REVIEWS

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CONVENTIONAL APPROACHES TO THE THERAPY OF HEREDITARY MYOPATHIES

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The aim of the work was to analyze the available therapeutic options for the conventional therapy of hereditary myopathies.
Materials and methods. When searching for the material for writing a review article, such abstract databases as PubMed and Google Scholar were used. The search was carried out on the publications during the period from 1980 to September 2022. The following words and their combinations were selected as parameters for the literature selection: “myopathy”, “Duchenne”, “myodystrophy”, “metabolic”, “mitochondrial”, “congenital”, “symptoms”, “replacement”, “recombinant”, “corticosteroids”, “vitamins”, “tirasemtiv”, “therapy”, “treatment”, “evidence”, “clinical trials”, “patients”, “dichloracetate”.
Results. Congenital myopathies are a heterogeneous group of pathologies that are caused by atrophy and degeneration of muscle fibers due to mutations in genes. Based on a number of clinical and pathogenetic features, hereditary myopathies are divided into: 1) congenital myopathies; 2) muscular dystrophy; 3) mitochondrial and 4) metabolic myopathies. At the same time, treatment approaches vary significantly depending on the type of myopathy and can be based on 1) substitution of the mutant protein; 2) an increase in its expression; 3) stimulation of the internal compensatory pathways expression; 4) restoration of the compounds balance associated with the mutant protein function (for enzymes); 5) impact on the mitochondrial function (with metabolic and mitochondrial myopathies); 6) reduction of inflammation and fibrosis (with muscular dystrophies); as well as 7) an increase in muscle mass and strength. The current review presents current data on each of the listed approaches, as well as specific pharmacological agents with a description of their action mechanisms.
Conclusion. Currently, the following pharmacological groups are used or undergoing clinical trials for the treatment of various myopathies types: inotropic, anti-inflammatory and antifibrotic drugs, antimyostatin therapy and the drugs that promote translation through stop codons (applicable for nonsense mutations). In addition, metabolic drugs, metabolic enzyme cofactors, mitochondrial biogenesis stimulators, and antioxidants can be used to treat myopathies. Finally, the recombinant drugs alglucosidase and avalglucosidase have been clinically approved for the replacement therapy of metabolic myopathies (Pompe’s disease).

Keywords: hereditary myopathies; Duchenne’s muscle dystrophy; metabolic therapy; pharmacological correction

Abbreviations: ETC – electronic transport chain; mRNA – matrix ribonucleic acid; tRNA – transport ribonucleic acid; siRNAs – small interfering ribonucleic acids; NAD, nicotineamide-adenine dinucleotide; FAD – flavin adenine dinucleotide; NADP – nicotinamide adenine dinucleotide phosphate; ATP – adenosine triphosphate; ADP – adenosine diphosphate; CTGF – connective tissue growth factor; TGFβ – transforming growth factor-beta; NSAIDs – non-steroidal anti-inflammatory drugs; XLMTM – X-linked myotubular myopathy; TCA – tricarboxylic acid cycle; TNF-α – tumor necrosis factor-alpha; CTGF/CCN2 – connective tissue growth factor.

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КОНВЕНЦИОНАЛЬНЫЕ ПОДХОДЫ К ТЕРАПИИ НАСЛЕДСТВЕННЫХ МИОПАТИЙ

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Цель. Проанализировать доступные терапевтические опции для конвенциональной терапии наследственных миопатий.

Материалы и методы. При поиске материала для написания обзорной статьи использовали такие реферативные базы данных, как PubMed и Google Scholar. Поиск осуществлялся по публикациям за период с 1980 г. по сентябрь 2022 г. Параметрами для отбора литературы были выбраны следующие слова и их сочетания: “myopathy”, “Duchenne”, “myodystrophy”, “metabolic”, “mitochondrial”, “congenital”, “symptoms”, “replacement”, “recombinant”, “corticosteroids”, “vitamins”, “tirasemtiv”, “therapy”, “treatment”, “evidence”, “clinical trials”, “patients”, “dichloracetate”.

Результаты. Врожденные миопатии представляют собой гетерогенную группу патологий, которые вызваны атрофией и дегенерацией мышечных волокон вследствие мутаций в генах. На основании ряда клинических и патогенетических особенностей наследственные миопатии разделяют на: 1) врожденные миопатии; 2) мышечные дистрофии; 3) митохондриальные и 4) метаболические миопатии. При этом, подходы к лечению значительно варьируют в зависимости от типа миопатии и могут быть основаны на 1) замещении мутантного белка; 2) увеличении его экспрессии 3) стимуляции экспрессии внутренних компенсаторных путей; 4) восстановлении баланса соединений, связанных с функцией мутантного белка (для ферментов); 5) воздействии на функцию митохондрий (при метаболических и митохондриальных миопатиях); 6) снижении воспаления и фиброза (при мышечных дистрофиях); а также на 7) увеличении мышечной массы и силы. В текущем обзоре представлены современные данные о каждом из перечисленных подходов, а также конкретные фармакологические агенты с описанием их механизмов действия.

Заключение. В настоящее время для лечения разных типов миопатий используются или проходят клинические исследования следующие фармакологические группы: инотропные, противовоспалительные и антифибротические препараты, антимиостатиновая терапия и препараты, способствующие трансляции через стоп-кодоны (применима при нонсенс-мутациях). Кроме того, для лечения миопатий могут быть применены метаболические препараты, кофакторы метаболических ферментов, стимуляторы митохондриального биогенеза и антиоксиданты. Наконец, клинически одобрены рекомбинантные препараты алглюкозидаза и авалглюкозидаза для заместительной терапии метаболических миопатий (болезнь Помпе).

