Metabolism Clinical and Experimental 102 (2020) 154008

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Mini-Review

Skeletal muscle adiponectin induction in obesity and exercise

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ARTICLE INFO

Article history:
Received 26 August 2019
Accepted 28 October 2019

Keywords:
AdipoQ
High-fat diet
Skeletal muscle
Exercise

ABSTRACT

Recent scientific efforts have focused on the detrimental effects that obesity has on the metabolic function of skeletal muscles and whether exercise can improve this dysfunction. In this regard, adiponectin, with important metabolic functions (e.g. insulin-sensitizer and anti-inflammatory), has been recently described as a myokine that acts in an autocrine/paracrine manner. Earlier studies reported that muscle adiponectin could be induced by pro-inflammatory mediators (e.g. lipopolysaccharide), cytokines, and high-fat diets, providing a protective mechanism of this tissue against metabolic insults. However, when metabolic insults such as high-fat diets are sustained this protective response becomes dysregulated, making the skeletal muscle susceptible to metabolic impairments. Recent studies have suggested that exercise could prevent or even reverse this process. Considering that most scientific knowledge on adiponectin dysregulation in obesity is from the study of adipose tissue, the present review summarizes and discusses the literature available to date regarding the effects of obesity on skeletal muscle adiponectin induction, along with the potential effects of different exercise prescriptions on this response in an obesity context.

Contents

Abbreviations: IL-6, interleukin-6; LMW, low-molecular weight; HMW, high-molecular weight; AdipoR, adiponectin receptor; I.P., intraperitoneal; LPS, lipopolysaccharide; TNF, tumor necrosis factor; HNE, 4-hydroxy-2-nonenal; HO-1, heme oxygenase 1; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, peroxisome proliferator-activated receptor γ; EDL, extensor digitorum longus; MMW, medium-molecular weight; HFD, high-fat diet; APPL, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper.

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1. Endocrine function of skeletal muscles

It has been well-described that skeletal muscle produces mediators named "myokines" that can have an endocrine or an autocrine/paracrine action [1]. The first study that demonstrated this secretory feature of muscles was published in 2000, where six healthy males performed one leg knee extensions at 40% of peak power output for 5 h, with the resting leg acting as a control. Exercise resulted in 19-fold systemic increases in arterial interleukin-6 (IL-6) levels, with a similar net IL-6 release in the

https://doi.org/10.1016/j.metabol.2019.154008
0026-0495/

exercising leg without changes in the resting leg, suggesting that the circulatory increase of this protein was exercise dependent and due to muscle production and secretion [2]. In this context, recent efforts have been focused on characterizing the secretome [3] or myokinome [4] of skeletal muscles during exercise, to identify potential therapeutic strategies, particularly in the context of metabolic dysfunctions. This is a complex challenge given >10,000 proteins can be identified in skeletal muscles after exercise, whereas >9000 can be found in the circulation during post-exercise periods [4], which suggest that the variety of proteins that could be considered myokines is large. Further validation is required to confirm which myokines are predominantly muscle-produced/secreted, given that 200–600 proteins have been identified when analyzing primary human skeletal muscle cells culture medium [5,6]. It has recently been proposed that series of myokines might have important local metabolic roles in skeletal muscle, by regulating glucose uptake and availability through autocrine/paracrine mechanisms, as well as through endocrine signalling in communicating with other tissues that regulate carbohydrates and lipid availability in the circulation, such as adipose tissue and liver [1].

In particular, some myokines have received more scientific attention given their potential metabolic functions. For instance, acute increases in fibroblast growth factor 21 (FGF21) have been reported in mice and humans as a response to single bouts of exercise [7], suggesting FGF21 as a myokine. From a metabolic point of view, FGF21 has functions in increasing lipolysis in adipose tissue and fatty acid oxidation in the liver [8]. Another recently described myokine is musclin, which has been reported to be a regulator of exercise tolerance in mice. Specifically, in animals lacking the gene (Ostn) that encodes musclin, profound decreases in exercise tolerance has been seen. These changes were associated with decreases in peroxisome proliferator-activated receptor-gamma coactivator 1-α (PGC-1α) in skeletal muscles after exposure to exercise [9]. Such findings highlight the potential influence of this myokine in exercise-derived metabolic adaptations. Another important myokine sensitive to the actions of high-fat diet (HFD) and exercise (reduction and restoration, respectively) is myonectin [10], a regulator of lipid homeostasis given its ability to stimulate fatty acid uptake from adipocytes and hepatocytes; however, the exact mechanisms are still unclear [10]. An additional myokine that has received increasing attention is irisin, a 112 amino acid peptide first described by Bostrom et al. in 2012 [11]. It has been suggested to be involved in glucose metabolism and thermogenesis, with improved glucose tolerance and decreased fasting insulin in mice treated with adenoviral vectors containing the gene that encodes irisin (FNDC5). In the clinical setting, lower levels of irisin have been described in people with type 2 diabetes, regardless of time of diagnosis, age, gender, and body mass index [12], findings that strongly suggest that this myokine could be involved in metabolic regulation.

