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REVIEW

The effects of obesity on skeletal muscle contractile function

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ABSTRACT

Obesity can cause a decline in contractile function of skeletal muscle, thereby reducing mobility and promoting obesity-associated health risks. We reviewed the literature to establish the current state-of-knowledge of how obesity affects skeletal muscle contraction and relaxation. At a cellular level, the dominant effects of obesity are disrupted calcium signalling and 5′-adenosine monophosphate-activated protein kinase (AMPK) activity. As a result, there is a shift from slow to fast muscle fibre types. Decreased AMPK activity promotes the class II histone deacetylase (HDAC)-mediated inhibition of the myocyte enhancer factor 2 (MEF2). MEF2 promotes slow fibre type expression, and its activity is stimulated by the calcium-dependent phosphatase calcineurin. Obesity-induced attenuation of calcium signalling via its effects on calcineurin, as well as on adiponectin and actinin affects excitation–contraction coupling and excitation–transcription coupling in the myocyte. These molecular changes affect muscle contractile function and phenotype, and thereby *in vivo* and *in vitro* muscle performance. *In vivo*, obesity can increase the absolute force and power produced by increasing the demand on weight-supporting muscle. However, when normalised to body mass, muscle performance of obese individuals is reduced. Isolated muscle preparations show that obesity often leads to a decrease in force produced per muscle cross-sectional area, and power produced per muscle mass. Obesity and ageing have similar physiological consequences. The synergistic effects of obesity and ageing on muscle function may exacerbate morbidity and mortality. Important future research directions include determining: the relationship between time course of weight gain and changes in muscle function; the relative effects of weight gain and high-fat diet feeding per se; the effects of obesity on muscle function during ageing; and if the effects of obesity on muscle function are reversible.

KEY WORDS: Myosin heavy chain, AMPK, HDAC, Calcineurin, Insulin, Work-loop, Force, Power, Ageing

Introduction

Obesity (see Glossary) is a major global health epidemic of the 20th and 21st centuries (Busutil et al., 2017; Hales et al., 2017). The World Health Organization defines obesity as abnormal or excessive fat accumulation that may impair health, indicated by a body mass index [BMI=mass (kg)/height^2 (m^2)]≥30 (Hales et al., 2017). Obesity has well-known metabolic effects, and leads to serious health complications by causing metabolic syndrome (see Glossary), cardiovascular disease, type 2 diabetes, and even increasing the risk of cancer (Muoio and Newgard, 2006). In addition to its metabolic effects, obesity can affect skeletal muscle function and thereby reduce mobility of obese individuals (Teasdale et al., 2013). There are two opposing trends. On the one hand, skeletal muscle of obese individuals has to work harder to move a greater body mass, which may result in a positive training effect (Garcia-Vicencio et al., 2016). On the other hand, obesity can also lead to a decrease in muscle mass and to lower muscle quality (Prado et al., 2008; Tallis et al., 2017). Overall, obesity is likely to lead to a reduced ability of skeletal muscle to maintain locomotor performance, which leads to lower mobility in obese individuals. Movement is important for maintaining a healthy body composition. Hence, the effects of obesity on the contractile performance of skeletal muscle may cause a negative obesity cycle: reduced mobility is likely to lead to lower activity levels and energy use, thereby causing further weight gain and consequently a reduction in quality of life (Busutil et al., 2017). Obesity accelerates the ageing process (Baumgartner et al., 2004), and it is particularly important to understand better the combined effects of obesity and ageing on skeletal muscle performance considering the ageing populations in many countries. Our aim here is to provide a summary of the cell signalling systems in skeletal muscle that are affected by obesity, and integrate these with current knowledge of the effects of obesity on skeletal muscle function and its interaction with ageing.

Muscle consists of different fibre types that determine metabolic and contractile properties (Fig. 1). Many of the effects of obesity on muscle function are mediated by its effect on fibre type composition. Muscle fibres are classified on the basis of their myosin heavy chain (MHC) isoform composition, which are broadly categorised into slow and fast fibres. In humans, these are slow type I and IIa fibres, which are poised towards oxidative metabolism with high fatigue resistance, but low shortening velocity, force and power production. At the other end of the spectrum are fast type IId/x and IIb fibres that are glycolytically poised with high shortening velocity, force and power production, but low fatigue resistance (Bassel-Duby and Olson, 2006). There is variation in the categorisation of fibre types and their mechanical properties among species (Berchtold et al., 2000; Schiaffino and Reggiani, 2011). However, while the details may change, the general categorisation of function into ‘slow’ and ‘fast’ fibre types remains valid.

Different fibre types have different isoforms of proteins involved in muscle excitation–contraction (see Glossary) and relaxation coupling. In addition to differences in the expression of myosin heavy chains, each fibre type may have different troponin and tropomyosin isoforms that translate the calcium signal to actin and myosin-mediated contraction. Fibre types can also differ in the sarco-endoplasmic reticulum ATPase (SERCA) isoforms that re-sequester calcium back into the sarcoplasmic reticulum to facilitate relaxation (Gordon et al., 2000; Gundersen, 2011). This variation ultimately leads to differences in metabolic and contractile function (James et al., 1995; Berchtold et al., 2000).

Obesity is associated with a shift to a faster muscle phenotype (Helge et al., 1999; Tanner et al., 2002; de Wilde et al., 2008; Stuart et al., 2013; Seebacher et al., 2017). Slow type I muscle fibres have

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List of abbreviations

AMP	adenosine monophosphate
AMPK	5′-adenosine monophosphate-activated protein kinase
ATP	adenosine triphosphate
BMI	body mass index
CaMK	calmodulin-dependent protein kinase
CnA	calcineurin
DAG	diacylglycerol
DAK-δ	diacylglycerol kinase delta
DHPR	dihydropyridine receptor
EDL	extensor digitorum longus
GLUT4	glucose transporter 4
HDAC	histone deacetylase
MEF2	myocyte enhancer factor 2
MHC	myosin heavy chain
NFAT	nuclear factor of activated T-cells
PGC-1α	peroxisome proliferator activated receptor gamma co-activator 1 alpha
PPARδ	peroxisome proliferator activated receptor delta
ROS	reactive oxygen species
RyR	ryanodine receptor
SERCA	sarco-endoplasmic reticulum ATPase
TGF-β1	transforming growth factor beta 1

greater insulin sensitivity and glucose uptake via the glucose transporter GLUT4 compared with fast fibres (Hickey et al., 1995; Bassel-Duby and Olson, 2006), so that fibre-type expression can be associated with metabolic as well as contractile characteristics of muscle (Zorzano et al., 2005; Gundersen, 2011; Wyckelsma et al., 2017). In addition, obesity-induced changes in contractile function may be associated with a reduction in myogenesis resulting from disruption of muscle satellite cell activation (Akhmedov and Berdeaux, 2013; D'Souza et al., 2015), changes in troponin isoforms that are involved in mediating cross-bridge cycling (see Glossary) (Ciapaite et al., 2015; Eshima et al., 2017), calcium handling and neuromuscular recruitment (Yoshida et al., 2012). However, these responses are not consistent across muscle groups, and experimentally established links between mechanisms and measures of contractility are lacking in an obesity model. Often, the responses to obesity are muscle specific, and the relatively small amount of literature means that understanding the effects of obesity on skeletal muscle contractile function is incomplete. It should be noted that changes in metabolic function can occur without fibre type transitions. For example, exercise training can lead to increases in metabolic capacities of muscle without changes in muscle fibre type (Rico-Sanz et al., 2003; Wyckelsma et al., 2017). Our aim here is to review the current state-of-knowledge, and to identify areas where research is currently lacking. We start by providing a mechanistic background and summarise the signalling processes that can mediate obesity-related changes in muscle fibre type (Fig. 2). A more thorough review of the signalling mechanisms that mediate muscle plasticity in general can be found in Hoppeler (2016). Changes in muscle fibre type are the most important mechanisms that alter contractile function as a result of obesity. The signalling processes we summarise in the first part of this Review therefore represent the mechanistic basis underlying changes in muscle contractile function *in vivo* and in isolated muscle preparations, which we review subsequently (Fig. 3). Lastly, we discuss the interaction between obesity and ageing, and identify future research directions.

