

## REVIEW

# Mechanisms governing the health and performance benefits of exercise

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Humans are considered among the greatest if not the greatest endurance land animals. Over the last 50 years, as the population has become more sedentary, rates of cardiovascular disease and its associated risk factors such as obesity, type 2 diabetes and hypertension have all increased. Aerobic fitness is considered protective for all-cause mortality, cardiovascular disease, a variety of cancers, joint disease and depression. Here, I will review the emerging mechanisms that underlie the response to exercise, focusing on the major target organ the skeletal muscle system. Understanding the mechanisms of action of exercise will allow us to develop new therapies that mimic the protective actions of exercise.

### Abbreviations

ACTN3,  $\alpha$ -actinin-3; AMPK, adenosine monophosphate kinase; EPO, erythropoietin; ERR, oestrogen-like receptor; HIF, hypoxia inducible factor; IGF-1, insulin-like growth factor; MET, metabolic equivalent; Pax, paired homeobox transcription factor; PEPCK-c, cytosolic phosphoenolpyruvate carboxykinase; PGC-1 $\alpha$ , PPAR $\gamma$  coactivator-1 $\alpha$ ; SIRT, sirtuin

## The health benefits of exercise

There is a strong argument that humans have evolved as endurance runners, potentially being among the best endurance land animals taking account size and distance (Bramble and Lieberman, 2004). Evolution has led to a highly efficient thermoregulation system in man, which allows us to travel over long distances while expending energy independent of all but the extreme climatic conditions (Bramble and Lieberman, 2004; Noakes and Spedding, 2012). Pressure for these evolutionary changes have been hypothesized as the need for long distant migration, the need to scavenge over greater distances and the potential also to persistence hunt, chase animals over long distances to exhaustion, or to get close enough to use weapons (Bramble and Lieberman, 2004). Over the last 100-50 years, physical activity in many populations has declined. This decline is also associated with an increase in the incidence of metabolic disorders such as type 2 diabetes, obesity and cardiovascular disease. Our evolutionary pressure to exercise therefore may underlie our sus-

ceptibility to these conditions when living a sedentary lifestyle (Noakes and Spedding, 2012).

The World Health Organization has now identified that physical inactivity is the fourth leading risk factor for global mortality just behind hypertension, tobacco use and hyperglycaemia ([http://whqlibdoc.who.int/publications/2010/9789241599979\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf)). As such, organizations such as the World Health Organization, the American Heart Association ([http://www.heart.org/HEARTORG/GettingHealthy/PhysicalActivity/StartWalking/American-Heart-Association-Guidelines\\_UCM\\_307976\\_Article.jsp](http://www.heart.org/HEARTORG/GettingHealthy/PhysicalActivity/StartWalking/American-Heart-Association-Guidelines_UCM_307976_Article.jsp)) and the British Heart Foundation (<http://www.bhf.org.uk/heart-health/prevention/staying-active.aspx>) recommend that individuals undertake an exercise regime of the order of at least 30 min of moderate-intensity aerobic activity at least 5 days per week, and moderate-to-high intensity muscle-strengthening activity for least 2 or more days per week for additional health benefits. This benefit of maintaining exercise capacity was highlighted in a recent study of 15 660 US veterans over 23 years, where it was shown that those individuals who could

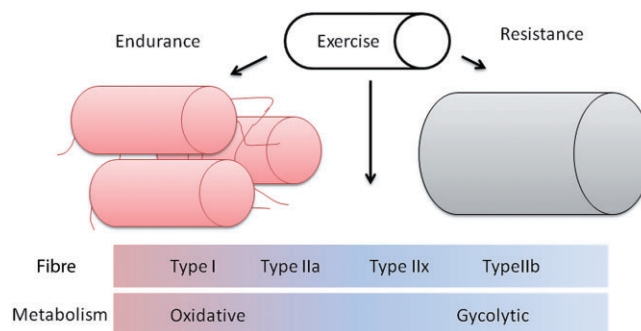
maintain a peak exercise task equivalent to gently running had a reduction in all-cause mortality (including cardiovascular diseases) by approximately 50% (Kokkinos *et al.*, 2008). Exercise level is measured in metabolic equivalents (METs). One MET is defined as the energy expended at rest, equivalent to an oxygen consumption of 3.5 mL.kg<sup>-1</sup> body weight per minute. The fitness level was strongly inversely related to mortality in individuals with and without cardiovascular disease, regardless of factors related to socioeconomic strata. Moreover, mortality was 13% lower for every 1-MET increase in exercise capacity up to 7 to 10 METs (Kokkinos *et al.*, 2008). Exercise has also been associated with a reduction in risk of developing diabetes (Wang and Reusch, 2012), obesity (Poirier and Despres, 2001), breast and colon cancer (Newton and Galvao, 2008); it aids in strengthening joints and bone (Nikander *et al.*, 2010), and is considered one of the best treatments for depression (Strohle, 2009). Exercise can however take many forms; at least experimentally it is often divided in to two main forms: resistance or strength type exercises and endurance types. Experimental examples of this are currently knee extensions for resistance exercise, and cycling (often stationary) or treadmill running for endurance. As discussed following, although the vast majority of the associations for health benefits of exercise come with endurance type activity, there is emerging evidence that resistance exercise or programmes such as high intensity training, where short 30 s periods of maximum activity a few times a week are being studied may also have benefits particularly in type 2 diabetes and glucose control (Gibala *et al.*, 2012).

In the context of both resistance and endurance exercise, I will therefore discuss the emerging pathways that underlie the exercise response. Over the last 20 years, there has been an explosion in the interest of the molecular and biochemical processes that mediate the response to exercise. These advances bring with them a host of novel therapeutic avenues for a wide variety of chronic diseases (that exercise is known to be protective in).

## Skeletal muscle as the major target for exercise

In this review, I will focus on the role of the skeletal muscle (Figure 1). Skeletal muscle is one of the most abundant tissues in the human body. At rest, skeletal muscle takes approximately 15–20% of cardiac output, during exercise however, it takes 70–85%. Compare this to the heart which takes 4–5% at rest and during exercise respectively (Saltin *et al.*, 1998). Skeletal muscle therefore requires the greatest adaptation to exercise and has one of the greatest adaptive responses to exercise.