The study of myokines in metabolic disorders has been an active scientific area in recent years, with increasing recognition of paracrine and autocrine mediated effects as well as endocrine signalling. A summary of the described functions and experimental models used for the myokines described here is shown in Table 1.

2. Muscle adiponectin

A protein that has received much scientific attention in the last decade is adiponectin. From a structural perspective, adiponectin is a 30 kDa protein with a carboxy-terminal globular domain and an amino-terminal collagen domain, which enables it to form multimers [13,14]. These multimers are mainly comprised by the low (LMW) and high-molecular weight (HMW) isoforms [15], with the latter proposed to be the most bioactive [14]. The metabolic relevance of adiponectin resides in its multiple described functions as an insulin-sensitizer, as well as its anti-inflammatory and antioxidant activities [15]. Most of the studies addressing this protein have been focused on adipose-tissue secreted adiponectin which can be found in the circulation [15]. However, it has been described that adiponectin is also produced by muscle cells, acting in an autocrine/paracrine manner through the stimulation of two adiponectin receptors: AdipoR-1 (enriched in skeletal muscle) and AdipoR-2 (enriched in liver) [16–18]. Remarkably, these tissue levels appear to not be associated with the systemic presence of this protein [19]. Delaigle et al. were one of the first groups to report the presence of adiponectin mRNA and protein in mouse *tibialis anterior* muscles. Interestingly, they found that inflammatory challenges such as intraperitoneal (I.P.) injections of LPS were able to induce increases in adiponectin mRNA (8-fold) and total muscle adiponectin protein (~2-fold), findings that were confirmed by cultivating C_2C_{12} myotubes with interferon ɣ plus TNF, where similar increases in mRNA (20-fold) were observed [20]. This suggests that muscle adiponectin induction might act as a protective measure against metabolic challenges. Moreover, the same research group tested this hypothesis further by comparing the metabolic consequences that I.P. injections of LPS could cause in *tibialis anterior* muscles from wild-type C57BL6 male mice and adiponectin KO mice. As expected, LPS reproduced the increases in total muscle adiponectin protein in wild-type animals, along with increases in the protein content of oxidative stress (4-hydroxy-2-nonenal (HNE), heme oxygenase 1 (HO-1), and peroxiredoxin −3 and −5), inflammation (TNF), and apoptosis (caspase-6) markers. Intriguingly, muscles from adiponectin KO animals exhibit further increases in those stress markers. Furthermore, electrotransfer through electroporation of the adiponectin gene to *tibialis anterior* of KO animals reversed these changes [17].

However, it seems that adiponectin induction in skeletal muscles in not homogenous throughout muscle the tissue, since muscle fibres with higher intramyocellular lipid content have higher levels of adiponectin (e.g. type IIA fibres) [18]. This suggests that adiponectin expression in skeletal muscles might be tightly related to oxidative pathways to produce energy.

In this context, Iwabu et al. investigated the pathways by which adiponectin induces its metabolic effects in skeletal muscle by analyzing the muscle phenotype of muscle-specific AdipoR1 KO mice. Mutant mice were glucose intolerant, insulin resistant, and showed lower endurance capacities. Their muscles exhibited a lower number of mostly oxidative type I fibres and lower levels of β-oxidation, changes that confirmed that adiponectin action on skeletal muscles influence its

Table 1
Summary of described functions and experimental models of some metabolism-involved myokines.

Myokine	Described functions	Experimental models		
		Cells	Rodents	Humans
IL-6	Regulates glucose homeostasis	✓ [39]	✓ [40]	✓ [39]
FGF21	Increases lipolysis in adipose tissue and fatty acid oxidation in liver	✓ [41]	✓ [7]	✓ [7]
Musclin	Regulates aerobic adaptations to exercise	✓ [42]	✓ [9]	✓ [43]
Myonectin	Regulates lipid homeostasis in adipose tissue and liver	✓ [10]	✓ [10]	✓ [44]
Irisin	Regulates glucose metabolism and thermogenesis	✓ [45]	✓ [46]	✓ [45]
Adiponectin	Insulin-sensitizer, anti-inflammatory, anti-oxidant	✓ [20]	✓ [30]	✗

IL-6: interleukin 6; FGF-21: fibroblast growth factor 21.

oxidative capacity. Furthermore, lower levels of mRNA (0.6-fold) and protein (0.6-fold) of PGC-1α were found in mutant animals compared with their wild-type peers, along with disturbances in the deacetylase activity of Sirtuin 1 (SIRT1), which also further facilitates PGC-1α activation [21]. Altogether, these findings highlight the metabolic relevance of adiponectin signalling in skeletal muscles, which seems to be mostly related to its influences on oxidative pathways and mitochondrial function. In support of this, a recently published review by Krause et al. [22] has thoroughly discussed the known-to-date specific effects of adiponectin on skeletal muscle physiology; highlighting its involvement in the intramyocellular calcium concentration and muscle mass regulation, its action as a negative regulator of inflammation and autophagy stimulator.

A summary of the muscle adiponectin induction process, along with its proposed functions is showed in Fig. 1.