Signalling processes affected by obesity

Muscle contractile function is largely determined by calcium signalling within the muscle cell (Fig. 1), and the activity of proteins

Glossary

Concentric muscle contraction
Force production while the muscle is shortening, e.g. shortening of the biceps while lifting an object.

Cross-bridge cycling
The binding between actin and myosin, leading to the shortening of the contractile part of the muscle cell, is termed a cross-bridge. Cross-bridge cycling is the repeated actin–myosin binding and detachment.

Eccentric muscle contraction
Force production while the muscle is lengthening, e.g. the quadriceps lengthens during walking while still producing power.

Excitation–contraction coupling
The process by which a neural signal leads to muscle contraction, which is mediated by calcium influx into the muscle cell.

Excitation–transcription coupling
Changes to gene transcription mediated by calcium influx into the muscle cell.

Isometric force
Force produced by a muscle of constant length.

Metabolic syndrome
A cluster of several medical conditions including obesity, high blood pressure, high blood glucose levels and high serum triglyceride levels.

Obesity
Abnormal or excessive fat accumulation that may impair health, indicated by a body mass index (BMI=mass [kg]/height^2 [m^2])≥30.

Stress
Stress is the force produced per muscle cross-sectional area.

Tetanus
Sustained isometric muscle contraction in response to high-frequency action potentials of the motor nerve, or electrical stimulation *in vitro*. A tetanus is characterised by the activation time or rate following stimulation, maximal tetanus force production, and a relaxation time or rate following stimulation.

Work loop technique
A specialised technique that measures *in vitro* muscle force production while the muscle is undergoing length changes. It is a more realistic indicator of *in vivo* muscle performance than isometric measures. The product of force and shortening velocity of the muscle is equal to the mechanical power produced.

responsible for muscle contraction and relaxation (Berchtold et al., 2000; Gundersen, 2011; Gehlert et al., 2015), both of which differ between fibre types. Obesity affects muscle force production and power output by altering fibre type composition and disrupting calcium cycling (Funai et al., 2013, 2016; Seebacher et al., 2017). Obesity often leads to a slow-to-fast muscle fibre transition (Tanner et al., 2002; DeNies et al., 2014; Lee et al., 2015; Seebacher et al., 2017). A similar shift in fibre types occurs in response to high-sugar and high-fat diets in the absence of obesity (Hyatt et al., 2016). The high-fat diet-induced reduction in absolute and relative force produced by the fast extensor digitorum longus (EDL) muscle in mice was not accompanied by changes in proteins related to calcium cycling (ryanodine receptor, dihydropyridine receptor, parvalbumin, SERCA), but there was a decrease in the fast troponin isoform (Ciapaite et al., 2015; Eshima et al., 2017), which mediates calcium sensitivity (Ogut et al., 1999). Below, we summarise the mechanisms by which obesity can alter muscle fibre composition and muscle mass. There are several intersecting signalling pathways that are affected by obesity, principally centred on calcium signalling and 5′-adenosine monophosphate-activated protein kinase (AMPK) activity.

Energy sensing: AMPK is a central signalling molecule in obesity

Obesity represents a disruption of whole-organism energy balance. In many animals, including humans, physiological signalling systems evolved in the context of high energy expenditure, often

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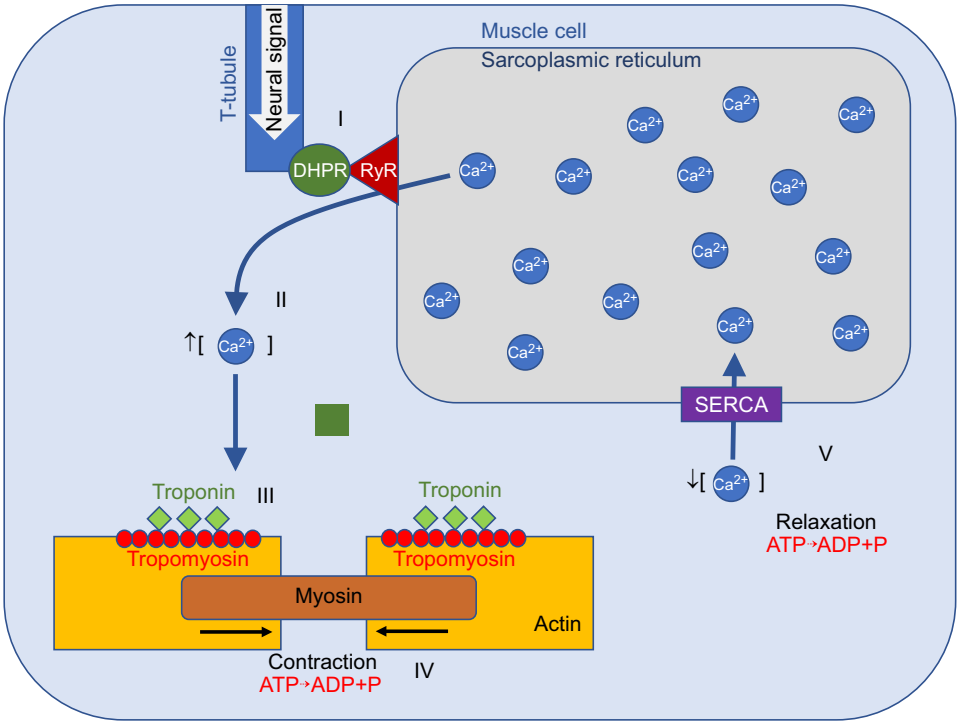

Fig. 1. Simplified description of the basic mechanisms that mediate muscle contraction and relaxation. Muscle contraction is initiated by a neural signal that stimulates specialised calcium channel proteins (dihydropyridine receptors, DHPR) situated in invaginations of the cell membrane projecting into the muscle cell, called t-tubules (I). Upon neural stimulation, DHPR physically interact with a second receptor, the ryanodine receptor (RyR), which is located in the membrane of the sarcoplasmic reticulum, an internal calcium store. When stimulated by DHPR, RyR releases calcium from the sarcoplasmic reticulum (II). Stimulation of DHPR also permits entry of extracellular calcium into the myocyte (not shown). Increased calcium concentrations inside the muscle cell lead to increased binding of calcium to troponin, a regulatory molecule that is associated with actin and myosin. Actin and myosin proteins represent the contractile apparatus of the muscle cell. Following calcium binding, troponin 'unlocks' tropomyosin, which in its unbound state prevents the interaction between actin and myosin (III). Once the inhibitory effect of tropomyosin is removed, myosin binds to actin via cross-bridges, which pull the myosin molecule along the actin molecule, thereby shortening the muscle fibre and causing muscle contraction. The sequence of events from nerve stimulation to contraction is termed excitation–contraction coupling. The actin/myosin-mediated contraction requires ATP, which is hydrolysed by myosin ATPase activity (IV). Calcium is re-sequestered into the sarcoplasmic reticulum by the sarco-endoplasmic reticulum ATPase (SERCA). The resultant decreases in calcium concentrations reverse the contraction process described above and cause muscle relaxation (V). SERCA hydrolyses ATP to pump calcium back into the sarcoplasmic reticulum. The basic mechanisms of contraction and relaxation are similar in fast and slow fibres, but the different muscle fibres possess different isoforms of the proteins involved such as myosin heavy and light chains, troponin and SERCA. In addition, there are some fibre type-specific proteins such as parvalbumin in fast fibres, which enhance calcium binding and thereby increase relaxation rates. More detailed descriptions of these mechanisms can be found in Berchtold et al. (2000), Gordon et al. (2000) and Gundersen (2011).

