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Role of Skeletal Muscle in Insulin Resistance and Glucose Uptake

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Abstract

The skeletal muscle is the largest organ in the body, by mass. It is also the regulator of glucose homeostasis, responsible for 80% of postprandial glucose uptake from the circulation. Skeletal muscle is essential for metabolism, both for its role in glucose uptake and its importance in exercise and metabolic disease. In this article, we give an overview of the importance of skeletal muscle in metabolism, describing its role in glucose uptake and the diseases that are associated with skeletal muscle metabolic dysregulation. We focus on the role of skeletal muscle in peripheral insulin resistance and the potential for skeletal muscle-targeted therapeutics to combat insulin resistance and diabetes, as well as other metabolic diseases like aging and obesity. In particular, we outline the possibilities and pitfalls of the quest for exercise mimetics, which are intended to target the molecular mechanisms underlying the beneficial effects of exercise on metabolic disease. We also provide a description of the molecular mechanisms that regulate skeletal muscle glucose uptake, including a focus on the SNARE proteins, which are essential regulators of glucose transport into the skeletal muscle.

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Introduction: Diabetes and Insulin Resistance

Overview of diabetes and insulin resistance

Diabetes mellitus, hereafter referred to as diabetes, is a suite of metabolic disorders that impair glucose homeostasis and cause persistent elevation of blood glucose levels. This impaired glucose homeostasis increases the risk of heart disease, stroke, and neuropathy, among other complications. Most instances of diabetes are divided into types 1 and 2. Type 1 diabetes (T1D) is an autoimmune disorder that leads to pancreatic β-cell dysfunction and demise; impeding their ability to provide insulin to the body. The lack of insulin prevents glucose uptake in the peripheral tissues, including adipose tissue, and skeletal muscle, resulting in high blood glucose levels. In type 2 diabetes (T2D), the pancreatic β-cells initially produce insulin, but the malfunctioning peripheral tissues are resistant and unable to respond to the insulin, and blood glucose levels remain high. The persistent high levels of blood glucose provoke the continued demand for insulin in this dysregulated signaling state, which eventually leads to β-cell dysfunction and defective insulin secretion. Other types of diabetes include gestational diabetes, which can occur in pregnant women with no history of the disease, and diabetes that is secondary to another medical condition.

Insulin resistance—also called prediabetes—is characterized by elevated fasting blood glucose levels ranging from 101 to 125mg/dL (5.6–6.9mM) or impaired glucose tolerance (140–199mg/dL or 7.8–11.1mM, 2 h after a 75-g oral glucose challenge) (6, 7); however, diagnosis of prediabetes is somewhat controversial due to the lack of a consensus on diagnostic criteria (104). Prediabetic individuals have a 50% chance of developing T2D within 5years of diagnosis (41) and are also at a higher risk of developing other metabolic disorders such as cancer, cardio-metabolic complications, neuropathy, and sarcopenia that can ultimately lead to death (41, 197).

Public health impact

In 2015, around 415 million adults worldwide were estimated to have diabetes, and this is expected to increase by over 250 million people in the coming three decades (347). T2D accounts for over 90% of diabetes cases. As of 2017, there were 30.3 million people in the USA with diabetes and 84.1 million people (more than one in three adults) with prediabetes, a condition that places them at risk for T2D (41).

Therapies for prediabetes

Prediabetes is thought to be reversible. Current treatments for prediabetes include lifestyle interventions in the form of exercise or dietary modifications (323) and anti-hyperglycemic drugs that can increase insulin sensitivity, like metformin (194). However, metformin has not been approved by FDA for use in prediabetes and is less effective than lifestyle intervention (diet and exercise) in minimizing the incidence of T2D (41). What is more, metformin can cause unpleasant side effects, such as gastrointestinal effects, including nausea, diarrhea and abdominal pain, and compliance is a challenge for prescribed exercise regimens (130, 217). Exercise prescription often fails because of poor adherence to a sustained exercise program. In addition, many individuals cannot exercise due to medical conditions, including conditions exacerbated by a sedentary lifestyle (125, 305). There is currently great research

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interest in developing new T2D therapies that target prediabetes, including therapies that mimic the effects of exercise.

Role of Skeletal Muscle in T2D

Overview of skeletal muscle

The skeletal muscle organ system is the largest in the body, comprising about 40% of the body weight of a young man (141). It is important for movement, posture, temperature and glucose homeostasis, soft tissue support, and metabolism. The skeletal muscle is a striated muscle tissue that is attached to the bones *via* tendons. Unlike the other two human muscle tissue types, smooth and cardiac muscle, skeletal muscle is under voluntary control by the somatic nervous system. Skeletal muscle is made up of a number of muscle fiber bundles that can vary in fiber type. Skeletal muscle fibers can be divided into slow-twitch Type 1 and fast-twitch Type 2 fibers based on their metabolic characteristics, and then are further defined by their myosin heavy chain (MHC) isoform expression (88).

Importance of skeletal muscle in insulin resistance

Skeletal muscle is essential for glucose clearance and is responsible for over 80% of glucose uptake from an oral glucose load, postprandial (59, 72, 307). Insulin resistance is caused by the desensitization of muscle to the insulin released by the pancreas to elicit glucose uptake, leading to elevated blood glucose levels. Skeletal muscle insulin resistance can appear decades before the onset of β-cell failure and symptomatic T2D (59, 336). In addition, lean nondiabetic, normoglycemic individuals with a high risk of developing T2D (such as children with parents who are both diabetic) have been reported to show moderate skeletal muscle insulin resistance (125, 305), supporting a role for insulin resistance as an early step in the development of T2D.

As the principal site of insulin-stimulated glucose uptake, skeletal muscle is also considered the primary driver of whole-body insulin resistance. When the primary defect is in skeletal muscle, remediating insulin resistance in the muscle alone is sufficient to restore whole-body glucose homeostasis (59). Although skeletal muscle insulin resistance is reversible, β-cell demise to date is not.

Insulin resistance disrupts both the amount of glucose uptake into skeletal muscle and the timing of that uptake (58, 307). Under normal conditions, postprandial glucose uptake into muscle increases linearly with time. However, with insulin resistance and T2D, there is a delay in insulin action and glucose uptake, causing diminished overall glucose uptake by the skeletal muscle. This has been demonstrated by hyperinsulinemic-euglycemic clamping studies in nondiabetic and type 2 diabetic humans (58).

Insulin Resistance and Skeletal Muscle

Links between aging and skeletal muscle insulin resistance

Aging (after 40–50 years of age) of the human skeletal muscle manifests as a gradual decline in mitochondrial function and reduced muscle mass, also known as sarcopenia (359). The loss of muscle mass is concomitant with a decline in strength and muscle function

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(158), and with a loss in regenerative capacity. While aging is a major risk factor for T2D, in part due to the muscle dysfunction of sarcopenia, there are additional suggested reasons that underlie T2D etiology beyond sarcopenia (291).

This age-associated muscle dysfunction can also be exacerbated by T2D and other diseases —a phenomenon known as secondary aging (24). Although there is currently no way to slow aging, secondary aging can be circumvented or delayed with increased physical activity or exercise (25). However, because sarcopenia can limit movement, a feed-forward cycle of increasing sedentary behavior can occur.

Combined effects of aging and obesity on insulin resistance

The aforementioned metabolic defects overlap and converge upon one another, with insulin resistance at the juncture of aging, muscle atrophy/sarcopenia and obesity. Indeed, these metabolic disorders are so intertwined that the term “sarcopenic obesity” has been coined to describe the toxic feedback loop between increased fat mass (obesity) and decreased skeletal muscle mass (sarcopenia), where one exacerbates the other (93).

Links between obesity/inflammation and skeletal muscle insulin resistance

There is a causal relationship between weight and insulin resistance that has been demonstrated by classical studies of nondiabetic, lean individuals. When these individuals were given a regimen of over-nutrition, they become insulin resistant, suggesting that obesity increases the risk of insulin resistance (89, 202). Chronic inflammation caused by obesity is thought to be a major contributor to the pathogenesis of insulin resistance and T2D. T2D is typically associated with elevated free fatty acids (particularly saturated), increased circulating pro-inflammatory cytokines, and elevated blood glucose which can all lead to insulin resistance (165).

For example, the adipose tissue releases adipokines, which act as signaling molecules, and facilitate tissue cross-talk. Adipokines have been shown to become dysregulated in obese and diabetic patients (192), with one of the most notable adipokines being leptin (186). The discovery of adipokines established the adipose tissue as an official endocrine organ. Similarly, in the last two decades, it has been shown that the skeletal muscle can act as an endocrine organ, secreting factors termed “myokines.” Myokines are proteins released by skeletal muscle, capable of cross-talk with other organs such as the bone, brain, and adipose tissue. Similarly, skeletal muscle can also become a target of obesityinduced inflammation. Obesity-induced inflammation and insulin resistance can also cause the release of particular cytokine hormones from both tissues (adipo-myokines) (Table 1). Skeletal muscle can secrete interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-15 (IL-15) as well as irisin, myonectin and myostatin, and unlike adipokines, muscle myokines are regulated by exercise and contraction (250). The release of these circulating factors can either increase or decrease obesity, inflammation, and insulin resistance.

Mechanisms of inflammation in skeletal muscle

Skeletal muscle can undergo infiltration by immune cells, such as macrophages and T cells, and in both humans and mouse models can become pro-inflammatory during obesity or

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T2D. The intramuscular adipose tissue depots, which expand with obesity and T2D and account for up to 10% of the total skeletal muscle mass (174), are thought to be the main contributors of pro-inflammatory immune cells (e.g. M1-like macrophages) to the skeletal muscle (68, 140). There are two adipose-type depots in skeletal muscle, which reside in an intramuscular or subcutaneous location. Separating the individual effects of these two depots is not yet technically feasible (81). Nevertheless, the cross-talk between adipose tissue and skeletal muscle drives the proinflammatory phenotype in skeletal muscle and is a major contributor to the development of insulin resistance due to the shift in myocyte metabolism imposed by inflammation (68).

There is growing research interest in the role of tissue cross talk in inflammation, including the influence of signaling factors from adipose tissue, circulating immune cells, and the gastrointestinal tract, on skeletal muscle metabolism. Progress is somewhat slow due to the technical challenge associated with isolating intramuscular adipose tissue away from skeletal muscles in the *in vivo* disease models (174). Recent work in mice has shown that in response to a high-fat diet, proinflammatory pathways are activated in endothelial cells, causing monocyte adhesion and transmigration (43). This promotes immune cell infiltration into muscle and other tissues. Skeletal muscle cells treated with saturated fatty acids attract monocytes and activate macrophage polarization to an M1-like pro-inflammatory state. These M1-like macrophages can cause insulin resistance (43). In muscle from mice fed high-fat diet, or in obese human skeletal muscle, there is also an increase in pro-inflammatory macrophages that is linked with increased adiposity and poor glucose tolerance (74).