3. Muscle adiponectin induction during obesity

The effect of muscle adiponectin on metabolism in animal models of obesity has been studied mainly for its systemic, endocrine effects. The use of dietary interventions [16,23–29] and leptin mutants [25,30] (e.g. *ob*/*ob* and *db*/*db* mice) have been useful in this field. For instance, after 20 weeks of high fat/high sucrose diet, rat *gastrocnemius* muscles exhibit decreases in total adiponectin (~0.5-fold), changes that were rescued by a peroxisome proliferator-activated receptor ɣ (PPARɣ) agonist [29]. These results are in concordance with studies that showed that muscle-specific overexpression of PPARɣ in mice induced muscle adiponectin production [31]. Others have also reported decreases in muscle adiponectin protein in the *soleus* muscles (0.6-fold) of *db*/*db* mice [25]. Interestingly, contrary findings have been described in mice after 8 weeks [16] and 16 weeks [23] of high fat/high sucrose consumption, and also in *ob*/*ob* mice [30] where increases of this protein (~1.6-fold) have been reported. These discrepancies could be due to the model used to study these responses, the muscles analysed, along with which adiponectin isoforms were measured, as results from all the previously mentioned studies either measured total adiponectin content (all isoforms altogether) or a single (monomer) isoform of adiponectin (30 kDa). Lack of measurement of the most bioactive isoforms of adiponectin might be considered as a limitation, given the physiological ability of adiponectin to form multimers. In support of this, Liu et al. in two different experiments, highlighted the relevance of measuring different muscle adiponectin isoforms, along with the comparison between different muscles. First, in Wistar rats they investigated the effect of 9 weeks of high fat/high sucrose diet on *gastrocnemius* adiponectin induction. Decreases of adiponectin mRNA were found (0.6-fold), despite no changes in total protein content. Interestingly, only the high-molecular weight (HMW, >250 kDa) isoform was reduced (~0.7-fold). Moreover, in a separate experiment in *db*/*db* mice, they compared muscle adiponectin profiles of *soleus* and *extensor digitorum longus* (EDL) muscles, by measuring total muscle adiponectin plus three different isoforms: HMW, medium-molecular weight (MMW, ~150 kDa), and low-molecular weight (LMW, ~100 kDa). Intriguingly, the highly oxidative *soleus* muscle showed decreases in total (0.8-fold) and HMW adiponectin (~0.6-fold) and increases in lower isoforms such as MMW (~1.3-fold), whereas the highly glycolytic EDL exhibited increases only in the LMW (~2-fold) compared to their wildtype peers [25]. Our group has found similar results. For instance, after 10 weeks [32] and 20 weeks [33] of high-fat diet (HFD), decreases in HMW isoform in quadriceps (as a partially oxidative muscle) were detected in mice, whereas no major changes were seen in LMW levels.