in environments with low nutrient and energy availability (Booth et al., 2002). Regulation of cellular energy balance, therefore, was a crucial evolutionary step in maintaining homeostasis within a fluctuating environment (Roustan et al., 2016). The principal regulator of energy balance, AMPK, is an ancient mechanism that evolved in prokaryotes and has maintained its function throughout evolution (Hardie et al., 2006, 2016). AMPK is activated by energy depletion, which in the cell is signalled by the decreasing ratio of the high-energy adenosine triphosphate (ATP) to the low-energy adenosine monophosphate (AMP) (Hardie et al., 2006; Cantó et al., 2009). ATP depletion resulting from muscle contraction during exercise, or from calorie restriction, for example, stimulates AMPK activity to facilitate catabolic processes and ATP synthesis (Narkar et al., 2008; Kristensen et al., 2015; Steinberg, 2018). In addition, activated AMPK itself can promote fast-to-slow muscle fibre transformation (Ljubicic et al., 2011), and thereby affect energy use (Irrcher et al., 2008; Steinberg, 2018) and contractile function (Gundersen, 2011).

Obesity suppresses AMPK activity (Steinberg et al., 2006), thereby reversing the actions of AMPK briefly described above and, among other effects, promoting fat deposition and a shift to fast muscle fibres. Obesity can also attenuate the exercise-stimulated activation of AMPK, thereby mediating exercise intolerance (Lee-Young et al., 2010). The obesity-induced suppression of AMPK activity may even be transferred between mother and offspring. Mesenchymal stem cells, which give rise to muscle cells and adipocytes, of human infants born to obese mothers have lower AMPK activity compared with those of infants from normal weight mothers (Du et al., 2010; Boyle et al., 2017).

AMPK interacts within complex signalling systems (Ross et al., 2016; Craig et al., 2017; Steinberg, 2018), and many of its actions are as yet poorly understood (Myers et al., 2017). However, with respect to muscle contractile function, the interaction between AMPK and histone deacetylases (HDAC) is of particular importance.

AMPK and histone acetylation

In eukaryotes, DNA molecules are condensed into nucleosomes by forming complexes with histone proteins. Access to DNA and regulation of gene expression is mediated by histone acetylation and methylation (Turner, 2012; Halsall and Turner, 2016). The balance between histone acetylation by histone acetylases and deacetylation by histone deacetylases (HDAC) modulates transcription (Wang et al., 2009). In mammals, class II HDACs are particularly important in determining muscle function by repressing expression of the transcription factor myocyte enhancer factor 2 (MEF2) (McGee and Hargreaves, 2011). MEF2, in conjunction with myogenic regulatory

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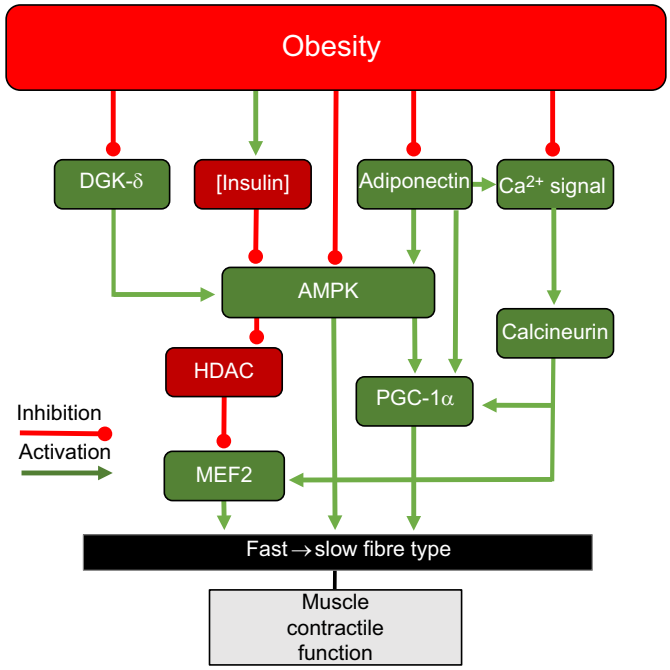

Fig. 2. Summary of regulatory pathways that are affected by obesity. The simplified diagram shows the major signalling pathways that are affected by obesity, and their downstream effect on muscle fibre type and contractile function. Obesity leads to increased insulin secretion and concentrations (green arrows indicate activation), and it inhibits (red lines) a number of processes that ultimately determine fibre type expression and thereby muscle function including metabolism, force production, power output and fatigue resistance. Green boxes indicate individual signalling molecules that overall promote slow fibre expression; red boxes indicate mechanisms that suppress slow fibre expression. DGK-δ, diacylglycerol kinase delta; Ca^{2+} signal, calcium signalling; AMPK, AMP-activated protein kinase; HDAC, histone deacetylase; MEF2, myocyte enhancer factor 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; SERCA, sarco-endoplasmic reticulum calcium ATPase.

factors such as myogenin and MyoD (Molkentin et al., 1995), plays a central role in determining slow fibre expression (McGee and Hargreaves, 2004; Potthoff et al., 2007). An important role of AMPK in modulating muscle composition and function lies in lifting the suppressive effect of class II HDAC on MEF2 by mediating the export of HDAC from the nucleus (Salminen et al., 2016; Vilchinskaya et al., 2017). By supressing AMPK, obesity increases the effect of HDAC and reduces MEF2 expression (Fig. 4).

MEF2 activity is sensitive to calcium signalling, and it promotes formation of slow-twitch type I muscle fibres that maintain higher calcium concentrations compared with fast-twitch fibres (McKinsey et al., 2002; Bassel-Duby and Olson, 2006). MEF2 is regulated by class II HDAC4 and HDAC5, which form a complex with HDAC3 to decrease slow muscle fibre gene expression by repressing MEF2 activity (Liu et al., 2005; Cohen et al., 2015). Conversely, slow fibre expression is stimulated by translocation of HDAC4 from the nucleus to the cytoplasm, thereby releasing the block on MEF2 (Liu et al., 2005). Calmodulin-dependent protein kinase (CaMK) and AMPK phosphorylate HDAC, and phosphorylated HDACs bind to chaperone protein 14-3-3 within the nucleus and are exported via a complex with the transport protein CRM1 (Grozinger and Schreiber, 2000; McGee and Hargreaves, 2010). Translocation of HDAC4 was blocked by inhibiting CaMK. In contrast, export of HDAC from the nucleus was stimulated by calcium signalling and energy imbalance, which activate CaMKII and AMPK, respectively (Liu et al., 2005; McGee and Hargreaves, 2011). Inhibition of AMPK also decreased expression of myogenin and myogenesis by reducing phosphorylation of HDAC5 and thereby increasing its repressive effects (Fu et al., 2013).

Calcium signals are disrupted by obesity

Calcium plays an important role in signalling changes to gene expression and muscle phenotype in addition to facilitating muscle contraction and relaxation (Fig. 1). For example, the calcium-dependent phosphatase calcineurin is stimulated by calcium release in the myocyte. Calcineurin is activated by prolonged low-frequency firing of motor neurons leading to low-amplitude calcium waves typical of slow muscle fibres (Michel et al., 2007). Calcineurin stimulates MEF2 and increases in slow fibre expression (Chin et al., 1998). Calcineurin stimulation led to increased transcription of slow type I fibre-specific genes, such as myoglobin and slow troponin isoforms (Bassel-Duby and Olson, 2006; Michel et al., 2007). Similarly, the endurance exercise-stimulated activation of MEF-2, which led to fast-to-slow fibre type transition and increased oxidative capacity, was dependent on calcineurin (Wu et al., 2001). Calcium release therefore mediates contraction and relaxation (excitation–contraction coupling), and leads to regulating gene expression (excitation–transcription coupling; see Glossary) and muscle phenotype (Michel et al., 2007).

