Evaluation of animal models for the study of exercise-induced muscle enlargement

BENJAMIN F. TIMSON
Department of Biomedical Sciences, Southwest Missouri State University, Springfield, Missouri 65804

TIMSON, BENJAMIN F. *Evaluation of animal models for the study of exercise-induced muscle enlargement.* J. Appl. Physiol. 69(6): 1935–1945, 1990.—Skeletal muscle is known to enlarge in response to high-resistance training programs in humans. Study of the cellular mechanisms of muscle enlargement and the adaptations of muscle to strength-training programs has been difficult because of the need to analyze entire muscles. This precludes the use of human subjects in many experiments of this nature. Several animal models have been developed for the study of muscle enlargement; these models basically fall into three categories: *1*) stretch hypertrophy, *2*) compensatory hypertrophy, and *3*) exercise-induced hypertrophy. This review attempts to analyze these models as models of muscle enlargement produced by strength training in humans. Three areas must be considered when evaluating animal models of human muscle enlargement produced by strength training: *1*) response topography, *2*) magnitude of enlargement, and *3*) muscle fiber adaptations produced as a result of the enlargement. Based on these considerations, it is concluded that none of the animal models currently in use truly represents the human strength-training situation under all conditions. All three models, however, provide valuable information about the plasticity of skeletal muscle in response to a broad spectrum of muscle enlargement.

compensatory hypertrophy; stretch hypertrophy; weight lifting; strength training

HISTORICALLY, investigations of skeletal muscle adaptations to exercise and training have broadly been focused on two areas: strength and endurance. Without question the greatest attention has been devoted to endurance training and performance of endurance events such as distance running, cycling, and swimming. One of the reasons for this imbalance in research between the two areas is that the steady-state nature of endurance activities makes it relatively easy to design and conduct experiments to investigate exercise of this type.

Much of the research into the mechanisms of the response of skeletal muscle to strength training necessitates analysis of entire muscles, as opposed to analysis of small biopsy samples, which are generally sufficient for the study of the effects of endurance training on skeletal muscle. This greatly limits the use of human subjects in meaningful experimentation into the cellular mechanisms of skeletal muscle enlargement that are known to occur with strength training. Because of this problem, investigators have turned to animal models to simulate muscle enlargement that occurs in humans in response to strength training.

Several animal models have been used to produce and study the mechanisms of muscle enlargement: tenotomy of synergistic muscles (15, 44, 66, 74); surgical removal, or ablation, of synergistic muscles (4, 6, 53–55); passive muscle stretch (1, 5, 51, 96, 97); and numerous exercise-induced models (17, 20, 33, 49, 62, 116). Exercise-induced models have had limited success in producing consistent and significant muscle enlargement in animals. The compensatory and stretch models have been more successful in producing increases in muscle mass but have been criticized as models of human strength training (102).

It is the purpose of this review to evaluate animal models for the production of skeletal muscle enlargement in terms of their adequacy as models of muscle enlargement produced by strength training in humans. The strength of a human is usually expressed as the maximum amount of resistance that can be overcome during a given exercise. Human strength gains as a result of a training program are the result of both neural adaptations and muscle enlargement, with early gains being associated

primarily with neural adaptations (19, 89). Animal models are used to study the mechanisms of skeletal muscle enlargement that take place during long-term strength training in humans. Therefore, human adaptations to strength training considered in this review are limited to those studies focusing on muscle enlargement rather than neural adaptations.

Throughout this review the term strength training will be used to refer to those training programs, usually high-resistance weight training, that result in increases in muscle strength. Weight lifting will be used to refer to animal models that require the animal to lift external weights (in addition to body weight). These programs may or may not lead to strength gains in animals. Enlargement will refer to an increase in the mass of a muscle without regard for mechanism. The term response topography refers to the nature of the action performed by the individual (human or animal) that brings about the muscle enlargement. The response topography of the human strength-training condition is lifting an external weight in a high-resistance low-repetition-type activity.

Human Studies

Before a discussion of animal models used for the production of muscle enlargement, it is necessary to briefly establish our current understanding of the adaptations of human skeletal muscle to strength training on the parameters of muscle cross-sectional area, fiber area, composition, and metabolic and contractile properties. A comparison can then be made between these studies and the studies using animal models. A complete review of this topic is beyond the scope of this paper (for a more in-depth treatment of this topic see Refs. 75, 91, 103).

Measurement of the cellular adaptations of skeletal muscle to strength training in humans is limited to the information that can be gained from muscle biopsy samples (measurement of fiber type, fiber area, and metabolic properties) and muscle-scanning techniques such as ultrasound and computed axial tomography scans (measurement of muscle cross-sectional area) and magnetic resonance imaging. Longitudinal studies have resulted in variable increases in muscle cross-sectional area in response to training programs. Ikai and Fukunaga (57) demonstrated a 23% increase in muscle cross-sectional area after 100 days of isometric training. Frontera and co-workers (23) found a 9.3% increase in the cross-sectional area of the quadriceps muscle group in older men who participated in a 12-wk strength-training program, and Cureton and co-workers (13) found a 16 and 23% increase in men and women, respectively, in the area of the muscles of the upper arm after a 16-wk progressive strength-training program. MacDougall and co-workers (71) demonstrated an 11% increase in arm circumference after a 5-mo strength-training program. Myofibrillar volume does not change in strength-training programs of ≤6-mo duration (68, 70).

