MALAYSIAN JOURNAL OF

Sport Science and Recreation

CONTENTS

UNIVERSITI TEKNOLOGI MARA

Faculty of Sports Science & Recreation

Volume 1 No. 1

Malaysian Journal of Sport Science and Recreation

Malaysian Journal of Sport Science and Recreation

Volume 1 • No.1 / 2005

FACULTY OF SPORTS SCIENCE AND RECREATION
Universiti Teknologi MARA

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The Specificity of Training: New Insights from Molecular Biology

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The key overload components of a training programme are volume, intensity and frequency, with the specific adaptive process occurring with exercise dependent on the training stimulus. Periodised training of sufficient overload initiates a cascade of events in muscle that results in modification of adaptive responses. Chronic adaptations are likely the result of the cumulative effects of repeated bouts of exercise with the initial cellular responses that lead to these long-term adaptations occurring after each training session. The training specific adaptive response is influenced by numerous factors including the overload stimulus and individual muscle fibre type. Comparing the distinct adaptive responses in skeletal muscle to endurance versus heavy resistance training highlights this process. This brief review summarises some of the specific adaptations associated with heavy resistance training, endurance training, and concurrent training.

Key words: *training impulse, fibre type, gene expression, mitochondria, hypertrophy*

INTRODUCTION

Habitual exercise training generates a multitude of integrated adaptive responses that are specific to the stimulus applied. This ability to adapt to repeated stimuli is a consequence of the inherent need to maintain homeostasis and minimize cellular disruptions/disturbances during subsequent exercise bouts. Skeletal muscle represents a physiological system that has extensive malleability enabling the tissue to alter its morphological and contractile properties in line with the type of overload stimulus (Adhihetty, Irrcher, Joseph, Ljubicic, & Hood, 2003). The key overload components of any training programme are the volume, intensity and frequency of training sessions. The sum of these inputs can be termed the "training stimulus" or "training impulse" that either enhances (fitness) or decreases (fatigue) performance capacity (Bannister, 1991). Accordingly, the plasticity of skeletal muscle enables athletes with the appropriate phenotype to selectively attain the biochemical and physical adaptations required to compete successfully in their chosen discipline (Figure 1).

Regular exercise training of sufficient overload initiates a cascade of events in muscle that upregulates gene expression and results in modification of adaptive responses ranging from DNA copying to the assembly of translation products (Figure 2). These biological actions ultimately produce a new steady-state in the protein synthesis of key mediators for altered tissue function and, therefore, overload induced adaptation to the stimulus (Flück & Hoppeler, 2003). Although chronic adaptations are likely the result of the cumulative effects of repeated bouts of exercise, the initial cellular responses that lead to these long-term adaptations are likely to occur after each training session.

The specificity of muscle adaptation is highlighted by comparing the distinct adaptive responses in skeletal muscle to endurance versus heavy resistance training. Heavy resistance training increases muscle size and strength (Häkkinen, 1989) while regular endurance training results in enhanced oxygen kinetics and improved resistance to fatigue (Hawley, 2002). However, optimal performance in a range of sporting disciplines often requires a muscle phenotype incorporating the combination of both endurance and strength adaptation. This brief review summarises some of the specific adaptations associated with heavy resistance training, endurance training, and concurrent training, and highlights the emerging role of molecular biology in helping to explain some of the training specific responses to such exercise-training regimens.