Ключевые слова: наследственные миопатии; миодистрофия Дюшенна; метаболическая терапия; фармакологическая коррекция

Список сокращений: ЭТЦ – электронно-транспортная цепь; мРНК – матричная рибонуклеиновая кислота; тРНК – транспортная рибонуклеиновая кислота; миРНК – малая интерферирующая рибонуклеиновая кислота; НАД – никотинамидадениндинуклеотид; ФАД – флавинадениндинуклеотид; НАДФ – никотинамидадениндинуклеотидфосфат; АТФ – аденозинтрифосфат; АДФ – аденозиндифосфат; CTGF – фактор роста соединительной ткани; TGFβ – трансформирующий фактор роста-бета; НПВП – нестероидные противовоспалительные препараты; XLMTM – X-сцепленная миотубулярная миопатия; ЦТК – цикл трикарбоновых кислот; ФНО-α – фактор некроза опухоли-альфа; CTGF/CCN2 – фактор роста соединительной ткани.

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INTRODUCTION

Hereditary myopathies are a clinically, histologically and genetically heterogeneous group of muscle pathologies that are caused by atrophy and degeneration of striated muscles due to mutations in genes whose role is closely related to the functioning of myocytes. Most often, the proteins encoded by these genes are involved in the formation or maintenance of the structural integrity of the cytoskeleton and plasma membrane. At the same time, myopathies associated with the pathology of cytoskeletal proteins are characterized by a progressive course (muscular dystrophies), and myopathies caused by a function loss of membrane proteins are fully manifested from birth (congenital myopathies). In addition, hereditary myopathies can be caused by mutations in the genes associated with the work of mitochondria (mitochondrial myopathies), or the genes encoding enzymes of intracellular metabolism (metabolic myopathies) [1].

Initially, classifications of hereditary myopathies were based on the clinical presentation or typical histological features found in muscle biopsy specimens. However, according to the current recommendations, the diagnosis of myopathy should be accompanied by the data from molecular genetic studies. In addition to precision diagnostics, this approach leads to an expansion list of the nosological group genetic correlates [2].

THE AIM of the work was to analyze the available therapeutic options for the conventional therapy of hereditary myopathies.

MATERIALS AND METHODS

When searching for the material for writing a review article, such abstract databases as PubMed and Google Scholar were used. The search was carried out on the publications during the period from 1980 to September 2022. The following words and their combinations were selected as parameters for the literature selection: “myopathy”, “Duchenne”, “myodystrophy”, “metabolic”, “mitochondrial”, “congenital”, “symptoms”, “replacement”, “recombinant”, “corticosteroids”, “vitamins”, “tirasemtiv”, “therapy”, “treatment”, “evidence”, “clinical trials”, “patients”, “dichloracetate”.

RESULTS AND DISCUSSION

1. General characteristics of hereditary myopathies

The most typical symptoms of myopathies are muscle weakness, myalgia, myopenia, and exercise intolerance. The clinical picture of myopathies can vary from asymptomatic forms with an increase in serum creatine kinase values and an increased tendency to hyperthermia to severe forms leading to skeletal deformities, as well as respiratory and heart failures. The groups of affected muscles can differ significantly – from an isolated lesion of the oculomotor muscles [3] to a systemic muscle atrophy involving myocardium and diaphragm. The variability of clinical signs is associated both with the diversity of causative genes and with the degree of their function loss. For example, a severe muscle phenotype in Duchenne’s muscle dystrophy is associated with neuropsychiatric disorders [4], and muscle symptoms in the phosphofructokinase deficiency (Tarui disease) are accompanied by hemolytic anemia and hyperuricemia [5]. Mitochondrial myopathies are characterized by especially high clinical heterogeneity [6]. Since multisystem disorders, nervous, digestive, urinary, cardiovascular, endocrine and reproductive systems, as well as the organs of vision and hearing often accompany a mitochondrial dysfunction, they can be involved in the pathological process (Table 1).

1.1. Muscular dystrophies

More than 30 muscular dystrophies have been identified, the most common of which are as follows: Duchenne’s muscle dystrophy, facioscapulohumeral muscular dystrophy, Becker muscular dystrophy, limb-girdle and myotonic kinds of muscular dystrophy. Etiologically, these diseases are very heterogeneous. For example, Duchenne’s muscle dystrophy and Becker dystrophy are caused by dystrophin mutations, while lumbar-limb muscular dystrophies can be caused by an impaired function of calpain, dysferlin, sarcoglycan, lamin, anoctamine, etc. [7]. In all cases, early signs of degeneration and then regeneration of some muscle fibers are usually found. The fibers that regenerate become larger than usual, and eventually the muscle is almost completely replaced by a fibrous scar tissue and fat.

The most classic type of such muscle disorders is Duchenne’s dystrophy. It is caused by frameshift mutations in the MDD gene encoding the dystrophin protein, which is a plasma membrane-associated protein that plays a critical role in sarcolemma stabilizing in mechanical shifts during the muscle contraction or stretching [8, 9]. The dystrophin absence leads to a decrease in the resistance of sarcolemma and the subsequent necrosis of the muscle fibers [10]. The muscle fibers destruction is exacerbated by a mechanical stress and improves while the muscle immobilization [11, 12]. Thus, the accumulation of the damaged muscle fibers is the cause of the progressive course of Duchenne’s myodystrophy. At the same time, the exact molecular mechanisms by which dystrophin plays the role of a mechanical stabilizer, are still unclear [13].

1.2. Congenital myopathies

Unlike muscular dystrophies, congenital myopathies are already manifested in the neonatal period [14]. This is due to the fact that the function of defective proteins is not associated with maintaining the integrity of already differentiated myocytes, but with

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the structural organization of the muscle tissue even at the stage of histogenesis. Basically, these are the proteins involved in the formation of the cytoskeleton or intercellular substance. At the same time, these can be such multifunctional proteins as myotubularin, which is involved in the transfer of endosomes, coupling of excitation and contraction, the organization of intermediate filaments, and apoptosis.

