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Exercise performance and health: Role of GLUT4☆

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ABSTRACT

The glucose transporter GLUT4 is integral for optimal skeletal muscle performance during exercise, as well as for metabolic health. Physiological regulation of GLUT4 translocation during exercise and increased GLUT4 expression following exercise involves multiple, redundant signalling pathways. These include effects of reactive oxygen species (ROS). ROS contribute to GLUT4 translocation that increases skeletal muscle glucose uptake during exercise and stimulate signalling pathways that increase GLUT4 expression. Conversely, ROS can also inhibit GLUT4 translocation and expression in metabolic disease states. The opposing roles of ROS in GLUT4 regulation are ultimately linked to the metabolic state of skeletal muscle and the intricate mechanisms involved give insights into pathways critical for exercise performance and implicated in metabolic health and disease.

The ongoing supply of ATP to energy-dependent processes that support skeletal muscle contractile activity is crucial for exercise performance. Various metabolic pathways for ATP generation are activated during exercise, their relative contribution to overall energy metabolism being primarily determined by exercise intensity and duration for review see Ref. [1]. At the exercise intensities undertaken by elite athletes during competition and training, carbohydrate degradation is the major source of ATP production, with a primary reliance on muscle glycogen, although blood glucose derived from liver glycogenolysis and gluconeogenesis and from the gut when carbohydrate is ingested can contribute significantly to skeletal muscle energy metabolism during exercise. Due to the dependence on carbohydrate during strenuous exercise and the relatively small endogenous carbohydrate reserves, there has been a focus on carbohydrate nutrition before, during and after such exercise to enhance athletic performance [2].

Skeletal muscle glucose uptake occurs via facilitated diffusion and increases during exercise as result of greater blood flow and glucose delivery, enhanced sarcolemmal transport mediated by the glucose transport protein GLUT4 and increased glucose disposal, the first step being glucose phosphorylation catalysed by hexokinase [3]. The primary metabolic fate of glucose during exercise is glycolysis, whilst during post-exercise recovery it is glycogenesis. The importance of GLUT4 is demonstrated by the complete abolition of exercise-induced skeletal muscle glucose uptake in transgenic mice with muscle-specific deletion of GLUT4 [4]. Skeletal muscle GLUT4 protein levels are higher in trained athletes compared with untrained subjects [5,6] and this contributes to an enhanced capacity for muscle glycogen storage [6] and improved insulin sensitivity [7,8]. Similar responses are seen in transgenic mice overexpressing GLUT4 [9]. Although exercise training is generally associated with reduced muscle glucose uptake during submaximal exercise at the same absolute power output, glucose uptake during intense exercise is increased, associated with greater GLUT4 expression [10]. This may partly contribute to the greater capacity for carbohydrate oxidation after intense training in athletes [11].

1. Exercise and GLUT4

Both acute and chronic exercise have major effects on skeletal muscle GLUT4 cellular distribution and expression. The translocation of GLUT4 to the plasma membrane and t-tubules during exercise [12–14] is a fundamental event for facilitating skeletal muscle glucose uptake and effectively removes glucose transport as a limiting factor [3]. It is generally believed that GLUT4 translocation accounts for the majority, if not all, of the increased skeletal muscle glucose transport during exercise; however, the possibility that GLUT4 transporter intrinsic activity is increased remains a somewhat open question [15]. GLUT4 sarcolemmal translocation is relatively normal during exercise in patients with type 2 diabetes [16] and is associated with an exercise-induced decrease in

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blood glucose [17], despite their insulin resistance. This emphasizes the importance of regular exercise/physical activity in the prevention and management of metabolic diseases, such as diabetes, and explains the considerable interest in potential pharmacological activators of the GLUT4 sarcolemmal translocation process. The molecular mechanisms responsible for GLUT4 sarcolemmal translocation and skeletal muscle glucose uptake more generally during exercise remain to be fully elucidated. Potential initiating factors include changes in muscle [Ca^{2+}] and energy charge, increased nitric oxide, and changes in muscle length and the cytoskeleton [18]. These factors can in turn activate kinases such as Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), AMP-activated kinase (AMPK) and Rho-GTPases such as Rac1 that ultimately result in the translocation of GLUT4 to the cell surface and insertion of GLUT4 into the sarcolemma [18]. It has been shown that reactive oxygen species (ROS) generated via NADPH oxidase 2 (NOX2) during exercise are involved in the regulation of skeletal muscle glucose transport [19]. NOX2 produces superoxide (O_2^-), which is rapidly converted to other ROS, particularly hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) enzymes [20].

