[S4-6] [10/19/2001(Fri) 17:00-17:30 / Hall B]

Effect of Growth Hormone on Lipid Metabolism: Age and Obesity

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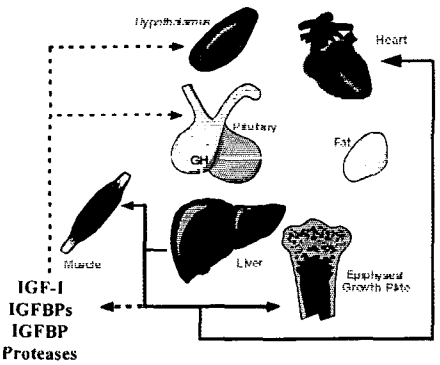
INTRODUCTION

Growth hormone (GH) is necessary for the normal growth and development of youth but normal growth occurs only in a relatively short time period while GH secretion continues throughout life. However, the biological significance of GH in adults had not been known until recently. The first success in human GH (hGH) therapy in pituitary dwarfism was reported in 1958[1], but the use of such replacement therapy was limited by the GH availbility. The rapid advent of recombinant hGH (rhGH) at the beginning of the 1980s[2] provided large quantities of non-immunogenic hGH. Thus, it has been possible to broaden the indications of GH therapy to other growth retardations in children[3]. More recently, it has been postulated that GH-deficient (GHD) adults could benifit from the metabolic effects of hGH[4]. In fact it has been shown that the life expectancy in hypopituitarism is shortened because of cardiovascular disorders[5], and it is known that the amount and the distribution of body fat are abnormal in GHD adults[6]. The most common pattern found during GH deficiency is an increase in total and low-density lipoprotein (LDL) cholesterol and apoprotein B (apoB) levels, an increase in triglycerides, and a decrease in high-density lipoprotein (HDL) cholesterol levels[7]. In this presentation, the metabolic effects of GH will be reviewed especially focusing on lipid metabolism as a function of sex, age and obesity.

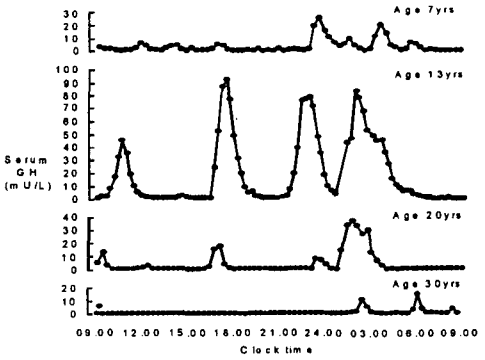
Metabolic Effect of Growth Hormone

(Scheme 1)



In adults growth hormone continues to play a role in the control of protein metabolism and body composition. It is generally accepted that most-promoting actions of growth hormone (GH) are mediated by insulin-like growth factor I (IGF-I)[7]. IGF-I may either circulate after production and secretion by hepatocytes[8] or it may produced by various other fetal, postnatal and transformed cells to act locally in an autocrine or paracrine manner[9]. Scheme 1 summarizes the mechanism of GH secretion and modulation in the

body[10]. In adult men and women, basal GH secretion is pulsatile. It has been estimated that GH is secreted with a periodicity of ~110 min[11], a pulse duration of ~60 min, and an average secretion rate of 0.18 and 0.27 umol kg-1 min -1 in adult men and women, respectively[11]. A typical GH daily secretion pattern is shown in Figure 1 as to ages[10].

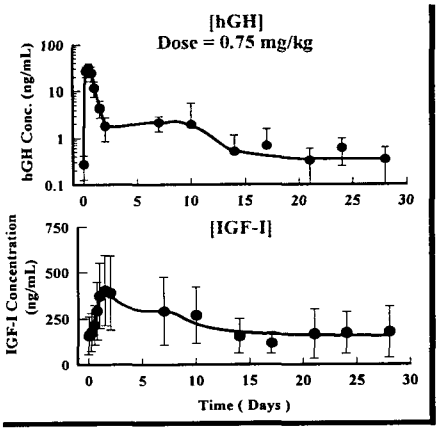


Due to a series of chain reaction among GH, IGF-I, and their binding proteins, the metabolic effect of GH is either directly or indirectly mediated via IGF-I[12]. Indirect effects of IGF-I may enhance or counteract the direct metabolic effects of GH. And the metabolic effects of IGF-I are regulated by the availability of binding proteins, which inhibit or enhance its effects. Table 1 summarizes the metabolic effects of GH together with the indirect contrasting effect through the elevation of IGF-I. Figure 2 demonstrates GH and corresponding IGF-I profiles following a month-long GH administration[13].

(Table 1)

Direct		Contrasting Indirect	
Increase	Decrease	Increase	Decrease
FFA			FFA
lipolysis	serum cholesterol		lipolysis
lipid oxidation	triglyceride		
HDL	LDL		
	glucose uptake	glucose uptake	
nitrogen balance	protein breakdown		
protein synthesis			
insulin sercretion			
glycogenolysis	glycogen synthesis		

(Figure 2)



Among the well known effects of GH on the lipid metabolism, the mobilization of free fatty acid (FFA) from adipose tissue is one of the more important[7]. From animal studies, especially in hypophysectomized models, a direct lipolytic effect of GH on adipose cells has been demonstrated[14]. It is not clear, however, whether in GHD humans, GH has a direct lipolytic action or simply a permissive action on the effects of other lipolytic agents.

Age and Sex

Aging in man is associated with reduced protein synthesis. decreased lean body mass and bone mass, and increased body fat[15]. These body composition changes are accompanied by a progressive decline of adrenal secretion of dehydroepiandrosterone (DHEA) and its sulfate ester (DS)[16] paralleling that of the GH-insulin-like growth

factor-I (GH-IGF-I) system[15]. In women before menopause, GH decrease, IGF-I axis increase in adiposity, loss of lean mass, and development of osteoporosis. Basal GH levels are positively correlated with age in women. But in women after menopause, basal GH levels are negatively correlated with age in postmenopausal women, possibly due to decrease in plasma E_2 levels that occurs during menopause[17].

Obesity

Studies in adult GH-deficient patients have demonstrated mean reductions in lean body mass of 7-8% corresponding to approximately 4 kg of lean tissue[6] while GH replacement of these patients has been shown to result in an increase in lean body mass after 6 months. A study which has investigated the effect of GH treatment for 3 yrs has shown that this increase in lean body mass by GH is maintained over this time. Obsesity (OB) and Cushing's syndrome (CS) are characterized by marked decrease of both spontaneous and stimulated GH secretion[18,19], but nevertheless total IGF-I levels have been reported normal or low normal[20] and free IGF-I levels even increased, at least in OB[21]. It has also been reported that total IGF-I levels in patients with subcutaneous OB are higher than those in patients with visceral OB[22]. Basal IGF-I levels in NS (239.3 +/- 22.9 ug/L) were similar to those in OB (181.5 +/- 13.7 ug/L) and CS (229.0 +/- 29.1 ug/L[22].

Thus, the present talk will review the effect of GH on lipid metabolism in the literature along with our laboratory data on the effect of GH on FFA levels and body weight gain following a short-term and a long-term treatment of GH in mice.

ACKNOWLEDGMENT

I thank Dr. Gwansun Lee and Mr. Sechang Kwon in Hanmi Pharmaceutical Co. for their generous hGH supply and financial aids.

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