Although the exact epidemiology of congenital myopathies is unknown, researchers estimate their incidence to be around 1:25 000 [15]. The classification of congenital myopathy is constantly being revised as more genes that are associated with its various phenotypic and histological manifestations, are identified. At the moment, it continues to be based mainly on the features observed in muscle biopsy [16]. Accordingly, congenital myopathy can be divided into the following five forms: rod myopathy; cardiac myopathy; centronuclear myopathy; congenital myopathy of a fiber type imbalance; myosin storage myopathy.

Clinically, congenital myopathies are manifested by muscle hypotonia and weakness, present at birth or appearing in infancy and not progressive during life. Depending on the causative gene and the nature of the mutation, the clinical spectrum varies from severe neonatal forms with congenital arthrogryposis to mild forms with isolated hyposthenia [14, 16]. In the neonatal period, symptoms tend to be more pronounced and may include reduced fetal movement and a subsequent development of arthrogryposis and clubfoot. Severe muscular hypotonia is often present at birth and in the first months of life (a sign of a lethargic baby) along with a frog-like posture, difficulty sucking, and a respiratory failure [17].

1.3. Metabolic myopathies

Metabolic myopathies are associated with mutations in the genes encoding energy metabolism enzymes. Biochemical disorders include disorders of fatty acids, glucose, or glycogen oxidation. As a result, the functional reserves of the muscle tissue are reduced, which is manifested by hypotension, increased fatigue, myalgia, convulsions, episodes of rhabdomyolysis, etc. [18]. At the same time, fatty acids utilization defects are characterized by a low tolerance to long-term endurance exercises, while disorders of glucose and glycogen metabolism are manifested by an intolerance to fast high-intensity exercises [19]. A separate feature of myopathies also associated with mutations of glycogenolysis enzymes, is the accumulation of intracellular glycogen inclusions [20].

1.4. Mitochondrial myopathies

The pathogenetic basis of mitochondrial myopathies is a violation of energy metabolism processes due to defects in the oxidative phosphorylation. In this regard, some authors consider mitochondrial myopathies as a subtype of metabolic ones. Nevertheless, a number of features of inheritance and pathogenesis, as well as some clinical characteristics, make it possible to distinguish them into a separate group. Thus, mitochondrial myopathies are always associated with impaired functioning of the electronic transport chain (ETC), most often with defects in complex 1 [21–23]. In addition, mitochondrial myopathies can be caused by mutations in both nuclear and mitochondrial genes. In case of mitochondrial DNA mutations, inheritance occurs almost exclusively maternally [24]. The severity of symptoms is determined not only by the pathogenicity of the mutation, but also by the number of the mutant mitochondrial DNA copies that the body has inherited from the mother [25]. The fact is that the mitochondrial genome is heterogeneous (the phenomenon of heteroplasmy) and, along with mutant ones, healthy mitochondria are always present in the cell. Thus, the proportion of defective mitochondria is determined randomly with a random distribution of mitochondria between the daughter cells, which is called the “bottleneck” phenomenon [26].

In general terms, mitochondrial myopathies are mitochondrial diseases, in the spectrum of clinical manifestations of which there are pronounced symptoms from the muscle tissue. Mitochondrial myopathies are characterized by a progressive course and a wide range of associated symptoms, including epilepsy, neuropathy, sensory impairments, etc. [27].

2. Treatment of hereditary myopathy

Treatment of hereditary myopathies varies widely depending on the type and specific disease. A significant proportion of therapeutic interventions in the treatment of myopathies patients are the approaches based on diet, exercise therapy and massage. For example, in metabolic myopathies associated with impaired glucose utilization, the most important therapeutic approach is a low-carbohydrate ketogenic diet [53]. When correcting congenital myopathies, patients are recommended a controlled physical activity, as well as the use of special corsets to prevent the development of bone deformities.

Pharmacological approaches occupy an important place in symptomatic, supportive, and pathogenetic-oriented kinds of therapy. In addition, high rates development of antisense and gene therapy have recently made it possible to focus on etiotropic approaches in the treatment of myopathies patients.

As with most monogenic diseases associated with the gene function loss, conventional specific therapy can be aimed at: 1) replacement of the mutant protein; 2) increase in its expression; 3) stimulation of the expression of internal compensatory pathways; 4) restoration of the balance of compounds associated with the function of the mutant protein (for enzymes).

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Table 1 – General clinical characteristics of hereditary myopathies

