Word count: 1350

Other Links and Extracts of Articles

by Geoffrey Goldspink

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About Goldspink:

Geoffrey Goldspink became a professor when still only 32. He was awarded the chair for his contribution to the understanding of how muscle grows and develops. He has held nine professorships, including a visiting professorship at Harvard University.

Links:

http://www.biochemsoctrans.org/bst/030/0285/bst0300285.htm

Gene expression in skeletal muscle

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Biochem. Soc. Trans. (2001) 30, (285–290) (Printed in Great Britain)

Abstract:

Muscle has an intrinsic ability to change its mass and phenotype in response to activity. This process involves quantitative and qualitative changes in gene expression, including that of the myosin heavy chain isogenes that encode different types of molecular motors. This, and the differential expression of metabolic genes, results in altered fatigue resistance and power output. The regulation of muscle mass involves autocrine as well as systemic factors. We have cloned the cDNAs of local and systemic isoforms of insulin-like growth factor-I (IGF-I) from exercised muscle. Although different isoforms are derived from the IGF-I gene by alternative splicing, the RNA transcript of one of them is only detectable following injury and/or mechanical activity. Thus this protein has been called mechano growth factor (MGF). Because of a reading-frame shift, MGF has a different 3´ sequence and a different mode of action compared with systemic or liver IGF-I. Although MGF has been called a growth factor, it may be regulated as a local repair factor.

http://www.annalsnyas.org/cgi/content/abstract/1019/1/294

Age-Related Muscle Loss and Progressive Dysfunction in Mechanosensitive Growth Factor Signaling

by Geoffrey Goldspink
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Annals of the New York Academy of Science
vol.1019: 294–298 (2004). doi: 10.1196/annals.1297.050

Abstract:
Loss of muscle mass and function (sarcopenia) is one of the most marked problems associated with aging because it has major healthcare as well as socioeconomic implications. The growth hormone/IGF-I axis is regarded as an important regulator of muscle mass. However, it is now appreciated that other tissues in addition to the liver express IGF-I. Also, there are local as well as systemic forms of IGF-I that have different functions. We cloned two different IGF-Is that are expressed by skeletal muscle, and both are derived from the IGF-I gene by alternative splicing. One of these is expressed in response to physical activity, which has now been called "mechanogrowth factor" (MGF). The other is similar to the systemic or liver type (IGF-IEa) and is important as the provider of mature IGF-I required for upregulating protein synthesis. MGF differs from systemic IGF-IEa in that it has a different peptide sequence that is responsible for activating muscle satellite (stem) cells. Therefore, it appears these two forms of IGF-I have different actions and that they are important regulators of muscle growth. Growth hormone treatment apparently upregulates the level of IGF-I gene expression, and when it is combined with resistance exercise more is spliced toward MGF. This results in an increase in muscle cross-sectional area in the elderly subjects who otherwise would produce less MGF. The possibility of ameliorating sarcopenia using MGF delivered as a peptide or by gene therapy will be discussed.

http://ajpendo.physiology.org/cgi/content/abstract/268/2/E288

Muscle growth in response to mechanical stimuli

D. F. Goldspink, V. M. Cox, S. K. Smith, L. A. Eaves, N. J. Osbaldeston, D. M. Lee and D. Mantle — Department of Clinical Medicine, University of Leeds, United Kingdom.

American Journal Physiology - Endocrinology and Metabolism,
vol 268: Issue 2 E288-E297, 1995; 0193-1849/95 $5.00

Abstract:
The relative merits of the separate and combined uses of stretch and electrical stimulation at 10 Hz in influencing the rates of protein synthesis in vivo, proteolysis, and the growth of the extensor digitorum longus muscle have been investigated after 3 days in the rabbit. Continuous electrical stimulation failed to change muscle protein turnover or growth. Static stretch caused significant adaptive growth, with increases in c-fos, c-jun, and insulin-like growth factor I (IGF-I; 12-fold) mRNA levels, and protein (19%), RNA (128%), and DNA (45%) contents. Both the fractional (138%) and total (191%) rates of protein synthesis increased with stretch, correlating with increased ribosomal capacities. Combining stretch and electrical stimulation increased the mRNA concentration of IGF-I (40-fold). The adaptive growth was greater (35%), with massive increases in the nucleic acids (185 and 300%), ribosomal capacities (230%), and the

rates of protein synthesis (345 and 450%). Large increases (i.e., 200-400%) in cathepsins B and L and dipeptidyl aminopeptidase I activities during stretch, with or without stimulation, suggest a role for these enzymes in tissue remodeling during muscle hypertrophy.

Extracts from articles:

http://slate.msn.com/id/2079406/

The Zero-Minute Workout - Cheat your way to a great body!
By David Plotz

from Slate: Posted Thursday, March 6, 2003, at 11:28 AM PT

Extract of one section of this article...

There's a treatment that could boost muscle mass without (much) work: a gene for something called Insulin-like Growth Factor.

The Project

The IGF gene is a multitasker. It makes different proteins, depending on the circumstances. When a muscle is exercised by a long-distance runner, the gene manufactures something called IGF-1. But when a muscle is intensely stretched or contracted, as by a weight lifter, the gene produces Mechano Growth Factor. MGF, which was discovered by University of London professor of anatomy Geoffrey Goldspink, instigates muscle growth by activating the "satellite cells" in the muscle, causing them to divide and fuse, creating the nuclei for new muscle cells.

Both MGF and IGF-1 encourage muscles to grow. (IGF-1 seems to activate protein synthesis necessary for new muscle cells.) Scientists have created mighty mice using both compounds. When Goldspink injected a gene for MGF into mouse muscles, he recorded a 20 percent increase in muscle mass in two weeks and a 25 percent increase in muscle strength—without the mouse hitting the weight room and without apparent side effects. Similar tests have been done on mice using IGF-1. They, too, became supermice, though it took longer.

