Effects of acute exercise and training on insulin action and sensitivity: focus on molecular mechanisms in muscle

Jørgen F.P. Wojtaszewski and Erik A. Richter

Copenhagen Muscle Research Centre, Institute of Exercise and Sport Sciences, University of Copenhagen, Denmark

Abstract

A single bout of exercise increases insulin sensitivity for several hours and the effect is mainly restricted to the muscles recruited during exercise. When exercise is repeated over time, adaptations to physical training occur that include more long-lasting increases in insulin sensitivity. The present review explores the molecular mechanisms involved in both the acute and chronic effects of exercise on insulin sensitivity in skeletal muscle.

Introduction

During dynamic exercise, the turnover of ATP in skeletal muscle increases greatly. This is mainly fuelled by the catabolism of carbohydrates (intramuscular glycogen and blood glucose) and fatty acids (intramuscular triglycerides and blood lipids) whereas protein oxidation does not increase significantly unless muscle glycogen stores are exhausted. During exercise in the postabsorptive state, the contribution of blood glucose to energy expenditure is initially relatively minor, but as exercise continues and muscle glycogen stores are depleted, the contribution of blood glucose becomes

1To whom correspondence should be addressed (email erichter@ifi.ku.dk).
more substantial, reaching about 35% of leg oxidative metabolism and close to 100% of muscle carbohydrate metabolism (for review see [1]). Following exercise, muscle glucose uptake decreases rapidly and, depending on the duration and intensity of the preceding exercise, glucose uptake reaches resting levels within a few hours if no food is ingested. However, the sensitivity of muscle towards insulin stimulation is enhanced for several hours (up to 48 h) after exercise [2]. This facilitates rapid glycogen resynthesis after exercise when food is ingested. In addition to the effect of a single bout of exercise, repeated exercise (physical training) leads to more long-lasting increases in insulin sensitivity [3]. The beneficial effect of both acute and chronic exercise on insulin sensitivity is the basis for recommending physical activity as an important tool in prevention and treatment of insulin resistance. In the present review we will discuss the possible mechanisms behind the increased metabolic effect of insulin in the period after a single bout of exercise, as well as after a period of regular training. This has been studied mainly from the perspective of insulin action on glucose transport, and to a somewhat lesser extent on GS (glycogen synthase) activity, whereas other potential metabolic roles of insulin, such as stimulation of amino acid transport and protein synthesis, have been studied remarkably little.

**Insulin signalling: a complex web**

The many biological effects of insulin are initiated by the binding of insulin to the α-subunits of the transmembrane heterotetrameric IR (insulin receptor), leading to autophosphorylation and activation of the kinase associated with β-subunits. A web of inter-related intracellular proteins then mediates the post-receptor signalling toward a diversity of both mitogenic and metabolic cellular bioeffects. Based on our limited knowledge, these signalling events are often depicted in a linear fashion but over recent years evidence has gathered to suggest a much more complex web-like arrangement, inhibiting and promoting cross talk within the web (Figure 1). For detailed information about the insulin signalling pathway the reader is referred to recent reviews [4,5].