A single bout of exercise has been shown to transiently increase GLUT4 transcription in rat skeletal muscle, as measured directly by nuclear run-on assays [21]. In human skeletal muscle, we have observed an increase in GLUT4 mRNA [22,23] most likely due to increased transcription, although changes in mRNA degradation cannot be entirely excluded. This was associated with an increase in GLUT4 protein levels 3 h after exercise [22]. It has been suggested that the transient increases in mRNA with repeated bouts of exercise result in increased translation and the sustained increase in GLUT4 protein expression [24]. We have some evidence in support of this hypothesis with short-term training [25]. The molecular signals that stimulate GLUT4 transcription during and following exercise are similar to those that enhance GLUT4 translocation and include activation of AMPK [26] and CaMKII [27,28]. In a series of studies in human skeletal muscle we have demonstrated that exercise increased nuclear AMPKα2 abundance [29], stimulated nuclear export of the class IIa HDACs, particularly histone deacetylase 5 (HDAC5) and reduced myocyte enhancer factor 2 (MEF2)-associated HDAC5 [30], increased MEF2 and GEF DNA binding [31] and increased GLUT4 mRNA [30]. Using a range of biochemical approaches and a human primary myotube model, we further showed that AMPK was the upstream kinase that phosphorylated HDAC5, leading to its nuclear export [32] and that p38 mitogen activated protein kinase (MAPK) potentially phosphorylated MEF2, thereby increasing transcriptional activity [30]. The relevant histone acetyl transferase involved in the exercise-induced increase in GLUT4 transcription remains to be identified but p300 has been proposed as a potential candidate [27]. It has been suggested that ROS activates kinases that phosphorylate the class IIa HDACs, including AMPK [33], PKD [34] and CaMKII [35] and may contribute to exercise-induced changes in skeletal muscle phenotype [36], including potentially increased GLUT4 expression. How ROS activates kinases such as these likely involves direct oxidation, particularly of cysteine residues resulting in the formation of stabilized protein structures. For example, H_2O_2 can oxidise cysteines 299 and 304 of the AMPK catalytic α subunit, which increases AMPK activity [37]. Deletion of NOX2 prevented the contraction-induced nuclear export of HDAC5 in isolated mouse muscle fibres [38], suggesting that H_2O_2 derived from NOX2 plays an important role in the signalling axis controlling GLUT4 expression. Similarly, ROS may also regulate the transcriptional coactivators thought to regulate GLUT4 expression by confering greater p300 transcriptional activity. Mechanistically, it has been shown that H_2O_2 induces disulfide bridge formation between p300 and its transcription factor targets to establish a stable complex [39]. Whether this occurs in skeletal muscle during exercise remains to be determined. That said, deletion of NOX2 from murine skeletal muscle did not alter muscle GLUT4 protein levels [19]. It is possible that sources of ROS other than from NOX2 and/or other signalling pathways compensated for reduced NOX2-generated ROS. Interestingly, NOX2 deletion is sufficient to prevent exercise-induced ROS generation [19]. In any event, it appears there is redundancy in the regulation of exercise-induced alteration in GLUT4 expression [28]. In addition to activation of kinases, increasingly oxidized cellular states are also associated with impaired phosphatase activity, including in skeletal muscle during exercise [40]. Inactivation of phosphatases could also potentiate the activity of kinases involved in enhancing GLUT4 sarcolemmal translocation and transcription. Furthermore, the PP2A phosphatase, which dephosphorylates HDAC5 in cardiomyocytes at the sites that control its nuclear export [41], is also inactivated by oxidants. The mechanisms involved could include both nitrosylation and oxidation [42] and confer control of transcriptional regulators of GLUT4 that would potentiate GLUT4 expression. A summary of our current understanding of the molecular regulation of exercise-induced changes in GLUT4 mRNA and protein expression is provided in Fig. 1.

