EFFECTS OF GROWTH HORMONE ON SKELETAL MUSCLES OF AGING SYSTEMS

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ABSTRACT

Growth Hormone (GH) is an anabolic hormone responsible for the somatic growth of young people. However, there is a progressive decline of the level of GH secretion with age where its level in old people is 20% of peak puberty level. Similarly, the level of Insulin-like Growth Factor I (IGF-I), the local mediator of GH action, is also reduced significantly with age. Several studies in the last decade have tried to use GH replacement therapy in attempts to alleviate some of the age-accelerated symptoms. GH administration to elderly people have improved nitrogen retention and reduced urinary excretion of phosphate, sodium and nitrogen. In elderly people over 60 y old, provision of GH for 6 mo improved lean body mass by 8.8% and decreased fat tissue by 14.4%. Other reports also claimed that GH had positive effect on increasing bone cortical strength in aging 24 mo old male rats. One of the main target tissues for GH is the skeletal muscle, especially in the process of differentiation of muscle cells to form postmitotic myotubes and myofibers. Studies on the effects of GH on skeletal muscles of aging systems have led to some mixed results. Some early studies have shown that GH administration to old rats can improve muscle mass and denervation associated with muscle atrophy. Other studies on GH-deficient adult humans also claimed that GH can considerably improve muscle volume in these patients. More recent studies in models of muscle immobilization of old animals have shown that GH had a very positive influence in reducing muscle damage associated with immobilization. However, studies on adult patients suffering from post polio syndrome of muscle weakness have shown no improvement by GH treatment. Similarly, studies on the effect of GH on muscle strength in elderly people subjected to resistance exercise demonstrated that training indeed increases muscle strength. But addition of GH to the regimen of elderly subjects did not further increase the effect of training alone. Thus, it appears that GH may have positive effect on aging and particularly in aging skeletal muscles; however, other studies could not corroborate this positive effect. More work is needed to ascertain the effect and mode of action of GH in aging animals and humans.

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INTRODUCTION

Growth hormone (GH) is one of the important hormones secreted from the pituitary gland and its main function is to control the somatic growth after birth. In essence, this hormone is a mixture of at least six different proteins of which the dominant type is a polypeptide of 191 amino acids with two disulfide bridges with molecular weight of 22,000 daltons (1, 2). The hormone is secreted in periodic rhythms of about 7-8 times in 24 h with peak secretion at the beginning of the sleep period at night (3).

GH amounts to about 10% of the dry weight of the pituitary. Traditionally, it was possible to isolate it from the gland by standard biochemical techniques. However, today, with the advance of genetic engineering techniques, a mass production of recombinant human GH and other recombinant animals GH(s) are being manufactured commercially.

The biological action of GH begins with its binding to GH receptors present on the membranes of the target cells (4, 5). Skeletal muscles are one of the most important target tissues for the action of GH. Other tissues like liver, adipose tissue, ovary, kidneys and cells like lymphocytes, chondrocytes, etc., were also shown to possess GH receptors.

Following GH binding to its target receptor, a cascade of events take place in those tissues which result in the production of family of protein called somatomedins. These are polypeptides that were first described by McConaghey (6); because of having characteristics similar to insulin, they were called insulin like growth factors, or IGF(s). The IGF(s) are the local mediators of GH action in the target tissues. Their main function is to accelerate tissue proliferation and growth.

Among the IGF(s), the most studied one has been IGF-I which was shown to be secreted by both paracrine

and autocrine mechanisms (7), and to be produced by tissues like liver, muscle and cartilage (8-10). Since IGF(s) levels and mode of action depend on GH secretion, it has been shown that in old people there was a marked reduction in IGF-I serum concentration compared to young ones (11).