The kinase of the IR phosphorylates other endogenous proteins on tyrosine residues. Such endogenous IR substrates (second messengers) are numerous, and include the IRS (insulin receptor substrate) family of proteins 1–4, CAP (c-Cbl associated protein) and APS (adapter proteins) associated with pleckstrin homology and SH2 (Src homology-2) domains [5]. Of these, the IRS family is by far the most studied group of substrates, and in fact the presence/function of the APS–Cbl–CAP complex in skeletal muscle is still unsolved. The IRS proteins do not themselves have catalytic activity. However, phosphorylation on tyrosine residues within specific motifs allow the IRS proteins to bind to other proteins containing the SH2 domain. In this fashion IRS proteins are thought to regulate and direct further signalling. The importance of IRS-1, and to a lesser extent IRS-2, to insulin-mediated glucose transport in muscle tissues/cells has
been underpinned by studies in which the protein has been eliminated by gene knockout or RNA silencing techniques \[siRNA (small interfering RNA)\] \[6\]. When tyrosine phosphorylated IRS interacts with the SH2 domain of the p85 regulatory subunit of the class IA PI3K (phosphatidylinositol 3-kinase), the p110 catalytic subunit of the enzyme is activated. This subsequently gives rise to an increased production of phosphatidylinositol-3-phosphate compounds \[\text{PI}(3,4,5)P_3, \text{PI}(3,4)P_2, \text{and PI}(3)P\] within the plasma membrane. The production of these compounds is also dependent on activation of additional lipid kinases acting on several of these sites as well. The essential role of class IA PI3K in glucose transport has been elucidated using many different techniques, including chemical poison and molecular inhibition \[7\]. Interestingly, increased levels of phosphatidylinositol-3-phosphate compounds seems to increase GLUT4 (glucose transporter 4) translocation to the plasma membrane, but does not increase glucose transport, raising the possibility that an additional signalling event is necessary for the full functionality of GLUT4 to be achieved at the plasma membrane. This could involve the newly identified protein AS160 (Akt substrate of 160 kDa) as discussed below.

Insulin stimulation leads to a PI3K-dependent dual phosphorylation and activation of the serine/threonine kinase, Akt, which exists in two isoforms in skeletal muscle, namely Akt 1 and Akt 2. Current evidence suggests that the

**Figure 1. Insulin signalling**
The figure depicts some of the events from insulin binding to its receptor to the activation of the effector proteins GLUT4 and glycogen synthase. aPKC, atypical protein kinase C; GSV, GLUT4 storage vesicles.
insulin induced increase in PI(3,4,5)P$_3$ content initiates a recruitment of the PDK1 (phosphoinositol-dependent protein kinase 1) to the plasma membrane, as well as its activation. Apparently, Akt is recruited to the plasma membrane in association with PDK1 [4,5]. Akt is subsequently phosphorylated by PDK1 on its Thr$^{308}$ site. The full activation of Akt, however, requires additional phosphorylation by another kinase PDK2 (phosphoinositol-dependent protein kinase 2), on the Ser$^{473}$ site, which in fact may be the Rictor–mTOR kinase complex. An important role of Akt in insulin-stimulated glucose transport has been confirmed using transgenic approaches, as well as knockout and siRNA techniques. Through such studies, Akt 2 has been suggested to be more important in regulating glucose transport than Akt 1 [8].

PKC$\delta/\zeta$ (protein kinase $\delta/\zeta$), atypical PKC isoforms, are also activated in response to insulin stimulation in a PI3K–PDK1-dependent manner. Phosphorylation by PDK1 induces autophosphorylation, and this is suggested to release auto-inhibition of these atypical PKCs. The role of PKC$\delta/\zeta$ in insulin stimulated glucose transport has also been verified using overexpression of both kinase dead and active constructs, as well as siRNA [9].

Both Akt and PKC$\delta/\zeta$ may regulate different aspects of the vesicular trafficking and membrane docking/fusion machinery enabling the GLUT4-containing vesicle translocation and fusion to the plasma membrane. Recently, a new substrate of Akt, AS160, was described. AS160 apparently links IR signalling and GLUT4 trafficking [10]. AS160 contains a GAP (GTPase-activating protein) homology domain, which has been shown to regulate the GTPase activity of certain Rab proteins in vitro. Phosphorylation of AS160 by Akt is likely to inhibit its GAP activity, such that as a consequence, the GTP form of this or these Rab protein(s) is/are formed, in turn increasing GLUT4 vesicle movement to, and/or fusion with, the plasma membrane. Insulin increases AS160 phosphorylation, likely in a PI3K-dependent manner, in 3T3-L1 adipocytes and skeletal muscle. Interestingly, AS160 is also phosphorylated (inactivated) during muscle contractions in an AMPK (AMP-activated protein kinase)-dependent manner [11].

