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PERIPHERAL DYSFUNCTIONS IN NEURODEGENERATIVE DISEASES: MECHANISMS AND CONTRIBUTION TO PATHOGENESIS

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Abstract

Neurodegenerative disorders (NDD) – Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis – affect about 10% of the elderly population worldwide, which makes them one of the most important medical and social problems. Numerous literature data confirm that NDD are related not only to CNS dysfunction, but also to dysregulation and pathological changes in peripheral tissues (neuromuscular synapses, skeletal, and cardiac muscles). These peripheral disorders may be important in the NDD pathogenesis by contributing to the pathological processes that directly lead to disability and death of patients (atrophy and paralysis of skeletal muscle, myocardial infarction, etc.). Notably, the pathology of neuromuscular and cardiovascular systems in NDD is currently underestimated und insufficiently studied, but it is not merely a "reflection" of degenerative changes in the nervous system, being rather a separate aspect of the pathogenesis of NDD. Several studies showed that peripheral dysfunctions in NDD can be either primary and/or reinforce degeneration in CNS, which further increases their importance in the development of the disease. In this paper, we reviewed the available literature data on the peripheral dysfunctions in NDD and their contribution to NDD pathogenesis.

Keywords: neurodegenerative diseases, Alzheimer's disease, neuromuscular system, peripheral dysfunction

Introduction

Neurodegenerative disorders (NDD) present a heterogeneous group of fatal chronic disorders of the nervous system, which are characterized by progressive neuronal loss. The most common and severe NDD are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. According to expert estimates, the number of people suffering from Alzheimer's disease amounted to more than 24 million in 2005 and may reach 80 million by 2040 [1]. Currently, more than 45 million, mostly elderly, people worldwide are suffering from NDD [1], which makes this group of disorders one of the most important medical and social problems. NDD are characterized by neuronal death in specific regions of the brain, thereby leading to multiple cognitive and/or motor disorders (depending on nosology),

disability, and, finally, to the patient's death. For example, in Alzheimer's disease and amyotrophic lateral sclerosis, death occurs in about eight and five years, respectively. Neuronal death, the main reason of NDD, is initiated by a variety of pathogenic factors, such as accumulation of toxic protein aggregates (ß-amyloid peptide, α-synuclein, etc.), oxidative stress, mitochondrial dysfunction, intracellular calcium imbalance [2]. Unfortunately, the detailed molecular mechanisms of NDD are still poorly understood. Thus, it is difficult to develop effective pathogenetic approaches to treatment of these diseases.

Most clinical therapeutic approaches to NDD treatment can only retard the disease progression, but do not cure the patient. The drugs act symptomatically, without affecting the primary cause of the disease. Furthermore, NDD are diagnosed mainly at advanced stages (decompensation), when most of the affected neurons are already dead and it becomes almost impossible to change or reverse the course of the disease [3]. Therefore, early diagnosis of NDD based on the identification of specific markers of the disease in the blood, cerebrospinal fluid, and peripheral tissues is desperately needed, but no such method has been successfully and widely implemented in clinical practice.

In recent years, severe dysfunction of excitable cells of the peripheral organs related to the neuromuscular and cardiovascular systems has been confirmed in animal models of NDD [2, 4–7]. Peripheral disorders in the neuromuscular and cardiovascular systems – atrophy and paralysis of skeletal muscles, cardiac infarction, etc. – are important, although underestimated, in the NDD pathogenesis, because they are often the direct cause of disability and death. Therefore, the pathology of the neuromuscular and cardiovascular systems during NDD is not merely a "reflection" of degenerative changes in the nervous system as they are fully involved in the NDD pathogenesis. Peripheral dysfunction can be either primary or reinforcing degenerative process in the central nervous system, which further increases its importance in the development of NDD.

In this review, we summarize the available data on the cellular and molecular mechanisms of dysfunction of the peripheral excitable structures (neuromuscular synapses and muscle cells) in the NDD development and estimate possible contribution of these disorders to the NDD pathogenesis.