Mechanisms of myokine action

Just as the discovery of adipokines established the adipose tissue as an endocrine organ, the identification of myokines hasestablishedthattheskeletalmusclecan actasanendocrine organ. Myokines mediate cross talk with organs including the bone, brain, and adipose tissue. Over 600 different peptides have been identified to be produced and secreted by the skeletal muscle (85, 96), and work is ongoing to characterize the complete secretome in muscle. Recent studies have shown that exercise or contraction of the skeletal muscle can induce the secretion of novel previously un-identified myokines (250), which have anti-inflammatory potential. Some of the most notable well-studied myokines are described below.

Interleukin-6 (IL-6)—IL-6, is a well-known pro-inflammatory cytokine released by skeletal muscle (226, 292), which, together with TNFα, contributes to the onset of insulin resistance. However, more recent evidence suggests that IL-6 can have anti-inflammatory effects, which are dependent on the signaling cascade and type of receptor binding. In macrophages, IL-6 release is caused by pro-inflammatory NFκB signaling and is accompanied by TNF activity. However, when IL-6 is released as a myokine in response to exercise, there is no NFκB signaling, but rather there is a calcium-dependent MAPK signaling pathway that leads to IL-6 release (340). This is thought to be regulated at the level of the IL-6 receptor, of which there are two types, IL-6R and sIL-6R. Classically, IL-6 binds to IL-6R, and this complex associates with gp130 (ubiquitously expressed) to stimulate the anti-inflammatory and anti-apoptotic MAPK signaling pathway (153). However, IL-6R

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expression is limited to hepatocytes and a limited number of lymphoid cells (124). In contrast, many cell types instead express a soluble IL-6R (sIL-6R), which has the same affinity for IL-6 and induces IL-6 trans-signaling. Thus, sIL-6R can induce IL-6 signaling through gp130 in cells without IL-6R (207). In human skeletal muscle, IL-6 release increases with exercise intensity and duration, this has been linked to lactate production. This IL-6 release depends on exercise-induced lactate production, and lactate alone without exercise, mimics the release of IL-6 from skeletal muscle (103).

Myostatin—Myostatin (growth differentiation factor 8) was the first identified myokine back in 1997, and its discovery has led to numerous secretome analyses, leading to the discovery of over 600 myokines (85). Myostatin, a highly conserved member of the transforming growth factor-beta (TGF-β) family of proteins (195) is highly expressed in skeletal muscle but can also be found in adipose and cardiac tissue. Myostatin is a negative regulator of muscle mass, and its ablation or mutation leads to muscle hypertrophy and a "hypermuscle" phenotype, like for example the Belgian blue cattle (195), or the whippet (205, 281). Myostatin protein abundance (135, 274) and expression (181, 190) decrease in humans after resistance exercise, with IL-6 plasma levels correlating with myostatin expression. Myostatin inhibits myogenesis and protein growth, and its inhibition leads to increased muscle growth (87, 204). Myostatin has also been associated with muscle sarcopenia, and females suffering from sarcopenia show increased serum levels (22). There is considerable research interest in exploring the therapeutic potential of myostatin inhibition to combat muscle atrophy. Indeed, since the early 2000s, there have been numerous agents tested as potential myostatin antagonists (99), including follistatin (22, 86, 105), and stamulumab [myostatin antibody, (330)], albeit with none found to be clinically successful in increasing muscle strength in muscle dystrophy patients (330), or, studies had to be discontinued for safety reasons (33). Some evidence does suggest that myostatin inhibition *via* the activin receptor extracellular domain fusion protein (ACVR2B-Fc) (21), or ActRIIB agonist (365), is able to inhibit cancer-induced cachexia in mice.

The effect of myostatin on skeletal muscle converges on the same pathway as does Activin A (both members of the TGF-β family of secreted factors). Myostatin binds to a multimeric receptor complex comprised of two type-I (ALK4 and ALK5) and two type-II (ActRIIA and ActRIIB) activin receptors. In skeletal muscle, ActRIIB is more abundant relative to ActRIIA, with a higher affinity for myostatin (167). Activation of the myostatin pathway and formation of the multimeric receptor complex leads to the phosphorylation of Smad2 and Smad3, and the recruitment of Smad4, to form a Smad 2/3/4 complex (276). The Smad complex then translocates into the nucleus where it inhibits genes that drive skeletal muscle proliferation and differentiation, leading to muscle cachexia and atrophy. In fact, myostatin levels are increased in cancer (13), and aging (diseases associated with muscle atrophy) (356). Furthermore, myostatin signaling can inhibit the AKT-mediated mTOR pathway involved in muscle protein synthesis (318). Inhibition of AKT leads to activation of autophagy *via* the FoxO pathway (166, 187, 188), and the ubiquitin-proteasome pathways, which are involved in protein degradation (179). Overall, elevated myostatin is associated with an increase in muscle atrophy and inhibition of muscle growth.

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Irisin—Expression of irisin, also known as cleaved FNDC5, is stimulated by PGC1α and is thought to mediate the beneficial effects of exercise by promoting the beiging of white adipose tissue. This beiging process activates the uncoupling protein UCP1, causing white adipose tissue to partially take on a brown adipose tissue phenotype (26). Brown adipose tissue is associated with increased thermogenesis. Irisin transcript levels have been shown to increase in both human and rodent exercise models, and this is thought to involve an increase in mitochondrial number and oxygen consumption by increasing the expression of PGC1α (85, 324). However, there is controversy surrounding the exercise-induced increase in serum irisin, primarily due to the difficulty in detecting irisin in the blood (due to low serum levels). Quantification of irisin levels has been challenging, but a recent study has shown that circulating irisin levels increase (as detected by tandem mass spectroscopy) with exercise (115). Recently, a mutant Fndc5 mouse model was created to assess the ability of irisin to mediate exercise and adipocyte "beiging." The mice showed no deficits in skeletal muscle development or function, but they showed reduced running capability, as well as reduced insulin sensitivity and glucose uptake in response to running, highlighting irisin's importance in mediating the metabolic effects of exercise (349). In addition, irisin treatment of mouse myotubes increases expression of PGC-1α and mitochondrial transcription factor A, both involved in increased mitochondrial content and function (324). However, harmful nutrients such as palmitate can decrease irisin expression and hence decrease its insulin-sensitizing benefits. Specifically, palmitate drives the binding of Smad3 to a Smad3 binding motif in the FNDC5 gene promoter to negatively regulate FNDC5 expression (313). This highlights one potential mechanism whereby insulin resistance in muscle is caused by the downregulation of insulin-sensitizing factors like irisin.

Myonectin—Myonectin belongs to the CTRP (C1q/TNF related protein) family (279) and is a nutrient-responsive myokine that is structurally homologous to adiponectin and is released by muscle contraction. Myonectin mimics insulin's ability to promote fatty acid uptake by upregulating the expression of fatty acid transport genes such as CD36 and Fabp1/4 in response to exercise (280). Myonectin can inhibit autophagy in the mouse liver (278). The ability of myonectin to inhibit autophagy is abolished when the phosphatidylinositol-3 kinase (PI3K)/AKT pathway is suppressed. Since the PI3K/AKT pathway is known to be important in skeletal muscle anabolism, it is through this pathway that myonectin may inhibit muscle atrophy to promote muscle growth (278). In addition, myonectin activates the nutrient-sensing AMP-activated protein kinase (AMPK) pathway in myocytes, leading to increased translocation of the GLUT4 glucose transporter and glucose uptake (229). Myonectin has also been associated with mitochondrial deoxyribonucleic acid (mtDNA) density, and decreased mtDNA levels in response to insulin resistance can upregulate myonectin (171, 229). Myonectin levels have been shown to be dependent on the skeletal muscle fiber type, with slow-twitch fibers expressing higher levels of the myokine compared to fast-twitch fibers (280).

Interleukin 15 (IL-15)—IL-15 is an exercise- and muscle contraction-regulated myokine that can decrease obesity and inflammation and is of interest as a candidate therapeutic target to combat the negative effects of obesity (155, 295). It is thought to mediate the benefits of exercise; however, the exact effect of exercise on expression, protein, and

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secretion of IL-15 varies from study to study (26, 213, 253, 353, 357). These studies differ in exercise intensity and type (acute vs. training), as well as IL-15 measurement protocols. The consensus is that moderate-intensity training has a positive impact on IL-15 serum levels in humans (251). IL-15 is upregulated during myoblast differentiation, and IL-15 enrichment in cultured skeletal muscle can induce differentiation and increase muscle mass (164, 242). In contrast, another group showed that IL-15 administration to young rats leads to reduced muscle mass and increased apoptosis (236), suggesting that the conditions of IL-15 administration can affect its role in skeletal muscle. IL-15 increases fatty acid oxidation and glycogen synthesis in skeletal muscle (5), and in adipose tissue, IL-15 has been shown to reduce lipid accumulation while increasing adiponectin secretion (similar to exercise) (243, 244). IL-15 has also been shown to increase glucose uptake into rat skeletal muscle and cultured skeletal muscle cells (31), *via* the STAT3 (152), and AMPK pathways (209) similar to the effect of exercise on these pathways (193, 319). The lack of consensus regarding IL-15 action indicates that more work needs to be done to understand the mechanism underlying its function as a myokine. Toward this, a recent publication (discussed below) has shed light on the potential mechanism of IL-15 regulation *in vivo* (282).

Other myokines—Other notable myokines include BDNF and Decorin, which play roles in fat metabolism, muscle regeneration, and differentiation (164, 251). In addition, new myokines have been identified that respond to exercise [termed exerkines (263)]. As for the effect of exerkines on insulin resistance, more work is needed to characterize the function of these exerkines, and understand their role in insulin resistance, before they can be leveraged for therapeutic purposes.

O-GlcNAc: Muscle Nutrient Sensor

O-GlcNAcylation (O-GlcNAc) has been proposed to increase IL-15 expression in skeletal muscle. β-Linked *N*-acetylglucosamine (O-GlcNAc) is a dynamic posttranslational modification of serine or threonine hydroxyl groups of proteins in the nucleus and cytoplasm. O-GlcNAc is regulated by two proteins: O-GlcNAcase (OGA), which removes O-GlcNAc from serine/threonine hydroxyl groups, and O-GlcNAc transferase (OGT), which adds O-GlcNAc. O-GlcNAc levels are real-time nutrient sensors in the skeletal muscle and other organs. This posttranslational modification was discovered over three decades ago, but its biological relevance, especially in skeletal muscle, was not known until very recently (282).

