GROWTH HORMONE: Understanding the Endocrinology and Ergogenics

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Ergogenics

Human Growth Hormone (hGH), a naturally-produced hormone in the body, is also considered an ergogenic drug and is banned by the World Anti-Doping Agency (WADA). Despite its ban, it has been purported to be in widespread use in sports dating back to the late 1980s. The reasons hGH has become so popular are because it is effective in benefiting athletic performance, has relatively mild side effects as compared to anabolic steroids (although substantial side effects accompany its use), and there is no detection system for determining its usage as an ergogenic drug (16). Furthermore, hGH is a particularly attractive alternative to anabolic steroid use in female athletes because of the relatively lower risk of undesired androgenic side effects (16).

Originally, hGH was obtained from the pituitary glands of cadavers and prepared as a medical injection (15). This process resulted in only limited quantities with the added risks of infection. Most notably, the use of hGH obtained from cadavers has been associated with a high risk of developing Creutzfeldt–Jakob disease, a slow progressing dementia. In the late 1980's genetic engineering lead to the synthesis of a recombinant form of human growth hormone (rhGH) (7). Athletes and bodybuilders use rhGH for its anabolic benefits to increase muscle mass, repair tissue, and decrease fat mass. While rhGH injection increases contractile protein synthesis in the muscle, it appears to have a more marked effect on the connective tissue, allowing strength to increase faster than muscle growth (6). Strength athletes are not the only ones benefiting from rhGH. Even endurance athletes use rhGH for its metabolic advantage on lipolytic and glycolytic metabolism (8). Recombinant human growth hormone appears to benefit endurance performance by enabling fat to be used as an energy source and preserving glucose. Furthermore, rhGH may aid in athletic performance by increasing cardiac output (10), improving thermoregulation, increasing blood volume, and stimulating endorphin release.

Use by Pro Athletes

Reliable information on the frequency, dosage and patterns of use by athletes are difficult to obtain because rhGH is a banned substance. But some information reveals that the athletes misusing rhGH will take 10 – 25 IU/day, three to four times a week (16). Many athletes combine rhGH use with other ergogenic drugs and it is estimated that these athletes will inject about 4 IU/day in combination with other doping agents (16). For instance, bodybuilders and strength/power athletes will frequently combine rhGH abuse with anabolic steroids (for muscle growth), and endurance athletes will use rhGH in conjunction with erythropoietin (EPO) to enhance aerobic capacity, making it difficult to isolate the effects of rhGH on performance. Recombinant human growth hormone use comes with a hefty price tag as a daily dose is estimated to run at between $75 – $150 (13).

Function

Human growth hormone is naturally produced by the somatotroph cells of the anterior pituitary gland and is released in a pulsatile pattern. It is sometimes considered a prohormone (preceeding a functional hormone) because after its genetic code is translated, hGH undergoes several modifications in the pituitary gland and circulation. The stimuli for the secretion of hGH from the anterior pituitary gland requires the release of growth hormone releasing factor (GHRF) from the hypothalamus (12,16). The release of GHRF comes in response to a variety of stressors such

as nutrition, sleep, emotion, and exercise. In normal, healthy adult men, hGH is produced at a rate of about 0.4 to 1.0 mg/day (7). Human growth hormone exerts both direct and indirect effects on the tissues, binding directly to specific receptors located on target cells throughout the body to exert direct effects. Additionally, indirect effects of hGH are mediated by another anabolic hormone, insulin-like growth factor (IGF-1), generated in the liver. Human growth hormone has a short half-life (length of time it takes for it to reach half of its original concentration in circulation) of about 20 minutes (9) with concentrations returning to baseline 8 – 16 hours after intramuscular injection and 11 – 20 hours after subcutaneous injection (4).

