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Effect of orally active growth hormone secretagogue, MK-677, on somatic growth in rats

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Effect of orally active growth hormone secretagogue, MK-677, on somatic growth in rats

Directed by Professor Ho-Seong Kim

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Medicine

Junghun Lee

December 2016

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This certifies that the Master's Thesis
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<Abstract>

Effect of orally active growth hormone secretagogue, MK-677, on somatic growth in rats

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(Directed by Professor Ho-Seong Kim)

Growth hormone secretagogues (GHSs) have been considered as alternative for the treatment of diseases related to growth hormone (GH) deficiency because of their ability to release GH in the body. As GH is a large peptide molecule, it must be injected into subcutaneous tissue or muscle to get it into the blood. However, some types of GHS can effectively stimulate GH release by administration through various routes such as intravenously, subcutaneously, intraperitoneally, and orally. The effects of MK-677, an orally active non-peptide mimic of GHS, on somatic growth were studied in rats. To confirm the GH stimulatory effect of MK-677, the concentration of serum GH was measured at regular intervals after oral administration of 0, 2, or 4 mg MK-677/kg. To investigate the growth-promoting effect of MK-677, body weight and body length were measured after oral administration of 4mg MK-677/kg for 6 weeks. Blood samples were collected from the tail vein every 2 weeks for insulin-like growth factor-I determination. After decapitation, tibia length and epiphyseal plate width were measured, and the pituitary gland and hypothalamus were collected and frozen for analysis of GH, GH releasing hormone, GHS receptor, somatostatin, and somatostatin receptor mRNA by real-time polymerase chain reaction. Oral administration of MK-677 at 4 mg/kg significantly increased peak GH concentrations by 1.8-fold, compared to baseline levels. However, oral administration of MK-677 at 4 mg/kg for 6 weeks did not increase the body length, body weight, width of tibia growth plate, and serum level of insulin-like growth factor-I. At 6 weeks after treatment, the GH response to oral administration of MK-677 was abolished. Pituitary GH mRNA and hypothalamic GHRH mRNA

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levels did not differ between the control and 6-week treatment groups. Treatment with MK-677 did not alter pituitary and hypothalamic GHSR mRNA expression. Somatostatin mRNA expression in the hypothalamus was markedly increased in the treatment group compare to in controls. In addition, somatostatin receptor-2 mRNA expression in the pituitary gland was decreased in the treatment group compare to the controls.

Although oral administration of MK-677 stimulated GH secretion, prolonged administration for 6 weeks attenuated the GH stimulatory effect of MK-677 and did not promote growth, which may be related to increased expression of somatostatin in the hypothalamus. Further studies are needed to overcome the desensitization of growth hormone-releasing peptide after the prolonged clinical treatment of growth disorders.

Key words: growth hormone secretagogues, treatment outcome, growth hormone, somatostatin

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Effect of orally active growth hormone secretagogue on somatic growth in rats

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I. INTRODUCTION

Growth hormone secretagogues (GHSs) have been considered as an alternative to treat diseases related to growth hormone (GH) deficiency because of their ability to release GH in the body.[1-3] GHSs enhance the pulsatile release of GH in the anterior pituitary gland with resulting sustained elevation in insulin-like growth factor (IGF)-I levels. As GH is a large peptide molecule, it must be injected into subcutaneous tissue or muscle to get it into the blood. However, MK-677, an orally active non-peptide mimic of GHSs, can stimulate the release of GH effectively by different ways such as intravenous, subcutaneous, intraperitoneal, and oral administration.[4,5] Growth hormone-releasing peptide (GHRP)-6, which is a synthetic hexapeptide, also shows potent GH-releasing activity after intravenous, subcutaneous, intranasal and oral administration in humans. MK-677 is a non-peptide spiropiperidine previously demonstrated to be functionally and mechanistically indistinguishable *in vitro* and *in vivo* from the potent peptide growth hormone secretagogue GHRP-6.[1] MK-677 elevates GH levels, as well as IGF-I and cortisol level in dogs after oral administration,[6] and this stimulatory effect depends on the presence of an intact pituitary.[7] Previous studies in humans demonstrated that daily oral administration of MK-677 in healthy elderly adults,[8] GH-deficient adults[9] for 4 weeks, and GH-deficient children[10] for 7 days increased serum GH, IGF-I, and IGF binding protein (IGFBP)-3 concentrations. Further, clinical trial studies of MK-677 have been conducted to improve body