These studies indicate increased muscle cross-sectional area in a range of 9–23% in response to strength training of ≤6-mo duration. On the other hand, athletes (i.e., football players, power lifters, wrestlers, and bodybuilders) subject themselves to strength-training programs of much longer duration, some in excess of a decade. Longitudinal studies on this population are limited, but observation of these athletes would seem to indicate a much greater magnitude of muscle enlargement than the 9–23% reported in studies of ≤6-mo duration (13, 23, 57, 71). These observations are supported by the study of MacDougall and co-workers (69) indicating a 76% greater cross-sectional area of the biceps brachii muscle in bodybuilders than in the normal population.

It has generally been considered that strength training results in a greater hypertrophy of fast-twitch fibers than slow-twitch fibers (11, 16, 18, 37, 83, 90, 92); however, other studies indicate that fiber hypertrophy is similar in both fiber types (23, 71, 93, 105). It has also been determined that muscle fiber type composition is not altered by strength training in humans (26, 59, 108).

Reports on the metabolic alterations in skeletal muscle to strength training in humans have indicated no change (18, 28) or a decrease (104) in the activities of enzymes of the oxidative and glycolytic pathways. Mitochondrial volume density is decreased with strength-training programs of ≤6-mo duration (68, 70). ATP and creatine phosphate concentrations are increased after 5 mo of strength training (71).

Attention has been focused on the effect of isometric, isotonic, and isokinetic strength-training programs on skeletal muscle contractile properties (see Ref. 89 for references). These studies have focused on short-term training programs in humans where voluntary strength gains are associated mainly with neural adaptations such as improved coordination or learning (88) and increased activation of prime mover muscles (45, 77). Alterations in muscle contractile properties resulting from muscle enlargement produced by strength training in humans are not well defined.

Animal Models

Stretch hypertrophy. In 1944, Thomsen and Luco (106) reported that if the ankle was immobilized with the soleus in a lengthened position, the muscle would undergo enlargement that was transient in nature. The enlargement peaked at ~7 days and then regressed, and eventually the muscle atrophied. Passive stretch was further implicated to be involved in muscle enlargement by Sola and Martin (97). Denervation of the left hemidiaphragm was used to produce stretch in the antagonistic right hemidiaphragm; in this model the enlargement peaked at 6–9 days and was followed by a continuous weight loss, with control weight being reached 23–38 days after denervation. This work was subsequently supported by others (22, 43). Stretch has also been shown to promote growth in vivo in intestinal (24) and myometrial (12) smooth muscle as well as cardiac muscle (84).

One of the most popular models for studying stretch hypertrophy has been the stretched avian wing; weights are hung from the tip (1, 27, 96) or a spring-loaded device is used (9, 51). Sola and co-workers (96), who were the first to use this model, reported a rapid increase in wet weight of the chicken anterior latissimus dorsi muscle

(ALD) of up to 80% in the 1st wk followed by a less dramatic increase in wet weight that peaked at ~180% by 5 wk. These increases in muscle wet weight were similar to those reported in subsequent investigations (1, 5, 9, 27, 51, 64, 65).

Holly and co-workers (51) found an increase in fiber area of 43 and 45% for the chicken ALD and patagialis muscle (PAT), respectively. Muscle length increased by 24 and 22% for the ALD and PAT, respectively. Alway and co-workers (1) reported a muscle fiber area increase of 57% and a muscle fiber length increase of 23% in the ALD of the Japanese quail after 30 days of stretch. The increase in muscle fiber length is presumed to be due to the addition of sarcomeres in series, as has been demonstrated to occur in stretch-immobilized cat soleus muscle (101).

Total muscle protein is increased in muscles enlarged by stretch. This is accomplished by an increase in the rate of protein synthesis with no change in protein degradation (9, 63, 65, 67, 98). Muscle protein concentration (mg protein/g wet wt) after stretch hypertrophy is similar to that of control muscles (9, 65). There is an increase in the absolute amount of connective tissue and the connective tissue concentration after stretch hypertrophy (1, 65).

Citrate synthase and succinate dehydrogenase activities increased markedly in the PAT after enlargement, whereas the same enzymes were not different from control muscles in the ALD. The activity of α-glycerophosphate dehydrogenase was decreased in both the ALD and PAT. Lactate dehydrogenase was decreased in the PAT but elevated in the ALD (51). These data indicate a different response in the oxidative capacities of the tonic PAT and the phasic ALD to stretch, whereas the glycolytic response to the two muscles appears to be similar.

