SKELETAL MUSCLE HEALTH IN METABOLIC DISEASES

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Skeletal Muscle Health in Metabolic Diseases

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PREFACE

Metabolic diseases such as obesity and diabetes cause disruption of systemic energy metabolism and are major public health problems, affecting at least 2 billion people worldwide. The energy metabolism of the whole body is mainly regulated by skeletal muscle, liver, and brain. This book, entitled "Skeletal Muscle Health in Metabolic Disease", aims to clarify organ and tissue alterations in metabolic diseases, such as obesity, diabetes, and fatty liver.

The book comprises six chapters. The first chapter gives a background of metabolic diseases that affect cellular mechanisms in muscle cells and muscle tissue, especially glucose metabolism in skeletal muscle.

The skeletal muscle and liver share functions as metabolic organs, contributing to systemic metabolic regulation through mutual cooperation. The second chapter discusses the latest findings on the crosstalk between metabolic dysfunction-associated steatotic liver disease (MASLD) and skeletal muscles, which starts and progresses in association with obesity and its associated systemic metabolic abnormalities.

The third chapter focuses on nutrition, especially carbohydrate metabolism. Lipids are stored in the body mainly in the form of triglycerides, whereas carbohydrates are primarily stored in the liver and skeletal muscles in the form of glycogen. Glycogen utilization has also been shown to increase during exercise. When glycogen is depleted, exercise performance is impaired. Therefore, carbohydrate metabolism is important for exercise and the maintenance of organ and tissue homeostasis.

Metabolic diseases are closely associated with brain health and noncommunicable diseases, including type 2 diabetes. By contrast, exercise exerts its beneficial effects on the brain by releasing bioactive substances. The fourth chapter presents how metabolic diseases affect brain health and how exercise mitigates these detrimental effects, focusing particularly on the molecular mechanisms in the brain.

The subsequent five and six chapters discuss muscle atrophy and weakness and cellular mechanisms in metabolic disease. Muscle oxidative stress has been implicated in lipid species composition in the development of type 2 diabetes. Therefore, the sixth chapter discusses the impact of metabolic disorders, such as obesity and type 2 diabetes, on the regulation of lipid species and oxidative stress.

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CHAPTER 1

Muscle Glucose Metabolism in Metabolic Diseases

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Abstract: Metabolic diseases such as obesity and diabetes cause disruption of systemic energy metabolism and are major public health problems, with at least 2 billion people affected worldwide. Skeletal muscle tissue makes a substantial contribution to promoting energy efficiency because it remodels cellular size, composition, and function in response to various nutritional changes. However, metabolic diseases such as impaired insulin sensitivity can dynamically affect the metabolism of skeletal muscle. A deeper understanding of myopathology in metabolic disorders may provide clues for therapeutic strategies to promote skeletal muscle health and improve the overall quality of life. This chapter presents how metabolic diseases *via* cellular mechanisms affect muscle cells and muscle tissue, especially glucose metabolism in skeletal muscle.

Keywords: Diabetes, Glucose, Obesity, Metabolism, Skeletal muscle.

INTRODUCTION

Diabetes and obesity have a high risk of leading to diseases, including myocardial infarction and stroke, which affect life expectancy, and thus therapeutic strategies are needed [1]. A major feature of metabolic disease is insulin resistance. Insulin resistance is associated with obesity and type 2 diabetes mellitus (T2DM). It is generally defined as a reduction in the ability of the body to absorb blood glucose from circulation in response to insulin. Glucose is the main nutrition for energy consumption, but excess blood glucose is an index for obesity and T2DM. Insulin resistance from skeletal muscle is commonly viewed as the critical component of whole-body insulin resistance because the muscle is the most important tissue for insulin-stimulated glucose disposal [2].

Carbohydrates, lipids, and proteins all ultimately break down into glucose and then serve as the primary metabolic fuel in a mammalian cell. Glycogen in skel-

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etal muscles contains approximately as much as 50,000 glucose moeties. However, the large increase in muscle glycogen is generally associated with insulin resistance in the glucose transport process [3, 4]. Insulin activates the glycogen synthase pathway, whereas glycogen synthesis in muscle is markedly reduced in T2DM [5, 6]. Despite many years of research, the molecular mechanisms by which metabolic disease promotes insulin resistance in skeletal muscle are not fully understood.

Recent research focused on how lipid species affect glucose metabolism in skeletal muscles. Lipids were also used as molecules to probe the basic mechanisms of ion fragmentation following electron ionization [7]. However, fundamental studies using mass spectrometry analysis of lipids demonstrate that lipid species are associated with insulin resistance in obesity and diabetes [8 - 11]. This chapter presents the cellular and molecular mechanisms of obesity- and diabetes-induced insulin resistance in skeletal muscle.

