Chapter 2

The Role of Glucose and Fatty Acid Metabolism in the Development of Insulin Resistance in Skeletal Muscle

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Abstract

The rapid rise in the prevalence of obesity and diabetes has significantly contributed to the increasing global burden of noncommunicable diseases. Insulin resistance is a major underpinning etiology of both obesity and type 2 diabetes. Insulin resistance is characterized by a reduced response of skeletal, liver, and fat tissues to the actions of insulin hormone. Although detailed mechanisms implicated in the development of insulin resistance remain plausible, skeletal muscles have been identified to play an integral role in the improvement of insulin sensitivity in the diseased state. The effective modulation of glucose and fatty acid metabolism in the skeletal muscle through exercise or by certain therapeutics has been associated with reversal of insulin resistance and amelioration of diabetes associated complications such as inflammation and oxidative stress. This chapter will briefly discuss the role of glucose and fatty acid metabolism in the development of insulin resistance in the skeletal muscle.

Keywords: skeletal muscle, insulin resistance, glucose and fatty acid metabolism

1. Introduction

According to the World Health Organization, type 2 diabetes mellitus (T2D) contributes to approximately 90% of all diabetes mellitus cases and is amongst the top 10 leading causes of death worldwide [1]. Symptoms such as enhanced thirst, polyuria, fatigue, and impaired wound healing are identified in those with T2D. The recent International Diabetes Federation (IDF) report projects an astonishing increase in cases of diabetes [2]. An estimated 425 million

people are currently living with diabetes, with a projected 1.5 fold increase in the prevalence of diabetes, while a total of 629 million adults are expected to be diabetic by the year 2045 [2]. In Africa, the prevalence of diabetes is estimated at 16 million and is expected to rise to 41 million by 2045 [2]. Diabetes is characterized by hyperglycemia resulting from an inadequate production of insulin and insulin utilization in a T2D state. An unhealthy lifestyle such as lack of physical activity and a diet containing excessive fat content, including refined carbohydrates has been associated with an increased risk for developing insulin resistance (IR) [2, 3]. Carbohydrate-rich diets with a high glycemic index may contribute to obesity, impaired glucose tolerance, and hyperinsulinemia. This consequence can impair glucose and lipid metabolism, and accelerate the progression of IR. During a state of IR, insulin levels are elevated due to the rising glucose levels, but over time, a state of relative inadequate production of insulin can develop [2]. IR is regarded as one of the early phenotypes associated with development of obesity, and it is normally present in high-risk individual's years before development of T2D. Although maintenance of healthy lifestyle, as well as the use of hypolipidemic and hypoglycemic drugs, remains effective at attenuating insulin-resistant complications, the escalating incidence of the metabolic syndrome (MetS) warrants further exploration into pathological mechanisms implicated in the development of IR. Accumulative evidence suggests that effective modulation of energy substrates such as glucose and free fatty acids (FFAs) remains crucial in the amelioration of lifestyle diseases, including T2D [4–6]. This chapter will discuss the role of glucose and lipid metabolism in the development of IR.

2. Skeletal muscle and its role in modulating insulin resistance

Skeletal muscles are comprised of an intricate tissue, with diverse network of fibers, which have different mechanical and metabolic functions. Skeletal muscles contribute to approximately 40% of the total body weight and contain 50–75% of all body proteins [7]. Skeletal muscles account for more than 80% of insulin-stimulated glucose uptake [8], and using combined oral and intravenous glucose tolerance testing, Himsworth and Kerr were able to demonstrate that tissue-specific insulin sensitivity was lower in T2D individuals [9]. Therefore, IR in skeletal muscle has a major impact on whole-body metabolic homeostasis and it is the main element for the development of T2D. However, the underlying molecular mechanisms remain elusive. Several mechanisms that play a role in the development of IR in skeletal muscle have been proposed, and these include accumulation of intracellular lipid derivatives (diacylglycerol and ceramides) as a result of elevated plasma FFAs, oxidative stress, pro-inflammatory signals, and impaired gene transcription [8, 10]. Moreover, mitochondrial dysfunction has associated with IR [11]. The following section will focus on glucose regulation and fatty acid metabolism, in relation to the development of IR in skeletal muscle.