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composition and metabolism in older adults[11] or increase bone mass.[12,13] However, the beneficial effect of MK-677 on growth promotion in children is controversial. The aims of this study were to investigate whether oral administration of MK-677 1) stimulates the secretion of serum GH and increases the serum level of IGF-I, 2) enhances the body length and width of the growth plate in rats, and 3) influences the mRNA expression of GH, GH-releasing hormone (GHRH), GHS receptor, somatostatin, and somatostatin receptor in the pituitary and hypothalamus.

I I. MATERIALS AND METHODS

1. Animals

The animals were allowed regular chow and water *ad libitum*, and were maintained at a temperature of 21 ± 2 ˚C and humidity of 60 ± 10% on 12-h light/dark cycles. Fermale Sprague-Dawley(SD) rats, approximately 4weeks of age,in each group were used for the experiment. The rats were fasted for 8 h before treatment and allowed water *ad libitum*. MK-677 was administered via a stomach tube, and blood samples were collected from the tail vein during the experiment, or from the heart after decapitation. Formulations of MK-677 were prepared at 1 mg/mL in distilled water. Distilled water was administered at 4 mL/kg as a placebo. All animal studies were approved by the Animal Care and Use Committee of the Yonsei University College of Medicine (No. 2013-0095).

2. Experimental design

A. Dose range study

To determine whether oral administration of MK-677 can stimulate GH secretion in rats, MK-677 was administered at 0, 2, or 4 mg/kg via the stomach tube. Distilled water was administered at the same volume as a placebo. Blood samples were collected from the tail vein at 0, 30, 60, 90, and 120 min after treatment. Plasma was harvested by centrifugation and stored in -70˚C for determination of GH. The same experiment was conducted after oral administration of 4 mg/kg MK-677 to determine

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whether the GH stimulatory effect was sustained after treatment with MK-677 for 6 weeks.

B. Efficacy of oral administration of MK-677 for 6 weeks

MK-677 was administered at 4 mg/kg via the stomach tube between 08:00- and 10:00 h for 6 weeks. Distilled water was administered at 4 mL/kg as a placebo. To evaluate the growth-promoting effect of MK-677, body weight and body length were measured daily. The body length of rats was measured as the length from the nose to the anus. Blood samples were collected from the tail vein every 2 weeks for determination of IGF-I. The width of the tibia growth palate was measured after decapitation at 6 weeks after treatment. Right tibia tissues were fixed in 4% paraformaldehyde for 24 h. Decalcification was performed with a EDTA-G solution (14.5 g EDTA, 1.25 g NaOH, and 15 mL glycerol dissolved in distilled water, pH 7.3. The solution was then brought to 100 mL and stored for 10–14 days at 4°C as previously described. The fixed and decalcified tibia was embedded in paraffin and sectioned at 5 μm. Paraffin bone sections were stained with hematoxylin and eosin (Sigma, St. Louis, MO, USA) according to the manufacturer's instructions.

C. Effect of MK-677 on expression of GH, GHRH, GHS receptor (GHSR), somatostatin, and somatostatin receptor mRNA in pituitary gland and hypothalamus

To determine whether MK-677 can alter GH, GHRH, GHSR, somatostatin, and somatostatin receptor mRNA expression, rats were sacrificed by decapitation at 6 weeks after treatment. The pituitary gland and hypothalamus were collected and frozen for analysis of GH, GHRH, GHSR, somatostatin, and somatostatin receptor mRNA by real-time polymerase chain reaction (RT-PCR).

3. Hormone analyses

All hormone analyses were performed by enzyme-linked immunosorbent assay (ELISA). GH was determined by ELISA(Elabscience Biotech, Wuhan, China) with a sensitivity of 0.188 ng/mL, intra-assay coefficient of variation of 3.87 - 5.15%, and inter-assay coefficient of variation of 7.04 - 8.45%.

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IGF-1 was determined by ELISA (Elabscience Biotech, Wuhan, China) with a sensitivity of 18.75 pg/mL, intra-assay coefficient of variation of 3.4 - 5.7%, and inter-assay coefficient of variation of 5.7 - 7.9%.