The basic unit of the skeletal muscle is the myocyte. Myocytes are formed from the fusion of precursor myoblasts giving rise to long cylindrical multinucleated myofibres that characterize skeletal muscle. The muscle fibres themselves can then be subdivided into subtypes dependant on their ability to undertake oxidative phosphorylation as well as the presence of different types of myosin (Schiaffino and Reggiani, 2011). Type 1 fibres are slow twitch fibres that utilize oxygen for aerobic oxidative phosphorylation to generate ATP for work. Type 1 fibres are dark/red due to the



**Figure 1**

Exercise induces changes to skeletal muscle. Exercise induces metabolic and phenotypic changes to skeletal muscle that gives us major health benefits to whole body physiology. Endurance type exercise favours the growth and expression of type I and type IIa (type IIx muscle fibres, which have increasing oxidative capacity (from type IIx to type I), are mitochondria rich and have an increased blood supply. Resistance exercise favours the growth and hypertrophy of type IIb muscle fibres, which are fast twitch, have increase glycolytic/anaerobic metabolism and produce power/strength over endurance.

presence of high levels of the oxygen carrying protein myoglobin, they are capillary dense, contain large amounts of mitochondria and use fats (triglycerides) as fuel (Schiaffino and Reggiani, 2011). Type 1 fibres therefore are strongly associated with endurance over power activity, and link fat utilization to activity. In contrast, type 2 fibres are more variable and are divided into more of a continuum of types IIa, IIx, IIb, with increasing concentration of fast twitch muscle myosin, increasing power production, high glycolytic activity, but decreasing myoglobin, capillary density, oxidative capacity, and resistance to fatigue (as you go from a to x to b). Type IIa fibres use creatinine phosphate and glycogen for energy, while type IIb use ATP and creatinine phosphate (Schiaffino and Reggiani, 2011).

All skeletal muscles have all three types of muscle fibre, but the composition changes with their role in the body and with activity, for example postural muscles have a higher proportion of type I fibres (Eriksson and Thornell, 1983), marathon runners have a high proportion of type I (Ludén *et al.*, 2012) while power athletes like sprinters have a high proportion of type II fibres (Fry, 2004). Real world exercise often combines endurance and resistance exercises, and the combination does lead to increase aerobic capacity and muscle size (Lundberg *et al.*, 2013). Since endurance exercise is linked most highly to the protective actions of exercise, it is likely that the beneficial effects of exercise are mostly linked to the muscles oxidative capacity, driven by the extent and activity of the type I and type IIa fibres.

In addition to the differentiated myocytes, small progenitor ‘satellite cells’ surround myofibres between the basal membrane (sarcolemma) and basal membrane (Relaix and Zammit, 2012). These satellite cells are activated upon damage, and have the ability to proliferate, differentiate and fuse in to the existing skeletal muscle, as well as self-regenerate. Moreover, the numbers of satellite cell increase with either resistance or endurance exercise in man (Relaix and Zammit, 2012).

Muscle growth/function can, however, occur by more than one mechanism: hyperplasia, hypertrophy and via new protein synthesis. Central to these processes are a core of transcription factors that drive the myogenic gene programme. The basic helix-loop-helix factor MyoD appears central to myotubule formation during development (Berkes and Tapscott, 2005), while related factors Myf5, Myf6 and myogenin can also drive myotubule differentiation (Berkes and Tapscott, 2005). The development of skeletal muscle relies on the expression of paired homeobox transcription factors (Pax); initially Pax3 to lay the patterning framework for which Pax 7 is then required incorporate tissue for complete muscular development (Ludolph and Konieczny, 1995; Berkes and Tapscott, 2005).

Skeletal muscle represents a major tissue type in the body. Important to whole body physiology therefore is its metabolic capacity, linking diet, both in terms of calories, but also different food groups required for fuel, new protein synthesis, etc. to general health. Skeletal muscle therefore also communicates with other metabolic tissues and reservoirs such as adipose stores and the liver, both through fuelling requirements, but also being the source of a wide variety of secreted muscle cytokines or 'myokines' including IL-6, IL-15 and brain-derived neurotrophic factor (Pedersen, 2009b).

As we continue the discussion, a note of caution should also be raised particularly surrounding the interpretation of mechanistic data found using animal, particularly rodent models and their translation in to man. Hypertrophy as opposed to hyperplasia is clearly the major response to exercise in man (Sjostrom *et al.*, 1991; McCall *et al.*, 1996). Rodents have inherently higher rates of muscle turnover and protein synthesis, so experimental effects can be far more dramatic (Phillips *et al.*, 2009). Moreover, although there are some similar gene changes in muscle aging in mice and men such as Rac-1, glucose-6-phosphate isomerase ATP synthase 6/8 and pro- $\alpha$ (III) collagen, there are as least as many differences (Welle *et al.*, 2001).

## Muscle pathologies

A sedentary lifestyle or conditions such as long-term immobilization or malnutrition leads to muscle atrophy. For everyone, the process of aging leads to sarcopenia and reduced muscle mass, and of course increases susceptibility to metabolic diseases. A component of aging itself may be a lack of sensitivity to exercise, potentially due to reduced exercised induced muscle satellite cell activation (Leiter *et al.*, 2011). Although beyond the scope of this review to discuss in detail, additionally, there are a number of common chronic conditions, pathologies and physiological processes associated with loss of muscle mass; including heart failure, chronic obstructive pulmonary disease, chronic kidney disease, AIDs, muscular dystrophies, sepsis, autoimmune diseases and cancer lead to cachexia/muscle wasting (Fanzani *et al.*, 2012). In addition to indirect health benefits, exercise may therefore have a direct benefit reversing the decline in these muscle wasting conditions.

Inflammation may underlie a number of these pathologies. Low grade inflammation occurs in obese visceral adipose tissue (Yudkin, 2007), while inflammatory processes underlie

the pathogenesis of cardiovascular disease and the development of insulin resistance and diabetes (Tabas and Glass, 2013). Common to cancer, metabolic and inflammatory conditions, are high proinflammatory cytokine levels, of which tumour necrosis factor- $\alpha$ , also originally called cachexin due to its wasting properties in cancer is elevated (Aggarwal *et al.*, 2002). Although chronic inflammation impairs exercise ability, exercise reduces the level of low grade inflammation (Michigan *et al.*, 2011; de Lemos *et al.*, 2012) and can even be beneficial in muscle specific inflammation (Nader and Lundberg, 2009).