Upon activation, calcineurin dephosphorylates the nuclear factor of activated T-cells (NFAT), leading to the translocation of NFAT from the cytoplasm to the nucleus (McGee and Hargreaves, 2004) (Fig. 4). In the nucleus, NFAT associates with other transcription factors to activate specific target genes, including MEF-2 (Wu et al., 2001). Overexpression of calcineurin led to suppression of fast contractile isoforms (Martins et al., 2012). In the reverse process,

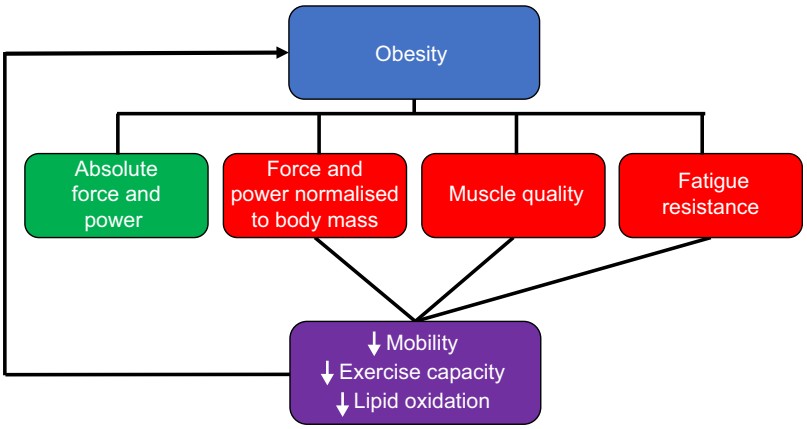

Fig. 3. Summary of obesity-mediated effects on contractile function of skeletal muscle. Obesity can lead to increases in absolute force production and power output of weight-bearing muscles resulting from the increased demand (green box). However, when normalised to body mass, force production and power output decrease with obesity, leading to decreased muscle quality and fatigue resistance (red boxes). As a result, obese individuals have reduced mobility, exercise capacity and lipid oxidation (purple box).

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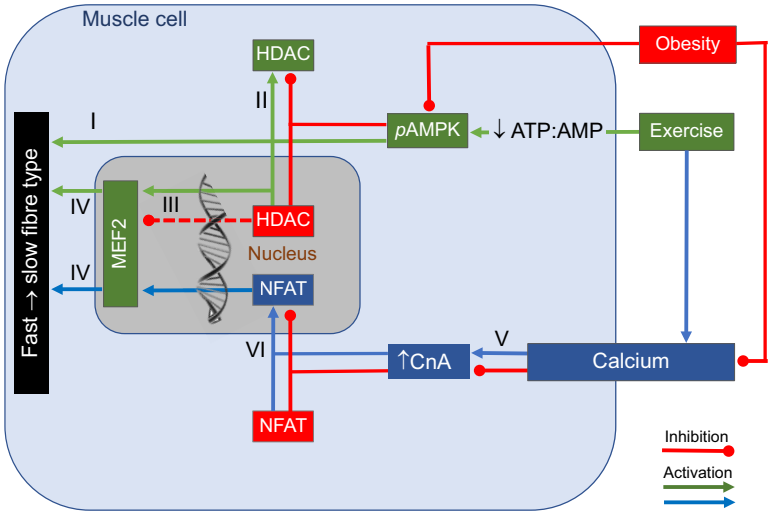

Fig. 4. Schematic summary of how obesity affects muscle fibre type composition by suppressing AMPK activity and disrupting calcium cycling. AMP-activated protein kinase (AMPK) activity is increased by phosphorylation (*p*AMPK) in response to a reduction in the ratio between ATP and AMP resulting from energy expenditure during exercise, for example. AMPK activity induces a shift from fast to slow muscle fibres directly (I; green arrow indicates activation), and causes nuclear export of class II histone deacetylases (II; HDAC). HDAC suppress (dashed red line) transcription of the myocyte enhancer factor 2 (III; MEF2), which mediates the shift from fast to slow fibre types (IV). Nuclear export of HDAC lifts their suppressive effect, allowing MEF2 expression and fast to slow fibre type transformation (III, IV; green lines). Obesity inhibits (red lines) AMPK activity, thereby preventing the direct effects of AMPK on fibre type, the nuclear export of HDAC (II) and expression of MEF2 (III). Calcium release into the myocyte from extracellular sources or from stores in the sarcoplasmic reticulum is stimulated by muscular activity and exercise (blue arrows indicate activation; see also Fig. 1), and it activates calcineurin (V; CnA). Calcineurin causes the nuclear factor of activated T-cells (NFAT) to enter the nucleus (VI), where it stimulates transcription of MEF2 and slow fibre type expression (IV). Obesity disrupts calcium cycling (red lines), and calcineurin-mediated translocation of NFAT into the nucleus (VI; red line). Note that calcineurin also activates the transcriptional co-activator PGC-1α, which interacts with MEF2 to promote slow fibre type expression (details not shown, see main text).

phosphorylation of skeletal muscle NFAT resulted in its nuclear export (Shen et al., 2007) and inhibition of NFAT-mediated increases in slow MHC gene expression (Jiang et al., 2006). Muscle phenotypes and contractile function therefore depend on the balance between MEF2 repression by HDACs and activation via calcineurin (McGee and Hargreaves, 2004). In addition, calcineurin regulates skeletal muscle mass (Michel et al., 2004; Hudson and Price, 2013), so that obesity-induced decreases in muscle mass could be partially explained by disrupted calcium signalling.

Obesity and ageing can disrupt calcium signalling by promoting excess production of reactive oxygen species (ROS) leading to oxidative stress (Espinosa et al., 2016; Di Meo et al., 2017). For example, oxidative stress can impair SERCA function, and induce calcium leak from the sarcoplasmic reticulum by its effect on ryanodine receptors (Matsunaga et al., 2003; Baumann et al., 2016). Disrupted calcium signalling could also result from lower sensitivity to motor stimulation in obese individuals (Maffiuletti et al., 2011). In addition, differential expression of muscle-specific structural actinin proteins can be associated with obesity (Insenser et al., 2012), and actinin is involved in fibre type transformation by mediating repression of calcineurin via calsarcins (Frey et al., 2008; Seto et al., 2013). Calsarcins (also known as Myoz) are associated with α-actinin (Frey et al., 2000), and calsarcin-1 suppressed calcineurin activity and thereby reduced slow fibre type expression (Lomonosova et al., 2016). Mice with a calsarcin-1 knock-out had excessive slow fibre expression (Frey et al., 2004), and mice deficient in calsarcin-2 had lower body mass, exhibited a shift from fast to slow muscle fibres, and showed improved endurance exercise performance (Frey et al., 2008). Similarly, actinin 3 deficiency increased calcineurin activity and hence slow fibre type expression and endurance exercise capacity in human and mouse muscle (Seto et al., 2013). Actinin 3 knock-out mice expressed greater slow type I muscle fibres, and gained less weight than wild-type mice. However, a naturally occurring null polymorphism in the actinin 3 gene did not affect body mass index or obesity in humans (Houweling et al., 2017).