O-GlcNAc is increased in the skeletal muscle of obese and T2D individuals, and this is consistent with its function as a nutrient sensor: O-GlcNAc levels positively correlate with nutrient availability; for example, high-fat diet-fed mice have elevated O-GlcNAc, and this is associated with disrupted angiogenesis (184). O-GlcNAc inhibits activity of many components of the insulin-stimulated glucose uptake pathway including AKT, PI3K and the insulin receptor (IR), making it an important signaling molecule in the mechanisms underlying insulin resistance and diabetes (338). Specifically, O-GlcNAc synthesis *via* the hexosamine biosynthesis pathway (HBP) is increased under hyperglycemic conditions and can lead to insulin resistance *via* the modulation of AKT signaling (230, 328). In hepatocytes, ablation of OGlcNAc by viral overexpression of OGA leads to increased AKT

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activity (284), while enhanced O-GlcNAc synthesis driven by glutamine treatment of endothelial cells inhibited angiogenesis *via* inhibition of AKT activity (184).

The effect of increased O-GlcNAc can also be inconsistent and dichotomous. For example, while elevated O-GlcNAc in the pancreata of young mice also associates with negative actions on serum and islet insulin contents and β-cell dysfunction, elevated O-GlcNAc in the pancreata of the mice at older ages was associated with increased AKT activation and improved β-cell function (283). Hence, O-GlcNAc modification can exert both positive and negative effects, depending upon the tissue/cell type, the specific proteins that are modified, and when the proteins are modified longitudinally. Furthermore, O-GlcNAc of glycogen synthase in 3T3-L1 adipocytes under high glucose conditions has been shown to contribute to insulin resistance, similarly, in hyperglycemic mice, O-GlcNAc of glycogen synthase was increased (231).

In addition, it has been shown that there is cross talk between O-GlcNAc and AMPK, whereby activation of AMPK can alter the substrate selectivity of OGT and lead to its nuclear localization (30). O-GlcNAc has also been associated with a vesicle trafficking protein, Munc18c, to impair GLUT4 vesicle translocation and glucose uptake in adipocytes (45). Munc18c that is O-GlcNAcylated remains clamped to syntaxin 4 (STX4), maintaining it in its closed conformation and blocking the activation of STX4. When STX4 activation is blocked, so is the formation of functional SNARE complexes in the adipocytes. Increased O-GlcNAc of Munc18c *via* glucosamine treatment in 3T3-L1 adipocytes leads to an inhibition of SNARE trafficking to the plasma membrane and blunted GLUT4 translocation. Interestingly, only Munc18c was found to be modified, none of the vesicle SNAREs (v-SNAREs) or target SNAREs (t-SNAREs) were O-GlcNAcylated (45).

The levels of O-GlcNAc are tightly regulated by OGT and OGA and the dysregulation of either of these enzymes can be detrimental in skeletal muscle. Loss of OGA leads to skeletal muscle atrophy, while OGT overexpression leads to insulin resistance, suggesting that O-GlcNAc plays a role in a signaling network in the muscle that can modulate a number of metabolic mechanisms and pathways. The precise role of O-GlcNAc in skeletal muscle is largely unknown, but it was recently shown that OGT knockout in mouse skeletal muscle improves insulin sensitivity, increases leanness, increases energy expenditure, and enhances glucose uptake (282). These mice also showed increased circulating IL-15 expression, which was accompanied by increased levels of adiponectin. Furthermore, OGT was found to control IL-15 expression *via* O-GlcNAc. This provides a mechanism for promoting IL-15 expression in skeletal muscle, which may be useful as a therapeutic target to combat insulin resistance and T2D.

Mechanisms of Glucose Uptake

Glucose transporters (GLUTs)

Multiple glucose transporters facilitate glucose movement across the plasma membrane. This membrane-spanning SLC2A family of proteins is integral to the transportation of glucose and other hexoses either to the inside or outside of the cell. There are over 14

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SLC2A-family glucose transporters present in human cells across three classes [class I, II, and III (310)] based on sequence similarity (206).

There is variable tissue expression of glucose transporters in humans. In skeletal muscle, there are three GLUTs responsible for mediating glucose uptake: GLUT4, GLUT1, and GLUT3 (expressed in fetal and neonatal muscle only), in order of abundance (147) (i.e. GLUT4>GLUT1). GLUT1 localizes to the plasma membrane, whereas GLUT4 primarily localizes to intracellular vesicles and is transported to the cell surface in response to stimuli. GLUT5 has also been found in the skeletal muscle (108), where it primarily localizes to the plasma membrane for facilitating fructose transport across the muscle.

GLUT4 is best known as the insulin-regulated glucose transporter (112). It is encoded by the SCL2A4 gene, and it is highly abundant in skeletal muscle and adipose tissue. GLUT4 is an intracellular protein that depends on stimulus (insulin or exercise) to translocate to the plasma membrane and facilitate glucose uptake. Under unstimulated conditions, glucose transport is restricted, due to the intracellular localization of GLUT4, and a limited expression of GLUT1 at the plasma membrane. There are reported to be two pools of intracellular GLUT4, one recruited by insulin stimulation (Figure 1), and the other by exercise (Figure 2) (55). Below we discuss the differences in GLUT4 translocation and uptake between the two stimuli.

GLUT4 regulation of insulin-stimulated glucose uptake

Insulin-stimulated glucose uptake is rate-limited by the translocation of GLUT4-laden vesicles from the intracellular compartments to the PM. The translocation of the GLUT4 vesicles occurs in response to the canonical insulin signaling pathway (and in muscle, *via* a second noncanonical insulin signaling pathway). Once GLUT4 proteins are integrated into the PM, the influx of glucose into the muscle or adipocyte ensues. While this process has been delineated in both muscle and adipose tissue, the skeletal muscle is the focus of this review article. As shown in Figure 1, insulin stimulates GLUT4 vesicle translocation *via* two pathways in the skeletal muscle that bifurcate shortly after insulin binds the IR and activates the intracellular signaling cascade. These two pathways are normally distinguished by the activation of the serine/threonine kinase AKT in the canonical pathway, or the Rho-family GTPase Rac1 in the noncanonical pathway. These pathways are independent of one another: inhibition of one pathway does not affect the other pathway. Both can function autonomously to stimulate GLUT4 translocation (301). The two pathways are discussed in detail below.

Canonical insulin signaling pathway—Insulin binds to the α-subunit of the IR, which localizes to the plasma membrane of the skeletal muscle (341). This leads to both a conformation change and tyrosine phosphorylation of the IR ß-subunit (163, 361). Once the IR is phosphorylated, the insulin receptor substrate-1 (IRS-1) is recruited to the IR (296). In the canonical insulin signaling pathway, IRS-1 binds the SH2 domain of PI3K (160, 208), allowing PI3K to phosphorylate phosphatidylinositol 4,5-biphosphate (PIP_2), and form phosphatidyl 3,4,5-triphosphate (PIP_3) (4). PIP_3 phosphorylation recruits AKT, which binds PIP_3, and AKT is phosphorylated and activated by phosphatidylinositoldependent kinase

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(PDK1) (3, 4, 334). AKT phosphorylates AS160 (133, 309), a Rab GTPase activating protein (GAP) (273). AS160 prevents the inactivation of the small GTPase Rab proteins Rab8A and Rab13 in muscle, which occurs when AS160 is dephosphorylated (110, 297). Rab8A is required for GLUT4 translocation in muscle cells, and its loss inhibits glucose uptake (297), whereas Rab13 enables tethering of GLUT4 vesicles to filamentous actin (298). In contrast, Rab10 is the main substrate of AS160 in adipocytes (271). The adipose-specific Rab10 is required for glucose uptake into adipose tissue, and genetic ablation of adipocyte Rab10 in mice diminishes glucose uptake and GLUT4 translocation both *in vivo* and *in vitro* (325). These findings show that while the adipose tissue is responsible for only a minor portion of glucose uptake, its systemic signaling affects whole-body glucose homeostasis. GLUT4 translocation, facilitated by Rab proteins, guides the GLUT4 vesicles to the plasma membrane where members of the SNARE complex, including synaptosomal-associated protein 23 (SNAP23) (77, 134), and STX4, bind to the v-SNARE VAMP2 to fuse the vesicles with the PM and integrate GLUT4 onto the PM (220). This process permits glucose to enter the cell *via* facilitated diffusion.

Noncanonical insulin signaling pathway—Unlike the canonical insulin signaling cascade, this pathway involves small GTPases of the Rho family. In muscle, this is the Ras-related C3 botulinum toxin substrate 1 (Rac1) (113, 114), whereas in adipocytes, Rac1, as well as the small GTPase TC10, is used (50, 303). Signaling is initiated in a manner similar to that of the canonical pathway: insulin binds the IR, resulting in PI3K activation, which in turn generates PIP3. PIP3 recruits AKT and becomes phosphorylated and therefore activated by PDK1. After this point, the pathways diverge. In the noncanonical pathway, Rac1 is activated *via* GTP-loading by PI3K activation of guanine nucleotide exchange factors (GEFs) or inactivation of GAPs. Once activated, Rac1-GTP leads to activation of its effector protein, p21-activated kinase 1 (PAK1) (114, 300), which in turn causes phosphorylation of p41-ARC, an ARP2/3 subunit required for GLUT4 translocation, and leads to filamentous actin polymerization *via* interactions with N-WASP (320, 321). Actin remodeling allows for GLUT4 translocation to the plasma membrane, where the two signaling arms converge with SNARE complex formation and glucose uptake (51).

Mechanisms of GLUT Translocation in Muscle

SNARE-mediated vesicle exocytosis

SNARE proteins mediate vesicle fusion during GLUT4 translocation. Traditionally SNAREs are of two types, v-SNAREs or t-SNAREs, which are located on the membrane of vesicles or at terminal membranes, respectively. There are 6 v-SNAREs, and 11 t-SNAREs, present in the muscle and adipocytes. However, only the t-SNAREs STX4 and SNAP23 and the v-SNARE VAMP2 are required for insulin-stimulated GLUT4 vesicle fusion and exocytosis in muscle and adipocytes (134, 220, 352). Given the promiscuity of some SNARE proteins, which can localize to both vesicles and target membranes, an alternate classification scheme exists R-SNAREs and Q-SNAREs. R-SNAREs contribute an arginine residue (R) in SNARE complex formation and usually act as v-SNAREs, while Q-SNAREs contribute a glutamine (Q) to the SNARE complex zero ionic layer. Q-SNAREs can be further sub-categorized to Q_a, Q_b, and Q_c (70). SNARE proteins are defined by a 60 to 70 amino acid SNARE motif,

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which has the propensity to form coiled-coil structures. Most SNARE proteins contain only one motif, but there are three identified SNAREs with two motifs: SNAP23, SNAP29, and SNAP47. In addition, v-SNARE proteins and syntaxin (STX) t-SNAREs have hydrophobic C-terminal transmembrane domains; however, some do not (SNAP23, SNAP29, SNAP47), and instead, they have posttranslational lipid modifications, such as palmitoylation, to anchor them into the plasma membrane. When t-SNAREs and v-SNAREs interact, they form a complex known as the SNARE core complex. A SNARE core complex is generally defined as having three Q-SNARE motifs and one R-SNARE motif and is notoriously SDS-resistant due to the induced high affinity binding of the four α-helices (e.g. two from SNAP23, one from STX4 and one from VAMP2). The helices create multiple hydrophobic layers and must be boiled to dissociate the protein complex (69).