MUSCLE GLUCOSE TRANSPORTER IN OBESITY AND DIABETES

Glucose is a key metabolic substrate for the whole body. Muscle tissues require glucose as an energy source for adenosine triphosphate (ATP) production [12]. Glucose metabolism starts with transport across the plasma membrane [13]. Skeletal muscles take up glucose in response to insulin stimulation and exercise. The insulin receptor (IR), insulin receptor substrates (IRS), and phosphatidylinositol 3-kinase (PI3K) activation are essential components of the insulin-induced response. Eventually, blood glucose is taken into intramyocellular through glucose transporter 4 (GLUT4) translocation [14, 15]. GLUT4 is an insulin-regulated glucose transporter that is responsible for glucose uptake in muscle. It is mainly located in intracellular vesicles in the absence of insulin [16]. Obesity and T2DM are strongly linked to the development of insulin resistance within the skeletal muscles [17]. In 1975, Kemmer *et al*. demonstrated that the skeletal muscles of obese rats are insulin-resistant with respect to both glucose-transport mechanisms and intracellular pathways of glucose metabolism [18]. Consistent with this, the expression of GLUT4 can explain the insulin-resistant glucose uptake characteristic of dietary-induced obesity [19]. A previous study revealed that transgenic overexpression of GLUT4 enhances glucose tolerance in lean and obese mice [20]. Taken together, increasing muscle GLUT4 content is an important target for improving glucose tolerance in obesity.

The main molecule pathway for glucose uptake through GLUT4 is the PI3K/AKT signaling pathway. The PI3K/AKT pathway is a central regulator in cellular physiology for growth factor signals and critical cellular processes [21]. PI3K and serine/threonine kinase 1 (Akt) signaling is important for insulin-stimulated

glucose uptake in skeletal muscle tissues. AKT phosphorylates are involved in the regulation of GLUT4 translocation [22]. PI3K/AKT signaling pathway exists in various organs, but obesity and T2DM impair PI3K/AKT signaling [22]. Sano *et al*. demonstrated that insulin increases the phosphorylation of AS160 and GLUT4 translocation in 3T3-L1 adipocytes [23]. In human skeletal muscles, exercise increases AS160 phosphorylation without insulin infusion [24]. Similarly, obese rodent muscles decrease glucose uptake with decreased AS160 phosphorylation on Ser588 with or without insulin stimulation [25].

AMP-activated protein kinase (AMPK) increases glucose uptake through PI3K/Akt signaling. For instance, loss of skeletal muscle AMPK exacerbates glucose intolerance and insulin resistance in obese people, resulting in a significant decrease in glucose uptake in skeletal muscles [26]. Indeed, loss of AMPK activity has been observed in the skeletal muscle of patients with obesity and diabetes [27, 28]. 5-Aminoimidazole-4-carboxamide ribonucleoside (AICAR) reportedly activates AMPK and stimulates glucose uptake by skeletal muscle [29], suggesting a drug target to facilitate muscle glucose uptake in obesity and diabetes [30]. Long-term AICAR improves glucose metabolism in insulin-resistant obese mice, which can be explained by effects on muscle glucose uptake [31]. However, a previous report has reported that the stimulatory effects of AICAR on glucose uptake are reduced in older men, irrespective of type 2 diabetes, suggesting that AICAR has only a limited therapeutic effect on older type 2 diabetic skeletal muscles [32].

TBC1D1 and TBC1D4, the two Rab GTPase-activating proteins, are closely related to the GLUT4 translocation to the plasma membrane, resulting in increased glucose uptake [33]. The phosphorylation of TBC1D1 and TBC1D4 has been defined as targets for the AKT and the AMPK [34]. Insulin increases in AS160 phosphorylation in skeletal muscle tissues [35] and cells [36]. Deletion of phosphorylated AS160 exhibits reduced insulin-induced GLUT4 translocation in adipocytes and muscle cells [23, 37]. Therefore, AS160 phosphorylation induces glucose uptake into muscles through the translocation of GLUT4 vesicles. On the other hand, insulin-stimulated AS160 phosphorylation is reduced in T2DM [38]. However, reduced muscle glucose uptake of obesity is not associated with the AKT/AS160 content [39]. Therefore, underlying mechanisms for the impaired glucose uptake in metabolic disease are not completely understood.

In type 1 diabetic rodent models induced streptozocin, NPC43 can effectively increase glucose uptake by activating PI3K, Akt, and AS160 pathways through insulin receptors [40]. Akt and AMPK phosphorylated proteins to vesicle traffic appear to be dependent on linking to small GTPase of the Rab family [41]. When activated, Akt by insulin or muscle contraction phosphorylates AS160 and

CHAPTER 2

The Role of Skeletal Muscles in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract: Skeletal muscles and the liver share functions as metabolic organs, and there are known crosstalk in their pathophysiology. In today's world, where obesity is rampant, many people suffer from metabolic abnormalities associated with obesity, posing a global health issue. This chapter summarizes the latest findings on the crosstalk between metabolic dysfunction-associated steatotic liver disease (MASLD) and skeletal muscles, which starts and progresses in association with obesity and its associated systemic metabolic abnormalities.

Keywords: Muscle-Liver axis, MAFLD/MASH, NAFLD/NASH, Skeletal muscle.

INTRODUCTION

Skeletal muscles are the largest organs in the body, and they have roles in locomotor function and metabolism of glucose and lipids. They also act as endocrine organs, secreting bioactive substances known as myokine. Decreases in muscle mass, such as sarcopenia and metabolic dysfunction, are associated with numerous diseases, including type 2 diabetes, lipid disorders, metabolic dysfunction-associated steatotic liver disease (MASLD), and cognitive impairment, among others [1 - 3]. The skeletal muscle and liver share functions as metabolic organs, contributing to systemic metabolic regulation through mutual cooperation (Muscle-Liver axis). There is a crosstalk between the dysfunction and pathology of skeletal muscle and liver. Regarding this pathophysiological crosstalk, it may be easy to understand that when dysfunction occurs in one organ, the other organ alone must process the same function, placing a significant burden on that organ. This chapter summarizes the relationship between quantitative and qualitative changes in skeletal muscle and the pathophysiology of MASLD, as

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well as introduces the mediators of the muscle-liver axis that have been elucidated thus far.

