



Metabolic disorder in a denervated muscle

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Abstract

A denervated muscle is a skeletal muscle that has completely lost its connection to the motor neuron (the spinal cord motor neuron or its axon).

Metabolic disorders in denervated skeletal muscles are a complex set of biochemical and structural changes that occur after the loss of nerve connection. This process leads to atrophy and changes in the functional properties of muscle tissue. The main metabolic shifts include:

disruption of energy metabolism, increased breakdown and altered protein synthesis, activation of oxidative stress, alteration of membrane lipid composition, and shift in metabolic pathways.

Keywords: muscle, neuron, metabolic, disorder.

Introduction

Skeletal muscle is the largest tissue in the human body, accounting for approximately 40% of the body's muscle mass. It is essential for movement and serves as the primary site for glucose and lipid metabolism, maintaining energy homeostasis and being closely linked to metabolic disorders such as diabetes and metabolic syndrome. This tissue exhibits remarkable adaptability, responding to mechanical stress and de-stressing through various mechanisms.[1]

The motor function of a muscle depends on the integrity of the motor unit with its main components. It is known that the neuromuscular junction (NMJ) is a dynamic formation with remarkable plastic ability, which is able to be reconstructed due to special requirements for ingrown axons (NMJ). In the native state, somatic efferent fibers are necessary for the functioning of breast cancer.[4]

Schwann cells are necessary for peripheral nerve regeneration, but at short distances in cell-free nerve grafts, extracellular matrix (ECM) molecules can support growth. ECM molecules are also present on denervated muscle surfaces, where they can support nerve growth.[14]

Mitochondria, critical intracellular organelles, have a significant impact on muscle plasticity. During muscle contraction, they produce

the necessary amount of energy. These organelles are organized into a network throughout the skeletal muscle to optimize energy supply. ATP, the primary energy source in cells, is generated through oxidative phosphorylation within the respiratory chain complexes in the inner membrane of mitochondria. Disruption of mitochondrial function can lead to reduced energy production, resulting in dysfunction and atrophy of skeletal muscles. For example, inactivation of the main regulator of mitochondrial biogenesis, the gamma coactivator of the peroxisomal proliferator 1-alpha PGC-1a, specifically in skeletal muscles, reduces the content of mitochondria and the cross-sectional area of muscle fibers[1]

Loss of motor innervation causes rapid degeneration of skeletal muscle fibers, with activation of atrophy-related signaling and subsequent disassembly of sarcomeres, altering normal muscle function. After denervation, the inflammatory stage is characterized by increased expression of pro-inflammatory cytokines that contribute to muscle atrophy.[18]

Denervation causes mitochondrial dysfunction and a significant increase in the production of reactive oxygen species (ROS). In response, compensatory mechanisms of antioxidant protection are activated in the muscle, particularly the increased expression of the enzyme catalase, which is particularly noticeable against the background of mitochondrial DNA (mtDNA) instability[1].

It is known that the production of ROS in skeletal muscles can be carried out in the respiratory chain of mitochondria, with the activation of xanthine oxidases, as well as NADPH oxidases (NOX, NADPH oxidase). Traditionally, mitochondria have been considered the main source of ROS in skeletal muscles, however, recent data suggest that muscle NADPH oxidases can also contribute significantly to the development of oxidative stress. It is known that skeletal muscles have two isoforms of enzymes: NOX2 (sarcolemma) and NOX4 (sarcoendoplasmic reticulum, mitochondria). Their activation, followed by the production of ROS, occurs through the assembly of membrane and cytosolic subunits. The role of NOX2 and NOX4 in the development of muscle dysfunctions, including atrophy due to inactivity, has been described in several studies.

The role of mitochondrial dysfunction in the development of oxidative stress during atrophic processes is also well-established. It has been shown that in the soleus muscle of mice, total levels of AFC increase as early as on the 3rd day of functional unloading, and mitochondrial AFC increase after 7 and 14 days, against the background of suppression of the activity of the respiratory chain enzyme complexes. Thus, the growth of free oxygen radicals can be induced from the earliest terms of unloading and, in addition to mitochondrial AFC, depends on the contribution of other sources.[5]

In denervated muscle, autophagy is suppressed due to the paradoxical activation of the mTORC1 complex. This activation depends on the functioning of the proteasome and is likely an adaptive anabolic response aimed at slowing down atrophy through protein and ribosome synthesis[2].