Skeletal Muscle Dysfunction in Neurodegenerative Diseases

Alzheimer's disease is characterized by memory impairment; however, it is often accompanied by non-cognitive symptoms as well, including muscle dysfunction. In most cases, motor defects are observed along with dementia and another NDD (for example, Parkinson's disease), but they may be also directly associated with Alzheimer's disease. Such impairments include bradykinesia, tremor, dysarthria, and rigidity [8, 9]. In patients with Alzheimer's disease, weight loss due to muscle weight reduction has been also observed, which can be an indirect indicator of degenerative processes in muscles [10]. Myoclonic movements, pathologic reflexes, and gait impairment have been revealed in transgenic mice with Alzheimer's disease model [11].

The key factor of Alzheimer's disease pathogenesis is an excess production and accumulation of β-amyloid peptide (βAP). βAP is an oligopeptide consisting of 38–42 amino-acid residues and formed in the extracellular space by cleavage of the transmembrane amyloid precursor protein (APP) when exposed to special enzymes – β- and

γ-secretases [12, 13]. βAP is polymerized with the genesis of long insoluble fibrils, a key component of senile plaques in the brain and some other tissues of patients with Alzheimer's disease and transgenic mice with the genetic model of this disease [12, 13]. One of the promising techniques for early diagnosis of Alzheimer's disease may be detection of different βAP forms or their ratio in blood, cerebrospinal fluid, and peripheral tissues (skin, muscles). However, numerous investigations of the toxic effects of βAP raise questions about the mechanisms of βAP action during NDD, thereby interfering in the development of diagnostic techniques based on quantitative estimation of βAP.

The attention of researchers has been focused on possible toxic effects of βAP on peripheral excitable cells. APP is expressed in neurons and almost all cell types of the organism [14]. Soluble βAP is present in the systemic circulation [15]. βAP deposits have been found not only in the brain, but also in the skin and skeletal muscles of patients with Alzheimer's disease [16, 17]. The increased frequency of motor and cardiovascular disorders has been observed in Alzheimer's disease [9, 18]. Considering these facts, the most likely targets of the peripheral toxic influence of βAP are excitable cells of the locomotor and cardiovascular systems. At the same time, these effects have been studied much less than the effect of βAP on neurons.

In the study with the use of frog sartorius muscle and mouse diaphragm, we found expressed depolarization of the skeletal muscle fibers under the influence of βAP (fragment 25–35) [19]. Impairment of the muscle contractility was revealed in frogs, but not in mice, which is explained by a higher reliability factor of neuromuscular transmission in warm-blooded animals [20]. In the electrophysiological experiments on mouse diaphragm, we found that βAP disrupts the processes of membrane resting potential generation and causes expressed depolarization of the muscle fibers due to the following two mechanisms: Na^+/K^+-ATPase inhibition resulting in the disappearance of the contribution of this pump to the formation of the resting membrane potential; increase of the cationic membrane permeability by forming "amyloid" channels in it, which are blocked by Zn^{2+} ions [6]. What is the clinical significance of the above-described βAP effects on the functioning of skeletal muscle fibers? On the one hand, the minimal concentration of βAP (10^{-8} M) used in that studies is several times lower than that one in the plasma of patients with Alzheimer's disease [15]. Besides, in vivo, defense reactions of the organism to the βAP influence in the form of immune response and βAP-degrading enzyme activity can be observed [12, 21]. On the other hand, muscles are exposed to βAP for a much longer period of time in case of Alzheimer's disease (years and decades). Furthermore, βAP effects may be more significant in the motor load when high-frequency activation of the neuromuscular synapse leads to the depression of endplate potentials and reduces the reliability factor of neuromuscular transmission. At the same time, patients in the late stages of Alzheimer's disease are almost bedridden due to deterioration of their general condition associated with the muscle pathology.

Myositis with inclusions – a disease characterized by weakness and atrophy of the muscles of extremities – is a striking example of the toxic effects of βAP on skeletal muscles [22]. The main process in the pathogenesis of myositis with inclusions is the intracellular accumulation of βAP in the muscle fibers. It has been shown that the latter reduces the amplitude of contractile force and the spike by affecting calcium

ion release mediated by the ryanodine receptor [23]. The influence of βAP on the processes of membrane electrogenesis may play some role in the development of myositis with inclusions [5].