Akt is at a crossroads at which insulin signals to regulate glycogen synthesis via regulation of GS activity. Upon insulin stimulation, Akt phosphorylates GSK3$\alpha/\beta$ (glycogen synthase kinase 3 $\alpha/\beta$) in a PI3K-dependent manner leading to inactivation of GSK3 activity. Although GS action is regulated by multiple phosphorylations, the sites purported to affect its activity the most are the N-terminal site two and the C-terminal site three. Of these, GSK3 is only directly phosphorylating site three. The importance of GSK3 for insulin-induced GS activation has recently been firmly established using knockin experiments of mutated GSK3 in murine muscle resulting in failure of insulin to regulate GS activity [12].

An important route of regulation of the insulin signalling cascade is likely to be via negative feedback loops within the cascade. Over recent years it has become apparent that during insulin stimulation IRS-1 is heavily serine
phosphorylated at the same time as it becomes tyrosine phosphorylated. Multiple serine residues have been described to undergo phosphorylation, and apparently these are induced by a variety of kinases [mTOR (mammalian target of rapamycin)/JNK (c-Jun N-terminal kinase), GSK3, Erk (extracellular signal-related kinase), Akt, S6K1 (ribosomal S6 protein kinase) and AMPK]. Although many aspects of these serine phosphorylations are unresolved, some seem to down-regulate whereas others appear to up-regulate the ability to signal through IRS-1. Another level of regulation occurs through the action of phosphatases acting on tyrosine residues, e.g. LAR (leukocyte antigen related phosphatase) and PTP1B (protein tyrosine phosphatase 1B) within the IR and IRS. In addition, insulin signalling may also be modified by the action of PP2A (serine/threonine phosphatases) acting on Akt, PKC, GSK3 and by the action of lipid phosphatases [PTEN (phosphatase and tensin homologue deleted on chromosome 10) and SHIP2 (SH2-containing inositol phosphatase 2)] down-regulating the levels of PI(3,4,5)P$_3$.

**Exercise/contraction signalling in muscle: a web distinct from insulin’s, but likely inter-woven**

The factors thought to be involved in exercise-induced glucose transport have recently been reviewed [1]. In brief, glucose uptake during exercise increases due to a coordinated increase in (i) muscle glucose delivery due to greatly increased capillary perfusion; (ii) increased sarcolemmal and t-tubular transport of glucose from the interstitium to the muscle interior, aided by increased membrane content of the glucose transporter GLUT4; and (iii) increased metabolism of the transported glucose. Whereas each of these events is important, in this review we will focus on the molecular mechanisms activated by exercise/muscle contractions that lead to GLUT4 translocation. The importance of GLUT4 has been shown using muscle tissue from mice with systemic or muscle-specific knockout of GLUT4 [13], in which muscle glucose transport during contractions *in vitro* was abolished.

The molecular events leading to translocation of GLUT4 during muscle contractions are incompletely understood. It has been suggested that the regulation of glucose uptake during exercise can be divided in to a Ca$^{2+}$/calmodulin-dependent feed-forward mechanism, that is responsible for increasing muscle glucose uptake at the onset of contractions, and an AMPK-related feedback mechanism, responsible for adjusting glucose uptake to the energy needs of the muscle [1] (Figure 2).

Early evidence for a role of intracellular Ca$^{2+}$ in increasing muscle glucose transport comes from older studies showing that pharmacologically induced increase in myoplasmic Ca$^{2+}$-concentration increases glucose transport in resting muscle [14]. More recently, Wright et al. in a series of studies based on inhibition of CaMK (Ca$^{2+}$/calmodulin dependent kinases) with the inhibitors KN62 and KN93 suggested that activation of CaMKII during muscle
contractions plays an essential role in activating glucose transport, especially in slow-twitch fibres [15]. Notably, it was shown that the KN inhibitors did not affect AMPK phosphorylation with exercise [16]. Other downstream Ca\(^{2+}\)-dependent kinases of possible importance for translocation of GLUT4 include the conventional isoforms of PKC and the atypical isoforms of PKC [17]. Since the atypical isoforms of PKC are involved in activating glucose transport during insulin stimulation, as discussed above, its activation in muscle during exercise may suggest that it is also involved in stimulating muscle glucose uptake during exercise.