Glycogen content in denervated muscles. One of the earliest biochemical changes observed within a few days after denervation, when no noticeable morphological changes in the muscles have yet been detected, is a decrease in glycogen content. Subsequently, the glycogen content in denervated muscles decreases even further. The assumption that the decrease in glycogen content in denervated muscle is caused by fibrillar contractions, which begin at the same time as the most pronounced decrease in glycogen content, is not supported by the work of D. L. Ferdman, P. M. Zubenko, and others. A decrease in glycogen content is observed to a similar extent in muscle atrophy that is not accompanied by fibrillar contractions, as well as in the administration of substances that eliminate these contractions. Further studies have shown that the decrease in glycogen levels in denervated muscle is associated with a disruption in its ability to produce glycogen. The production of lactic acid from glycogen by the denervated muscle paste under anaerobic conditions is very low, but it increases significantly in the presence of glucose.

Significant disturbances in the metabolism of phosphorus compounds are also observed during muscle denervation. The content of labile phosphorus in ATP and ADP changes little in the first days after denervation, but then decreases sharply.

Information about the activity of enzymes involved in the metabolism of macronergic phosphorus compounds is of great interest. Most authors note that the activity of adenosine triphosphatase decreases after denervation, especially in the later stages of the atrophic process. In experiments on cats with motor fibers of the sciatic nerve cut off, it was found that 2-4 weeks after surgery, there was an increased breakdown of ATP in the mush of the deafferented muscles compared to the control by 20-30%. The data of S. E. Severin and his colleague L. V. Slozhenikina regarding the increase in ATPase activity in denervated muscles are in known contradiction with the results of studies by a number of other authors. However, it is possible that this contradiction is only apparent. It can be assumed that since the ATPase activity of muscle pulp is due to the total activity of myosin and water-soluble ATPase, the amount (or activity) of

water-soluble ATPase increases in parallel with the decrease in myosin content during denervation. For example, the following observations indicate the possibility of changes in the ratios of myosin and non-myosin ATPase activities during muscle denervation. ATPase activity does not change in myofibrils during the first few hours after denervation, but increases in sarcosomes. After 12 to 16 hours, activity decreases in both myofibrils and sarcosomes.

After denervation, the muscle's water content increases. R. Y. Yudelovich (1940) observed no changes in the dry matter content of muscle tissue in dogs within a few days after nerve transection. In experiments on rats, Lulman and Mushol found an increase in muscle weight in the early stages of denervation, but a noticeable loss of weight in the later stages. Denervated muscles absorb and release water more slowly than normal muscles. Water accumulation is largely due to an increase in connective tissue in denervated muscles. The water content in muscle cells does not change. The loss of K by muscles and the retention of Na, Ca, and Cl during perfusion with a mixture of blood and saline solutions or incubation in saline solutions in denervated muscles is more intense than in normal muscles. Several authors also associate changes in the electrolyte composition of denervated muscles with changes in the ratio between muscle and connective tissue. According to A. N. Leporsky, the decrease in Mg content in denervated muscle is associated with a decrease in the concentration of ATP and other phosphorus compounds that form complex compounds with Mg. The loss of K by muscles increases with intra-arterial administration of acetylcholine, and this process is significantly more pronounced in denervated muscle. The process that limits the release of K in normal muscle is the diffusion of acetylcholine from the extracellular fluid into the space between the nerve endings and the membrane of the end plates. Denervation leads to the loss of this process. In this case, it is not so much the above-mentioned consideration about the membrane mechanism of K release by the muscle (these ideas are disputed by some authors) that is of greatest interest, but rather the fact that acetylcholine affects the electrolyte composition of muscle cells. It is also interesting to note that the opposite process, i.e., the uptake of K into the muscle from the surrounding solution, is hindered during denervation.

The content of glycogen, lactic acid, phosphocreatine, and ATP, as well as catalase, glutathione, ascorbic acid, and myoglobin, did not change significantly during muscle deafferentation. A slight decrease in the binding intensity of inorganic phosphorus by the mush of deafferented muscle was observed. Bound inorganic phosphorus accumulated mainly in the form of fructose diphosphate, which, according to L. V. Slozhenikina (1957), indicates a relatively slow course of the subsequent stages of carbohydrate breakdown and, in particular, the glycolytic oxyreduction reaction. No impairment of respiratory phosphorylation was detected.

The retinol-binding protein RBP4 promotes fatty infiltration and muscle atrophy through the activation of the STRA6/JAK2/STAT3 pathway. This mechanism leads to increased expression of atrophy markers (Atrogin-1, MuRF1) and suppression of myogenesis factors (MyoD, MyoG). Inhibition of RBP4 is considered a potential therapy[3].