Group of congenital myopathies	Examples of diseases	Clinical manifestations	Proteins with impaired function	Pathogenesis
Muscular dystrophies	Miyoshi myopathy	Distal skeletal muscle weakness Elevated levels of creatine kinase in the blood First symptoms occur during adolescence [28, 29]	Dystrophin [30]	Dysferlin is a membrane-associated linker protein; its function is to mediate calcium-dependent regeneration of mechanical damage to sarcolemma. With mutations that disrupt the dysferlin function; the accumulation of damage to sarcolemma occurs, which leads to progressive dystrophy of skeletal muscles [31].
	Limb-girdle muscular dystrophy type 2B (LGMD2B)	Proximal skeletal muscle weakness Elevated levels of creatine blood kinase Manifestation at the age from 10 to 30 years [32, 33]		
	Duchenne's myodystrophy	Muscular hypotension Heart failure Respiratory distress Debut in early postnatal or postnatal age Death before age of 20 [34, 35]	Dystrophin [36]	Dystrophin is involved in the mechanical stabilization of sarcolemma. In case of loss of the protein product dysferlin due to large deletions or a shift in the reading frame, sarcolemma becomes vulnerable to mechanical deformations that occur during muscle contraction or stretching [37]. Since dystrophin plays an important role in the processes of mitotic division, Duchenne's disease disrupts cell polarity and myogenic differentiation of stem cells. Stem cells lacking functional dystrophin undergo aberrant asymmetric division with centrosome amplification, spindle orientation errors, and an extended cell cycle [38, 39].
Congenital myopathies	Myosin storage myopathy	Muscular hypotension Hypertrophic or dilated cardiomyopathy Manifestation in the neonatal or postnatal period	MYH7 (heavy chain of slow/β-cardiac myosin)	MYH7 is the main myosin isoform in slow oxidative type 1 muscle fibers of skeletal muscles and myocardium. Numerous missense mutations in the MYH7 globular head lead to disruption of the structural protein function and the formation of large inclusions consisting of myosin chains.
	Bethlem muscular dystrophy	Weakness of proximal muscles Joints contracture Hypotension progresses slowly, and more than two-thirds of patients older than 50, continue to move independently. Possible damage to the respiratory muscles [40].	Type VI collagen	Collagen VI is an extracellular matrix protein that forms a microfibrillar network. The protein consists of three different α-chains encoded by separate genes named COL6A1, COL6A2 and COL6A3 in humans. Potential effects on muscles include progressive dystrophic changes, fibrosis, and signs of increased apoptosis [41].
Metabolic myopathies	Pompe's disease	Muscular hypotension Hepatomegaly Heart failure Neurological disorders Debut at any age (an early debut correlates with a more severe course) [42]	Acid maltase [43]	After entering the lysosomes, acid maltase mediates the catalytic breakdown of glycogen by interacting with the mannose-6-phosphate receptor [44]. More than 500 mutations including insertions, deletions, splicing site mutations, nonsense and missense mutations, have been found. They disrupt the functional activity of acid maltase, leading to glycogenosis and energy deficiency of the muscle tissue [45, 46].
	Tarui disease	Muscle weakness Muscle cramps Encephalopathy Hemolytic anemia Rhabdomyolysis risk Debut at any age [47]	Phosphofructokinase [48]	Phosphofructokinase catalyzes the transfer of a phosphate group from ATP to fructose-6-phosphate, which is one of the key elements of glycolysis. In humans, three isozymes named M (muscle), L (liver), and P (platelets), have been identified, Mutations in phosphofructokinase-M lead to muscle weakness due to an energy deficiency in working muscles [49].
Mitochondrial myopathies	Myoclonus epilepsy with myopathy and sensory ataxia (MEMSA)	Proximal and/or distal myopathy Muscular hypotension Myoclonic epilepsy Encephalopathy Sensory ataxia Debut at any age [50]	Polymerase gamma (POLG) [51]	Gamma polymerase is a key enzyme of a mitochondrial DNA replication Mutations in the POLG gene lead to the energy deficiency due to the accumulation of defective mitochondria and a decrease in the number of mtDNA copies (mtDNA depletion), especially in muscle, brain, or liver cells [52].

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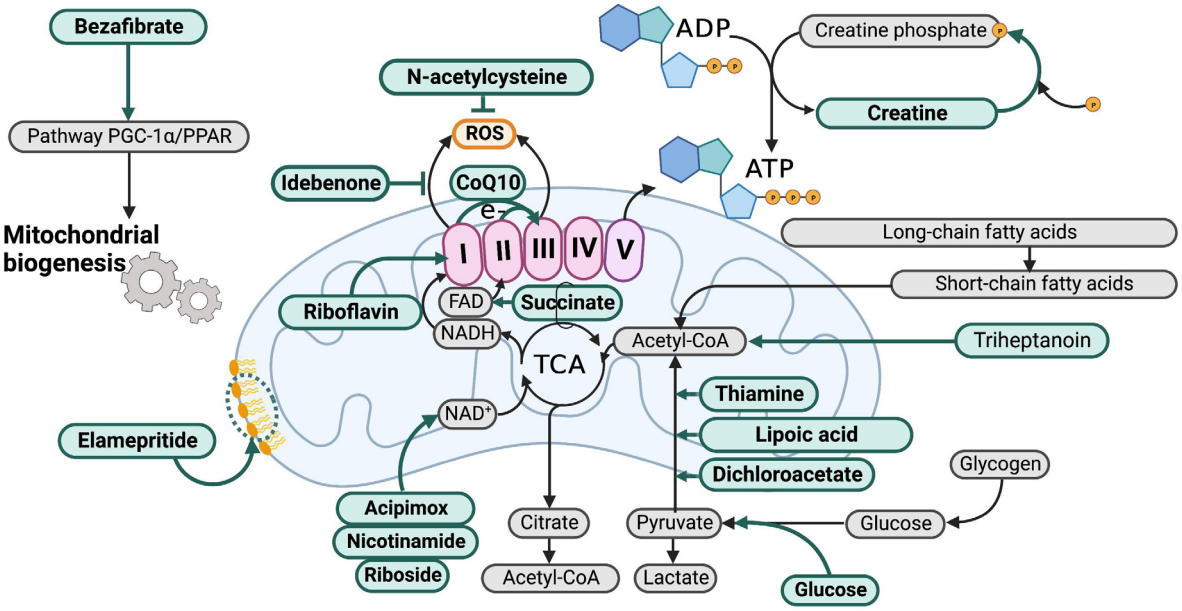

Figure 1 – Classical pharmacological methods to compensate for inadequate functioning of mitochondria