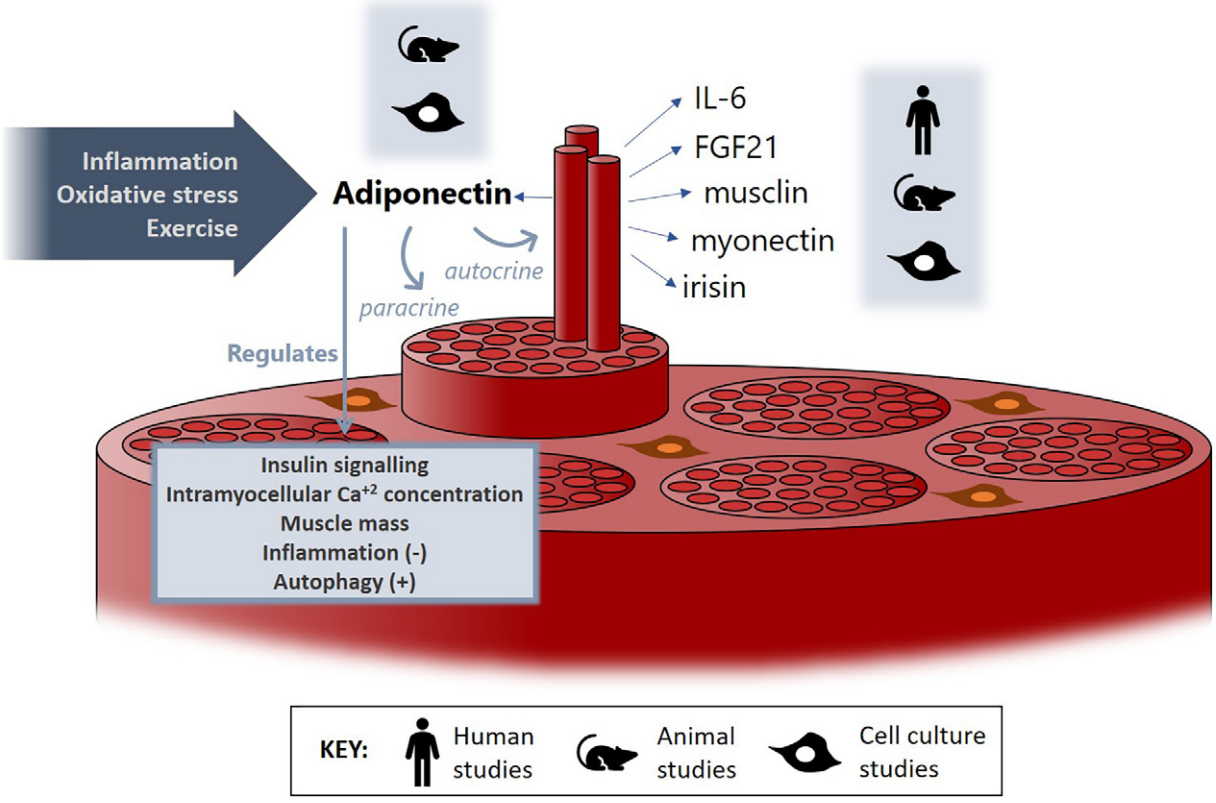

Fig. 1. Characteristics of muscle adiponectin induction. Under several types of metabolic stress (e.g. inflammation, oxidative stress, and exercise), skeletal muscles produce adiponectin in an autocrine/paracrine manner. This myokine is proposed to regulate several functions in this organ, such as: insulin signalling, intramyocellular Ca^{+2} concentration, muscle mass, inflammation, and autophagy. However, in comparison with other metabolically relevant myokines (e.g. IL-6, FGF21), no human studies are known on this topic. IL-6: interleukin 6; FGF21: fibroblast growth factor 21.

In a subsequent study, we investigated the effects of 10 weeks of HFD on the adiponectin profile of glycolytic muscles (*gastrocnemius* and *masseter*) in mice. Here, increases in LMW adiponectin protein levels (~1.5-fold) were seen without major effects on the HMW isoform [34]. These findings suggest that in order to reach valid conclusions regarding muscle adiponectin induction, the type of muscle analysed, along with analysis of various adiponectin isoforms, are essential requirements for ensuring accurate reporting and interpretation of studies in this field.

Fewer studies have been focused on the analysis of the mediators of adiponectin signalling in skeletal muscle during obesity. These studies have mostly focused on the effects of HFD on the expression of skeletal muscle adiponectin receptors and one of its immediate downstream factors such as adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 and 2 (APPL1-2) [24,26,28]. This protein has been associated with the regulation of the insulin receptor signalling pathway, particularly under adiponectin signalling [35]. In swiss mice after 12 weeks of HFD, Farias et al. found lower levels of AdipoR1 protein (~0.3-fold) in their skeletal muscles. Unfortunately, the specific muscle used for analysis was not described, and muscle-specific adiponectin measurements were not conducted. Nevertheless, decreases of APPL1 protein (~0.25-fold) were also found in those animals [24], suggesting that HFD also promoted dysregulations in downstream factors of muscle adiponectin. However, there were discordant findings between different studies, given that no changes in muscle AdipoR1 and AdipoR2 protein were found in C57BL6 mice after 10 weeks of HFD. Notably, no changes in APPL1 or APPL2 were seen; however, the specific muscle analysed was also not reported [28], which hinders further interpretation. Moreover, differential responses between AdipoRs have been described after 10 weeks of HFD in C57BL6 mice, where *gastrocnemius* muscle showed mild increases in protein levels of AdipoR2 (1.3-fold) whereas no changes were seen in AdipoR1 [26]. In contrast, our studies have found consistent decreases of AdipoR1 protein levels (~0.5-fold) after 10 and 20 weeks of HFD in *quadriceps* and *gastrocnemius* muscles from mice [32–34].

Future research should elucidate if the differential response described here was because of an eventual differential response to metabolic stress, particularly HFD, between different muscles. This is plausible given the previously described specificity of metabolic actions regarding muscle adiponectin induction and its downstream factors. Table 2 provides a summary of previous studies examining the effects of obesity on the induction of muscle adiponectin in animal models.

4. Effects of exercise on muscle adiponectin induction

In terms of therapeutic strategies that could induce muscle adiponectin, various modalities and durations of physical exercise have been tested in animal models with promising results. In lean Sprague-Dawley rats, 6 months of treadmill training resulted in increased adiponectin mRNA (~6-fold) as well as the protein monomer (30 kDa; ~1.3-fold) in *gastrocnemius*. Interestingly, these changes were associated with increases of AdipoR1 (~2-fold) protein levels [36], suggesting a multifaceted role for exercise on muscle adiponectin induction and its mediators. Using a different experimental approach, Goto et al. investigated the effects of different levels of mechanical loads on muscle adiponectin induction. First, they overloaded *soleus* muscles in C57BL6 mice by excision of agonists (*plantaris* and *gastrocnemius*), finding that after 3 weeks in this condition, increases of the adiponectin monomer were found (~1.5-fold), changes that were associated with increases in APPL1 protein (~3-fold). Secondly, they investigated the effect of decreases in mechanical load on *soleus* muscle through hindlimb suspension for 2 weeks in C57BL6 mice with a subsequent recovery period of 2 and 4 weeks. Decreases of AdipoR1 mRNA levels were seen after 2 weeks of suspension (~0.8-fold), whereas in the recovery process, increases adiponectin monomer (~1.3-fold) and APPL1 protein levels (~1.7-fold) were described after 2 weeks [37]. These findings highlight the relevance of muscle adiponectin and its signalling when skeletal muscles are challenged to different levels of mechanical loads. In that context, our group has reported that 10 weeks of constant-moderate intensity exercise resulted in significant increases of LMW adiponectin (~1.5-fold) in the *gastrocnemius* of lean mice [34]. Nevertheless, other studies have reported that *soleus* muscles from Wistar rats did not exhibit changes in total muscle adiponectin protein after 12 weeks of treadmill training at low, moderate, and high intensities [19], finding that could highlight that the animal model (mouse vs rat, and its respective strains) could have an influence on these outcomes and should be explored. In this regard, one of the main difficulties in interpreting these results is the outcome discrepancies between the different studies (e.g. total adiponectin vs isoforms). However, in the understanding that adiponectin isoforms could have different bioactivity [38], the different complexes should be measured in order to achieve interpretable conclusions.

