hereditary forms of PD [16]. The change in this residue is sufficient to prevent alpha-synuclein conformation, which accumulates in hereditary forms of PD, from adopting any of the conformations that alpha-synuclein protofibrils have in MSA.

Alpha-synuclein under physiological conditions can be found in the cell in a membrane-bound and soluble stable state; the latter was discovered by examining the proteins in human erythrocytes using analytical centrifugation [17, 18]. In cells, alpha-synuclein binds to lipid membrane structures such as liposomes, lipid droplets and lipid rafts, which require the presence of oxidised lipids [19] such as phosphatidylserine or phosphatidylinositol and involves membrane interaction with lysines found in the structure of this protein. Binding to negatively charged lipid membrane structures causes alpha-synuclein to acquire a helical conformation [20]. This form of alpha-synuclein is thought to be observed in cells as two variants: a single elongated α-helix and a broken α-helix represented by two antiparallel non-interacting helices [21]. Molecular modelling methods have been used to reveal that the formation of an elongated α-helix is promoted by the interaction of alpha-synuclein with membrane structures of large diameter (~100 nanometres or more), while its interaction with membrane structures of smaller diameter promotes the formation of a broken α-helix

[22]. The above spiral shapes appear to be characteristic of native alpha-synuclein under physiological conditions, whereas under pathological conditions it takes the form of a β-sheet. This alpha-synuclein conformation is associated with the processes of aggregation of this protein, formation of fibrils and their deposition in Lewy's bodies, which are formed in the black substance neurons of the brain as a result of PD [23]. The β-sheet alpha-synuclein conformation is thought to be neurotoxic, but the exact genesis of this form remains unclear [24].

ALPHA-SYNUCLEIN TOXICITY AND ITS INTERACTION WITH NEURONAL DYSFUNCTION

Serine phosphorylated alpha-synuclein (α-Syn-p129) was found experimentally to be highly toxic regardless of the size of its aggregates accumulating in nerve cells and neuropil [25]. Accordingly, it was revealed that if both single oligomers of α-Syn-p129 and its larger aggregates (fibrils) obtained from PD patients were stereotactically injected into the brain shell structures of adult baboons, which in turn were isolated from Lewy's bodies of autopsy brains of individuals with PD (brain donation programme of the Brain Bank 'GIE NeuroCEB'), then in 2 years in experimental animals, regardless of the size of alpha-synuclein fractions administered to them, neurodegeneration developed in the compact part of the black substance of the brain, leading to the death of not only dopamine neurons, but also other neurons. The cytotoxicity of alpha-synuclein may be attributed to its ability to bind to large curvature membranes [26], which is a common property for amphipathic α-helices and is explained by the fact that, compared to flattened membranes, large curvature membranes provide a higher density of binding sites for helix-shaped proteins when interacting with lipid membrane structures [27]. Furthermore, it is suggested that in impairment, alpha-synuclein, by acting on mitochondrial membranes, may cause their fragmentation [28]. At the same time, binding mainly to the inner mitochondrial membrane, it can interact with complex I, which reduces mitochondrial activity and increases autophagy (mitophagy) of these structures [29].

The neurotoxicity of α-Syn-p129 is also manifested in the fact that it can induce the influx of calcium ions into the cell both directly, through the formation of pore-like ring structures in the plasma membrane [30], and indirectly, through the activation of potential-dependent N-type calcium channels [31], as a result of which the concentration of calcium ions in neurons increases, and the cell membrane of the nerve cell depolarises, which leads to the release of neurotransmitters.

The toxicity of alpha-synuclein conformation may be associated with the loss of the helical conformation by this protein [32]. The relative stability of helicality was demonstrated in an in vitro experiment in which the addition of small single-layer negatively charged lipid vesicles did not induce significant conformational changes in the native alpha-synuclein tetramer [17]. However, exposure to a number of factors, such as genetic mutations, aging, inflammatory process, and environmental toxins, can contribute to the fact that it loses the orderliness of its structure and consequently loses its helical conformation, taking the form of an insufficiently structured protein, i.e. β-sheet [33]. Such alpha-synuclein conformation is adopted in neurodegenerative diseases, the development of which is induced by oxidative stress and accumulation of nitric oxide (II) in nervous tissue [34]. Alpha-synuclein oligomers formed during oxidative stress are phosphorylated and as a result hydrogen peroxide molecules are released [35]. This process results in the presence of transition metal ions exhibiting redox properties: Fe (II), Cu (I) and others. Metal ions, binding to the alpha-synuclein molecule, form specific oxygen bridges that are destabilised when the alpha-synuclein conformation changes and oligomerises. This releases superoxide anion, which subsequently undergoes reversible conversion to hydrogen peroxide [36]. Nitrosative stress, in which the formation of active nitrogen forms exceeds the possibilities of their neutralisation or elimination, leads to the formation of covalent bonds between nitric oxide (II) and specific thiol groups of proteins and can be considered as a probable mechanism, contributing to NO-induced incorrect aggregation of various proteins, including alpha-synuclein [37], which is confirmed by the detection of nitrosylated alpha-synuclein in Lewy's bodies, which are localised in brain structures during PD [38].