3. Glucose metabolism in skeletal muscle

Glucose is a monosaccharide used as a biological fuel during aerobic and anaerobic respiration or fermentation. Aerobic respiration is the most efficient means of glucose utilization, yielding

32 molecules of ATP during the processes of glycolysis and oxidative phosphorylation. Glycolysis is the metabolic whereby glucose is metabolized into pyruvate or to lactate; this process yields higher capacity for ATP generation [12]. During glycolysis, glucose 6-phosphate is converted to fructose-6-phosphate by phosphohexose, and then to fructose-1,6-biphosphate by phosphofructokinase. This reaction is irreversible and is a major point of regulation during glycolysis. Energy utilization by adult skeletal muscle is tightly controlled, with muscle fibers having the ability to switch between different substrates for ATP production. This is highly dependent on the availability of energy substrates and the energy requirements [13, 14]. Skeletal muscles are able to utilize both glucose and FFAs as a source of ATP production. However, utilization of glucose and FFAs as a primary source of ATP production depends on the metabolic state of an individual, i.e., whether the individual is at a fed or fasting state [15]. During the fasting state, glucose uptake in skeletal muscle is reduced while plasma FFA levels are increased due to lipolysis in adipose tissue. This subsequently leads to the utilization of FFAs as the predominant source of ATP production [16]; whereas, during a fed state, plasma glucose levels are elevated, which stimulates insulin secretion and enhances glucose uptake by skeletal muscle. This also leads to reduced lipolysis in adipose tissue and a reduction in plasma FFAs. The ability of switching between substrates in the fasted and fed state is crucial in promoting skeletal muscle glucose oxidation. Consequently, it has been reported that muscle of insulin-resistant or diabetic subjects fails to switch between the substrates, showing metabolic inflexibility [8]. This metabolic inflexibility can result in impaired glucose and fatty acid metabolism, leading to the development of IR.

Several mechanisms, which include glucose transportation, are implicated in the regulation of skeletal muscle glucose metabolism and have been a therapeutic target for the reversal IR and improvement of skeletal muscle function. Briefly, postprandial glucose is transported actively across the plasma membrane by specific carrier proteins, which belong to the glucose transporter (GLUT) family. There are several types of glucose transporters located in the plasma membrane of myocytes. Each glucose transporter isoform plays a specific role in glucose transportation that is determined by its tissue distribution, substrate specificity, and transport kinetics [17]. Glucose transporter isoform 1 (GLUT1) is present in all cells and is largely responsible for regulating basal glucose and ensuring a steady influx of glucose into cells. The glucose transporter isoform 2 (GLUT2) is a high-Km glucose transporter expressed in hepatocytes, pancreatic beta cells, and the basolateral membranes of intestinal and renal epithelial cells. In contrast to other transporters, GLUT2 facilitates bidirectional glucose transport into and out of the cell [17]. GLUT3 is a low-capacity glucose transporter that is responsible for glucose uptake in neurons, while glucose transporter protein isoform 4 (GLUT4) is expressed exclusively in muscle and fat cells, and is responsible for increased glucose uptake into these tissues postprandially, thereby maintaining normoglycemia [17].

In skeletal muscle, insulin stimulation induces translocation of GLUT4 from intracellular vesicles within the cytoplasm to the plasma membrane and thereby increases glucose uptake [18, 19]. When insulin levels decrease in the blood and insulin receptors are no longer occupied, the glucose transporters are recycled back into the cytoplasm. Failure of GLUT4 to translocate to the plasma membrane results in IR [20]. The crucial step for effective modulation of GLUT4 translocation has been the binding of insulin or insulin-like growth factor 1 (IGF1) to its receptor or IGF1 receptor, leading to the activation of phosphatidylinositol-4,5-bisphosphate

3-kinase (PI3K)/protein kinase B (AKT) pathway. Activation of this pathway has been subject to ongoing research for its role in skeletal muscle tissue growth, and most importantly, in the regulation of insulin signaling [21]. This has been verified on various models showing that knockout of insulin receptor, PI3K and AKT genes, especially in skeletal muscle, is associated with growth retardation as well as with impairment of insulin action [22, 23]. Therefore, effective modulation of glucose transportation and activation of PI3K/AKT pathway remains important to improve glucose tolerance and also skeletal muscle function.