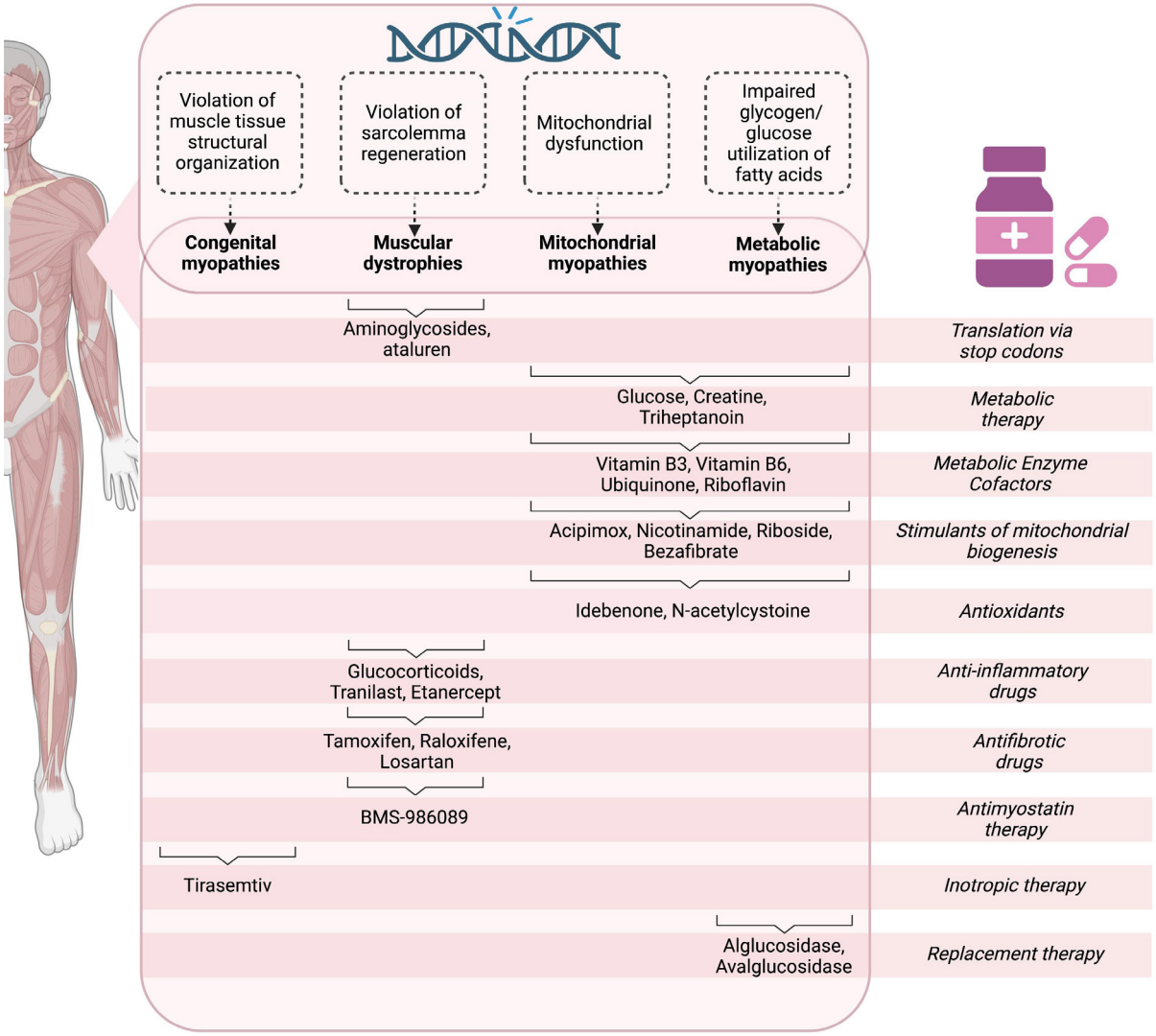

Figure 2 – Varies of existing pharmacological methods for hereditary myopathies correction depending on disease type

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2.1. Mutant protein substitution

Currently, a number of recombinant enzymes have been approved for the specific myopathies therapy. One of the approved approaches is the enzyme replacement therapy for type II glycogenosis (Pompe's disease) with recombinant human alglucosidase alfa (rhGAA; Myozyme© (ex-US) and Lumizyme© (USA), which has been available since 2006, or with avalglucosidase alfa (NEXVIAZYME™; avalglucosidase alfa-ngpt) available since 2021 [54, 55].

Obviously, replacement therapy with recombinant forms of proteins is not the main strategy, since most exogenous proteins cannot penetrate intracellularly to carry out their functions. However, the approaches to directly modify proteins and peptides to enhance cytosolic translocation, continue to be a promising method for improving the delivery efficiency and extending the viability of intracellular protein therapeutics. Among the proposed approaches to improve the cytosolic delivery of exogenous proteins, there have been such as chemical recharging or the inclusion of intracellular internalization motifs [56]. For example, the enzyme replacement therapy with a modified recombinant protein has been proposed for the treatment of X-linked myotubular myopathy. In the preclinical study on Mtm1 δ4 mice with a myotubularin gene knockout, the replacement therapy with recombinant 3E10Fv-MTM1 protein (0.1 mg/kg) into the tibialis anterior muscle twice a week significantly improved the muscle function [57].

2.2. Increase in expression

Some nucleotide substitutions called nonsense mutations, lead to the formation of a stop codon in the coding gene region, resulting in the premature termination of the desired protein synthesis. In addition, mRNA resulting from nonsense mutations is destabilized by a nonsense-mediated decay [58]. Similar mutations are often the cause of hereditary myopathies. Such mutations are found in approximately 10% of Duchenne's patients [59] and in 20% of individuals with X-linked myotubular myopathy (XLMTM) [60].

To restore the expression of the full amino acid sequence, the drugs that force the reading of termination codons were proposed [61]. For example, these were aminoglycosides containing a 2-deoxystreptamine ring bind to the small ribosomal RNA subunit, reducing the accuracy of translation [62]. This property made it possible to propose the use of aminoglycosides for the treatment of Duchenne's myodystrophy [63] and a number of other monogenic diseases caused by premature stop codon mutations [64, 65].