Histochemical analysis of chicken ALD has indicated that there are two fiber populations, one dark staining and one light staining for myosin adenosinetriphosphatase (ATPase). Holly and co-workers (51) reported a conversion of dark-staining to light-staining fibers in the enlarged ALD after stretch hypertrophy. This finding was supported by the work of Gollnick and co-workers (27). It has been demonstrated that the chicken ALD contains two major myosin bands that can be separated by pyrophosphate gel electrophoresis of the proteins in the native state (14, 50). These bands have been designated as SM-1 and SM-2 based on their speed of migration. There is almost a complete conversion of the SM-1 to the SM-2 isoform after enlargement produced by 28 days of stretch hypertrophy of the chicken ALD (60, 61). It appears that stretch hypertrophy results in a shift in fiber type in the same direction as that seen in compensatory hypertrophy.

Compensatory hypertrophy. The compensatory hypertrophy model was first devised by Denny-Brown (15). This model entails severing the tendon of a synergistic muscle or complete removal of a synergistic muscle. The remaining muscles must produce the same tension that was originally produced by the entire muscle group, thereby increasing the functional demand resulting in enlargement. The two models producing compensatory hypertrophy, tenotomy (severing the tendon of the synergistic muscle) and ablation (complete removal of the synergistic muscle), result in different adaptations and are discussed separately for the purpose of this review.

Tenotomy. Severing the gastrocnemius or tibialis anterior tendons has been used by several investigators to produce compensatory enlargement in the plantaris, soleus, and extensor digitorum longus muscles (39, 41, 42, 44, 46, 47, 58, 72–74, 94, 95, 110, 111). Generally, use of this method results in a rapid transient initial weight gain in the experimental muscle that peaks 4–7 days after surgery and is followed by a decrease in weight to values slightly greater than control (66, 74, 95). Mackova and Hnik (74) found a 30% increase in rat soleus muscle weight 7 days after tenotomy of the gastrocnemius. This increase receded and became stabilized at 10–15% above control muscle weight 2–3 wk after tenotomy. It was concluded that the enlargement produced during the first 7 days was not a true working hypertrophy; however, the authors suggested that the enlargement that remained after 2–3 wk may indeed be a true working hypertrophy. Seiden (95) found a 34% increase in wet weight of the extensor digitorum longus muscle 7 days after tenotomy of the tibialis anterior. The increase in muscle wet weight was only 9% 21 days after tenotomy. The studies of compensatory hypertrophy using the tenotomy model have generally focused on the 4- to 7-day time period following surgery, because this is when the greatest increase in muscle wet weight occurs (66, 74, 95).

It appears that the peak increase in muscle wet weight in the 4- to 7-day period after tenotomy is due to stretch rather than an increased functional demand on the muscle. Stretch is produced on the remaining muscles of a functional group after tenotomy, because the tension produced by the antagonistic muscle group becomes greater relative to the group with the incapacitated muscle. Evidence for stretch as the mechanism for enlargement comes from studies indicating that when the antagonistic muscles are denervated, thereby eliminating the stretch on the remaining synergistic muscles, enlargement is eliminated (44, 74).

Lesch and co-workers (66) studied the relationship between compensatory enlargement and muscle contractile properties in the soleus muscle. Enlargement peaked at 48% 4 days after tenotomy of the gastrocnemius. Tetanic tension was not altered at the time of peak enlargement; twitch tension and the maximum rate of tension development were slightly reduced 6 days after surgery. When standardized for muscle cross-sectional area, tetanic tension, twitch tension, and maximum shortening velocity were all reduced in the enlarged muscle. The ratio of twitch tension to tetanic tension was unaltered. There are reports of significant reductions in muscle protein concentration (4, 53, 55) during this period as well as a decrease in the myofibrillar protein fraction (53, 95). Metabolic potential, demonstrated by succinate dehydrogenase and phosphofructokinase activities, of the enlarged muscle is also decreased (55). These changes are the result of a "dilution effect" due to the muscle edema that results from tissue inflammation that takes place during the initial rapid increase in muscle weight (4). The data of Lesch and co-workers (66) also indicate a dilution effect, because the increase

in wet weight of the soleus muscle greatly exceeded the increase in dry weight during the first 6 days after tenotomy of the gastrocnemius.

Muscle fiber area of the extensor digitorium longus muscle was only 4.2% greater than that of the contralateral control muscle 7 days after tenotomy in the presence of a 34% increase in muscle wet weight (95). This finding is consistent with the observation that muscle edema is primarily responsible for the early enlargement during compensatory hypertrophy (4).

One problem with the tenotomy model is that the resectioned tendon has a tendency to reattach or adhere to the remaining musculature after 10–14 days, thus allowing for tension development of the muscle that was intended to be functionally eliminated (44). In an effort to circumvent the problems associated with tendon reattachment, investigators have utilized ablation (complete removal) of the synergistic muscles (4, 6, 7, 29, 53–55, 80, 87).

Ablation. The general finding of studies using ablation is that enlargement increases for 4–6 wk, at which time a steady state is reached. Baldwin and co-workers (6) observed a steady-state enlargement of 40% in the plantaris muscle compared with control animals 5 wk after bilateral ablation of the gastrocnemius muscles. Ianuzzo and Chen (55) observed a steady-state enlargement of 80% for the same muscle compared with that of the contralateral control limb 30 days after unilateral ablation of the gastrocnemius. The response of ablation is different from that of tenotomy, in that the increase in muscle wet weight is much greater in magnitude and is consistent rather than transient (55). This is more likely due to the elimination of the possibility of the tendon reattaching and thus removing the overload.