Calcineurin interacts with PGC-1α

The peroxisome-proliferator activated receptor gamma co-activator-1α (PGC-1α) is a master controller of metabolism with pronounced influences on skeletal muscle. PGC-1α is positively associated with oxidative energy metabolism and transition to slow muscle fibres (Wu et al., 1999; Lin et al., 2002), and is induced by endurance exercise and in response to cold (Egan et al., 2010; Little et al., 2010; Philp et al., 2011; Smiles and Camera, 2015). In addition, calcineurin induced the expression of PGC-1α and its target, the nuclear receptor peroxisome proliferator activated receptor δ (PPARδ) in mice (Long et al., 2007). PGC-1α co-activates PPARδ, which promotes type I fibre expression and endurance performance, and genetically increased PPARδ phenotypes possessed resistance to obesity even without exercise (Wang et al., 2003). PGC-1α also induces MEF2 (Puigserver, 2005), and there is a positive feedback loop between PGC-1α and MEF2: when co-activated by PGC-1α, MEF2 binds to the PGC-1α promoter to stimulate its expression (Handschin et al., 2003). Hence, there is a link between muscle calcium and PGC-1α signalling, which can be disrupted by the effects of obesity on calcium cycling in the myocyte. Muscle PGC-1α expression is also regulated by AMPK (Jäger et al., 2007; Irrcher et al., 2008; Lira et al., 2010), which is sensitive to obesity as described above. Increased PGC-1α expression also protects from sarcopenia in ageing (Wenz et al., 2009), and from muscle disuse atrophy (Sandri et al., 2006; Cannavino et al., 2015). The association between obesity and ageing, which we discuss in more detail below, may therefore be explained at least partly by calcineurin–AMPK–PGC-1α signalling.

Consequences of obesity-induced decreases in adiponectin and insulin sensitivity

Obesity reduces the secretion of adiponectin, a hormone secreted in adipocytes, as well as its receptors, AdipoR1 and AdipoR2, which together influence metabolism, insulin sensitivity and muscle fibre type expression (Yang et al., 2001; Pérez et al., 2016). Adiponectin and its receptors mediate extracellular calcium influx into the muscle cell, which leads to subsequent activation of metabolic regulators such as the NAD^+-dependent histone deacetylase (SIRT1), AMPK and PGC-1α (Yamauchi et al., 2002; Iwabu et al., 2010). Adiponectin thereby represents an additional signalling mechanism that is negatively affected by obesity, and which has a pronounced influence on muscle fibre types by influencing calcium signalling. Obesity leads to increased visceral adipose tissue deposits, which display disrupted secretions of adiponectin (Pérez et al., 2016), as well as increased production of inflammatory cytokines and chemokines that can decrease production of contractile proteins in myotubes, and affect muscle fibre size distribution (Pellegrinelli et al., 2015). Adiponectin can be produced in muscle cells directly, and mice with a knock-out of muscle adiponectin showed lower peak tetanic force, but no effect on fatigue resistance (Krause et al., 2008).

Obesity-induced decreases in adiponectin led to decreased insulin sensitivity, but increased circulating insulin levels (Kadowaki et al., 2006; Gaur et al., 2017). Increased insulin levels inhibit AMPK activity in muscle and thereby slow fibre type expression (Valentine et al., 2014). It is possible, therefore, that the observed shift from slow to fast muscle fibres in obese individuals is partly caused by an insulin-mediated decrease in AMPK activity. Insulin responsiveness and metabolic rates correlate positively with the proportion of type I fibres; fewer type I fibres and more mixed type IIa fibres are typical in metabolic syndrome (Stuart et al., 2013).

In the insulin-resistant state, ligands of transforming growth factor beta 1 receptor (TGF-β1) are up-regulated (Watts et al., 2013). One of these ligands, myostatin, was up-regulated during obesity in mice (Allen et al., 2008b) but not in humans (Watts et al., 2013). However, altered concentrations and phosphorylation of the TGF-β1 signal transducers Smad2, Smad3 and Smad4 during obesity in humans was associated with a decrease in transcription of MyoD, a muscle regulatory factor that promotes muscle growth (Watts et al., 2013). Reduced muscle mass in obesity is therefore at least partly mediated through the TGF-β1 pathway. In addition, obesity-induced insulin resistance and type 2 diabetes are associated with increased levels of diacylglycerol (DAG), a precursor to triglycerides, and reduced diacylglycerol kinase delta (DAK-δ) activity (Chibalin et al., 2008). DAK-δ are lipid kinases that break down DAG, and are associated with fat deposition and obesity (Chibalin et al., 2008). DAK-δ deficiency in mice impaired AMPK activity, lipid metabolism and muscle contractile function (Jiang et al., 2016), indicating that disrupted lipid metabolism in obese individuals leads to impaired muscle function and locomotor activity via AMPK signalling (Fig. 1).

In summary, obesity influences muscle contractile function via a range of signalling pathways, but its most dominant influence is via disrupted calcium cycling and reduced AMPK activity, which leads to slow-to-fast fibre type transformation. Below, we review the consequences of these molecular changes on muscle function *in vivo* and in isolated muscle preparations.

Effects of obesity on *in vivo* skeletal muscle function in humans

Obesity can affect muscle isometric, concentric and eccentric force (see Glossary) (Fig. 3) (Maffiuletti et al., 2013; Tomlinson et al., 2016; Bollinger, 2017). Isometric strength is needed for postural control, but during locomotion and functional tasks (e.g. walking, rising from a chair, and ascending stairs) muscle undergoes length changes and can perform a range of functions such as powering locomotion, acting as a brake, spring or strut (Dickinson et al., 2000). Hence, isometric measurements (i.e. measurements taken at a constant muscle length) are not necessarily good approximations for muscle power, which necessitates length changes. The necessity to generate both muscular strength and power have important biomechanical implications. Obesity-induced changes in contractile performance could therefore have serious biomechanical consequences for many tasks performed during daily living.

The effect of obesity is not uniform across muscles or contractile modalities, and anatomical location and *in vivo* function of skeletal muscle can influence changes in mechanical performance (Maffiuletti et al., 2013; Bollinger, 2017). There are three important indicators of muscle function that have been reported in the literature: (1) absolute force or power-producing capacity of a muscle group; (2) force or power normalised to body mass or fat free mass; and, to a lesser extent, (3) muscle quality, defined as force or power normalised to muscle mass. Obesity can be associated with an increase in the capacity of weight-bearing skeletal muscles to produce absolute force and power for locomotion and postural control (e.g. knee extensor and trunk musculature) (Hulens et al., 2001; Rolland et al., 2004; Lafortuna et al., 2005; Maffiuletti et al., 2007; Abdelmoula et al., 2012; Tomlinson et al., 2014), but it does not affect performance of other skeletal musculature (Hulens et al., 2001; Rolland et al., 2004; Lafortuna et al., 2005). Excess body mass of obese individuals increases the demand placed on the skeletal muscles during standing and locomotion, and this can lead to a beneficial training adaptation in some muscles (Hulens et al., 2001; Lafortuna et al., 2005). However, obesity does not always lead to changes in absolute force and power (Pescatello et al., 2007; Gadducci et al., 2017). Discrepancies between studies at least partly relate to the specific muscle examined, participant physical activity levels, age, and duration and magnitude of obesity (i.e. duration and extent of overloading), which can affect the scope and magnitude of mechanistic responses. Importantly, obesity has been associated with a reduction in skeletal muscle protein synthesis (Akhmedov and Berdeaux, 2013), which would substantially reduce any positive adaptation evoked via an overload stimulus. Functional impairment associated with obesity (Pataky et al., 2013) and the resultant modified movement strategy (Runhaar et al., 2011) may place greater demand on some muscles, which can contribute to disparity in adaptation between muscles (Bollinger, 2017).