Skeletal muscle dysfunction is found not only in the β-amyloid model, but also in the genetic model of Alzheimer's disease. In particular, electrogenesis impairment of the skeletal muscle fibers in APP/PS1 transgenic mice exhibited by pronounced muscle membrane depolarization and explained by the decreased activity of membrane ion pumps (primarily, Na/K pump) has been observed [7].

Dysfunction of Neuromuscular Synapses in Neurodegenerative Disorders

Synapses are the basis of intercellular communication in the nervous system. In the recent years, it has been found that synaptic transmission is a "weak link" in the development of nervous system pathology and its disruption underlies the pathogenesis of a number of neurological and psychiatric diseases. Synaptic dysfunction plays a key role in the development of Alzheimer's disease, which, thus, can be regarded as a "synaptic disorder" [24]. In a number of the latest studies, it has been established that the dysfunction in NDD develops in both central and neuromuscular synapses.

It has been shown that the degradation of neuromuscular synapses may be a key factor in the pathogenesis of amyotrophic lateral sclerosis – a progressive incurable NDD affecting mainly the motor neurons of the spinal cord and brain. The prevalence of amyotrophic lateral sclerosis is the third highest among all NDD, being the most formidable among them, as 50% of patients die within three years from diagnosis [25]. The etiology of amyotrophic lateral sclerosis has been studied insufficiently. It is known that "gain-of-function" mutations in the genes encoding antioxidant enzymes Cu/Zn-superoxide dismutase (SOD1) are the basis of 20% of familial and 5% of sporadic cases of the disease; transgenic models of the disease in mice were created, particularly, by using a mutant gene SOD1 (mSOD1) [26]. However, the etiology of the vast majority of sporadic and more than half of familial forms of the disease remains unclear.

It has been established that the pathology of motor neurons in patients with sporadic amyotrophic lateral sclerosis and mSOD1-transgenic mice begins with degeneration of the neuromuscular synapse long before the appearance of clinical symptoms and progresses in a retrograde fashion [4, 27, 28]. At the same time, prevention of apoptosis of the bodies of motor neurons has little effect on the dynamics of the disease in mSOD1-transgenic mice [29–31], and the selective expression of mSOD1 in motoneurons does not cause a severe clinical picture [32, 33]. These and other findings have led to the formation of a rising "dying-back" theory of the pathogenesis of amyotrophic lateral sclerosis, according to which the pathological process starts in the skeletal muscle or neuromuscular junction and initiates motoneuron degeneration due to the lack of retrograde acting trophic factors released from the muscle [26]. It has been found that neuromuscular synaptic transmission in mSOD1-transgenic mice is improved in the asymptomatic stage, and two functionally distinct populations of synapses have been revealed in the symptomatic stage, which is consistent with the hypothesis of cycles of denervation-reinnervation changes in the skeletal muscle with the disease progression [28]. A decrease in the number of synapses positively stained for presynaptic protein SV-2 and cholinergic receptors has been observed in the asyptomatic stage

of the disease, while the number of cholinergic receptor clusters does not reduce even at the terminal stage; these data indicate the disconnection of nerve terminals from skeletal muscle endplates [34]. In neuromuscular synapses of mSOD1-transgenic *Caenorhabditis elegans* roundworms, the reduction of both numbers of synapses and synaptic vesicles in the active zones has been demonstrated [35].

Using the muscle biopsy samples from the patients with clinical symptoms of amyotrophic lateral sclerosis, a reduction of the amplitude of miniature endplate potentials without affecting their frequency, as well as reducing the quantum structure of endplate potentials, has been revealed [36]. In the electromyographic study, the patients have experienced a decrement of the M-response amplitude during the rhythmic stimulation and other disruptions similar to those in myasthenia and those occurring as a result of the poor reliability of neuromuscular transmission [37].

Thus, there is strong evidence that the dysfunction of the neuromuscular synapse is a key event in the pathogenesis of amyotrophic lateral sclerosis. Probably, neuromuscular synaptic pathology correction is a promising therapeutic approach for treatment of this disease. However, the dysfunction of peripheral synapses in other NDD has been covered insufficiently in the available literature.

