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Review

Effects of Acute Muscle Contraction on the Key Molecules in Insulin and Akt Signaling in Skeletal Muscle in Health and in Insulin Resistant States

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Abstract: Insulin signaling plays a key role in glucose uptake, glycogen synthesis, and protein and lipid synthesis. In insulin-resistant states like obesity and type 2 diabetes mellitus, these processes are dysregulated. Regular physical exercise is a potential therapeutic strategy against insulin resistance, as an acute bout of exercise increases glucose disposal during the activity and for hours into recovery. Chronic exercise increases the activation of proteins involved in insulin signaling and increases glucose transport, even in insulin resistant states. Here, we will focus on the effect of acute exercise on insulin signaling and protein kinase B (Akt) pathways. Activation of proximal proteins involved in insulin signaling (insulin receptor, insulin receptor substrate-1 (IRS-1), phosphoinoside-3 kinase (PI3K)) are unchanged in response to acute exercise/contraction, while activation of Akt and of its substrates, TBC1 domain family 1 (TBC1D1), and TBC domain family 4 (TBC1D4) increases in response to such exercise/contraction. A wide array of Akt substrates is also regulated by exercise. Additionally, AMP-activated protein kinase (AMPK) seems to be a main mediator of the benefits of exercise on skeletal muscle. Questions persist on how mTORC1 and AMPK, two opposing regulators, are both upregulated after an acute bout of exercise.

Keywords: insulin signaling; AKT; acute exercise; insulin resistance; glucose uptake

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1. Introduction

Skeletal muscle comprises 30–40% of a human body weight [1] and plays a crucial role in locomotion, and in metabolic and endocrine functions [1]. It is the most insulin-responsive tissue in the body and plays a major role in maintaining systemic glucose homeostasis [2,3]. In conditions like insulin resistance, obesity and type 2 diabetes mellitus (T2DM), insulin signaling is blunted in skeletal muscle, leading to a reduction in insulin-mediated glucose uptake, reduced glycogen synthesis, impaired protein synthesis and the accumulation of muscle lipid deposits and their associated derivative products that further deteriorate insulin sensitivity [4–6]. Exercise is a powerful therapeutic tool that can attenuate and even reverse skeletal muscle insulin resistance in various conditions of apparent health and disease [7,8].

Exercise training or "chronic" exercise is defined as repeated bouts of exercise during a short or long period of time, while "acute" exercise is defined as a single bout of exercise [9]. The effect of exercise training on insulin signaling has been extensively studied, as it increases insulin-mediated whole-body glucose disposal [10–12]. This improvement correlates with an increase in protein expression of glucose transporter type-4 (GLUT-4) [10–14], and an increase in the activation of insulin-signaling molecules such as insulin receptor substrate-1 (IRS-1), phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) [13,14]. An acute bout of exercise can also have therapeutic effects, as it reduces blood glucose levels [15], even when insulin action is impaired [16]. Here, we will examine how an acute bout of exercise/contraction can affect insulin signaling and Akt pathways. An

understanding of the acute effects of exercise on insulin and Akt signaling can improve our knowledge of the mechanisms of the beneficial effects of exercise in the management of insulin resistance and associated human chronic disease conditions.

2. Methods

Databases used to find information for this review include Pubmed and Google Scholar.

3. Insulin Signaling within Skeletal Muscle

3.1. Insulin Receptor and Insulin Receptor Substrates

A simplified schematic of insulin signaling and its links to diverse metabolic processes in skeletal muscle, including glucose transport, glycogen synthesis and protein synthesis is shown in Figure 1. Insulin receptor is a heterotetrametric glycoprotein consisting of two α and two β subunits. The subunits are linked by disulfide bonds in an α-β-β-α arrangement. The α subunit on the extracellular side of the membrane contains an insulin binding site. The β subunits are located on the intracellular side of the membrane to propagate the insulin signaling downstream [17]. Once insulin binds to the α subunit, it results in a conformational change in the insulin receptor, stimulating phosphorylation on the Tyr960 residue of the β subunit. This further activates the β subunit and its kinase activity, allowing for recruitment of receptor substrates.

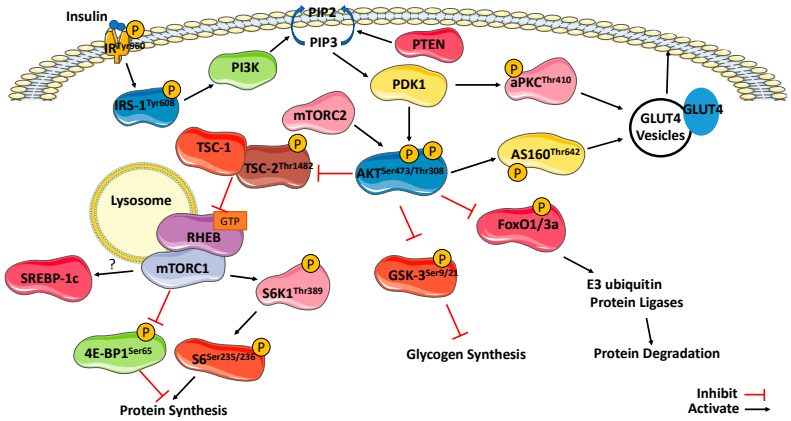

Figure 1. Simplified overview of insulin signaling in the skeletal muscle. Insulin binds to the insulin receptor, resulting in the phosphorylation of the insulin receptor, which then phosphorylates tyrosine residues of IRS-1. Then, IRS-1 interacts with PI3K, phosphorylating it. Subsequently, activated PI3K produces PIP3, which then leads to PDK1 activation. PDK1 phosphorylates Akt and aPKC. Akt phosphorylates AS160, which interacts with 14-3-3, thus inhibiting Rab-GTPase activity, allowing for Rab proteins to be GTP loaded (not shown). This results in the translocation of GLUT4 to the plasma membrane, and ultimately the uptake of glucose by the cell. Akt also phosphorylates TSC2, removing TSC2′s inhibition on Rheb. This results in the activation of mTORC1 which then phosphorylates S6K1 and 4E-BP1, thus increasing anabolic processes like protein synthesis. mTORC1 activation can also lead to increased fatty acid synthesis [18] for example by activating muscle SREBP-1c, and nucleic acid synthesis [19] (not shown). Akt also inhibits GSK-3 (Ser9/21) and FoxO1/3a (Thr32, Ser253 or Ser315 of FoxO3a and Thr24, Ser256 or Ser319 of FoxO1) in response to insulin by phosphorylating them. (*IR, insulin receptor; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PDK1, phosphoinositide-dependent kinase-1; TSC-1/2, tuberous sclerosis-1/2; Akt, protein kinase B; AS160, Akt substrate of 160 kDa; aPKC, atypical protein kinase C; GLUT4, glucose transporter 4; Rheb, Ras homolog enriched in brain; mTORC1/2, mechanistic/mammalian target of rapamycin complex 1/2; 4E-BP1, 4E-binding protein 1; S6K1, S6 Kinase 1; S6, Ribosomal protein S6. FoxO, Forkhead box O transcription factors; GSK-3, glycogen synthase kinase-3; SREBP-1c, sterol-regulatory element-binding protein-1c; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PTEN, phosphatase and tensin homolog*). Figure was generated using images assembled from Servier Medical Art (https://smart.servier.com).

