REVIEW / SYNTHÈSE

Molecular responses to strength and endurance training: Are they incompatible?[1]

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Abstract: Simultaneously training for both strength and endurance results in a compromised adaptation, compared with training for either exercise mode alone. This has been variously described as the concurrent training effect or the interference effect. It now appears that the genetic and molecular mechanisms of adaptation induced by resistance- and endurance-based training are distinct, with each mode of exercise activating and (or) repressing specific subsets of genes and cellular signalling pathways. This brief review will summarize our current understanding of the molecular responses to strength and endurance training, and will examine the molecular evidence for an interference effect when concurrent training is undertaken. A better understanding of the activation and interaction of the molecular pathways in response to these different modes of exercise will permit sport scientists to develop improved training programs capable of maximizing both strength and endurance.

Key words: Akt, AMPK, endurance training, mTOR, PGC-1, strength training, skeletal muscle adaptations.

Résumé : L'entraînement simultané à la force et en endurance engendre une adaptation particulière comparativement à une seule modalité d'entraînement. C'est ce qu'on appelle « l'effet convergent de l'entraînement » ou « l'effet de superposition ». Il semble clair maintenant que les mécanismes génétiques et moléculaires de l'adaptation suscitée par l'entraînement à la force et par l'entraînement en endurance sont distincts; chaque modalité d'entraînement active ou réprime de façon spécifique des sous-ensembles de gènes et des voies cellulaires de signalisation. Cette brève synthèse présente les mécanismes des réponses moléculaires aux modalités respectives d'entraînement à la force et en endurance et analyse les faits moléculaires à l'appui de « l'effet de superposition » quand on combine les deux modalités d'entraînement. C'est par une meilleure compréhension des mécanismes d'activation et d'interaction des voies moléculaires en réponse aux diverses modalités d'entraînement que les scientifiques du sport pourront développer des programmes d'entraînement afin d'améliorer simultanément la force et l'endurance.

Mots-clés : Akt, AMPK, entraînement en endurance, mTOR, PGC-1, entraînement à la force, muscle squelettique, adaptations.

[Traduit par la Rédaction]

Background

Adaptations to exercise training and the resultant performance improvements are highly specific to the mode of activity performed. Thus, undertaking resistance training stimulates the myofibrillar proteins responsible for muscle hypertrophy, culminating in increases in maximal strength (Fry 2004; Tesch 1988). In contrast, endurance training elicits increases in the mitochondrial content and respiratory capacity of the trained muscle fibers (Holloszy 1967), resulting in a slower rate of utilization of muscle glycogen and blood glucose, a greater reliance on fat oxidation, and less lactate production during submaximal exercise (Holloszy and Coyle 1984). These metabolic adaptations underlie the large increase in exercise capacity that occurs in response to endurance training (Hawley 2002; Holloszy et al. 1977).

Since the pioneering work of Hickson (1980), conducted over a quarter-century ago, it has been known that simultaneously training for both strength and endurance results in a compromised adaptation, compared with training for either exercise mode alone. This has been variously described as the concurrent training effect or interference effect (Coffey and Hawley 2007; Coffey et al. 2009; Hickson 1980; Nader 2006). Unknown to Hickson at the time, it now appears that the genetic and molecular mechanisms of adaptation induced

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by resistance and endurance training are distinct, with each mode of exercise activating and (or) repressing specific subsets of genes and cellular signalling pathways (Atherton et al. 2005; Coffey et al. 2006*b*, 2009). This brief review will summarize our current understanding of the molecular responses to strength and endurance training, and will examine the molecular evidence for an interference effect when concurrent training is undertaken. A better understanding of the activation and interaction of the molecular pathways in response to these different modes of exercise will permit sport scientists to develop improved training programs capable of maximizing both strength and endurance.