It has been shown that βAP and APP are found in the neuromuscular synapse of rat by immunohistochemistry, and only the aggregated form of βAP (25–35) influenced the neuromuscular synaptic transmission by inhibiting the quantal release of acetylcholine at the long low-frequency activity [38]. There is evidence of neuromuscular synapse dysfunction in the model of Huntington's disease – NDD that is characterized by a gradual onset between the ages of 35–50 years and a combination of progressive trochaic hyperkinesis and psychiatric disorders. In the model of Huntington's disease in the R6/1 transgenic mice, an increase in the amplitude and the quantum structure of endplate potentials at constant parameters of spontaneous neurosecretion and absence of violations in the amount and dynamics of a recycling pool of synaptic vesicles have been described. Furthermore, the increase of the expression of several synaptic proteins, in particular VAMP/synaptobrevin and SNAP-25, has been found [39].

Cardiovascular Pathology in Neurodegenerative Disorders

Recent studies indicate that there is a correlation between Alzheimer's disease and cardiovascular system pathology. The risk factors for Alzheimer's disease are stroke, hypertension, diabetes, hypercholesterolemia, heart failure, atrial fibrillation, and others [40, 41]. Increased risk of atherosclerosis in the middle age leads to increased risk of developing Alzheimer's disease in the old age [42]. Our studies proved that cardiac surgery causes a syndrome similar to Alzheimer's disease, which is manifested by reduced cognitive abilities and changes in the biochemical composition of cerebrospinal fluid [43, 44].

The experimental data indicate the relationship between the metabolic disturbance of βAP and the pathology of the cardiovascular system. β-amyloid angiopathy of the brain vessels is one of the most common pathologies in the elderly, affecting the majority of patients with Alzheimer's disease and about 30% of healthy people [45]. βAP can be accumulated in the vascular wall in the form of insoluble fibrils [46], while its source are neurons, degenerating myocytes, and blood [13]. βAP increases arterial vasoconstriction, exerts a toxic effect on endothelial and vascular smooth muscle

cells [47, 48]. It has been shown that βAP enhances the endothelin-1 induced contraction of human isolated cerebral arteries, and this effect is removed by the inhibitors of cyclooxygenase 2 or MAP-kinases, suggesting the involvement of inflammatory mechanisms [49]. It was found that βAP (25–35) application impairs the carbachol- and histamine-induced contractile activity of the rat abdominal aorta, resulting in a distortion of the contractile response (relaxation instead of contraction) [50]. The same study shows that βAP (25–35) disrupts the contractile activity of rat ventricular myocardium, resulting in a decrease of the duration of the relaxation phase and increasing the speed of relaxation (positive lusitropic effect), herewith positive lusitropic effect of noradrenaline disappeared at the background of βAP [50]. The relationship between βAP metabolism and cardiovascular disorders may be mediated by the blood system – it has been found that βAP retards dissolution of fibrin clots by changing the structure of fibrin and weakening of the binding of plasminogen and fibrin [51].

Despite the large amount of experimental data, the mechanisms of the relationship between Alzheimer's disease and cardiovascular pathology are not well understood. On the one hand, cardiovascular disorders leading to hypoperfusion and hypoxia of the brain promote the development of dementia (both vascular and Alzheimer's type). On the other hand, Alzheimer's disease, as a systemic disease, probably contributes to the development of cardiovascular pathology. This is indirectly supported by the clinical evidence of increased rates of cardiovascular events in patients with dementia [52–57]. Eventually, Alzheimer's disease and cardiovascular pathology reinforce each other, thereby forming a "vicious circle" of pathogenesis. For this reason, that may be difficult for clinicians to make a differential diagnosis between Alzheimer's and vascular types of dementia, and quite often there are mixed dementias.

The impairment of myocardial contractility manifested in the reduction of the peak amplitude of myocardial contraction and reduction of the maximum speed of shortening/lengthening of cardiomyocytes, as well as impaired calcium signaling in cardiomyocytes has been found in transgenic mice with the Alzheimer's disease model; the use of antioxidant N-acetylcysteine reduced the contractile dysfunction of cardiomyocytes, indicating the involvement of oxidative stress [58].