The relationship between the accumulation of highly toxic α-Syn-p129 in neurons and their dysfunction, however, remains unclear [39]. The number of neurons in the black substance significantly decreases even before the development of the main clinical symptoms of PD or at early stages of the disease (from 50 to 90 %) [40], which, according to studies of the relationship between neuronal loss and the accumulation of α-Syn-p129 in dopamine neurons of the black substance in this impairment, suggests that its accumulation in brain structures is not as significant as the loss of nerve cells [39]. In other nervous system entities, such as the enteric nervous system, the clinical manifestations of Parkinsonism are not related to neuronal death but to the accumulation of α-Syn-p129 in nervous tissue [41]. Simultaneously, transgenic mice with high expression of wild-type alpha-synuclein showed impaired behavioural responses associated with changes in olfaction, intestinal peristalsis and motor activity, but they did not reveal morphological signs of neurodegenerative process [42]. Besides, morphological signs of alpha-synuclein accumulation were observed in autopsy material of the midbrain of elderly people who died from intercurrent diseases, but no neurological symptoms were revealed in these people during their lifetime [43]. Accordingly, it is suggested that the accumulation of aggregated alpha-synuclein in the brains of neurologically healthy individuals is an adaptive response of the organism, and the increase in morphochemical indicators of the neurodegenerative process

in the brains of PD patients is the result of the accumulation of toxic α-Syn-p129.

Consequently, despite the high toxicity of α-Syn-p129, the excessive accumulation of this protein in nervous tissue alone is clearly insufficient for the development of neurodegeneration, and its actual role in the development of this process remains to be determined.

The information about the structural characteristics of aggregated alpha-synuclein and its neurotoxicity outlined above was obtained mainly in experimental animal studies. Accordingly, they do not provide a complete picture of the morphological basis and possible mechanisms of pathogenesis of alpha-synucleinopathies. Meanwhile, these data significantly expand and supplement the data of pathomorphological studies performed by immunohistochemical methods on autopsy material of patients with alpha-synucleinopathies.

ALPHA-SYNUCLEIN LOCALIZATION AND ACCUMULATION IN PARKINSON'S DISEASE

Localisation of α-Syn-p129 during PD, considered as an alpha-synucleinopathy, is observed not only in the central (CNS) but also in the peripheral nervous system [44], and in the latter this protein often starts to accumulate earlier than in the CNS [45]. This can probably explain the earlier appearance during PD of symptoms indicating peripheral cranial nerve damage (hyposmia, reduced visual contrast and colour discrimination), symptoms of gastrointestinal and cardiovascular dysfunction, and the later appearance of symptoms of motor disorders, which are considered to be the main clinical manifestations of the disease [44].

The sequence of α-Syn-p129 deposition in different parts of the nervous system revealed in pathomorphological studies formed the basis for the scheme of clinical and morphological stages of PD, which considered the involvement of both peripheral and central parts of the nervous system in the pathological process and postulated the spread of pathological changes from caudal brain formations to cortical formations [46]. Furthermore, the "double hit" hypothesis has been proposed to explain the progression of PD in terms of matching the sequence of stages of the clinical picture of the disease with the morphological changes observed [47]. Based on this hypothesis, an unknown neurotropic pathogen (presumably a virus) can penetrate through the olfactory tract and the fibres of the vagus nerve innervating the digestive system into brain structures: in the first case into the temporal lobe, in the second case into the medulla oblongata, pons cerebelli and mesencephalon. In the latter formation, namely in the compact part of the black substance, there is a secondary accumulation of α-Syn-p129 in the form of Lewy's bodies localised both in the cytoplasm of neurons and outside the cells, resulting in the death of dopamine neurons. Initially, α-Syn-p129 accumulates either in the olfactory bulbs or in the dorsal motor nucleus of the glossopharyngeal and vagus nerves. The hypothesis was confirmed by cross-sectional analysis of pathological changes in brain samples from individuals with PD who died as a result of intercurrent diseases. The scheme of PD stages and the "double hit" hypothesis, despite its popularity, have been repeatedly and justifiably criticised by the scientific community. Consequently, α-Syn-p129 accumulations were revealed simultaneously in various brain formations, thus refuting the possibility of this protein spreading only in the direction from the medulla oblongata to the mesencephalon and cerebrum structures [48]. Besides, the concept did not explain the presence of oligomeric alpha-synuclein in elevated amounts in the plasma and liquor of PD patients [49]. Finally, the scheme to define the clinical and morphological stages of PD was questioned by the author himself [50].

It is currently believed that impaired alpha-synuclein aggregation, and subsequently its accumulation, occurs simultaneously in several structures of the central and peripheral nervous system already at the latent stage of the neurodegenerative process [51]. Furthermore, single-photon emission computed tomography revealed that different clinical scenarios of PD course correspond to the involvement of different structures of the nervous system in the pathological process [52], and the accumulation of α-Syn-p129 in the nervous tissue is not always the cause of dopamine neuron death in this disease [53]. The accumulation of α-Syn-p129, however, can activate microglia whose activity level corresponds to the degree of neurotoxicity [54], and, in addition, oligomeric alpha-synuclein enhances the phagocytic function of microglia [55].