It should be noted that MASLD is a newly defined concept of a disease introduced in 2023, which redefines previously known conditions such as nonalcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated fatty liver disease (MAFLD). First, I will briefly outline the definitions, name changes, and the process of redefinition for each condition. However, evidence and reviews mentioning MASLD are limited to date. Unless otherwise specified, I will treat these conditions in the chapter as synonymous. However, since the definition of each disease is strictly different, the names of the diseases used in the original texts are used when referring to previous studies.

DEFINITION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

It is known that overweight and obesity induce fat deposition in the liver, which in turn leads to hepatic inflammation and fibrosis. Hepatic inflammation and fibrosis can lead to more serious diseases such as cirrhosis and hepatocellular carcinoma, and their pathogenesis has been attracting attention with the increase in the obese population. Hepatic inflammation and fibrosis based on the fatty liver caused by obesity or overweight were first reported and named “non-alcoholic steatohepatitis (NASH) ” by Jurgen Ludwing in 1980. The term “non-alcoholic fatty liver disease (NAFLD) is used to distinguish non-alcoholic fatty liver (NAFL), which is a benign fatty liver that shows lipid deposits in the liver from NASH, and to describe the progression of the disease from NALF to NASH. NAFLD is used as a disease concept to describe a chronic liver disease that progresses to hepatitis and fibrosis with systemic metabolic abnormalities based on obesity and ectopic fat deposition in the liver without a clear history of alcohol consumption (less than 30g/day in men and 20g/day in women in terms of ethanol). In today's society, the number of obese people continues to increase, and the number of patients with NAFLD is also growing worldwide. It is recognized as one of the most common chronic liver diseases [4, 5].

NAFLD presents two distinct conditions: benign NAFL and malignant NASH. In addition, given that liver biopsy is required for definitive diagnosis, it is unsuitable for the efficient screening of high-risk fatty liver patients in clinical practice. There is also a concern that the relatively low alcohol intake standard may exclude patients with a drinking habit. Therefore, a new disease concept focusing on metabolic abnormalities involved in the progression from fatty liver to hepatitis and fibrosis, “Metabolic dysfunction-associated fatty liver disease (MAFLD)”, was proposed in 2020. In addition to fatty liver, MAFLD is defined

by the presence of obesity or type 2 diabetes or meeting two or more criteria indicating abnormalities in glucose or lipid metabolism. As mentioned above, although NAFLD and MAFLD have different diagnostic criteria, they represent concepts that are shared by many patients in reality. However, when comparing MAFLD with NAFLD, MAFLD allows for the exclusion of low-risk fatty liver patients without metabolic abnormalities while identifying high-risk fatty liver patients with metabolic abnormalities and a history of alcohol consumption. Additionally, since liver biopsy is not required for diagnosis, MAFLD was expected to be a useful disease concept for screening high-risk fatty liver patients. However, many people are resistant to the terms “alcoholic” and “fatty” used in NAFLD and MAFLD, and the problem that there is a group of patients who are excluded from screening in NAFLD and MAFLD remains unresolved. There have always been calls by medical doctors and medical researchers toredefine the disease concept.

Against this background, efforts were made to create a new concept of the disease in 2023 through the cooperation of institutions around the world, led by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) [6]. The concept of steatotic liver disease (SLD) was proposed as a generic term for fatty liver diseases of various etiologies. These are classified into five categories according to pathogenesis and cause. The concept of MASLD was proposed as a concept similar to the conventional NAFLD or MASLD. MASLD was defined as a fatty liver with an abnormal level of one or more of the following cardiometabolic risk factors (BNI or waist diameter), abnormal glucose metabolism (blood glucose level or HbA1C), blood pressure, blood triglycerides, and blood HDL cholesterol (Fig. **1**). In addition, metabolic dysfunction-associated steatohepatitis (MASH) was also proposed as an alternative to conventional NASH. Although MASLD/MASH is expected to replace NAFLD/NASH or MAFLD in clinical practice in the future, it would be more meaningful to treat these disease concepts as synonymous to some extent for the time being in terms of accumulation of scientific knowledge.

MECHANISM OF ONSET AND PROGRESSION OF NASH (MASH): THE MULTIPLE PARALLEL HITS HYPOTHESIS

Although NASH is a serious liver disease that can progress to cirrhosis and hepatocellular carcinoma, there are few preventive and curative measures to date. One reason for this is the complexity of the pathogenesis and progression mechanism. “The multiple parallel hits hypothesis” proposed in 2010 is supported as a mechanism for the onset and progression of NASH [7, 8]. This hypothesis suggests that multiple extrahepatic organ abnormalities are involved in the onset and progression of NASH in parallel hits.

