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hGH Transgenic Rats Expressing Severe Obesity and Effect of Treatment with hGH in a Pulsatile Manner

AKIHIRO IKEDA, KYU-TAE CHANG, TAKAHIRO NAKANO, SHIGEMI MATSUYAMA, MASUGI NISHIHARA, AND MICHIO TAKAHASHI

Department of Veterinary Physiology, Veterinary Medical Science, The University of Tokyo, Tokyo 113, Japan

GH affects not only body growth but also carbohydrate and lipid metabolism [1]. Though the majority of the effects are believed to be brought about by enhancing the production of insulin-like growth factor-I (IGF-I) in hepatic cells [2], some direct effects of GH on adipose tissue are also proposed [3]. Various experimental observations indicate that GH has both insulin-like and anti-insulin-like effects [1], but no simple and straightforward explanations of the GH action on carbohydrate and lipid metabolism are yet available. The significance of pulsatile and sexually differentiated secretory patterns of GH observed in mature animals has not been well analyzed [4], but these secretory patterns of GH appear to be important for regulating growth and metabolic function in the liver and adipose tissue [4, 5]. We previously produced hGH transgenic rats expressing relatively low circulating levels of hGH constantly [6]. In these transgenic rats, pulsatile secretory no pattern in either transgene-derived hGH or endogenous rGH could be detected [6]. One of the most striking phenotypes in these transgenic rats is severe obesity with hyper-insulinemia, -glycemia and hyperlipidemia. In this study, to study the significance of GH pulsatility, these transgenic rats were treated with hGH in a pulsatile manner.

Correspondence to: Dr. Akihiro IKEDA, Department of Veterinary Physiology, Veterinary Medical Science, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113, Japan

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Materials and Methods

Animals and generation of transgenic rats

Wistar strain rats purchased from Imamichi Institute for Animal Reproduction (Tsuchiura, Japan) were used. The animals were housed at 23 ± 1 °C under a lighting schedule of 14 h light/10 h darkness (lights on at 0500 h).

hGH transgenic males with a low and constant peripheral level of hGH [6] were mated with normal females, and the resulting transgenic animals and non-transgenic littermates were used.

hGH treatment

hGH transgenic rats were treated i.p with hGH (Pharmacia, Sweden) at a dose of 100 mg/body, 4 times per day at 4 h intervals from 0700 h to 1900 h for 7 days. Another group of the transgenic rats and normal rats were treated similarly with a vehicle solution (0.3 m*l*) for 7 days. The blood and tissue samples were collected 3 h after the final injection.

Analytical methods

Plasma glucose, triglyceride and free fatty acids (FFA) were measured with commercial kits (Wako, Tokyo), and plasma insulin was also measured with commercial kits (Amersham Life Science, Tokyo).

Results

The hGH transgenic rats with obesity had high-

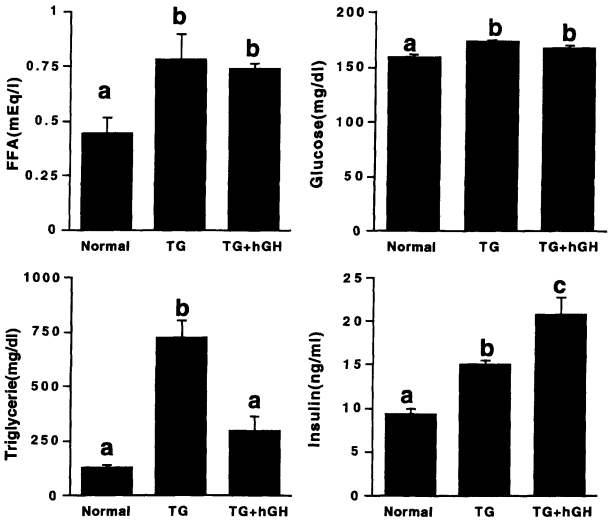

Fig. 1. The effects of pulsatile hGH treatment for 1 week on plasma glucose, insulin, triglyceride and FFA concentrations. Normal: nontransgenic littermates treated with a vehicle solution (n=3); TG: transgenic rats treated with a vehicle solution (n=3); TG + hGH: transgenic rats treated with hGH (100 μg/body) 4 times a day at 4 h intervals between 0700 and 1900 h for 7 days (n=3). Each column represents the mean ± SEM. Values having a different superscript are significantly different from each other ($P<0.05$).

er plasma triglyceride, FFA, glucose and insulin levels than their normal control littermates did. After hGH treatment, the plasma triglyceride concentration had noticeably decreased to 41% of the level in the non-treated transgenic rats, and this level was not significantly different from that in the normal controls. In contrast, the plasma insulin level increased to 138% of the level in the non-treated transgenic rats, and this level in the hGH treated transgenic animals was 222% of that in the normal controls. FFA and glucose levels did not change after treatment and these levels are significantly higher than those in the normal controls (Fig. 1).

Discussion

The hGH transgenic rats developed obesity and characteristics of insulin resistance. Since the effect of GH on the adipose tissue is generally known as lipolytic [1], this lipolytic effect of GH should be much attenuated in these transgenic rats due to both a low level of peripheral hGH and the absence of endogenous rGH pulses, and thus could induce obesity. It is known that monosodium glutamate (MSG) administration to neonatal rats alters GH secretory pattern to low and flat [7], and also induces obesity [8]. The coincidence observed in MSG-treated animals suggests that the low and constant levels of GH are responsible for the induction of obesity in our transgenic rats.

The pulsatile treatment of the transgenic rats with hGH noticebly decreased plasma triglyceride to almost normal levels and eliminated the major factor responsible for induction of obesity. The pulsatility in GH secretion seems to contribute substantially to the synthesis of triglyceride in the liver and uptake of triglyceride into the adipose tissue as a form of FFA, and thus could normalize the plasma concentration of triglyceride.

The pulsatile hGH treatment in this study increased plasma insulin levels. This enhancement of insulin level could be temporarily induced to compensate antagonistic GH action to insulin that induces hyper-glycemia [1].

Our present study showed that pulsatile GH could decrease the plasma triglyceride level. This indicates that pulsatile GH is important in modifying carbohydrate and lipid metabolism. The transgenic rats used in this study seems to be a good model to elucidate the mechanisms of GH action on carbohydrate and lipid metabolism.

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