Implications of Obesity on Neuromuscular Functions-The Known And Unknown

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Abstract

The global obesity pandemic is due to an imbalance between energy intake and expenditure and is attributed to increased intake of sugary beverages and increased portion size associated with a decrease in physical activity. Obesity is associated with an increase in whole body fat reserve in adipose and non-adipose tissues. The fat processing organs like adipose tissue, liver, and skeletal muscle undergo enlargement due to fat overload in obesity, often associated with increased secretions of inflammatory cytokines, which progressively lead to atrophy of these organs. There is ample literature on the metabolic implications of fat accumulation in these tissues but the knowledge on how obesity impacts neuromuscular functions still remains scarce. It is well known that body composition abnormalities affects gait, posture, and balance posing a major concern to daily functional activities. Obese people also suffer from respiratory inefficiencies and develop sleep apnea and hypoventilation. Posture, gait, and respiration are coordinated by nerves, which control the voluntary muscles. But there is no evidence directly associating the complications of obesity with neuromuscular junction (NMJ). Besides, most NMJ disorders are autoimmune disorders. It is also well known that obesity is a chronic low-grade inflammatory disorder and it is very difficult to speculate whether obesity triggers these disorders. Currently, the knowledge on the implications of metabolic diseases like obesity on proteins, which take part in maturation and clustering of acetylcholine receptors and thereby regulating neuromuscular transmission, is limited. This review focuses on the implications of obesity at the NMJ and highlights need for future research to understand the effects of metabolic dysfunctions on neuromuscular functions.

Obesity and Neuromuscular Functions-The Known

Obesity is considered as a global epidemic [1-7], which is now becoming a global pandemic [8-10]. According to World Health Organization reports, there are more than 1 billion overweight adults, at least 300 million of them obese [11]. Obesity occurs due to an energy imbalance between intake and expenditure. Excess energy intake is attributed to high consumption of sugar and sweetened beverages [12,13] and the decreased energy output can be attributed to sedentary life style. Body mass index (BMI) is commonly used to assess the prevalence of overweight and obesity and is defined as weight in kilogram divided by the square of height in meters (kg/m²). BMI over 25 Kg/m² is defined as overweight and a BMI over 30 Kg/m² is considered obese [11,14]. Although BMI and similar markers are used as benchmarks to assess the risk of contracting obesity-related diseases, it is worth noting that segments of the population with high BMI also run the risk of suffering from the comorbidities related to overweight and obesity. Obesity leads to adverse metabolic effects on blood pressure and dyslipidemia [15] leading to increased cholesterol and triglyceride levels in the blood circulation, which progressively causes atherosclerosis [16-18], insulin resistance, myocardial infarction [19-25], and stroke [25-27]. Further, comorbidities including certain types of cancers, especially hormone-related [28-34] and large bowel cancers [35, 36], and gall bladder disease [37, 38] are often associated with obesity. The non-fatal but debilitating problems associated with obesity include respiratory difficulties [39-41], chronic musculoskeletal problems [42-47], skin diseases [46-50], and infertility [51-55].

Complications Arising from Fat Accumulation in Tissues

Fat is the largest energy reserve in mammals. There is whole body fat accumulation in obesity, both in adipose and non-adipose tissues and in organs including liver, pancreas, heart, skeletal muscle, and bone etc. Although fat metabolism occurs in several tissues, adipose tissue, skeletal muscle and liver are largely involved in lipogenesis and lipolysis processes. Each of these tissues has a store of triacylglycerol that can be hydrolyzed (mobilized) in a regulated fashion to release fatty acids. In the case of adipose tissues, stored fatty acids may be released into the circulation for delivery to other tissues, whereas in muscle the fatty acids are substrates for oxidation [56] while in the liver the fatty acids undergo re-esterification within the endoplasmic reticulum to make triacylglycerol that is secreted as a very-low-density lipoprotein [57]. Under normal conditions these tissues work in synchrony to maintain metabolic homeostasis.

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During obesity, the adipocytes become enlarged, recruit macrophages, promote inflammation, and secrete a wide range of factors that lead to insulin resistance and other complications. Excessive fat accumulation leads to fatty liver, which progressively leads to hepatitis, portal fibrosis and cirrhosis. In the skeletal muscle, overload of lipids results in impaired insulin signaling and also perturbs muscle maintenance and regeneration resulting in muscle wasting or atrophy [58]. Even though there is ample literature suggesting the role of fat accumulation in these tissues and consequences associated with it [59, 60], there is lack of evidence for the role of fat accumulation in neuromuscular junctions and how the fat accumulation modulates neuromuscular functions.