4. RT-PCR analysis

Total RNA was isolated from the cells using the Trizol reagent (Invitrogen, Carlsbad, CA, USA). Five micrograms of total RNA was subjected to reverse transcription using the Superscript TM III first-strand synthesis system (Invitrogen) according to the manufacturer's instructions. Real-time PCR was conducted in 20 μL of reaction mixtures containing cDNA, Taqman primer pairs, and Taqman universal PCR master mix (Applied Biosystems, Foster City, CA, USA). The primer pairs were obtained from Applied Biosystems (Rn01495894 for GH, Rn00580832 for GHRH, Rn00821417 for GHSR, Rn00561967 for somatostatin, Rn01464950 for somatostatin receptor-2, Rn02535169 for somatostatin receptor-5, Rn01775763 for GAPDH). Amplification was performed in duplicate with the ABI 7300 system (Applied Biosystems) with the following profile: 50°C for 2 min, 95°Cfor 10 min, and 40 cycles of 95°C for 15 s and 60°C for 1 min. The gene expression in each sample was expressed in terms of the threshold cycle (C_t) normalized to GAPDH (ΔC_t). The ΔC_t values were compared between samples from MK-677 treated tissues (hypothalamus and pituitary gland)and control samples, to calculate $\Delta\Delta C_t$. The final comparison of the transcript ratios between samples is given as $2^{-\Delta\Delta Ct}$.[14]

5. Statistical analyses

All statistical calculations were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Two-tailed *t* test was used to test for differences between the treatment group and controls. *P*-values <0 .05 were considered statistically significant.

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III. RESULTS

1. GH response to MK-677 at baseline and 6 weeks after treatment

Serum GH concentrations after oral administration of 2 and 4 mg/kg of MK-677 or placebo at baseline are shown in Fig.1A. Oral administration of MK-677 at 4 mg/kg significantly increased GH concentrations with a 1.8-fold increase in peak GH concentration (45.7 ng/mL), whereas administration of distilled water did not increase GH concentrations. The GH area under the curve (AUC) showed a similar significant increase after administration of 4 mg/kg of MK-677 compared to the distilled water control group (1090±00 vs. 206±00 ng/min/mL, $P<0.05$). The peak GH concentration was observed at 60 min after treatment and returned to near-pretreatment levels by 120 min. The increased response of GH after administration of MK-677 was abolished in animals treated with MK-677 for 6 weeks. Oral administration of MK-677 at 4 mg/kg in rats treated with MK-677 for 6 weeks did not increase the GH concentrations (Figure 1B).

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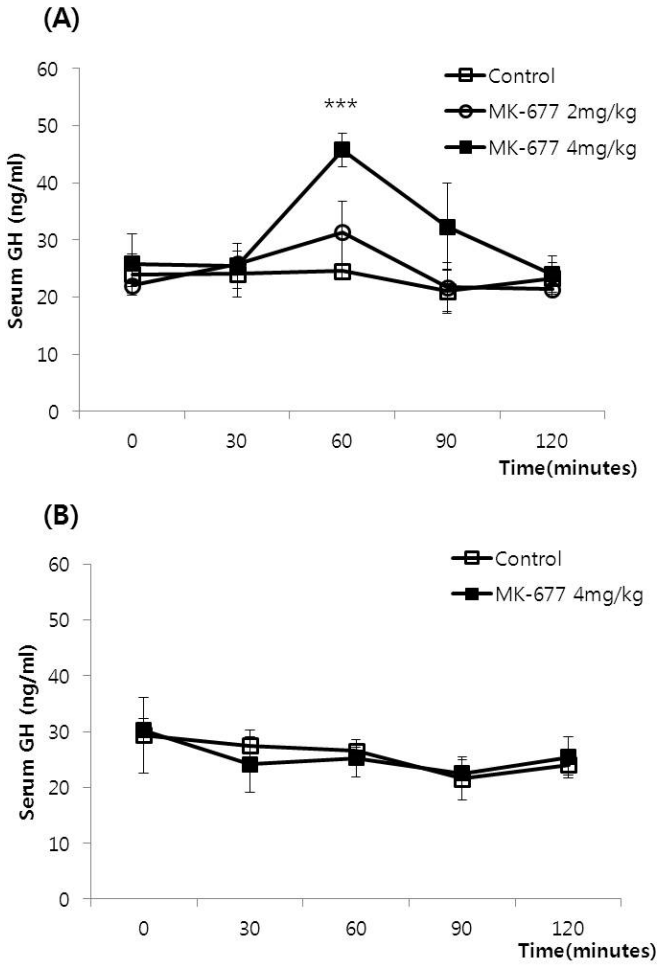