CHAPTER 3

Impact of Nutrition and Exercise on Carbohydrate Metabolism

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Abstract: People consume nutrients such as carbohydrates, fats, proteins, vitamins, and minerals in their diet. Among these, carbohydrates and fats are mainly used by the body as energy. Lipids are stored in the body mainly in the form of triglycerides, whereas carbohydrates are primarily stored in the liver and skeletal muscles in the form of glycogen. Compared to fat, glycogen can be stored in much smaller quantities in the body. Glycogen utilization has also been shown to increase during exercise. When glycogen is depleted, exercise performance is impaired. Glycogen is, therefore, a valuable source of energy, and much research has been conducted on how to store glycogen and how to enhance glycogen recovery after exercise. In addition, managing glucose and glycogen through proper nutrition and exercise training is very important not only for improving athletic performance but also for maintaining and improving health. Therefore, this chapter focuses on the impact of nutrition and exercise on carbohydrate metabolism.

Keywords: Glycogen, Glucose, Liver, Metabolism, Skeletal muscle.

INTRODUCTION

People consume nutrients such as carbohydrates, fats, proteins, vitamins, and minerals in their diet. Among these, carbohydrates and fats are mainly used as energy for the body. Ingested carbohydrates are broken down by digestive enzymes such as amylase and are absorbed primarily in the small intestine. Carbohydrates absorbed in the small intestine are transported throughout the body in the form of glucose. This glucose is used for ATP (adenosine triphosphate) production or stored as glycogen. Glycogen is stored mainly in the liver and skeletal muscle, and the amount is approximately estimated to be 100 g in the liver and 500 g in skeletal muscle, for a total of about 600 g [1, 2].

It has been shown that glucose utilization increases during exercise compared to resting conditions [3]. This increase is due to a greater reliance on the glycolytic

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system for energy production. Carbohydrates provide 4 kcal of energy per gram, but the body can store only a few thousand calories. This is a small amount compared to the vast amount of energy stored in the body in the form of triglycerides. Glycogen is a particularly important energy source because of the limited amount that can be stored. Much research has focused on strategies for pre-exercise glycogen storage and post-exercise glycogen replacement. In addition, managing glucose and glycogen through proper nutrition and exercise training is critical not only for improving athletic performance but also for maintaining and improving health. Therefore, this chapter focuses on the impact of nutrition and exercise on carbohydrate metabolism.

EXERCISE AND GLYCOGEN DEPLETION

During exercise, carbohydrates and lipids are the main sources of energy. Lipids have 9 kcal of energy per gram, while carbohydrates have 4 kcal per gram. Lipids have a high energy density, which has the advantage that when energy is stored in the form of triglycerides, they are less likely to gain weight. However, it takes more effort than carbohydrates to metabolize lipids and use them as energy. Therefore, during exercise, which requires quick movements, more readily available carbohydrates are used. In previous studies, it has been reported that prolonged exercise decreases glycogen in skeletal muscle [4]. Skeletal muscle glycogen is also reduced by brief periods of high-intensity exercise, such as 30 seconds of all-out exercise [5].

The decrease in skeletal muscle glycogen content associated with exercise occurs in an exercise intensity-dependent manner [3, 6, 7]. For example, Van Loon *et al*. examined changes in the percentage of energy substrate utilization during 40, 55, and 75% maximal workload (Wmax) exercise in elite cyclists. The results showed that at rest, lipid oxidation and carbohydrate oxidation accounted for 56% and 44% of total energy expenditure, respectively, whereas at 40% Wmax, lipid oxidation and carbohydrate oxidation accounted for 55% and 45%, respectively. At 55% Wmax, lipid oxidation was 49% and carbohydrate oxidation was 51%, and when exercise intensity was increased to 75% Wmax, lipid oxidation was 24% and carbohydrate oxidation was 76% [3]. Romijn *et al*. similarly evaluated energy substrate utilization during exercise at 25, 65, and 85% VO2max and reported increased glucose oxidation with increasing exercise intensity [6]. These data indicate that glucose utilization increases with increasing exercise intensity. It has also been reported that glucose tissue uptake increases with increasing exercise intensity and that at 65 and 85% VO2max exercise, carbohydrate oxidation greatly exceeds glucose uptake [6]. In other words, glucose utilization in skeletal muscle increases with exercise, and glycogen is more likely to be depleted than glucose uptake. In fact, it has been reported that glycogen decreases

significantly in competitions such as soccer, in which long periods of running and short periods of sprinting are repeated [8].

Effects of Muscle Glycogen Depletion

Glycogen can be stored in the body in much smaller quantities than fat. For example, Guezennec *et al*. reported that A man whose weight is near 70 kg has approximately 15 kg of fat as triglycerides in adipose tissue, representing about 140,000 kcal [9]. In humans, on the other hand, given that the majority of glycogen is stored in skeletal muscle (~500 g) and liver (~100 g) [1], the amount of carbohydrates in the body is only a few thousand kcal. Also, with exercise, glycogen stores decrease significantly.

So, what are the effects of reduced glycogen in skeletal muscle? In a previous study, Xirouchaki *et al*. examined the impact on exercise capacity in mice in which glycogen synthase was knocked out, specifically in skeletal muscle.

The results showed that exercise performance decreased when skeletal muscle glycogen levels were reduced [10]. There are several factors that contribute to reduced exercise performance when skeletal muscle glycogen levels decrease, but they are not yet fully understood. One possibility is that reduced glycogen levels affect ATP resynthesis in the glycolytic system, which would be a limiting factor in exercise, especially during high-intensity exercise. In addition, glycogen is involved in Na^+, K^+, and ATPase activity [11], and reduced skeletal muscle glycogen is involved in Ca^{2+} release from the sarcoplasmic reticulum [12]. Furthermore, it has been reported that reduced Ca^{2+} release leads to reduced muscle tensile strength [13]. Thus, a decrease in skeletal muscle glycogen content may inhibit muscle contraction.

