

Metabolic and endocrine response to exercise: sympathoadrenal integration with skeletal muscle

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Abstract

Skeletal muscle has the capacity to increase energy turnover by ~1000 times its resting rate when contracting at the maximum force/power output. Since ATP is not stored in any appreciable quantity, the muscle requires a coordinated metabolic response to maintain an adequate supply of ATP to sustain contractile activity. The integration of intracellular metabolic pathways is dependent upon the cross-bridge cycling rate of myosin and actin, substrate availability and the accumulation of metabolic byproducts, all of which can influence the maintenance of contractile activity or result in the onset of fatigue. In addition, the mobilisation of extracellular substrates is dependent upon the integration of both the autonomic nervous system and endocrine systems to coordinate an increase in both carbohydrate and fat availability. The current review examines the evidence for skeletal muscle to generate power over short and long durations and discusses the metabolic response to sustain these processes. The review also considers the endocrine response from the perspective of the sympathoadrenal system to integrate extracellular substrate availability with the increased energy demands made by contracting skeletal muscle. Finally, the review briefly discusses the evidence that muscle acts in an endocrine manner during exercise and what role this might play in mobilising extracellular substrates to augment the effects of the sympathoadrenal system.

Key Words

- ▶ muscle energetics
- ▶ endocrine
- ▶ sympathoadrenal
- ▶ cytokine

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Introduction

Over 60 years ago, *Morris et al. (1953)* published data examining the relationship between the occupation of London bus drivers and conductors with the incidence of cardiovascular disease (CVD) and sudden cardiac death. Their report revealed that the incidence rate of the first clinical manifestations of CVD in the active conductors was half of that observed in the sedentary drivers. They subsequently published findings showing a cardioprotective effect of physical activity in relationship with the incidence of sudden cardiac death (*Heady et al. 1961*). The conclusion from these studies was that the greater

physical demands placed on the conductors resulted in a lower incidence of CVD when compared with the more sedentary drivers. Although exercise is now widely recognised as an effective counter measure to the development of diseases such as CVD, diabetes, cancer and obesity, our understanding of the interrelationships between the mechanisms of systemic and peripheral responses to exercise and the underlying reasons for disease prevention are largely incomplete.

Our understanding of the metabolic, hormonal and genetic responses to exercise has increased substantially

since the work of Morris *et al.* (1953). Repeated exercise has been shown to improve insulin sensitivity (Borghouts & Keizer 2000, Kirwan *et al.* 2009, Malin *et al.* 2013, Goyaram *et al.* 2014), reduce the catecholamine response to exercise (Kjaer & Galbo 1988), increase lipid catabolism (Phillips *et al.* 1996, Henderson & Alderman 2014), improve arterial compliance and endothelial function (Seals *et al.* 2008, Pierce *et al.* 2011) and maintain both bone density and skeletal muscle mass during ageing (Layne & Nelson 1999) and maintain muscle metabolic capacity with ageing (Olesen *et al.* 2014). Recent work has suggested that both skeletal muscle and adipose tissue function as integrated endocrine organs in response to an exercise stimulus (Pedersen 2013). Exercise therefore continues to be an effective methodological tool to study the body's response to metabolic stress, and from a clinical perspective, offers an alternative treatment choice to drug intervention strategies. Exercise also provides a quantifiable and controllable mechanism to examine the effects of

increasing the demands for ATP production and the integration of several organ systems to meet these demands (see Fig. 1). Finally, exercise facilitates our understanding of the emerging role of muscle and adipose tissue as endocrine organs.

The rising incidence of diseases related to physical inactivity and the links to endocrine dysfunction continue to challenge worldwide health care programmes in addressing the deleterious effects of low physical activity on population health (Global Strategy on Diet, Physical Activity and Health' WHO 2004). The current review describes the metabolic capacity of skeletal muscle in the transition from rest to maximum energy turnover. The review also discusses the process of responding to this metabolic stress through the co-ordinated utilisation of intra and extra-muscular energy stores that skeletal muscle employs. Finally, the review discusses the established view of the endocrine response to exercise from the perspective of sympathoadrenal activity and introduces the concept

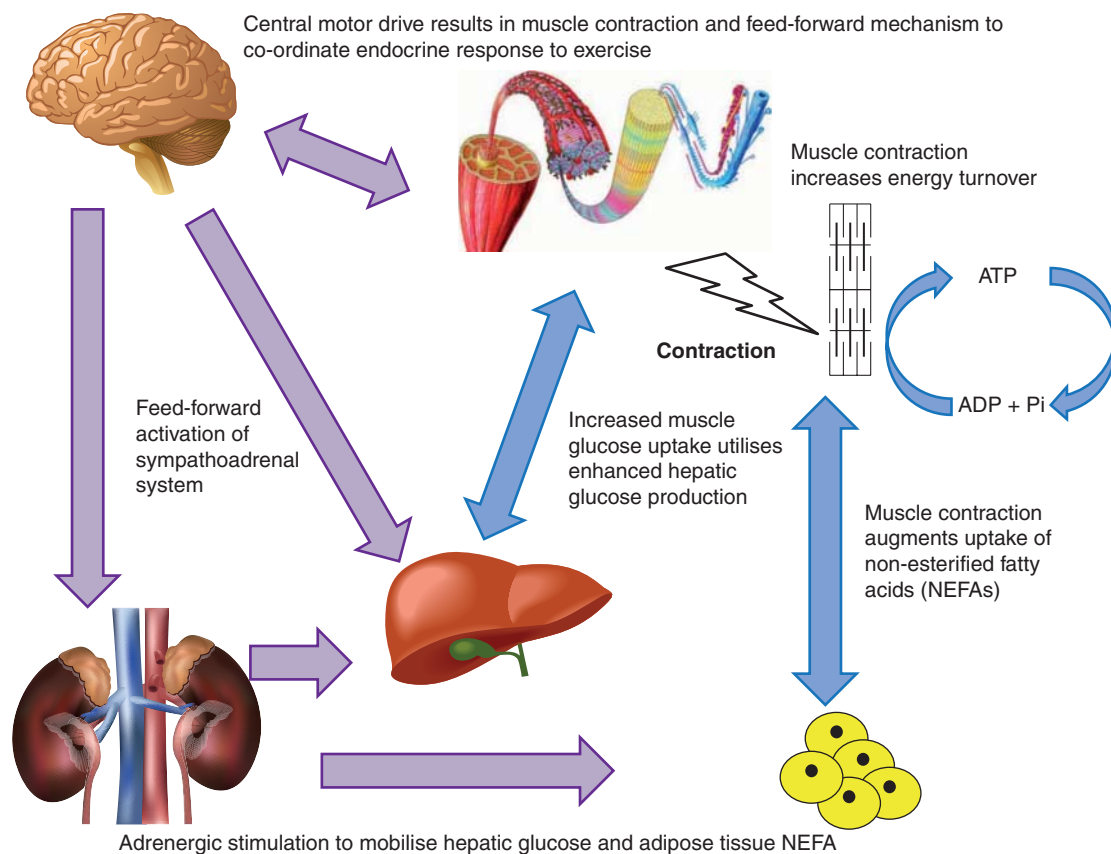


Figure 1

The activation of the CNS to initiate muscle contraction leads to an integrated response from the sympathoadrenal, cardiovascular, hepatic and adipocyte systems to mobilise and deliver oxygen and substrate to maintain energy turnover.

of muscle and adipose tissue as endocrine organs that participate in the co-ordinated endocrine response to exercise stress.