Insulin receptor substrates (IRS)s are a family of proteins, from IRS-1 through to IRS-6, and are recruited to the insulin receptor through pleckstrin homology (PH) and phosphotyrosine binding (PTB) domains [20]. IRS-1 becomes activated when tyrosine sites are phosphorylated by the insulin receptor [21]. In skeletal muscle, IRS-1 is necessary for glucose uptake in L6 myoblasts [22], while IRS-2 is not required for glucose uptake and its role in skeletal muscle is not well understood [23]. IRS-3 is present in adipocytes, liver and lung in rodents, while IRS-3 is not present in humans [24]. IRS-4 mRNA is present in skeletal muscle, liver, heart, brain, and kidney [24]. IRS-5 and IRS-6 have limited tissue expression and are relatively poor insulin receptor substrates [25].

3.2. IRS-1/PI3K/Akt Pathway

IRS-1 propagates the insulin signal downstream through PI3K to the Akt and the extracellular signal-regulated kinase (ERK) pathways [26]. We will focus on the PI3K/Akt signaling pathway as it regulates a network of proteins involved in stress, mitochondrial biogenesis, protein synthesis, glycogen synthesis and fatty acid metabolism in response to exercise. PI3K is a heterodimer consisting of a regulatory and a catalytic domain [27]. The regulatory domain binds to the tyrosine phosphorylated IRS-1 through two src homology 2 (SH2) domains. This activates the catalytic domain, which then phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate a lipid second messenger, phosphatidylinositol (3,4,5)-triphosphate (PIP_3). Phosphate and tensin homolog deleted on chromosome 10 (PTEN) is a phosphatase that opposes PI3K. It converts PIP3 into PIP2 to prevent further insulin signaling. The loss and mutation of PTEN leads to hyperactive PI3K signaling, emphasizing the importance of PTEN in regulating insulin signaling [28]. Once PIP_3 is formed, it activates 3-phosphoinositide-dependent protein kinase 1 (PDK1) by interacting with the PH domain of PDK1. Activated PDK1 then phosphorylates Akt at Thr308 [29]. However, for full activation, Akt also needs to be phosphorylated on Ser473, which is catalyzed by mammalian/mechanistic target of rapamycin complex 2 (mTORC2) [30]. Akt has three different isoforms [31]. Akt2 is the most predominant isoform in skeletal muscle, as Akt2 knockout mice are insulin resistant and develop T2DM while knockout of Akt1 or Akt3 does not develop T2DM [32].

In insulin signaling, atypical protein kinase C (aPKC) is critical in both the translocation and docking/fusion of GLUT4 to the plasma membrane [33], and aPKC is required for insulin-mediated glucose uptake in skeletal muscle [34]. It is activated by the allosteric binding of PIP3 and phosphorylation of Thr410 of aPKC by PDK1 [35–37].

3.3. Substrates of Akt

Akt plays an important role in glucose metabolism including glucose transport and glycogen synthesis [38]. Two major mediators of the effects of Akt in these processes are GLUT4 and glycogen synthase kinase-3 (GSK-3), respectively.

Akt is a crucial regulator in insulin-mediated translocation of GLUT4 from intracellular vesicles to the plasma membrane [39]. This is evident, as overexpression of a constitutively active Akt results in the translocation of GLUT4 to the plasma membrane [40] while inhibition of Akt blocks insulin-mediated translocation of GLUT4 [41–43]. There is a link between Akt and GLUT4 translocation through a substrate of Akt known as Akt substrate of 160 kDa (AS160). In response to insulin stimulation, Akt phosphorylates AS160, also called TBC1 domain family 4 (TBC1D4), and its homolog TBC1D1 [44–46] at Thr642 and Thr596, respectively. This enhances the binding of AS160/TBC1D1 to 14-3-3 and thus inhibits the Rab-GTPase activating protein activity toward Rab proteins. Rab proteins are necessary for membrane trafficking in insulin signaling [47]. Ultimately, this results in Rab being more GTP loaded than GDP loaded, allowing for the GLUT4 storage vesicles to translocate and fuse with the plasma membrane (Figure 2). Furthermore, the importance of AS160 is emphasized with a reduction in basal and insulin-mediated glucose uptake in skeletal muscle of AS160 deficient mice [48].

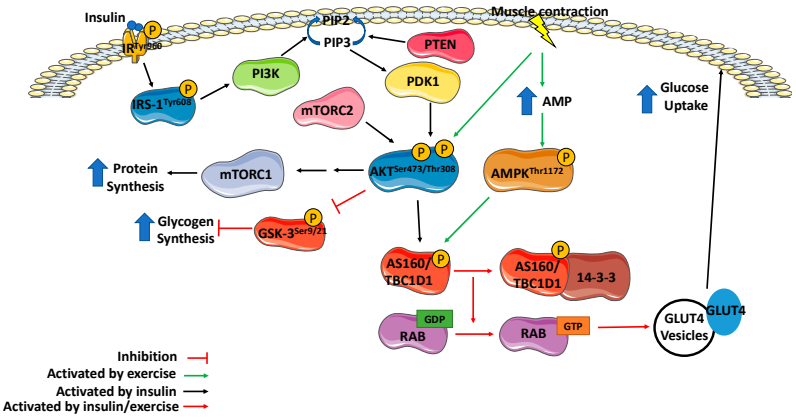

Figure 2. Effect of exercise on AS160/TBC1D1. Muscle contraction leads to an increase in AMP, leading to the activation of AMPK. Like AKT, AMPK then phosphorylates AS160 and TBC1D1, independent of insulin signaling. Once AS160 and TBC1D1 are phosphorylated, 14-3-3 binds to either of them, which inhibits Rab-GTPase activity allowing for RAB to be GTP loaded, resulting in the translocation of GLUT4 vesicles to the plasma membrane. (*IR, insulin receptor; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PDK1, phosphoinositide-dependent kinase-1; TSC-1/2, tuberous sclerosis-1/2; Akt, protein kinase B; AS160(TBC1D4), Akt substrate of 160 kDa; TBC1D1, TBC1 domain family member 1; GLUT4, glucose transporter 4; mTORC1/2, mechanistic/mammalian target of rapamycin complex 1/2; AMP, adenosine monophosphate; AMPK, adenosine monophosphate kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; Rab, Ras associating binding*). Figure was generated using images assembled from Servier Medical Art (https://smart.servier.com).

GSK-3 has two isoforms that Akt phosphorylates: Ser21 of GSK-3α and Ser9 of GSK-3β resulting in their inhibition and the activation of glycogen synthase, and glycogen accumulation [49]. Mice with mutation of Akt target phosphorylation sites Ser9 and Ser21 of GSK-3 exhibit impaired insulin-mediated glycogen synthesis, emphasizing the role of Akt in glycogen synthesis [50].