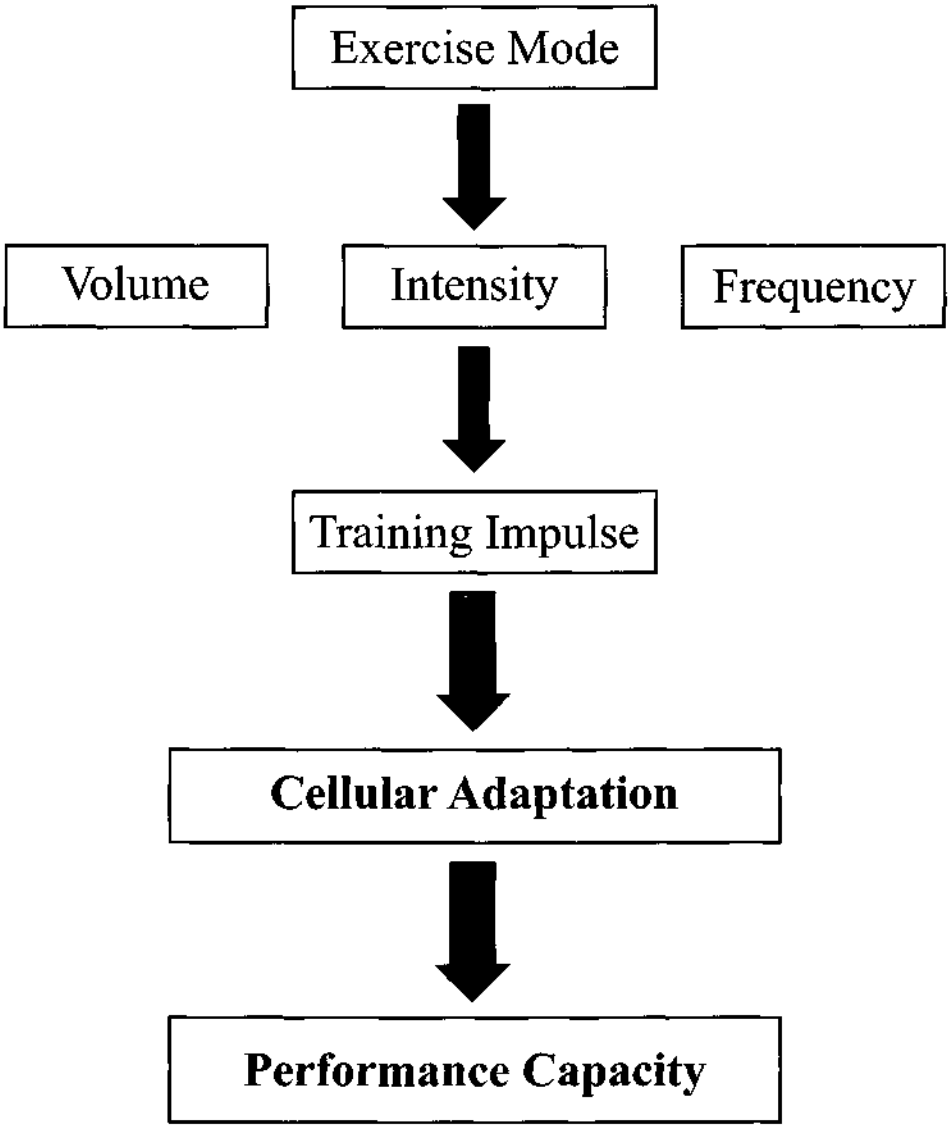

Figure 1.
Key components of periodised training that induce training-specific cellular adaptations.