However, serious side effects of aminoglycosides, such as nephrotoxicity and ototoxicity, limit their long-term use. In this regard, alternative agents have been proposed, including suppressor tRNAs and small interfering RNAs (siRNAS) [66] and ataluren [67]. However, only ataluren is currently approved for a clinical use [68].

Theoretically, the termination forcing approach could help treat all hereditary myopathies associated with premature stop codons. Restoration of translation does not always lead to the formation of a functional protein, which, apparently, is associated with impaired intracellular traffic and post-translational modifications of the product [69]. To date, the termination-forcing strategy has been approved for only use with nonsense mutations that cause Duchenne's muscular dystrophy. In addition, despite a high proportion of nonsense mutations in myopathies, their heterogeneity and a low prevalence of each specific disease in the general population make it difficult to conduct full-fledged clinical studies [57].

2.3. Stimulation of internal compensatory pathways expression

In some cases, a decrease or absence of protein expression can be partially compensated for hyperactivation of internal pathways that can functionally mitigate the defect. For example, the severity of muscle pathology in dystrophin defects can be reduced due to the myogenic stimulation, which leads to an increase in the expression of myocyte structural proteins. Non-clinical studies demonstrate that inhibitors of histone deacetylases have a pronounced therapeutic effect in some myopathies. Apparently, due to the regulatory activity in relation to epigenetic modifications, such compounds increase the activity of myogenic differentiation of myocyte precursors. *In vitro* studies have found out that inhibitors of histone deacetylases enhance myogenesis and the formation of enlarged skeletal myotubes [70, 71]. When administered to the dystrophy mice, the drugs had similar beneficial effects. In the mdx mice, the inhibitors increased the cross-sectional area of myofibrils, reducing the histological signs of inflammation and remodeling [72]. Interestingly, among the compounds with an inhibitory activity against histone deacetylases, such well-known drugs as trichostatin A and valproic acid can be distinguished. Herewith, computational biology methods have shown that trichostatin A has the ability to weaken the posttranscriptional repression of utrophin, which has a significant similarity in sequence and functional motifs with dystrophin, including the ability to bind the same dystrophin-associated glycoprotein complex [73, 74]. Utrophin is expressed in fetal tissues at high levels and is inhibited during its development in adults. It was found out that in mice, a decrease in the level of utrophin programmed in embryogenesis corresponds to the onset of muscle necrosis [75]. At the same time, the gene therapy approaches aimed at the

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delivery of utrophin, significantly improve the condition of Duchenne's myodystrophy mice [76]. Trichostatin A is currently undergoing clinical trials for the treatment of Duchenne's muscular dystrophy. At the same time, the specific utrophin modulator ezutromid/SMT C1100 demonstrated unsatisfactory results in phase II clinical trials and was withdrawn [77]. At present, the search for an optimal candidate for increasing utrophin expression continues [78].

2.4. Restoring Balance of Compounds Associated with Mutant Protein Function

In some cases, in addition to repairing the deficiency of the protein itself, a strategy for the delivery of compounds related to its catalytic function can be used (Fig. 1). Obviously, such an approach can be implemented in only metabolic and mitochondrial myopathies, where the cause of the disease is the metabolic enzyme deprivation function, and not the one of structural protein or kinase. The main principle of this approach is based on the fact that the use of an exogenous metabolite compensates for its endogenous deficiency, restoring the efficiency of the entire biochemical chain. For example, it has been known since the 1960s that intravenous glucose improves the exercise tolerance in patients with McArdle's disease, which is associated with a defect in the conversion of glycogen to glucose [79]. Glucose therapy is also effective in some other diseases associated with mutations in the proximal enzymes of glycogen catabolism [80–82]. Another example is the use of triheptanoin, a synthetic medium-length triglyceride that restores the energy efficiency of long-chain fatty acid oxidation in the presence of mutations in proximal catabolism enzymes [83]. Triheptanoin has demonstrated a significant improvement in cardiac and muscle symptoms in VLCAD syndrome patients and in patients with carnitine palmitoyltransferase 2 deficiency [84, 85]. In some cases, an effective strategy to increase the concentration of compounds that serve as substrates for the bypass or an alternative biochemical cascade is also used. Thus, for example, in case of a defect in the formation of ATP along the pathway of fatty acid oxidation, an increase in glucose concentration can compensate for the total energy deficiency due to glycolysis [86]. A similar effect can be achieved with the use of creatine. Creatine is a skeletal muscle amino acid that serves as a substrate for the formation of creatine phosphate, a phosphate group donor for the conversion of ADP to ATP by the enzyme creatine kinase. In a number of studies, the administration of exogenous creatine has shown a therapeutic effect on the muscle symptoms in metabolic myopathies [62, 63].

2.5. Mitotropic drugs

Various cofactors, including riboflavin, coenzyme Q10, vitamins B6 and B3, can be used to partially compensate for the disorders caused by a dysfunction of one of the metabolic pathways (Fig. 1). These drugs can partially increase the energy efficiency of cells due to a positive effect on oxidative phosphorylation in mitochondria [88]. It is known that vitamin B3 (nicotinic acid) serves as a substrate for the formation of NAD and NADP, thereby facilitating the transfer of hydrogen from the tricarboxylic acid cycle to complex 1. Coenzyme Q10 (ubiquinone), in turn, is directly involved in the transfer of electrons from the NADH dehydrogenase complex (complex I) and succinate dehydrogenase complex (II) to complex III.

