Training for Endurance and Strength: Lessons from Cell Signaling

KEITH BAAR

Division of Molecular Physiology, University of Dundee, Dundee, UNITED KINGDOM

ABSTRACT

BAAR, K. Training for Endurance and Strength: Lessons from Cell Signaling. *Med. Sci. Sports Exerc.*, Vol. 38, No. 11, pp. 1939–1944, 2006. The classic work of Hickson demonstrated that training for both strength and endurance at the same time results in less adaptation compared with training for either one alone: this has been described as the concurrent training effect. Generally, resistance exercise results in an increase in muscle mass, and endurance exercise results in an increase in muscle capillary density, mitochondrial protein, fatty acid–oxidation enzymes, and more metabolically efficient forms of contractile and regulatory proteins. In the 25 yr since Hickson's initial description, there have been a number of important advances in the understanding of the molecular regulation of muscle's adaptation to exercise that may enable explanation of this phenomenon at the molecular level. As will be described in depth in the following four papers, two serine/threonine protein kinases in particular play a particularly important role in this process. Protein kinase B/Akt can both activate protein synthesis and decrease protein breakdown, thus leading to hypertrophy, and AMP-activated protein kinase can increase mitochondrial protein, glucose transport, and a number of other factors that result in an endurance phenotype. Not only are PKB and AMPK central to the generation of the resistance and endurance phenotypes, they also block each other's downstream signaling. The consequence of these interactions is a direct molecular blockade hindering the development of the concurrent training phenotype. A better understanding of the activation of these molecular pathways after exercise and how they interact will allow development of better training programs to maximize both strength and endurance. **Key Words:** HYPERTROPHY, MITOCHONDRIAL, BIOGENESIS, EXERCISE

While completing his postdoctoral fellowship at Washington University in St. Louis, Dr. Robert Hickson noticed that the runs he did with his mentor, Dr. John Holloszy, seemed to cause him to lose muscle mass. The two men agreed that this should be the first thing that Dr. Hickson studied when he took up a position of his own. In 1980, Dr. Hickson published the first experimental demonstration of the specificity of training (20). In this article he showed what athletes and coaches had believed for years: training to improve strength was negatively affected by concurrent endurance exercise. At the time, very little was known about how resistance training increased muscle mass or how endurance exercise increased mitochondrial density, so Hickson could only hypothesize as to how the two processes interacted. In the intervening 25 yr, the mechanisms underlying muscle adaptation to exercise have been better elucidated, and we can now propose a model to explain the concurrent training effect. The articles that follow are the proceedings of a symposium entitled "Training for Endurance and Strength: Lessons from Molecular Biology," which was part of the ACSM annual meeting in Nashville in 2005. This paper will introduce many of the molecular players and provide the background for the specific papers that follow.

Exercise is a general term used to describe a wide variety of activities and sports that can be classified into three subtypes: endurance, resistance, and patterned movements. Patterned movement exercises deal largely with a motor program in the central nervous system and result in relatively small biochemical changes in muscle, whereas resistance and endurance exercise have a profound impact on muscle phenotype. In the past 2500 yr, many myths and a great deal of scientific research have focused on the phenotypic and functional changes of muscle in response to exercise. A classic fable concerns Milo of Crotona, the Greek farmer who would do his morning exercises every day with a calf draped across his shoulders. As the calf grew, so did Milo's strength. At the time of the Olympiad, he could complete his exercises with what had become a full-grown bull on his shoulders, making his strength unparalleled. The theory described in this fable has been termed the overload

Address for correspondence: Keith Baar, Ph.D., Functional Molecular Biology Lab, Division of Molecular Physiology, University of Dundee, MSI/WTB Dow Street, Dundee DD1 5EH, UK; E-mail: k.baar@dundee.ac.uk.
Submitted for publication December 2005.
Accepted for publication April 2006.

0195-9131/06/3811-1939/0
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DOI: 10.1249/01.mss.0000233799.62153.19

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principle: muscle hypertrophy occurs as a result of systematic and progressive exercise of sufficient frequency, intensity, and duration, causing adaptation.

The overload principle has been thoroughly investigated during the past 100 yr. The conclusion from these studies is that exercise of a short duration and high intensity produces skeletal muscle hypertrophy (10). Duration denotes the length of time that work is occurring; intensity denotes the resistance or tension across the muscle. For muscle growth, duration is kept under a minute per exercise, and tension is the maximum that will allow completion of the exercise. The results of this type of high-resistance training include increases in wet mass (6), fiber cross-sectional area (51), protein content (56), RNA content (56), and the capacity to generate force (12,28).

In contrast, decreasing the intensity and increasing the duration of exercise results in different adaptations within the muscle. This type of exercise results in an endurance phenotype characterized by increased mitochondrial mass (21), increased oxidative enzymes (23), decreased glycolytic enzymes (38), increased slow contractile and regulatory proteins (38,49), and a decrease in fast-fiber area (47).