Muscle energetics and the metabolic demands of exercise

The potential for skeletal muscle to induce metabolic stress is reflected by its capacity to increase resting energy turnover by 1000 times to meet the needs of maximum exercise (Turner & Hoppler 1999). The concentration of ATP in mixed skeletal muscle is ~25 mmol/kg of dry muscle (d.m.; Hultman *et al.* 1967) and in contrast to other intramuscular substrates indicates that ATP is not stored in any large quantity. As a consequence of its limited availability, ATP is resynthesised at a rate for meeting the metabolic demands placed upon the cell. Stimulation of the muscle cell to contract initiates both ATP hydrolysis and resynthesis, and depending on the rate of ATP degradation, the cell will employ different metabolic strategies in an attempt to match the resynthesis rate with the rate of hydrolysis.

During ATP hydrolysis, the free energy that is released is used to generate force, which depending on the external load placed upon the muscle produces force, and shortening in length (concentric contraction), or force but no change in length (isometric contraction) or alternatively, force and a lengthening of muscle (eccentric contraction). The maximum amount of work done by skeletal muscle is reported to be 24 kJ/mol of ATP (di Prampero *et al.* 1988).

The theoretical maximum rate of ATP hydrolysis by myosin ATPase is reported to be 10 mmol/kg d.m. per s, with the highest rate found to be ~8.6 mmol/kg d.m. per s during isometric contraction (Hultman & Sjöholm 1983). This rate of ATP breakdown represents 70% of the total ATP turnover in skeletal muscle, a further 2.4 mmol/kg d.m. per s is utilised in the process of Ca²⁺ and proton handling and the maintenance of Na⁺ and K⁺ balance (Hultman *et al.* 1987). Other studies (Hultman & Sjöholm 1983, Bangsbo *et al.* 2001) have reported a lower rate of ATP hydrolysis and these discrepancies are probably due to the differences in exercise modality, which will have different patterns of motor unit and muscle fibre recruitment. Hydrolysis of ATP leads to an increase in the concentration of ADP, AMP and Pi, although this would reduce the ATP:ADP ratio, the accumulation of these by-products of ATP hydrolysis serves to co-ordinate the metabolic response to exercise by stimulating substrate level and oxidative phosphorylation, the activation of

creatine kinase and the expression of AMP-activated protein kinase (AMPK).

The most immediate substrate source for ATP resynthesis in skeletal muscle is phosphocreatine (PCr). Skeletal muscle has sufficient PCr (~85 mmol/kg per d.m., Harris *et al.* (1976)) to sustain the maximum ATP turnover rate for about 7–10 s. In addition to this metabolic pathway, the myokinase reaction utilises ADP to resynthesise ATP with the production of AMP (Spriet *et al.* 1987). The rise in AMP concentration is now understood to play a key role in activation of AMPK, a metabolic protein that is considered to play a central role in energy sensing in cells (Gowans *et al.* 2013), although AMP is rapidly deaminated to inosine monophosphate and ammonia through the purine nucleotide cycle (Lowenstein 1972, Meyer & Terjung 1979).

Not only is PCr energetically favourable in the resynthesis of ATP but it has a higher concentration than ATP at rest (~85 mmol/kg of d.m., Hultman *et al.* (1967)). Employing an *in-vivo* isometric exercise model, Spriet *et al.* (1987) reported that a 50% decline in force production coincided with 90% depletion of PCr, at the same time ATP concentration had decreased by 30%. During exercise, there is sufficient PCr to sustain the maximum rate of ATP hydrolysis for about 3–5 s before a decline in power production (Karatzafiri *et al.* 2001a,b). In this study, muscle biopsy samples revealed that after only 10 s of maximum power production, the concentration of ATP in the fast contracting muscle fibres had declined by over 30%. These data demonstrate that although skeletal muscle can generate a high power output, there is a limited metabolic capacity to do so.

Skeletal muscle also utilises both fat and carbohydrate as substrates for ATP resynthesis. The rates at which these substrates can resynthesise ATP are significantly lower than that from either PCr or ADP. However, their capacity for ATP resynthesis is significantly greater and consequently there is a trade-off between the power to produce ATP and the capacity for ATP resynthesis. The balance between substrate level phosphorylation (glycolysis) and oxidative phosphorylation (pyruvate and fatty acyl-CoA utilisation) is in part determined by the match between glycolytic flux and mitochondrial respiration. The maximum ATP resynthesis rate from glycogenolysis/glycolysis is reported to be 3.4 mmol/kg d.m. per s (Hultman & Spriet 1986) during electrical stimulation of the quadriceps when producing 70–75% of maximum tetanic force. In contrast, the maximum rate of ATP resynthesis from the utilisation of fatty acids alone is reported to be ~1.0 mmol/kg d.m. per s (McGilvery 1975; given in Table 1).

Table 1 Substrate availability and maximum ATP resynthesis capacity during exercise. Data from McGilvery (1975) and Maughan & Gleeson (2004)

Metabolic fate	Intracellular substrate availability (mmol/kg muscle)	Maximum rate to produce ATP (mmol/kg dry matter per s)
ATP, PCr→ADP, Cr	32	9.0
Glycogen→lactate	240	4.5
Glycogen→CO ₂ , H ₂ O	3000	2.8
Fatty acids→CO ₂ , H ₂ O	7–25	1.0