Skeletal muscle atrophy occurs in various situations, such as denervation, starvation, and aging. The imbalance between protein synthesis and degradation plays a crucial role in muscle atrophy, and the disruption of Akt phosphorylation is considered crucial in this process. The regulation of protein function involves the attachment of the O-linked N-acetylglucosamine (O-GlcNAcylation) motif, which is a post-translational modification mediated by the biosynthesis of hexosamine, an alternative pathway of glycolysis. Akt O-GlcNAcylation interacts with Akt phosphorylation, thereby regulating its function.[6]

Decreased bone morphogenetic protein (BMP) signaling is observed in the early stages of skeletal muscle wasting associated with cancer cachexia in mouse models and in cancer patients. Cancer-mediated factors, including activin A and IL-6, trigger the expression of the BMP inhibitor Noggin in muscles, which blocks the action of BMP on muscle fibers and motor nerves, subsequently causing neuromuscular junction (NMJ) dysfunction, denervation, and muscle wasting. Increasing BMP signaling in tumor-bearing mouse muscles by gene delivery or pharmacological means can prevent muscle atrophy and preserve NMJ function[7].

Denervation causes a sharp increase in CTMP expression in muscle. CTMP inhibits the phosphorylation of Akt (a key survival and growth kinase). The phosphorylation of ribosomal proteins S6 and 4E-BP1 is reduced, which leads to a slowdown in translation and the assembly of new muscle proteins.

The decrease in Akt activity stimulates the expression of E3 ubiquitin ligases (MuRF-1) and myostatin, which accelerates proteolysis (the breakdown of protein)[8].

Denervation causes endoplasmic reticulum stress (ER stress) and mitochondrial dysfunction. In response to ER stress, the transcription factor C/EBP β is activated, which triggers the expression of SESN2. SESN2 has a dual function:

1. Protein synthesis inhibition: It inhibits the mTORC1 complex to reduce the load on the damaged ER (preventing the accumulation of misfolded proteins).

2. Mitochondrial clearance: Activates mitophagy (mitochondrial autophagy) through the p62 protein, removing damaged sources of reactive oxygen species.[9]

It has been shown that denervation activates the transcriptional co-regulators YAP/TAZ in FAPs. Activation of YAP/TAZ leads to proliferation of FAPs and deposition of extracellular matrix components (fibrosis). It contributes to the replacement of muscle parenchyma with adipose tissue. This explains why, with prolonged denervation, the muscle not only loses weight (protein) but is also replaced by connective tissue and fat, making the process irreversible in the later stages. [10]

In denervated patients (compared to spastic innervated patients), the following was found:

1. A decrease in the cross-sectional area of the thigh muscles by 38-61%.
2. An increase in intramuscular fat (IMF%) by 15.5% (there is almost no fat in healthy muscles).

A decrease in bone mineral density (BMD) in the knee area by 17-23%, which is a result of the lack of mechanical muscle traction and impaired local metabolic processes. [11]

The denervation model is the standard for studying the ubiquitin-proteasome pathway (the Atrogin-1/MuRF1 ubiquitin-ligase system) and autophagy.[12]

The formation of densely packed clusters of acetylcholine receptors (AChR) on the postsynaptic membrane is a distinctive feature of the neuromuscular junction (NMJ), the synapse between the motor axon and the muscle fiber. Studies on mice depleted of essential components of the basic complex (agrin, low-density lipoprotein receptor-related protein 4 (Lrp4), and muscle-specific kinase (Musk)), or proteins located below tyrosine kinase 7 (Dok7) and receptor-associated protein (rapsin), have revealed their importance in the initial stages of NMJ formation, as their absence leads to impaired NMJ formation (rapsin). Conversely, auxiliary

proteins such as dystrophin-glycoprotein complex (DGC), neuregulin, members of the ErbB receptor family, and Wnt signaling molecules play a crucial role in the maturation and maintenance of the NMJ in mice. Denervation enhances the expression of microRNA-206 levels in both synaptic and non-synaptic regions. Due to the distribution of miR-206 expression in synaptic regions, we investigated whether miR-206 can target specific mRNAs that encode proteins crucial for NMJ formation and stability. To achieve this goal, we used the miR-206 oligonucleotide as a primer in a reverse transcriptase reaction to identify potential miR-206 mRNA targets, as described previously. We verified the specificity of this approach by using the utrophin transcript as a miR-206 target (positive control), which was previously predicted to be a target using bioinformatics tools and confirmed as a target by experiments[13]