The training response and adaptation

From a molecular perspective, any training adaptation can be viewed as the accumulation of specific proteins induced by a given exercise stimulus (Hansen et al. 2005). Accordingly, the altered gene response that initiates changes in protein concentration is of major importance for any subsequent training adaptation. While a single bout of resistance or endurance exercise is insufficient to produce either hypertrophy or mitochondrial biogenesis, there are transient alterations in the cellular milieu that, when repeated over time, generate the specific exercise-induced phenotype associated with long-term training. Converting a mechanical signal generated during contraction to a molecular event that promotes adaptation in a muscle cell involves the upregulation of a number of primary and secondary messengers that initiate a cascade of coordinated events, resulting in the activation and (or) repression of specific signalling pathways regulating exercise-induced gene expression and protein synthesis and (or) degradation (for reviews, see Coffey and Hawley 2007; Williams and Neufer 1996). In brief, exercise generates transient increases in the quantity of messenger (m)RNA, which, for most contraction-induced genes, peaks in the first 4–8 h postexercise, typically returning to basal levels within 24 h (Bickel et al. 2005; Neufer and Dohm 1993; Pilegaard et al. 2000; Yang et al. 2005). This directional change in mRNA is generally the same as the encoded protein during adaptation to a new steady-state level (Booth and Baldwin 1996). However, because the half-life of many exercise-induced proteins is greater than that of the message (Neufer and Dohm 1993), the transient increase in mRNA synthesis has a longer lasting effect on the protein. Therefore, exercise repeated on a daily basis has a cumulative effect, leading to a change in the steady-state level of specific protein and a new functional threshold (MacLean et al. 2000; Williams and Neufer 1996). This observation has led to the paradigm that exercise-training-induced adaptations in skeletal muscle are the result of the cumulative effects of repeated bouts of contractile activity, with the initial signalling responses that lead to long-term adaptations presumably occurring during and (or) after each single training session (Widegren et al. 2001). While such a hypothesis is attractive, it should be noted that, currently, there is a paucity of data in humans to convincingly demonstrate that a tight coupling exists between early exercise-induced gene responses, the phosphorylation status of regulatory signalling pathway proteins, and the phenotypic adaptations to chronic training programs.