The role of the AMPK in contraction-induced glucose uptake is at present somewhat controversial. Pharmacological activation of AMPK with AICAR (5-aminimidazole-4-carboxamide-1-\(\beta\)-d-ribonucleoside) in resting muscle results in activation of muscle glucose transport independently of insulin (for review see [18]). Since AMPK is also activated in skeletal muscle during contractions/exercise in both rodent and human skeletal muscle [18], it has been speculated that AMPK may in fact be ‘the’ contraction activated kinase responsible for increasing glucose transport. More definitive mechanistic answers necessitate the use of genetically manipulated animals. Overexpression of a dominant negative form of AMPK (a dead kinase) has in mice been shown to inhibit electrically induced muscle glucose transport by 30–40\% in fast-twitch muscle of the kinase dead muscles compared with the wild type [19]. This finding may suggest that contraction-induced glucose transport...
is partly dependent upon AMPK via a feed-back pathway. Interestingly, however, knockout of either the α1 or the α2 catalytic subunit of AMPK, or the γ3 regulatory subunit, does not cause any inhibition of glucose transport in electrically stimulated incubated mouse muscle [20,21]. A recent study has added weight to the role of AMPK in contraction-induced glucose uptake. In LKB-1 knockout mice, in which the activation of AMPK during electrical stimulation is virtually abolished, uptake of glucose was also markedly inhibited [22]. Drawing conclusions from these experiments is difficult, but it would seem the sum of evidence supports a role for AMPK in contraction-induced glucose uptake. How significant this role is, and whether it varies in different kinds of contractions/exercise, awaits determination.

The regulation of GS activity during exercise has received less attention than glucose uptake. Nevertheless, GS is influenced by both stimulatory and inhibitory factors during exercise and the consequent effect of exercise on GS activity is a result of the relative strength of the various stimuli. Several human studies have shown that muscle GS activity is higher in a glycogen-depleted state compared with a glycogen-loaded state, and it has been suggested that exercise-induced GS activation is dependent on, and merely a result of, glycogen breakdown [23]. The mechanism behind this dependency is unknown, but at least in rodents seems to involve dephosphorylation of GS on site 3a and 3b and changes in the sub-cellular localization of GS [23]. Whether these two changes are linked is unknown, but cellular redistribution of GS induced by glycogen depletion could, for instance, make GS more susceptible to dephosphorylation. Conversely, the covalent modifications of GS, seen during conditions with high muscle glycogen content, are only partly reversible by phosphatase treatment, indicating the involvement of phosphorylation dependent regulatory mechanisms in addition to other unknown factors.

**Effect of a single bout of exercise on insulin sensitivity**

It has been shown that a single bout of cycle exercise, or stair climbing, improved insulin sensitivity of glucose clearance at the whole body level under hyperinsulinaemic euglycaemic clamp conditions (for review see [23,24]). These changes have been observed as long as two days after the bout of exercise. This effect is likely to be the result of increased insulin sensitivity localised to the muscles that performed the work, as shown in rats [25] and humans [2,26]. Increased insulin action seems to be mainly a result of a leftward shift in the dose–response curve for insulin action on glucose uptake (Figure 3). However, it should be noted that exercise does not always increase insulin action. For example, immediately after intense exercise, insulin action is impaired *in vivo* possibly due to elevated concentrations of catecholamines and non-esterified fatty acids. Likewise, eccentric exercise or physical activities with a dominant component of eccentric contractions elicit a prolonged decrease in insulin action, which may be caused by muscle damage and inflammation leading to
altered protein expression and function [27,28]. Nevertheless, non-damaging dynamic exercise of a moderate intensity usually results in increased insulin sensitivity in the post-exercise period.

What are the mechanisms behind this effect of exercise on insulin sensitivity? A simple hypothesis is that exercise somehow potentiates the insulin signalling cascade. This could theoretically be via the exercise-induced muscle glycogen depletion, since a low glycogen concentration in rat skeletal muscle has been shown to enhance insulin signalling at the level of Akt [29]. However, when the proximal part of the insulin signalling cascade, from the IR through IRS-1 associated PI3K to Akt and GSK3, was analysed in human skeletal muscle, exercise-induced increased insulin action was not accompanied by enhanced signalling in this cascade [30]. On the contrary, IRS-1 associated PI3K activity was stimulated slightly less in the exercised muscle compared with the contralateral control muscle [2].