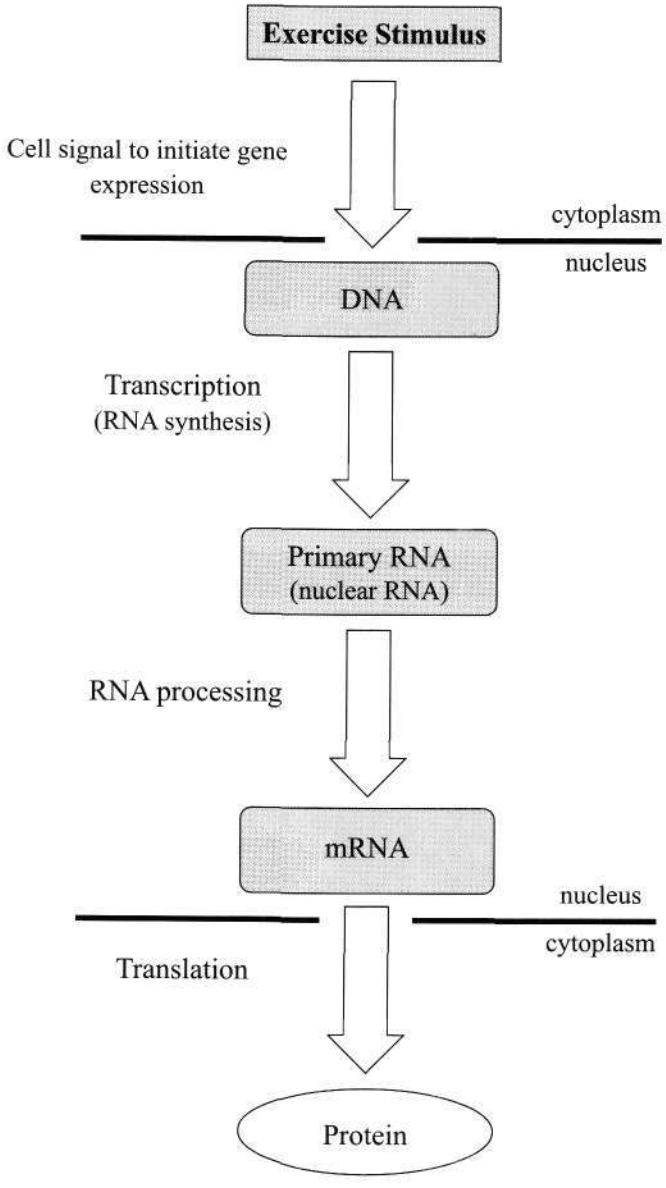

Figure 2.
Summary of exercise-induced molecular events producing an adaptive response via the synthesis of specific proteins.

The Training Stimulus

Endurance exercise is characterised by prolonged periods of low-resistance, high repetition muscular contraction. Exercise modes routinely associated with endurance training include running, cycling and swimming with the principle aims of increasing maximum oxygen uptake ($\dot{V}O_2max$), economy of movement and muscle resistance to fatigue. Volume is a key component of the overall training impulse for endurance athletes who often undertake very large amounts of training in belief of a direct relationship between work performed and subsequent performance enhancement (Hawley, 2002).

In contrast, resistance training is recognised as the primary mode of training for increasing muscle strength and power. Resistance exercise is associated with large muscle groups performing short bouts of high-load, low-repetition exercise to increase the force-generating capacity of the muscle. Exercise intensity represents an important component of the training impulse with loads >75% of an individual's one repetition maximum routinely required for overload induced performance enhancement (Häkkinen, 1989).

Although there is obviously a training impulse beyond which any additional load or stimulus does not induce further adaptation, the control mechanisms for the adaptive process require regular periods of overload regardless of the exercise mode. Therefore, in addition to the type of exercise performed the volume, intensity and frequency of overload is important in defining the training impulse with adequate recovery to ensure optimal muscle adaptation (Figure 1).

Muscle Fibre Type as a Marker for Exercise Capacity

All individuals have vastly different inherent abilities to perform aerobic or anaerobic exercise. Part of the reason for such differences in performance capacity is because of muscle fibre composition (Zierath & Hawley, 2004). Three main fibre types have been established i.e. slow twitch (ST), fast twitch *a* (FTa), fast twitch *b* (FTb); and each fibre type has its own specific functional characteristics (Table 1). Due to the innate nature of the fibre characteristics, their relative abundance has been associated with specific athletic endeavour. The relative content of ST fibres is related to an individual's predisposition for endurance capacity and training adaptation. This is a consequence of the oxidative potential and metabolic properties of these fibres. Conversely, muscle composed of mainly FT fibres produces higher and more rapid force outputs than muscle predominantly composed of ST fibres. This adaptation enhances performance of tasks of short duration requiring high levels of muscular power.