The effects of exercise on muscle adiponectin induction in animal models of obesity have also been explored. *Gastrocnemius* muscles from diabetic (streptozotocin-induced) albino rats fed with HFD for 12 weeks, exhibited increases of adiponectin mRNA levels (~3-fold) following 9 weeks of swimming training in comparison with untrained peers, however no protein data was given [27]. Furthermore, increased protein levels of AdipoR1 (~2-fold) and APPL1 (~2.5-fold) were seen in skeletal muscles (specific muscle not indicated) from Swiss mice that were fed with HFD and simultaneously undergoing swimming training for 12 weeks, compared to its untrained counterparts [24]. Notably, these results differ from what Pierard et al. reported in *gastrocnemius* muscles from C57BL6 mice where, after 10 weeks of HFD and simultaneous treadmill training at moderate intensity for the last 8 weeks, AdipoR1 protein levels were unchanged [26]. These discrepancies raise questions about the relevance of the muscle groups analysed, along with the eventual importance that the type of exercise program could have on muscle adiponectin induction, particularly in a model of metabolic dysfunction such as obesity. In this context, previous studies have described that exercise (constant-moderate intensity more so than high-intensity interval training) normalized the HFD driven decreases of HMW adiponectin in the *quadriceps* of mice [32]. Interestingly, in glycolytic muscles (*gastrocnemius* and *masseter*), HFD induced increases in LMW adiponectin, and 10 weeks of constant-moderate exercise normalized this response by reducing this isoform to lean equivalent levels. Furthermore, exercise in the form of running at moderate or high intensities did not change the finding that non-locomotor muscles, such as *masseter* did not exhibit HMW adiponectin [34], which suggests that any exercise-induced changes in this isoform are dependent on the intervention and not associated with systemic modifications driven by exercise. In terms of timing of sample collection, it is interesting to highlight that the studies which described increases in AdipoR protein levels collected their samples 24 h after the last training session [26,36]. In contrast, in our studies, samples were collected at least 72 h after the last exercise session, and no major changes were found in AdipoR1 [32,33]. It may be that AdipoR levels are dynamic, and they might change depending on the presence or absence of the metabolic challenge, in this case, exercise.

Collectively, these studies highlight that future research should compare different exercise protocols on muscle adiponectin induction during obesity, particularly from a clinical perspective, given that no human studies have reported on this topic. From a pre-clinical point of view, muscle-specific adiponectin KO animals could also shed some light on the relevance of muscle adiponectin induction after exercise, particularly in an obesity context. A summary of the studies regarding the effects of exercise and different levels of mechanical loads on muscle adiponectin induction is displayed in Table 3.

5. Final comment

Skeletal muscles are recognised as an endocrine organ, given their ability to produce myokines. One of them that has received little

Table 2
Effects of obesity on skeletal muscle adiponectin induction.