However, in human skeletal muscle two isoforms of IRS are expressed. Both IRS-1 and IRS-2 contribute to activation of PI3K during insulin stimulation [6], but the physiological role of IRS-2 associated PI3K activity in human skeletal muscle is not well described. Data from IRS knockout mice seem to indicate that IRS-1 is the major isoform mediating insulin-stimulated glucose uptake in skeletal muscle [31]. Still, knockout of IRS-2 results in the development of peripheral insulin resistance, but this could to some extent be a
secondary consequence of prolonged exposure to hyperglycaemia due to hepatic insulin resistance and β-cell failure. Interestingly, immediately after in vivo exercise, activation of IRS-2 (but not IRS-1) associated PI3K activity in mouse skeletal muscle is markedly increased in response to a supraphysiological insulin stimulus compared with rested muscle [32]. Furthermore, we have recently shown that IRS-2 associated PI3K activity is increased for 60 min in human skeletal muscle 4 h after a single bout of knee-extensor exercise, but the effect of insulin on stimulation of IRS-2 associated PI3K activity is unchanged by prior exercise (unpublished observations by the authors). This results in a generally higher activity of IRS-2 associated PI3K activity in the exercised leg both at basal and during insulin stimulation. Theoretically, this should lead to a higher production of PIP_3 (phosphatidylinositol-3,4,5-trisphosphate). Downstream of PI3K, atypical PKC has emerged as an important signalling component stimulating GLUT4 translocation as discussed previously in this review. One way to activate atypical PKC is via PIP_3. Thus, increased IRS-2 associated PI3K activity in the exercised leg would be assumed to cause increased allosteric activation of atypical PKC. Interestingly, whilst the effect of insulin to activate atypical PKC is not enhanced by prior exercise, we have recently shown that exercise increases the ability of PIP_3 to activate atypical PKC (unpublished observations by the authors). Together, the increase in IRS-2 associated PI3K activity, and the increased ability of PIP_3 to activate atypical PKC in the exercised leg, may be the first indication of direct molecular interactions between exercise and insulin signalling.

Exercise leads to activation of AMPK in the contracting muscles as described above. It has been hypothesized that activation of AMPK is involved in increased sensitivity to insulin. Thus, in rats, pharmacological activation of AMPK by AICAR increased muscle insulin sensitivity in the absence of muscle contractions, suggesting that activation of AMPK increases subsequent insulin sensitivity [33]. However, proof of this concept requires studies utilizing genetic manipulation of muscles such as knockout of AMPK.

Exercise leads to expenditure of energy and decreased muscle glycogen levels. The duration of enhanced insulin sensitivity after a single bout of exercise has in some rodent studies been found to depend on the feeding status of the animals after exercise, such that the duration of enhanced insulin sensitivity is prolonged when carbohydrate intake is restricted after exercise. In humans, the amount of muscle glycogen degraded during exercise correlates significantly with insulin action determined 4 h after the cessation of exercise [24], suggesting that muscle glycogen plays a role in insulin sensitivity although the molecular mechanisms behind such an effect of glycogen remains to be established and may in fact not be directly causative.

Muscle contractions cause changes in gene expression. However, it is generally believed that the increase in insulin sensitivity after a single bout of exercise is not caused by exercise induced increases in the expression of signalling proteins or GLUT4 protein.
**Effects of exercise training on insulin action**

Whilst a single bout of exercise increases insulin action as discussed above, chronic changes in muscle use or disuse also causes more prolonged changes in insulin action. It should, however, be realised that by simply repeating a single bout of exercise regularly, the muscle will be maintained at a level of improved ‘post-exercise’ sensitivity. Still, exercise training also leads to changes in gene expression of key proteins involved in glucose handling which potentiates the action of insulin stimulation. Thus, discussing effects of exercise training cannot be done without taking into account that trained muscle is, more or less, chronically in a ‘post-acute’ exercise state.

