10) MUSCLE FIBER HYPERTROPHY VS HYPERPLASIA
Has the debate been settled? by Jose Antonio PhD

editors note: One of the fundamental questions in exercise physiology has been the mechanism of muscle adaptation to increased force demands (i.e. strength training). The simple and generally correct answer remains that muscles grow in size due to the growth of existing muscle fibers. However, under extreme conditions of muscle size and workload, there is substantial evidence that muscles can take advantage of a more spectacular mechanism; they can split to form additional new fibers, a mechanism termed hyperplasia. Dr. Antonio has been at the center of this controversial research and did his doctoral work in this area. I think this article is an excellent resource for beginning exercise physiology student and an interesting glimpse into the challenges of physiological research for all. His contribution adds significantly to the teaching value of this site.
-- Stephen Seiler

WHAT IS HYPERPLASIA?

Hypertrophy refers to an increase in the size of the cell while hyperplasia refers to an increase in the number of cells or fibers. A single muscle cell is usually called a fiber.

HOW DO MUSCLE FIBERS ADAPT TO DIFFERENT TYPES OF EXERCISE?

If you look at a good marathon runner's physique and compared him/her to a bodybuilder it becomes obvious that training specificity has a profound effect. We know that aerobic training results in an increase in mitochondrial volume/density, oxidative enzymes, and capillary density (27). Also, in some elite endurance athletes the trained muscle fibers may actually be smaller than those of a completely untrained person. Bodybuilders and other strength-power athletes, on the other hand, have much larger muscles (14,40). That's their primary adaptation, their muscles get bigger! All the cellular machinery related to aerobic metabolism (i.e. mitochondria, oxidative enzymes, etc) is not necessary for maximal gains in muscle force producing power, just more contractile protein. We know that this muscle mass increase is due primarily to fiber hypertrophy; that is the growth of individual fibers, but are there situations where muscles also respond by increasing fiber number?

EVIDENCE FOR HYPERPLASIA

Scientists have come up with all sorts of methods to study muscle growth in laboratory animals. You might wonder what relevance this has to humans. Keep in mind that some of the procedures which scientists perform on animals simply cannot be done on humans due to ethical and logistical reasons. So the more convincing data supporting hyperplasia emerges from animal studies. Some human studies have also suggested the occurence of muscle fiber hyperplasia. I'll address those studies later.

DOES STRETCH INDUCE FIBER HYPERPLASIA?

This animal model was first used by Sola et al. (38) in 1973. In essence, you put a weight on one wing of a bird (usually a chicken or quail) and leave the other wing alone. By putting a weight on one wing (usually equal to 10% of the bird's weight), a weight-induced stretch is imposed on the back muscles. The muscle which is usually examined is the anterior latissimus dorsi or ALD (unlike humans, birds have an anterior and posterior latissimus dorsi). Besides the expected observation that the individual fibers grew under this stress, Sola et al. found that this method of overload resulted in a 16% increase in ALD muscle fiber number. Since the work of Sola, numerous investigators have used this model (1,2,4-8,10,19,26,28,32,43,44). For example, Alway et al. (1) showed that 30 days of chronic stretch (i.e. 30 days with the weight on with NO REST) resulted in a 172% increase in ALD muscle mass and a 52-75% increase in muscle fiber number! Imagine if humans could grow that fast!

More recently, I performed a study using the same stretch model. In addition, I used a progressive overload scheme whereby the bird was initally loaded with a weight equal to 10% of the its weight followed by increments of 15%, 20%, 25%, and 35% of its weight (5). Each weight increment was interspersed with a 2 day rest. The total number of stretch days was 28. Using this approach produced the greatest gains in muscle mass EVER recorded in an animal or human model of tension-induced overload, up to a 334% increase in muscle mass with up to a 90% increase in fiber number (5,8)! That is pretty impressive training responsiveness for our feathered descendants of dinosaurs.

But you might ask yourself, what does hanging a weight on a bird have to do with humans who lift weights? So who cares if birds can increase muscle mass by over 300% and fiber number by 90%. Well, you've got a good point.

Certainly, nobody out there (that I know of), hangs weights on their arms for 30 days straight or even 30 minutes for that matter. Maybe you should try it and see what happens. This could be a different albeit painful way to "train." But actually the physiologically interesting point is that if presented with an appropriate stimulus, a muscle can produce more fibers! What is an appropriate stimulus? I think it is one that involves subjecting muscle fibers to high tension overload (enough to induce injury) followed by a regenerative period.

WHAT ABOUT EXERCISE?