As described earlier, there is a trade-off between the power to produce ATP and the capacity for ATP production. Increasing exercise duration is achieved at the expense of the rate of ATP turnover. The lower rate of ATP turnover can be matched by oxidative phosphorylation that employs a combination of glucose/glycogen and fatty acids as the substrates. Early studies demonstrated the balance between fat and carbohydrate oxidation through indirect calorimetry method using expired gases (Christensen & Hansen 1939, Asmussen 1971). The use of the needle biopsy technique by Bergstrom & Hultman (1966) permitted direct measurement of intramuscular substrates, primarily glycogen and the glycolytic intermediates. Further studies using muscle biopsies provided a means to delineate the utilisation of glycogen in different muscle fibre populations (Gollnick *et al.* 1974). These early studies illustrated that utilisation of muscle glycogen was both fibre type and exercise intensity specific. At low exercise intensities (30–45% VO_{2max}), glycogen utilisation is primarily confined to type 1 (slow) muscle fibres. However, as the exercise intensity increases so too does the utilisation of glycogen in type 2 (fast) muscle fibres (Fig. 2). Whilst at very high exercise intensities, the rate of glycogen utilisation is also accelerated in type 1 fibres (Greenhaff *et al.* 1994). Utilisation of intramuscular triglycerides (IMTG) has also been reported, but determining the concentration of this substrate is technically challenging (Van Der Vusse & Reneman 1996), and there is an ongoing debate concerning the most appropriate method for measuring this substrate. As a consequence, there are limited data, in humans, that directly examines IMTG utilisation during exercise. An alternative method employed to measure the rate of IMTG has been achieved through the use of stable isotopic tracers. Romijn *et al.* (1993) and Van Loon *et al.* (2001) demonstrated the reliance on extracellular and intracellular fat and carbohydrates across a range

of exercise intensities by employing stable isotope tracers (Fig. 3).

The locus of control for balancing the mix of carbohydrate and fatty acid oxidation is still unresolved, with several candidate mechanism(s) being proposed. In 1963, Randle *et al.* proposed the 'glucose–fatty acid cycle', which suggested that a reciprocal relationship exists between the availability of fatty acids and glucose and their oxidation. A rise in plasma fatty acid availability, as a function of exercise, was postulated to limit glucose oxidation and increase fat oxidation and *vice versa* if plasma glucose availability increased with exercise.

Randle *et al.* (1963) focussed on the effects of fatty acid and ketone body availability because their principle interest was in studying the mechanism of the glucose fatty-acid cycle in relation to diabetes mellitus; however, some of their observations seemed to fit an exercise model and they postulated that increasing ketone body and fatty acid oxidation would inhibit key steps in glycolysis, namely phosphofructokinase (PFK), hexokinase and pyruvate dehydrogenase complex (PDC) activity. In terms of a mechanistic explanation, they argued that altering the acetyl CoA:CoA ratio would inhibit PDC, resulting in an upstream effect on both PFK and hexokinase through citrate and glucose-6-phosphate accumulation. However, the role of citrate, an essential element of the original glucose–fatty acid cycle hypothesis, was brought into question by work that demonstrated that the intracellular level of citrate was not different during intense exercise (85% VO_{2max}) with elevated plasma fatty acids, compared with a control (Dyck *et al.* 1993). Activation of the PDC through dichloroacetate has demonstrated that pyruvate

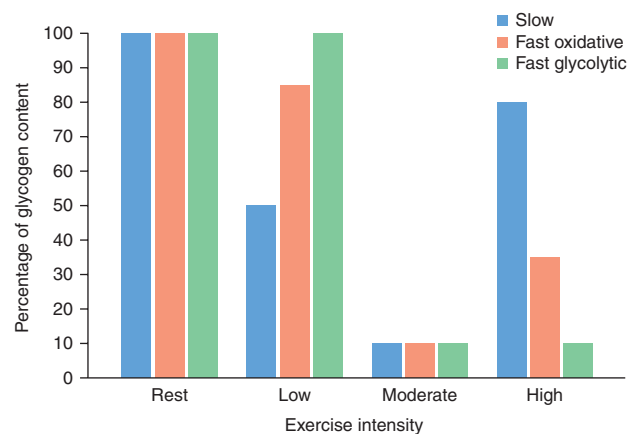


Figure 2 Muscle glycogen utilisation as a function of muscle fibre type and exercise intensity. Data from Gollnick *et al.* (1974).

flux is increased with a concomitant reduction in lactate production and stockpiling of acetyl groups (Timmons *et al.* 1998), hence any process that inactivates PDC would be expected to decrease carbohydrate oxidation. The availability of carnitine has been suggested as a mechanism that governs the oxidation of carbohydrate and fatty acids as a reduction in free carnitine would limit the transport of fatty acids into the mitochondria (Van Loon *et al.* 2001, Stephens *et al.* 2007) and increase the reliance upon carbohydrate. Along a related theme, increases in acetyl-CoA carboxylase (ACC) activity and malonyl CoA concentration and thus inhibition of carnitine palmitoyl transferase 1 have also been proposed as a mechanism that would limit the oxidation of free fatty acids during exercise (Merrill *et al.* 1998, Båvenholm *et al.* 2000). However, some studies have observed a decrease in ACC activity and malonyl CoA concentration as a function of exercise/muscle contraction (Rasmussen & Winder 1997, Dean *et al.* 2000) that would corroborate a shift to increase fatty acid oxidation, whereas others report no change in malonyl CoA concentration with exercise in humans (Odland *et al.* 1996). Other putative mechanisms that govern the signalling and transport of non-esterified fatty acids (NEFAs; Bonen *et al.* 1998) and insulin-independent glucose transport (Ploug *et al.* 1984, Hargreaves *et al.* 1991) have been proposed as mechanisms that might limit the intracellular availability of substrate and hence their oxidation. Taken together, these studies highlight the complexity of metabolic integration during exercise in relationship with substrate utilisation and ATP resynthesis.

Substrate utilisation is a product of both exercise intensity and duration. The effects of exercise intensity on substrate utilisation in well-trained cyclists was elegantly demonstrated by Romijn *et al.* (1993) when employing a stable isotope method to determine the rates of carbohydrate and fat oxidation at exercise intensities that elicited 25, 65 and 85% of maximum oxygen uptake (VO_{2max}). These authors reported that at 25% of VO_{2max} , the primary contribution to energy turnover was through plasma NEFA utilisation with a smaller but significant contribution from plasma glucose oxidation and little if any contribution from the intramuscular store of glycogen or triglyceride. The metabolic response to exercise at 65% VO_{2max} resulted in an increase in the utilisation of the intramuscular stores of both glycogen and triglyceride, and it was reported that at this intensity the rate of fat oxidation was higher than either that at 25 or 85% of VO_{2max} . The metabolic response to exercise at 85% VO_{2max} induced almost a complete reliance on

carbohydrate utilisation, whilst there was evidence of some fat oxidation this substrate contributed <30% to the total energy turnover. In support of these findings, Van Loon *et al.* (2001) examined the metabolic response to 30 min of exercise at 40, 55 and 75% of maximal workload (equivalent to 44, 57 and 72% of VO_{2max}). Again employing stable isotope methods and enhanced by muscle biopsies, they measured intramuscular substrate oxidation and extramuscular substrate provision. Their results supported those of Romijn *et al.* (1993) but also suggested that at the highest exercise intensity employed that the reduction in fat oxidation could have been due to a limitation in the availability of free carnitine. Collectively, these data demonstrate that at exercise intensities below 30% of VO_{2max} the principle energy source is fatty acids, between 40 and 65% of VO_{2max} there is approximately a 50:50 balance between carbohydrate and fat oxidation and beyond 70% of VO_{2max} there is an exponential rise in carbohydrate oxidation with a concomitant decrease in fat oxidation (see Fig. 3). For a more comprehensive review of fat metabolism during exercise, the reader is referred to Jeukendrup *et al.* (1998). More recently a metabolomics approach is being adopted to explore the metabolic response to exercise. A wide range of metabolites present in plasma and serum has been determined using liquid chromatography mass spectrometry and/or gas-chromatography mass spectrometry collected pre- and post-exercise. In most cases, a wide range of metabolites have been reported (Pohjanen *et al.* 2007, Lewis *et al.* 2010, Peake *et al.* 2014) to exist and that with exercise changes in metabolites related to carbohydrate, triglyceride and markers of the tricarboxylic acid have been reported.