Structure and Function of Neuromuscular Junction (NMJ)

The neuromuscular junction (NMJ) is the interface at which signals from myelinated motor nerves are transmitted to skeletal muscle. Minute action potentials are transformed into muscle contractions and thus NMJ serves as an integral part of an efficient biological amplification system. NMJ represents the simplest synapse between a muscle and the innervating motor nerve. The mature NMJ consists of a presynaptic terminal, a synaptic cleft and a postsynaptic terminal [61]. The presynaptic nerve terminal contains calcium, potassium, sodium channels, and synaptic vesicle proteins [SVs with 5000-10000 molecules of neurotransmitter acetylcholine (ACh)]. The quanta of vesicle release refer to the release of ACh from a single vesicle. The change in potential caused due to the spontaneous release of ACh without stimulation is called miniature end plate potential (mEPP). The generation of an action potential results in an increase of Ca$^{2+}$ within the nerve terminal to initiate a cascade of events, resulting in docking, priming, fusing of SVs at the active zones and release of ACh. Acetylcholine esterase (AChE) catalyzes the hydrolysis of ACh at the synaptic cleft into acetate and choline.

Located postsynaptically on the skeletal muscle are nicotinic ACh receptors (nAChR), pentameric channels composed of α, 2β, δ and ε subunits. Binding of ACh to N-terminal of α6 and αε subunits results in pore opening and sodium/calcium entry, which cause skeletal muscle contractions.

Implications of Metabolic Diseases on NMJ

The extent to which body composition abnormalities contributing to the motor problems is best manifested in Prader-Willi syndrome (PWS). PWS is a neurogenetic disorder characterized by hypotonia, muscle weakness and severely delayed motor development. The causes of these symptoms are attributed to abnormal body composition in PWS patients, with an increase in fat mass, a decrease in muscle mass, and neuromuscular abnormality. PWS adults suffer from hyperphagia and therefore the balance between energy intake and expenditure is lost leading to decrease in lean body mass and basal metabolic rate. This results in impaired neuromuscular functioning in PWS characterized by hypo excitability [62], atrophy [63], fiber deficiency and increased amount of immature muscle fibers [64], morphological abnormalities of contractile elements, and mitochondrial dysfunction [65], leading to decrease muscle strength and function. Altered body composition is considered as the major factor contributing to PWS. Beneficial results have been reported from administration of growth hormone on body composition in PWS and hence positively affect muscle strength and performance in patients suffering from PWS [66-68].

Obesity and NMJ

The nerves that control voluntary muscles are affected in neuromuscular disorders. Voluntary muscles are the ones that control the movement of limbs and respiration.

Posture and Gait

Neuromuscular deficit impacts the normal gait (locomotion) and posture. It has been shown that overweight reduces the performance of subjects and compromises the gait initiation and increases difficulty in controlling vertical stability of the body. Increased body fat mass composition decreases postural stability [69] and increases the risks of falling [70]. Poorer body balance due to overweight was also confirmed by a greater sway area as well as variability in the medial/lateral direction [71] in obese individuals. A decreased balance control has important functional limitations as balance does not refer only to the upright position but also regulates most of the daily activities. A proper balance control for stability is required for aiming or reaching movements in an upright position. Daily functional activities will be a major limitation for obese subjects due to decreased stability control.

Metabolic diseases affect postsynaptic nAChR

Nicotinic acetylcholine receptors are ligand gated ion channels and are tonically present in the NMJ. The alpha 7 nAChR (α7nAChR) has been shown to exert central and peripheral effect on the nervous system to alter appetite and energy expenditure, leading to changes in body weight [72-74]. α7nAChR expression levels are significantly decreased in obese subjects [75]. Obesity is associated with chronic low-grade inflammation and previous research suggests that α7nAChRs activation may mediate anti-inflammatory effects [75]. Further, α7nAChRs agonists improved insulin sensitivity in wild type but not in α7nAChRs knockout animals. These observations suggest that α7nAChRs are critical for the anti-inflammatory effects. Investigating α7nAChRs as therapeutic targets to minimize inflammatory comorbidities associated with obesity such as diabetes, arthritis, and ulcerative colitis [76] will be a good strategy.

Obesity and respiration

Obesity presents severe respiratory complications. It causes hypoventilation and breath-exhaustion, due to inefficiency of respiratory muscle and leads to sleep apnoea syndrome [77]. Higher respiratory rate, lower tidal volume and lung volume and decreased expiratory rate reserve volume have been reported in obese patients [78]. However, the role of respiratory center to increase nerve-drive of the respiratory muscles to overcome abnormal mechanical load has not been thoroughly understood [79]. In particular, alterations in the expression and function of metabolic proteins in phrenic nerve, which innervate diaphragm,
alteration in synaptic cleft composition and postsynaptic AChR in diaphragm during metabolic disease, are not known.

**Obesity and Neuromuscular Functions-The Unknown**

**Presynaptic, synaptic cleft and postsynaptic proteins and obesity**

Clustering of AChR at the postsynaptic muscle membrane is a determinant of accurate synaptic transmission at the NMJ. Different mechanisms regulate assembly and stabilization of AChR, which includes synaptogenic factors from muscle fibers and nerve terminals and perisynaptic Schwann cells [80].