SNARE proteins dock and fuse vesicles to the plasma membrane, but there is no consensus on the cargo of docked vesicles. For example, although STX4 is associated with GLUT4 vesicle docking, the potential for STX4 docked vesicles to mediate more than just glucose homeostasis has been proposed. STX4 was found to dock/fuse vesicles carrying the enzyme acid sphingomyelinase (A-SMase), which is central to sphingolipid metabolism, cancer drug cytotoxicity (e.g. cisplatin),and apoptosis (234). A-SMaseactivation and transport are dependent on STX4 abundance, and loss of STX4 can diminish A-SMase activity.

v-SNAREs—v-SNAREs are located on the GLUT4 vesicle membrane. In skeletal muscle, the following v-SNAREs have been found: VAMP2, VAMP3, VAMP5, and VAMP7. Although VAMP2 is the only v-SNARE implicated in insulin-stimulated GLUT4 translocation, during exercise, VAMP2, VAMP5, and VAMP7 have all been shown to co-immunoprecipitate, and translocate to the sarcolemma with GLUT4, and the transferrin receptor (256). This result suggests that all three VAMP proteins play a role in exercise-stimulated GLUT4 translocation and glucose uptake.

t-SNAREs—t-SNARE proteins, such as STX4 and SNAP23, reside on the sarcolemma in muscle. To anchor themselves into the sarcolemmal membrane, STX proteins contain a transmembrane C-terminal domain, whereas SNAP23 proteins associate with the membrane *via* palmitoylation of four cysteine residues in the central linker region of the protein allowing the formation of thioester linkages to the membrane (227). t-SNAREs are known to form binary sub-complexes (e.g. STX4-SNAP23), which aid v-SNARE binding by acting as templates. These sub-complexes are very stable, and usually contain three SNARE motifs residing within the same membrane (also called a t-SNARE complex) (64). The STX proteins have one SNARE motif and the SNAP23 proteins have two motifs separated by a linker region. The t-SNARE intermediate complex, a heterodimer, can be partially or completely zippered to form the receptor for v-SNARE binding (363).

SNARE zippering and complex formation—Once the v-SNARE and t-SNAREs are in close proximity, they form the SNARE complex. This process occurs *via* zippering, bringing the membranes (vesicle and plasma membranes) into position and facilitating fusion. The SNARE motifs, which are α-helical coiled -coils, assemble in a 4-strand parallel coiled-coil (237), with 15 layers of interacting hydrophobic side chains, in a 1:1:1 heterotrimeric ratio (285). At the center of the complex is one arginine residue from the v-SNARE and three

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glutamine residues from the t-SNARES, which represent the R and Q classifications mentioned above (70, 180). This is a conserved feature of SNARE complex formation. The term “zippering” is used to describe the interaction between the proteins, as it is believed that they assemble from the N-terminal region toward the C-terminal region, similar to a zipper closing a jacket. This brings the membranes close together to facilitate fusion (288).

SNARE accessory proteins

DOC2B—The double C2 domain-containing protein β (DOC2B) and two other DOC2 isoforms—DOC2α and DOC2γ—were originally discovered in the brain as synaptic proteins involved in calcium-dependent exocytosis (80, 223, 224). DOC2B functions as a priming protein that increases the number of fused vesicles in response to calcium. DOC2B lacks a transmembrane domain. In response to calcium, which binds both the C2A and C2B domains, a direct interaction between the DOC2B C2A domain and the plasma membrane can occur (150). DOC2 proteins also interact with Munc13 proteins (222).

DOC2B is also expressed in pancreatic β-cells, adipocytes and skeletal muscle. It has been shown to regulate glucosestimulated insulin secretion in β-cells (136), and insulin-stimulated glucose uptake in skeletal muscle (362). Enrichment of DOC2B promotes insulin secretion (12), and peripheral insulin sensitivity (246), by acting as a scaffold for Munc18 proteins to associate and promote SNARE complex assembly (245).

DOC2B deficiency in mice impairs GLUT4 translocation to the sarcolemmal surface and reduces SNARE complex formation (247). DOC2B is believed to recruit Munc18c away from STX4, allowing STX4 to adopt an open conformation (Figure 3), and allowing SNARE complex formation to continue (136). Without DOC2B, STX4 is maintained in a sequestered closed conformation by Munc18c (247). Indeed, DOC2B protein is reduced in human diabetic skeletal muscle, further implicating DOC2B as a key regulator of glucose homeostasis in muscle (362). DOC2B is a potential therapeutic candidate in T2D because of its ability to promote and protect functional beta-cell mass and to enhance and protect glucose homeostasis *in vivo*.

Munc18c—Mammalian uncoordinated-18 protein C (Munc18c or MUNC18–3) is the mammalian homolog of Unc-18c, an important component in exocytosis. The Munc18 family of proteins is 66 to 68kDa soluble proteins that localize to the plasma membrane and cytosolic compartments; two of the three Munc18 family, Munc18c and Munc18b, are expressed in muscle and fat cells (306). Munc18 proteins have both positive and negative roles. Munc18 proteins play a positive required role in SNARE-mediated fusion, wherein Munc18 protein reduction impairs SNARE-mediated fusion. Munc18 proteins can also play a negative role when over-expressed, by clamping their cognate STX partners in a closed conformation that impedes SNARE complex formation. For example, Munc18c binds to STX4 and is required for insulin-stimulated GLUT4 vesicle docking and fusion in 3T3L1 adipocytes (290, 304, 311), and mediating peripheral insulin action in skeletal muscle *in vivo* (216, 290). The high affinity of Munc18c for STX4, on the order of 12nM [entire cytoplasmic region, (120, 203)] is thought to localize Munc18c to the plasma membrane (360). It has been reported that Munc18c binds to the N-terminal region of STX4 (360), or

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to the C-terminal region (120, 252). Recognizing this, another report suggests that Munc18c binds to both domains of STX4, keeping STX4 in its closed conformation, similar to the interaction demonstrated for the neuronal Munc18–1 and STX1A proteins (203).

It was later discovered that Munc18c is rapidly tyrosine phosphorylated at Tyr219 and Tyr521 in response to insulin stimulation, serving as an IR substrate (121). Interestingly, Munc18c Tyr219 phosphorylation occurs independently of PI3K suggesting that Munc18c activation occurs in a parallel pathway to IRS-1 activation (121). Upon Munc18c's tyrosine phosphorylation, STX4 binding to Munc18c is decreased by 60%, releasing the clamp on STX4 and promoting SNARE complex formation and GLUT4 vesicle fusion (121). This decrease is accompanied by a twofold increase in the association between Munc18c and another SNARE accessory protein, DOC2B (120, 121), and STX4 activation and assembly into SNARE complexes. In essence, Munc18c switches binding partners depending upon its phosphorylation status. Munc18c levels in healthy muscle and fat cells are tightly controlled, as is common for key regulatory factors, with 2 to 3nM of Munc18c found to be required to maintain glucose homeostasis. Munc18c levels that are reduced or increased are associated with insulin resistance (290).

Syntaxin 4 interacting protein (synip)—Syntaxin 4 interacting protein (synip) is a STX4 binding protein which regulates glucose transport and GLUT4 vesicle translocation and was first identified in adipocytes (199). Synip binds to STX4 under resting/basal conditions, and insulin stimulation reduces the binding affinity of synip for STX4. Both the v-SNARE VAMP2 and synip compete for the same binding site on STX4. Therefore, when synip is bound to STX4, GLUT4 vesicles cannot dock and SNARE complexes cannot form (199). Insulin modulates synip binding to STX4 by activating AKT2, which phosphorylates synip at Ser99, leading to its dissociation from STX4 (350). Expression of a Ser99Phe synip mutant blocked GLUT4 translocation in response to insulin (350). While a follow-up study using a Ser99Ala mutation of synip resulted in congruent findings regarding ablation of insulin-stimulated GLUT4 translocation (219), this outcome was contested by a different group that also used the Ser99Ala mutant (272). The underlying cause of this discrepancy remains unresolved.

Although synip is an important modulator of insulin-stimulated GLUT4 translocation in adipocytes (199) and podocytes (350), and of glucose-stimulated insulin secretion in the pancreas (264, 265), no studies have evaluated synip function in the skeletal muscle, despite report of abundant synip mRNA expression in skeletal muscle and heart (199). Hence, whether synip plays a parallel role in insulin-stimulated skeletal muscle glucose uptake as has been demonstrated in adipocytes, remains to be tested.

STX4 in SNARE-mediated exocytosis: trafficking versus docking versus fusion—the rate-limiting step

Insulin-stimulated GLUT4 translocation requires the interaction of VAMP2 with STX4 and SNAP23 to form the SNARE complex (327). However, it was unknown whether trafficking (movement of the GLUT4 vesicle to the plasma membrane), docking (arriving at the plasma membrane) or fusion (fusing with the plasma membrane) constituted the rate-limiting step in

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this process. Using a temperaturesensitive Munc18c mutant as a novel tool to address this question, it was demonstrated that the rate-limiting step for insulin-stimulated GLUT4 translocation is principally vesicle trafficking (312). In brief, overexpression of wildtype Munc18c inhibited insulin-stimulated GLUT4 translocation, as had been previously reported (304, 311), the overexpression of a Munc18c mutant (Arg240Lys) also inhibited GLUT4 translocation at the permissive temperature, and was rapidly reversible upon shifting to the nonpermissive temperature. Evaluation of the rate of GLUT4 translocation following temperature shifts demonstrated that the ratelimiting step in insulin-stimulated GLUT4 translocation is the trafficking of the vesicles to the PM (312). The concept of the rate-limiting step preceding docking and fusion steps was later supported using TIRF microscopy in adipocytes (16). However, another group also using TIRFM suggested that the rate limiting step was vesicle fusion to the PM (176). Further studies will likely be required to reconcile the differences in TIRFM methodological differences to yield a consensus.