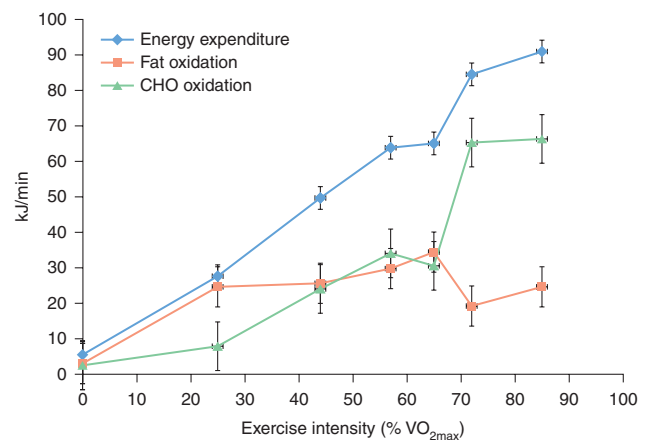


Figure 3

Increasing energy expenditure and the switch in substrate oxidation as a function of exercise intensity. Data taken from Romijn *et al.* (1993) and Van Loon *et al.* (2001).

Yan *et al.* (2009) examined the serum metabolite profile in athletes and compared this with healthy age-matched men. They concluded that the profiles of 13 metabolites and analysed using a principal component analysis technique allowed them to differentiate between the athletes and sedentary controls. With the exception of work by Peake *et al.* (2014), these studies were not hypothesis driven and are more observational in nature. However, the use of metabolomics could provide a unique insight into the co-ordinated metabolic response to exercise in terms of substrate mobilisation, utilisation and the production of metabolic by-products.

Efforts to understand the metabolic response to exercise have centred on how substrate utilisation is matched to ATP turnover and from a historical perspective the current review has presented this literature. Attention has now turned towards the intracellular signalling pathways related to the mechanism of glucose uptake and the expression of glucose transporters (Richter *et al.* 2003); the expression of differing myosin isoforms and muscle plasticity (Chin 2005); control of protein degradation and synthesis (Baar & Esser 1999, Hornberger *et al.* 2001, Parkington *et al.* 2003) and mitochondrial biogenesis (Wu *et al.* 1999, Baar *et al.* 2003), all of which contribute either to ATP hydrolysis or substrate oxidation and ATP resynthesis. Substantial efforts have been taken to clarify the role of AMPK since it was first proposed as the major fuel/energy sensor by Hardie *et al.* (e.g. Davies *et al.* 1992, Hawley *et al.* 1996, Hardie & Hawley 2001, Jorgensen *et al.* 2004). In a review of the many processes that AMPK is reported to influence, Hardie (2011) concluded that AMPK regulates all cell function. From the perspective of exercise/muscle contraction, a key element to AMPK activity is the energy charge (ATP:ADP ratio) of the cell, which will change with the onset of contraction. Utilising experimental designs that either increase AMPK activity through administration of AICAR (Jessen *et al.* 2003) or ablate AMPK expression (Lee-Young *et al.* 2009), AMPK is now understood to increase skeletal muscle glucose uptake through downstream phosphorylation of Akt/PKB (Cartee & Wojtaszewski 2007) and increase oxidative phosphorylation by elevating PGC1 α expression (Sasaki *et al.* 2014) and stimulating fatty acid oxidation through the simultaneous increase in mitochondrial respiration and a decrease in ACC activity (Park *et al.* 2002, Bonen *et al.* 2007).

The maintenance of blood glucose during exercise represents a significant challenge because the rate of muscle glucose uptake increases several fold (Ahlborg *et al.* 1974) and it is a process that is insulin independent

(Ploug *et al.* 1984). The principle organ for regulating blood glucose is the liver, which in the face of increased blood glucose disposal will increase the rate of hepatic glucose production through glycogen catabolism and gluconeogenesis (Ahlborg *et al.* 1974, Wahren *et al.* 1977). Ahlborg & Felig (1982) reported that during prolonged moderate intensity exercise ($\sim 60\%$ VO_{2max}), the rate of hepatic glucose output barely matched the rate of leg glucose uptake during the first 40 min of exercise. Skeletal muscle was reported to increase glucose uptake greater than tenfold from a resting value of 0.22 mmol/min. Crucially, during the following 140 min, the disparity between hepatic glucose output and leg glucose uptake became wider to the point whereby leg glucose uptake was double that of hepatic glucose production and as a consequence blood glucose had fallen below 3 mmol/l. These findings suggest that the decrease in hepatic glucose output is a function of depletion of the hepatic store of glycogen and that gluconeogenesis is unable to provide glucose at a rate to match the demand of contracting muscle. Increasing exercise intensity is also a potent stimulus to increase both the rate of glucose uptake and the rate of hepatic glucose production (Wahren *et al.* 1975, Katz *et al.* 1986). Van Loon *et al.* (2001) demonstrated that the rate of glucose appearance and disappearance increased as a function of increasing exercise intensity and that at their highest workload (72% VO_{2max}) the rate of plasma glucose oxidation was almost three times that measured at 44% VO_{2max} . The liver plays an important role in the maintenance of euglycaemia, but as these studies indicate the potential for skeletal muscle to utilise extracellular glucose is higher than the maximum rate of hepatic glucose output.

The mobilisation and delivery of endogenous substrates located other than in muscle, primarily glucose derived from the liver and NEFA released from adipose tissue, appear to be under endocrine control. The traditional view is that increasing sympathoadrenal activity, as a function of exercise, results in an increase in glycogen catabolism to release glucose from the liver and triacylglycerol to NEFA and glycerol in adipose tissue. Wahren *et al.* (1977) and Ahlborg & Felig (1982) independently reported the effect of increasing exercise intensity on the rate of hepatic glucose release and confirmed that hepatic glucose production increases by sevenfold, as a mechanism to match the rate of muscle glucose uptake that had increased by tenfold. These findings indicate that despite the concerted efforts of the liver to match the rate of skeletal muscle glucose disposal, there is always a deficit and the effects of this during prolonged exercise

may result in hypoglycaemia. It is also worth noting that the increase in hepatic glucose occurs despite a 50% decrease in hepatic blood flow (Wahren *et al.* 1977).