4. Fatty acid metabolism in skeletal muscle

FFAs are elongated hydrocarbon chains with a terminal carboxylate group. Apart from being one of the major sources of fuel in the body, FFAs can perform a number of other functions, including serving as building blocks for phospholipids and also acting as hormones as well as intracellular messengers [24]. FFAs can exist in unsaturated or saturated form, depending on the number of bonds the hydrocarbon chain contains. While unsaturated fats such as oleic acid, mostly available in vegetable oils, are considered beneficial to the body [25], saturated fats, namely palmitic acid, are associated with the development of IR [26]. For the latter, it is widely used in experimental models to induce IR [19, 27]. Exposure of cultured skeletal muscle cells to high palmitate concentrations has been linked with the activation of protein kinase C (PKC), one of the main enzymes involved in impaired insulin signaling [26, 28]. Briefly, by phosphorylating insulin receptor substrate 1, PKC can alter the whole downstream effect of insulin response, ultimately leading to impaired GLUT4 translocation and reduced glucose uptake in skeletal muscle. Evidence shows that PKC activation by 12-deoxyphorbol 13-phenylacetate 20-acetate is associated with a reduction in insulin-stimulated glucose uptake, whereas PKC inhibition with GF 109203X results in enhanced insulin action in cultured human skeletal muscle [29]. An abnormal reduction of glucose uptake in skeletal muscle, mainly due to an impaired switch in substrate preference, as explained by Randle [6], remains an important contributing factor to the development of IR and subsequent metabolic complications. Thus, it is a viable option to target glucose uptake improvement, concomitant to reducing glycogen stores to reverse IR in skeletal muscle.

Beta oxidation, the main catabolic process by which fats are broken down in the body, is another system crucial for the control of substrate switch within many cells, including skeletal muscle (**Figure 1**). Generally, during periods of fasting, a substrate switch occurs where FFAs become a predominant source for ATP production via beta oxidation [30]. Although FFAs are hydrophobic in nature and can passively diffuse across the lipophilic cell membrane, transporters such as plasma membrane fatty acid-binding protein (FABP), fatty acid transport protein 1 (FATP1), and cluster of differentiation 36 (CD36) are widely expressed in rodent and human skeletal muscle [31, 32]. By controlling entry of long chain fatty acids across the barrier of the inner mitochondrial membrane for subsequent beta oxidation, the carnitine shuttle system can influence skeletal muscle substrate switch. Some of the well-investigated components of the system include the malonyl-CoA sensitive carnitine palmitoyltransferase 1 (CPT1) that resides on the mitochondrial outer membrane (**Figure 1**).

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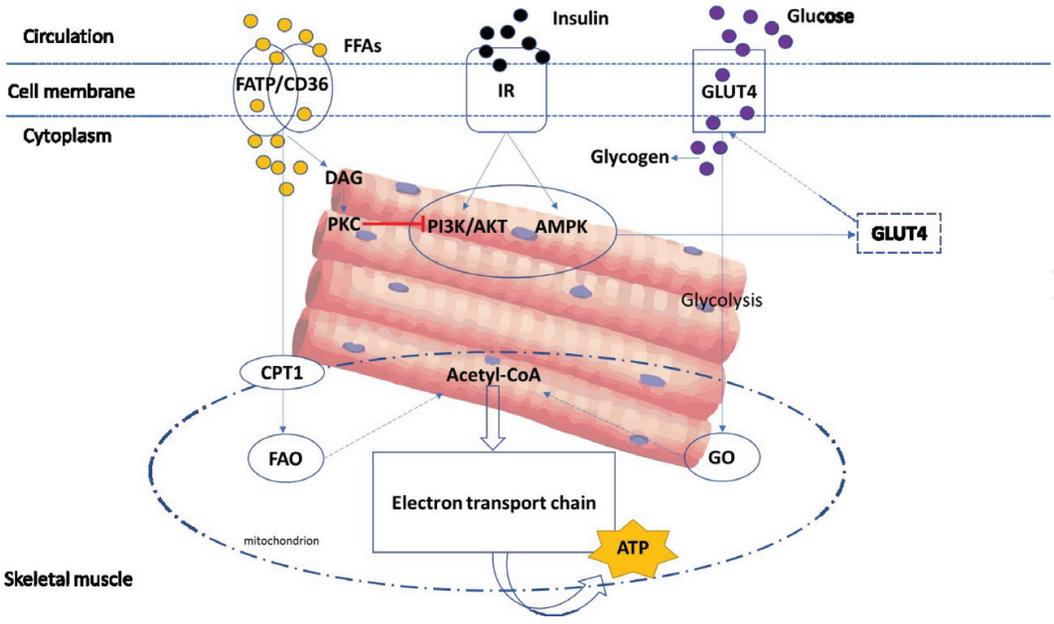