Another substrate of Akt is mTORC1, a complex that is regulated by exercise [51–53]. mTORC1 is important in the regulation of protein synthesis and other processes involved in growth, glucose, and lipid metabolism. Activated Akt phosphorylates Thr1462 of tuberous sclerosis complex 2 (TSC-2), resulting in the degradation of a complex formed between TSC-2 and TSC-1. The degradation of this complex allows for Ras homologue enriched in brain (Rheb) to become GTP loaded, as TSC-2 GTPase activity inhibits Rheb by keeping it GDP-loaded. GTP loading of Rheb allows for the activation of mTORC1. Activated Akt can also phosphorylate proline-rich Akt substrate 40 kDa (PRAS40), an inhibitor of mTORC1, thereby alleviating the inhibition on mTORC1 [54].

Other substrates of Akt in the skeletal muscle include Forkhead box O (FoxO) transcription factors, sterol-regulatory element-binding proteins (SREBPs) (Figure 1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). FoxOs increase the transcription of lipogenic and gluconeogenic genes. They reside in the cytoplasm and must enter the nucleus to regulate these genes. Akt phosphorylates Thr32, Ser253 or Ser315 of FoxO3a and Thr24, Ser256 or Ser319 of FoxO1 [55,56], which provides docking sites for 14-3-3 proteins, ultimately leading to the exclusion of FoxOs from the nucleus and blocking their transcriptional activity [56]. Insulin downregulates PGC-1α mRNA expression through the activity of Akt, and this is consistent with reduced FoxO1 phosphorylation. The authors suggest that insulin reduces the transactivation of PGC-1α by FoxO1 through Akt phosphorylation of FoxO1 [57]. Muscle PGC-1α mRNA expression is increased in mice with muscle specific FoxO1 overexpression [58]. However, a review by Ruegseggar et al. stresses the importance of insulin in mitochondrial function [59], complicating the relationship. Interestingly, in liver, Akt phosphorylates PGC-1α at Ser570 [60], but this has not been shown in skeletal muscle.

Akt is also implicated in lipid metabolism, as through mTORC1 it can activate SREBPs. There are three different isoforms of SREBP. SREBP-1c and SREBP-1a activate fatty acid synthase (FAS). SREBP-2 and SREBP-1a activate cholesterol-related genes, such as the gene for 3-hydroxy-3- methylglutaryl coenzyme A (HMG-CoA) reductase for cholesterol biosynthesis, and the gene for low-density lipoprotein-receptor (LDLR), which imports cholesterol from the blood [61]. Insulin upregulates SREBP-1c mRNA in skeletal muscle [62,63], which may be mediated by Akt signaling in skeletal muscle, as there is a consistent increase in Akt activation with SREBP-1c [64]. However, there is no FAS in skeletal muscle [65], which poses the question of SREBPs role in skeletal muscle.

3.4. mTORC1

As discussed above, Akt activates mTORC1. mTOR is a serine/threonine protein kinase that forms the catalytic subunit of two complexes, mTORC1 and mTORC2 [66]. mTORC1 has six components: mTOR, the catalytic subunit of the complex; regulatory-associated protein of mTOR (Raptor); mammalian lethal with Sec13 protein 8 (mLST8, also known as G protein beta subunit-like (GbL)); PRAS40; FK506 binding protein 12 (FKBP12) and DEP-domain-containing mTOR-interacting protein (Deptor) [67–69]. Raptor is a scaffolding protein that plays an important role in the regulation of mTORC1, as it interacts with upstream regulators like Rheb [70] and RagB [71] and substrates like ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) [72]. The function of mLST8 seems unclear, as its deletion does not affect mTORC1 activity. PRAS40, and FKBP12 are negative regulators of mTORC1. Deptor inhibits both mTORC1 and mTORC2 [67,73]. Activated mTOR phosphorylates PRAS40 and Deptor, reducing the physical interaction of these negative regulators with mTORC1 and further activating mTORC1 [67,74].

3.5. Substrates of mTORC1

Once mTORC1 is activated, it can promote protein synthesis, lipid metabolism, and inhibit autophagy. Since the increase in protein synthesis in skeletal muscle is a key benefit of both endurance [75] and resistance exercise [76], we will focus on substrates of mTORC1, ribosomal protein S6 kinase-1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 [4E-BP1] that are involved in regulating protein synthesis [77]. These two are also amongst the best characterized substrates of mTORC1.

mTORC1 phosphorylates the Thr389 site of S6K1. Once S6K1 is phosphorylated, it can activate key substrates involved in mRNA translation initiation like eukaryotic initiation factor (eIF)4B, a positive regulator of the 5′cap binding eIF4F complex [78]. S6K1 also phosphorylates programmed cell death 4 (PDCD4), which results in its degradation, relieving the inhibition on eIF4B [79]. The best characterized substrate of S6K1 is ribosomal protein S6 (rpS6). S6K1 phosphorylates rpS6 at its five serine residues, Ser235, Ser236, Ser240, Ser244 and Ser247, activating it. Activated rpS6 is an important ribosomal protein involved in the initiation of mRNA translation [80,81].

Another substrate of mTORC1 involved in regulating protein synthesis is 4E-BP1. This binding protein inhibits translation by binding and sequestering eIF4E to prevent assembly of the eIF4F complex. mTORC1 phosphorylates 4E-BP1 at Thr37, Thr46, Ser65 and Ser70, resulting in its dissociation from eIF4E, allowing for mRNA translation to occur [82].

4. Effect of Exercise on Insulin Signaling

Exercise is an important intervention for insulin resistant individuals, and it is important to assess if it does this by modulating specific components of insulin signaling. Chronic exercise leads to increases in resting skeletal muscle glucose uptake, and skeletal muscle GLUT4 protein expression [83–85], even in type 2 diabetic patients [86,87]. Similarly, an acute bout of exercise can ameliorate insulin resistance as seen by reduced blood glucose levels both during and after the event [15]. While the effects of chronic exercise on muscle insulin signaling have been much studied, comparatively less is known about the effects

of acute exercise/muscle contraction. We review available studies here (summarized in Table 1), but also include a summary of the effects of chronic exercise. In a cohort of type 2 diabetic individuals, acute exercise induces GLUT4 translocation from intracellular vesicles to the plasma membrane in skeletal muscle similar to nondiabetic subjects [68]. Exercise-mediated increase in glucose uptake can take place even when insulin action is impaired [16], and this can persist for 48 h post exercise [20]. Paradoxically, very intense exercise training (i.e., overtraining (152 min of high intensity training/week for 4 weeks) has recently been shown in healthy humans to initiate insulin resistance and a deterioration in blood glucose homeostasis, perhaps because of a reduction in intrinsic mitochondrial function [88].

Table 1. Summary of the effect of acute exercise on insulin signaling proteins.