It is well known that the motor neurons are affected in the first place during amyotrophic lateral sclerosis, but it has been confirmed that sympathetic neurons innervating the heart are involved in the pathological process. The number of neurons of the intermediate-lateral nucleus of the sympathetic nerves in the thoracic spinal cord in patients is significantly lower compared with the control group, and has an inverse linear correlation with the degree of increase in the duration and QT interval dispersion. In general, sympathetic denervation in amyotrophic lateral sclerosis increases the risk of sudden cardiac arrest [59]. In another study, average or moderate postganglionic sympathetic or parasympathetic denervation in all patients with amyotrophic lateral sclerosis has been found [60].

It is believed that accumulation of the mutant huntingtin protein in the neural tissue plays a key role in the pathogenesis of Huntington's disease. There are reasons to believe that huntingtin causes not only neuronal dysfunction, but also can adversely affect the performance of other excitable cells (such as cardiomyocytes). It should be noted that the cardiovascular disorders are the second leading cause of death in patients

with Huntington's disease [61, 62]. The electron microscopy showed a significant increase in the presence of nuclear and mitochondrial polyglutamine and changes of mitochondrial ultrastructure in cardiomyocytes of R6/2 transgenic mice with the Huntington's disease model. Such signs of cardiac remodeling as hypertrophy, fibrosis, apoptosis, reduced sensitivity of the beta-1 adrenergic receptors have been identified in Huntington's disease transgenic mice [63, 64].

Conclusions

In current paper, we reviewed the available literature on the dysfunctions of peripheral excitable structures in the most common NDDs. Peripheral disorders were divided into three groups: dysfunctions of skeletal muscles, neuromuscular synapses, and cardiovascular disorders. The analysis showed that virtually all common NDD are accompanied by peripheral dysfunction at the level of the neuromuscular system and/or cardiovascular system. This analysis was not aimed to cover the full range of dysfunctions and dysregulatory processes in peripheral excitable tissues during NDD, because in many NDD peripheral manifestations have hardly been studied. We described the examples of dysfunction in the peripheral excitable structures during the NDD, which are not merely interesting experimental findings, but represent the important and previously undocumented aspects of the pathogenesis of these diseases, in some cases being key factors of the pathogenesis. These aspects should be considered in the diagnosis and treatment of patients with NDD. We believe that the correction of the impaired functions of peripheral excitable structures will improve the results of complex therapy of neurodegenerative disorders.

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Периферические дисфункции при нейродегенеративных заболеваниях: механизмы и вклад в патогенез

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Аннотация

Нейродегенеративные заболевания (НДЗ), такие как болезнь Альцгеймера, болезнь Паркинсона, боковой амиотрофический склероз, поражают около 10% пожилого населения, что делает их одной из важнейших медико-социальных проблем современного общества.

Многочисленные литературные данные свидетельствуют о том, что НДЗ связаны не только с дисфункцией центральной нервной системы (ЦНС), но и с дизрегуляцией и патологическими изменениями в периферических структурах, в частности в нервно-мышечных синапсах, скелетных и сердечной мышцах. Периферические нарушения могут играть важную роль в патогенезе НДЗ и связанными с ними патологическими процессами, которые напрямую приводят к инвалидизации и смерти пациентов (атрофия и паралич скелетных мышцы, инфаркт миокарда и др.). Таким образом, патология нервно-мышечной и сердечно-сосудистой систем при НДЗ является не только «отражением» дегенеративных изменений в нервной системе, но и представляет собой отдельный, малоизученный аспект патогенеза НДЗ, значение которого в клинической медицине недооценивается. Ряд исследований свидетельствует о том, что периферические дисфункции при НДЗ могут быть первичными и/или усиливать дегенерацию в ЦНС, что еще более повышает их значимость в развитии заболевания.

В настоящей статье мы проводим детальный обзор имеющейся литературы о периферических дисфункциях при НДЗ и их вкладе в патогенез данных недугов.

Ключевые слова: нейродегенеративные заболевания, болезнь Альцгеймера, нервно-мышечная система, периферические нарушения

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