Consequently, α-Syn-p129, which accumulates in brain structures during PD, can apparently have the same toxic effect on dopamine neurons of the black substance as other pathogenic factors: metal ions, pesticides, etc. [56].

ALPHA-SYNUCLEIN ACCUMULATION IN OTHER NEURODEGENERATIVE DISEASES

Clinically, DLB is very similar to dementia during PD [57], and they are distinguished using the "1-year rule": if dementia occurs against the background of PD at least 1 year after diagnosis, the case is considered as 'dementia in Parkinson's disease'; if dementia precedes or occurs simultaneously with the appearance of clinical symptoms of Parkinsonism or it develops within a year after their appearance, DLB is diagnosed. Both diseases are characterised by the accumulation of aggregated alpha-synuclein in the form of Lewy bodies and Lewy neurites, which in autopsy brains of individuals with PD are revealed only in brainstem and limbic system structures, while in DLB and dementia developed on the background of PD, they are also found in the neocortex [58]. Positron emission tomography and pathomorphology revealed that cortical atrophy in DLB was more pronounced

than in dementia developed on the background of PD [59]. However, the number of Lewy bodies in the limbic region, especially in the CA2 field of the hippocampus, and in the temporal region of the neocortex was significantly higher during DLB than in dementia developed on the background of PD [60], and in the latter case there was significantly higher death of dopamine neurons in the black substance [61]. Moreover, DLB is characterised by loss of dopamine neurons in the medioventral segment of the black substance, whereas dementia in PD is characterised by loss of dopamine neurons in its dorsolateral segment.

Along with the fact that aggregated alpha-synuclein in the structures of nervous tissue was revealed in PD and DLB, it was also observed in MSA [62], but, unlike PD and DLB, alpha-synuclein deposits in MSA were mainly accumulated in the cytoplasm and nuclei of oligodendrocytes, and they were also observed in the bodies and outgrowths of neurons [63]. Autopsy samples from the cerebrum ($n = 14$) and spinal medulla ($n = 11$) of MSA patients revealed alpha-synuclein inclusions in the cytoplasm of glial cells in structures of the motor cortex, putamen, pontine, medulla oblongata, and suprasegmental centres of the autonomic nervous system [64], as well as in the caudate nucleus, external pallidum, black substance, locus coeruleus, and cerebellum [65]. Considering that alpha-synuclein is not expressed in significant amounts in oligodendrocytes under physiological conditions, it is not clear how its aggregated form accumulates in the cytoplasm of glial cells in impairment [66]? In addressing this issue, some authors believe that pathological inclusions in neuroglia can be formed on the basis of aggregated alpha-synuclein, which is released from neurons and then captured by neighbouring astrocytes [67], while others suggest that the cause of accumulation of alpha-synuclein aggregates in oligodendrocytes is *SNCA* gene activation [66]. In addition, in vivo experiments demonstrated that oligodendrocytes can internalize aggregated alpha-synuclein when administered to mice [68].

AD in a significant number of cases (up to 50 %) manifests accumulation of aggregated alpha-synuclein in brain structures [69], mainly in the amygdala [70], albeit its accumulation is not considered a characteristic pathomorphological sign of this disease. For instance, on autopsy brains by immunohistochemical methods, Lewy bodies were found during AD in 10 out of 22 cases [71] and were detected in the bodies rather than in the outgrowths of neurons [72]. It is suggested that alpha-synuclein during AD directly interacts with Aβ-peptide and tau-protein, and this contributes to the mutual aggregation of these proteins [73]. Meanwhile, it has been also revealed that injection of tau-protein grains and preformed fibrils derived from purified recombinant alpha-synuclein into the hippocampus and cortical plate region of laboratory mice significantly increases the number of tau-positive neurons but does not affect the number of alpha-synuclein-positive neurons [74].

Consequently, alpha-synuclein can modulate the aggregation and expression of other proteins functionally relevant for the development of neurodegeneration during AD, but the effect of these proteins on alpha-synuclein aggregation has not been proven to date.

CONCLUSION

It has therefore been established to date that alpha-synuclein under physiological conditions is found in the cytoplasm of neurons and presynaptic terminals of axons. In impairment it can change its conformation and acquire neurotoxic properties, which are being realised as a result of its interaction with elements of neuroglia, primarily with microglial cells and astrocytes. Moreover, it can modulate the expression of other neuronal proteins functionally relevant in neurodegenerative diseases such as PD, DLB, MSA and AD. Along with this, the data about the accumulation of aggregated alpha-synuclein in the structures of nervous tissue do not allow us to fully establish its role in the pathogenesis of these diseases, but this seems possible if we continue to study the mechanisms of its interaction with other proteins and clarify the relationship between its accumulation in brain structures and neuronal dysfunction.

Conflict of interest

The authors of this article declare no conflicts of interest.

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