The genetic predisposition and developmental variation combine with training specific adaptations to produce distinct fibre type shifts and subsequent muscle phenotype.

Part of any training-induced adaptation in muscle is due to a triggering of specific changes in gene expression. Although no single generic transcription factor has been identified that initiates this process, recent studies in animals highlight the importance of muscle phenotype to performance capacity. Wang et al. (2004) over expressed PPARδ, a major transcriptional regulator of fat oxidation, in wild type mice. They showed that such over expression of PPARδ stimulated mitochondrial biogenesis and oxidative function and lead to a two-fold increase in ST muscle fibres. More importantly, such changes in muscle phenotype and functional characteristics resulted in a 92% increase in endurance running capacity in these engineered mice, compared with their normal littermates. The results of this study support the concept that skeletal muscle fibre type transformations can occur by altering transcriptional factors, and raise the possibility of genetic engineering of human muscle for enhancement of athletic performance.

Endurance Training

Prolonged, intense endurance training elicits both central and peripheral adaptations, alters neural recruitment patterns, causes profound changes in muscle bioenergetics as a result of alterations in cell signalling and subsequent gene expression of specific adaptive proteins, and thus produces an enhanced morphological, metabolic substrate and acid-base status (for review see Hawley, 2002). Briefly, endurance adaptation results in increased muscle glycogen stores and glycogen sparing at submaximal workloads via increased fat oxidation, enhanced lactate kinetics and morphological alterations including greater type I fibre proportions per muscle area, and increased capillary and mitochondrial density (Table 1).

Since the pioneering study of Holloszy (1967) it has been well established that transformation of the components implicated in mitochondrial biogenesis are important responses in the cellular adaptation to endurance training (Holloszy, 1967; Holloszy, Oscai, Don, & Mole, 1970). While investigations of training-induced mitochondrial biogenesis have been reported for over 30 years, the molecular machinery and subsequent mechanisms of adaptation have only recently begun to be elucidated (Adhihetty et al., 2003). The complex process of exercise-induced mitochondrial biogenesis (i.e. expansion of the mitochondrial reticulum)

Table 1.
Physiological and functional characteristics of the different muscle fibre types in humans.

	Muscle Fibre Type		
Characteristic	**ST**	**FTa**	**FTb**
Relative Mitochondrial Density	High	Intermediate	Low
Mitochondrial Enzyme Activity	High Oxidative	Oxidative	Low Oxidative
Myoglobin	High	Intermediate	Low
Cross-sectional Area	Small	Large	Large
Fatigue Resistance	High	Intermediate	Low
Force Output	Low	High	Very High
Contraction Velocity	Slow	Intermediate	Fast
Capillary Density	High	Intermediate	Low
Metabolic Potential	Oxidative	Oxidative-Glycolytic	Glycolytic
Myosin Heavy Chain	Type I	Type IIa, x/d	Type IIb

involves a sequence of events initiated seconds after starting exercise (e.g. ATP turnover, calcium flux) and concludes days or weeks later with increased protein expression (for review see Hood, 2001; Irrcher, Adhihetty, Joseph, Ljubicic, & Hood, 2003). Mitochondria are found both at the centre (intermyofibrillar) and periphery (subsarcolemmal) of the muscle fibre yet their location specific functional properties and differential responses to various stimuli remain unclear (Hoppeler & Flück, 2003). Nevertheless, the marked improvement in endurance performance that parallels mitochondrial biogenesis is a result of increased total mitochondrial content (ranging from 50-100%) which enhances muscle metabolism during exercise (Hood, 2001).