The stretch induced method is a rather artificial stimulus compared to normal muscle activity. What about "normal" muscular exercise? Several scientists have used either rats or cats performing "strength training" to study the role of muscle fiber hyperplasia in muscular growth (9,13,17,18,20-22,25,33,34,39,41,42). Dr. William Gonyea of UT Southwestern Medical Center in Dallas was the first to demonstrate exercised-induced muscle fiber hyperplasia using weight-lifting cats as the model (20,21,22). Cats were trained to perform a wrist flexion exercise with one forelimb against resistance in order to receive a food reward. The non-trained forelimb thus served as a control for comparison. Resistance was increased as the training period progressed. He found that in addition to hypertrophy, the forearm muscle (flexor carpi radialis) of these cats increased fiber number from 9-20%. After examining the training variables that predicted muscle hypertrophy the best, scientists from Dr. Gonyea's laboratory found that lifting speed had the highest correlation to changes in muscle mass (i.e. cats which lifted the weight in a slow and deliberate manner made greater muscle mass gains than cats that lifted ballistically) (33).

Rats have also been used to study muscle growth (25,39,47). In a model developed by Japanese researchers (39), rats performed a squat exercise in response to an electrical stimulation. They found that fiber number in the plantaris muscle (a plantar flexor muscle on the posterior side of the leg) increased by 14%. Moreover, an interesting observation has been made in hypertrophied muscle which suggests the occurrence of muscle fiber hyperplasia (13, 17, 28, 47). Individual small fibers have been seen frequently in enlarged muscle. Initially, some researchers believed this to be a sign of muscle fiber atrophy. However, it doesn't make any sense for muscle fibers to atrophy while the muscle as a whole hypertrophies. Instead, it seems more sensible to attribute this phenomenon to de-novo formation of muscle fibers

(i.e. these are newly made fibers). I believe this is another piece of evidence, albeit indirect, which supports the occurrence of muscle fiber hyperplasia.

EXERCISE-INDUCED GROWTH IN HUMANS

The main problem with human studies to determine if muscle fiber hyperplasia contributes to muscle hypertrophy is the inability to make direct counts of human muscle fibers. Just the mere chore of counting hundreds of thousands of muscle fibers is enough to make one forget hopes of graduating! For instance, one study determined that the tibialis anterior muscle (on the front of the leg) contains approximately 160,000 fibers! Imagine counting 160,000 fibers (37), for just one muscle! The biceps brachii muscle likely contains 3 or 4 times that number!

So how do human studies come up with evidence for hyperplasia? Well, it's arrived at in an indirect fashion. For instance, one study showed that elite bodybuilders and powerlifters had arm circumferences 27% greater than normal sedentary controls yet the size (i.e. cross-sectional area) of athlete's muscle fibers (in the triceps brachii muscle) were not different than the control group (47). Nygaard and Neilsen (35) did a cross-sectional study in which they found that swimmers had smaller Type I and IIa fibers in the deltoid muscle when compared to controls despite the fact that the overall size of the deltoid muscle was greater. Larsson and Tesch (29) found that bodybuilders possessed thigh circumference measurements 19% greater than controls yet the average size of their muscle fibers were not different from the controls. Furthermore, Alway et al. (3) compared the biceps brachii muscle in elite male and female bodybuilders. These investigators showed that the cross-sectional area of the biceps muscle was correlated to both fiber area and number. Other studies, on the other hand, have demonstrated that bodybuilders have larger fibers instead of a greater number of fibers when compared to a control population (23,30,36). Some scientists have suggested that the reason many bodybuilders or other athletes have muscle fibers which are the same size (or smaller) versus untrained controls is due to a greater genetic endowment of muscle fibers. That is, they were born with more fibers. If that was true, then the intense training over years and decades performed by elite bodybuilders has produced at best average size fibers. That means, some bodybuilders were born with a bunch of below average size fibers and training enlarged them to average size. I don't know about you, but I'd find that explanation rather tenuous. It would seem more plausible (and scientifically defensible) that the larger muscle mass seen in bodybuilders is due primarily to muscle fiber hypertrophy but also to fiber hyperplasia. So the

question that needs to be asked is not whether muscle fiber hyperplasia occurs, but rather under what conditions does it occur. I believe that the scientific evidence shows clearly in animals, and indirectly in humans, that fiber number can increase. Does it occur in every situation where a muscle is enlarging? No. But can it contribute to muscle mass increases? Yes.

HOW DOES MUCLE FIBER HYPERPLASIA OCCUR?