Exercise-stimulated GLUT4 translocation and glucose uptake

When muscle contracts, it stimulates the translocation of GLUT4 vesicles to the plasma membrane, to facilitate the uptake of glucose into the muscle. Exercise duration and intensity determine the amount of glucose uptake by the skeletal muscle. Increased intensity and time lead to increased glucose uptake (331). Exercise increases blood flow (8), which further increases glucose uptake from the blood into the skeletal muscle.

Exercise is an important regulator of glucose metabolism and uptake (332) and is considered a therapeutic for insulin resistance and T2D (337). This is because exercise-stimulated glucose uptake is maintained during insulin resistance, as it does not rely on the AKT signaling arm of the GLUT4 translocation pathway (52, 344). Instead, the pathways are additive: glucose uptake can be further enhanced by combining muscle contraction and insulin stimulation (183). However, some studies suggest that the pathways for insulinand exercise-stimulated GLUT4 translocation may converge downstream (146, 339).

During exercise, an exercise-sensitive pool of GLUT4 vesicles is induced to translocate to the sarcolemma, and GLUT4 endocytosis from the sarcolemma is coordinately reduced in both skeletal muscle and cardiomyocytes, as demonstrated by the use of exercise mimetics (71, 132, 354). The exercise-stimulated GLUT4 pool is distinguished from the insulin-stimulated GLUT4 pool by the presence of the transferrin receptor selectively on the exercise-stimulated GLUT4 vesicles (169). The precise signaling mechanism used to elicit exercise-stimulated GLUT4 translocation is not well known. Implicated signaling pathways in exercise-induced GLUT4 vesicle translocation are described below.

AMP-activated protein kinase (AMPK)—AMPK is involved in mediating glucose uptake *via* exerciseinduced GLUT4 vesicle translocation (144, 221). AMPK is a cellular energy sensor, serving as a nexus for impacting multiple metabolic pathways such as fatty acid synthesis, glucose uptake, and fatty acid oxidation (19, 66, 221). AMPK is a heterotrimer made up of AMPK-α, -β, and -γ subunits, with α being a catalytic subunit, and the β and γ being regulatory subunits (65). There are multiple subtypes of each type of subunit, and the skeletal muscle has been shown to primarily express the α2β2 subtypes, and

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the α1β1 subtypes to a lesser extent (48). Exercise triggers activation of both α1 and α2 subtypes; α1 is activated during high-intensity acute exercise bouts, while α2 is activated during lower-intensity exercise (79). AMPK-β subunits are also important for glucose uptake and exercise capacity, as evidenced by muscle-specific β1β2 double knockout mice that exhibit noted physical inactivity (221), and have reduced exercise capacity and exercise-induced glucose uptake into skeletal muscle (302). An increase in the ADP:ATP ratio (i.e. low energy status as is induced by exercise) in the cell leads to activation of AMPK. AMPK is activated by phosphorylation of the α-subunit at Thr172 (91, 215, 268). This phosphorylation is mediated by upstream kinases, including calmodulin-dependent protein kinase (CAMK) (92, 109, 346); liver kinase B1 (LKB1) is the principle upstream kinase to phosphorylate AMPK in skeletal muscle (149, 266, 308). The pharmacological activator of AMPK is AICAR (5-aminoimidazoel-4-carboxamide1-D-riborfuronosil-5′monophosphate), which can mimic exercise-stimulated GLUT4 translocation and glucose uptake (AICAR details are discussed in greater detail in the section titled “Therapeutic Development of Exercise Mimetics”).

AMPK regulates exercise-stimulated glucose uptake *via* its phosphorylation of two downstream targets, AS160 and TBC1D1 (tre-2/USP6, BUB2, cdc16 domain family member 1, a member of the TBC1 Rab-GAP family of proteins) (47). AS160 was implicated in exercise-stimulated glucose uptake by evidence showing that *ex vivo* contraction of rat skeletal muscle leads to AS160 phosphorylation (29), and that mutation of AS160 phosphorylation sites reduces exercise-stimulated glucose uptake in rodent and human skeletal muscle (151, 317). While AS160 is central to both exercise- and insulin-stimulated glucose uptake, AMPK is the upstream regulator of AS160 in the exercise-stimulated pathway, while AKT regulates AS160 in response to insulin stimulation (151). In brief, AICAR treatment was shown to increase phosphorylation of AS160 at four sites, and that expression of an AS160 mutant (with all four phosphorylation sites mutated) reduced AICAR-induced glucose uptake (29). AMPK phosphorylates TBC1D1 at several sites, with the predominant phosphorylation site being Ser237, a site also phosphorylated in response to exercise (78). Inhibiting the phosphorylation of TBC1D1 decreases exercise-stimulated glucose uptake (145, 232).

Most recently, a novel myokine-ATP synthase inhibitory factor 1 (IF1) has been identified as a downstream target of AMPK activation, *via* reactive oxygen species (ROS), which leads to Rac1 activation (162). This further highlights the breadth of AMPK’s regulation of exercise-stimulated glucose uptake, and that additional facets and factors may be yet to be discovered.

Beyond exercise-stimulated glucose uptake, AMPK also contributes to insulin sensitivity in skeletal muscle, *via* its linkage to IRS1 phosphorylation (111), mTOR inhibition (67, 127, 142), adiponectin activation (351), and through its interaction with the myokine IL-6 (38). AMPK modulates insulin-stimulated glucose uptake *via* the phosphorylation and inhibition of glycogen synthase (39), a key enzyme for the conversion of glucose into glycogen (238).

Calcium-activated signaling—Calcium influx into the muscle leads to muscle contraction *via* a process known as excitation-contraction coupling (269). When an action

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potential is created upon depolarization of the skeletal muscle, this spreads throughout the cell, eventually depolarizing the T-tubules. This opens the voltage-gated calcium channel $Ca_v1.1$ at the sarcolemma, also known as the dihydropyridine receptor. $Ca_v1.1$ is a voltage-dependent, L-type α1S subunit calcium channel, and interacts with calcium release channels in the sarcoplasmic reticulum known as ryanodine receptors (RyRs) (10). There are three RyR isoforms, with RyR1 (skeletal muscle calcium release channel) being the isoform primarily expressed in skeletal muscle. Specifically, $Ca_v1.1$ undergoes a conformational change that activates RyR1 in the skeletal muscle (241), and causes calcium release into the muscle, leading to a "calcium spark." Several thousand calcium sparks increase the calcium concentration within the muscle (49). The calcium can bind proteins like troponin C to lead to cross bridge cycling, a mechanism of muscle contraction. A regulator of this process that controls the duration of contraction is the sarco/endoplasmic reticulum calcium ATPase (SERCA), which removes the calcium from the cytosol and returns it to the sarcoplasmic reticulum, allowing the muscle to relax (32).

Calcium has been shown to enhance muscle GLUT4 translocation, and subsequently glucose uptake (9). For example, calcium induced by caffeine addition to rat L6 myotubes leads to an increase in GLUT4 translocation; this effect can be blocked by a CAMK inhibitor (calmodulin-dependent kinase protein, a protein activated by calcium), or induced by the AMPK activator AICAR (218). Interestingly, the effect of AICAR and caffeine, that is activation of calcium and AMPK, were additive and their combined effects were similar to the effects achieved by exercise (348). Contrary to these data, use of RyR inhibitors failed to support a direct role for calcium release in the process of exercise-stimulated glucose uptake into skeletal muscle (117, 119). Given the importance of calcium in muscle contraction and the number of calcium-sensing proteins that are known to be modulated with exercise, it is plausible that calcium is an important modulator of exercise-stimulated glucose uptake, perhaps through an indirect mechanism (348). For example, inhibition of CAMKII reduces contraction-stimulated glucose uptake in mouse muscle (343).

Nitric oxide (NO) signaling—Exercise increases the activity of nitric oxide synthase (NOS) (18), which produces the gaseous signaling molecule nitric oxide (NO) from L-arginine, oxygen, and NADPH (76). Inhibition of NOS using L-NMMA blunts glucose uptake in skeletal muscle during exercise in both healthy and T2D individuals (27, 143). nNOSμ is the main isoform expressed in skeletal muscle (210), is constitutively active, and muscle contraction causes a twofold increase in NO production (233). However, there is some disagreement in the field as to whether NOS inhibition decreases exercise-stimulated glucose uptake (27, 143), as this is not universally observed (94, 138).

The mechanism linking NO to increased GLUT4 translocation is not known. NO has been suggested to modulate the GLUT4 translocation pathway, since it was found to be independent of an increase in blood flow in either rodents (257), or humans (95). Some reports also suggest that NO could be acting *via* the soluble guanylate cyclase/cyclic guanosine monophosphate/protein kinase G pathway, or by posttranslational modifications such as s-nitrosylation, which leads to nitrosylation of proteins in adipocytes (128) and tyrosine nitration, which activates PI3K, PKC, and AMPK (173). All of these pathways increase glucose uptake. The SNARE protein STX4 is s-nitrosylated in human islets and

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MIN6 (mouse insulinoma cell line) β-cells. In pancreatic islets, STX4 is nitrosylated at Cys141, impacting SNARE complex assembly; nitrosylation can be induced by exposure to damaging proinflammatory cytokines (342). However, it remains unknown whether STX4 can be nitrosylated in other tissue types, such as the skeletal muscle.

In addition to NO, the generation of peroxynitrite through the s-nitrosylation of proteins induces ROS, which stimulates GLUT4 translocation and glucose uptake in cardiomyocytes (106). Exercise-stimulated ROS in skeletal muscle is discussed in greater detail in the subsequent section.

Reactive oxygen species (ROS)—Exercise increases ROS in the skeletal muscle, yet until recently, this has only been demonstrated *via ex vivo* contraction-mimicking stimuli (i.e. hydrogen peroxide, a potent ROS producing reagent), which increases AMPK activation (366), as well as AKT phosphorylation, and glucose uptake (118). While these stimuli implicated ROS in the mechanism of exercise-stimulated glucose uptake, whether the source of ROS in skeletal muscle during exercise was mitochondrial or cytosolic, limited elucidation of the mechanism. In a very recent study (97), cytosolic ROS was identified as the predominant source. Using vivo fluorescent dyes and biosensors, ROS was shown to be generated during moderate-intensity exercise in both humans and mouse models (97). Moreover, cytosolic ROS production was shown to be dependent upon NADPH oxidase 2 (NOX2), with NOX2 loss-of-function models showing defective exercise-stimulated GLUT4 translocation and glucose uptake (97). Indeed, NOX2 activity was also recently shown to be essential for exercise-induced glucose uptake (98), and this newest evidence shows that this is linked to NOX2-dependent ROS production. Upstream of this, NOX2 is activated by the Rac1 GTPase, which can lead to the assembly of a NOX2 complex in other cell types (2, 148, 170). It has been suggested that Rac1 can regulate muscle glucose uptake through NOX2, based on shared phenotypes between Rac1 and Nox2 knockout mice (289). However, this data is correlative and we can only extrapolate that Rac1 is a vital upstream mediator of NOX2, impinging upon the downstream GLUT4 translocation pathway.