Effects of Liver Glycogen Depletion

The main storage tissues for glycogen are the liver and skeletal muscles, with the liver holding 100 g and skeletal muscles holding 500 g, for a total of about 600 g [1, 2]. Therefore, the liver, like skeletal muscles, stores a large amount of glycogen. The glycogen in skeletal muscles is broken down to produce ATP, which can then be used to contract muscles. On the other hand, the primary role of glycogen in the liver is to supply glucose to extrahepatic tissues and maintain blood glucose levels [14]. When blood glucose levels decrease, the liver acts as a glucose sensor, degrading glycogen and supplying glucose to the blood. The ability of the liver glycogen to maintain blood glucose levels for some time without causing immediate hypoglycemia during fasting is due to the function of liver glycogen. However, liver glycogen stores are also limited. Exercise raises the degradation of liver glycogen [15]. Wahren *et al*. reported that splanchnic

CHAPTER 4

Brain Health in Metabolic Disease and Exercise

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Abstract: Modern lifestyles, such as a Western diet, excessive food consumption, and physical inactivity, are closely associated with brain health and noncommunicable diseases, including type 2 diabetes. Epidemiological evidence suggests that an unhealthy lifestyle leads to impaired brain health, manifesting in conditions such as depression and anxiety. Conversely, mental illness can contribute to the development of type 2 diabetes. Thus, it has been suggested that there is a bidirectional relationship between brain health and metabolic diseases, but the detailed mechanisms remain unclear.

Exercise is considered the primary choice for the treatment of obesity or type 2 diabetes. This is attributed to the fact that increased physical activity contributes to a reduction in body weight and the accumulation of excess adipose tissue. Furthermore, it has long been recognized that exercise enhances brain health. Recent studies have revealed that, in addition to these indirect effects, exercise exerts its beneficial effects by releasing bioactive substances. This chapter presents how metabolic diseases affect brain health and how exercise mitigates these detrimental effects, focusing particularly on the molecular mechanisms in the brain.

Keywords: Anxiety, Brain, Cognitive function, Diabetes, Depression, Hippocampus, Obesity.

INTRODUCTION

Obesity is defined as an excess of body adiposity. According to a report from the World Health Organization, worldwide obesity has nearly tripled since 1975, and 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. From this situation, in 2023, WHO advocated the *WHO acceleration plan to stop obesity* [1]. Overweight and obesity are central to the risk of metabolic syndrome, predisposing individuals to insulin resistance, hypertension, and dyslipidemia, all of which are risk factors for metabolic syndrome [2], and then progresses to the pathology of type 2 diabetes. Epidemiological research suggests that depression rates are twice as high among persons with diabetes as among

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persons without diabetes [3]. In addition, diabetes is associated with an increased risk of psychological disturbance, especially for those with more diabetes-related complications [4]. Based on these studies, it has been considered as evidence that diabetes (and its complications) increases the risk of mental disorders. The causal relationship between metabolic and mental disorders remained unclear, but accumulating evidence suggested that it might appear to be bidirectional [5]. It is well known that physical activity, such as regular exercise, is beneficial for our health. It remained unclear whether the effect was simply due to the improvement of obesity or the effect of exercise itself. Very recent studies have revealed that exercise has its effects on the whole body, including the brain, through diverse mechanisms.

This chapter outlines the negative effects of metabolic diseases on brain health, especially in depression and anxiety, and the beneficial effects of exercise in improving them.

IMPAIRED BRAIN HEALTH IN METABOLIC DISEASE

With the recent westernization of diets, obesity has been increasing on a global scale and is already well-known to be a risk factor for various diseases [6]. In the 1980s, the ideal body weight approach was replaced by BMI, and the commonly used cutoffs for overweight (BMI 25–30) and obesity (BMI >30), for both men and women, were adopted to define obesity in adults [7]. Excess energy due to excessive lipid intake leads to obesity and the associated skeletal muscle insulin resistance and impaired glucose tolerance, which are major factors in type 2 diabetes mellitus. Although previous studies on obesity and glucose metabolism have focused on adipocytes [8 - 10] and skeletal muscle [11 - 13], recent studies have revealed that obesity also has important effects on brain function. For example, epidemiological studies reported that Western eating habits and being overweight are associated with reduced hippocampal volume [14, 15]. Western eating habits have also been found to be associated with psychiatric disorders such as depression and anxiety [16]. Insulin resistance is a prediabetic stage. A systematic review revealed a small but significant cross-sectional association between depression and insulin resistance [17]. In a study that investigated the association between metabolic syndrome and mood disorders, metabolic syndrome is associated with depressive symptoms but not anxiety in both men and women, irrespective of overweight/obesity status [18]. Further, patients with diabetes with both minor and major depression are associated with increased mortality [19].

Meanwhile, evidence suggests that a bidirectional relationship, in other words, mental illness, increases the risk of type 2 diabetes [5]. Eaton *et al*. reported in the

90s that major depressive disorder signals an increased risk for the onset of type 2 diabetes [20]. Also, individuals with newly diagnosed diabetes were 30% more likely to have had a previous history of depression compared with people without diabetes [21]. Interestingly, this relationship between mental illness and metabolic dysfunctions is observed not only in adulthood. According to Shomaker *et al*., children's depressive symptoms were a significant predictor of follow-up HOMA-IR, fasting insulin, and fasting glucose levels [22]. A more recent study reported that persistently high fasting insulin levels from age 9 years were associated with psychosis at 24 years, and puberty-onset body mass index increase was associated with depression at 24 years [23].