The use of cofactors is one of the main therapeutic options for mitochondrial myopathies. However, due to the lack of full-fledged clinical studies, it is impossible to judge the effectiveness of this approach in terms of evidence-based medicine. Moreover, the vast majority of these compounds are registered as food additives [89]. Obviously, the approaches based on the use of cofactors do not have a dramatic clinical effect due to e thweak mitochondrial transport, nonselectivity of the action, and a weak overlap with the pathogenetic mechanisms of the disease [90, 91]. The use of vitamin and cofactor cocktails is more justified when the number of factors considered is reduced due to their deficiency or transport defect now when this approach can be considered as replacement therapy [42, 68, 69].

In general, there are still not so many effective methods for restoring a mitochondrial function in mitochondrial mutations from the point of view of evidence-based medicine. In addition to cofactors, mitotropic compounds are represented by antioxidants, mitoprotectors, incl. dichloroacetate, arginine, coenzyme Q10, idebenone, etc. [70, 71]. Pharmacological approaches aimed at improving the function of mitochondria are based on the use of a very wide range of drugs [89, 90, 94]. Some of the most requested connections are shown in Fig. 1.

Classical pharmacological methods of compensating for inadequate functioning of mitochondria are based on increasing the activity of mitochondrial metabolic cascades and reducing the content of toxic agents such as lactate and reactive oxygen species (ROS). E.g., bezafibrate has been shown to stimulate mitochondrial biogenesis by activating the PGC-1a/PPAR pathway. In addition, acipimox, nicotinamide and riboside restore the content of NAD^+, increasing the efficiency of electron transfer to the ETC.

Thiamine, lipoic acid and dichloroacetate activate pyruvate dehydrogenase, which leads to a decrease in the lactate accumulation due to the conversion of pyruvate to another metabolite, acetyl-CoA. Succinate, riboflavin, and CoQ10 promote the ETC electron transfer or restore the function of complexes I and II. Some

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compounds, such as idebenone, N-acetylcysteine, and lipoic acid, have the ability to reduce or inactivate the ROS production. Elamepritide stabilizes mitochondrial membrane lipids, preventing a mitochondrial destruction.

In case of a deficiency of certain lipid or carbohydrate metabolism enzymes, the deficiency replenishing strategy of compounds in the biochemical chain after the reaction catalyzed by the mutant enzyme, has a therapeutic efficacy. E.g., with a defect in the utilization of long-chain fatty acids, the use of heptanoin, a more proximal component included in the tricarboxylic acid (TCA) cycle, is justified. Similarly, in case of glycogen cleavage defects, the therapeutic potential is the use of exogenous glucose. Finally, the defects in the oxidative phosphorylation and mitochondrial function can be partially compensated for by the use of creatine, which acts in muscles as an alternative carrier of the high-energy phosphate bond in the formation of creatine phosphate.

2.6. Anti-inflammatory therapy

Anti-inflammatory therapy is one of the key approaches to the treatment of muscular dystrophies [96]. Inflammatory changes may accompany other types of myopathies, but this is extremely rare [97].

Currently, the only approved approach aimed at suppressing the inflammatory process in myodystrophy is corticosteroid therapy. However, it is important to emphasize that, despite the progressive death of muscle fibers, anti-inflammatory therapy is not necessary for all muscular dystrophies. E.g., treatment with deflazacort in dysferlinopathies patients neither improved nor showed any trend towards a decrease in muscle strength [98].

Corticosteroids have been shown in clinical trials to improve muscle strength and function without clinically serious side effects [99, 100]. Moreover, glucocorticoids have been shown to increase the utrophin expression [101].

In view of the serious side effects developed during a long-term use of corticosteroids, the search for other anti-inflammatory therapy strategies continues. For example, among the strategies tested in myodystrophy, inhibitors of cyclooxygenase (COX), tumor necrosis factor-alpha (TNF-α) and its receptor, as well as TRPV2 channels, can be distinguished.

Non-steroidal anti-inflammatory drugs (NSAIDs) have shown a relatively modest efficacy in a mouse model of Duchenne's dystrophy. Despite the fact that the use of aspirin and ibuprofen improved the morphological picture of muscles and reduced the inflammatory infiltration and necrosis, the percentage of regenerating myofibrils and isometric tension did not change significantly [102].

The spectrum of the pharmacological activity of the antiallergic drug tranilast includes blockade of TRPV2 [103], therefor its use led to a decrease in fibrosis in skeletal muscles and an increase in the exercise tolerance [104, 105].

Inhibitors of TNF-α have shown some potential in the treatment of myodystrophy. The use of etanercept or an anti-TNF-α antibody slowed down the course of the disease and also reduced the inflammation and destruction of dystrophic muscles in mdx mice without the development of pronounced side effects [106, 107].

2.7. Antifibrotic therapy

An extracellular matrix is an important component of skeletal muscles. It provides a scaffold structure that holds the myofibrils and vessels. In addition, it plays a major role in the processes of biomechanical contraction, as well as in maintaining the integrity and repair of muscle fibers. An excessive accumulation of extracellular matrix components, especially collagen, is defined as fibrosis. An excess formation of the connective tissue as a result of death and defect in muscle cells proliferation is the most important distinguishing feature of muscular dystrophies. Since the dynamics of fibrotic replacement in myodystrophy strongly correlates with the development of muscle symptoms, antifibrotic therapy is one of the main approaches to treating such patients [108].

Tamoxifen is a prodrug, and some of its metabolites interact with the nuclear estrogen receptor, mediating antifibrotic and myoprotective effects. A multicenter, prospective study in 13 outpatient boys aged 6–14 years with genetically confirmed Duchenne's muscular dystrophy demonstrated that patients treated with tamoxifen 20 mg/daily maintained a motor and respiratory functions, compared with a significant deterioration in the patients of the same history of age who had been administrated with only corticosteroids [109].