Ianuzzo and co-workers (56) found a 45% increase in muscle mass of the soleus muscle after enlargement produced by ablation. Mean fiber area was increased by 40%. Timson and co-workers (109) found muscle mass increases of 47 and 31% in the soleus muscle of male and female mice, respectively. These increases corresponded very well with the 49 and 34% increases in mean fiber area for the male and female mice, respectively. Fiber area analysis of the individual fiber types after compensatory enlargement indicates a similar increase in area of both fiber types (109).

Studies investigating the effect of enlargement produced by ablation on contractile properties of the plantaris muscle indicate increases in absolute peak tension and maximal tetanic isometric force (10, 87). The absolute speed of contraction, measured as time to peak tension and half-relaxation time, is decreased when steady-state enlargement has been reached using the ablation model (87). Binkhorst and van't Hof (10) reported that maximal tetanic isometric force remains constant when standardized for muscle cross-sectional area. However, Roy and co-workers (87) found this parameter to decrease when standardized for muscle cross-sectional area. The reason for this discrepancy is unclear. Numerous studies have demonstrated a histochemical shift in fiber type in the direction of increased percentage of slow-twitch fibers in both the soleus and plantaris muscles (7, 40, 56, 80, 109). There is also a shift in the myosin light chain pattern toward the slow isozyme in plantaris muscle subjected to long-term compensatory hypertrophy produced with the ablation model (7, 38, 80, 112–114).

Muscle protein concentration in enlarged muscles 4–6 wk after ablation is similar to that of control muscles (6, 7, 55, 80). The metabolic profile of the enlarged muscles appears not to be altered, because activities of enzymes of the oxidative and glycolytic pathways are similar to control muscles (2, 55, 86). Also the ability of the enlarged muscle to oxidize α-glycerophosphate, palmitate, and pyruvate per unit mass is not different from that of the control muscle (8). These findings are not universal; however, as Baldwin and co-workers (6, 7) found, the activities of citrate synthase, phosphofructokinase, and myofibrillar ATPase were consistently depressed in the plantaris muscle compared with muscles of control animals 5 wk after bilateral ablation of the gastrocnemius. The reason for this discrepancy is unclear. Similar muscle protein concentration in the enlarged muscles makes it unlikely that the reduced enzyme activities reported by Baldwin and co-workers (6, 7) were due to increased water content of the enlarged muscles. Muscle blood flow (3) and glycogen concentration (3, 86) are similar in control and in enlarged plantaris and soleus muscle after ablation.

Exercise-induced enlargement in animal models. One of the earliest reports of exercise-induced enlargement in animals was that of Morpurgo (78). He ran two dogs for a period of 60 days, 7–50 km for the first 20 days and 60–80 km for the remaining 40 days. The sartorius muscle was removed from one leg before the training period, and the muscle from the contralateral leg was removed after the training period. There was a 53% enlargement in one dog and a 55% enlargement in the other. The reason for these rather dramatic increases in muscle mass in response to running (generally considered to be an endurance activity) is not clear. This finding was not supported by subsequent investigators who were not able to demonstrate increases in muscle mass by running (36, 48, 52, 82, 99, 100, 107) or swimming (95) animals.

Isometric training has been used in an attempt to produce muscle enlargement with limited success. Exner and co-workers (20, 21) placed rats in a large tube where they were not able to support themselves by pressing their bodies against the wall. The tube was placed at a 60° incline and had a wire bottom so that the rats could hold themselves in position with their hindlimbs. Weights (90–200 g) were attached to the tails of the animals, resulting in a force attempting to pull the animal out of the tube. The rats were forced to generate tension with the hindlimbs to maintain their position in the tube. The training program consisted of three sessions twice daily. Each session was continued until exhaustion. Weights were adjusted so that exhaustion occurred within 5 min. The animals were trained 7 days/wk for 25 days. Muscle weight of the rectus femoris and soleus was not different between trained and nontrained rats. In a similar study, Muller (79) also found no muscle enlargement with isometric training in rats.

Gordon and co-workers (36) used a system of dynamic contraction in an attempt to produce muscle enlarge-

ment. Rats were forced to climb a vertical distance of 16 in. 50 times daily for 7 wk with weights strapped to their backs. The weight was increased from 30 g at the beginning to 70 g for the final 4 wk of the training period. This program was unsuccessful in producing enlargement of the quadriceps muscle. A similar approach was used by Yarasheski and co-workers (117). They trained rats to climb a 40-cm vertical incline, 20 times daily, 5 days/wk. The animals carried progressively heavier weights, beginning at 43 g and ending at an average weight of 406.3 g, during an 8-wk training session. The final weight used during this regimen was 156% of the animal's body weight. This program resulted in a 7.6% increase in the muscle wet weight-to-body weight ratio of the rectus femoris muscle. The obvious differences between these studies is the amount of weight carried by the rats. The study of Yarasheski and co-workers (117) indicates that enlargement of skeletal muscle will occur in this type of exercise if sufficient weight is placed on the animal.