The endocrine response to exercise

The complexity and diversity of the entire hormonal response to exercise is too large to be covered in detail in this review. Therefore the context and focus on the metabolic effects of exercise in relationship with the endocrine response will be confined to the sympathoadrenal system. This element of the review will also consider the evidence that skeletal muscle responds to exercise in an endocrine manner by releasing myokines that have been purported to be involved in the mobilisation of extramuscular substrates. For a wider discussion on the hormonal response to exercise, readers are referred to a series of excellent reviews edited by Warren & Constantini (2000).

The neuroendocrine system controls a plethora of systemic functions that range from metabolism and fluid balance to cardiovascular and pulmonary function, in the context of this review the aim is to examine the endocrine response to exercise in relationship with the maintenance of an increase in energy demand. An early but classic description of the hormonal response to exercise was comprehensively reviewed by Galbo (1983) and similar to the current review substantial focus was devoted to sympathoadrenal activity, metabolism and exercise. The sympathoadrenal system releases the hormones epinephrine, norepinephrine and cortisol, although norepinephrine is often referred to as a hormone more accurately, it acts as a neurotransmitter. When discussing the sympathoadrenal response to various stimuli, it is worth noting that this is frequently reported as the changes in plasma norepinephrine and epinephrine, but that these variables may not precisely reflect the release of norepinephrine from the neuronal terminals of the sympathetic nervous system at the target organ, or methylated norepinephrine (epinephrine) from the chromaffin cells in the adrenal medulla (Galbo 1983, Kjaer & Lange 2000). However, due to the technical difficulties in directly measuring the release of these neurotransmitter/hormones, it is widely accepted that any increase or decrease in their plasma concentration indicates a change in sympathoadrenal activity (Galbo 2000).

Increases in sympathetic nervous activity as a function of exercise have been reported to be intrinsically linked to increased activity of the motor cortex of the brain (Kjaer *et al.* 1987, Victor *et al.* 1995) and to some degree a

metaboreflex from the contracting muscle (Victor *et al.* 1987). A novel but effective methodology to demonstrate the link between central activation of the motor centre and sympathetic activity is through the use of partial neuromuscular blockade by the i.v. administration of tubocurarine (Kjaer *et al.* 1987). These authors examined the effects of neuromuscular blockade (assessed as a 25% reduction in handgrip strength) during submaximal and maximal dynamic exercise. Under control conditions (i.e. no neuromuscular blockade) an increase in exercise intensity from rest to ~55% VO_{2max} and to that which elicited maximum oxygen uptake (100% VO_{2max}) resulted in a two- and fourfold increase in the plasma norepinephrine and epinephrine concentration respectively. Under partial neuromuscular blockade (curarisation), there was a higher concentration in both norepinephrine and epinephrine at the power output that demanded 55% VO_{2max} and the volunteers perceived the exercise to be harder. A further consequence of curarisation was that subjects were unable to match the higher power output during the graded exercise test, although their perceived exertion during these trials was no different than the control, but in contrast to the response observed at the lower exercise intensities the plasma epinephrine and norepinephrine concentration was depressed at this higher workload when compared with that found under control conditions. Galbo *et al.* (1987) reported similar effects of partial neuromuscular blockade (reported as a decrease in handgrip strength of 45%) during submaximal and maximal dynamic exercise on the plasma concentration of epinephrine and norepinephrine. Using a different exercise modality, Victor *et al.* (1995) measured central drive by recording muscle sympathetic activity through the peroneal nerve. They observed that during partial neuromuscular blockade the central drive to try and achieve the same isometric force output was maintained even though force production was only 25% of that attained under control conditions. The overriding conclusion from these studies is that there is a feed-forward element in terms of activating the sympathoadrenal system as a function of increased activity in the motor cortex of the brain. As mentioned previously, volitional motor unit recruitment initiates a feed-forward response of the sympathoadrenal system that mobilises endogenous substrates. A consequence of this neural-hormonal activity also affects cardiovascular function, which is integrated to the delivery of extracellular substrates for the exercising muscle. The importance of neural control of the circulation was presented in a series of papers published where exercise was the primary experimental

model and summarised as furthering our understanding of the role and location of central command (Basnayake *et al.* 2012, Matsukawa 2012) expanding the role of muscle afferents (Kaufman 2012) and the effects of neural blockade on the pressor response (Secher & Amann 2012). Owing to the innate potential to increase muscle blood flow by over tenfold from resting muscle conditions, control over blood flow during exercise is essential to avoid compromising central blood volume and pressure (González-Alonso *et al.* 2008). Sympathetic regulation of muscle blood flow assists in matching oxygen demand and substrate delivery to the exercising muscle whilst simultaneously helping to maintain blood pressure.

The effects of exercise on circulating catecholamine (epinephrine and norepinephrine) release are summarised: exercise induces a rise in catecholamines that is observed across a wide range of exercise modalities (Christensen & Brandsborg 1973, Galbo *et al.* 1975, Vecht *et al.* 1978, Hickson *et al.* 1979), is exercise-intensity dependent (Galbo *et al.* 1975, Kjaer *et al.* 1987) and is diminished with training (Winder *et al.* 1978, Phillips *et al.* 1996) and is lower in trained individuals compared with untrained individuals (Bloom *et al.* 1976, Kjaer & Galbo 1988). Interpretation of the effects of training status on the sympathoadrenal response to exercise requires careful consideration in relationship to whether the response is based on the absolute workload or is relative to the maximum workload. In general, when based on the absolute workload, the sympathoadrenal response is lower in trained individuals; however, when expressed as a percentage of the maximum workload (i.e. relative workload), trained individuals possess an augmented sympathoadrenal response to exercise.