There are two primary mechanism in which new fibers can be formed. First, large fibers can split into two or more smaller fibers (i.e. fiber splitting) (6,25,39). Second satellite cells can be activated (11,16,17,43,44).

Satellite cells are myogenic stem cells which are involved in skeletal muscle regeneration. When you injure, stretch, or severely exercise a muscle fiber, satellite cells are activated (16,43,44). Satellite cells proliferate (i.e. undergo mitosis or cell division) and give rise to new myoblastic cells (i.e. immature muscle cells). These new myoblastic cells can either fuse with an existing muscle fiber causing that fiber to get bigger (i.e., hypertrophy) or these myoblastic cells can fuse with each other to form a new fiber (i.e. hyperplasia).

ROLE OF MUSCLE FIBER DAMAGE

There is now convincing evidence which has shown the importance of eccentric contractions in producing muscle hypertrophy (15,24,45,46). It is known that eccentric contractions produces greater injury than concentric or isometric contractions. We also know that if you can induce muscle fiber injury, satellite cells are activated. Both animal and human studies point to the superiority of eccentric contractions in increasing muscle mass (24,45,46). However, in the real world, we don't do pure eccentric, concentric, or isometric contractions. We do a combination of all three. So the main thing to keep in mind when performing an exercise is to allow a controlled descent of the weight being lifted. And on occasion, one could have his/her training partner load more weight than can be lifted concentrically and spot him/her while he/she performs a pure eccentric contraction. This will really put your muscle fibers under a great deal of tension causing microtears and severe delayed-onset muscle soreness. But you need that damage to induce growth. Thus, the repeated process of injuring your fibers (via weight training) followed by a recuperation or regeneration may result in an overcompensation of protein synthesis resulting in a net anabolic effect (12, 31).

HAS THE DEBATE BEEN SETTLED?

In my scientific opinion, this issue has already been settled. Muscle fiber hyperplasia can contribute to whole muscle hypertrophy. There is human as well as rat, cat, and bird data which support this proposition (1-3, 5-8, 13, 17, 20-22, 25, 29, 35, 37, 47), a veritable wild kingdom of evidence. Does muscle fiber hyperplasia occur under all circumstances? No. There are several studies which show no change in fiber number despite significant increases in muscle mass (4,18,19,23,26,30,36,41). Is it possible that certain muscles can increase fiber number more so than others? Maybe. Can any Joe Schmoe off the street who lifts weights to get in better shape increase the number of fibers for instance in their biceps? Probably not. What about the elite bodybuilder who at 5'8" tall is ripped at a body weight of 250 lbs.? Are his large muscles purely the result of muscle fiber hypertrophy? I think it would be extremely naive to think that the massive size attained by elite bodybuilders is due solely to fiber hypertrophy! There is nothing mystical about forming new muscle fibers. Despite the contention that fiber number is constant once you're born (18, 19), we now have an abundance of evidence which shows that muscle fiber number can increase. Besides, there is nothing magical at birth which says that now that you're out of the womb, you can no longer make more muscle fibers! A mechanism exists for muscle fiber hyperplasia and there is plenty of reason to believe that it occurs. Of course, the issue is not whether fiber number increases after every training program, stress, or perturbation is imposed upon an animal (or human). The issue is again, under which circumstances is it most likely to occur. For humans, it is my speculation that the average person who lifts weights and increases their muscle mass moderately probably does not induce fiber hyperplasia in their exercised muscle(s). However, the elite bodybuilder who attains the massive muscular development now seen may be the more likely candidate for exercise-induce muscle fiber hyperplasia. If you are interested in a comprehensive scientific treatise on this subject, read a scientific review article that I wrote a few years ago (7).

KEY TERMS

• **anabolic** - in reference to muscle, a net increase in muscle protein

• **catabolic** - in reference to muscle, a net decrease in muscle protein

• **concentric** - shortening of a muscle during contraction

• **eccentric** - lengthening of a muscle during contraction

• **hyperplasia** - increase in cell number

• **hypertrophy** - increase in cell size

• **isometric** - no change in muscle length during a contraction

• **mitochondria** - is an organelle ("little organ") found within cells and is involved in generating ATP via aerobic processes

• **muscle fiber** - also known as a myofiber; is the multinucleated cell of skeletal muscle

• **myoblast** - an immature muscle cell containing a single nucleus

• **myogenesis** - the development of new muscle tissue, esp. its embryonic development

• **satellite cell** - are the cells responsible in part for the repair of injured fibers, the addition of myonuclei to growing fibers, and for the formation of new muscle fibers.

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