Calpain-activated signaling pathways are important for the degradation of skeletal muscle structural (sarcomeric) proteins. Muscles and bones function as a single musculoskeletal unit. When skeletal muscle is functionally and structurally damaged, it leads to bone abnormalities and vice versa. Bone remodeling/resorption releases TGF-beta, which contributes to muscle fibrosis and atrophy. Given that severe trauma causes significant damage to bones as well as muscle fibers, the large amount of TGF-beta released during bone regeneration/remodeling could potentially have a negative impact on muscle recovery after trauma. The breakdown of muscle collagen is inhibited after denervation, leading to the accumulation of collagen. The activation of muscle stem cells (satellite cells) during prolonged denervation helps to preserve the integrity of muscle fibers. These processes allow small atrophic skeletal muscle fibers to survive even after a very long period of denervation. Denervation not only leads to muscle atrophy, but also affects the metabolic functions of muscles. A study by Dr. Witschak's laboratory, published in the current Special Issue, describes the impact of denervation on insulin resistance. Although both the slow (soleus) and fast (extended digital longus or EDL) muscles atrophied to about 40% after 28 days of denervation, the changes in insulin sensitivity were quite different. The GLUT 4 transporter increased in the fast EDL muscles and decreased in the slow soleus muscles. This correlated with the development of insulin resistance in the soleus muscle, but increased insulin sensitivity in the EDL muscle. Given that age-related denervation of skeletal muscles predominantly affects fast muscle fibers with relative preservation of slow muscle fibers, it is interesting to consider the potential impact on glucose metabolism in older individuals.[15]

We have identified muscle-secreted fibroblast growth factor 21 (FGF21) as a key inducer of atrophy after muscle denervation. In denervated skeletal muscles, Fgf21 is the most highly activated member of the Fgf family and acts autocrinely/paracrinally to promote muscle atrophy. Silencing Fgf21 in muscles prevents muscle wasting caused by denervation by preserving the innervation of neuromuscular junctions (NMJs). Conversely, forced expression of FGF21 in muscles reduces NMJ innervation, leading to muscle atrophy.[16]

After denervation, myocytes undergo molecular changes within a few hours, activating signaling pathways that lead to muscle fiber degeneration and long-term atrophy. Macrophages play a crucial role in these processes, mediating tissue repair through pro-angiogenic and anti-angiogenic mechanisms. Additionally, denervation leads to hypoxic conditions within the muscle, caused by factors such as impaired blood flow regulation, increased metabolic demands, reduced capillary density, and insufficient angiogenesis.[17]

Hypoxia-inducible factors (HIFs), the main regulators of angiogenesis, play a central role in modulating the behavior of macrophages in these hypoxic conditions. HIFs regulate genes involved in oxygen homeostasis,

cell survival, inflammation, and angiogenesis. These HIF1-regulated genes mediate the cellular response to low oxygen levels and, when activated, activate pro-angiogenic genes that promote the development of blood vessels. Angiogenesis is vital not only for physiological processes such as wound healing, but also plays a central role in pathological conditions such as cancer, diabetic retinopathy, and rheumatoid arthritis. [17]

Using magnetic resonance spectroscopy, it has been shown in humans that the ratio of phosphocreatine to inorganic phosphate (PCr/Pi), a key indicator of energy status, decreases in denervated muscle. At the same time, intracellular pH increases. The extent of these changes correlates with the severity of denervation. This is supported by animal experiments, which also show a decrease in ATP and phosphocreatine levels. [19,20]

The paradox is that, despite increased basal glycolysis and glucose transport, the muscle becomes resistant to insulin action. In particular, there is resistance to insulin-stimulated glycogen synthesis, and there are defects in insulin's effect on protein synthesis. However, interestingly, insulin's effect on proteolysis is not impaired, suggesting multiple specific defects rather than a general signal failure. [20]

Conclusion

Skeletal muscle denervation triggers a complex cascade of interconnected metabolic disorders that go beyond simple atrophy from inactivity. Denervation leads to a decrease in ATP and creatine phosphate levels, disruption of the mitochondrial respiratory chain, and accumulation of reactive oxygen species (ROS). In denervated muscle, there is a paradoxical suppression of autophagy (due to activation of mTORC1) accompanied by increased ubiquitin-proteasome degradation of proteins (via MuRF-1 and Atrogin-1 ligases). Prolonged denervation activates fibro-adipogenic progenitors (FAPs) through the YAP/TAZ signaling pathway, leading to fibrosis and fatty infiltration of the muscle, making the atrophy partially irreversible. The decrease in bone mineral density confirms the disruption of the skeletal-muscular unit's integrity. Denervation causes multidirectional changes in insulin sensitivity: insulin resistance develops in slow fibers (soleus muscle), while sensitivity may increase in fast fibers. Key molecular regulators of denervation atrophy have been identified: FGF21, RBP4/STRA6, SESN2, CTMP, as well as microRNA (miR-206). These molecules represent potential therapeutic targets for preventing muscle mass loss.

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