The effect of increasing exercise intensity on the catecholamine response is an important feature in terms of mobilising both intracellular and extracellular substrates that are required to meet the energetic demands made by the contracting muscle. The exercise-induced increase in catecholamine concentration is of sufficient magnitude to stimulate glycogenolysis in both the liver (Kjaer *et al.* 1993, Kreisman *et al.* 2003) and skeletal muscle (Richter *et al.* 1981, Spriet *et al.* 1988). Under resting conditions, Chasiotis *et al.* (1983) demonstrated that infusing epinephrine resulted in an increase in skeletal muscle phosphorylase *a* and decrease in glycogen synthase I activity with a modest but significant decrease in glycogen content. During exercise, the effects of increasing plasma epinephrine concentration on the metabolism response in muscle is equivocal, with some studies suggesting an increase in carbohydrate utilisation

(Richter *et al.* 1981, Chasiotis & Hultman 1985, Jansson *et al.* 1986, Febbraio *et al.* 1998) and others reporting no effect (Chesley *et al.* 1995). The i.v. injection of epinephrine has been shown to accelerate the glycolytic rate in type 1 muscle fibres but not type 2 fibres (Greenhaff *et al.* 1991), which might account for the apparent discrepancy in previous findings because they were based on mixed muscle biopsy data. The effects of adrenergic stimulation on carbohydrate metabolism have also been examined in relationship with glucose uptake by skeletal muscle. Infusion of epinephrine has been reported to decrease glucose uptake (Watt *et al.* 2001); however, the rate of carbohydrate utilisation was enhanced demonstrating a shift towards intracellular carbohydrate utilisation and away from the utilisation of extracellular glucose. Employing either surgical or pharmaceutical adrenalectomised animal or human models is an interesting experimental approach due to the possibilities afforded by infusing exogenous epinephrine at rates that reflect those observed in normal controls during exercise and comparing the effects with the metabolic response to exercise in their normal (control) state. Kjaer *et al.* published work evaluating the metabolic response to exercise in adrenalectomised humans (Howlett *et al.* 1999, Kjaer *et al.* 2000) and reported that during exercise the adrenalectomised subjects maintained euglycaemia at ~ 70 and $\sim 85\%$ $\text{VO}_{2\text{max}}$. They also observed that in comparison with age matched controls they maintained the same rate of glycogen utilisation; this despite a lower glycogen phosphorylase *a* activity. When the adrenalectomised subjects subsequently received an infusion of epinephrine to double that observed in the control subjects the exercise-induced increase in muscle glucose uptake was depressed (Howlett *et al.* 1999). The effects of epinephrine are not confined to skeletal muscle because a rise in catecholamine concentration coincides with an increase in hepatic glucose output suggesting that the two might be related. Howlett *et al.* (1999) reported that in adrenalectomised subjects hepatic glucose output was substantially enhanced during the early stages of exercise when receiving an adrenaline infusion and that this effect of an increase in hepatic glucose output resulted in an elevated plasma glucose concentration. However, they also noted that during exercise with the adrenaline infusion, the metabolic clearance rate of glucose was lowered, which would also have an effect of elevating plasma glucose. Kjaer *et al.* (1993) examined the effects of blockade of the sympathetic nerves innervating the liver and adrenal medulla on the metabolic response to low- and moderate-intensity exercise. Blockade of celiac

ganglion resulted in a 50% reduction in plasma epinephrine when compared with the control (no blockade) condition; however, the plasma concentration of nor-epinephrine was not affected by celiac blockade. When the subjects exercised under conditions of sympathetic blockade, neither the rate of glucose appearance nor disappearance was different when compared with the control condition. The rate of glucose disappearance was higher than glucose appearance, resulting in a decline in plasma glucose during low-intensity exercise and this was not affected by blockade. However, during blockade and infusion with supraphysiological concentrations of epinephrine, they reported that hepatic glucose production increased by ~30% and this resulted in an elevated plasma concentration of glucose; under these conditions the rate of glucose uptake by skeletal muscle was similar between all conditions. The findings suggest that the plasma concentration of epinephrine or direct innervation of the liver has little effect on hepatic glucose production and that alternative factors may play a role in co-ordinating the release of the hepatic store of carbohydrate.

Adrenergic activation of the receptors on adipose tissue is known to increase the lipolytic rate to liberate NEFAs from stored triacylglycerol (Arner 2005). An increase in circulating epinephrine and nor-epinephrine would therefore be expected to increase NEFA availability. Romijn *et al.* (1993) reported that the peak oxidation of fatty acids occurred 65% of VO_{2max} when comparing the effects of exercise intensity at 25, 65 and 85% of VO_{2max} and this metabolic response coincided with an increase in plasma epinephrine concentration. However, at 85% VO_{2max} the plasma concentration of epinephrine increased further, but the rate of fatty acid oxidation had declined. During the latter stages of intermittent but prolonged (6 h) of moderate intensity exercise there is a shift in fuel utilisation from carbohydrate to fatty acids (Edwards *et al.* 1934). Other studies have confirmed these observations and explained the increase in fat utilisation partly as a consequence of the depletion of endogenous carbohydrate stores but also due to a rise in plasma NEFAs (Ahlborg *et al.* 1974) and this has been positively correlated with an increase in the plasma concentration of epinephrine (Ahlborg & Felig 1982, Romijn *et al.* 1993). A rise in plasma epinephrine in itself does not constitute a cause and effect on fatty acid availability, but Arner *et al.* (1990) demonstrated that during exercise, β -adrenergic stimulation is the principle mechanism for activating lipolysis in adipose tissue. Infusion of epinephrine has been shown to stimulate an increase in NEFAs during low-intensity exercise (40% VO_{2max} ; Mora-Rodriguez &

Coyle 2000). Despite the increased availability of fatty acids, the rate of fat oxidation remained unchanged thus providing further evidence of a limitation in substrate utilisation despite an increase in substrate availability, as previously discussed.

Under resting conditions, the rate of glucose uptake by skeletal muscle is ~0.2 mmol/min (Ahlborg & Felig 1982). It is postulated that the presence of the GLUT1 transporter is the mechanism responsible for the baseline rate of glucose uptake (Ciaraldi *et al.* 2005) and in the post-absorptive state is insulin independent. At rest, a rise in plasma insulin concentration results in an increase in glucose uptake into muscle through insulin-stimulated GLUT4 transport (James *et al.* 1988) and an inhibition in hepatic glucose production (DeFronzo *et al.* 1981). Exercise reduces circulating insulin concentration (Ahlborg *et al.* 1974, Hilsted *et al.* 1981, Galbo 1983), but as discussed earlier the rate of muscle glucose uptake can increase by tenfold during exercise. The link between exercise-induced skeletal muscle glucose uptake and an increase in GLUT4 expression demonstrates that there is an insulin-independent mechanism for increasing glucose transport (Ploug *et al.* 1992). It has been established that rises in contraction-induced AMP and increased AMPK activity result in a signalling cascade to increase the expression of GLUT4 at the sarcolemmal membrane and hence increase glucose uptake (Richter & Hargreaves 2013).