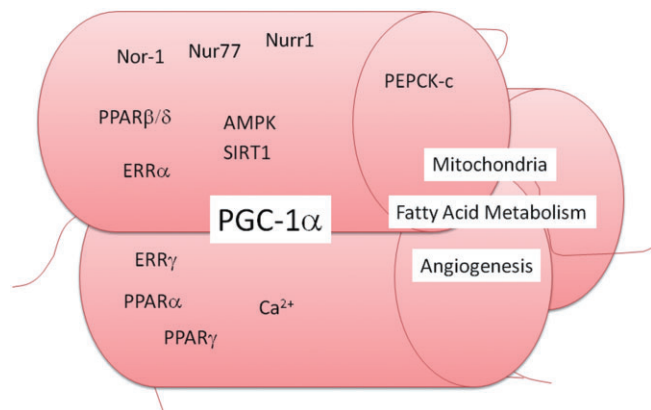
## General mechanisms of exercise

There are a number of pathways that mediate the benefits of exercise in terms of muscle biology, growth and metabolism: these including inputs such as mechanical activation, neuro-hormonal, steroids, growth factors, cytokines and other local mediators. Inside the cell, these pathways lead to changes in specific transcription factors and their co-regulators, oxidant stress, induction of cytoprotective proteins, muscle specific regulatory proteins, oxygen carry proteins, and proteins involved in intracellular recycling and degradation of proteins and organelles. Inputs include the levels and type of physical exertion, nutrition status, genetic predisposition along with emerging epigenetic mechanisms. Although muscle mass clearly alters with development, particularly in infancy and during puberty through the actions of hormones such as growth hormone and testosterone, it is beyond the scope of the review to go through these pathways in great detail (see Supporting Information Appendix S1 for more detail on these pathways). Rather than the developmental aspects, here we will focus on the emerging pathways directly related predominantly to endurance exercise, and their potential for use for therapy and misuse in doping.

The discovery of exercise pathways have come from multiple scientific directions, from directly studying muscle biology, naturally variations in the population, for example single nucleotide polymorphisms, and more recently from the application of omic' technologies to look for global changes in gene expression and metabolites released.

## Health benefits of resistance exercise

Although we will focus on endurance exercise, resistance exercises are important for reversing the loss of muscle function and structure, and joint weakness, associated with age and chronic illnesses. The cardiovascular health benefits of exercise are generally attributed to endurance exercise (Chudyk and Petrella, 2011). Resistance exercise alone is, however, commonly associated with a better glycaemic control in particular (Hurley *et al.*, 2011); by example, in a in a recent study of 100 type 2 diabetic patients, endurance and resistance exercise led to a greater insulin sensitivity and lower triglycerides levels compared to controls. Individuals who just undertook the endurance exercise protocol, also had significant improvements in circulating lipids, blood pressure, inflammation (decreased high-sensitivity C-reactive



**Figure 2**

Control of endurance exercise muscle phenotype. The increase in oxidative fatty acid metabolic, fatigue resistance muscle fibre generation seen with endurance exercise are mediated by several signalling processes: (i) activation of the master regulator of mitochondrial biosynthesis the PPAR $\gamma$  coactivator-1 (PGC-1 $\alpha$ ) appears to be a central process. (ii) Several nuclear receptors have also been implicated in the endurance phenotype, which PGC-1 $\alpha$  may co-activate, including the PPAR $\alpha$ , PPAR $\gamma$ , but in particular PPAR $\beta/\delta$ ; the oestrogen-like receptors (ERR) $\alpha$  and ERR $\gamma$ , and members of the NR4A family, nor-1, nur77 and nur1. (iii) Like resistance exercise, rises in intracellular Ca<sup>2+</sup> induced with work are also important. (iv) Also controlling the activation of PGC-1 $\alpha$  are the activation of the AMP kinase (AMPK), which is activation with an increase in the AMP : ATP ratio, and the deacetylase sirtuin (SIRT)-1. (v) Downstream, overexpression of cytosolic phosphoenolpyruvate carboxykinase (PEPCK-c), an enzyme key to central gluconeogenesis, induces an extreme endurance phenotype in mice.

protein) and a reduction in carotid intima-media thickness progression (Kadoglou *et al.*, 2013). So, although endurance exercise does have major cardiovascular benefits, a number of trials suggest a combination of resistance and endurance exercise may be better than endurance exercise alone for the reduction of cardiovascular risk factors (Chudyk and Petrella, 2011); findings reflected in the exercise recommendations of the World Health Organization (see above).

## Endurance exercise

Endurance exercise results in the metabolic switching of the skeletal muscle to a more oxidative phenotype (Figure 2). Underlying this activation are a variety of inputs such as physical activity and intracellular Ca<sup>2+</sup> release, the fuel status of the muscle, for example the ratio of ATP to AMP, which when favouring AMP, leads to AMPK activation, the redox status of the cell (NAD/NADH), and the relative hormone/nutrition status of the environment. Training with different nutritional status tends to adaptations, for example a low carbohydrate, tends to increase pathways of carbohydrate uptake and metabolism to compensate (Hawley *et al.*, 2011). In contrast, a high fat diet acutely may aid fatty acid oxidation over when switched back to a more balanced diet, but a continuous high fat diet appears detrimental to exercise per-

formance (Hawley *et al.*, 2011). The first gene identified to have polymorphic influence over exercise, however, was ACE. The mechanism by which it exerts this effect is still not known.

## ACE

In the late 1990s, polymorphisms in the ACE gene were identified as being linked to exercise performance (Montgomery *et al.*, 1997). ACE is responsible for the conversion of the angiotensin I to the vasoconstrictor peptide angiotensin II, along with the inactivation of the peptide mediator bradykinin (Regoli *et al.*, 2012). In particular, an insertion (I) polymorphism, associated with higher levels of circulating bradykinin (and therefore a reduced ACE activity), was found more prevalent in some endurance athletes including triathletes, experienced mountaineers and elite lightweight rowers (Puthuchery *et al.*, 2011), but not elite cyclists or lightweight rowers (Muniesa *et al.*, 2010). In contrast, individuals with a deletion (D) ACE polymorphism had more of an association with more strength/power resistance exercise including elite sprint swimmers (Puthuchery *et al.*, 2011), and football (soccer) players (Juffer *et al.*, 2009). Similar mutational differences may also exist across species. Alaskan sled dogs divided into endurance dog (1000 + miles in 10 days) or sprinters (30 miles, 18–25 mph), also have a polymorphism within the ACE gene that significantly distinguishes the sprint from endurance phenotypes (Huson *et al.*, 2011). Although these ACE polymorphisms are associated with some of these elite athlete populations, it is also clear that any effect is likely to be due to polygenetic contribution. When examined in healthy volunteers (non-elite), there was no evidence for an association of either polymorphism with baseline strength, but with training there were larger strength gains with individuals with the I/I genotype (Thomis *et al.*, 2004).