Muscles of obese individuals may produce greater absolute force or power when performing knee extensions or similar movements, but when normalised to body mass muscle performance is significantly lower than in lean individuals (Hulens et al., 2001; Lafortuna et al., 2005; Maffiuletti et al., 2007; Abdelmoula et al., 2012). These dynamics explain the lower performance of obese individuals in functional movement tasks, demonstrating that any improvement in absolute skeletal muscle performance does not counterbalance the substantial increase in body inertia. Similarly, the benefit of greater absolute muscle strength and power in obese individuals usually disappears when performance is normalised to fat free mass or muscle mass (Blimkie et al., 1990; Lafortuna et al., 2005; Maffiuletti et al., 2007). However, this is not always the case (Hulens et al., 2001; Hilton et al., 2008; Abdelmoula et al., 2012; Rahemi et al., 2015; Choi et al., 2016), and the effect of obesity on the intrinsic force-producing capacity of skeletal muscle is unresolved (Maffiuletti et al., 2013; Bollinger, 2017).

Advantages of isolated muscle preparations

Measuring the effect of obesity on isolated skeletal muscle function (Table 1) can enhance understanding of the mechanisms underpinning altered *in vivo* muscle performance. Most significantly, an isolated skeletal muscle approach permits direct assessment of the effects of obesity on muscle quality (force or power normalised to muscle size). Understanding obesity-associated changes in muscle quality is important, as obesity appears to result in larger muscles of lower quality (i.e. less contractile force per unit of cross-sectional area and lower power output per unit of muscle mass), which has the same absolute force and power output of smaller muscles in lean individuals (Tallis et al., 2017). This reduction in muscle quality results in two significant limitations: firstly, although obesity may not decrease absolute muscle performance, muscles of obese individuals are responsible for transporting and controlling the movement of a larger body mass. Secondly, larger muscles will contribute to an already elevated body mass, and therefore further increase the force required to overcome body inertia (Tallis et al., 2017). *In vivo* assessments of muscle quality in humans have estimated the volume of a muscle group using computed axial tomography scans (Blimkie et al., 1990), magnetic resonance imaging (Hilton et al., 2008), or ultrasound (Choi et al., 2016). The variation in assessment method may have contributed to the ambiguity with respect to the effect of obesity on muscle quality reported in previous *in vivo* studies. In an isolated skeletal muscle model, the mass of the contractile tissue can be measured directly to achieve greater accuracy in the assessment of muscle quality. Furthermore, *in vivo* assessments of muscle function consider the effect of obesity on whole muscle groups. Considering that each muscle varies in its form, function and fibre type distribution, *in vivo* methods are less suitable for determining muscle-specific effects.

An isolated skeletal muscle approach allows the examination of direct effects of obesity on muscle contractile function. Obesity-related changes in muscle function can be caused by changes in neural activation (Blimkie et al., 1990). An isolated muscle preparation can be stimulated directly to produce a contractile response, so that the influence of neural factors is removed. In addition, electrical stimulation results in complete muscle activation so that contractile responses are not confounded by motivation or central inhibition. Similarly, treatment conditions such as the diet of the animal model, drugs administered to the muscle, and thermal conditions can be controlled much more tightly in an isolated muscle preparation.

The effect of obesity on *in vitro* muscle function

Comparing studies examining the effect of obesity on the contractile performance of isolated skeletal muscle is challenging, given the varied methodological approaches that likely contribute to a lack of consistency amongst findings (Table 1). The muscle examined, contractility mode, feeding duration, diet composition and temperature at which performance is assessed appear to have profound effects on the obesity response. Ambiguities remain even though studies share similarity in the assessment of maximal isometric tetanus (see Glossary) force, and the use of rodent soleus and EDL muscles to represent slow and fast fibre types, respectively (Ayre and Hulbert, 1996; Ciapaite et al., 2015; Bott et al., 2017; Eshima et al., 2017; Tallis et al., 2017).

Despite evidence of a reduction in isometric stress (force relative to muscle cross-sectional area; see Glossary) of mouse soleus, and elevated isometric activation and relaxation times of both the EDL and soleus (Warmington et al., 2000), skeletal muscle contractile responses to genetically induced obesity are limited (van Lunteren, 1996; Matsakas et al., 2015). Moreover, obesity-associated changes in contractile responses and their underpinning mechanisms differ between genetic obesity models and dietary-induced obesity models (Matsakas et al., 2015). Typically, genetically induced obesity is associated with decreased muscle mass (Stickland et al., 1994; Warmington et al., 2000; Kemp et al., 2009). In contrast, obesity induced by high-fat diets results in either no change (Ciapaite et al., 2015; Eshima et al., 2017) or an increase in muscle mass (Ciapaite et al., 2015; Tallis et al., 2017). Diet-induced obesity is more relevant to the potential effects of the obesity epidemic in humans, therefore we will focus this Review on diet-induced obesity models.

Diet-induced obesity is commonly associated with a reduction in isometric stress, and changes in the rate of relaxation of skeletal muscle (Ayre and Hulbert, 1996; Ciapaite et al., 2015; Eshima et al., 2017; Tallis et al., 2017). However, available data are inconsistent. Unlike for humans, there are no clear criteria to classify obesity in rodents. There is large variability in the duration of high-fat diet administration in the literature (3–16 weeks; Table 1). Unsurprisingly, the severity of the effects appears to increase with feeding duration, and the shortest time course (3 weeks of high-fat diet consumption) had little effect on contractile performance (Thomas et al., 2014). Animal models with muscles that have a faster phenotype prior to high-fat diet consumption become more oxidative after treatment (Trajcevski et al., 2013; Ciapaite et al., 2015; Eshima et al., 2017). The obesity-induced change in muscle fibre type and metabolic profile may be affected by feeding duration. Short-term high-fat diet may cause an increase in slow MHC isoform and proteins involved with oxidative phosphorylation as a positive adaption to elevated lipid accumulation, but in the longer term genes involved in oxidative phosphorylation are down-regulated (de Wilde et al., 2008). The potential for a dose–response relationship between feeding duration and contractile performance is yet to be explicitly explored.

It is likely that the effects of obesity vary among different dietary fat sources (Mizunoya et al., 2013). For example, consumption of a high-fat palm oil diet led to a reduction in isometric twitch and tetanus force when normalised to muscle mass, but this result was not mirrored in a group receiving a high-fat lard diet for the same duration (Ciapaite et al., 2015). In many studies, diet quality is confounded by obesity. A common approach in the literature is to expose an obese treatment group (mice or other models) to a high-fat diet, while the control group is kept on a regular, low-fat diet (DeNies et al., 2014; Nitti et al., 2016). However, high-fat diet per se can have physiological effects in the absence of obesity (Bhagat et al., 2015; Hyatt et al., 2016; Burke et al., 2017). Hence, the effect of obesity may be masked or altered by different diet qualities. In humans, a high-fat diet is often associated with obesity so that this treatment combination may be relevant. However, hypotheses and interpretations of data should consider the potentially confounding effects of altering two experimental variables (diet quality and body mass) concurrently.

It is clear from the evidence that obesity effects are not uniform across muscles (Table 1). However, the outlined methodological discrepancies present a challenge when trying to establish the nature of a muscle-specific effect. For example, there was an obesity-induced decrease in the relative maximal isometric force of mouse soleus muscle (Ciapaite et al., 2015), which was not seen in other studies on mouse or rat soleus (Ayre and Hulbert, 1996; Bott et al., 2017; Tallis et al., 2017). Similarly, an obesity-induced reduction in the maximal isometric stress of mouse EDL in the studies by Tallis et al. (2017) and Eshima et al. (2017) was not found in other studies (Ayre and Hulbert, 1996; Ciapaite et al., 2015; Bott et al., 2017).