In the post-absorptive state, euglycaemia is maintained through a steady state hepatic output of glucose that is mediated through glucagon, stimulating both glycogenolysis and gluconeogenesis (Stevenson *et al.* 1987). Owing to the reciprocal nature of insulin and glucagon release, one would expect the concentration of glucagon to increase during exercise. Galbo *et al.* (1975) reported that a 35% rise in glucagon concentration was positively correlated with an increase in exercise intensity, from ~45 to 100% VO_{2max} ; however, Wahren *et al.* (1977) reported that plasma glucagon concentration did not change from rest when exercising at 60% VO_{2max} for 40 min. The duration of exercise appears to be an important factor in the stimulation of glucagon release because Galbo *et al.* (1975) observed that plasma glucagon increased threefold during the later stages of exercise at 70% VO_{2max} . The metabolic effects of increasing glucagon concentration during exercise appear to be confined to the liver (Wasserman *et al.* 1989, Wasserman & Cherrington 1991) and there are no studies, to the authors' knowledge, that demonstrate a direct effect of glucagon on lipolysis during exercise. Overall, an increase in contractile activity of muscle will accelerate the rate of glucose uptake and

in an effort to maintain euglycaemia hepatic glucose production is accelerated through an increase in glycogenolysis and gluconeogenesis.

Exercise also leads to an increase in the production and release of growth hormone, testosterone, adrenocorticotrophic hormone, cortisol and prolactin that each has local and systemic effects. However, discussing the scope of the effects of changing these hormones on factors such as muscle growth and repair is beyond the scope of this review and the reader is referred to the following papers (Galbo 2000, Kjaer & Lange 2000, Crewther *et al.* 2011).

The effect of exercise on cytokine expression

Based upon the increases in circulating catecholamines (epinephrine, norepinephrine and cortisol), increases in cell numbers related to the immune system (white blood cells) and an acute inflammatory response, i.e. an increase in cytokines (such as interleukin 6 (IL6), IL10 and tumour-necrosis factor alpha) the metabolic challenge presented by exercise could be viewed as a stress response. The initial interpretation of the exercise-induced increases in white blood cell number was thought to be due to a systemic inflammatory response or due to exercise-induced muscle damage (Brenner *et al.* 1999, Fischer 2006). Interest in the systemic role of cytokine expression has gathered pace since the early observation that the circulating cytokine concentration increases after moderate prolonged exercise (Fischer 2006). The pleiotropic result of increasing cytokine concentration appears to be mediated through either a chronic or acute stimulus that induces a pro-inflammatory or anti-inflammatory outcome. Comparisons between the increases in circulating cytokines associated with sepsis with those following exercise have been made with the conclusion that the magnitude and temporal pattern of cytokine expression differs and is dependent on whether the stimulus is through infection or exercise (see Fig. 4, Pedersen & Febbraio 2008). Separate observations on the expression of cytokines in relationship with disease status have also attracted interest due to the reported elevated plasma cytokine IL6 expression observed in type 2 diabetic patients (Kristiansen & Mandrup-Poulsen 2005). The causal link between IL6 expression and glucose/carbohydrate metabolism and exercise has yet to be fully established; however, there is a growing interest in the link between the two (Kristiansen & Mandrup-Poulsen 2005, Franckhauser *et al.* 2008, Sarvas *et al.* 2013).

From the perspective of an inflammatory response to exercise, the focus of attention has centred on the increase

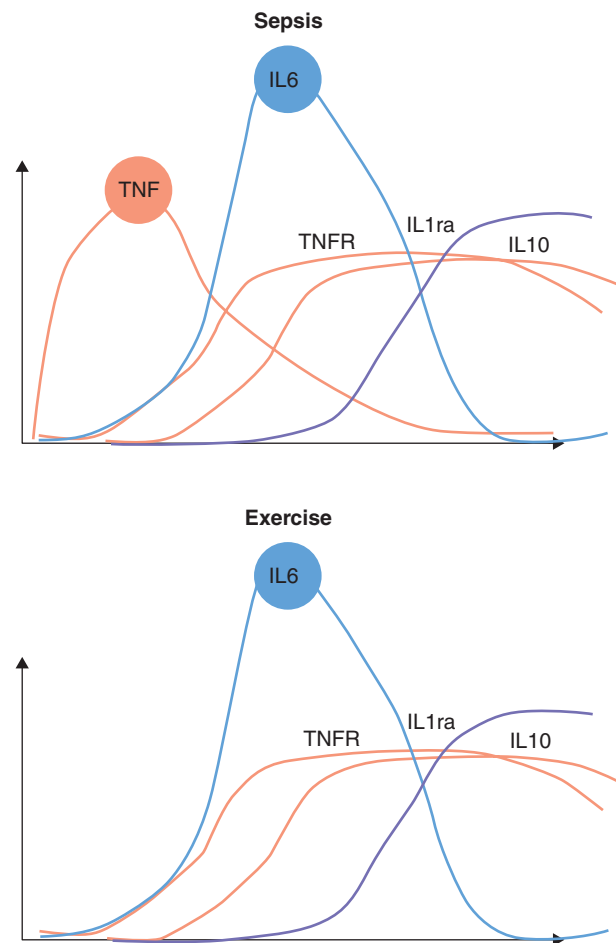


Figure 4

The effects of sepsis and exercise on cytokine expression, note that the magnitude of effect differs between stimulus. Figure from Pedersen & Febbraio (2008).

of the inflammatory cytokine, IL6, as a function of exercise (see Figs 4 and 5, Li & Gleeson 2004, Fischer 2006, Pedersen & Fischer 2007). It has been suggested that muscle may release secretory factors related to contractile activity that have systemic effects (Pedersen & Febbraio 2008). Several review papers that examined the evidence for an endocrine role of skeletal muscle (Pedersen *et al.* 2007) have been published and concluded that skeletal muscle expresses several myokines including IL6, IL8 and IL10 (Pedersen *et al.* 2001, Febbraio & Pedersen 2005, Pedersen 2009). There are numerous papers supporting an increase in IL6 expression with exercise but relatively fewer investigations reporting a relationship between IL10 and exercise (Nieman *et al.* 2006, Ropelle *et al.* 2010). Fischer (2006) conducted a systematic review of the relationship between exercise and IL6 expression. Of the 65 studies that Fischer reviewed, eight employed a

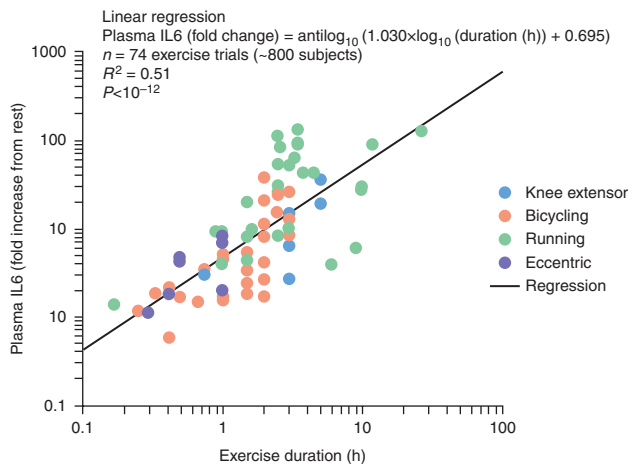


Figure 5
IL6 expression increases as a function of exercise duration. Figure from Fischer (2006).