ACE inhibitors are front line anti-hypertensive drugs that are commonly used in patients with ongoing cardiovascular diseases. Whether the effects of ACE in exercise are due to the control of blood pressure are not known. ACE inhibitors do appear to reverse the decline in physical performance due to congestive heart failure and slow the decline in muscle strength, particularly in elderly women (Gray *et al.*, 2012), and in hypertensive subjects, result in better exercise performance (Onder *et al.*, 2006). The mechanism of action of ACE in exercise is far from clear. Angiotensin II is angiogenic in the repair process of toxin-induced muscle damage (Bellamy *et al.*, 2010); however, ACE knockout mice also have an increased capillary density around type IIa (oxidative) fibres (Zhang *et al.*, 2005), suggesting the contribution of ACE to vascularization may play a role.

## $\alpha$ -Actinin-3 (ACTN3)

The skeletal-muscle actin-binding protein ACTN3 is specifically expressed in fast-twitch myofibres. In 18% of healthy white Australians, and approximately 1 billion individuals worldwide, ACTN3 is absent due to a homozygous stop-codon polymorphism (R577X). Male and female elite sprint athletes express functional ACTN3 compared to controls (Yang *et al.*, 2003; Eynon *et al.*, 2009). Moreover, endurance athletes (Eynon *et al.*, 2009; 2012) and centenarians (Fiuza-Luces *et al.*, 2011) appear to lack ACTN3. So far, there

has been no particular association of ACTN3 expression with ironman triathletes (Saunders *et al.*, 2007), elite swimmers (Wang *et al.*, 2013) or professional endurance cyclists (Lucia *et al.*, 2006). One potential mechanism for this endurance phenotype has been suggested a better ability to recover from multiple exercise bouts (Venckunas *et al.*, 2012).

When looking at the muscle fibre localization of ACTN3, individuals homozygous for ACTN3 had higher relative knee power, compared with those lacking ACTN3. At the structural levels, there does not appear to be a significant difference in oxidative capacity or type I or type II muscle fibres with the presence or absence of ACTN3 (Vincent *et al.*, 2012), but as potentially expected, ACTN3 does appear to be type II fibre specific (Ichinoseki-Sekine *et al.*, 2012).

An ACTN3 knockout mouse has been generated and shows, similar to the observations of elite athletes, an endurance phenotype, with increased aerobic oxidative metabolism (MacArthur *et al.*, 2007), increased glycogen content, altered Ca<sup>2+</sup> signalling (Quinlan *et al.*, 2010) reduced force generation, and enhanced recovery from fatigue (Chan *et al.*, 2008; MacArthur *et al.*, 2008), but an increased susceptibility to damage (Seto *et al.*, 2011).

### Glucocorticoids

The long-term therapeutic use of glucocorticoids is associated with side effects of decreased muscle mass, a suppression of myogenesis and increased skeletal muscle catabolism (Hanaoka *et al.*, 2012). The role of endogenous glucocorticoids or acute use glucocorticoid steroids (used in injury management to decrease inflammation) is less understood. Endogenous glucocorticoids, for example cortisol are, however, increased with exercise, and appears to have a small but significant effect on endurance exercise, and in learning and memory in rodents (Hajisoltani *et al.*, 2011). In man, in a number of studies, there appears little beneficial effect of acute glucocorticoid use. The acute stimulated release of cortisol using the banned synthetic adrenocorticotropic hormone Synacthen, in trained cyclists had no effect on performance over a 20k time trial (Baume *et al.*, 2008). Similarly, 4 weeks of corticosteroid or placebo inhalation in healthy, well-trained athletes did not affect maximal power output in cycle ergometer tests or mood state by questionnaire (Kuipers *et al.*, 2008). In contrast, studies examining submaximal exercise in recreational athletes, 1 week of oral prednisolone dosing, but not acute prednisolone (Arlettaz *et al.*, 2008) did show an increase in cycling endurance and recovery (Arlettaz *et al.*, 2007); whether this effect was due to the population studied (recreational vs. trained athletes) or the different protocols (1 week dosing, submaximal training) is not known.

### Erythropoietin (EPO)

The oxygen carrying capacity of the blood is critically important for endurance exercise. This has led to many elite endurance athletes training at altitude to increase their haematocrit. Although this is common practise, the evidence for a beneficial effect of high altitude training has not been tested in a randomized control trial, and benefits are commonly only ascribed to a subset of responders (Chapman *et al.*, 1998).

EPO is a glycoprotein hormone produced by the kidney in response to hypoxia, including exercised induced hyperoxaemia (Roberts and Smith, 1999). EPO binding its specific EPO receptor stimulates erythrocyte production in the bone marrow (Watowich, 2011). EPO may also act centrally to improve performance independent of effects on haematocrit (Schuler *et al.*, 2012).

Although the benefits of EPO doping for endurance exercise has recently been questioned (Heuberger *et al.*, 2013), anecdotal contemporary reports from elite cyclists such as David Millar and Tyler Hamilton at the time of widespread doping indicated a strong communal belief in long-term endurance performance benefits of EPO and/or blood doping, as evidenced by the number of winners and leading cyclists subsequently found to have doped at the time. Additionally, of particular note is the rare EPO receptor mutation, such as found in the Finnish multi-Olympic cross-country ski champion Eero Mäntyranta (1937-). The EPO receptor mutation exhibited by Mäntyranta results in a greatly increased haematocrit and an increase in oxygen carrying capacity of up to 50% (de la Chapelle *et al.*, 1993).

EPO treatment of mice increases maximal oxygen uptake (VO<sub>2</sub> max) but not voluntary running (Kolb *et al.*, 2010), it also increases exercise performance in small scale studies healthy volunteers (Rasmussen *et al.*, 2010), in patients with chronic heart failure (Mancini *et al.*, 2003) and standard bred horses (McKeever *et al.*, 2006). In addition to pharmacological approach, EPO gene-modified mesenchymal stem cells have been implanted to treat anaemic induced by chronic kidney disease. Mice that had chronic renal failure and received these EPO producing cells showed significantly greater haematocrit and swimming exercise capacity (Eliopoulos *et al.*, 2006). Conversely, functional EPO knockout mice exhibit a decrease in the aerobic exercise capacity, correlated with a decreased haematocrit, reflecting poor oxygen supply to the muscles. Moreover, the muscles of EPO receptor knockout mice exhibit gene changes in muscle hypoxia, oxidative stress, glycolysis and mitochondrial oxidative phosphorylation pathways (Mille-Hamard *et al.*, 2012).

