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Invited Editorial

Does blood flow restriction enhance hypertrophic signaling in skeletal muscle?

IN THE LAST DECADE, there was a dramatic increase in our knowledge of the molecular events that accompany changes in skeletal muscle mass in response to resistance exercise training or to chronic unloading. For example, the role of myostatin in limiting skeletal muscle growth during development was dramatically demonstrated in knockout animals, and myostatin's role in modulating growth of adult muscle was demonstrated by the administration of anti-myostatin antibodies (14). The key autocrine and paracrine roles of muscle insulin-like growth factor I [or mechano-growth factor (9)] in stimulating muscle hypertrophy were clearly established, and many details of the intracellular signaling cascades that link insulin-like growth factor I -receptor binding to increased muscle protein synthesis and satellite cell activation were worked out (8, 15). Similarly, other signaling pathways by which either mechanical force (10) or calcium changes (6) might regulate muscle growth were identified. Conversely, the loss of muscle mass during chronic unloading is now understood to arise not just from the down-regulation of hypertrophic signals but also from the activation of additional intracellular signaling cascades that specifically activate muscle protein degradation (8, 15).

Concurrent with these molecular advances, there was also a dramatic increase in applied research aimed at devising exercise programs to optimize muscle hypertrophy or to minimize atrophy in response to muscle unloading. Much of this applied research was directed toward counteracting the sarcopenia of normal aging or the muscle loss that occurs during prolonged spaceflight or bed rest. Thanks to these applied studies, the response of human muscle to almost every conceivable variation in resistance exercise training paradigm (e.g., number of repetitions, number of sets, interval between sets, interval between training sessions, eccentric vs. concentric motions, etc.) has been explored by at least one study (see Ref. 13 for review).

Although these applied and molecular studies of muscle hypertrophy sometimes seem to proceed relatively independently of each other, there is one issue on which applied exercise physiologists and molecular biologists have agreed: to obtain substantial hypertrophy from a resistance training program, the target muscles must be subjected to substantially increased load. Therefore, the American College of Sports Medicine recommended that, during resistance training, the load should exceed 70% of the one repetition maximum to achieve maximum hypertrophy (4). Correspondingly, most of the molecular literature hypothesizes that the initiating signaling event that ultimately results in, for example, increased muscle insulin-like growth factor I expression is the activation of a mechanical sensor mechanism, which unfortunately is so far not clearly identified. In view of this consensus that increased mechanical load is crucial to hypertrophy, few would have predicted that significant thigh muscle hypertrophy could be observed in healthy subjects after 3 wk of walking just 1 km/day, as is reported by Abe et al. (1) in this of the *Journal of Applied Physiology*.

The report by Abe et al. is the latest in a series of studies that show that restriction of muscle blood flow during low-intensity resistance exercise results in muscle hypertrophy and increased strength, whereas training at the same low intensity with normal flow has no effect (2, 18, 19). The hypertrophic response to low-intensity exercise with flow restriction is detectable within 1 wk, and it is accompanied by proportional increases in maximum force generation. Therefore, it cannot be dismissed as a volume change due to fluid accumulation. Both the Abe et al. (1) paper and a previous study (17) also show that a single bout of training with restricted flow causes a dramatic rise in serum growth hormone, comparable to that observed during resistance training at much higher intensities (12). Interestingly, there is also evidence that the adaptations to aerobic training are enhanced by modest flow restriction (11). In fact, it is well established from animal models that flow restriction amplifies angiogenesis in response to moderate aerobic exercise.

From the applied point of view, it is not clear that low-intensity resistance training with restricted flow has any advantage for healthy subjects over more conventional training with higher loads. Exercise of ischemic muscle can be uncomfortable, and certainly it would be difficult to apply the method to training trunk or neck muscles! Nonetheless, the method is apparently quite popular in Japan, where it is known as "Kaatsu," and advocates of the method argue that it would be clinically useful in subjects for whom high-load exercise is not indicated, for example, in the frail elderly or during rehabilitation after cast immobilization (16). In any case, from the molecular point of view, the phenomenon deserves further investigation, because it may provide insight into the initial signaling events that trigger muscle growth. Specifically, the enhanced response to ischemic training suggests that intracellular metabolic changes may be an important signal for hypertrophy.

There is no doubt that resistance training with restricted flow would amplify high-energy phosphate depletion and lactic acid production compared with training at the same load with normal flow. In fact, insofar as there is a good correlation between high-energy phosphate depletion and acid production vs. load during resistance exercises (20), the recommendation that hypertrophy requires a load $>70\%$ of one repetition maximum might just as well be recast as a recommendation that the training must result in substantial anaerobic metabolism. The observation that resistance training with shorter rest periods between sets results in greater hypertrophy than the same training program with long rest periods (but the same total mechanical work) is consistent with this view (13). The mechanism by which acute changes in high-energy phosphates or other linked metabolites might trigger the hypertrophic signaling cascade is unknown. However, there is ample evidence that metabolic sensors such as AMP-dependent protein kinase can play important regulatory roles in skeletal muscle (5). Thus it seems just as reasonable to hypothesize an unidentified metabolic sensor as a mechanical sensor (7).

Of course, there are other possible explanations for the hypertrophic response to exercise with flow restriction besides a hypothesized metabolic sensor. For example, insofar as the

smaller, more aerobic motor units normally recruited at light loads would be expected to fatigue more rapidly during flow restriction, it is likely that exercise with flow restriction requires recruitment of the larger, fast motor units, which are normally only recruited during stronger efforts. In fact, greater integrated electromyograph amplitudes were recorded during exercise with flow restriction compared with the same exercise without restriction (17, 19). Thus it may be that the enhanced hypertrophic response to exercise with flow restriction simply results from enhanced mechanical load on the muscle fibers in large motor units. This hypothesis would be easy to test by examining the effect of flow restriction on hypertrophy after resistance training by electrical stimulation of muscle, either in humans or in an animal model of resistance exercise (3). If flow restriction enhances the hypertrophic response to training independent of changes in recruitment, then the phenomenon deserves serious consideration from those interested in the molecular biology of hypertrophy.

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