Protein	Effect of Exercise	Reference
Insulin receptor phosphorylation	No change	[89–91]
IRS-1 tyrosine phosphorylation	No change	[90,92]
PI3K activity	No change	[92–95]
aPKC activity	No change	[96]
Akt S473 phosphorylation	No change	[97–102]
Akt S473 phosphorylation	Increased	[99,103–105]
AS160 phosphorylation	Increased	[101,106–108]
AS160 phosphorylation	No change	[101,109–111]
TBC1D1 phosphorylation	Increased	[46,112,113]
mTOR activation	Increased	[51–53,114–120]

4.1. Effect of Exercise on Insulin Receptor and Insulin Receptor Substrate

Chronic exercise has different effects on the insulin receptor and IRS-1 compared to an acute bout of exercise. Insulin receptor phosphorylation is increased by ~50% after 5 days of exercise, but not after 1 day in rat epitrochlearis [14]. Rats trained for 9 weeks on a treadmill show an increase in insulin receptor and IRS-1 (~60%) mRNA content [121] and a decrease in IRS-1 Ser636/639 phosphorylation (~50%) in the soleus muscle [122]. In rats receiving angiotensin II to induce insulin resistance, there was no effect of drug or exercise (6 weeks of wheel running) on the phosphorylated or total insulin receptor. Angiotensin II increased IRS-1 Ser307 phosphorylation, while exercise attenuated this [123].

In contrast to chronic exercise, an acute bout of exercise does not seem to have a beneficial impact on the insulin receptor or IRS-1. An acute bout of electrical stimulation of rat hindlimb muscles does not result in an increase in insulin receptor or IRS-1 tyrosine phosphorylation [92]. Mice 3 h post a single bout of treadmill exercise at 60–70% maximum oxygen consumption (VO_{2max}) display no change in phosphorylation of the insulin receptor in the soleus muscle. This is consistent with reduced blood glucose and insulin, suggesting that exercise-mediated changes in insulin sensitivity are independent of the insulin receptor [89]. Interestingly, 6 h post electrical stimulation of rat gastrocnemius, there is an increase in IRS-1 Ser632/635, Ser1100 and Ser612 phosphorylation, which would indicate a decrease in insulin signaling [124]. However, aged rats subjected to swimming show a decrease in IRS-1 Ser307 phosphorylation in the gastrocnemius compared to aged controls, but this does not correlate with a reduction in blood glucose or insulin levels [125]. High intensity interval exercise for 30 min does not affect IRS-1 Ser307 phosphorylation in human vastus lateralis [126]. This suggests differences in exercise and insulin signaling in humans versus rodents. Endurance exercise lasting 60 min at 65% of VO_{2max} does not increase insulin receptor phosphorylation, IRS-1 phosphorylation, or PI3K and IRS-1 association in skeletal muscle of obese or diabetic individuals [90]. In another study, an acute bout of endurance exercise for 60 min at 75% of VO_{2max} results in no change in insulin receptor phosphorylation in skeletal muscle [91]. Mice running on a treadmill for 30 min show a decrease in tyrosine phosphorylation and IRS-1 association with PI3K 24 h post exercise in skeletal muscle, which correlates with oxidative modification of IRS-1 [127]. An acute bout of exercise also has no effect on insulin receptor and IRS-1 gene expression in

human vastus lateralis [128]. Most of the studies reported above show that acute exercise does not increase insulin receptor or IRS-1 activation as one would expect, although a few show a decrease in insulin signaling, stressing the importance of further investigation. The available data do indicate that the beneficial effects of exercise on glucose metabolism are dependent on IRS-1. Unfortunately, studies on the effect of exercise on insulin resistant states have used chronic exercise models. Due to a lack of effect of acute exercise on IRS-1 phosphorylation in healthy individuals, one might predict a similar lack of effect in insulin resistant states. On the other hand, because insulin sensitivity is reduced in such states and therefore there is greater room for improvement, one might also hypothesize that acute exercise may elevate IRS-1 phosphorylation to induce insulin signaling.

4.2. Effect of Exercise on PI3K

Trained individuals exhibit greater PI3K activation (~50%) compared to sedentary individuals [129]. However, in another study, Frosig et al. demonstrate that 3 weeks of one-legged-knee-extensor exercise increases glucose uptake, but with a decreased association of IRS-1 with PI3K [130]. The effects of chronic exercise on PI3K seem to be inconsistent.

Inhibition of PI3K does not influence glucose transport in muscles that are contracted acutely by electrical stimulation in rats [131,132]. This is consistent with PI3K activity being unchanged after acute exercise/contraction in skeletal muscle [92–95]. Related to this, exercise has no effect on PTEN, a negative regulator of PI3K. In one study, endurance exercise has no effect on PTEN mRNA levels in vastus lateralis of humans [133]. In non-diabetic lean Zucker rats EDL muscle, PTEN protein levels are unchanged immediately after and 1 h post electrical stimulation. However, 3 h post electrical stimulation, PTEN protein levels are increased by ~25%. There is also a reduction (~20%) in PTEN Thr382/383 phosphorylation, which renders it functionally inactive, immediately after and 1 h post electrical stimulation, but not at 3 h post electrical stimulation [134]. Overall, there are few studies that assess the effect of acute exercise on PTEN expression or phosphorylation, as much of the focus is on PI3K. Nevertheless, available studies suggest that just like for IRS-1, the effects of acute exercise are mediated by the regulation of events downstream of PI3K.

In vitro studies demonstrate that aPKC activity increases in response to acute electrical stimulation of the muscle [135–138], but this has not been established in vivo. In one study [96], aPKC activity in human skeletal muscle did not increase in acutely exercised leg versus a rested leg. PIP3 supplementation increases aPKC activity, and acute exercise further increases this effect compared to the rested leg [96]. It is unlikely aPKC increases in response to acute exercise, as the activity of upstream regulator PI3K is not increased in response to an acute bout of exercise as described above.

4.3. Effect of Exercise on AKT

Muscle specific knockout of Akt in mice results in reduced insulin sensitivity, and induces muscle atrophy [38]. On the other hand, constitutively active Akt induces muscle hypertrophy [139] and increases basal glucose uptake [140]. This highlights the significance of studying proteins involved in the Akt signaling network to the discovery of interventions to manage disease states like insulin resistance, T2DM and sarcopenia. Below, we will outline how exercise affects Akt and its substrates.

During chronic exercise Akt phosphorylation is unchanged [122,130], but total Akt is increased [130,141], consistent with findings in db/db mice, where the ratio of phosphorylated Akt (Ser473) to total Akt is unchanged in response to 8 weeks of moderate treadmill exercise [142]. However, another study showed that 15 weeks of intense treadmill exercise attenuates the reduction of Akt Ser473 phosphorylation in db/db mice [143]. Contrary to what one might expect, these studies suggest that chronic exercise has minimal effect on muscle Akt phosphorylation, but might increase the abundance of the protein, which is in line with the effect of an acute bout of exercise on Akt as discussed below.