In summary, obesity and overweight and the resulting metabolic disorders and psychiatric disorders, including depression, are bidirectional. Furthermore, childhood depression (or metabolic parameters such as high insulin levels) may be a predictor of future metabolic parameters (or depressive symptoms).

IMPAIRED NEUROGENESIS AND MOLECULAR MECHANISMS IN THE BRAIN IN METABOLIC DISEASE

Metabolic disorders are associated with impairment of brain health; however, these regulating mechanisms are not fully understood. In this section, we focus on mature hippocampal neurogenesis and molecular signaling within the hippocampus as the underlying mechanisms. As the hippocampus is a site of structural and functional pathology in most psychiatric disorders, it plays a crucial role in their manifestation. Therefore, a hippocampal-based treatment approach has been proposed to combat the cognitive deficits and mood dysregulation that are hallmarks of psychiatric disorders [24]. Adult hippocampal neurogenesis, the generation of new neurons in the adult dentate gyrus (DG), is an important event for the maintenance or regulation of brain function. Adult hippocampal neurogenesis is first discovered by Joseph Altman in 1963 [25]. In animal studies, mice lacking adult neurogenesis increased response to stress, which elevated blood glucocorticoid corticosterone [26]. Chronic high corticosterone reduces adult hippocampal neurogenesis in both males and females [27]. In addition, the above-mentioned adult neurogenesis-deficient mice also showed increased anxiety and depression-like behaviors [26]. In contrast, antidepressant treatment increased adult hippocampal neurogenesis [28, 29] and reduced depressive behaviors [30].

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family of proteins and is one of the key factors that affect cognitive functions and mental illness. BDNF is expressed in the central nervous system and is highly in the limbic area, which is important for effective regulation. BDNF regulates the

CHAPTER 5

Muscle Atrophy and Weakness in Metabolic Disease

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Abstract: Obesity and diabetes are associated with changes in skeletal muscle quantity and quality, such as increased ectopic fat, muscle atrophy, and decreased muscle strength. Skeletal muscle tissue is often affected by metabolic insult because it remodels cellular size, composition, and function in response to a variety of nutritional changes. Declining muscle quantity and quality are directly linked to falls and bedriddenness; understanding the intracellular mechanisms may provide clues for therapeutic strategies. How metabolic diseases *via* cellular mechanisms affect muscle quality and muscle quantity are presented in this chapter.

Keywords: Contraction, Calcium, Diabetes, Fiber type, Motor neuron, Myofibrillar, Obesity, Skeletal muscle, Satellite cell.

INTRODUCTION

Skeletal muscle is one of the largest organs in humans and accounts for ~40% of body mass in healthy-weight individuals, which is important for maintaining metabolic health [1]. Carbohydrates and fats are the primary nutrients that provide the necessary energy required during exercise. However, the metabolic insults in the regulation of glucose and lipids cause skeletal muscle abnormalities. As fat increases in the body due to lipid accumulation, the risk of type 2 diabetes mellitus (T2DM) increases, which is associated with insulin resistance in skeletal muscle [2]. Previous studies have focused on the cellular and molecular mechanisms of obesity- and diabetes-induced insulin resistance in skeletal muscle. On the other hand, recent studies have focused on the effect metabolic insult has on the loss of muscle size, strength, and physical function.

Skeletal muscle tissues are heterogeneous in their composition and mainly divided into slow-twitch and fast-twitch myofibers. The differences between slow- and

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fast-twitch fibers are the contractile proteins and types of energy metabolism, such as ATP production from mitochondria [3]. Furthermore, skeletal muscle adapts to numerous stimuli such as exercise, nutrition, disease, and aging, and these responses are manifested through changes in muscle size, fiber-type distribution, and metabolism. In contrast, muscle atrophy and weakness decrease the quality of life and increase the risk of injuries, falls, and the development of diseases. Indeed, diabetes and obesity cause loss of muscle mass and decrease muscle strength [4, 5]. Pharmacologic therapy for muscle loss induced by metabolic disease does not exist, and current diet/exercise therapeutic approaches are often ineffective and/or unfeasible.

This chapter will address skeletal muscle metabolism in metabolic disease through a brief comprehensive summary and describe the potential mechanisms of dysfunction of contractile force (weakness) and muscle atrophy induced by metabolic disease in skeletal muscle.

MUSCLE ATROPHY IN METABOLIC DISEASE

Lipids often ectopically accumulate in non-adipose tissues, including skeletal muscle [6]. Muscle lipids have been extensively studied in the context of metabolism, such as insulin sensitivity [7 - 9]. However, muscle lipid overload appears to affect not only metabolism but also muscle quantity, such as muscle maintenance and regeneration. There is evidence that diabetic myopathy is unfavorable for muscle growth and regeneration [10 - 12]. The loss of muscle mass in metabolic disorders is partly accounted for by an altered balance between synthesis and degradation in protein [13, 14]. Previous studies have reported that obesity causes the loss of muscle mass due to a decrease in muscle protein synthase and activation of protein degradation [15 - 17]. On the other hand, a high-fat diet (HFD) does not change the muscle protein synthase [18]. The lipid overload increases protein synthesis in skeletal muscle in rodent models [19]. These findings suggest that the mechanism underlying the muscle atrophy in metabolic disorders has not been fully elucidated.