Study	Design	Muscle	Results	Adiponectin	AdipoRs	Downstream factors
Yang et al. [29]	Sprague-Dawley rats. 20 weeks of high fat/high sucrose diet.	Gastroc	Protein mRNA	↓ total –	– –	– –
Delaigle et al. [30]	*ob*/*ob* mice.	Tibialis anterior	Protein mRNA	↑ total ↑ total	– –	– –
Bonnard et al. [23]	C57BL6 mice. 4 weeks of high fat/high sucrose diet. C57BL6 mice. 16 weeks of high fat/high sucrose diet.	Gastroc Gastroc	Protein mRNA Protein mRNA	↔ monomer – ↑ monomer –	– – – –	– – – –
Liu et al. [25]	Wistar rats. 9 weeks of high fat/high sucrose diet. *db*/*db* mice.	Gastroc EDL Soleus	Protein mRNA Protein	↔ total ↓ HMW ↓ Soleus ↓ total ↓ HMW ↑ MMW ↔ LMW EDL ↔ total ↔ HMW ↔ MMW ↑ LMW	– – –	– – –
Farias et al. [24]	Swiss mice. 12 weeks of HFD (60% fat)	Not declared	Protein mRNA	– –	↓ −1 –	↓ APPL1 –
Jortay et al. [16]	C57BL6 mice. 8 weeks of high fat/high sucrose diet	Tibialis anterior	Protein mRNA	↑ total –	– –	– –
Safwat et al. [27]	Albino rats. 12 weeks of HFD (42% fat) + 1 I.P. injection of STZ.	Gastroc	Protein mRNA	– ↓	– –	– –
Vu et al. [28]	C57BL6 mice. 10 weeks of HFD (60% fat).	Not declared	Protein mRNA	– –	↔ −1 ↔ −2 –	↔ APPL1 ↔ APPL2 –
Pierard et al. [26]	C57BL6 mice. 10 weeks of HFD (60% fat)	Gastroc	Protein mRNA	– –	↔ −1 ↑ −2 –	– –
Martinez-Huenchullan et al. [32]	C57BL6 mice. 10 weeks of HFD (45% fat)	Quad	Protein mRNA	↔ LMW ↓ HMW ↑	↓ −1 ↔ −1	– ↔ Sirt1 ↓ Pgc-1a ↑ Ucp2
Martinez-Huenchullan et al. [34]	C57BL6 mice. 10 weeks of HFD (45% fat)	Gastroc Masseter	Protein mRNA	Gastroc ↑ LMW ↔ HMW Masseter ↑ LMW HMW undetectable Gastroc ↑ Masseter ↔	 ↓ −1 ↔ −1 ↔ −1 ↔ −1	– ↔ Sirt1 ↔ Pgc-1a ↑ Ucp2 ↔ Sirt1 ↓ Pgc-1a ↔ Ucp2
Martinez-Huenchullan et al. 2018	C57BL6 mice. 20 weeks of HFD (45% fat)	Quad	Protein mRNA	↔ LMW ↓ HMW ↔	↓ −1 ↔ −1	– ↔ Sirt1 ↓ Pgc-1a ↔ Ucp2

Abbreviations: AdipoRs, adiponectin receptors; mRNA: messenger RNA; Gastroc: gastrocnemius; EDL: extensor digitorum longus; Quad: quadriceps; HMW: high-molecular weight; MMW: medium-molecular weight; LMW: low-molecular weight; HFD: high-fat diet; APPL: adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; Pgc-1a: peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; Ucp2: Uncoupling protein 2; Sirt1: sirtuin 1; I.P.: intraperitoneal; STZ: streptozotocin.

attention is adiponectin, probably because this protein is classically described as an adipokine. Interestingly, it seems that muscle levels of adiponectin are not associated with its circulating levels, highlighting a potential independent process in skeletal muscles. Given that muscle adiponectin has been described to act through an autocrine/paracrine manner, it suggests that this protein might have regulatory functions in muscle that don't rely on cross-talk with other insulin-sensitive tissues. Considering that its induction seems to be associated with the

Table 3
Effects of exercise and increases of mechanical loads on skeletal muscle adiponectin induction.