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Table 1. Summary of studies examining the effect of obesity on isolated skeletal muscle contractile function

Study	Animal	Feeding protocol	Muscle(s) examined	Experimental protocol	Change in muscle function	Mechanisms
Ayre and Hulbert (1996)	3 week old male Wistar rats	9 weeks for 3 groups: (1) Diet deficient in essential fatty acids (EFAD) (2) Diet high in essential (*n*-6) fatty acids (3) Diet enriched with (*n*-3) essential fatty acids Some animals subjected to further 6 weeks standard laboratory chow	Isolated whole EDL and soleus	Isometric twitch force, isometric tetanus force, high frequency and low frequency fatigue via repeated tetani at 33–34°C	EDL: EFAD↓fatigue time during high-frequency stimulation,↑fatigue resistance during low-frequency stimulation Soleus: EFAD↓twitch stress, twitch activation time, twitch relaxation time, stress during low-frequency stimulation *n*-3 diet resulted in↓whole animal treadmill running endurance After 6 weeks of standard laboratory chow changes in contractility were reversed	n/a
van Lunteren (1996)	3–4 month old genetically obese Zucker rats	n/a	Isolated strips of sternohyoid and diaphragm	Isometric twitch force, isometric tetanus force frequency curve, submaximal fatigue via repeated tetani at 37°C	Sternohyoid: no effect Diaphragm:↓twitch-to-tetanic force ratio	n/a
Warmington et al. (2000)	5 month old genetically obese male mice (inbred Aston strain) and genetically normal lean control	n/a	Isolated whole soleus and EDL	Isometric twitch force, isometric tetanus force frequency curve, fatigue resistance induced via repeated tetani	Soleus:↑activation and relaxation time,↓tetanus stress,↑twitch-to-tetanic tension ratio,↑stress at submaximal stimulation frequency,↓stimulation frequency for maximal tetanic stress,↑fatigue resistance EDL:↑activation and relaxation time,↑twitch-to-tetanic tension ratio,↑stress at submaximal stimulation frequency,↑fatigue resistance	Leptin did not affect contractility measures Shift to slow oxidative fibre types
Shortreed et al. (2009)	10 week old male C57BL/6J mice	HFD for 8 weeks compared with a lean control	*In situ* assessment of gastrocnemius/plantaris complex Biochemical analysis of soleus, EDL, peroneus longus and tibialis anterior	Isometric tetanus force frequency curve pre- and post-low-frequency fatigue induced via repeated tetani	No effect	↑ Type I and IIA fibre type No change in SDH activity EDL:↓palmitate and glucose oxidation rates Soleus:↑SCHAD enzyme activity
Thomas et al. (2014)	4 week old male C57BL/6J mice	HFD for 3 weeks compared with a lean control	*In situ* assessment of triceps surae Biochemical analysis of tibialis anterior and soleus	Isometric fatigue protocol consisting of 5 min of 100 Hz stimulation lasting 100 ms in 1 s trains, followed by 5 min of 300 ms of 100 Hz stimulation in trains of 400 ms	No effect	HFD did not affect performance during a progressive treadmill test Tibialis anterior:↑type IIa/x fibres,↓type IIb fibres, no change in SDH density or capillary density Soleus:↑type IIa fibres and SDH density,↓capillary density
Ciapaite et al. (2015)	12 week old male C57BL/6J mice	HFD containing lard (HFL) or palm oil (HFP), or low-fat diet (LFD) for 5 weeks	Isolated whole soleus and EDL	Isometric twitch and tetanus force at 20°C	EDL:↑twitch relaxation time for HFL and HFP Soleus:↓normalised twitch force, twitch relaxation time, normalised tetanus force in HFP	EDL:↑PGC1α and mitochondrial oxidative phosphorylation pathway complexes III, IV and ATP synthase Soleus:↑Tnnt1,↓Tnnt3 No change in MHC isoform or SERCA isoform

Continued

Table 1. Continued

Study	Animal	Feeding protocol	Muscle(s) examined	Experimental protocol	Change in muscle function	Mechanisms
Matsakas et al. (2015)	4–5 month old C57Bl/6 (WT) and Mstn$^{-/-}$ mice	HFD for 10 weeks compared with a lean control	*In situ* assessment of EDL	Isometric twitch and tetanus force	WT:↓absolute twitch force, absolute and normalised tetanus force Mstn$^{-/-}$: no effect	WT:↓exercise-induced fatigue,↑SDH activity and gene products that regulate fatty acid uptake and oxidation Mstn$^{-/-}$:↓exercise-induced fatigue, gene products that regulate fatty acid uptake and oxidation
Bott et al. (2017)	20 week old male C57BL/6J mice	(1) Baseline lean control group (2) Ageing (33 weeks) lean control group (3) Ageing (33 weeks) HFD group	Isolated whole EDL and soleus	Isometric twitch and tetanus force at 25°C	EDL:↑twitch activation and relaxation time,↓tetanus relaxation time compared with baseline Soleus:↓tetanus relaxation time compared with baseline	n/a
Eshima et al. (2017)	8 week old male C57BL/6J mice	HFD for 4 or 12 weeks compared with a lean control	Isolated whole EDL	Isometric twitch and tetanus force	12 weeks HFD:↓absolute and normalised tetanic force across maximal and submaximal stimulation frequencies	12 weeks HFD:↑percentage of type IIa/x myosin heavy chain fibres at the expense of decreased type IIb fibres,↑mitochondrial oxidative enzyme activity,↓fast-troponin T-protein expression No change in expression levels of calcium handling-related proteins and myofibrillar proteins (myosin heavy chain and actin)
Seebacher et al. (2017)	9–10 week old zebrafish (*Danio rerio*)	(1) Control fish fed once a day to satiety for 9–10 weeks (2) Obese fish fed three times per day to satiety for 9–10 weeks (3) Obese-lean fish fed three times per day for 4–5 weeks, then once per day for 4–5 weeks	Isolated section of rostral (anterior dorsal) muscle fibres	Isometric tetanus force, WL power and fatigue resistance via repeated tetani at 20°C	Obese group:↓tetanus stress and normalised work loop power and relaxation rate and locomotor performance Obese-lean group:↓tetanus stress and normalised work loop power and relaxation rate and locomotor performance	Obese group:↑resting metabolic rate,↓maximal metabolic rate which was reversed in the obese lean group Obese and obese-lean groups:↓fast:slow MHC expression
Tallis et al. (2017)	4 week old CD1 female mice	HFD for 16 weeks compared with a lean control	Isolated whole EDL, soleus and diaphragm	Isometric tetanus force, WL power and fatigue resistance (50 consecutive WLs) at 37°C	Soleus:↑absolute tetanus force and fatigue resistance, ↑relaxation time EDL:↓tetanus stress and WL power normalised to muscle mass Diaphragm:↓tetanus stress and relaxation time and WL power normalised to muscle mass	No change in fast:slow MHC expression, ↓AMPK activity of soleus

AMPK, 5′-adenosine monophosphate-activated protein kinase; EFAD, enriched with fatty acid; HFD, high-fat diet; MHC, myosin heavy chain; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase; SDH, succinate dehydrogenase; SERCA, sarco-endoplasmic reticulum Ca^{2+}-ATPase; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1alpha; Tnnt1, troponin T; Tnnt3, troponin T3; WT, wild type; n/a, not applicable.

Such discrepancies may further relate to a difference in the temperature at which measurements were taken (James, 2013). Isometric force, activation time, relaxation time and mechanical power are improved at higher test temperatures, and optimal performance in mice occurs at around 35–40°C, which reflects the common *in vivo* temperature range (James et al., 2015). Test temperatures vary widely in the literature, from 20 to 37°C in rodents, or have not been reported (Table 1). Studies that have examined contractility in multiple muscles provide clearer evidence of a muscle-specific effect (Ayre and Hulbert, 1996; Ciapaite et al.,

2015; Bott et al., 2017; Tallis et al., 2017). Interestingly, 5 weeks of high-fat diet (HFD) feeding caused a greater reduction in the contractile performance of relatively slow twitch soleus compared with relatively fast twitch EDL (Ciapaite et al., 2015). This result is contradictory to evidence using a 16-week HFD feeding regime (Tallis et al., 2017). It has been considered that the muscle-specific effect may be confounded by feeding duration as well as possibly being influenced by not only fibre type, but also anatomical location and *in vivo* function (Tallis et al., 2017), the latter of which is likely to be modified by a greater body mass.