Some studies demonstrate an increase in skeletal muscle Akt phosphorylation on its two phosphorylated residues during acute exercise/contractions [99,102,103], while others

show no change [97,98,100]. There is no change in Akt Ser473 phosphorylation or Akt activity in response to acute exercise in isolated rat soleus (slow-twitch) muscles [97,98]. Brozinick and Birnbaum did not see an effect of acute exercise on Akt phosphorylation in the fast twitch epitrochlearis muscle of rats either, but this was because muscles were harvested 20 min post-acute exercise [98], at a time point when Akt activity had returned to baseline [99]. The timing in which the muscle is assessed post-acute exercise could be the reason for the conflicting reports on the effect of an acute bout of exercise on Akt signaling. Widegren et al. also demonstrated no change in Akt kinase activity, and this could be because muscles were incubated with or without insulin for 40 min post-acute exercise, at which time the transient increase in Akt Ser473/Thr308 phosphorylation would have been diminished in rats [99] and humans [100]. Sakamoto et al. show an increase in Akt activity in human skeletal muscle. In their study; biopsies were obtained 10–15 s after cessation of an acute bout exercise [103].

The intensity of exercise also plays a role in Akt activation, as the greater the intensity of the exercise, the higher the increase in Akt activity [102,103]. Other studies in rodents involving acute electrical stimulation of the muscle with 2–5 V of stimulation, 120 min of swimming, or 60 min of running at a speed of 22 m/min and incline of 10% show an acute increase in the phosphorylation of Akt Ser473 [99,104,105]. There is also a discrepancy in Akt phosphorylation as a function of the type of exercise as acute endurance exercise (cycling at 70% of VO_{2max} for 60 min) increases Akt Ser473 phosphorylation. However, acute resistance exercise does not increase Akt Ser473 phosphorylation in normal individuals (8 sets of 5 repetitions of maximal isokinetic leg extension, with 3-min rest periods between sets) [101], but does so in type 2 diabetic rats [144]. In other studies, acute electrical stimulation causes a quick transient increase in phosphorylation of Akt Thr308 and Ser473 in the TA and EDL of rats (~13 fold) [99] while acute treadmill exercise results in a delayed prolonged increase in Akt activity in the gastrocnemius of rats (~50%) [102]. Both muscle fibers in in vitro and in situ experiments display an increase in Akt phosphorylation, which suggests that local intrinsic factors in the muscle play a role in activating Akt, not neural or systemic factors [99,102]. The lack of effect of contraction/exercise on PI3K activation and these in vitro studies support the notion that exercise-mediated increases in Akt activation are not from increases in insulin signaling, but through other mechanisms. This is consistent with the fact that Akt can be activated by additional pathways, including stress and survival signaling pathways [49], which could be upregulated during exercise. Nevertheless, how Akt is activated during exercise without PI3K activation is an area that requires further investigation. Unfortunately, studies focus on the effect of chronic exercise on insulin signaling when comparing healthy and insulin resistant states, and not acute exercise. One would expect greater activation of Akt with more intense acute exercise in insulin resistant states, as in healthy individuals, more intense exercise induced Akt activation [102,103]. In diabetic mice, more intense chronic exercise increases Akt phosphorylation [143] while moderate exercise does not [142].

4.4. Effect of Exercise on Akt substrates

GLUT4 is necessary for insulin-stimulated glucose uptake, and in insulin resistance there is a reduced level of GLUT4 translocation to the membrane [145–147]. Additionally, its overexpression attenuates the reduction in insulin sensitivity in high fat diet fed mice [148]. The review by Richter and Hargreaves outlines that, in addition to its stimulation by insulin, GLUT4 expression and translocation is upregulated in response to chronic exercise [84]. Acute exercise too can induce its translocation independent of Akt [98]. Mice with GLUT4 muscle-specific knockout exhibit a suppression of glucose uptake in the EDL (~75%) after muscles are acutely electrically-stimulated [149]. Interestingly, there are separate GLUT4 vesicle pools that respond to either insulin or exercise/contraction [150,151]. Consistent with this, stimulation with insulin and acute electrical stimulation of the muscle result in additive translocation of GLUT4 to the plasma membrane of rat soleus muscle [152].

AS160 total protein levels are unchanged, but Akt phosphorylated sites of AS160 are increased in trained individuals compared to sedentary, with no change in Akt Ser473 phosphorylation [130,153]. Similarly, five minutes of contractile activity of isolated rat epitrochlearis muscle increases phosphorylation of AS160 (3.5 fold increase) [107]. There is also an increase in AS160 phosphorylation and glucose uptake in female rat epitrochlearis muscle 3 h post exercise [108]. Similar changes are seen in vastus lateralis muscle following moderate intensity cycling for 60 or 90 min at 70% VO_2 [101,106]. However, acute sprint cycling [111] and acute resistance exercise [101,109,110] do not increase the phosphorylation of AS160 in muscles of humans, but there is a trend towards an increase in AMPK phosphorylation (~21%), and an increase in the phosphorylation of AMPK substrate acetyl-CoA carboxylase (ACC) (~60%) [110].

Once phosphorylated, AS160 interacts with 14-3-3 for GLUT4 to translocate from vesicles to the plasma membrane. An acute bout of endurance [106], but not resistance exercise [110], enhances the affinity of AS160 for 14-3-3 in the vastus lateralis of humans. Another study supports this as AS160 phosphorylation in the vastus lateralis of humans increases in response to an acute bout of endurance exercise but not resistance exercise [101]. Although the phosphorylation of AS160 does not increase immediately after acute resistance exercise, Dreyer et al. show an increase (~2-fold) in the phosphorylation of AS160 1 h post and a trend for significance (~1.8-fold, $p < 0.07$) 2 h post an acute bout of resistance exercise in the vastus lateralis of humans [109]. The importance of AS160 in exercise-stimulated glucose uptake is emphasized with a recent study that shows that AS160 knockout rats exhibit reduced skeletal muscle glucose uptake in response to swimming exercise compared to control rats. This effect was partially restored with the expression of a phosphomimetic amino acid and fully restored with the expression of a wild-type AS160 [154]. In an insulin resistant state (angiotensin II administration), AS160 Thr642 phosphorylation is reduced, but exercise (6 week wheel running program) attenuates this reduction [123]. No study has looked at the acute effect of exercise on AS160 phosphorylation in an insulin resistant state.

The effect of exercise on phosphorylation of AS160 may be mediated by other factors. For example, exercise increases AMP levels [155], leading to the activation of the cellular energy sensor, AMP-activated protein kinase (AMPK) [156]. Once activated, AMPK can phosphorylate Akt targets TBC1D1 and AS160 [157] (Figure 2). AMPK muscle specific knockout attenuates the increase in TBC1D1 Ser231 phosphorylation that is seen during and after exercise, emphasizing the role of AMPK in phosphorylating TBC1D1 during and after exercise. In response to chronic exercise, there is an increase in AMPK phosphorylation [158–160]. This is also seen in response to moderate chronic exercise in db/db mice [142] and after an acute bout of exercise, which is consistent with increases in glucose uptake that we will discuss below.