Study	Animal|diet|intervention	Muscle	Results	Adiponectin	AdipoRs	Downstream factors
Garekani et al. [19]	Wistar rats|Chow standard diet| Treadmill training (0% slope, 60 min/day, 5 days/week, for 12 weeks) at three different intensities: Low: 20 m/min Moderate: 28 m/min High: 34 m/min	Soleus	Protein	↔ total (in all intensities)	–	–
			mRNA	–	–	–
Farias et al. [24]	Swiss mice|12 weeks of HFD (60% fat)| Swimming training (2 × 30 min/day, 5 days/week, for 12 weeks)	Not provided	Protein	–	↑ -1 (vs HFD untrained)	↑ APPL1 (vs HFD untrained)
			mRNA	–	–	–
Dai et al. [36]	Sprague-Dawley rats|Chow standard diet|Treadmill training (15% slope, 20 m/min, 60 min/day, 5 days/week, 6 months)	Gastroc	Protein	↑ monomer	↑ -1	–
			mRNA	↑	–	–
Safwat et al. [27]	Albino rats|12 weeks of HFD (42% fat) + 1 I.P. injection of STZ|Swimming training (10–40 min × 1–4 sessions/day, 5 days/week, for 9 weeks)	Gastroc	Protein	–	–	–
			mRNA	↑ (vs HFD untrained)	–	–
Goto et al. [37]	C57BL6 mice|Chow standard diet| Overloading of soleus muscle by excision of agonists for 1 and 3 weeks.	Soleus	Protein	↑ monomer (after 3 weeks)	–	↑ APPL1 (after 3 weeks)
			mRNA	↑ (after 1 and 3 weeks)	↔ −1 ↑ −2 (after 1 and 3 weeks)	
	C57BL6 mice|Chow standard diet| Hindlimb suspension for 2 weeks and recovery for 2 and 4 weeks.	Soleus	Protein	↑ monomer (after 2 weeks of recovery)	–	↑ APPL1 (after 2 weeks of recovery)
			mRNA	↔	↓ −1 (after 2 weeks of hindlimb suspension) ↔ −2	–
Pierard et al. [26]	C57BL6 mice|10 weeks of HFD (60% fat)|Treadmill training (70% of MRC, 60 min/day, 5 days/week, for 8 weeks)	Gastroc	Protein	–	↑ −1 (vs Chow untrained) ↔ −1 (vs HFD untrained) ↔ −2 (vs Chow untrained) ↔ −2 (vs HFD untrained)	–
			mRNA	–	–	–
Martinez-Huenchullan et al. [32]	C57BL/6 mice|10 weeks of HFD (45% fat)|Treadmill training (0% slope, 70% of MRC (END) or 8 bouts at 90% of MRC intercalated by 8 active rest periods at 50% of MRC (HIIT)), 40 min/day, 3 days/week, for 10 weeks)	Quad	Protein	↔ LMW ↑ HMW (vs HFD untrained after END and HIIT)	↔ −1	–
			mRNA	↑ (vs HFD untrained)	↔ −1	↔ Sirt1 ↔ Pgc-1a ↔ Ucp2
Martinez-Huenchullan et al. [34]	C57BL/6 mice|10 weeks of HFD (45% fat)|Treadmill training (0% slope, 70% of MRC (END) or 8 bouts at 90% of MRC intercalated by 8 active rest periods at 50% of MRC (HIIT)), 40 min/day, 3 days/week, for 10 weeks)	Gastroc Masseter	Protein	↑ LMW (vs Chow untrained; Gastroc after END) ↔ HMW (Gastroc) ↓ LMW (vs HFD untrained after END; Masseter) HMW undetectable (Masseter)	↓ −1; Gastroc ↔ −1; Masseter	–
			mRNA	↓ (vs HFD untrained; Gastroc) ↔ (Masseter)	↓ −1 (vs HFD untrained; Gastroc) ↓ −1 (vs HFD untrained; Masseter)	↓ Sirt1 (vs HFD untrained; Gastroc) ↓ Pgc-1a (vs HFD untrained; Gastroc) ↓ Ucp2 (vs HFD untrained; Gastroc) ↓ Sirt1 (vs HFD untrained; Masseter) ↓ Pgc-1a (vs HFD untrained; Masseter) ↔ Ucp2 (vs HFD untrained; Masseter)
Martinez-Huenchullan et al. 2018	C57BL/6 mice|20 weeks of HFD (45% fat)|Treadmill training (0% slope, 70% of MRC (END) or 8 bouts at 90% of MRC intercalated by 8 active rest periods at 50% of MRC (HIIT)), 40 min/day, 3 days/week, for the last 10 weeks)	Quad	Protein	↔ LMW ↔ HMW (normalized HFD driven changes after both training programs)	↔ −1 (normalized HFD driven changes after HIIT)	–
			mRNA	↔	↔ −1	↔ Sirt1 ↓ Pgc-1a (vs Chow untrained) ↔ Ucp2

Abbreviations: AdipoRs, adiponectin receptors; mRNA: messenger RNA; HFD: high-fat diet; APPL: adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; HMW: high-molecular weight; MMW: medium-molecular weight; LMW: low-molecular weight; Gastroc: gastrocnemius; Quad: quadriceps; Pgc-1a: peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; Ucp2: Uncoupling protein 2; Sirt1: sirtuin 1; I.P.: intraperitoneal; STZ: streptozotocin.

presence of metabolic challenges (e.g. inflammation, obesity) it is plausible that adiponectin production in skeletal muscle might be a protective mechanism.

Particularly from an obesity-exercise perspective, muscle adiponectin induction is not simple to study, given that several factors such as diet, muscle type, and exercise intensity seem to influence this response (Fig. 2).

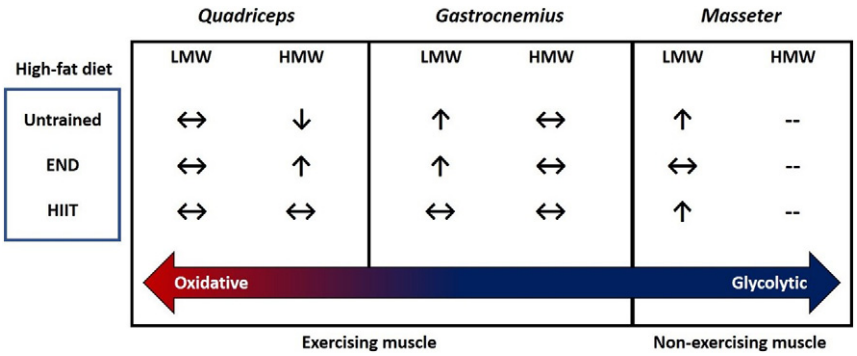

Fig. 2. Interactions between high-fat diet, muscle type/activity, and exercise on skeletal muscle adiponectin in mice. Arrows indicate changes in protein levels compared to CHOW untrained animals. – indicates that this isoform was not detectable. LMW: low-molecular weight; HMW: high-molecular weight.
Adapted from Martinez-Huenchullan et al. [33].