Effects of GH on Skeletal Muscles

The axis of action of GH starts with the release of growth hormone releasing hormones (GHRH) from the hypothalamus. The latter triggers the release of GH from the pituitary to the bloodstream where a GH binding protein (BP) was identified which partially carries some of the GH in blood to its target organs. Eventually, GH is recognized and is bound to the GH receptors, which initiate the intracellular cascade of events leading to the induction of IGF(s) in these target tissues, to the synthesis of new proteins and other intracellular metabolic events.

It has been shown that IGF-I is an important factor in regeneration and growth of skeletal muscles (12-13). Ewton, et al. (14), using *in vitro* studies, found that in early developmental stages of skeletal muscle from the stage of myoblast to myotubes, IGF(s) have direct effect on development. However, in later stages of differentiation from myotubes to myofibers, GH has direct effect on muscle development. Other researchers have found that IGF-I may have effect on muscle differentiation also in the absence of GH by activating satellite cells which are muscle progenitor cells capable of differentiating into myoblasts (15-17).

In a later work (18), it was shown that IGF-I was responsible for specific induction of gene expression of muscle protein called myogenin. It is this protein that was implicated in the terminal myogenic differentiation of muscle cells to form postmitotic myotubes (18). In other studies of muscle injury and ischaemia, there was a proliferation of muscle satellite cells and elevation of IGF-I which led to prompt muscle regeneration (17).

While IGF-I is now considered important for muscle growth and development (myogenesis), it is believed that IGF-II is an important growth factor prenatally and is mostly associated with forming the connection between nerve cell branches and muscles (synaptogenesis) (19). The interrelation between exercise, GH and muscle buildup has been studied extensively. Exercise and intense muscle activity tend to raise the levels of human GH (20, 21). Other studies have found that also the level of IGF-I is elevated as a consequence of physical activity (8, 22). However, Yarasheski and co-workers could not find any positive effect of GH on muscle anabolism in young men subjected to resistance training (23).

The effect of GH administration to rats on glucose transport and utilization in skeletal muscle has been studied by several investigators. Dimitriadis *et al.* (24) have found that a single injection of GH did not increase the rate of glucose transport within 1-2 h after injection, but 12 h later, the sensitivity of glucose transport to insulin was increased. However, prolonged treatment with GH decreased the rate of glucose transport and glycogen synthesis at physiological levels of insulin (24). Similar observations were made by Cartee and Bohn (25), who showed that 10 d of twice daily injections of GH decreased by 20-30% the basal glucose transport in rats of various ages (9, 20 and 31 mo). Thus, evidence indicates that skeletal muscle is one of the prime tissues influenced directly by GH. Through proteins, carbohydrate and fat metabolism, GH controls the growth and proper maintenance of skeletal muscles.

Aging and Growth Hormone

Rudman et al. (26) have investigated the progressive decline of GH secretion and decline in the level of IGF-I from the third to the ninth decades in humans. In 55% of subjects over 69 y old, no release of GH (<4 ng/mL) was detected, either at day or at night.

In subjects whose IGF-I levels were around 0.98 u/mL, peak day release of GH was 5.39 ng/mL and peak night release was 14.10 ng/mL. These values were found to be much lower than the peak day and night release of young people ages 20-29, which were 7.27 mL and 20.38 mg/mL, respectively. This consistent decline in GH levels with age was further discussed in earlier reviews (26, 27). However, in a more recent review by Ho and Hoffman (28), a description of six different studies was reported which showed that mean GH secretion in 24 h increases by 100% from early puberty to late puberty and then declines rapidly in the twenties, reaching only 20% of secretion of late puberty value in people over 60 y old (28).

From the above findings it was quite natural to assume that GH replacement therapy should be attempted on aging populations. Indeed several works have been published in the last decade where provision of GH to aging animals and humans have been tried. In a study of elderly adults who lost weight due to nonmalignant illness, a well balanced nitrogen sufficient diet was given in the control periods. Afterwards, in the experimental periods of four days each, a supplement of 25 and 50 mg/Kg of GH was administered to these patients. Significant increase in nitrogen retention was observed after the experimental periods which led to the conclusion that even during adequate nutritional intake, low doses of GH improve nitrogen retention in underweight adults (29).