Molecular responses to resistance exercise

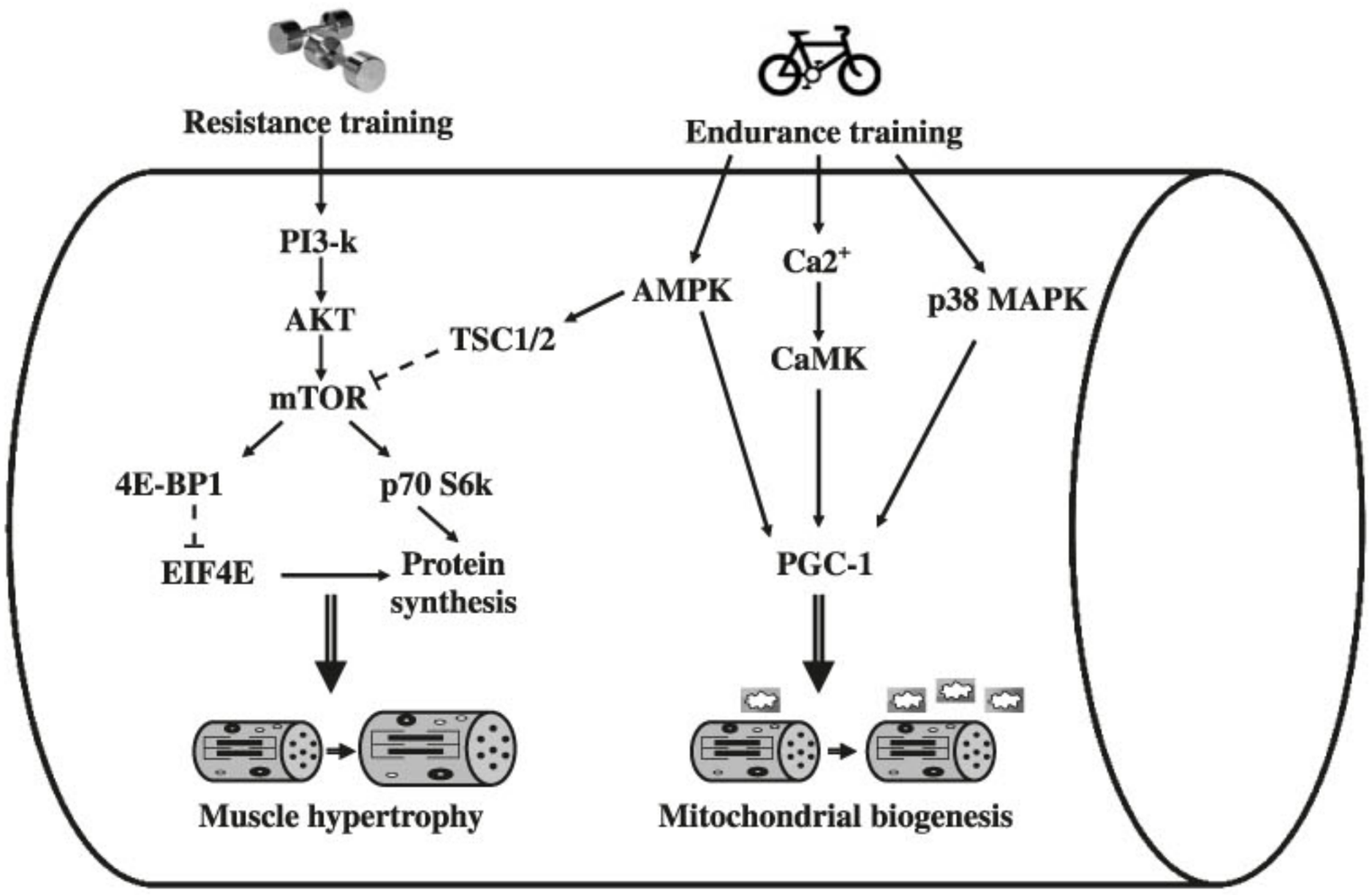
Muscle protein anabolism takes place when the rate of protein synthesis is greater than the rate of protein breakdown, resulting in a net accretion of muscle protein over time. Muscle hypertrophy is a relatively slow process, because protein synthesis must exceed protein breakdown for an extended period (i.e., weeks to months). An acute bout of resistance training increases skeletal muscle protein turnover for up to 48 h after completion of exercise, with both concentric and eccentric contractions similarly effective in promoting this effect (Phillips et al. 1997). A single bout of resistance exercise increases the fractional rate of mixed muscle protein synthesis by ~50% 4 h postexercise, and by 115% 24 h postexercise (Chesley et al. 1992). These changes in protein synthesis are the result of an increase in the amount of protein synthesized per molecule of RNA, rather than an increase in total RNA product (i.e., increased efficiency of translation), as there is no measurable increase in the RNA content of the muscle 4 or 24 h following exercise (Chesley et al. 1992).

The chronic resistance training-induced adaptations that culminate in muscle hypertrophy are the result of an integrated pattern of gene responses and coordinated molecular events that promote the enlargement of pre-existing muscle cells via the incorporation of additional myonuclei (Flück and Hoppeler 2003). For example, 1 bout of resistance exercise induces a rapid (~2 h) activation of several genes involved in muscle hypertrophy (muscle regulatory factor 4), with the peak induction for the majority of myogenic genes occurring 4–6 h after exercise (Psilander et al. 2003; Willoughby and Nelson 2002; Yang et al. 2005). The translation control mechanisms that regulate muscle gene expression in response to resistance exercise have been reviewed elsewhere (Baar et al. 2006; Bolster et al. 2003; Kimball and Jefferson 2006), but it appears that chronic training subtly coregulates numerous genes from important functional groups that may be part of the long-term adaptive process to repeated training stimuli (Stepto et al. 2009).