However, there is some evidence to suggest that AS160 is not necessary for exercise-stimulated glucose uptake. Wortmannin treatment eliminates exercise-stimulated increases in AS160 phosphorylation, but without changing glucose uptake in rat epitrochlearis [112]. Furthermore, 3–4 h post-acute exercise, rat epitrochlearis muscle AS160 phosphorylation remains elevated, but exercise-mediated glucose transport does not [161]. Acute resistance exercise increases glucose uptake, but not AS160 phosphorylation immediately after exercise in human vastus lateralis muscle [109]. An AMPK inhibitor, Compound C, reduces exercise-mediated glucose transport without reducing AS160 phosphorylation in rat epitrochlearis [112]. These data demonstrate that, unlike for insulin signaling, AS160 phosphorylation might not be required for exercise-induced increase in muscle glucose transport.

TBC1D1 may be more important in exercise-stimulated glucose transport than AS160. TBC1D1 phosphorylation increases in the TA of mice with in situ contraction [46], and with acute electrical stimulation of rat epitrochlearis muscle [112]. Unlike for AS160, wortmannin does not reduce exercise-mediated TBC1D1 phosphorylation or glucose transport, and the loss in TBC1D1 phosphorylation after 3–4 h correlates with the loss in glucose transport [112]. Additionally, regulation of TBC1D1 by AMPK is more pronounced as

the AMPK inhibitor, Compound C, suppresses exercise-mediated glucose transport and TBC1D1 phosphorylation [112].

Two different phosphorylation sites in TBC1D1 that are responsive to exercise have been identified (Ser237; Thr596) [162,163]. In running mice, knockout of two AMPK subunits, β_1 and β_2, decreases TBC1D1 Thr596 phosphorylation (~33%) and exercise-mediated glucose uptake in the soleus (~33%) and EDL (~43%) [164]. Two studies in particular further support this. Both studies mutated TBC1D1 phosphorylation sites of AMPK. In one study, four AMPK target phosphorylation sites on TBC1D1, Ser231, Thr499, Ser660 and Ser700 in mice were mutated [165], while in the other study, Thr569, an Akt site, and three AMPK sites, Ser231, Thr499, and Ser621, were mutated [45]. Both studies show a reduction in exercise-mediated glucose uptake, suggesting that the phosphorylation of these sites on TBC1D1 is necessary for glucose uptake during exercise. Finally, Funai et al. show that insulin treatment shows a correlation between AS160 Thr642 phosphorylation and insulin-mediated glucose uptake. However, TBC1D1 phosphorylation does not correlate with glucose uptake in response to insulin treatment. Instead, TBC1D1 phosphorylation correlates with an insulin-independent mechanism of glucose uptake in response to exercise in rats [113].

It is important to note that that although TBC1D1 phosphorylation is necessary for exercise-mediated glucose uptake as discussed above [45], the AMPK-TBC1D1 axis is not the only contributor to exercise-mediated glucose uptake. Nitric oxide, produced from the action of nitric oxide synthase (NOS), may also play a role. Nitric oxide is increased in response to exercise [166] and electrical stimulation [167] in rodent skeletal muscle. Pharmacological inhibition of NOS inhibits exercise-mediated glucose transport in human [168,169] and rodent [167,170] skeletal muscles. However, other studies show that NOS inhibitors do not affect exercise-mediated glucose transport [171,172]. The discrepancy in the literature could be due to the intensity of the exercise, as studies suggest that glucose uptake at rest and low-moderate intensity are not nitric oxide mediated [171,173], while it is for high intensity exercise [168,169].

Another mechanism involved in exercise-stimulated glucose transport is the effect of reactive oxygen species (ROS). Electrical stimulation in isolated skeletal muscle [174–176] and high intensity exercise [177–179] increase ROS levels. This increase may be mediated by NADPH oxidase 2 (NOX2). During an acute bout of exercise of moderate intensity, ROS production from NOX2 stimulates glucose uptake by promoting GLUT4 translocation to the plasma membrane in mice quadricep, soleus and TA, as depletion of NOX2 attenuates this effect. AMPK-TBC1D1 signaling pathway does not appear to mediate the effect of NOX2 [180]. These findings suggest that no single signal transduction pathway fully accounts for exercise-mediated increase in glucose uptake. While this complicates an understanding of mechanisms of effect of exercise on glucose transport, the existence of these multiple options of regulation likely confers some robustness on the regulation of glucose transport to ensure that this important function can be targeted from different angles.

4.5. Additional Substates of Akt

T2DM is characterized by reduced glycogen synthesis, and reduced glycogen synthase activity [181,182]. Exercise can increase glycogen synthesis by inhibiting GSK-3, an inhibitor of glycogen synthesis. Sufficient glycogen stores is necessary to control glucose homeostasis and prevents excess glucose to be used in de novo lipogenesis [183].

In exercise training, phosphorylated GSK-3α is reduced after endurance exercise in rat skeletal muscle, consistent with increased glycogen content [184], but a study by Frosig et al. show no change in GSK-3α/β total levels or phosphorylation in human skeletal muscle post resistance exercise [130]. The mechanisms of exercise and insulin differ in the regulation of GSK-3. Markuns et al. compared the effect of insulin versus acute exercise on GSK-3α and Akt [185]. Rats running 25 m/min at 10% grade exhibit a decrease in GSK-3α activity 10 min after exercise and for up till 60 min post-acute exercise in the gastrocnemius (~40–60%). Animals injected with insulin show decreases in GSK-3α activity after 5 min

(~40–60%). During insulin signaling, Akt is activated, which then phosphorylates GSK-3 to inhibit its activity. Here, they demonstrate that Akt phosphorylation is consistent with decreases in GSK-3 activity during insulin treatment, but not during acute exercise, suggesting that GSK-3 is regulated differently in exercise than in insulin signaling [185]. However, another study in humans showed that exercise increases phosphorylation of Ser21 of GSK-3α in the vastus lateralis. This is consistent with increases in glycogen synthase activity and Akt phosphorylation in response to acute exercise [103].

One explanation of why Ser21 phosphorylation in GSK-3α, a phosphorylation site of Akt, is not consistently observed in response to acute exercise could be because of the role of glycogen. Markuns et al. hypothesize that glycogen acts as an allosteric activator of GSK-3, and during acute exercise when glycogen is depleted, GSK-3 cannot be phosphorylated, a condition that would favor glycogen synthesis [185]. However, Lai et al. demonstrated that varying concentrations of glycogen do not alter GSK-3β phosphorylation in soleus muscles, but higher glycogen content does result in lower glycogen synthesis in an exercised and insulin-mediated condition in rat soleus muscles [186]. In another study, they demonstrated that after acute electrical stimulation of the muscle, greater glycogen content correlates with greater GSK-3β Ser9 phosphorylation, but no change in Akt phosphorylation [187]. Greater GSK-3 phosphorylation is consistent with increased glycogen synthase activity during and post 3.5 h an acute bout of an exercise, suggesting that glycogen synthesis is increased [188]. This demonstrates that the regulation of GSK-3 by exercise is independent of Akt unlike in insulin signaling.