Moreover, HFD decreases more bioactive isoforms (HMW adiponectin) in muscles with higher oxidative fibres (e.g. *quadriceps* and *soleus*), whereas in more glycolytic muscles (e.g. *gastrocnemius* and *EDL*) it induces an increase in less bioactive isoforms (e.g. monomer, LMW adiponectin), probably as a protective mechanism against an increase in fat influx. Interestingly, certain isoforms (e.g. HMW adiponectin) were only present in muscles associated with locomotion/running, suggesting that muscle activity is a strong factor regulating this response. Furthermore, AdipoR1 seems to be susceptible to HFD by decreasing its expression on muscle, which might decrease its signalling in this tissue. However, recent reports have suggested that exercise can prevent or even reverse this change (Fig. 3).

To date, only preclinical studies are available on this topic, which makes the development of human studies important to corroborate the findings described in such studies, and most importantly, to assess the clinical significance of this feature of skeletal muscles, particularly in the context of metabolic dysfunction. The described effects of exercise on this response in an obesity context are promising however, the lack of studies focused on the comparison of different exercise protocols on this response is concerning. Future clinical trials regarding the effects of exercise during obesity should include muscle adiponectin induction outcomes (different isoforms, receptor content, and downstream factors), as a potential mediator of the classically described beneficial effects of exercise.

Financial disclosure

SM-H is supported in this work by a National Commission for Scientific and Technological Research (CONICYT) Becas Chile Scholarship for foreign Ph.D. programs (Resolución Exenta #2185/2015). CST is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (#1037275).

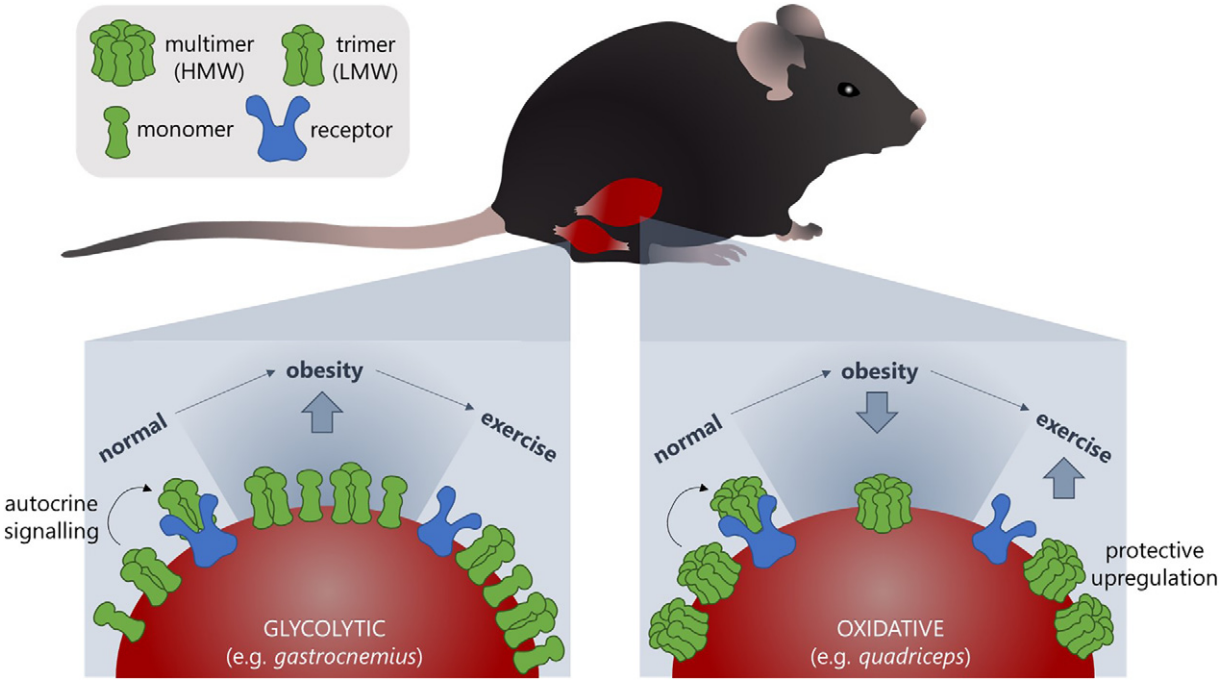

Fig. 3. Summary of changes in skeletal muscle adiponectin expression. Under normal circumstances, adiponectin (green) interacts with its receptor (AdipoR1; blue) on myocytes via autocrine and paracrine signalling. In the context of obesity, the adiponectin monomer and low molecular weight (LMW) trimer are increased in expression on predominantly glycolytic muscles, whereas exercise intervention has no effect on this change. In contrast, the high molecular weight (HMW) multimer is decreased in predominantly oxidative muscles during obesity. Since this is the most bioactive form of adiponectin, there is a protective upregulation following exercise intervention. AdipoR1 is reported to be decreased in both muscle types during obesity, whereas exercise prevents or reverses this downregulation. Arrows refer to changed expression of adiponectin ligand.

Author contributions

Manuscript drafting: S.M—H., C.S.T., S.M.T. Editing and revision of manuscript: S.M-H., C.S.T., L.A.B., P.E—S., S.V.M., S.M.T. Final version of manuscript approved by: S.M—H., C.S.T., L.A.B., P.E—S., S.V.M., S.M.T.

Declaration of competing interest

The authors have no conflict of interest to declare.

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