Concurrent training (training for both strength and endurance) results in decreased strength gains, suggesting that, in some way, the endurance training limits skeletal muscle growth (20).

As described above, a change in muscle phenotype is the result of repeated bouts of exercise. Although each individual bout of exercise is necessary, it alone is not sufficient to alter muscle phenotype. After a single bout of exercise, there is a transient alteration within muscle that, when repeated at sufficient frequency, produces a new steady state within skeletal muscle. This acute effect could be the result of an alteration in the metabolic state of muscle, the activation of a mechanosensor within the muscle, or the local effect an autocrine factor such as IGF-1 or mechano growth factor that is released by muscle cells in response to exercise (17,55,58).

Resistance Exercise

The primary acute response to resistance exercise is an increase in the rate of protein synthesis. In humans, a single bout of resistance exercise increases the rate of protein synthesis by 50% at 4 h and by 115% at 24 h before returning to basal again by 36 h (32). This increase in protein synthesis occurs without a change in the RNA content, suggesting that the changes in protein synthesis after resistance exercise are the result of an increase in the amount of protein synthesized per molecule of RNA (18). This has been confirmed in isolated muscles from chickens (30) and rabbits (45), *in vivo* in rat muscle (56), and in cell free extracts (18). Interestingly, rapamycin, a bacterial macrolide that specifically inhibits mTOR when bound to raptor (see below), blocks the resistance exercise–stimulated increase in protein synthesis, even though it has little effect on basal protein synthesis (29). This suggests that basal and growth-related synthesis are controlled by different mechanisms and that mTOR is essential for the increase in protein synthesis after resistance exercise.

The rate of protein synthesis is regulated primarily at the initiation phase by a number of proteins that are controlled by posttranslational modification (9). Three key proteins expressed in all cell types (eukaryotic initiation factor 2 (eIF2), 4E binding proteins (4E-BP), and the 70-kDa S6 protein kinase (S6K1)) are believed to be the primary controls of initiation. eIF2 is thought to regulate general protein synthesis, and 4E-BP and S6K1 are believed to control growth-related protein synthesis (34). As described below, the activity of all three proteins requires mTOR and/or PDK1 and is modulated by exercise.

PDK1 is a constitutively active protein kinase whose downstream signaling is controlled by its subcellular localization and/or the conformation of its targets (33). mTOR, on the other hand, is activated by a complex series of phosphorylation events. To add to the complexity, mTOR exists in two protein complexes (57). TOR complex 1 (TORC1) consists of mTOR, the G-protein beta-like protein (GβL/LST8) and raptor and is responsible for cell growth, whereas TORC2 contains mTOR, GβL, and rictor and is important in cytoskeletal organization (57). The different function of the two complexes is dictated by the ability of raptor or rictor to bind to downstream targets (4). Three mechanisms have been identified for the activation of TORC1 and its downstream targets (Fig. 1). The most widely studied mechanism of TORC1 activation is growth factor stimulation, but TORC1 can also be activated by amino acid stimulation and Vps34 mediated autophagy. The growth factor–stimulated pathway works through phosphoinositol 3-kinase (PI 3-kinase)–mediated production of phosphoinositol 3,4,5 tris phosphate (PIP3) at the cell membrane (33). PIP3 increases the protein kinase B/akt (PKB) and PDK1 at the membrane by interaction with the pleckstrin homology domains (3,33). When colocalized at the membrane, PKB is phosphorylated and activated by successive phosphorylation on Thr308 by PDK1 (33) and on Ser473 by TORC2 (43). Active PKB is then able to phosphorylate its targets, which include glycogen synthase kinase 3β (GSK3β) (13), the forkhead (FOXO) transcription factors (42,48), and the GTPase-activating protein TSC2 (Tuberin) (25). PKB-dependent phosphorylation inactivates GSK3β, FOXO, and TSC2. Inactivation of GSK3β increases the rate of translation by increasing eIF2B activity (54), phosphorylation of FOXO removes it from the nucleus and decreases FOXO-dependent transcription of atrogenes (42,48), and phosphorylation of TSC2 blocks its GTPase activity towards the Ras-like protein, Rheb, keeping it in the active GTP-bound form (24). GTP-bound Rheb stimulates the activation of TORC1 and, through interactions with raptor, mTOR phosphorylates its downstream targets, S6K1 and 4E-BP (24,44).

The second mechanism of activation of TORC1 is observed in the case of nutrient deprivation and refeeding of amino acids. The refeeding of amino acids inactivates TSC1/2 in an unidentified PKB-independent manner (50).