EPO is not without side effects. EPO elevates the arterial blood pressure even in healthy subjects (Lundby and Olsen, 2011). Increased haematocrit increases blood viscosity, which can reach levels that not only severely limit exercise capacity (Schuler *et al.*, 2010) but also increase the risk of thrombosis, heart attack, stroke and sudden death (Clyne *et al.*, 1995; Lage *et al.*, 2002). Indeed, it is believed the introduction of EPO in cycling was associated with close to 20 sudden deaths in this period (late 1980s to early 1990s) of cyclists such as Johannes Draaijer.

### Metabolic nutrition nuclear receptors and tier co-regulators

There is a strong link between aerobic capacity mitochondria, fatty acid metabolism and the endurance exercise phenotype (Wisloff *et al.*, 2005). Conditions, such as obesity associated insulin resistance may result of the imbalance between beta-oxidation pathway induction (increased lipids) and lack of up-regulation of tricarboxylic acid (TCA) cycle activity (lack

of exercise, so no need to generate more ATP). Endurance exercise training enhances mitochondrial performance, favouring tighter coupling between beta-oxidation and the TCA cycle, and concomitantly restores insulin sensitivity in animals fed a chronic high-fat diet. A number of energy-sensing molecules exist that sense changes in nutrition and energy homeostasis to trigger compensatory gene expression. Nuclear receptors such as the PPARs and their co-regulators, AMP-activated protein kinase, and sirtuin (SIRT)1 are all known to play important roles (Freyssenet, 2007). The exercise-activated nuclear receptor transcriptional co-activator, PGC-1 $\alpha$ , appears to play a key role in coordinating metabolic flux through a number of these pathways (Muoio and Koves, 2007).

### PPARs

The PPAR subfamily of nuclear receptors has three members: PPAR $\alpha$  (NR1C1), PPAR $\beta/\delta$  (NR1C2) and PPAR $\gamma$  (NR1C3), all of which are expressed in skeletal muscle (Bishop-Bailey, 2000). PPAR $\alpha$  and PPAR $\beta/\delta$  induce  $\beta$ -oxidation pathways, while PPAR $\gamma$  is critical for adipocyte differentiation programme (Bishop-Bailey, 2000). Since their discovery, PPARs have been shown to be expressed in monocytes/ macrophages, the heart, vascular smooth muscle cells, endothelial cells, and in atherosclerotic lesions, and all experimentally appear to be cardioprotective (Bishop-Bailey, 2000). PPARs can be activated by a vast number of compounds including clinically used drugs, such as clofibrate (PPAR $\alpha$ ), and the anti-diabetic thiazolidinedione classes (PPAR $\gamma$ ), polyunsaturated fatty acids, and a number of eicosanoids, including prostaglandins, lipoxygenase and epoxygenase products, and oxidized low density lipoprotein components (Bishop-Bailey and Wray, 2003). Although there is evidence for a role for all the PPARs, in exercise there is considerable evidence that PPAR $\beta/\delta$  in particular is a critical signalling component of the endurance response.

### PPAR $\beta/\delta$

PPAR $\beta/\delta$  is more highly expressed in type I compared to type II myofibres (Lunde *et al.*, 2007). Endurance exercise (Luquet *et al.*, 2003) or electrical stimulation of slow type I fibres (Lunde *et al.*, 2007) induces PPAR $\beta/\delta$  expression in skeletal muscle. Electrically stimulation mimicking fast/glycolytic IIb activation (Lunde *et al.*, 2007) or age (Giordano *et al.*, 2009) decreases the expression of PPAR $\beta/\delta$ .

Muscle-specific PPAR $\beta/\delta$  (Luquet *et al.*, 2003) or constitutively active PPAR $\beta/\delta$  (Wang *et al.*, 2004) transgenic mice, or overexpression of a constitutively active PPAR $\beta/\delta$  in adult muscle (Lunde *et al.*, 2007) results in a profound hyperplasia and shift to more oxidative fibre (Luquet *et al.*, 2003), accompanied by an increased blood supply due to a rapid angiogenic response (Piqueras *et al.*, 2007; Wagner *et al.*, 2009; Bishop-Bailey, 2011). These changes in muscle are accompanied by a reduction of body fat mass, mainly due to a large reduction of adipose cell size (Luquet *et al.*, 2003), and a dramatic reduction in high fat-diet induced obesity and insulin resistance. Importantly, these PPAR $\beta/\delta$  muscle mice have an endurance phenotype being able to run for twice as long and twice as far as control mice (Wang *et al.*, 2004).

In contrast to PPAR $\beta/\delta$  overexpression, activation of PPAR $\beta/\delta$  by a highly selective agonist (GW501516) did not

enhance endurance performance by itself. The PPAR $\beta/\delta$  agonist did, however, synergize with treadmill training to increase oxidative myofibres and running endurance similar to that seen with the transgenic mice (Narkar *et al.*, 2008). Moreover, PPAR $\beta/\delta$  activation activated adenosine monophosphate kinase (AMPK), and an orally active AMPK agonist AICAR alone could partially mimic the induction of metabolic genes and enhanced running endurance (Narkar *et al.*, 2008). Recently, in the mdx mouse model of muscular dystrophy, a combination of exercise, with pharmacological activation of PPAR $\beta/\delta$  and AMPK over a month showed a significant improvement in exercise performance, compared to training alone (Bueno Junior *et al.*, 2012).

Activation of PPAR $\beta/\delta$  by overexpression or by selective agonists promotes a rapid myonuclear accretion via the calcineurin/NFAT pathway, to induce fusion rather than proliferation (Giordano *et al.*, 2009). In terms of metabolism, not only is fatty acid metabolism optimized, PPAR $\beta/\delta$  in conjunction with AMPK and MEF-2 induce lactate dehydrogenase b which diverts pyruvate into mitochondria for the final steps of glucose oxidation (Gan *et al.*, 2011). The skeletal muscle from PPAR $\beta/\delta$  transgenic mice have high glycogen stores, increased levels of the glucose transporter GLUT4, and augmented capacity for mitochondrial pyruvate oxidation (Gan *et al.*, 2011). Activation of PPAR $\beta/\delta$  therefore appears to effectively re-integrate  $\beta$ -oxidation and the TCA cycle to optimize metabolism that becomes uncoupled by diet induced obesity.