Attempts have been made to produce muscle enlargement in animals with weight-lifting exercise. Probably the most well known of these models is the operant-conditioning program used by Gonyea and co-workers (30–35). In this model, cats were trained to flex their right wrists against increasing resistance. The cats exercised 5 days/wk against a constant resistance; each week the resistance was increased by 50 g. This procedure was followed until the cat could no longer perform a minimum of five repetitions per exercise session. When this occurred the total weight load was reduced to 90% of the maximum and then increased weekly by 20 g. This protocol was repeated with smaller weight increments of 10 g, until increases in maximum weight could no longer be achieved. At this point the training period was terminated. The average time that the animals were on the training program was 101 wk (35). The average weight that the cats were able to lift at the end of the training program was 57% of body weight. Muscle enlargement produced by this training procedure varied from 6 (34) to 16% (30).

Ho and co-workers (49) and Klitgaard (62) trained rats to perform weight-lifting exercise similar to squats performed by humans. Ho and co-workers (49) placed a chain around the waist of the rat and attached weights to the chain. The rats were trained to respond to a light (visual) stimulus by standing upright on the hindlimbs to grasp a vertical bar projecting from the top of the chamber. If the rat did not respond to the light stimulus within a specified time, a mild current was applied through the grid floor. The training program was administered 4 days/wk for 8 wk and consisted of 16 successful lifts daily. During the last 2 wk of training, each rat lifted a weight equal to 130% of body weight. This training program resulted in a 21% increase in the muscle weight-to-body weight ratio of the adductor longus muscle. There was no increase in the same ratio of the rectus femoris muscle. In the model of Klitgaard (62) the rat performed a similar movement to obtain a food pellet with a weighted harness around its neck. The initial weight lifted by the rats was equal to 90% of body weight. At the end of the 36-wk training program the rats were lifting weights equal to 200% of body weight. After the training program, muscle weight-to-body weight ratio was 45% greater in the soleus muscle and 33% greater in the plantaris muscle than in the same muscles in animals from a control group. Of interest in this study is that very old rats were used: the rats were 19 mo old at the beginning of the study and 29 mo old at the end of the study. The body weights of the rats decreased from 509 g at the beginning to 418 g at the end of the study. In contrast, 9-mo-old rats from the same strain had a mean body weight of 693 g. The increased muscle weight-to-body weight ratios for the muscles used in this study are the largest reported for any of the studies using exercise-induced models in animals. The extent to which these enlargements were affected by the age of the rats utilized (i.e., increased muscle weight-to-body weight ratio is a function of exercise decreasing the rate of age-related muscle deterioration rather than increasing muscle mass) is difficult to determine.

Wong and Booth (116) have recently developed a unique model to simulate human weight lifting in rats. The right foot of the rat was strapped to a metal plate with adhesive tape. Weight was attached to a free-moving pulley that was soldered to the same bar as the foot plate. Any movement of the foot plate due to plantar flexion of the foot made by the rat resulted in a comparable movement of the pulley, thus lifting the weight. The animals, which were anesthetized with ether throughout each training bout, were secured in a prone position onto a wooden platform with the right foot attached to the foot plate. Muscle contraction was elicited by an electrical stimulus of 1-ms pulses at 100 Hz and 15 V with a 2.5-s train duration. The stimulus was supplied through two Teflon-coated platinum electrodes that were subcutaneously inserted and positioned bilaterally along the surface of the plantar flexor muscles of the lower right leg. The basic regimen consisted of four sets of six repetitions per set. By the end of the 16-wk training period, rats were lifting 600- to 1,100-g loads per repetition. Gastrocnemius, plantaris, and soleus muscle weights increased 18, 18, and 13%, respectively, compared with the muscle of the contralateral control limb after the 16-wk training period.

Treadmill running in combination with gastrocnemius ablation has been used to produce a significant exercise-induced enlargement in addition to that produced by the compensatory hypertrophy alone (29, 85, 115). Using this method, Gollnick and co-workers (29) were able to demonstrate a 44% increase in plantaris muscle weight and a 21% increase in soleus muscle weight above that produced in animals that were subjected only to compensatory hypertrophy. The 44% exercise-induced enlargement of the plantaris muscle represents the greatest mean exercise-induced enlargement for a group of animals reported in the literature. The response topography, although not similar to strength training in the human in that an external weight is not being moved, is similar in that dynamic contractions are a significant component of this model.