In order to evaluate hGH levels in the blood its molecular characteristics must be considered. With hGH this is not an easy task because it exists in several isoforms and fragments. In fact, it has been estimated that there are as many as 100 different variant forms of hGH present in human circulation (1). In other words, hGH exists in many functionally similar forms that differ slightly by their amino acid sequences, genes, or RNA transcripts. Also, fragments or pieces of the hGH protein are created by protolytic cleavage at susceptible sites in the amino acid chain. So, hGH should be considered a hormone "family," including all isoforms and fragments when examining its multifunctional role. Four major isoforms of hGH have been identified in the human pituitary ranging in amino acid number and include 191 aa = 87.5%; 176 aa = 8.1%; 153 aa=3.3%; and 145 aa = 11% (Zhan et al., 2005). The largest intact molecule (191 aa), is what has been typically referred to as hGH and is most predominant. It is likely responsible for the growth-promoting effects of hGH, while the fragments likely act on lipid and carbohydrate metabolism (1). The molecular weight of the 191 aa form is 22kDa (kilodaltons). There is a 20kDa isoform which is co-secreted from the anterior pituitary gland with the 22kDa form, but does not have amino acid residues 32 – 46, for example (5). Another hGH fragment, known as 1-43, is a ~5kDa fragment but it is unclear whether it is naturally formed, created by proteolysis, or by laboratory techniques (5). Furthermore, there is speculation that other fragments are formed by proteolytic cleavages at other vulnerable sites on the hGH molecule (5). Despite this progress, it is still unknown as to exactly how these variants of hGH interact with the target tissue. Some evidence suggests that a 'spectrum of hGH molecules' is required for hGH to exert its effects on the target tissue (11).

Detection Strategies

To date, detection of exogenously administered hGH has not been possible. Since hGH is naturally synthesized by the body, it is difficult to distinguish endogenously produced hGH from exogenously administered hGH. Additionally, because hGH responds markedly in a pulsatile manner to stress, including nutrition, sleep, emotion, and exercise, it is difficult to determine supraphysiologic levels, indicative of doping. Moreover, hGH has a short half life in the blood and low concentration in the urine being 100 to 1000 times less than in blood (16). Thus, simply quantifying the amount of hGH is not sufficient to detect exogenous rhGH. Finally, despite persistent research, scientists are far from unraveling the complexity of the entire hGH family. Therefore, detection of exogenously administered hGH will also not likely be possible in the foreseeable future

The understanding of the different isoforms of hGH may bring us one step closer to detecting exogenous use. The injected form of hGH contains only the 22kDa form, which is also the predominant form produced by the body. Yet, based on the presumption that the isoforms and fragments are released in proportion to the 22kDa form, assess-

ment of all fragments and isoforms has the potential to provide strategies to allow us to detect hGH abuse. Measuring the serum amounts of the 20kDa form may give us some insight to distinguish naturally produced hGH from rhGH, because in normal samples the 20kDa isomer should be about 10%, but is suppressed when rhGH is given. Injection of the recombinant form of hGH increases the proportion of the 22kDa form in comparison with all other circulating forms. Furthermore, long term use also favors the ratio of the 22kDa form, due to back-regulation of the naturally produced form. Despite the potential, this method is unable to detect hGH from cadaver sources. Furthermore, current knowledge is so lacking in the understanding of the complexity of the hGH family, scientists are perplexed by the possibility of the binding of exogenously administered rhGH to binding proteins, further complicating these strategies.

Another attempted method to detection of exogenously administered hGH has tried to rely on "pharmacodynamics" to measure evidence of supraphysiologic doses based on the notion that other biological factors are less variable or less sensitive than hGH itself and should have a longer half-life in the body. Furthermore, recent advancements have shown promise in producing methodology to be able to detect hGH abuse in up to 86% of men and 60% of women using blood markers of hGH action (14). Nevertheless, individual variation continues to make quantifying cut-off levels difficult.

Side Effects of Excess GH in Adults

Like other ergogenic drugs, hGH abuse comes with various side effects, which are considered relatively mild compared to those associated with anabolic steroid use. Because the epiphyseal growth plates of adult bone are fused, excess hGH in adults results in a condition called acromegaly, which is characterized by thickening of the bones in the forehead, jaw, hands, and feet. Because rhGH is injected, the usual risks of transmitted diseases, such as HIV/AIDS and hepatitis apply via cross-infection if syringes are non-sterile. Additionally, soft tissues and organs are affected by hGH, resulting in noticeable enlargements of the nose, lips, and internal organs. Chronic use may lead to more severe side effects such as diabetes, high blood pressure, cardiovascular disease, fluid retention, excessive sweating, osteoporosis, menstrual irregularities (in females), cardiomyopathy, impotence, and an abbreviated lifespan (3,16). Some of these side effects will disappear after withdrawal of the drug.

Conclusions

Although prohibited, hGH is widely used as an ergogenic drug in competitive sports. Human growth hormone does not exist as a single protein, but rather it exists as a large family of variants. This makes understanding its functions on target tissue very complex. Scientists are diligently working on understanding the roles of these forms in the body, which may lead to detection strategies. Nevertheless, detection of exogenous rhGH administration is not yet possible, and athletes will likely continue to use rhGH for its ergogenic benefits in competitive sports.

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