GH administration to elderly men and women over 60 for a period of one week increased the levels of IGF-I and reduced the daily urinary excretion of nitrogen, phosphate and sodium (30). In another study Rudman et al. (31) have given h-GH to 21 healthy people ages 61 to 81 y who had plasma IGF-I concentration of less than 350 u/L for a period of 6 mo treatment. The results showed that IGF-I level rose to youthful range of 500 to 1500 u/L. In the control group who received no treatment there was no change in IGF-I values. In the group receiving h-GH there was an 8.8% increase in lean body mass, a 14.4% decrease in fat tissue and a 7.1% increase in skin thickness ($p < 0.05$ in all cases). No significant changes were observed in the control group. The authors concluded "that diminished secretion of GH is responsible,

in part, for decrease of lean body mass, the expansion of adipose-tissue mass, and the thinning of the skin that occur in old age (31)." However, some criticism of the above study was that this work was lacking a placebo control group (32).

Another recent work has studied the effect of h-GH on the composition cortical strength of bones from 2 y old male rats (33). Daily injection of h-GH for 20, 40 and 80 days to these rats compared to control saline injected animals showed 400 and 800% increase in mineral deposition rate at 40 and 80 day groups, respectively. The mechanical analysis showed increased strength of the diaphyseal bone after h-GH administration (33).

From the above studies it appears that administration of GH to older individuals increased the level of IGF-I and subsequently there was an increase in tissue buildup and protein synthesis. However, a recent paper by Zachwieja et al (34) could not detect any increase in albumin synthesis in older adults treated with h-GH (34).

Growth Hormone and the Aged Muscle

The aging skeletal muscle has been a subject of extensive research in the past decade. The physiology and biochemistry of muscles in aging systems has been reviewed recently (35). As we have seen in the previous sections, skeletal muscle is one of the prime target tissues responsive to GH action.

Since the level of GH and IGF-I are significantly diminished with age, the issue as to how responsive are muscles of old animals and humans to GH has been studied quite extensively in the past few years. Early studies in adults and old rats have shown that GH administration can improve muscle regeneration (36, 37). In rats that underwent denervation of muscles, GH treatment could reduce to some extent the denervation-associated muscle atrophy (36). In another work, Jorgensen et al. (38) have reported that GH administration to GH-deficient adult humans can considerably improve muscle volume in these patients.

Using the hind limb muscles of aging rats, a model of plaster of paris cast immobilization has been developed (39-42). Using this model it was possible to show that cast immobilization for 4 weeks causes a 30-40% reduction in muscle mass of mist hind limb muscles. Application of rat-GH could ameliorate to a great extent this muscle degeneration. Other criteria for muscle damage, such as changes in muscle enzyme activities and oxidation of muscle proteins due to immobilization, were also protected by GH administration (39-42).

External fixation (EF) of the limbs has been shown to be a more drastic technique of immobilization than plaster of paris. (43) Using the EF technique, old rats were immobilized and treated with rat-GH. Table 1 shows the loss of weights of gastrocnemius and quadriceps muscles. Indeed both muscles lose a significant weight due to EF. But provision of GH slows down this weight loss, especially in the gastrocnemius muscle.

Table 1. Changes in the gastrocnemius and quadriceps muscles weights of 26 mo old female Wistar rats after right hind limb external fixation for 4 weeks and 3 weeks of rat-GH administration.

	4 weeks external fixation		4 weeks external fixation # 3 wks r-GH	
	control leg (Lt.)	immobilized leg (Rt.)	control leg (Lt.)	immobilized leg (Rt.)
gastrocnemius weight (mg) (N=5)	1117±116*	623±65*	1198±70*	879±56*
average weight loss (mg)	494		319	
significance control vs. immobilized leg	*p <0.001		*p <0.001	
% change	-43.3±10**		-26.5±3.8**	
significance of % change of EF vs. EF + GH	**p<0.02			
quadriceps weight (mg) (N=4)	1629±184*	1046±152*	1613±78*	1204±52*
average weight loss (mg)	583		409	
significance control vs. immobilized leg	*p <0.01		*p <0.01	
% change	-35.8±3.5		-25.5±4.9	
significance of % change EF vs. EF + GH	**p <0.05			

* P was calculated using paired student's t-test.
** P was calculated using independent student's t-test.