Goldspink hopes MGF could be a therapy for the sick and frail: Muscular dystrophy and age-related muscle loss are the obvious targets. But he has no doubt "there will be misuse of MGF" by athletes and bodybuilders. (In fact, the International Olympic Committee has already commissioned him to develop a test for MGF, IGF-I, and human-growth hormone abuse.) But it won't just be hard-core muscleheads who experiment with MGF; if it turns out that MGF is safe and effective in 65-year-olds with sarcopenia, 50-year-olds will start asking for it, then all the rest of us. If you could get 25 percent bigger pecs without a visit to the gym, wouldn't you consider it?

The Obstacles

No clinical trials of MGF have started yet. The technique for inserting the gene into muscles is not complicated, but gene therapy is never easy. Although Goldspink's

experiment resulted in Schwarzenegger mice, that doesn't mean that MGF will successfully pump up normal humans. Goldspink saw no side effects in his mice tests but wonders if prolonged application of the gene would cause damage. (Goldspink expects a single dose of the gene would last about a year.) And as for IGF-1, it may have health risks that MGF does not. For example, it could damage the heart if it is injected directly into the bloodstream.

The Timeline

Goldspink hopes MGF will be used therapeutically within five years. Athletes are already experimenting with IGF-1, which is widely sold on the Internet (mostly by companies that seem less than concerned about its safety). So far, MGF hasn't found its way to the gym black market because Goldspink has tightly limited its distribution and because MGF is tricky to make, but it's just a matter of time before MGF slips out to athletes.

http://www.cheshire.mmu.ac.uk/exspsci/research/effects.htm

Effects of activity and ageing on muscle mass and connective tissue
Geoffrey Goldspink

Our group have for a good number of years carried out studies on the cellular aspects of muscle fibre growth, hypertrophy, atrophy and fibrosis. During the last decade we have used molecular biology methods to determine the link between mechanical signals and gene expression that result in changes in muscle mass and phenotype.

It has been shown that muscle fibres increase in girth by hypertrophy in response to exercise and overload and that this is due almost entirely to an increase in the number of myofibrils within the fibre. This is a local mechanical effect that results in the myofibrils splitting into two or more daughter myofibrils when they reach a certain size. This is preceded by an increase in synthesis of the muscle proteins associated in response to the production of insulin-like growth factors.

As well as increasing in diameter muscle fibres increase in length during post-natal growth. It has been shown that they elongate by adding new sarcomeres serially to the ends of existing myofibrils. Even mature muscles have been shown to be capable of adapting to a new functional length by adding or removing sarcomeres in series. In this way sarcomere length is adjusted back to the optimum for force generation, velocity of contraction and hence power output.

The change in the length of the fibres involves a remodelling of the connective tissue. This actually precedes the change in the number of sarcomeres in series. When the muscle is held at a shortened length there is an increase in the concentration of collagen which results in an increase in stiffness which may be a protective role. An increase in connective tissue content also occurs during ageing and this is particularly so when there is decreased activity. Using in situ hybrisation it was shown that collagen gene expression decreases with age and this implies that age-related fibrosis is not due to the accumulation of collagen within the muscle. Experiments showed that the latter could be ameliorated with exercise.

In recent years we have studied the regulation of muscle mass in relation to exercise and ageing. For some time it has been appreciated that there is local as well as systemic regulation of muscle mass. We have cloned the cDNA of two isoforms of IGF-1 which are derived from the IGF-1 gene by alternate splicing. The expression of one of these is only

detectable after mechanical stimulation. For this reason this has been called mechano growth factor (MGF). This has different exons, is not glycosylated, is smaller, has a shorter half life in the unbound state than the systemic liver type IGF-1. As the result of a reading frame shift the MGF peptide also has a different C terminal sequence and thus has different binding protein/receptor affinities. The other splice variant expressed in muscle during rest but is also upregulated by exercise, is similar to the systemic liver type IGF-1. The evidence suggests that MGF has a high potency for inducing local protein synthesis and preventing apoptosis and therefore has an important role in local tissue repair and remodelling. Our physiological experiments show that stretch and particularly stretch combined with electrical stimulation rather than stimulation per se are important in inducing MGF expression. The mechanotransduction mechanism involved is believed to involve the muscle cytoskeleton. During ageing the production of growth hormone and IGF-1 by the liver declines markedly. The discovery of MGF and muscle IGF-1 provides a link between physical activity and gene expression and underlines the need for the elderly to remain active as the locally produced growth factors supplement the circulating IGF-1 levels. However, data for humans and animals indicate that older muscles are less able to respond to mechanical stimuli by producing MGF than younger ones and thus the threshold for maintaining muscle mass increases.

The group at the Royal Free has shown that the injection of the cDNA of MGF in an engineered gene into muscles in the mouse resulted in a 25% increase in muscle mass within two weeks. Hence this local growth factor is very potent. Specific antibodies have been developed to MGF and using these in 2D Western blots that the MGF peptide binds to a specific binding protein that is specific to muscle tissue. This binding protein stabilises the MGF and provides a time release mechanism so even though MGF gene expression occurs only during or just after exercise the effects of exercise continue for a day or so after the exercise bout. Recent experiments also show that MGF as well as increasing protein synthesis also induces the muscle satellite (stem) cells to multiply. Although muscle is regarded as a post-mitotic tissue the extra nuclei required for growth are provided by the satellite cells fusing with the existing muscle fibres and a decline in muscle stem cells is associated with disease states such as Duchenne muscular dystrophy as well as age-related muscle loss.

This work was supported by grants from the Wellcome trust and from the EC Biomed programme for studying loss of function in respiratory muscle in COPD.