single-leg knee extensor exercise mode, 30 utilised cycling and the remaining 27 used running as the exercise modality. The increase in IL6 expression varied between a onefold increase and a 128-fold increase, with the higher levels of IL6 expression generally observed as a function of the longer duration of exercise. Whilst this may seem a prodigious increase in IL6 expression due to exercise, severe infection induced can result in levels of circulating IL6 that are up to ten times higher, i.e. a 1000-fold increase from basal levels (Friedland *et al.* 1992). The mode of exercise also appears to be important in determining the IL6 response with running resulting in the highest level of IL6 expression (Fischer 2006). While it should be noted that the duration of exercise tended to be longer in the running studies; two experiments, Nieman *et al.* (1998) and Starkie *et al.* (2001) employed both running and cycling and reported higher levels of IL6 expression when running was completed by subjects compared with cycling, despite the fact that the exercise was at the same relative intensity and for the same duration.

The source of the increased circulating IL6 continues to be a source of debate since it is known that circulating monocytes release IL6 (Gleeson 2000). However, Starkie *et al.* (2001) reported that despite a marked increase in circulating white cell number following completion of a marathon (42.2 km), the number of cells producing the cytokines IL1 and IL6 decreased, suggesting that white blood cells are not the source of IL6 following exercise. An early study examining the effects of prolonged exercise on cytokine expression suggested that the source of IL6 may stem from skeletal muscle (Ostrowski *et al.* 1998).

They reported that 60% of the participants exhibited an increase in mRNA expression of *IL6* in muscle; however, the method of measuring mRNA was semi-quantitative. A later report from the same group (Steensberg *et al.* 2000) measured the release of IL6 from human contracting muscle by determining the femoral vein–arterial difference and demonstrated, for the first time, that IL6 is released by exercising muscle. Whilst the strong evidence from this study demonstrates that skeletal muscle releases cytokines, the actual source of IL6 was not identified and as highlighted by Gleeson (2000) there are numerous types of cells that could account for the production of IL6. The evidence for skeletal muscle as the principle source of IL6 release appears to be strong but other cell types, such as endothelial cells, connective tissue, adipose tissue, interstitial macrophages may also contribute to the release of cytokines.

One factor that appears to be important in an exercise-induced cytokine release is a reduction in the availability of intramuscular glycogen. Almost all studies that have measured the circulating concentration of IL6 report that depleting the intramuscular store of glycogen before exercise augments the circulating IL6 concentration (Nehlsen-Cannarella *et al.* 1997, Bishop *et al.* 2001, Keller *et al.* 2001, Steensberg *et al.* 2001, MacDonald *et al.* 2003). Gleeson *et al.* (1998) reported a significant increase in white cell count and granulocyte activity following prolonged submaximal exercise and that this response was augmented when preceded by the consumption of a diet low in carbohydrate. In a follow-up study, they also measured the plasma cytokine concentration and reported that in a glycogen depleted state there was an increase in the plasma concentration of cortisol and IL1r, IL6 and IL10 expression in the first hour following strenuous exercise (Bishop *et al.* 2001). The proposition that carbohydrate availability is linked with cytokine expression is further strengthened by the observation that the provision of exogenous carbohydrate has a suppressive effect on plasma IL6 concentration (Nieman *et al.* 1998, Febbraio *et al.* 2003). The activity of AMPK has been proposed as an intracellular signal that governs skeletal muscle cytokine expression (Weigert *et al.* 2007), but another study suggests that AMPK activity is increased by IL6 (Yuen *et al.* 2009). Furthermore, Lihn *et al.* (2008) reported that cytokine expression is reduced by AMPK activity. Clearly, the energy status of the cell, in terms of substrate availability and intracellular signalling, is linked to cytokine expression but exact the nature of the relationship is still not fully understood.

It has been postulated that IL6 release is associated with the mobilisation of extracellular substrates. [Febbraio *et al.* \(2004\)](#) examined the effects of administering recombinant human IL6 (rh-IL6) during 2 h of low-intensity exercise (40% $\text{VO}_{2\text{max}}$). Using stable isotope tracer techniques, to determine hepatic glucose production (Ra) and rate of glucose disposal (Rd), they reported that infusion of rh-IL6 resulted in an increase in both Ra and Rd when compared with low-intensity exercise alone. They also compared the metabolic effects of rhIL6 at low-intensity exercise with exercise at 70% $\text{VO}_{2\text{max}}$. Despite the fact that Ra and Rd were not different between low-intensity exercise with rhIL6 and exercise at 70% $\text{VO}_{2\text{max}}$, the metabolic clearance rate of glucose was higher during exercise at 70% $\text{VO}_{2\text{max}}$. In support of the role of IL6 in promotion of skeletal muscle glucose uptake [Glund *et al.* \(2007\)](#) reported that IL6 increased *in vitro* skeletal muscle glucose uptake by 1.3-fold, a prodigious improvement in glucose transport; however, the concentration of IL6 used in the study was supraphysiological. Other observations, however, have been unable to demonstrate any effect of IL6 on hepatic glucose output ([Wolsk *et al.* 2010](#)). Any increase in plasma glucose following the administration of recombinant IL6 could also be due to a decline in skeletal muscle glucose uptake rather than an increase in hepatic glucose output. Increasing the plasma concentration of IL6 has been linked to an increase in plasma non-esterified concentration according to [Wolsk *et al.* \(2010\)](#). Examining the effects of rhIL6 they reported that following IL6 infusion both the rate of palmitate appearance and oxidation increased when compared with a saline infusion. Taken together, these effects of IL6 suggest some augmentation of the sympathoadrenal system, as it has been shown that an increase in catecholamine release during exercise results in an increase in lipolysis ([Arner 2005](#)) with the effects of IL6 resulting in a similar increase in NEFA availability.

Conclusion

Skeletal muscle can increase the rate of energy turnover from rest to maximum force/power output that requires an integrated response both from within the cell and systemically to match the rate of ATP degradation with the ATP resynthesis. The metabolic co-ordination required to do this incorporates the demand on different substrates to maintain ATP production to support muscle contraction. In addition, the sympathetic system is activated in a feed-forward manner by the motor centre in the brain with the

consequence of initiating an endocrine response to exercise as reflected by the increases in sympathoadrenal activity. Focus has now switched to the role that skeletal muscle plays in a systemic endocrine response that appears to be related to substrate availability within the exercising muscle. The equivocal role of cytokine expression during and after exercise and the contrasting effects to cytokine expression related to disease remain a fertile area for research.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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