From Table 1 and the above discussion it seems that GH has a positive effect in slowing down muscle damage due to immobilization. It should be noted, however, that GH did not have any effect on soleus muscle of hind limb suspended young rats (44). Soleus hypertrophy due to h-GH administration was observed only in the control rats (44). Interestingly, work in our laboratory (unpublished) also showed that young rats were less responsive to exogenous GH administration, probably due to the endogenous high level secretion of GH.

Other recent reports have claimed that GH may have a positive effect on aging muscles. De Luca et al. (45) have shown that chronic treatment of 23 mo old female Wistar rats resulted in an improved membrane electrical properties of extensor digitorum longus muscle. In a very recent report (33), administration of h-GH to 2 y old rats for 80 d increased muscle weight of injected animals by a range of 19-31%. Thus the weights of soleus, anterior tibialis and extensor digitorum longus increased by 28%, 31% and 19.2% respectively in GH treated old rats compared to saline injected rats. All these elevations were statistically significant (33). Effect of administration of GH to adult rats ages 9, 20, 31 mo on skeletal muscle glucose transport was studied by Cartee and Bohn (25). Although skeletal muscle level of Glut-1 and Glut-4 did not change with GH treatment, maximal glucose transport was reduced 40% by h-GH treatment only in the 31 mo old rats (25).

Growth hormone replacement therapy has been attempted in growth hormone deficient hypopituitary adults. These people quite often complain of being tired and muscle weakness. In a recent study GH was given to 14 such patients and other 14 age- and sex-matched patients served as controls (46). Following GH replacement, muscle isometric strength increased significantly ($p < 0.05$) as did other parameters of muscle function such as half relaxation time which was shorter in GH treated patients (46). A similar study was conducted by Sartorio and Narici (47) who provided h-GH to GH-deficient adults (GHD patients) for 6 mo. They concluded that GH treatment did have some positive influence in increase of muscle size and strength in GHD patients. Similarly to GHD patients, many polio survivors develop what is now known as post-polio syndrome manifested by muscle weakness and fatigue. Several reports in the last few years have shown that polio survivors have lower levels of IGF-I compared to age-matched controls (48). However, although administration of h-GH to polio survivors tended to raise the IGF-I serum levels to normal ranges, no consistent changes in muscle strength were observed in the GH-treated groups (49).

Finally, several studies on the effect of h-GH on muscle growth and strength in elderly people subjected to resistance exercise have been attempted (50, 51). Although strength training did increase muscle strength and decreased fat mass, treatment of elderly subjects with GH did not further improve the effect of training alone (50, 51). These final results with strength training were similar to the findings with polio patients, but were in contrast to the positive effects that GH had on GHD patients.

CONCLUSION

GH is responsible for the somatic growth after birth. However, its level of secretion and action is drastically reduced after puberty and after cessation of bodily growth. Also, the level of insulin like growth factor-1 (IGF-I), which is the local mediator of GH, is also diminished considerably in advanced age. Thus, attempts to replace and provide GH to elderly humans and animals have shown positive results in some cases, while in other studies effects were less impressive.

Some studies have indicated that long-term provision of GH may increase muscle mass during aging. Also in models of muscle immobilization of old animals, GH had a very positive influence in curtailing muscle damage associated with immobilization. However, no effect of GH on exercising muscles of aging individuals were observed. In conclusion, the effect of GH on aging systems in general and on aged muscles in particular is still not clear. More work and repetitions of some studies are needed to ascertain the influence and mode of action of GH in aging systems.

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