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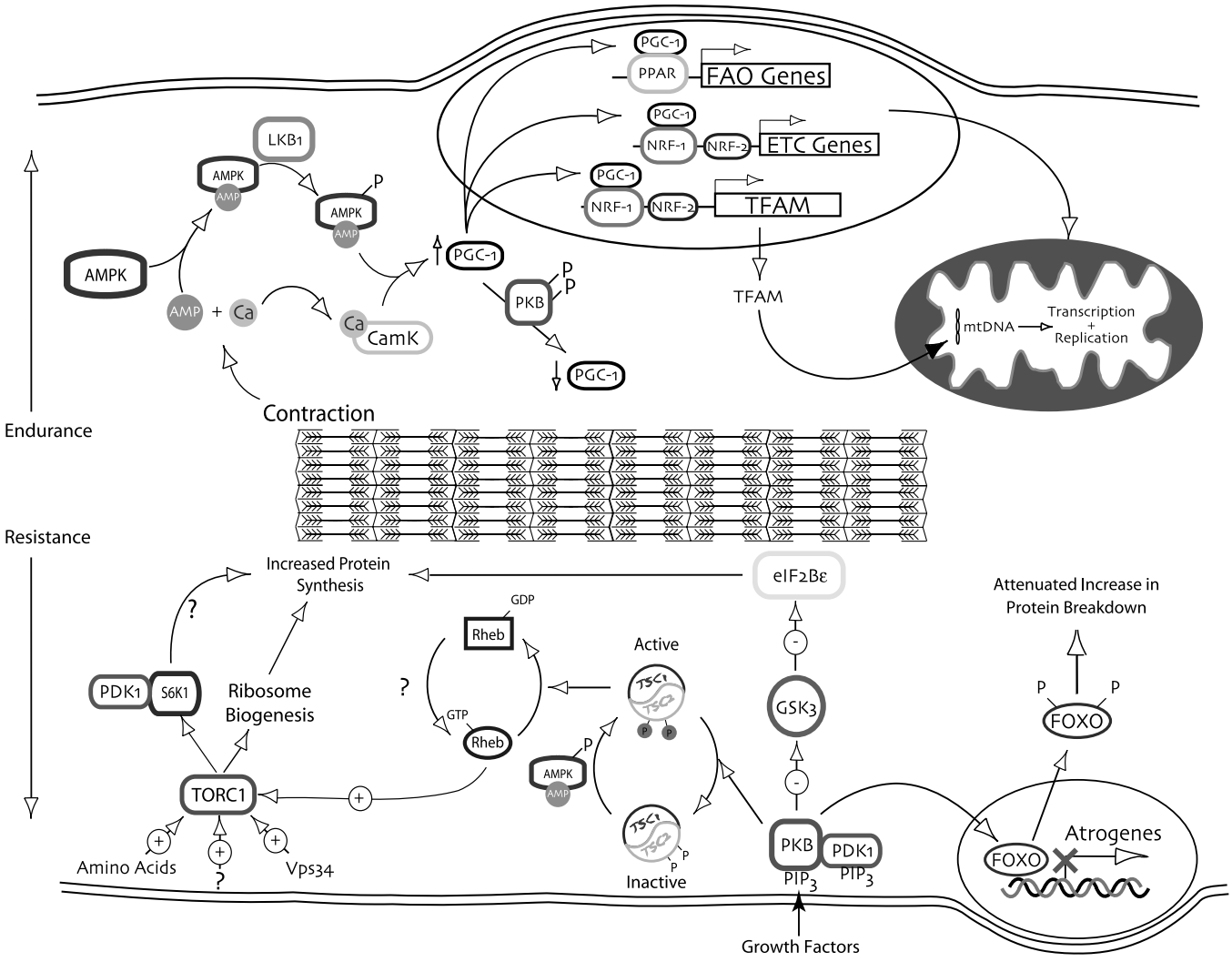

FIGURE 1—Representation of the molecular pathways activated by (*top*) endurance and (*bottom*) resistance exercise. AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; Ca, calcium; CamK, calcium-calmodulin kinase; eIF2B, eukaryotic initiation factor 2B; FOXO, forkhead transcription factor; GSK3, glycogen synthase kinase; LKB1, serine-threonine kinase 11; TORC1, mammalian target of rapamycin complex 1; NRF-1 and NRF-2, nuclear respiratory factors; PPAR, peroxisome proliferator activating receptor; PGC-1, PPARγ coactivator; PDK1, 3-phosphoinositide-dependent protein kinase; PKB, protein kinase B/akt; Rheb, ras-like protein enriched in brain; S6K, 70KDa ribosomal S6 protein kinase. The tuberosclerosis complex includes hamartin (TSC1) and tuberin (TSC2). The interaction of the two types of exercise is denoted by the ability of PKB to decrease PGC-1α in the top half of the figure and the ability of AMPK to activate TSC2 in the bottom half of the figure.