The relationship between muscle enlargement produced in exercise-induced animal models and fiber area has been inconsistent at best. Morpurgo (78) demon-

strated a very close relationship between increase in muscle mass and fiber area. A similar relationship was demonstrated by Gonyea and Ericson (33) and Gonyea (30). Both studies demonstrated similar increases in area of slow-oxidative (SO), fast-oxidative-glycolytic (FOG), and fast-glycolytic (FG) fibers in response to exercise-induced enlargement (9–11%). Yarasheski and co-workers (117) found a 15% increase in FG fibers with no change in SO or FOG fibers as a result of a 7.6% enlargement of the rectus femoris muscle. Goldspink and Ward (25) reported a 50% increase in FG fiber area, 47% in FOG, and 29% in SO in rats that lifted 50% of their body weight for 60 days. They did not, however, report whether there was an increase in muscle weight after the training regimen. On the other hand, Ho and co-workers (49) found a 24% decrease in FOG fiber area and a 19% decrease in SO fiber area in the adductor longus muscle in conjunction with a 14% increase in muscle weight. The decreased area of both fiber types in conjunction with the increased muscle weight was explained by an increased number of fibers present per unit cross-sectional area in the exercised animals. Fiber type composition of muscle undergoing enlargement does not seem to be altered in exercise-induced animal models (30).

Studies investigating the effect of exercise-induced enlargement on muscle contractile properties indicate increased isometric twitch and tetanic tension development (32, 62). Muscle protein concentration is not altered as a result of exercise-induced enlargement in animals (116).

Evaluation of Animal Models for the Study of Muscle Enlargement Produced by Weight-Lifting Exercise in Humans

When evaluating animal models to be used for the study of muscle enlargement produced by strength training in humans, three factors must be considered: *1*) response topography, *2*) magnitude of muscle enlargement, and *3*) adaptations in muscle fiber characteristics brought about as a result of the enlargement. Based on lack of similar response topography alone, it has been suggested that the compensatory and stretch hypertrophy models should not be utilized for the study of human muscle enlargement in response to strength training (102). Although response topography is an important consideration in the evaluation of animal models for the production of exercise-induced enlargement, it is certainly not the only consideration. Degree of muscle enlargement, as well as the response of muscle fiber parameters to the enlargement (i.e., fiber type, fiber area, metabolic potential), is of extreme importance when evaluating animal models. If the response topography of a particular animal model is similar to that of human strength training but the model produces little or no muscle enlargement, it is difficult to argue that the model is effective for studying cellular adaptations to strength training in humans. Similarly, if the adaptation of the muscle fiber parameters to the enlargement is different from that observed after human strength training, the effectiveness of the model would be questionable.

The relationships between the stretch hypertrophy model, compensatory hypertrophy using ablation, exercise-induced animal models, and human strength training are summarized in Table 1. The response topography between stretch hypertrophy and human strength training is obviously different. The stretch model employs a constant stretch on the muscle for the duration of the treatment period, whereas the human response is one of short-term dynamic movements. Stretch hypertrophy results in an increase in muscle mass of 150–200% within 30 days (5, 9, 27, 51, 64, 96), which is larger than the increase of 9–23% seen in human longitudinal studies of ≤6-mo duration (13, 23, 57, 71). It is also larger than the 76% increase in cross-sectional area of arm muscles of elite bodybuilders compared with untrained controls (69). Muscle enlargement in the stretch model is accompanied by possible increases in oxidative capacity, increases in the percentage of ATPase light-staining fibers, and an increase in connective tissue concentration, all of which are not present in the human strength-training condition. There is also a significant increase in muscle length in the stretch model. It is not known whether there is an increase in length in human muscle after strength training; however, it is unlikely that this occurs. The differences between the stretch hypertrophy model and the human condition in the response topography, muscle mass changes, and the selected cellular adaptations to the enlargement make this model questionable as a good model of muscle enlargement produced by strength training in humans.

The question of whether compensatory hypertrophy is a good model of human muscle enlargement produced by strength training is not a simple one to answer because of the different methods used to produce compensatory enlargement. As in the case of the stretch hypertrophy model, the response topography of the compensatory hypertrophy model is different from strength training in humans. The tenotomy model has been criticized as a model of human strength training based primarily on the time course of the enlargement produced (74, 95). The rapid increase in muscle wet weight peaking at 4–7 days, as well as the transient nature of the increase, makes this model suspect as a true model of muscle enlargement produced by strength training in humans. Decreased twitch and tetanic tension, muscle protein concentration, and metabolic potential that occur during this time period do not enhance the image of tenotomy as a model of human strength training. The study of Armstrong and co-workers (4) clearly demonstrates that during the rapid phase of muscle enlargement the increase in muscle wet weight is primarily due to muscle edema caused by an inflammatory response brought about by surgical trauma.

Studies utilizing ablation to produce compensatory hypertrophy have been far more successful in the production of a large and consistent increase in muscle wet weight. This weight increase reaches a steady state 4–6 wk after the surgical procedure. Once steady-state enlargement has been attained, the enlarged muscles exhibit increased peak tension and maximal tetanic force as well as similar protein concentration and metabolic properties as control muscles. There is a shift in the fiber type profile of muscles undergoing enlargement with the

TABLE 1. *Relationships between animal models for the production of muscle enlargement and human strength training*