A focus on fixed length isometric contraction may present limitations of this body of work when considered in relation to muscle activity *in vivo*. Locomotion in humans and other animals relies on dynamic muscle activity, where muscles that generate or absorb net power undergo cycles of length change while active (Josephson, 1993; James et al., 1996). Isometric measurements of force production are poor predictors of force production during concentric/eccentric contraction. Dynamic muscle activity can be determined using the work loop technique (see Glossary) to determine power during cycles of muscle lengthening and shortening (Josephson, 1993; Caiozzo, 2002). Use of the work loop technique is, as yet, relatively rare in studies relating to obesity. However, obesity may elicit a reduction in power output normalised to locomotor muscle mass in zebrafish and mice (Seebacher et al., 2017; Tallis et al., 2017), although absolute muscle power output was not affected in mice (Tallis et al., 2017). Interestingly, the absolute isometric force of isolated soleus was greater in obese mice, supporting previous human work suggesting a training adaptation for weight-bearing muscles (Tallis et al., 2017). This finding implies that obesity induces a contractile-specific adaptation in muscle function, with reduced plasticity in dynamic power-producing muscle activity. In addition, increases in absolute force and power are proportionally less than the magnitude of body mass increase so that locomotor performance is still likely to decrease with obesity (Seebacher et al., 2017; Tallis et al., 2017).

Most locomotor and functional tasks of daily living require sustained muscle contractility, so that muscle fatigue can be an important constraint on locomotion and activity (Allen et al., 2008a). The effects of obesity on muscle fatigue resistance are not well resolved (Maffiuletti et al., 2013; Tallis et al., 2017), and the available data on fatigue resistance *in vivo* are equivocal (Maffiuletti et al., 2007, 2008; Mayer et al., 2012; Paolillo et al., 2012; Minetto et al., 2013). As above, discrepancies between studies can be attributed largely to variation in experimental design (i.e. differences in muscle groups tested, mode of exercise, age and gender). In isolated muscle models, the effect of obesity on fatigue resistance changes with contraction type and muscle group (Table 1). Fatigue resistance has been assessed via repeated tetani at low and high simulation frequencies, or by subjecting isolated muscle to repeated maximal work loops (Table 1). Generally at the muscle level, fatigue resistance in obese individuals is unchanged or reduced when muscle is stimulated to produce maximal or near-maximal force or power (Thomas et al., 2014; Seebacher et al., 2017; Tallis et al., 2017), indicating that the obesity-associated reduction in sustained activity *in vivo* is not wholly related to an increase in force requirement to overcome an elevated body weight.

Contribution of obesity to muscle ageing

There is a parallel between the physiological changes associated with ageing and obesity; obesity can produce a physiological phenotype typical of ageing even in relatively young individuals (Pérez et al., 2016). Obesity-related changes may also exacerbate the ageing process (Baumgartner et al., 2004). Increasing age is associated with substantial changes in body composition, and in humans maximal fat mass is reached by 60–70 years of age (Villareal et al., 2005). Moreover, there is a global trend for an increased prevalence of obesity in older adults (Samper-Ternent and Snih, 2012), and it is estimated that around 40% of older (>60 years) Americans (USA) are obese (Hales et al., 2017). In humans, ageing is associated with a reduction in isometric and concentric muscle function, but eccentric performance appears to be well maintained (Doherty, 2003; Raj et al., 2010). The synergistic impacts of obesity and ageing may exacerbate the risk of morbidity and mortality. However, the evidence evaluating the effects of obesity on *in vivo* muscle function in older adults is limited and equivocal (Maffiuletti et al., 2013). The small number of studies in this area have been reviewed recently (Maffiuletti et al., 2013; Tomlinson et al., 2016; Bollinger, 2017), and in general the effects of obesity in the elderly mirror those in younger obese individuals, although older individuals may be disproportionately worse affected at a functional level (Baumgartner et al., 2004).

Obesity may result in reduced absolute strength in the elderly (Zoico et al., 2004), although these data need to be normalised to physical activity levels (Rolland et al., 2004). Reduction in absolute strength in the elderly may be partly explained by a synergistic reduction in protein synthesis in obesity and ageing that limits the ability of muscle to adapt to an elevated body mass (Tomlinson et al., 2016). The single study to date that measured the synergistic effects of ageing and obesity on isolated skeletal muscle function (Bott et al., 2017) demonstrated that obesity reduced the isometric activation and relaxation times in 33 week old mice. However, these animals were relatively young given that rodents, and in particular C57BL/6J strain mice, tend to have a lifespan in excess of 100 weeks (Kunstyr and Leunenberger, 1975). It is not clear if the increased functional impairment of older and obese individuals, compared with older and lean individuals (Zoico et al., 2004; Rolland et al., 2009), results from an accelerated reduction in muscle function, or the greater demand placed on already weakened muscles due to the elevated body mass. Given that both obesity and ageing share some common mechanistic characteristics, such as chronic inflammation, reduced protein synthesis, denervation and change in calcium kinetics (Navarro et al., 2001; Akhmedov and Berdeaux, 2013; Pérez et al., 2016; Bollinger, 2017), obesity has the potential to exacerbate skeletal muscle ageing. In addition to these common responses of ageing and obesity, there may be opposing effects on factors that mediate fibre type composition, given that obesity is associated with a faster fibre type composition (Bollinger, 2017) and ageing with slower fibre types (Deschenes, 2004).

Future directions

In summary, the principal effects of obesity are a shift in muscle fibre type that is mediated by disrupted calcium cycling and energy sensing, and which leads to altered *in vivo* and *in vitro* muscle function. Contradictory findings from *in vitro* and *in vivo* studies are at least partly owing to lack of standardisation in methodology. Based on our review of the literature we suggest the following to be important areas for future work.

Determining the effects of obesity on eccentric muscle function

Eccentric muscle performance is important in movement control and it is therefore fundamental in tasks of daily living (e.g. stair descent, postural control) (Choi, 2016). The elevated body weight of obese individuals is likely to increase the demand on this form of muscle action and any reduction in performance could result in functional impairment and increased injury risk.

Measuring the time course of effects of feeding on a high-fat diet on *in vivo* and isolated skeletal muscle performance

There is some evidence demonstrating that longer duration feeding on a high-fat diet increases the severity of the effects of obesity (Table 1). The longest feeding duration used in the literature is 16 weeks and it is likely that the magnitude of the resultant effects could be exacerbated with even longer duration feeding. Future work should examine muscle-specific mechanisms resulting in the change in muscle function across a range of feeding durations. In addition, as pointed out above, experiments should explicitly differentiate between the relative effects of high-fat diet per se and obesity.

Assessing the contribution of obesity to skeletal muscle ageing

In vivo evidence in this area is limited and ambiguous. There are a number of studies examining the effect of ageing on isolated skeletal muscle contractility, but the contribution of obesity is as yet unresolved. Understanding any synergies between the effects of ageing and obesity are particularly important considering that adiposity increases with age.

Determining whether the effects of obesity on skeletal muscle performance are reversible

Ayre and Hulbert (1996) demonstrated that a 6 week dietary intervention effectively reversed detrimental changes in muscle function induced by a diet deficient in essential fatty acids. In contrast, and despite improvement in metabolic scope, a similar dietary intervention failed to reverse obesity-induced changes in skeletal muscle function and fibre type expression (Seebacher et al., 2017). Future work should examine the effectiveness of caloric restriction, exercise, and their combination, on reversing the detrimental effects of obesity on skeletal muscle performance.

Competing interests

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