The inactivation of TSC2 leads to more GTP-bound Rheb, activating mTOR and its downstream targets as described above. The most recently identified mechanism for activating TORC1 is through the class III PI 3-kinase Vps34 (11), which is required for autophagy (protein breakdown within the cell). Vps34 overexpression can activate TORC1 in kidney cells, and using an antibody to block Vps34 activation decreases insulin-stimulated mTOR activity (11). One important role of Vps34 may be to sense the availability of amino acids within the cell, because its activity decreases when amino acids are withheld. However, whether Vps34 is involved in exercise signalling has yet to be addressed.

We and others have shown that muscle strain or resistance exercise can transiently activate mTOR (37), PKB (36), S6K (6), inactivate GSK3β (53), and increase eIF2B activity (15,29). Furthermore, rapamycin treatment has been shown to prevent skeletal muscle hypertrophy in mice, indicating that TORC1 activity is required for skeletal muscle enlargement (8). However, it is still unclear which TORC1 targets are important in the development of hypertrophy. Also unclear is whether the activation of TORC1 is the result of PKB activation, stimulation of the amino acid or autophagy pathways, or an altogether separate mechanosensory pathway. Overexpression of PKB *in vitro* in muscle cells (40) and in mice results in an increase in muscle size (8), suggesting that the activation of PKB after resistance exercise is sufficient for muscle hypertrophy.

Endurance Exercise

During exercise of long duration, there is a progressive increase in the AMP:ATP ratio and the level of intracellular free calcium (22). Both of these intracellular changes are

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signals for muscle adaptation. The rise in the AMP:ATP ratio increases the amount of AMP bound to AMPK (19). This causes a conformational change in AMPK that makes it a better substrate for its constitutively active upstream kinase LKB1, resulting in an increase in AMPK activity after endurance exercise (55). The rise in intracellular free calcium activates a number of calcium-sensitive signaling molecules, including the calcium- and calmodulin-activated protein kinase (CamK) (16). Active AMPK and CamK are able to phosphorylate histone deacetylases (HDAC) and permit myocyte-enhancing factor (MEF) 2 binding to the promoter of PGC-1α (14). MEF2 binding to the PGC-1α promoter increases the expression of this critical mitochondrial-regulating gene. PGC-1α coregulates the expression of respiratory genes, mitochondrial transcription factor A, GLUT4 (35), the fatty acid–oxidation enzymes (14), and, possibly, the slow myosin heavy chain (5,31). Because all of these factors also change with endurance exercise, it is not surprising that this type of exercise has been shown to increase both PGC-1α mRNA (1,2,7) and protein (27).

Concurrent Effect

Recent advances have provided possible molecular targets that may explain the concurrent training effect identified by Hickson (20). First, TSC2 can be phosphorylated and activated by AMPK (26). Activation of TSC2 by AMPK is dominant over PKB-mediated inactivation and leads to the inactivation of mTOR and a decrease in the rate of protein synthesis (26). The hypothesis that concurrent high levels of AMPK activity would reduce hypertrophy after resistance exercise was supported by experiments in old animals that underwent overload hypertrophy. A higher level of AMPK activity correlated with diminished hypertrophy in the old animals (52). However, a muscle-specific knockout of LKB1, the enzyme that activates AMP kinase, does not induce an increase in cell size (41), as would be expected from this hypothesis. For this reason, the role of AMPK in preventing muscle growth remains uncertain.

Another potentially interesting mechanism to explain the concurrent training effect was suggested by recent work by Southgate and colleagues (46). This study demonstrated that PKB could control PGC-1α expression by phosphorylating FOXO1 and removing it from the nucleus. This suggests that when PKB is activated after resistance exercise, in the process of decreasing the expression of atrogenes and attenuating the increase in protein degradation (39,42,48), PKB might prevent mitochondrial biogenesis. However, in his original paper on the concurrent training effect, Hickson (20) did not observe that resistance training impaired endurance capacity, only that endurance training impaired strength gains. Whether there is an effect of strength training on decreasing mitochondrial biogenesis has yet to be determined.

SUMMARY

As complex as the molecular interactions after exercise are, they are still far from complete. Even so, we can already see how understanding these pathways can improve the way that we combine endurance and resistance training. The papers that follow focus on how these pathways are activated by exercise and diet and how they interact to alter skeletal muscle phenotype. Each paper summarizes the most recent work in the area, including the role of AMP kinase in the molecular adaptation to endurance exercise (Winder), mTOR signaling and the molecular adaptation to resistance exercise (Bodine), the interaction between the AMP kinase and mTOR signaling pathways (Kimball), and how to use this information for improving training for strength and endurance (Nader). Although we have progressed from the seminal work of Dr. Hickson, there remain significant challenges to completely understand how exercise alters skeletal muscle phenotype.

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