	Human Strength Training	Stretch Hypertrophy	Compensatory Hypertrophy (Ablation)	Exercise-Induced Animal Models
Response topography		Not similar to HST	Not similar to HST	Similar to HST
Magnitude of muscle enlargement, %		150–200 (1, 96)	50–100 (4, 55)	
Short-term training	9–23 (13, 57)			0–30 (20, 62)
Long-term training	76 (69)			11 (35)
Relative response of muscle fiber characteristics				
Fiber area	Increase (71, 90)	Increase (27, 51)	Increase (56, 109)	Increase/decrease (33, 49)
Fiber length	?	Increase (1, 51)	No change (87, 109)	?
Oxidative capacity	No change/decrease (18, 104)	No change/increase (51)	No change/decrease (6, 55)	?
Glycolytic capacity	No change/decrease (18, 104)	No change (51)	No change/decrease (6, 55)	?
Fiber composition (%ST)	No change (59, 108)	Increase (27, 51)	Increase (7, 56)	No change (32)
Protein concn	?	No change (9, 65)	No change (4, 55)	No change (116)
Connective tissue concn	No change (69)	Increase (1, 65)	No change (58a)	?

Numbers in parentheses represent reference numbers. HST, human strength training; ST, slow twitch; ?, not measured.

ablation model toward a greater slow-twitch population. This shift has been demonstrated both histochemically and biochemically and results in a slowing of contraction time of the muscle expressed as time to peak tension and half-relaxation time. Fiber type conversion has not been demonstrated in humans after strength-training programs; however, this has not been studied in a longitudinal manner in individuals undergoing the long-term highly intense programs of bodybuilders. It is interesting to note that bodybuilders tend to display a high percentage of slow-twitch fibers relative to the normal population (105). These data, however, do not indicate whether this is because of a training effect or genetic predisposition. The obvious disadvantage of compensatory hypertrophy is that the response topography is not that of the human strength-training condition.

It is apparent that compensatory hypertrophy (produced by either ablation or tenotomy) studied during the 4- to 7-day period following the surgical procedure is not a good model of muscle enlargement produced by strength training in humans. If, however, enlargement is allowed to reach a steady state, compensatory hypertrophy, using ablation, becomes a much better model for the study of human strength training. The differences in response of muscle fiber characteristics between this model and the human condition are reduced to the alteration in fiber type profile with compensatory hypertrophy and possibly a greater increase in muscle wet weight. The increase in muscle wet weight in the compensatory hypertrophy model is greater than the 9–23% increase in muscle cross-sectional area measured by scanning techniques in humans as a result of periods of training of $\leq$6 mo (13, 23, 57, 71). However, muscle cross-sectional area of bodybuilders who have trained for much longer periods of time was 76% greater than that of control subjects (69). This difference is much more in line with the enlargement produced by the compensatory hypertrophy model.

It has been argued that stretch is the main mechanism of enlargement in the compensatory hypertrophy model, thereby making it an ineffective model for the study of muscle enlargement produced by strength training in humans (74, 102). This argument has generally been made concerning the enlargement produced during the 4- to 7-day period immediately following tenotomy. Evidence for stretch as the mechanism for enlargement during short-term compensatory hypertrophy produced by tenotomy comes from studies indicating that when the antagonistic muscles are denervated, thereby eliminating the stretch on the remaining synergistic muscles, enlargement is eliminated (44, 74).

Evidence against stretch as the major mechanism of enlargement in long-term compensatory hypertrophy produced by ablation includes the following: *1*) enlargement does not occur after ablation if the animal is placed in a non-weight-bearing situation (112–114), *2*) enlargement is further enhanced if the animal is placed on a forced running program after ablation (29, 85, 115), and *3*) muscle fiber length is not increased in this model (87, 109). Placing the animal in a non-weight-bearing position after gastrocnemius ablation would eliminate the functional overload component on the plantaris muscle (produced during normal locomotion of the animal) but would not affect stretch placed on the muscle from the relatively greater tension produced by the antagonistic muscle group. If stretch were a factor in muscle enlargement produced by this model, the wet weight of the plantaris muscle in the experimental leg of the non-weight-bearing animals would have been enlarged. Similarly, the finding that plantaris muscle enlargement is enhanced by increasing the functional overload (29) by treadmill running is evidence for a major role of this factor in the production of muscle enlargement in the ablation model.

Exercise-induced models for the production of muscle enlargement have the obvious advantage of a similar response topography to human strength training. The greatest disadvantage of these models has been in their ability to produce enlargement. Many studies utilizing these models have failed to produce increases in muscle mass (20, 21, 36, 79, 95, 99, 100). Several studies (30, 35, 49, 62, 116) have been able to produce enlargement on

the order of the increase in muscle cross-sectional area seen in human studies utilizing programs of <6-mo duration in previously untrained subjects (13, 23, 57, 71). However, exercise-induced animal models have yet to produce the kind of enlargement seen after long-term training in human bodybuilders (69). It is discouraging to note that even in the study of Gonyea and co-workers (35) where the cats lifted weights for nearly 2 yr the enlargement produced was only 11%.

Fiber area adaptations in exercise-induced animal models are somewhat analogous to those reported in human studies. It has been demonstrated that fast-twitch fibers enlarge to a greater extent than slow-twitch fibers (25, 117), which is consistent with the general consensus from human studies (11, 16, 18, 37, 83, 92). On the other hand, it has been demonstrated that similar enlargement occurs in all fiber types in exercise-induced animal models (30, 33), which is consistent with other human studies (23, 71, 93, 105).