Exercise training improves whole body insulin sensitivity in both healthy subjects and in people suffering insulin-resistant diseases. This effect is largely attributable to enhanced insulin induced glucose clearance in peripheral tissues, in particular in the trained skeletal muscle [34].

Skeletal muscle is a heterogeneous tissue composed of fibres with different metabolic and contractile characteristics. Use/disuse of skeletal muscle, i.e. contractile activity of the individual fibres affects these characteristics. For example, use/activity (endurance and strength training) induces changes in myosin heavy chain protein expression toward type IIa (from IIx), whereas disuse induces changes in the opposite direction. A shift in fibre type from IIx towards type IIa also means a shift to more oxidative fibres, generally thought to be more insulin sensitive than the mainly glycolytic fibres. Along the same lines, but not necessarily linked to changes in fibre types [35], use/disuse changes the expression profile of a range of other proteins. This includes the GLUT4 glucose transporter protein, known to be essential for insulin induced glucose uptake into skeletal muscle [13]. Thus, in rodents, exercise training increases GLUT4 protein and mRNA expression in skeletal muscle, an effect that seems to be rather early in onset. In human muscle similar plasticity is observed. Thus, both strength and endurance training increases, and physical inactivity decreases muscle GLUT4 mRNA and protein expression, and data suggest that those fibres recruited during the actual exercise performed are also those in which these adaptations are occurring [35]. In addition, endurance training induces increased capillarization of muscle leading to a generally lower mean diffusion distance from capillary to muscle, in this way facilitating delivery of insulin and glucose to the muscle. That this adaptation may be important is indirectly indicated by the fact that insulin sensitivity in a large sample of subjects has been shown to be related to capillary density [36].

In rodent muscle, insulin responsiveness to activate glucose transport is positively correlated with GLUT4 expression. Thus, a graded response of glucose uptake to insulin stimulation has been observed among rodent muscles expressing variable amounts of GLUT4, e.g. in genetically modified mice in which GLUT4 expression was manipulated (heterozygous and homozygous...
knockout of the GLUT4 gene), and in animals treated with streptozotocin in which muscle GLUT4 expression is decreased. In humans, a decrease in GLUT4 expression with age correlates with decreased whole body insulin sensitivity. Still, in type 2 diabetes, muscle insulin resistance is present in the face of normal muscle GLUT4 expression suggesting that other mechanisms may also be important for insulin action. In accordance, several studies have addressed the idea that exercise training not only increases the amount of GLUT4 in the muscle, but also leads to changes in insulin signalling capacity enabling the muscle cell to respond to insulin with an enhanced sensitivity.

In rodents, exercise training increases muscle mRNA encoding proteins within the signalling cascade (e.g. IR, IRS-1, P85/P110), as well as mRNA encoding ‘effector proteins’ (e.g. GLUT4 and GS). However, not all of these effects seem to be translated into changes in actual protein levels. Although increases in IR, p85 and IRS-2 protein levels have been reported [37], the vast majority of studies in rodents have reported no changes in insulin signalling protein expression (e.g. IR, IRS-1, IRS-2, Akt and PKC) despite increases in ‘effector proteins’ like GS and GLUT4, as well as insulin action. In human skeletal muscle available data is sparse. Short-term (a few weeks) exercise training studies have revealed no apparent changes in IR, IRS-1 or IRS-2 protein levels, whereas long-term training (endurance or strength) reveal increases in expression of IR and Akt protein levels, as well as the ‘effector proteins’ GLUT4 and GS, in addition to insulin action in muscle [38]. These responses to exercise training in muscle of both human and rodents are likely to be dependent on training mode (intensity and duration), animal species etc., yet the prevailing adaptive responses observed suggest that changes in the expression of the ‘effector proteins’ GLUT4 and GS are likely to be more important for the adaptive response in muscle (at the level of insulin action) than altered expression of the signalling proteins. Still, neither mRNA nor protein expression necessarily reflects adaptive responses in the signalling cascade upon activation. Thus, to address the question as to whether exercise training changes signalling sensitivity, a range of studies have also applied measurements at the signalling level, involving measurements of either activity or phosphorylation of different signalling elements.