NO is also increased with passive stretching, and it was previously postulated that passive stretching increases glucose uptake *via* NOS activation (18). However, more recent work has demonstrated that glucose uptake stimulated by passive stretching is independent of NOS (138). Mechanical stress has also been shown to activate AMPK and ROS production, which stimulates glucose uptake into the skeletal muscle (42).

Therapeutic Development of Exercise Mimetics

Given the ability of exercise-stimulated glucose uptake to bypass insulin resistance, there is great interest in developing exercise mimetic therapies. However, progress has been limited by technical and conceptual challenges. From a technical perspective, there is a lack of *in vitro* models of contraction, and it is difficult to conduct live analysis in the contracting muscle of animal models.

From a conceptual perspective, it is unclear how GLUT4 is mobilized to the sarcolemma in response to exercise, and current models are probably overly simplistic. In addition, recent proteomic analyses have identified thousands of proteins that are changed with exercise

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(154, 157), with many of those likely to contribute to exercise-stimulated glucose uptake, suggesting that many key components of the mechanism remain to be discovered. With no defined mechanism for exercise-stimulated glucose uptake, it is challenging to leverage any one aspect of the contributing pathways and recapitulate the benefits of exercise for therapeutic purposes.

There have been multiple attempts to develop exercise mimetics, as outlined in Table 2. In 2007, it was reported that GW501516, a PPARδ receptor agonist, improves training performance in mice (211). This result was widely publicized by media outlets as "exercise-in-a-pill." However, this drug had previously been in clinical trials as a therapeutic for T2D (NCT00388180, NCT00841217) and cardiovascular disease (CVD, NCT00318617) and was abandoned by the manufacturer when two abstracts reported that this agonist causes cancer in rodents (rats and mice), even though these studies were never published in peer-reviewed journals at the time. Later, studies emerged demonstrating the tumor-promoting effects of GW501516 (239, 240, 333, 358).

Numerous different types of AMPK activators have been explored as potential exercise mimetics, given that AMPK elicits insulin-sensitizing effects and increases glucose uptake. Drugs that have been found to agonize AMPK include Compound 14 (11), Metformin (28), R419 (189, 196), and O304 (293), and AICAR. AICAR increases glucose uptake and fatty acid oxidation (198), enhances endurance *via* regulation of PPARδ-dependent genes and protects against obesity (211). AICAR is a direct activator of AMPK, as it is converted into an analog of adenosine monophosphate (AMP) that is required for stimulation of AMPK (262). AICAR primarily activates the AMPKα2 isoform (209), although it can also activate AMPKα1 but to a much lesser extent (126). AICAR has the capacity to elicit a multi-faceted array of signals that culminate in an "exercise phenotype," given that AMPK can impinge upon an array of signaling pathways, and that AMPK-defective mouse models have reduced exercise capacity, supporting this concept (221, 302). Indeed, AICAR is such a potent exercise mimetic that it, and all activators of AMPK, have been officially declared banned substances by the World Anti-doping Agency, due to its supposed performance-enhancing capabilities (http://www.wada-ama.org).

Although it has already been suggested that metformin works by activating AMPK to elicit its insulin-sensitizing capabilities in adipose, liver and skeletal muscle (75, 168, 299), a recent report suggests that metformin's mechanism of action is dependent on the dosage: pharmacological concentrations improve mitochondrial respiration, whereas supra-pharmacological concentrations of metformin inhibit mitochondrial activity (335).

Although multiple exercise mimetic targets and drugs/agonists have been studied, there are no confirmed candidates that can function as "exercise-in-a-pill." This is in part because many candidate exercise mimetic therapies are in the early stages of development, with promising studies in rodents or *in vitro* models, but they have not been tested in *in vivo* exercise studies *per se*. In addition, early clinical trial results have not always supported the conclusions from animal studies. For example, the SIRT1 agonist nicotinamide riboside (NR) improved insulin sensitivity and exercise capacity in rodents (35, 316). However, when tested as a supplement in obese human males, the drug did not improve exercise endurance,

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insulin sensitivity, or any of the other parameters tested (61). In addition, as mentioned for GW501516, many exercise mimetics have severe side effects that prevent progress in clinical trials. That being said, exercise in excess can also be harmful to the body, leading to conditions like rhabdomyolysis, which can cause severe muscle damage and kidney failure (315). As the technical and conceptual challenges are overcome, it is anticipated that more candidate exercise mimetics will enter the development pipeline for further evaluation.

Role for Mitochondria in Insulin Resistance

Mitochondria, the powerhouses of the cell, are dynamic organelles that cycle between fusion and fission states. Mitochondrial dynamics are central to mitochondrial function and integrity and are carefully regulated. When mitochondrial fission is too high there is an increase in mitophagy, and subsequently, apoptosis. Increased fission is associated with aging and aging-related diseases like sarcopenia (100), heart failure (46), and neurodegeneration (287). In contrast, when fusion outweighs fission, there is an increase in mtDNA and mitochondrial bioenergetics. Fusion is usually associated with improved mitochondrial function, and exercise increases mitochondrial elongation (14). However, excessive mitochondrial enlargement and elongation can be associated with starvation and cell stress, which can damage mitochondria and increase ROS production (83). These changes have been linked with muscle aging (161), though many counter-studies have found fission to be associated with sarcopenia and aging (Figure 4).

The skeletal muscle has a high mitochondrial density that is second only to the heart, as measured by mtDNA copy number in humans; mtDNA copy number positively correlates with mitochondrial mass and respiratory activity (60). The mitochondria play a vital role in skeletal muscle metabolism, energy supply, and apoptosis. As such, mitochondrial dysfunction in skeletal muscle is associated with a variety of diseases, like muscular dystrophies (322), aging (57, 172), sarcopenia (100), and insulin resistance (23, 200).

High-fat diet causes mitochondrial dysfunction, decreases mitochondrial number in human skeletal muscle (23, 200, 254), changes the mitochondrial structure, and reduces oxidative phosphorylation and mitochondrial respiration (15, 44). Another hallmark of high-fat diet-fed mice is increased mitochondrial fission and mitophagy (314). In addition, mitochondrial dynamics and structure play a large role in mitochondrial function and integrity. Changes in mitochondrial size and structure, mediated by changes in fission or fusion, are central to complications in obesity and diabetes (Figure 4). Indeed, a 40% high-fat diet-fed to mice for only 4weeks was reported to increase mitochondrial fission and vacuolization in oocytes (185). Similarly, increases in mitochondrial fission and dysfunction in palmitate-treated skeletal muscle cells (122), and muscle of obese mice (175) is observed.

Exercise appears to improve mitochondrial function. For example, exercise can induce mitochondrial elongation (14). Exercise-trained mice show improved mitochondrial function and have increased spontaneous physical activity levels compared to untrained controls (53). Also, mitochondrial dynamics are tailored to muscle fiber type, with oxidative fibers (Type I, IIA) having elongated and highly fused mitochondria relative to glycolytic (Type IIX, IIB) fiber types (201).

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Mitochondria are of special interest when considering exercise mimetics and insulin resistance therapeutics. Mitochondrial dysfunction can cause disease, and some view mitochondrial bioenergetics and remodeling as crucial elements of a successful exercise mimetic, due to the importance of mitochondria in the metabolic benefits of exercise. It has been proposed that an ideal exercise mimetic would mimic the benefits of fitness by inducing mitochondrial remodeling, increased oxidative phosphorylation, and fatty acid metabolism (68).

Concluding Remarks

Insulin action on skeletal muscle is pivotal in metabolic homeostasis, and insulin action in skeletal muscle is an important target in generating therapeutics that can combat metabolic disease. In this article, we have discussed the interplay among obesity, aging, exercise, and the skeletal muscle. We have described the importance of exercise as a therapeutic, not only for insulin resistance but also for a variety of skeletal muscle metabolic disorders, as well as general health. We have highlighted the therapeutic potential of exercise mimetics and the current limitations in producing these therapeutic agents.

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Didactic Synopsis

Major teaching points

- Type 2 diabetes is a worldwide epidemic characterized by peripheral insulin resistance and insulin insufficiency.
- Skeletal muscle plays a major role in metabolic disease, including insulin resistance, diabetes, obesity, aging, and sarcopenia.
- Skeletal muscle can function as an endocrine organ that releases myokines to facilitate tissue cross talk. Myokine release is increased with exercise, with some myokines having anti-inflammatory potential.
- Glucose uptake into the skeletal muscle can occur *via* multiple signaling pathways that lead to the translocation of the glucose transporter GLUT4; there are separate pathways for exercise-stimulated and insulin-stimulated glucose uptake.
- Exercise can reverse insulin resistance, and researchers are seeking exercise mimetic therapies that target the mechanisms underlying the benefits of exercise.
- The SNARE proteins regulate GLUT4 translocation and there is a growing understanding that the SNAREs, especially STX4, regulate metabolism and disease through glucose uptake.