Although there appears to be a gender difference in PPAR $\beta/\delta$  expression, with women expressing higher amounts in the vastus lateralis than men (Maher *et al.*, 2009), PPAR $\beta/\delta$  is readily induced after gently or strenuous exercise independent of nutrition or condition state (Russell *et al.*, 2005). Even relatively low intensity exercise such as walking for greater than 150 min per week over a 4-month period is sufficient to induce PPAR $\beta/\delta$  (Fritz *et al.*, 2006). Induction of PPAR $\beta/\delta$  is even seen in highly trained individuals such as elite cyclists after training bouts (Psilander *et al.*, 2010).

These finding have led to a huge interest in PPAR $\beta/\delta$  activators as exercise mimetics and the illegal use of PPAR $\beta/\delta$  in training regimes in man. The first doping case has now been reported with GW501516, which has also been nicknamed 'Endurobol'. In April 2013, the European track cycling champion Valery Kaykov was sacked by the Rusvelo team after failing a drugs test for GW501516. GW501516 has been trialled in man for dyslipidaemia for which it effectively elevates high-density lipoprotein (HDL) (Olson *et al.*, 2012). However, GW501516 clinical development has now been stopped for safety reasons, due to long-term carcinogenesis in rodents (Olson *et al.*, 2012), which has led to World Anti-Doping Agency taking the unprecedented step to issue an alert about safety of the compound.

### PPAR $\alpha$ and PPAR $\gamma$

PPAR $\alpha$  and PPAR $\gamma$  are induced in the adipose (Ruschke *et al.*, 2010) and skeletal muscle (Fatone *et al.*, 2010; Ruschke *et al.*, 2010; Sixt *et al.*, 2010), of type 2 diabetic patients following exercise prescription (Sixt *et al.*, 2010). PPAR $\alpha$  and its target genes, hepatocyte nuclear factor-4, carnitine palmitoyltransferase 1, catalase and ABCA1 are also induced by exercise in the liver of diabetic Otsuka Long-Evans Tokushima Fatty rats, again indicating potentially important metabolic targets for

these receptors outside the skeletal muscle system (Zhang *et al.*, 2011). Although little is known regarding the direct endurance modulating role of PPAR $\alpha$ , single nucleotide polymorphisms (SNPs) in man do indicate a potential role. A G/C polymorphism in intron 7 of the PPAR $\alpha$  gene appears to significantly influence athletic performance (Ahmetov *et al.*, 2006). In a large cohort of Russian athletes, the C allele was associated with increasing resistance/strength performance, while the GG genotype was associated with endurance athletes. These GG genotypes had approximately 20% more slow-twitch fibres than CC individuals (Ahmetov *et al.*, 2006).

Similarly, little is known about PPAR $\gamma$  and the exercise phenotype, particularly in skeletal muscle. In a low-intensity exercise (8 weeks walking) study, volunteers had a significant reduction in total serum cholesterol and oxidized low-density lipoprotein, an increase in HDL, and a significant increase in leukocyte PPAR $\gamma$  expression and activation (Butcher *et al.*, 2008). In mice, PPAR $\gamma$  is activated in adipose tissue after of 8 weeks of voluntary wheel running (Petridou *et al.*, 2007), and PPAR $\gamma$  may mediate anti-depressant activity due to exercise (Eissa Ahmed and Al-Rasheed, 2009; Sadaghiani *et al.*, 2011). The Pro12Ala polymorphism in the PPAR $\gamma$  gene, Pro12 was significantly associated with type 2 diabetes in those with low physical activity (Nelson *et al.*, 2007). PPAR $\gamma$  Pro12Ala carriers also experience greater improvements in glucose and insulin metabolism in response to a 20-week endurance training programme (Ruchat *et al.*, 2010).

It is important to note, that PPAR response overall may, however, be dependent on the muscle type being studied, and the type of training programme. In different muscles, either glycolytic (plantaris; type II fibre dominant) or oxidative (soleus- type I fibre dominant) in the rat, PPAR $\alpha$  and PPAR $\gamma$  mRNAs were expressed to a greater extent in the soleus muscle than in the plantaris muscle, while PPAR $\beta/\delta$  was equally expressed. PPAR $\gamma$  was the least abundantly expressed PPAR. After 12 weeks of training, only PPAR $\gamma$  mRNA expression increased in the soleus muscle, while PPAR $\beta/\delta$  and gamma mRNA levels increased in the plantaris muscle (Spangenburg *et al.*, 2009).

### PGC-1 $\alpha$

The PPAR $\gamma$  co-activator (PGC) family are central transcriptional co-activators for induction of mitochondrial biogenesis (Spiegelman, 2007). Although, originally identified as a cold-activated co-activator of PPAR $\gamma$ , PGC-1 $\alpha$  co-activates a number of nuclear receptors (Spiegelman, 2007). PGC-1 $\alpha$  and can be up-regulated and/or activated by a number of pathways that induce skeletal muscle exercise phenotype including:  $\beta$ 2-adrenoceptor activation (Miura *et al.*, 2007), Akt signalling, cAMP-cAMP response element binding protein activation or intracellular coupling of Ca<sup>2+</sup>/calmodulin-dependent protein kinase in a p38-dependent manner (Wright *et al.*, 2007), or as the case of adiponectin via a Ca<sup>2+</sup>/calmodulin-dependent protein kinase beta-AMPK-SIRT pathway (Iwabu *et al.*, 2010), or oxidant stress via a similar AMPK-SIRT dependent pathway. Antioxidants such as vitamin C or E supplementation may therefore blunt the response to exercise training (Ristow *et al.*, 2009).

The capacity of muscle mitochondria to fully oxidize fatty acid correlates with the extent of type I fibres expression

(Koves *et al.*, 2005). PGC-1 $\alpha$  is activated by exercise, and its expression alone is sufficient to produce the endurance phenotype (Baar, 2004) and lipid  $\beta$ -oxidation *in vitro* (Koves *et al.*, 2005). Muscle-specific PGC-1 $\alpha$  transgenic mice have increased mitochondrial gene expression, mitochondrial DNA, and mitochondrial enzyme activity and improved exercise performance and peak oxidative capacity (Calvo *et al.*, 2008). Increased mitochondrial biogenesis, capillaries (Chinsomboon *et al.*, 2009) and fatty acid transporters all contribute to this improved exercise capacity via an increase in fatty acid utilization (Tadaishi *et al.*, 2011). Angiogenesis is particularly important for supplying oxygen to oxidative type I (and type IIa) fibres. One of the most important recent findings in vascular biology is that PGC-1 $\alpha$  induces VEGF and angiogenesis in a hypoxia inducible factor (HIF-1)-independent manner [via co-activation or oestrogen-like receptor (ERR) $\alpha$ ] (Arany *et al.*, 2008). HIF-2 $\alpha$  (endothelial PAS domain-containing protein 1) is a hypoxia inducible gene, which is transcriptionally activated by the PGC-1 $\alpha$ -ERR $\alpha$  complex. The PGC-1 $\alpha$ -mediated switch to slow, oxidative fibres *in vitro* and *in vivo* is dependent on HIF-2 $\alpha$  activation (Rasbach *et al.*, 2010).