Mechanisms that may contribute to lower muscle mass of metabolic disease can include decreases in the satellite cell. A previous study has reported that the differentiation of myoblasts is impaired in patients with diabetes, suggesting that one of the underlying causes of muscle loss [20]. Diabetic myoblasts had a reduced ability to differentiate into skeletal muscles, whereas administration of myogenic oligodeoxynucleotide improved skeletal muscle differentiation exacerbated by diabetes [20]. In obese rodent models, obese Zucker rats reduce the number of satellite cells, which may be a factor that contributes to the reduced muscle mass [12]. Interestingly, satellite cell proliferation can be restored with

compensatory loading with surgery. Similar results were obtained in mice models of T2DM, and impaired muscle regeneration in T2DM mice was associated with reduced accumulation of macrophage and angiogenesis [21]. This cytokine was increased in muscle in patients with T2DM, suggesting a possible mechanism by which muscle function is compromised in diabetes [22]. These findings suggest that metabolic disease severity will mainly influence the functions of satellite cells.

Insulin resistance is associated with increased lipolysis and the release of free fatty acids from adipose tissue, which may lead to the inhibition of muscle regeneration through the growth hormone/insulin growth factor-1 [5, 23]. Furthermore, oxidative stress, mitochondrial dysfunction, inflammation, and protein degradation pathways have been implicated in muscle atrophy and weakness. Indeed, these factors are increased in skeletal muscle of metabolic diseases [24]. For example, metformin is a commonly prescribed medication for T2DM patients due to decreased hepatic glucose production and intestinal absorption of glucose. A previous study showed that metformin ameliorates muscle atrophy due to decreased muscle atrophy-related genes in HFD-induced obese rats [25]. However, a long-term administration of metformin causes accelerates muscle atrophy through the activation of phosphorylated AMPK in *db/db* mice [26]. Metformin should be prescribed to patients with T2DM because of its great efficacy in reducing hyperglycemia and other diabetes-related complications, but there is no effective treatment for muscle wasting that has been established. Metformin might induce muscle atrophy that is regulated in an AMPK-dependent manner [27 - 30]. AMPK is not only associated with the glucose transporter system but also inhibits anabolic processes such as protein synthesis and increases protein degradation and autophagy [31]. Thus, it is skeptical whether antidiabetic drugs are necessarily effective against muscle atrophy.

MUSCLE CONTRACTILE ADAPTATION IN METABOLIC DISEASE

Rodent studies demonstrate that obesity induced by HFD impairs contractile function with electrical stimulation, enhanced fatigability, and increased muscle fragility [32 - 34]. A previous study demonstrated that middle-aged mice fed HFD exhibited decreased grip strength [35]. Consistent with this, another study also shows that the contractile force was lower in aged mice fed HFD [36]. These findings suggest that the synergistic effects of obesity and aging may exacerbate muscle contractile dysfunction. Consistent with these findings, Eshima *et al*. recently demonstrated that chronic HFD feeding significantly reduced contractile force in fast-twitch dominant muscles but not slow-twitch dominant muscle in aged skeletal muscle [33] (Fig. **1**).

CHAPTER 6

The Cellular Mechanism in Skeletal Muscle in Metabolic Disease: Lipid Species and Oxidative Stress

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Abstract: Obesity and diabetes impair skeletal muscle metabolism, muscle atrophy, and contractile function, but the intracellular mechanisms have not been clarified fully. Increasing evidence suggests that oxidative stress is associated with obesity and diabetes. Depending on the pathological condition, stress may be affected to a greater extent. Muscle oxidative stress has been implicated in lipid species composition in type 2 diabetes. This chapter discusses the impact of metabolic disease on the regulation of lipid species and oxidative stress.

Keywords: Ferroptosis, Lipid species, Oxidative stress, Phospholipid, Skeletal muscle.

INTRODUCTION

Under obesogenic conditions such as feeding a high-fat diet (HFD), the excessive abundance of fat leads to intramyocellular (IMCL) accumulation [1]. IMCL disrupts muscle function, resulting in muscle atrophy in obese [2, 3] and diabetic mice [4]. These results from IMCL accumulation are associated with increased reactive oxygen species (ROS) production that can compromise the antioxidant defense system of skeletal muscle [5]. However, the specific effect of lipid species on oxidative stress in skeletal muscle has not been clarified fully.

Oxidative stress is important for skeletal muscle atrophy [6]. For example, long-term inactivity, such as tail suspension, immobilization, and small cage housing, promote oxidative stress and result in muscle atrophy [7 - 9]. This inactivity-induced muscle atrophy increases intracellular ROS production. Recent studies have indicated that redox signaling is an important regulator of cell signaling pat-

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hways [10]. Similar to these findings, increased ROS production is an important signal for muscle atrophy induced by aging [11] and cancer [12]. Recent evidence indicates obesity and diabetes induce ROS production [13 - 15], suggesting that metabolic imbalance is linked to dysfunction of the cellular redox system.