2. GLUT4 in health and disease

In addition to its role in athletic performance, regulation of GLUT4 also has a major influence on systemic metabolism. Translocation of GLUT4 from intracellular locations to the plasma membrane in skeletal muscle, adipose tissue and the heart occurs in response to insulin in the post-prandial period. Interestingly, transient ROS production by insulin is important for the effects of insulin on GLUT4 translocation in a variety of cell types [43,44]. The role of transient ROS production in mediating the effects of insulin and its potential targets have recently been reviewed elsewhere [45]. The importance of GLUT4 for maintaining systemic glucose homeostasis and normal tissue function is best highlighted by mouse models with various deletions of the GLUT4 gene. Global heterozygous GLUT4 knockout mice that have an ~50 %

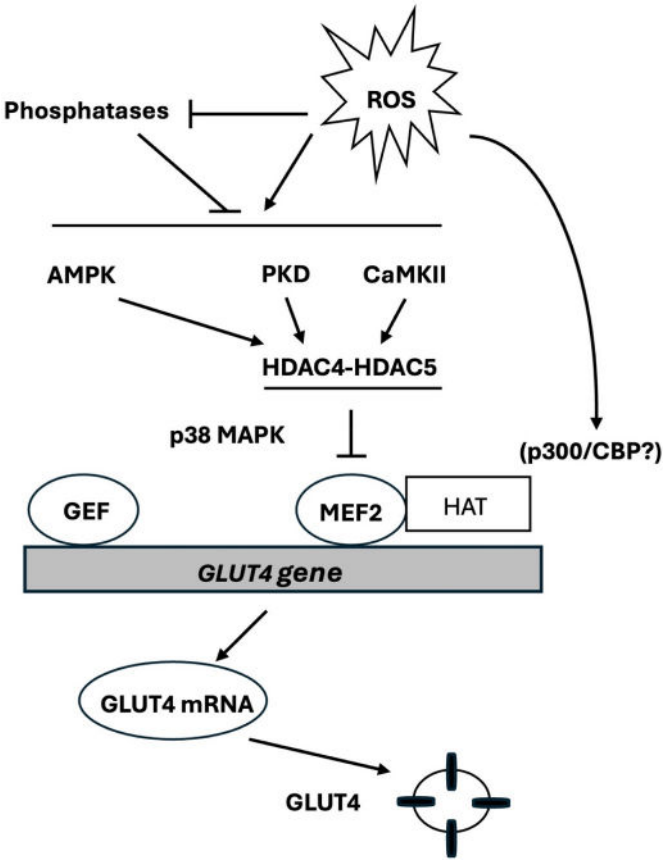

Fig. 1. Molecular regulation of exercise-induced GLUT4 expression in human skeletal muscle and potential involvement of ROS. Adapted from Ref. [71] with permission.

reduction in GLUT4 protein in skeletal muscle and adipose tissue develop systemic insulin resistance, hypertension and cardiomyopathy [46]. Mice with complete knockout of GLUT4 in both skeletal muscle and adipose tissue also manifest with systemic lipid abnormalities [47]. In the context of human health and disease, impaired translocation of GLUT4 to the plasma membrane in skeletal muscle and adipose tissue is a conserved feature of insulin resistance [48], which leads to glucose intolerance, hyperinsulinemia and can progress to type 2 diabetes [49]. While defective translocation of GLUT4 to the sarcolemma is central to insulin resistance in skeletal muscle and adipose tissue, the role of GLUT4 expression in metabolic disease states is less clear. Humans with type 2 diabetes have reduced GLUT4 protein in adipose tissue [50], while GLUT4 in skeletal muscle is unchanged [50,51]. However, reduction of GLUT4 protein has been noted in specifically in type I fibres of skeletal muscle in both obesity and diabetes [52]. Although mouse models with reduced GLUT4 expression manifest with a range of metabolic abnormalities, it is generally accepted that reduced GLUT4 expression is not the primary driver of metabolic abnormalities in diseases such as type 2 diabetes [48].