Mitochondrial biogenesis requires genetic information from both the cell nucleus and the mitochondria to ensure the accurate assembly and expansion of proteins to increase mitochondrial content (Adhihetty et al., 2003). A key regulatory step in this adaptive process is control of the procedure for copying nuclear and mitochondrial genetic material (i.e. transcription). While it is logical to assume that no single factor could control such an integrated process, a recently discovered transcription factor, peroxisome proliferator-activated receptor-gamma (PPARδ) coactivator-1 (PGC-1) has emerged as a potential master regulator of mitochondrial biogenesis (Baar et al., 2002). Current research indicates the alpha isoform of PGC-1 is involved in control of mitochondrial function. PGC-1α exhibits tissue-enriched expression in slow-twitch skeletal muscle and is rapidly and transiently induced by exercise (Lin et al., 2002; Pilegaard, Saltin, & Neufer, 2003). The exercise-induced activation of PGC-1a mediates multiple events within the mitochondria that can ultimately lead to an enhanced oxidative capacity of the cell. Therefore, PGC-1α represents an excellent molecular marker for monitoring the specific cellular adaptation to endurance training.

Strength Training

Increased muscle cross-sectional area and altered neural recruitment patterns represent the principal adaptations to repeated bouts of heavy resistance training. Increased cross-sectional area (i.e. hypertrophy) is a result of an increase in protein mass per tissue and this adaptive process is regulated by a complex network of physiological mechanisms (for review see Rennie, Wackerhage, Spangenburg, & Booth, 2004). Fundamentally, the hypertrophy response to overload is qualitatively and quantitatively controlled via the production of cellular proteins and new muscle cells.

Adaptation to resistance training includes increased protein synthesis via regulatory changes in translational mechanisms and in the production of muscle cells that are added to existing myofibres or less frequently combine and form new contractile filaments, each providing additional contractile machinery with which to generate more force (Glass, 2003; Rennie et al., 2004). In addition to protein synthesis from ribosomal production, new muscle cells form via the activation of non-specialised satellite cells (also referred to as muscle stem or precursor cells) that lie inactive at the periphery of existing muscle fibres. The mechanical stress and damage that occurs to muscle with resistance training overload triggers a cascade of events that ultimately result in the activation of this otherwise dormant pool of non-specialised cells. The satellite cells respond to the stimuli and consequently proliferate via mitosis and/or differentiate for their specialised role as mature muscle cells (Adams, Caiozzo, Haddad, & Baldwin, 2002; Rathbone, Wenke, Warren, & Armstrong, 2003).

Recently, two genes have been identified that play important roles in the regulation network of human muscle mass; insulin-like growth factor (IGF) and myostatin (Rennie et al., 2004). IGF isoforms are positive regulators of muscle hypertrophy that are understood to be primarily involved in both translation regulation and satellite cell activation. Specific roles for different IGF isoforms include muscle generated systemic IGF retained in local extracellular compartments producing an increase in cell density and myoblast fusion, and local autocrine/paracrine IGF related to mechanotransduction growth and repair that results in an increase in the number of myoblasts (Goldspink, 2003). Myostatin is a transforming growth factor and negative regulator of muscle mass. The specific mechanisms by which myostatin exerts it's effect remain unclear but the regulation of expression and subsequent targets appear to depend on major growth pathways such as glucocorticoids, androgens, and myogenic differentiation factors (Rennie et al., 2004). However, the powerful regulatory role of myostatin has been established in animal knockout models and more recently in humans (Schuelke et al., 2004) where genetic deletion or mutation results in profound increases in muscle mass.

While the specific quantitative and qualitative exercise-induced adaptations with IGF and myostatin gene expression are still to be clearly defined, both expression profiles are altered with training and culminate in a change in the adaptive profile and muscle hypertrophy. The functional outcome of such changes represents an important area of future research for interpreting training specific adaptation to resistance training.

Concurrent Endurance and Resistance Training

The concomitant prescription of endurance and resistance training in a periodised training plan is termed concurrent training. To date results of research investigating the adaptation and performance changes in individuals undertaking concurrent training has been equivocal. There are several possible reasons for this, including differences in the design of the concurrent training interventions, the influence of dependent variable selection, small sample sizes and inadequate statistical power (for review see Leveritt, Abernethy, Barry, & Logan, 2003).