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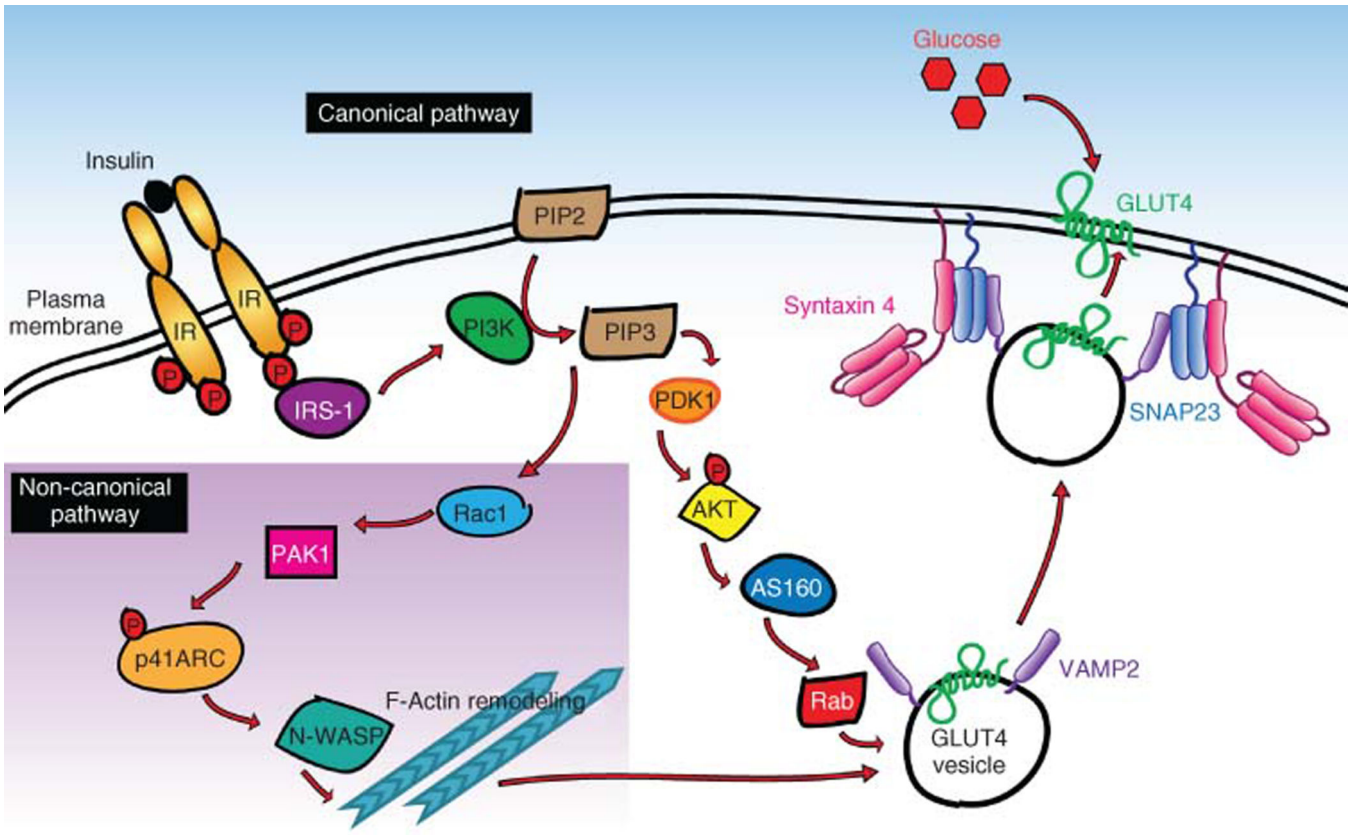

Figure 1.

A simplified model of insulin-stimulated translocation of the GLUT4 glucose transporter in skeletal muscle. Shown is the canonical insulin signaling pathway, and a noncanonical pathway (inset in purple). Both signaling pathways culminate with SNARE protein (Syntaxin 4, SNAP23, and VAMP2)-mediated vesicle trafficking and fusion with the plasma membrane. Vesicle fusion allows GLUT4 to integrate into the plasma membrane and transport glucose from the blood into the skeletal muscle.

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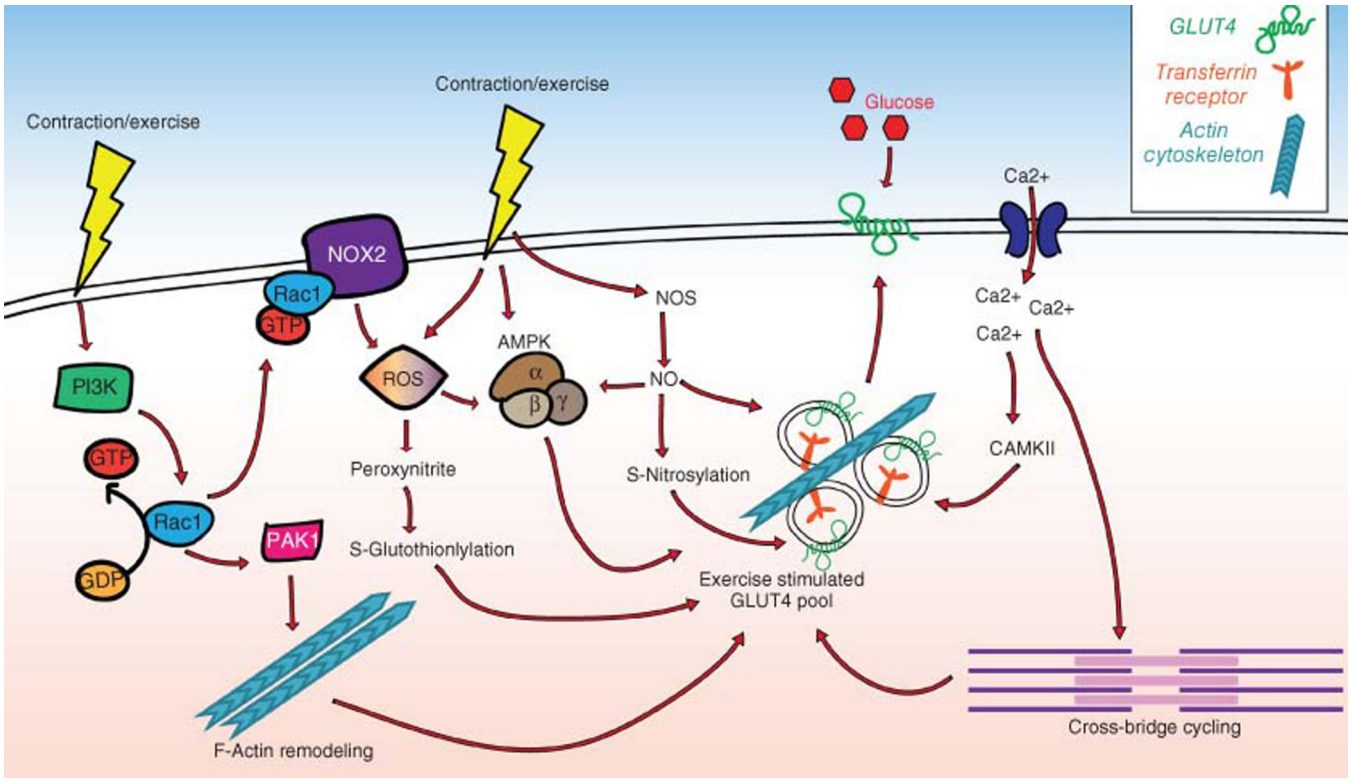

Figure 2.

Contraction-mediated GLUT4 translocation. When contraction occurs *via* exercise (depicted by yellow lightning bolts) multiple pathways are activated, which can all lead to GLUT4 translocation and glucose uptake. Left: contraction causes Rac1-GTP loading/activation, which induces PAK1 phosphorylation/activation, and F-actin remodeling to activate the exercise stimulated GLUT4 vesicle pool; it can also activate NOX2 which causes reactive oxygen species (ROS) formation. ROS can also be stimulated directly by contraction, leading to peroxynitrite and subsequent GLUT4 translocation, or can cause AMPK activation. Nitric oxide (NO) production can lead to S-nitrosylation of proteins that cause GLUT4 translocation. Muscle excitation can also cause calcium influx into the muscle cell (far right), which can activate CAMKII and lead to glucose uptake. Calcium influx can also stimulate cross-bridge cycling, the process of muscle fiber contraction, which leads to GLUT4 translocation and glucose uptake into the cell.

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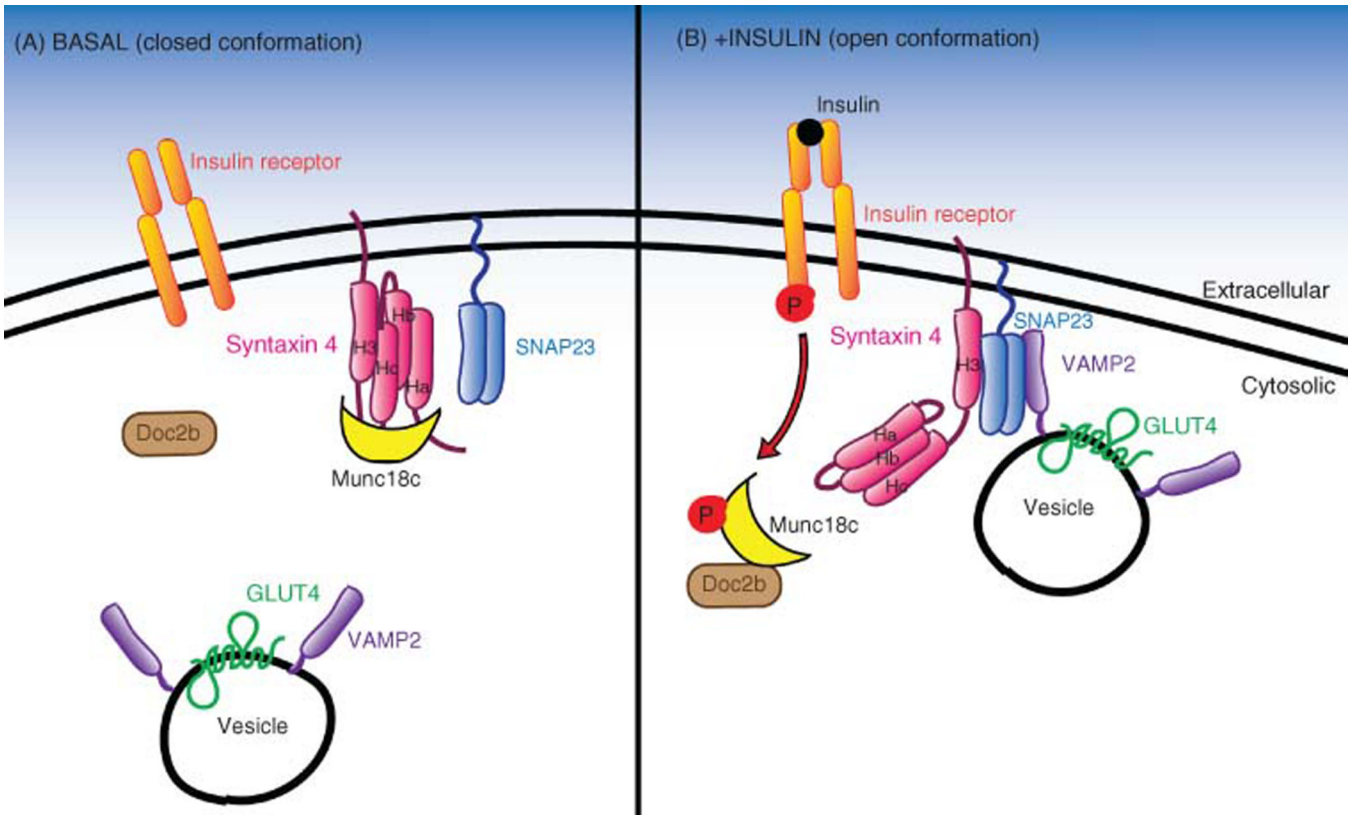

Figure 3.