Characterization of muscle enlargement that occurs in exercise-induced animal models is not as clearly defined as it is for the stretch and compensatory models. For instance, the response of skeletal muscle oxidative capacity, glycolytic capacity, muscle length, and connective tissue has not been characterized in exercise-induced animal models. The apparent reason for this is that, with the exception of Gonyea and co-workers (30–35), no laboratory has dedicated itself to the study of muscle enlargement utilizing a model of this nature. Many laboratories have developed a model that has been used for one study, generally to measure fiber area and number, and do not use the model to continue investigation in the area of strength development.

Many of the exercise-induced animal models have utilized an operant-conditioning program. Operant conditioning is an effective method for producing a desired response topography in an animal; however, it is virtually impossible to use this method to determine the maximum amount of weight that an animal can lift using the trained response. The amount of effort that the animal will put into the task is proportional to the motivation the animal has for the stimulus.

Classic operant-conditioning literature indicates that the greatest motivation for an animal is direct electrical stimulation of the septal area of the brain (81). When reinforced by direct electrical stimulation to the brain, the performance of the animal far exceeds that of even the hungriest animal when rewarded by food (81). Pain avoidance has been demonstrated to be a greater stimulus than food or water reward (76). The animal will perform a task only until the effort involved in the task performance exceeds his desire for the stimulus. This makes it difficult, if not impossible, to conclude that when an animal will no longer increase the amount of weight lifted, it is because the weight is greater than one repetition maximum. More than likely, it is not a maximum lift but it is the maximum effort the animal is willing to make in response to the operant stimulus. The limited enlargements produced in operant-conditioning weight-lifting models (30, 32–35, 49, 62) tend to support this hypothesis. If during the daily sessions the animal is only performing lifts with 50–60% of its maximum, limited, if any, enlargement would be expected to occur.

In the human strength-training condition, the maximum amount of weight an individual is capable of lifting can be determined with a much greater degree of certainty. A strength-training program can then be performed based on this knowledge. Observation clearly indicates that individuals involved in these programs over a number of years have achieved much greater muscle enlargement than has been produced by the operant-conditioning models in animals. If progress is to be made in the investigation of long-term human strength-training programs, an operant-conditioning animal model will need to be developed that will stimulate an animal to make a maximum effort.

Conclusion

Stretch hypertrophy is probably the least applicable model for the study of exercise-induced skeletal muscle enlargement in humans (Table 2). The response topography is different, the magnitude of enlargement is greater, and the adaptations in muscle length, fiber com-

TABLE 2. *Summary of advantages and disadvantages of animal models for the study of muscle enlargement produced by strength training in humans*

Model	Advantages	Disadvantages	Comments
Stretch hypertrophy		Response topography not similar to HST Magnitude of enlargement greater than HST Adaptations in fiber length, composition, and connective tissue concn different from HST	Not a good model for study of HST
Compensatory hypertrophy (ablation)	Magnitude of enlargement similar to long-term HST	Response topography not similar to HST	Possibly the best animal model for study of long-term HST
	Enlargement stimulus (functional overload) similar to HST	Increase in ST fiber composition not similar to HST	
Exercise-induced animal models	Response topography similar to HST	Magnitude of enlargement significantly less than long-term HST	Best model for study of short-term but not long-term HST

position, and connective tissue concentration are all different from the human strength-training situation. This model does, however, demonstrate that skeletal muscle has the ability to respond in many ways to severe stress that is normally not imposed in the human condition.

The compensatory hypertrophy model, using ablation, may be the best model for the study of muscle enlargement that occurs in long-term strength training such as in power lifters and bodybuilders but not for the study of short-term (<6 mo) strength-training programs. The response topography is different, but the magnitude of the enlargement produced in this model is very similar to the enlargement seen in bodybuilders. The alterations in muscle characteristics are similar, with the possible exception of the fiber type conversion seen in the compensatory hypertrophy model.

The advantages and disadvantages of the exercise-induced animal models are exactly opposite of those of the compensatory model. Response topography is similar to the human strength-training situation, but the magnitude of the muscle enlargement produced is far less than that produced by long-term strength training in humans. Some of these models do, however, appear to be good for the study of short-term strength-training programs.

The best model for the study of the cellular mechanisms of human skeletal muscle enlargement in response to strength-training programs would be an animal model that would mimic the human condition in topography and magnitude of enlargement in a similar time course (relative to the life span of the animal). To meet the response topography criteria, this would need to be a model that employs a movement similar to an exercise typically done by humans. It is also necessary that this motion be accomplished by only one limb of the animal if an assessment of fiber number is to be made as part of the investigation. A great deal has been learned about the ability of skeletal muscle to adapt to high-resistance stresses through the collective information obtained using the stretch hypertrophy, compensatory hypertrophy, and exercise-induced animal models. None of these models have proven to be ideal in the study of muscle enlargement produced by strength-training programs utilized by humans. It would be a mistake, however, to suggest that information obtained in any of these models is not of value in the study of exercise-induced skeletal muscle growth.

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