Nevertheless, since the original investigative work of Hickson (1980) numerous studies have reported a variety of positive/negative physiological adaptive consequences when combining resistance and endurance training (for review see Leveritt, Abernethy, Barry, & Logan, 1999).

The conundrum of variable results with concurrent training research found in available literature is not surprising given the distinct adaptive processes described previously. Indeed, it is reasonable to suggest that the specific adaptations to the divergent exercise modes appear to be incompatible, at least at the cellular/ molecular level. Heavy resistance training does not lead to mitochondrial biogenesis and the larger myofibril cross sectional area increases diffusion distances for oxygen and substrates (Hood, 2001). Therefore, with respect to alterations in the muscle milieu, this does not induce a favourable adaptation for endurance capacity. Likewise, chronic endurance training does not have a significant effect on myofibril size and the muscles altered metabolic status and subsequent residual fatigue may have a negative effect on muscle protein synthesis and the ability to generate force. Accordingly, this does not produce an adaptation conducive for increased muscular size and strength.

Much of the research of concurrent training practices has focused on performance outcome variables; as a result there has been little or no elucidation of the mechanisms of training specificity or interference in subsequent adaptation.

Our current understanding of the specific exercise-induced adaptations that occur with concurrent training highlights the difficulty for the trainer or coach working with athletes involved in sports that require components of both endurance and strength/power (i.e. team sports). Performance that is predominantly governed by a singular adaptive state that may benefit from occasional concurrent training periods (e.g. high intensity resistance training to enhance movement economy in endurance athletes) represents a lower complexity in exercise prescription.

However, for performance that requires adaptations for both strength and endurance (e.g. rugby, basketball, rowing, tennis etc) the prescriptive guidelines are less clear. Given the apparent distinct adaptive pathways with endurance versus resistance overload, the training impulse devoted to each mode of training represents the basis for manipulating the chronic training adaptation response. Indeed, considering the time required for adaptive processes the training frequency, and therefore recovery, appears to be paramount in the periodised plan where concurrent training is unavoidable.

To date, exercise programming for simultaneous increases in muscle mass and aerobic capacity has required an artistic approach due to the limitations in interpreting concurrent research: most studies have involved cycling, with only a few studies using running or swimming protocols, and have employed untrained or moderately trained male volunteers, who undergo short-term (8 to 16 wk) training interventions in which the total training impulse is low. Hence, results from these investigations are not likely to be applicable to highly trained competitive athletes with superior genetic predisposition, individuals with a prolonged training history, or those athletes with a consistently high training impulse. Periodised training approaches vary and may utilise block periods (macro-cycles) of single mode training for optimal adaptation followed by maintenance while the secondary mode is developed, or simultaneous training of the divergent exercise modes by skilful manipulation of each micro-cycle in an attempt to gain adaptive benefits for each mode concurrently. While these and other approaches to concurrent training are well established much of the training specific adaptation process remains to be elucidated. Progress in understanding the mechanisms of training-induced adaptation with concurrent resistance and endurance training has previously been impeded by the difficulty in establishing important markers of adaptation. However, the emergence of vital molecular markers of adaptation (such as IGF and PGC-1α) represent an exciting new means to determine mechanisms in this adaptive process.