The intracellular signalling pathways that mediate the resistance-exercise-induced increase in protein synthesis revolve around the phosphatidylinositol 3-kinase (PI3-k)–Akt–mammalian target of rapamycin (mTOR) cascade (Fig. 1). The mTOR complex integrates signals of the energetic status of the cell and environmental stimuli (nutrient and growth factors, mitochondrial signals, and exercise) to control protein synthesis, protein breakdown and, therefore, cell growth (Deldicque et al. 2005). Studies in humans elucidating a role for Akt–mTOR signalling by resistance exercise have yielded contrasting results (Coffey et al. 2006*a*; Deldicque et al. 2008), but, in general, provide support for the involvement of this pathway in anabolic processes following both acute (Dreyer et al. 2006) and chronic (Léger et al. 2006; Wilkinson et al. 2008) resistance exercise training.

Perhaps the most well-defined effectors of Akt–mTOR signalling are the proteins implicated in translational control: ribosomal protein S6 kinase (p70 S6k) and eIF4E-binding protein (4E-BP1). S6k exerts its effect through multiple substrate targets, and has been implicated in orchestrating the regulation of numerous cellular functions, including cell size and protein synthesis (Coffey and Hawley 2007). Nu-

Fig. 1. Intracellular signalling networks mediating exercise-induced skeletal muscle responses to resistance- and endurance-based exercise training programs. Resistance-based exercise induces an increase in the activity of the phosphatidylinositol 3-kinase (PI3-k)–Akt–mammalian target of rapamycin (mTOR) signalling cascade to modulate rates of protein synthesis and (or) breakdown and, over a prolonged period (weeks to months), muscle hypertrophy. Endurance-based exercise activates signalling pathways involved in metabolic homeostasis, comprising the adenosine-monophosphate-activated protein kinase (AMPK)–p38 mitogen-activated protein kinase (MAPK)–peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 axis. Activation of AMPK by endurance exercise may inhibit mTOR signaling via tuberous sclerosis complex (TSC) and suppress resistance-exercise-induced muscle-protein synthesis. Endogenous and exogenous substrate availability before, during, and after resistance- and endurance-based exercise can modulate the transcriptional activity of selected myogenic and metabolic genes, as well as the regulation of signalling pathways that promote myofibrillar and mitochondrial protein synthesis. 4E-BP1, eukaryotic initiation factor 4E-binding protein 1; CaMK, calmodulin-dependent protein kinase; EIF4E, eukaryotic translation initiation factor-binding protein; S6k1, ribosomal protein S6 kinase; TSC1/2, tuberous sclerosis complex 1 and 2.



merous studies provide compelling support for the fundamental role of p70 S6k in skeletal muscle hypertrophy (for review, see Coffey and Hawley 2007). Early work by Baar and Esser (1999) in a rodent model established a strong association between increased p70 S6k activity and skeletal muscle hypertrophy following 6 weeks of resistance-training-like stimulus (high-frequency electrical stimulation). Bodine and coworkers (2001) used surgical ablation and pharmacological intervention to demonstrate the important role for p70 S6k in skeletal muscle hypertrophy in a variety of in vivo animal models. Terzis et al. (2008) recently reported that increases in p70 S6k phopshorylation after a single bout of resistance exercise in humans was significantly correlated with the percentage increase in whole-body fat-free mass, several maximal strength measures, and type IIA muscle fiber cross-sectional area after a 14-week resistance training program. This latter finding is important because the long-term regulation of hypertrophy and other cell processes by S6k1 is not currently well understood. Indeed, it has been proposed that p70 S6k may promote reciprocal effects on protein synthesis and repress insulin-like growth factor signalling via a negative feedback loop through insulin receptor substrate-1 phosphorylation (Ruvinsky and Meyuhas 2006).