The excess lipids are susceptible to oxidation induced by free radicals. Lipid hydroperoxides (LOOH) are one of the primary products of lipid hydroperoxidation and induce oxidative stress. Recently, Stockwell identified that ferroptosis is a novel cell death mechanism characterized by iron-dependent lipid peroxidation [16]. Ferroptosis is associated with a variety of diseases, including cancer, kidney diseases, atherosclerosis, and liver diseases, suggesting that ferroptosis can provide insights and treatment strategies for metabolic diseases [17].

In this chapter, we will discuss the evidence that oxidative stress, particularly lipid peroxidation, contributes to the cell signaling pathways for skeletal muscle homeostasis.

LIPID SPECIES IN SKELETAL MUSCLE

Lipids act as structural components of cell membranes and energy storage sources and participate in signaling pathways. They are also ubiquitous in the organism and play diverse biochemical and physiological functions. Lipid species are present in many classes and can transduce signals to influence cell function (Table **1**).

Table 1. Categories of lipid molecular species.

Category	Specific Lipid Species
Fatty acyls	Fatty acids, elcosanoids, endocannabinoids
Glycerolipids	TAG, diacylglycerols
Glycerophospholipid	PC, PE, PI, PS, PG, PA, CL
Sphingolipids	Sphingomyelin, sulfatides, sphingosine, ceramides, ganglioside
Sterol lipids	Cholesterol, estradiol, testosterone, bile acids
Prenol lipids	Farnesol, dolichols, vitamin K
Saccharolipids	Lipid A, acyltrehaloses
Polyketides	Aflatoxins, tetracyclines, erythromycin

In metabolic disease, obese and type 2 diabetes mellitus (T2DM) patients increase concentration of plasma free fatty acid (FFA) [18]. An increased FFA was observed in skeletal muscles from obese rodents [19 - 21] and in obese and T2DM

patients [22, 23]. Plasma FFA enters intramyocellular lipids*via* protein transporters, such as fatty acid translocase, fatty acid binding protein, and fatty acid transport protein family [24]. Then, fatty acids attach coenzyme A in a reaction catalyzed by acyl-Co synthase and formatted of long-chain acyl-CoA. These are used as a substrate in *de novo* synthesis of other lipids, including triacylglycerols (TAG), diacylglycerols (DAG), and ceramides [25, 26].

In skeletal muscle, a previous study demonstrates that lipid extracts using mass spectrometry analysis have the presence of lipid species, including phospholipids, sphingolipids, and cholesterol esters [27]. The main fatty acid is TAG, and most extracellular-derived fatty acids enter the pool of intracellular TAG [28, 29]. Obesity generally changes lipid species content, including fatty acids of phospholipid and triglyceride [30, 31] (Figs. **1**-**3**). Particularly, obese muscle exhibits increased polyunsaturated (PUFA) from phospholipid and triglyceride fractions [31]. Indeed, analyzing fatty acid-related metabolism, many genes are significantly changed in obese muscle. Consistent with this, obesity increases the fatty acid of phospholipid molecular species.

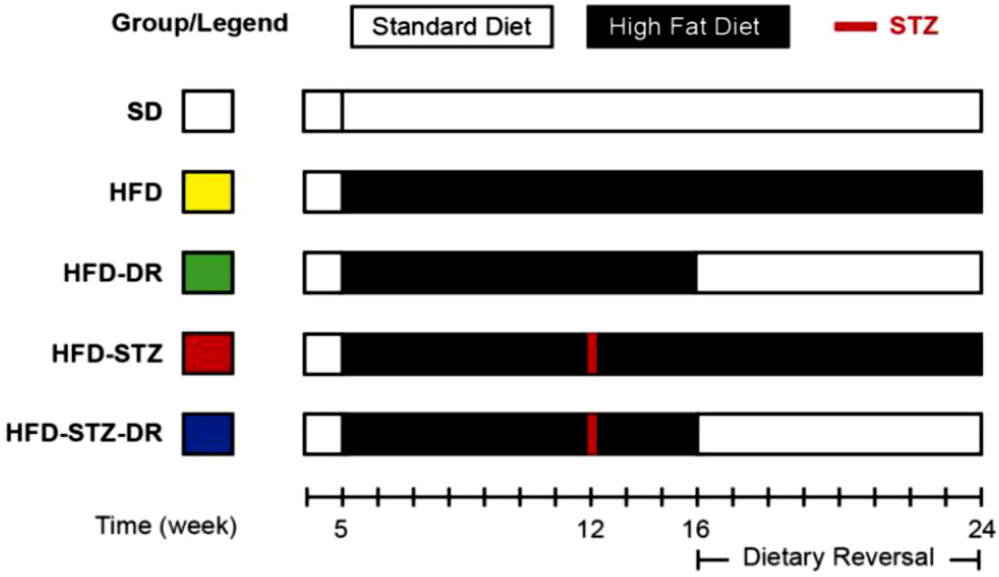

Fig. (1). Experimental design from a previous study. Animals began HFD at 5 and 12 weeks; two cohorts were administered STZ to induce a T2D phenotype. At 16 weeks, a cohort of HFD and HFD-STZ mice were placed on the standard diet (SD) for 8 weeks. From [32].

In humans, triglyceride and phospholipid content in skeletal muscle have been linked to insulin sensitivity [33 - 35]. Indeed, skeletal muscle phospholipids are inversely related to body fat [35] (Fig. **4**). Skeletal muscles are also influenced by

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