A similar approach has also shown off its efficacy in a mouse model of dystroglycanopathy. In the studies by Wu B. et al. it has been demonstrated that tamoxifen and raloxifene significantly alleviate a disease progression in the animals with the c.1343C>T mutation of the FKRP gene, demonstrating a pronounced phenotype of a limb-girdle muscular dystrophy [110].

A primary profibrotic signal in skeletal muscles, as in other tissues, is a transforming growth factor-beta (TGFβ) [111]. A high expression of TGFβ is a characteristic feature of dystrophic muscles [112] and is considered one of the main therapeutic targets for reducing fibrosis. It has been shown that Wnt-TGFβ2 is one of the key factors mediating the differentiation of dystrophin-deficient muscle cell precursors in the fibrogenic direction. Antibodies stabilizing LTBP4, which is a TGFβ binding factor, demonstrated a high efficiency.

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Anti-LTBP4 treatment also reduced muscle fibrosis and increased muscle strength, including the ones in the diaphragm muscles [113].

The renin-angiotensin system plays an important role in the transmission of profibrotic signals. In particular, the activation of the angiotensin 1 receptor stimulates fibrosis. At the same time, it has been shown that the antihypertensive drug with an inhibitory activity against TGFβ2 losartan led to an increase in the level of myogenic factors with a reduced expression of fibrogenic genes in mdx mice (Duchenne's myodystrophy model) [112].

Interestingly, another drug that blocks the renin-angiotensin-aldosterone axis, enalapril, also exhibits inhibitory effects on the connective tissue growth factor (CTGF/CCN2) [114] and is another regulator of profibrotic signaling [115, 116]. Pharmacological blockade of CTGF has been shown to slow the progression of fibrosis and improve a muscle function in mdx mice [114]. Moreover, anti-muscle CTGF therapy is currently undergoing clinical trials for the treatment of Duchenne's muscular dystrophy [117].

2.8. Means with a positive effect on muscle strength

A decreased muscle strength is the main symptom of myopathies. In this regard, in addition to other approaches, strategies have been developed to increase the effectiveness of the muscle contraction or the prevention of myopenia.

For example, tirasemtiv, fast skeletal troponin activator acting on thin filaments, has been shown to be effective as an agent that increases muscle strength, and can be used to compensate for hypotension in the muscle dysfunction. In the studies on genetically modified mice and cells from a patient with rod myopathy carrying an actin mutation (ACTA1H40Y), treatment with tirasemtiv increased inotropic parameters to those comparable to healthy controls [118].

One of the most popular targets for regulating a muscle mass is myostatin. A decrease in signaling of this myokine leads to a sharp increase in the muscle mass due to the intensification of the muscle fiber growth [119]. The first similar drug, domagruzumab (PF-06252616, Pfizer), which is a recombinant humanized antibody to myostatin, was withdrawn during the second phase of clinical trials, despite the fact that in the first phase, a 6.1% increase in the muscle mass after treatment was shown compared with a placebo group [120]. Another antimyostatin drug, BMS-986089, has demonstrated its high efficacy in preclinical test systems in mice and cynomolgus monkeys, and is currently undergoing clinical trials. However, in general, despite the theoretical promise of the approach and positive initial results, the recent clinical data demonstrate that antimyostatin therapy is less effective than expected. In addition, the long-term effects of antimyostatin therapy require a particularly close study, due to the possible negative impact on the pool of myosatellite cells [121].

CONCLUSION

Hereditary myopathies are a group of incurable diseases with a wide range of symptoms and a high variability in the clinical course. Currently, a large number of therapeutic approaches have been developed and approved for the use in various types of myopathies (Fig. 2). The most developed are the methods for the correction of muscular dystrophies, which, due to the progressive nature of the course, have the largest number of pathogenetic pathways that can be targets for therapy. At the same time, the smallest number of therapeutic options is available for the treatment of congenital myopathies, where the hereditary defect is permanently manifested throughout life, and there are no secondary alteration factors, such as inflammation and fibrosis. In addition, with the exception of some nosologies, there are no effective approaches to correct metabolic and mitochondrial myopathies.

In the treatment of all myopathies, an important role is played by symptomatic and supportive therapy aimed at treating pain and symptoms from other organs and systems. Osteoporosis [122] and pneumonia are regular consequences arising from hypodynamia myopathies, which are treated according to standard schemes.

It should be notified that in recent years, gene therapy approaches that correct or compensate for a defect at the gene level have become increasingly important. These approaches were not been covered in the work, the aim of which was to analyze the existing conventional strategies. However, to date, it is gene and cell therapy that constitute the most growing and promising layer of pharmacological agents for the treatment of hereditary myopathies.

In congenital myopathies, tirasemtiv, rapid skeletal troponin activator acting on thin filaments, has been shown to be effective. Theoretically, this approach can be effective in other types of myopathies. For the treatment of muscular dystrophies, anti-inflammatory and antifibrotic drugs, as well as antimyostatin therapy and a strategy aimed at translation through stop codons (applicable for nonsense mutations), can be used. In addition, metabolic drugs, metabolic enzyme cofactors, mitochondrial biogenesis stimulants, and antioxidants can be used to treat mitochondrial and metabolic myopathies. Finally, the recombinant drugs alglucosidase and avalglucosidase have been clinically approved for the replacement therapy of metabolic myopathies (Pompe's disease).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

MVP – idea creating, article concept planning, advising on writing of individual manuscript sections; MVK – idea development, article writing; AMK –literature analysis, article writing; NSZ – literature analysis, article writing; KNL – article writing, graphic material preparing; MOS – literature analysis, article writing; EAK– literature analysis, article writing; OSG – literature analysis, article writing; ISK – literature analysis, article writing; AVD – article concept planning, article writing.

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