**Proteins involved in synthesis and clustering of AChRs:** Muscle specific Kinase (MuSK) is a receptor tyrosine kinase and component of agrin receptor. Agrin interaction with MuSK via Lipoprotein receptor-related protein 4 (LRP4) is important for the prepatternning of AChR clusters [81-83]. Rapsyn - an AChR-associated anchoring protein plays a crucial role in postsynaptic assembly [84]. Extracellular neuregulin1 binds to its receptor ERBB to promote synthesis of AChR [85,86].

**Proteins involved in Presynaptic Maturation:** Laminins[87], Fibroblast growth factors (FGF7, FGF10 and FGF22), type IV and XIII collagen [88,89], Glial derived neurotropic factors (GDNF), and Brain-derived neurotropic factors (BDNF) [90, 91] play an important role in presynaptic maturation. Matrix metalloproteases present in extracellular matrix of Schwann cells play an important role in regulating the levels of agrin and conversion of mature BDNF[92, 93] for proper AChR clustering and function[94, 95].

Acute and prompt changes are critical at transcriptional/translational, and at post-translational levels of proteins in response to various metabolic stimuli to maintain cellular homeostasis. In obesity, the metabolism of carbohydrate and lipid is drastically affected, indicating loss of control of genes at transcriptional, translational, and post translational levels leading to altered functions.

There are only a few evidences suggesting a cross talk between some of the proteins involved in synaptic function and obesity [96-98]. More work has to be done to evaluate how these proteins are altered due to excess fat accumulation in NMJ. This will help in developing targets to decrease weight gain and to improve motor functions that are compromised in obesity.

**Does Obesity trigger Neuromuscular Diseases?**

Some of the diseases that affect NMJ are autoimmune neuromyotonia (associated with muscle cramps and stiffness), Lambert-Eaton Myasthenic syndrome (associated with weak proximal limb muscles, respiratory muscle weakness/failure, erectile dysfunction, low gastrointestinal motility), and Acquired Myasthenia Gravis (decreased muscle contraction), which are all autoimmune disorders.

Obesity is a chronic, low-grade inflammatory disease, which affects the immune system and produces autoantibodies. Although there are no established links between obesity and the autoimmune disorders associated with NMJ, the prevalence of neuromuscular autoimmune diseases in obese patients triggers the focus of new research to investigate these mechanisms.

**Conclusions and Future Directions**

Currently, efforts are underway to develop drug targets to prevent weight gain and comorbidities associated with it. Obesity is associated with change in body composition due to accumulation of fat in tissues. This decreases postural balance and increases rates of falling and injury. Obesity down-regulates respiratory functions and often exacerbates an existing respiratory disease. The voluntary muscles constitute nearly the whole of the fleshy parts of the body. The limbs and respiratory muscle are classic examples of effective functioning of NMJ and their functions are potentially decreased during obesity.

In this review, we focused on what is known about NMJ and identified the targets, which might be affected by over weight and obesity. Although several research works have highlighted the implications of diabetes [99-103], specific research evaluating the effects of obesity on neuromuscular functions and the modulations of expression of specific presynaptic and postsynaptic proteins that regulate neuromuscular transmission is currently lacking. NMJ is a complex organization that involves interactions between nerve and muscle. Pleiotropic effects of obesity may modulate the expression and functions of presynaptic and postsynaptic proteins, which orchestrate neuromuscular functions. Specifically, the effects of obesity on the synaptic proteins that regulate ACh release at the motor nerve terminals and proteins that assemble, stabilize, cluster, and prepattern AChR have not been studied so far. Further studies are needed to evaluate the effects of obesity on these mechanisms. PWS model emerges as a good model system to evaluate the effects of obesity on motor neuron functions. Presynaptic complications associated with obesity can be best studied in people suffering from PWS as growth hormone administration has beneficial effects on body composition and motor performance in patients suffering from PWS.

Further, autoimmune diseases are some of the major diseases affecting the neuromuscular functions. Numerous studies have documented the secretory properties adipocytes under obese conditions to be proinflammatory mediators containing interleukin-6, tumor necrosis factor alpha (TNFα), leptin, and adiponectin. A strong association between obesity and autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, psoriatic arthritis, and Type-1 diabetes has also been suggested [104]. Even though the pathophysiological mechanisms are complex, obesity clearly promotes pro-inflammatory Th1 profile, autoantibodies, and reduces immune suppressive Treg and Breg cells. However, how obesity serves as a contributing factor for autoimmune diseases still remains to be investigated.

In conclusion, even though NMJ is most studied of all synapses and neuromuscular functions are affected during obesity, literature evidence analyzing the mechanisms by which obesity modulates...
the expression and functions of neuromuscular proteins remains scanty. In the light of recent advances in developing drug targets against obesity, understanding the molecular mechanisms by which obesity affects target neuromuscular proteins will help in the identification and development of new strategies to prevent and treat neuromuscular dysfunction during obesity and its comorbidities.

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