Figure 1. Glucose and free fatty acids (FFAs) are the predominant substrates that are oxidized to generate acetyl-CoA, which is then utilized by the electron transport chain to generate adenosine triphosphate (ATP). An insulin-resistant state is characterized by an impaired substrate utilization, a process termed metabolic inflexibility. Modulation of phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT) and 5′ AMP-activated protein kinase (AMPK) signaling mechanisms are increasingly targeted by various pharmacological compounds to reverse insulin resistance and improve skeletal muscle function. Abbreviations: CD36: cluster of differentiation 36, CPT1: carnitine palmitoyltransferase 1, DAG: diacyl glycerol, FAO: fatty acid oxidation, FATP: fatty acid transport protein 1, GLUT4: glucose transporter isoform 4, GO: glucose oxidation, IR: insulin receptor, and PKC: protein kinase C.

Some polyphenols, including those from grape extracts, can influence muscle lipid metabolism by reducing CD36 and regulating CPT1 expression in high fat diet (HFD) fed rats, leading to upregulated GLUT4 protein expression and improved insulin signaling [33]. Similarly, metformin, a commonly used antidiabetic drug, has demonstrated increased capacity to reverse IR and improve skeletal muscle function through the modulation of CPT1 and 5′ AMP-activated protein kinase (AMPK) [34, 35]. Like PI3K/AKT, AMPK is also a target of ongoing research for its role in preventing metabolic disease through modulation of substrate metabolism in various tissues [36, 37]. Intracellular energy fluctuations, represented by changing AMP/ATP ratio, such as those identified in an IR state, remain monumental for the activation or deactivation of AMPK activity [38]. A number of natural products [39–41], including metformin, are known to activate AMPK, leading to the phosphorylation of acetyl-CoA carboxylase and to effective modulation of beta oxidation. However, the activity of AMPK is tissue specific and is tightly controlled in a T2D state, with its activation demonstrated to be important in reversing IR and improving signaling in skeletal muscle [19, 36].

5. Conclusions

Skeletal muscle forms the largest insulin-sensitive tissue in the body and remains the key site for insulin-stimulated glucose uptake. Glucose and FFAs are the prominent substrates

responsible for ATP production in the skeletal muscle. However, in an insulin-resistant state, the utilization of both glucose and FFAs is impaired, leading to abnormally enhanced intramuscular substrate storage. Modulation of the PI3K/AKT and AMPK signaling appears to be the driving mechanism responsible for the regulation of substrate metabolism, as well as associated downstream effects such as generation of oxidative stress. Interestingly, some pharmacological compounds such as metformin are known to exert their therapeutic effects through the modulation of these pathways, leading to improved control of energy substrates. Therefore, it is imperative that more research be directed at exploring signaling mechanisms implicated in the control of energy substrates, especially in the skeletal muscle, since it is known to be the major "hub" for energy metabolism.

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Conflict of interest

The authors report no conflict of interest. All authors are responsible for the content and writing of the paper.

Abbreviations

AKT	protein kinase B
AMPK	5′ AMP-activated protein kinase
ATP	adenosine triphosphate
CD36	cluster of differentiation 36
CPT1	carnitine palmitoyltransferase 1
FABP	fatty acid binding protein
FATP1	fatty acid transport protein 1
FFAs	free fatty acids

GLUT	glucose transporter
HFD	high fat diet
IDF	International Diabetes Federation
IGF-1	insulin-like growth factor 1
IR	insulin resistance
MetS	metabolic syndrome
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PKC	protein kinase C
T2D	type 2 diabetes mellitus
UCP	uncoupling protein

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