An important question to resolve is why are insulin-stimulated GLUT4 translocation and, in some tissues, GLUT4 expression reduced in metabolic diseases? Recently, persistent mitochondrial ROS production that induces oxidative stress has emerged as a major driver of impaired GLUT4 translocation and insulin resistance [53,54]. Nutrient overload and excessive beta oxidation place reductive pressure on the mitochondrial electron transport chain, increasing electron transfer to molecular oxygen at specific mitochondrial complexes, resulting in formation of $O_2^{\cdot-}$ before it is converted to H_2O_2 [55]. The mechanisms by which mitochondrial ROS impair GLUT4 sarcolemmal translocation, and other mechanisms of insulin resistance more broadly, have proved difficult to clearly define [56]. Recent comprehensive interrogation of insulin signalling in numerous models of adipocyte insulin resistance have revealed dysregulation of a signalling a node surrounding glycogen synthase kinase 3 (GSK3) of the insulin signalling network [57]. This work also identified the likely involvement of non-canonical components of the insulin signalling pathway [57], indicating that more work is required before we can understand how ROS has negative impacts on GLUT4 sarcolemmal translocation. Nonetheless, it has therefore been proposed that insulin resistance is a negative feedback mechanism to prevent further oxidative stress driven by nutrient excess [54,58]. This raises the question whether a reduction in GLUT4 protein expression is a feedback mechanism to reduce cellular stress during nutrient oversupply. In support of this hypothesis, we recently established that lipotoxicity increases class IIa HDAC protein in skeletal muscle [59]. The increase in class IIa HDACs repressed a broad transcriptional program of metabolic and oxidative genes, including GLUT4, and reduced mitochondrial oxidative capacity and $O_2^{\cdot-}$ production. This metabolic reprograming was ultimately linked to suppression of cell death pathways, particularly ROS-mediated ferroptosis, and preservation of muscle integrity during lipotoxicity [59]. These findings are consistent with broad transcriptional reprograming of oxidative metabolism in skeletal muscle of people with type 2 diabetes [60,61] and indicate that aspects of metabolic reprogramming that occur in response to nutrient excess are protective, rather than pathogenic *per se* [62]. Whether there is a role for oxidative stress in driving the increase in the class IIa HDACs under these conditions remains to be deciphered. To our knowledge, there are no reports that have described a mechanism by which ROS can increase the class IIa HDACs. However, a potential mechanism is that elevated production of mitochondrial-derived H_2O_2 can acutely disassemble the 26S proteosome in yeast by oxidation of cysteine residues within proteosome proteins [63]. The 26S proteosome controls the degradation of the class IIa HDACs and determines steady state levels of these transcriptional repressors in skeletal muscle [64]. Collectively these observations highlight that persistent nutrient excess dysregulates both GLUT4 cellular distribution and expression and that ROS plays an integral role in these responses.

3. Divergent effects of ROS on GLUT4 localisation and expression

As redox-sensitive cellular signalling pathways play a role in both physiological regulation of GLUT4 sarcolemmal translocation and expression, and in inhibition of GLUT4 sarcolemmal translocation and reduced GLUT4 expression in response to persistent nutrient overload, an important question to consider is how ROS can have these divergent effects on GLUT4? The temporal dynamics of ROS in these different contexts could be important. Both exercise and insulin transiently stimulate ROS production to amplify signalling that mediates GLUT4 translocation [65,66]. A recent paper suggests that NOX2 is integral for both the effects of insulin and exercise in mouse skeletal muscle [67]. In contrast, chronic nutrient overload induces a persistent oxidative stress response [68]. The cellular compartmentalization of redox-sensitive cellular signalling pathways could be equally important. Exercise and insulin tend to have the most profound effects on cytosolic ROS, while ROS driven by chronic nutrient overload are produced mainly by mitochondria [68], although cytosolic NOX2 might also play a role [69]. While the exact signalling mechanisms underlying these differential temporal and compartmentalized effects of ROS on GLUT4 remain to be determined, the distinct biological effects of ROS from cytosolic and mitochondrial sources have been previously noted in other biological systems [70].

4. Conclusions

The glucose transporter GLUT4, through its impact on tissue glucose uptake and subsequent effects on whole body metabolism, is integral for optimal skeletal muscle performance during exercise, as well as for optimal metabolic health. Physiological regulation of GLUT4 involves redox-sensitive cellular signalling pathways – during exercise, ROS contributes to GLUT4 translocation to increase glucose uptake to working muscles and stimulates signalling mechanisms that increase GLUT4 expression. Conversely, ROS also plays a role in inhibition of GLUT4 translocation and expression in metabolic disease states. The opposing roles of ROS in GLUT4 regulation is ultimately linked to the metabolic state of skeletal muscle and the intricate mechanisms involved give insights into pathways for exercise performance, metabolic health and disease.

CRediT authorship contribution statement

Sean L. McGee: Writing – review & editing, Writing – original draft. **Mark Hargreaves:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

Professor Sean McGee and Professor Mark Hargreaves own equity in Imitex Pty Ltd. Professor Sean McGee also owns equity in Ambetex Pty Ltd. The activities of these companies have no relationship to the content of this article.

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