Finally, it is becoming clear that endogenous and exogenous substrate availability before and after resistance exercise can modulate the transcriptional activity of selected myogenic genes and the regulation of signalling pathways that promote the resistance-exercise-induced increase in protein synthesis (Churchley et al. 2007; Creer et al. 2005). Indeed, feeding and resistance exercise independently activate translation initiation events involved in determining the specific nature of the protein synthetic response (Fujita et al. 2007; Karlsson et al. 2004; MacKenzie et al. 2009; Moore et al. 2009; Wilkinson et al. 2008). In this regard, it appears that, to promote maximum cellular growth and adaptation to resistance exercise, nutrient provision (in the form of amino acids) is critical to fully activate protein synthetic signalling in muscle (Deldicque et al. 2005).

Molecular responses to endurance exercise

Endurance is the ability of an individual to perform repeated, continuous skeletal muscle contractions for prolonged periods (i.e., >30 min) at a given submaximal power output or speed (Hawley 2002). While enhanced oxygen kinetics, substrate transport, and muscle buffering capacity all contribute to enhanced endurance, the improved performance capacity after a program of endurance training is mostly associated with the increase in mitochondrial density and oxidative enzyme activity, termed mitochondrial biogenesis (Holloszy and Coyle 1984). Endurance training can in-

crease steady-state mitochondrial protein content 50%–100% within 6 weeks, but a protein turnover half-life of ~5–7 days means a repeated training stimulus is required to maintain elevated mitochondrial content (Zierath and Hawley 2004). As such, the chronic endurance-training-induced adaptations that result in mitochondrial biogenesis and enhanced performance capacity are the consequence of the gene-specific transcriptional activation during and after a single bout of exercise. Although the entire transcriptional response to endurance exercise has not been demonstrated, a single bout of exercise has been shown to increase mRNA expression in a growing number of genes, the majority of which are involved in mitochondrial biogenesis and metabolism (Mahoney et al. 2005).

Mitochondrial biogenesis requires the coexpression of both the nuclear and mitochondrial genomes for assembly and expansion of the reticulum, and 95% of the genes necessary for biogenesis are encoded in the nucleus (Goffart and Wiesner 2003). Thus, an important aspect of mitochondrial biogenesis is the machinery regulating the transport of nuclear-encoded precursor proteins into the organelle (Irrcher et al. 2003) However, expression of genes promoting mitochondrial biogenesis is predominantly controlled by the global principles of gene regulation, that is, transcription initiation and interaction at the gene promoter (Goffart and Wiesner 2003). Therefore, transcription factors and transcriptional coactivators represent critical regulators of mitochondrial biogenesis.

The initial breakthrough in elucidating how mitochondrial biogenesis is regulated was the discovery of the transcription factors that regulate expression of the nuclear genes that encode mitochondrial proteins (Scarpulla 2006). These include nuclear-respiratory factor 1 and nuclear-respiratory factor 2, which bind to the promoters and activate transcription of the genes that encode mitochondrial respiratory chain proteins (Kelly and Scarpulla 2004). Nuclear-respiratory factor 1 also activates expression of the nuclear gene that encodes mitochondrial transcription factor A, which moves to the mitochondria, where it regulates transcription of the mitochondrial DNA (i.e., the mitochondrial genome). Another important transcription factor involved in regulating expression of mitochondrial proteins is the peroxisome proliferator-activated receptor coactivator, which regulates expression of the mitochondrial fatty acid oxidative enzymes (Kelly and Scarpulla 2004; Scarpulla 2006). The discovery of an inducible coactivator, the peroxisome proliferator-activated receptor gamma coactivator (PGC-1α), shed further light on the complex process of mitochondrial biogenesis. PGC-1α docks on and activates various transcription factors and, thus, activates and regulates the coordinated expression of mitochondrial proteins encoded in the nuclear and mitochondrial genomes (Lin et al. 2005). A single bout of exercise induces a rapid increase in PGC-1α gene and protein in skeletal muscle (Baar et al. 2002; Irrcher et al. 2003; Mathai et al. 2008). The initial phase of the increase in mitochondrial biogenesis induced by exercise appears to be mediated by activation of PGC-1α, while the second phase is mediated by the increase in PGC-1α protein (Wright et al. 2007).