PGC-1α is another substrate of Akt in skeletal muscle. PGC-1α is a key mediator in exercise-mediated changes in mitochondrial capacity [189]. Its overexpression protects against muscle atrophy [190,191] and regulates skeletal muscle hypertrophy in response to resistance exercise training [192].

Chronic exercise increases PGC-1α protein levels [193–195]. In db/db mice, PGC-1α protein levels are reduced compared to healthy controls. An 8 week exercise program attenuates this effect of T2DM [142]. Likewise, an acute bout of exercise increases PGC-1α mRNA content in rodent [196–198] and human [199] skeletal muscles. The increase in PGC-1α mRNA content is greater with more intense exercise [200–202]. These changes in mRNA content come hours after exercise [196–198], so it is unlikely that these changes in response to acute exercise are due to Akt signaling as the activation of Akt peaks 5 min post exercise, and persists for only ~10–15 min as described above [99]. Instead, the increase in PGC-1α mRNA content seems to be through an AMPK dependent mechanism, as AMPK phosphorylation persists for longer [198], and directly phosphorylates PGC-1α to activate it [203]. Studies also show that increased AMPK activation improves PGC-1α expression [198,204]. AMPK phosphorylation on PGC-1α makes it more susceptible to deacetylation by Sirtuin (Silent mating type information regulation 2 homolog) 1 (SIRT1) [205]. SIRT1 is also activated in response to exercise [206]. SIRT1 plays an important role in the deacetylation of PGC-1α. Deacetylation of PGC-1α results in enhanced mitochondrial activity, which in turn improves exercise performance [207]. AMPK is necessary for SIRT1 to deacetylate PGC-1α. During exercise PGC-1α acetylation is decreased, and this effect is attenuated when AMPK is knocked down in skeletal muscle of mice [208]. On the other hand, SIRT1 is required for AMPK activation and the benefits of resveratrol on mitochondrial function [209] suggesting that SIRT1 and AMPK are both necessary to carry out their respective roles.

Akt also phosphorylates FoxO1 Ser256 and FoxO3a Ser253 to inhibit their activity. In chronic endurance exercise, FoxO1/3a mRNA content is unchanged [210], however, in another study, FoxO1 mRNA content is unchanged in the soleus, but is reduced in the vastus lateralis (~50%) [211]. Eight hours post-acute resistance exercise, FoxO3 mRNA expression in human skeletal muscle is reduced 3-fold, but no changes in response to acute endurance exercise [212]. This heterogeneity in response of muscle FOXO mRNA to exercise is also seen in the phosphorylation of the proteins. For example, in acute exercise, FoxO1 Ser256 phosphorylation increases 5 h after acute exercise in human vastus lateralis (~30%) [213], but in another human study its phosphorylation increases (~40%) only at

40 min post-acute exercise, but not at 5 h post-acute exercise in human vastus lateralis [214]. Ultimately, the effect of an acute bout of exercise on FoxO1 or FoxO3a phosphorylation in skeletal muscle requires further investigation.

SREBP-1c mRNA content is unchanged, and protein levels are decreased in response to 90 min of cycling at moderate intensity in human skeletal muscle [64]. There have been studies showing how chronic exercise (exercise training) increases SREBP-1c mRNA and protein levels [215,216], but little work has been done in regards to the effect of an acute bout of exercise. However, it is likely that exercise reduces the expression of STREBP genes, as lipogenesis is reduced after an acute bout of exercise in the liver [217] and adipose tissue [218].

4.6. Effect of Exercise on mTORC1 and Its Substrates

Muscle specific mTOR knockout mice exhibit myopathy and premature death [219]. Skeletal muscle specific ablation of raptor, a key component of mTORC1, leads to skeletal muscle becoming dystrophic and impaired in their oxidative capacity [220]. mTORC1 is also implicated in exercise-mediated effects on muscle mass and metabolism. It is a key regulator in controlling skeletal muscle mass in response to contraction, mechanical load-mediated hypertrophy, synergistic ablation, and amino acids [221]. Resistance exercise-(single bout and training) mediated increases in protein synthesis and ribosome biogenesis are attenuated with mTORC1 inhibition [222].

During chronic exercise, mTOR Ser2448 phosphorylation is reduced (~35%) [122,158]. However, Edgett et al. showed that chronic electrical stimulation increases mTOR protein levels (~1.5 fold), but no change in mTOR Ser2448 phosphorylation in rat skeletal muscle [114]. Stuart et al. demonstrated an increase [50%] in mTOR Ser2448 phosphorylation in human quadriceps after six weeks of stationary cycling [223]. This discrepancy is also seen after an acute bout of exercise. Some studies found no change in mTOR Ser2448 phosphorylation in response to acute endurance exercise in skeletal muscle of mice [224] and rats [225] or in response to low-frequency acute electrical stimulation of rat [52]. However, mTOR Ser2448 phosphorylation increases post-acute endurance exercise in muscles of both rodent [114] and humans [53,115], consistent with increased protein synthesis up to 3 h post exercise [115].

While the evidence for an effect of exercise on mTORC1 activation seems strong, the same cannot be said of the phosphorylation of mTOR on this residue. Others have questioned the significance of Ser2448 of mTOR based in part on the fact that this residue is phosphorylated in response to glucagon, a hormone that normally inhibits mTORC1 actions [226].

There are significant increases in the phosphorylation of substrates of mTORC1 (S6K1, and 4E-BP1) in response to acute exercise [118]. In one study, acute endurance exercise reduces the phosphorylation of S6K1 (6 h post-exercise), 4E-BP1 (0.5, 3, 6 h post-exercise) and S6 (0.5 and 3 h post-exercise), but surprisingly myofibrillar protein synthesis is still increased [224]. Furthermore there seems to be no difference between training models, as endurance [53,114–116], contracted in situ [52,117,118] and resistance exercise [51,119,120] all increase mTORC1 activation.

Differences in training intensities and modalities could play a factor in mTORC1 activation or mTOR phosphorylation in response to acute endurance exercise. Steady-state exercise >60% Wmax in human skeletal muscle [116,227], high-intensity interval exercise in rat hindlimb [228] and exercise to exhaustion in rat gastrocnemius [114] all lead to increases in mTORC1 signaling, while acute exercise at a lower intensity (30% Wmax for 1 h) does not increase phosphorylation of mTOR Ser2448 even though protein synthesis increases in human vastus lateralis [227]. Atherton et al. supports this, as they show an increase in mTORC1 activity from acute high frequency (100Hz) electrical stimulation, but no change from acute low frequency (10 Hz) electrical stimulation in rat EDL [52]. Besides training intensity, the degree of mTORC1 activation post exercise can be attributed to time of testing post exercise. Numerous studies show mTORC1 activation immediately after and up till 1 h post exercise [52,53,114,116–118], but not at 90 min [115] or 3–4 h post exercise [52,114,115,117].