Activation of muscle PGC-1 $\alpha$  by exercise may also direct benefit metabolism in adipose depots by the inducing myokine production. A recent report showed that exercised induced PGC-1 $\alpha$  induces the expression FNDC5, a membrane protein that is cleaved and secreted as a newly identified myokine termed irisin. Circulating irisin binds white adipose tissue and stimulates uncoupling protein-1 expression and a broad programme of brown fat-like development, increasing energy expenditure without increasing activity or food intake (Bostrom *et al.*, 2012).

Interestingly, a novel splice variant of PGC-1 $\alpha$ , which results from alternative promoter usage and splicing, has been recently identified and called PGC-1 $\alpha$ 4 (Ruas *et al.*, 2012). PGC-1  $\alpha$ 4 is highly expressed in resistance exercised muscle but unlike expected for canonical PGC-1 $\alpha$  activation, PGC-1 $\alpha$ 4 induces insulin-like growth factor (IGF-1) and represses myostatin leading to skeletal muscle hypertrophy. Skeletal muscle-specific PGC-1 $\alpha$ 4 transgenic mice in contrast to PGC-1 $\alpha$  show increased muscle mass and strength, and a dramatic resistance to muscle wasting induced by cancer cachexia (Ruas *et al.*, 2012).

## Other nuclear receptors and co-regulators

### ERR $\gamma$ (NR3B3)

Like ERR $\alpha$ , the sister orphan nuclear receptor ERR $\gamma$  is highly expressed in type I skeletal muscle. ERR $\gamma$  when overexpressed in anaerobic type II muscles induces fatty acid metabolism, mitochondrial respiration (Rangwala *et al.*, 2010), and a type I fibre gene programme (Narkar *et al.*, 2011), along with angiogenesis to support the increased oxidative requirements (Narkar *et al.*, 2011). Consequently, similar to PPAR $\beta/\delta$  transgenic mice, ERR $\gamma$  transgenic mice have a doubling in running endurance. Interestingly, these fibre switching actions of ERR $\gamma$  were independent of PGC-1 $\alpha$ , but were still partially dependent on AMPK activation (Narkar *et al.*, 2011). Mice

lacking ERR $\gamma$  in contrast showed decreased mitochondria and reduced exercise capacity (Rangwala *et al.*, 2010).

### *Neuron-derived orphan receptor 1 (Nor-1; NR4A3)*

Nor-1 is commonly found as an exercised induced nuclear receptor by transcriptomic analysis of endurance exercise in man (see below). Nor-1 is also induced by  $\beta$ 2-adrenoceptor activation and is up-regulated after exercise and down-regulation with limb immobilization in mice (Kawasaki *et al.*, 2009). siRNA targeted knockdown of Nor-1 in skeletal muscle cells *in vitro* reduced oxidative metabolism. Skeletal muscle specific constitutively-active Nor-1 transgenic mice have been generated (Pearen *et al.*, 2012). In the skeletal muscle, active Nor-1 resulted in induction of myoglobin, mitochondria, oxidative enzymes and various subunits of electron transport chain complexes, leading to type IIa and IIx fibres switching from type IIb fibres, and increased MEF-2 and phospho-histone deacetylase 5 and cytoplasmic HDAC5 staining (Pearen *et al.*, 2012). Indicative of this fibre-switching phenotype, Nor-1 skeletal muscle transgenic mice had significantly improved glucose tolerance, oxygen consumption and running endurance (Pearen *et al.*, 2012).

### *Nerve growth factor IB (Nur77; NR4A1)*

Nur77 is decreased in the skeletal muscle from obese individuals. *In vitro*, Nur77 overexpression in skeletal myoblasts induces glucose oxidation and glycogen synthesis, GLUT4 and glycogenin and increased hexokinase and phosphofructokinase activity (Kanzleiter *et al.*, 2010). Endurance exercise training of rats (Kawasaki *et al.*, 2009) or man (Lewis *et al.*, 2010) induces skeletal muscle Nur77. Nur77 is also particularly sensitive to induction by the  $\beta$ 2-adrenoceptor–cAMP/PKA pathway, but not AMPK (Kanzleiter *et al.*, 2009).

### *Rev-erb $\beta$ (NR1D2)-retinoic acid receptor-related orphan receptor alpha (ROR $\alpha$ ; NR1F1)*

Rev-erb $\beta$  is an orphan nuclear receptor that functionally antagonizes the ROR $\alpha$  nuclear receptor. Rev-erb $\beta$  and ROR $\alpha$  are both expressed in skeletal muscle. Dominant negative Rev-erb $\beta$  expression in skeletal muscle cells *in vitro* decreased the expression of fatty acid transporter CD36, and the fatty acid binding proteins-3 and -4, and resulted in a dramatic repression (>20-fold) of myostatin mRNA (Ramakrishnan *et al.*, 2005). Whether, this effect of Rev-erb $\beta$  is ROR $\alpha$  dependent is not known, nor whether this effect is seen *in vivo* or in man.

### *Nuclear receptor co-repressor 1 (NCoR1)*

The nuclear receptor co-repressor is a common co-repressor regulator of a wide range of nuclear receptors. Muscle-specific deletion NCoR1 in mice enhanced exercise endurance which is associated with increased muscle mass mitochondrial number and the activation of transcriptional regulators of muscle function: MEF2, PPAR $\beta$ / $\delta$  and ERRs (Yamamoto *et al.*, 2011).