The other important exercise-induced signal that leads to increased mitochondrial biogenesis is the increase in AMP concentration in muscle during exercise, which results in activation of the enzyme AMP-activated protein kinase (AMPK). AMPK functions as a metabolic fuel gauge in skeletal muscle, because when it becomes activated in response to decreased energy levels (i.e., muscle contraction), it inhibits ATP-consuming pathways and activates pathways involved in carbohydrate and fatty acid catabolism to restore ATP levels (Hardie and Sakamoto 2006). AMPK promotes fatty acid oxidation in skeletal muscle during exercise by inhibiting acetyl-CoA carboxylase and activation of malonyl-CoA, thus removing inhibition of mitochondrial fatty acyl-CoA translocation by carnitine palmitoyltransferase-1. Numerous studies have reported that these exercise-induced effects on acetyl-CoA carboxylase and malonyl-CoA are closely paralleled by activation of AMPK (Rasmussen and Winder 1997; Yu et al. 2003).

As is the case for resistance exercise, substrate availability exerts profound effects on the endurance-training-induced adaptation. However, in contrast to resistance training, in which adequate nutrient provision (amino acids) is critical for muscle hypertrophy, selected markers of training adaptation (i.e., resting muscle glycogen content, the maximal activities of several mitochondrial enzymes, and the protein content of COX IV) may be augmented when individuals commence selected exercise sessions with low muscle glycogen levels, compared with training in a normal glycogen condition. (Hansen et al. 2005; Yeo et al. 2008).

Molecular responses to concurrent resistance and endurance exercise

The concomitant integration of endurance- and resistance-based exercise in a training program is termed concurrent training. Since the work of Hickson (1980), contemporary studies have investigated a variety of metabolic and performance measures after combining resistance and endurance training. However, the majority of these experiments have been confined to end-state measures, such as maximum strength and (or) power, maximal aerobic capacity, and (or) maximal enzyme activities. Consequently, it is not possible to deduce the timing and identity of the regulatory events that orchestrated the observed endpoint adaptations. As a result, there has been little or no elucidation of the mechanisms underlying the specificity of training adaptation or interference to these pathways during concurrent training (Coffey and Hawley 2007).

The first clues that resistance and endurance training might induce different types of signalling responses in skeletal muscle came from the work of Atherton and colleagues (2005). These workers used isolated rat muscles, electrically stimulated with either high frequency (to mimic resistance exercise) or low frequency (to mimic endurance exercise), to determine exercise-specific signalling events. Resistance-like exercise specifically increased the phosphorylation of the anabolic Akt–mTOR signalling cascade, along with the activation of the translation initiation regulators p70 S6k, 4E-BP1, and eIF2B, but had little effect on the AMPK–PGC-1 pathway. In contrast, endurance-like exercise increased AMPK phosphorylation and PGC-1 protein levels. Atherton et al. (2005) proposed that selective activation of either the Akt–mTOR or AMPK–PGC-1 signalling pathways

can explain specific adaptive responses to resistance- or endurance-like exercise responses. From a regulatory perspective, the notion of an AMPK–Akt master switch is attractive. However, major differences exist between rodent and human responses to exercise (extra- vs. intramuscular substrate preference, fiber type homogeneity, and prior training history), which make extrapolations from animal models to humans difficult.

To determine the early signalling responses to divergent exercise stimuli in humans, we studied skeletal muscle from resistance-only trained and endurance-only trained athletes (Coffey et al. 2006*b*). One experiment was undertaken in the athletes' habitual training disciplines (resistance or cycling exercise), while the other was performed in the nonfamiliar mode. Muscle biopsies were taken at rest, immediately postexercise, and after 3 h of passive recovery. AMPK phosphorylation increased after cycling in resistance- (54%; $p < 0.05$) but not endurance-trained subjects. Conversely, AMPK was elevated after resistance exercise in endurance- (114%; $p < 0.05$) but not strength-trained subjects. Akt phosphorylation increased in endurance- (50%; $p < 0.05$) but not strength-trained subjects after cycling, but was unchanged in either group after resistance exercise. p70 S6k phosphorylation increased in endurance- (118%; $p < 0.05$) but not strength-trained subjects after resistance exercise, but was unchanged in both groups after cycling. Similarly, phosphorylation of S6 protein, a substrate for p70 S6k, was increased immediately following resistance exercise in endurance- (129%; $p < 0.05$) but not strength-trained subjects. These results do not support the hypothesis of a selective activation of the AMPK–PCG-1–Akt pathways in response to divergent stimuli; rather they support the notion that a degree of response plasticity is conserved at opposite ends of the strength-endurance adaptation continuum. Indeed, the increases in AMPK phosphorylation in cyclists after resistance exercise and in strength-trained athletes after cycling strongly suggests that the adaptive phenotype and overload stimulus, rather than the mode of exercise per se, alters the AMPK signalling response.