Future Directions

How do muscles know how to adapt to the variety of overload stimuli with different modes of training? Should endurance athletes perform resistance training? What is the optimal recovery time between concurrent exercise sessions? Clearly, the amplitude and duration of molecular events within the muscle cell represent a significant component in elucidating the complex mechanisms of training specific adaptation. Although the major disruptions to cellular homeostasis occur during a training bout, the time-course responses of important

signalling cascades and subsequent gene expression during recovery from exercise are likely to be of major significance for determining training specific adaptation (Figure 3). Future research should incorporate the monitoring of molecular markers during exercise and recovery while manipulating the mode, frequency, volume and intensity in well-designed research studies to elucidate the foundational mechanisms of training specific adaptation. This information will be invaluable for the intricate task of exercise prescription for optimal athletic performance. While still in the realm of fantasy, we are closer than ever to a genomic future that may involve the prospect of a molecular myostatin knockout / PGC-1α over-expression transgenic super-athlete who has the potential for extremes in both endurance and strength performance, and to redefining known paradigms of training specific adaptation.

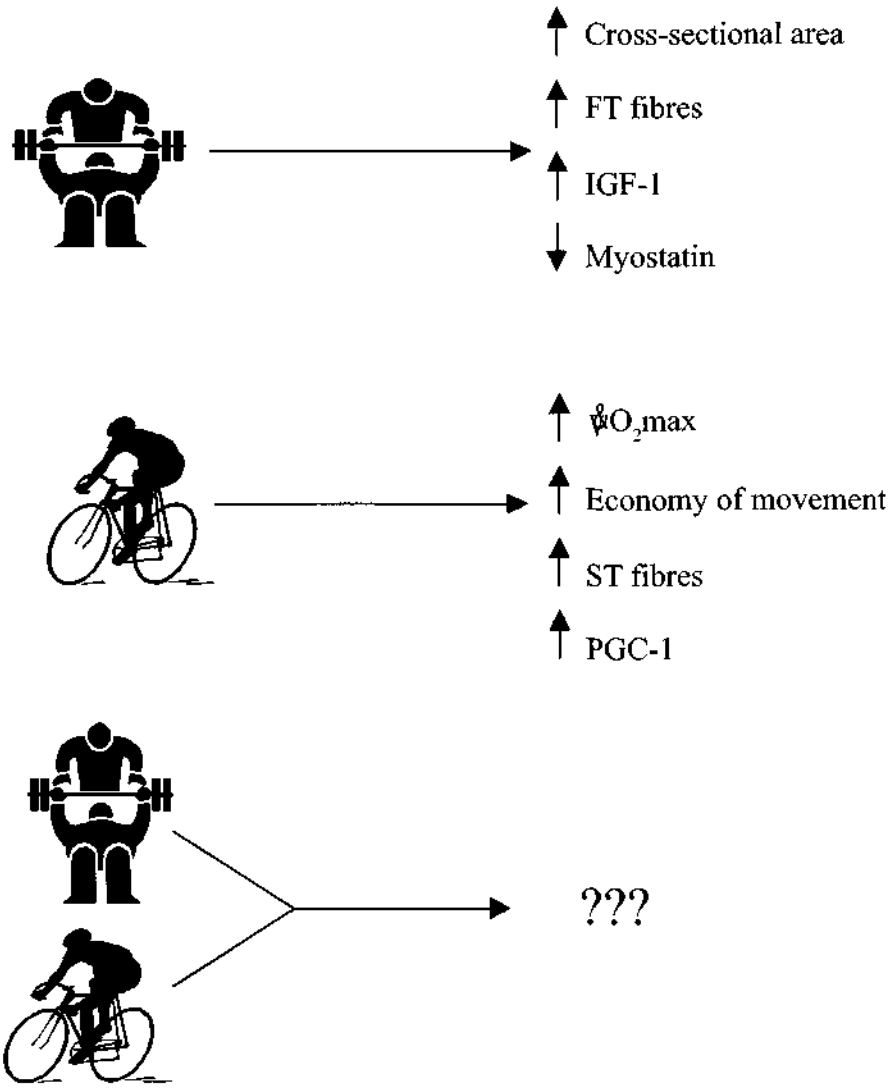

Figure 3.
Schematic of the specificity of training responses with heavy resistance training and endurance training modes, and the undefined adaptive responses generated by concurrent training.

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