Earlier studies investigating IR function in vitro using a wheat germ preparation have not reported any increases in IR tyrosine kinase activity after training in human skeletal muscle [39]. However, a recent study in humans [40] indicates that in vitro IR autophosphorylation capacity is increased after 7 days of training. In none of the studies did exercise training lead to changes in the amount of IR protein present. Similarly, some, but not all, studies in muscle of rodent models suggest improved receptor signalling after training [37]. Thus, from the available literature it can be concluded that exercise training under some conditions improves receptor function, and this may improve muscle sensitivity to insulin. In some of the rodent studies the improved IR function translates into increased activity at the post-receptor signalling
level (IRS-1/IRS-2 PI3K activity), whereas in other studies this has not been found [41]. In human studies the picture is also not clear, as two studies have observed improved signalling at the level of PI3K and two have reported no improvement.

It is likely that this diversity of findings reflects the complexity of exercise training as a stimulus as well as our limited understanding of the intracellular signalling mechanism. A factor influenced by training is muscle glycogen content which is often increased by training. Glycogen has been shown to be a negative regulator of insulin signalling, at least at the level of Akt phosphorylation [29], and thus some of the variable signalling responses observed in different studies may relate to differences in glycogen modulation by the training regime used. Still, common to nearly all of these training studies is that besides improved muscle insulin action to glucose handling, the amount of ‘effector proteins’ like GLUT4 and GS is increased. One interpretation of this is that these adaptations are very important for the improved insulin action in trained muscle.

As discussed above, AMPK is activated during exercise, and may have important roles in regulating metabolic events both acutely and chronically. AMPK activation may also to some extent improve muscle insulin sensitivity [33]. Interestingly, we recently observed that AMPK activity in trained human muscle is increased at rest. Chemical activation of AMPK regulates a variety of genes involved in mitochondria biogenesis as well as GLUT4 in resting muscle. However, the obvious extension of these findings i.e. that AMPK is a regulator of insulin sensitivity by regulating the expression of the GLUT4 gene during training has not been verified in studies of genetic animal models. For example, both acute exercise- and training-induced GLUT4 gene transcription is AMPK independent [42,43]. Thus, the mechanisms behind the up-regulation of ‘effector proteins’ during exercise training are unclear at present.

Interestingly, a recent study in which subjects trained for 7 days showed that enhanced insulin sensitivity was only found if the subjects did not compensate for the training induced increase in energy expenditure [44]. In contrast, when the amount of calories expended during exercise training was carefully replaced by increased dietary intake mainly in the form of carbohydrates, no improvement in insulin sensitivity could be shown. Thus, decreased energy balance induced by exercise training may be important for development of increased insulin signalling, at least during short term training studies.

Conclusions

Insulin and exercise each stimulate muscle glucose uptake via distinct molecular mechanisms which eventually converge on GLUT4 translocation to the plasma membrane. A single bout of exercise increases insulin sensitivity for several hours maximally up to 48 h, and the effect is mainly found in
the muscles recruited during exercise. The molecular mechanism behind this effect of exercise is presently largely unresolved, but is likely to be a complex phenomenon involving exercise induced changes in several signalling parameters as well as changes in muscle energy stores.

When exercise is repeated over time, adaptations to physical training occur, which include increased protein expression of GLUT4 and GS, muscle fibre type changes and increased capillarization. Changes in the expression or activation of signalling proteins are less consistently described. Because a single bout of exercise and regular physical training enhances insulin sensitivity, physical activity is considered a cornerstone in prevention and treatment of conditions of low insulin sensitivity such as the metabolic syndrome and type 2 diabetes.

Summary

- Insulin and exercise each stimulate muscle glucose uptake via distinct molecular mechanisms.
- A single bout of exercise increases insulin sensitivity for several hours maximally up to 48 h.
- Adaptations to physical training include increased protein expression of GLUT4 and GS, muscle fibre type changes and increased capillarization.
- Changes in the expression or activation of signalling proteins are less consistently described.
- Physical activity is considered a cornerstone in prevention and treatment of conditions of low insulin sensitivity such as the metabolic syndrome and type 2 diabetes.

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