To further examine this question, Coffey et al. (2009) determined the acute molecular responses to divergent contractile stimuli (resistance vs. endurance exercise) by combining consecutive bouts of resistance and endurance exercise in subjects who had a training history in both modes of exercise. Subjects completed trials consisting of either resistance exercise (8 × 5 repetitions of leg extension at 80% of 1 repetition maximum) followed by a bout of endurance exercise (30 min cycling at 70% of peak O_2 uptake), or vice versa, with muscle biopsies taken before and 15 min after the exercise bouts, and following 3 h of recovery. The cumulative effect of the combined exercise protocols resulted in disparate mRNA responses. For example, modest increases in PCG-1 mRNA did not reveal any order effect. With regard to signalling, there was increased Akt^{ser473} phosphorylation 15 min following resistance exercise, with the greatest magnitude of change taking place when resistance exercise was undertaken after cycling. The isoform-specific increase in Akt1 phosphorylation with resistance but not endurance exercise is indicative of the capacity for high-intensity, low-volume contractions to promote an anabolic response in muscle (Atherton et al. 2005; Bodine et al. 2001). Subtle changes in tuberous sclerosis complex 2 and mTOR phosphorylation did not match those observed for Akt activation. Phosphorylation of AMPK (above rest) was higher 3 h after cycling was undertaken following resistance exercise, indicating that the metabolic stress may have been exacerbated when exercise was performed in this order. Taken collectively, these results provide support for the contention that (acute) concurrent training does not promote optimal activation of pathways that simultaneously promote both anabolic and endurance responses. Furthermore, undertaking divergent exercise modes one after the other clearly influences the molecular profile typically associated with exercise in either mode alone.

Finally, it is known that both resistance and endurance exercise stimulate the rate of mixed muscle protein synthesis, an aggregate measure of all muscle proteins (Carraro et al. 1990; Chesley et al. 1992). However, resistance training results in increases in the myofibrillar proteins (actin and myosin), whereas endurance training increases mitochondrial proteins. From a teleological perspective, and given their vastly divergent functional outcomes, it would seem incongruous to suggest that resistance- and endurance training-induced responses could be compatible from a molecular standpoint.

Summary and directions for future research

The aim of training is to provide an overload stimulus that generates specific molecular responses to enhance the adaptive phenotype. From a performance perspective, it is clear that alternating exercise modes during concurrent training reduces the capacity for the simultaneous acquisition of hypertrophy and (or) mitochondrial training-induced adaptation responses, compared with single-mode training. While the molecular blueprint associated with either resistance- or endurance-based training is, to some degree, unique, there are many factors that independently activate translation initiation by acutely (and possibly chronically) altering the phosphorylation state of multiple signalling proteins (e.g., nutrient availability, training status). Clearly, the biggest challenge for exercise biochemists will be to directly link the acute metabolic and intracellular signalling events that occur after different types, durations, and intensities of exercise to specific changes in gene and protein expression in skeletal muscle. This will be complicated by the fact that these pathways are not linear, but rather constitute a complex network with a high degree of cross-talk, feedback regulation, and transient activation. Clearly, there is much work to be undertaken in this field in the next decade if we are to gain a better understanding of the molecular bases of training adaptation.

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