SNARE complex formation under basal versus insulin-stimulated conditions. (A) Under basal conditions, Syntaxin 4 (STX4, pink) is in a closed conformation, which is maintained by the accessory protein Munc18c (yellow). (B) Upon insulin stimulation, the insulin receptor (IR) is phosphorylated, after which phospho-IR binds to and phosphorylates Munc18c. Phospho-Munc18c then lets go of STX4 and binds to DOC2B (brown), allowing STX4 to adopt its open conformation. In its open conformation. In its open conformation, the STX4 H3 domain is exposed, enabling STX4 to associate with SNAP23 and VAMP2 (purple) on the GLUT4 vesicle, leading to the formation of the SNARE complex, mediating vesicle docking and fusion to the plasma membrane.

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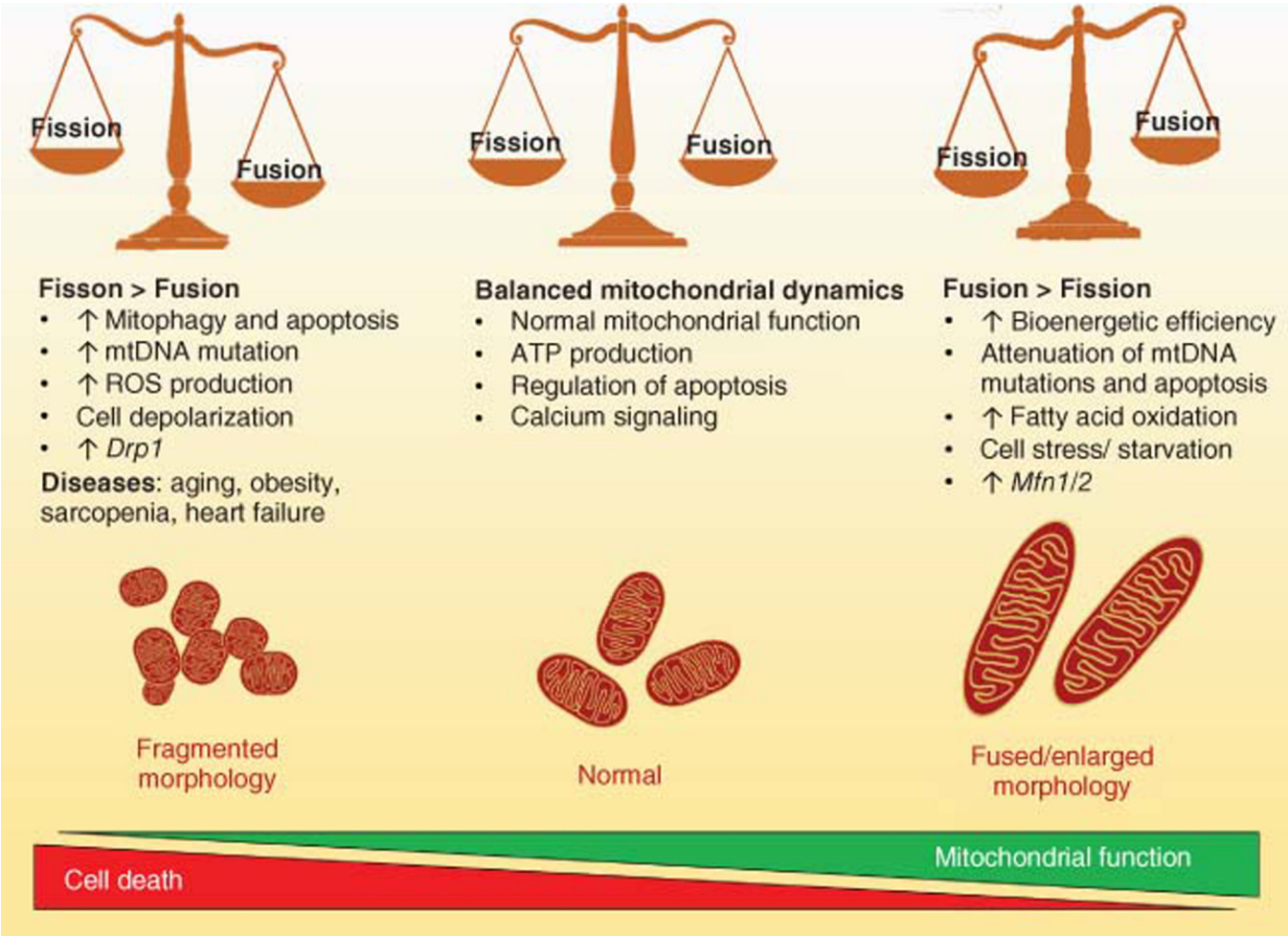

Figure 4.

The role of mitochondrial dynamics in maintaining skeletal muscle function and preventing disease. Center: mitochondrial fission and fusion are balanced and under these conditions, there is normal mitochondrial function, ATP production, and cell death. Left: fission outweighs fusion, so mitochondria become fragmented, there is an increase in mitophagy and cell death, a reduction in mitochondrial function, and increased ROS production. This contributes to diseases including aging, obesity, and insulin resistance. Right: mitochondrial fusion outweighs fission, leading to increased mitochondrial function, reduced cell death, elongated mitochondria, and increased fatty acid oxidation. However, this can also cause cell stress and starvation due to the high demands of the large mitochondria.

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Table 1

Effects of Exercise and Obesity on Myokines, Adipokines, and Adipo-Myokines (Secreted by Both Muscle and Adipocytes)

	Secreted factors	Effect of obesity	Effect of exercise
Myokines	BDNF	↔ (270)	↑ (73, 191, 255)
	IL-7	? (182, 192)	↑ (90)
	IL-15	? (155, 295)	↑ (26, 213, 253, 353, 357)
	Irisin	↑ (248)	↑ (26)
	Myonectin	↓ (278, 280)	? (171, 279)[a]
Adipo-myokines	ANGPTL4	↑ (17)[b]	↑ (40, 139)
	FGF21	↑ (364)	? (82, 355)[c]
	Fstl1	↓ (105)	↑ (86, 214)
	IL-6	↑ (20, 37, 329)	↑ (137, 228)
	IL-8	↑ (259, 267)	↑ (225, 326, 357)
	MCP-1	↑ (275)	↑ (40, 54, 326)
	Myostatin	↑ (101)	↓ (159, 181, 190, 258, 260, 274)
	PAI-1	↑ (1)	↑ (214)
	PEDF	↑ (116, 261)	↑ (214)
	VEGF	↑ (178)	↑ (102)
Adipokines	Adiponectin	↓ (107, 177)	? (84, 123, 277)
	Leptin	↑ (56)	↓ (131)
	Resistin[d]	↑ (294)	↓ (129)

↑, Enhanced in serum or muscle mRNA after exercise or in obesity; ↓, decreased in serum or muscle mRNA after exercise or in obesity; ?, contradicting evidence—some report enhancement and others report a decrease or no change; ↔, no change

[a] Different results reported for mouse versus human.

[b] E40K variant protective against dyslipidemia.

[c] Sex differences reported.

[d] Released by adipocytes in rodents but not humans.

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Table 2

Candidate Exercise Mimetic Targets and Drugs

Target	Function	Drug	Drug function	Drug effect	Natural/synthetic	References
AMPK	Master metabolic sensor-induces mitochondrial biogenesis and fatty acid oxidation	AICAR	Directly activates AMPK	Increased glucose uptake and fatty acid oxidation, enhanced endurance, protection against obesity	Synthetic	(211)
		Compound 14 (Cpd14)[a]	Increases ZMP via ATIC inhibition, a metabolite that activates AMPK	Reduced weight gain, improved glucose tolerance	Synthetic	(11)
		Metformin[a]	Mildly inhibits mitochondrial complex 1 and activates AMPK	Increased glucose tolerance via reduced hepatic production, increased glucose uptake	Synthetic	(28)
		R419	Activates AMPK by inhibiting mitochondrial complex 1; decreases MAPK signaling in neurons	Improved insulin sensitivity, insulin-stimulated glucose uptake, mitochondrial function, and exercise capacity; in neurons can inhibit pain	Synthetic	(189, 196)
		O304	Suppresses dephosphorylation of pAMPK	Increased glucose uptake in skeletal muscle; reduced β-cell stress, plasma glucose, and blood pressure; exercise mimetic effects in rodent hearts	Synthetic	(293)
SIRT1	Mediates gene activity in response to nutrient availability, enhances fat oxidation	Resveratrol	Indirectly activates SIRT1 *via* AMPK activation	Increased PGC1α in skeletal muscle, mitochondrial biogenesis, fatty acid transport, and oxidative metabolism; protection against obesity	Natural—found in red grapes	(34, 36, 156)
SIRT1	Mediates gene activity in response to nutrient availability, enhances fat oxidation	Resveratrol	Indirectly activates SIRT1 *via* AMPK activation	Increased PGC1α in skeletal muscle, mitochondrial biogenesis, fatty acid transport, and oxidative metabolism; protection against obesity	Natural—found in red grapes	(34, 36, 156)
		NR (nicotinamide riboside)	NAD+ precursor that activates SIRT1	Increased oxidative metabolism; improved insulin sensitivity, exercise performance, and glucose tolerance; reduced weight gain	Natural—found in milk, form of vitamin B3	(35, 61, 62, 316)
		MRL-45696	Inhibits PARP1 (NAD+ consuming enzyme)	Blunted weight gain, reduced fat accumulation, higher energy expenditure, enhanced mitochondrial function, longer running, and higher VO_2 max	Derived from niraparib (ovarian cancer treatment)	(235)
REV-ERBα	Nuclear receptor important in metabolism, exercise, and circadian rhythm	SR9009/SR9011	REV-ERBα ligands that inhibit REV-ERB target gene expression	Improved endurance and stamina, increased mitochondrial abundance and function in skeletal muscle	Synthetic	(286, 345)
PPARδ	Regulates fatty acid metabolism	GW501516	PPARδ ligand	Increased fatty acid oxidation and energy expenditure; works synergistically with AICAR to improve oxidative metabolism; poor pharmacokinetics, causes tumors	Synthetic	(211)
ERRγ	Regulates mitochondria	GSK4716[a]	ERRγ ligand	Improved mitochondrial biogenesis and fatty acid oxidation	Synthetic	(63, 212, 249)

[a]Elicits the same effects as exercise training but not yet tested in exercise models.