In insulin resistance, mTORC1/S6K1 is activated and phosphorylates serine residues of IRS-1 [229]. This also complicates the role of mTORC1 in exercise-induced glucose uptake. One study showed that in response to resistance exercise, mTORC1 signaling was increases 6 h post exercise, along with increased serine phosphorylation of IRS-1 in rat skeletal muscle [124]. Furthermore, rapamycin attenuated this response and lead to increased Akt Ser473 phosphorylation [124]. Rats that received rapamycin showed a greater increase in skeletal muscle glucose uptake 6 h post exercise compared to rats that received placebo [124]. This is interesting, as although mTORC1 regulates anabolic processes, it is highly expressed in aging skeletal muscle, and rapamycin treatment protects against age-related muscle loss [230].

A protein that is important in regulating mTORC1 in response to exercise could be regulated in DNA damage and development 1 (REDD1). Endoplasmic reticulum stress, starvation, glucocorticoids and hypoxia activate REDD1 [231–234], while anabolic stimuli suppress it [235]. REDD1 inhibits mTORC1 by sequestering 14-3-3 proteins away from TSC-2. In turn, TSC-2 is not inhibited by 14-3-3 and can therefore inhibit mTORC1 [236]. Acute exercise reduces REDD1 abundance in human vastus lateralis [237], suggesting that exercise-mediated activation of mTORC1 may be in part due to suppressed REDD1. Gordon et al. show that acute exercise decreases REDD1 expression (~33%) and this correlates with an increase in S6K1 Thr389 phosphorylation (~75%) in mice TA [238]. However, in another study, REDD1 increases in response to acute endurance exercise and this is concomitant with a reduction in mTORC1 signaling in mice gastrocnemius [224]. REDD1 activity inversely correlates with mTORC1 signaling [224,238], but in low intensity exercise, there seems to be no inverse correlation [237]. This is consistent with the discussion above showing how higher intensity exercise activates mTORC1 while low intensity exercise does not.

Since mTORC1 is regulated by numerous proteins, assessing TSC-2 phosphorylation in response to exercise can give a better sense of the specific input of Akt into mTORC1 signaling. Treadmill running had no effect on TSC-2 phosphorylation in mice gastrocnemius, consistent with the exercise not having an effect on Akt phosphorylation, but inducing greater raptor association with mTOR [239]. In another study, 1 h post resistance exercise, there is a reduction in TSC2 Thr1462 phosphorylation (~33%) even though Akt Ser473 (~45%) and mTOR Ser2448 (~29%) phosphorylation are increased [240]. However, others have shown that low frequency electrical stimulation reduces TSC-2 Thr1462 phosphorylation (~60%), along with an increase in AMPK phosphorylation. High frequency electrical stimulation increases TSC-2 Thr1462 phosphorylation (~60%) along with a decrease in total TSC-2 protein levels (~20%). These effects of high frequency electrical stimulation occurred in parallel with increased Akt Ser473 phosphorylation (~80%) and mTOR Ser2448 phosphorylation (~44%) in the soleus and EDL of rats [52]. The authors of that study suggest that in response to low frequency stimulation, AMPK activates TSC-2 while in response to high frequency, Akt is activated to phosphorylate TSC-2 and thereby inhibit it, resulting in increased mTORC1 activation [52]. Ultimately, the intensity of exercise dictates which player (AMPK vs. Akt) is maximally activated, which in return influences downstream activation of key proteins (TSC-2 and mTORC1).

4.7. Exercise Prescription

An exercise prescription, like a prescription for a drug has a dose, type, dosing frequency, a duration of treatment and anticipated adverse effects [241]. The frequency and intensity of prescribed exercise will depend on an individual's strength, endurance, and recovery. An adverse effect could be, for example, delayed onset of muscle soreness, or joint pain for individuals with arthritis [241].

Exercise can attenuate and even reverse skeletal muscle insulin resistance in various conditions of apparent disease [7,8]. Only 10% of current trials focus on preventative measures of T2DM, while 63.1% and 11.7% of studies focus on drug interventions and behavioral modifications, respectively [242]. Published guidelines recommend 150 minutes of moderate to vigorous intensity aerobic exercise weekly, spread over for at least 3 days. In addition to

aerobic exercise, resistance exercise is recommended for at least 2 days a week for T2DM [243]. For sarcopenia, whole-body resistance exercise is recommended 2–3 times a week [244].

Our findings have implications for improving exercise prescriptions. The greater the intensity of the exercise, the higher the increase in Akt activity [102,103]. Also, in healthy individuals, acute endurance exercise (cycling at 70% of VO_{2max} for 60 min) increases Akt Ser473 phosphorylation while acute resistance exercise does [101]. However resistance exercise does increase Akt Ser473 phosphorylation in type 2 diabetic rats [144]. This emphasizes the importance of tailoring exercise prescription towards certain conditions. These data also point to the beneficial effects of combining different types of exercise.

For mTORC1 activation, there seems to be no difference between training models, as endurance [53,114–116], contracted in situ [52,117,118] and resistance exercise [51,119,120] all increase mTORC1 activation. We also show that higher intensities increase mTORC1 phosphorylation, but even in low intensities protein synthesis is increased [227]. One should take this molecular signaling with a grain of salt, as fatigue and weakness are common symptoms of sarcopenia [245] and T2DM [246], which may make more intense exercise difficult.

5. Conclusions

In summary, although phosphorylation of many of the proximal proteins involved in insulin signaling (insulin receptor, IRS-1, PI3K) are increased in response to chronic exercise, available evidence indicate that these proteins are not activated in response to an acute bout of exercise/contraction. The fact that some of the benefits of exercise training are seen with an acute exercise suggests the existence of a network of proteins/regulators that serve to not only co-ordinate physiological adaptations to exercise of diverse durations, but also modulate the nature and degree of associated physiological benefits. For acute exercise, in the absence of consistent changes in proximal components of insulin signaling cascade, distal proteins like AS160 and TBC1D1 seem to play a role in mediating some of the benefits of acute exercise, including the translocation of GLUT4 to the plasma membrane and increased glucose transport. Parallel upstream regulators that are not components of the canonical insulin signaling cascade include AMPK acting on AS160 and TBC1D1. While there seems to be some controversy on whether exercise/contraction activates Akt and mTORC1, the activation of these two regulators appears to depend on training mode, intensity, and time of measurement post exercise.

Further work is required in understanding mechanisms of Akt and mTORC1 activation in exercise when upstream proteins like the insulin receptor, IRS-1 and PI3K are not altered. Additionally, in some studies, Akt/mTORC1 and AMPK, proteins that are antagonistically regulated, are simultaneously activated during exercise, thus further work is required to determine other mechanisms/proteins that may impinge on these proteins.

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