Insulin-like growth factor in muscle growth and its potential abuse by athletes

Skeletal muscle is an inherently plastic tissue. Evidence suggests that muscles are constantly adapting in both quantity and quality to the changing functional demands imposed by the types and amounts of physical activity routinely performed. To date, the evidence suggests that in adults, activity-induced adaptations of skeletal muscle are orchestrated by local—that is, tissue-level as opposed to systemic—mechanosensitive mechanisms, which appear to include several growth factors and hormones. Of particular recent interest is the growth hormone (GH) and insulin-like growth factor-I (IGF-I) system. In the context of skeletal muscle homoeostasis, IGF-I is thought to mediate most of the growth-promoting effects of circulating GH. In addition, it appears to function in a GH-independent autocrine–paracrine mode in this tissue.[1]

As information on the mechanisms that modulate muscle adaptation becomes available in the scientific literature, it is tempting for athletes to apply this knowledge to enhance muscle mass, and hence function, by artificially manipulating these systems. In some cases, this misapplication of information has led to the simplistic notion that exogenous anabolic agents can be used to safely and effectively stimulate or augment muscle. Unfortunately, many of these attempts have been unsuccessful, and in truth, they ignore our understanding of the integrated nature of physiologic systems.

The most obvious problem with misusing anabolic substances is that they are invariably nonspecific. Agents that can stimulate muscle cells to hypertrophy will undoubtedly have effects on other cells and tissues—for example, the effects of GH on prostatic hypertrophy. Another problem is that just as the body is made up of tissues

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Striving to reach peak athletic form, typified by US sprinter Jon Drummond, tempts athletes to misuse anabolic substances

and organs that function as an integrated whole, so muscle comprises different cell types that must also function in unison. For example, a treatment that stimulates muscle cells to hypertrophy must also recruit fibroblasts to strengthen the connective tissues that will transmit the force generated by the muscle cells and must enhance angiogenesis and mitochondrial function. Without this coordination, larger (therefore stronger) muscle cells may develop, but the application of this enhanced contractile function would only damage the structure of the muscle when the unenhanced connective tissue fails.

Results from animal studies are instructive with regard to manipulating IGF-I either directly or through GH. Researchers have long sought ways to mitigate the atrophy-inducing effects of unloading on skeletal muscle. An animal model used to study this effect involves suspending rats by their tails with only their front feet touching any surface of the cage. The muscle atrophy that results mimics that seen in humans after space flight. When GH or IGF-I has been supplied exogenously during tail suspension, the results indicated that the mass of the normally weight-bearing muscles was, in fact, conserved. Owing to the effects of these treatments on other tissues, however, the overall body weight of the rats had increased. It was as if the growth and development program from an earlier developmental stage had been reactivated. When compared with their body weight changes, however, the muscles had actually grown less—that is, the normalized muscle mass was less in treated than untreated animals—the end result being that the IGI-I-treated rats would actually be less well adapted to normal ambulatory activity than the rats that received no treatment at all.

In humans, the effects of attempts to augment muscle mass using IGF-I have been less dramatic. In studies designed to overcome the loss of muscle in the elderly, the overall effect of increasing circulating IGF-I levels experimentally has been negligible.[2-4] In 1 study, the investigators managed to double the circulating IGF-I levels in elderly subjects but found no effect on the rate of protein synthesis in muscles and no augmentation of strength.[4] In addition to this disappointing result, the supplementation of IGF-I in otherwise healthy—that is, GH-normal—people is associated with moderate-to-severe hypoglycemia (it is, after all, insulin-like),[5] decreased GH secretion,[6,7] a shift from lipid to carbohydrate oxidation for energy,[7] and a general disruption of the insulin–glucagon system.[5,7] The issue of augmenting IGF-I is rendered even more complex because the biologic activity of IGF-I in the body is substantially influenced by the family of IGF-binding proteins.[8] For example, recent work on the effects of hypoxia on rat growth suggests that it is the effect of IGF-binding protein-3 that is more closely related to overall growth than is IGF-I itself.[9]

A more troubling aspect of IGF-I has recently emerged. In addition to a direct anabolic effect on skeletal muscle—for example, the production of more protein—IGF-I is also capable of stimulating the proliferation and differentiation of muscle stem cells (satellite cells). Results of animal studies suggest that this process is obligatory for muscle hypertrophy to proceed. Evidence that IGF-I is mitogenic should serve as a cautionary note to those who would use this agent to promote an anabolic state. Additional evidence suggests that IGF-I signaling may also participate in cellular transformation.[10] Specifically, elevated IGF-I levels have been linked to prostate, colorectal, and lung cancers.[11]

Given its potentially adverse effects, ranging from disruption of the insulin system to cancer, the exogenous augmentation of IGF-I is not an attractive or effective method of increasing muscle mass or function. Clearly, a prerequisite to the therapeutic use of these powerful growth factors is focused research on the mechanisms through which these mediators actually influence growth in the context of the whole organism.

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