### *Other metabolic pathways: the phosphoenolpyruvate carboxykinase (PEPCK)-cytosolic muscle transgenic mice*

Clearly altering metabolism is critical to changing the function and phenotype of skeletal muscle, which then impacts also on whole body health. Endurance exercise increases concentrations of the hexose phosphates and phosphoenolpyruvate and depresses those of fructose 1,6-bisphosphate, triose phosphates in the liver (Dohm and Newsholme, 1983). These changes are associated with were increased maximal activity of PEPCK, which increases with exercise (Dohm *et al.*, 1985). PEPCK is strongly up-regulated by glucocorticoids, agents that elevated cAMP (Friedman, 1994; Nizielski *et al.*, 1996). Skeletal muscle-specific PEPCK-c transgenic mice were subsequently generated and found to have probably the most extreme endurance phenotype yet described (Hakimi *et al.*, 2007). PEPCK-c muscle transgenic mice were found to be seven times more active than control mice, and the male mice extremely aggressive. With treadmill testing, the PEPCK-c transgenic mice ran up to 6 km at a speed of 20 m·min<sup>-1</sup>, whereas control mice stopped at 0.2 km. The PEPCK-c transgenic mice ate 60% more than controls but had half the body weight and 10% the body fat as determined by magnetic resonance imaging, while the skeletal muscle were greatly enriched with mitochondria, store up to five times more triglyceride than control mice, and have a greatly extended life span (females are reproductively active up to 35 months), and up to an age of 2.5 years ran twice as fast as 6–12-month-old control animals (Hakimi *et al.*, 2007; Hanson and Hakimi, 2008).

### *Myokines and local mediators*

Skeletal muscle release several cytokines, including IL-6, IL-8 and IL-15. IL-6 and IL-8 are induced upon muscle contractions. IL-6, in particular, increases insulin-stimulated glucose disposal and fatty acid oxidation in man, whereas IL-8 is only released in small amounts locally from contracting muscle, suggesting that IL-8 may exert its effects locally in the muscle that is by exerting a pro-angiogenic effect (Nielsen and Pedersen, 2007). The role of IL-6 in muscle, although one of the best characterized myokines, is poorly understood. IL-6 is a mediator of muscle wasting in models of cancer cachexia (Baltgalvis *et al.*, 2009) and heart failure (Janssen *et al.*, 2005), but also appears to be an important regulator of satellite cell mediated muscle hypertrophy (Serrano *et al.*, 2008). IL-15 is also expressed at high levels by skeletal muscle. IL-15 appears to have little effect on myoblast proliferation or differentiation *in vitro*. However, IL-15 does appear to have anabolic activity, by increasing myosin heavy chain and myotubes hypertrophy, and synergizing with IGF-1 to increase myosin heavy chain (Quinn *et al.*, 1995).

### *IL-15*

IL-15 serum levels negatively correlates with obesity in man (Nielsen and Pedersen, 2007). Plasma IL-15 protein is significantly elevated in man immediately after acute resistance exercise, but did not appear to change with further resistance training, and a SNP in exon 7 of IL-15 receptor is strongly associated with muscle hypertrophy (Riechman *et al.*, 2004). Due to its anabolic activity in myofibres, the initial studies



with IL-15 focused on resistance training; however, recent evidence to a greater role mediating the endurance response. A 30-min treadmill running protocol at resulted in a significant increase in circulating IL-15 level in untrained healthy young men (Tamura *et al.*, 2011). However, the role for IL-15 in endurance exercise is far from clear, as both IL-15 receptor knockout and IL-15 overexpression both lead to an endurance phenotype. Whether there is an alternative IL-15 receptor that could account for this is not known. In mice lacking the IL-15 receptor, there is a fibre switch to an oxidative phenotype including markers of mitochondrial biogenesis and increasing resistance to fatigue and increased exercise capacity (Pistilli *et al.*, 2011; 2013). These IL-15 receptor knockouts have greater running endurance and greater ambulatory activity. Consistent with a role in man, a genetic association was found between a SNP in the IL-15 receptor gene and endurance in athletes stratified by sport (Pistilli *et al.*, 2011). In contrast to the receptor knockout, IL-15 transgenic mice, with elevated skeletal muscle and circulating IL-15 levels also have an endurance phenotype, being able to run twice the distance as control mice (Quinn *et al.*, 2013). The muscles of these IL-15 transgenic mice had increased markers for oxidative metabolism, including SIRT1, PGC-1 $\alpha$  and PGC-1 $\beta$ , and preferentially metabolized fatty acids, while still maintaining higher levels of myosin heavy chain and troponin I (Quinn *et al.*, 2013).

### Brain-derived neurotrophic factor (BDNF)

Exercise clearly has not only effects on muscle but central effects.  $\beta$ -endorphins are released upon exercise and provide effective analgesia for a number of painful conditions (Nijs *et al.*, 2012). In addition, the ability to tolerate pain is clearly also associated with exercise training and performance. Exercise also leads to central adaptations. Of particular importance appears to be an increase in BDNF which via its receptor TrkB leads to long-term potentiation and an increase in both excitatory and inhibitory synapses, new nerve cell growth and an increase in respiration and mitochondrial activity particularly in the hippocampus (Mattson, 2012; Spedding and Spedding, 2008) and learning (Rothman *et al.*, 2012). BDNF levels in the brain and plasma are elevated after exercise (Spedding and Spedding, 2008), and in the brain at least, this appears secondary to IGF-1 (Chen and Russo-Neustadt, 2007); see Supporting Information Appendix S1. Conversely, circulating BDNF levels are reduced in individuals with obesity, type 2 diabetes, cardiovascular disease, depression and with diagnosed Alzheimer's disease (Pedersen, 2009a). BDNF is a critical central regulator of food intake (Rothman *et al.*, 2012). However, BDNF treatment improved insulin resistance in obese (ob/ob) mice independent of effects on food intake suggesting additional peripheral actions (Pedersen, 2009a). BDNF has also now been recently identified as a myokine, being increased in human skeletal muscle after exercise, or in electrically stimulated muscle cells (Matthews *et al.*, 2009). This induced BDNF via TrkB induced an increase in  $\beta$ -oxidation via the activation of AMPK and Akt dependent pathways (Matthews *et al.*, 2009). At this stage, however, it is not known how much BDNF contributes to endurance phenotype of exercising muscle.

## Summary and conclusions

Exercise is a vastly underused therapy. No pharmaceutical intervention has the overall benefit on mortality and reduction in risk factors as aerobic fitness. Understanding the underlying mechanisms that mediate exercise will give us new therapeutic leads to mimic some of these important health benefits. Such therapies could provide novel treatments for life-long health in an increasingly aging population, as well as for muscle specific pathologies, where chronic disease or immobilization invariably leads to muscle wasting. The overall benefit of exercise in its entirety is not going to be replaced by a pill, but the pathways described do allow multiple opportunities for pharmacologists to test and develop new exercise mimetic therapies.

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## Conflict of interest

No conflict of interest.

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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**Appendix S1** Supporting information text.

**Figure S1** Signalling of muscle hypertrophy with resistance/strength type exercises.