Figure 1.Serum GH levels after oral administration of MK-677. (A) Dose range study at baseline. MK-677 at 0, 2, and 4 mg/kg were administered. (B) MK-677 at 4 mg/kg was administered in rats after treatment of MK-677 for 6 weeks. n=4/treatment.*** $P<0.001$.

2. Efficacy of oral administration of MK-677 for 6 weeks

The treatment group showed no increase in body weight, body length, and width of the tibia growth plate at 6 weeks of MK-677 treatment, compared to the control group (Figure 2 A, B, C). Serum IGF-I levels at 2, 4, and 6 weeks were not changed compared to the level at baseline, and did not differ between the treatment group and control group at each time point (Figure 3).

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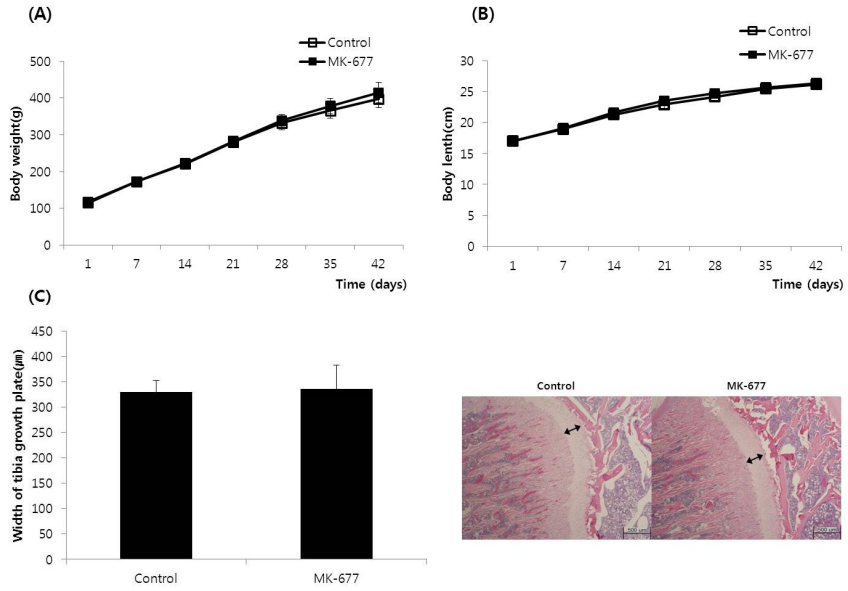

Figure 2.Efficacy of oral administration of MK-677 for 6 weeks.(A) Body weight, (B) body length, and (C) width of tibia growth plate. n=4/treatment.

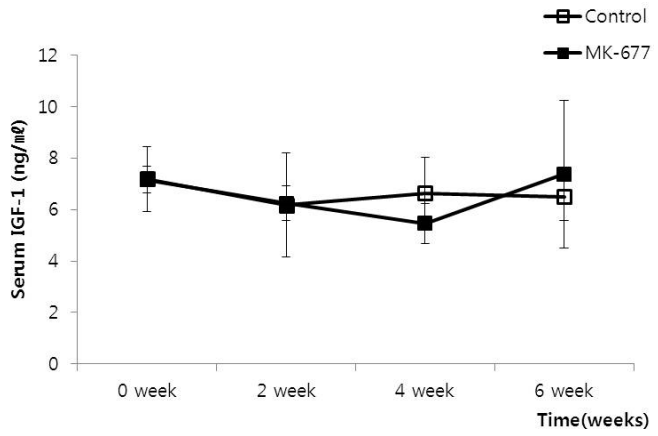

Figure 3.Serum IGF-I levels after oral administration of MK-677. n=4/treatment.

3. Effect of MK-677 on expression of GH, GHRH, GHSR, somatostatin, andsomatostatin receptor mRNA in pituitary gland and hypothalamus

Pituitary GH and hypothalamic GHRH mRNA levels did not differ between the control and treatment groups (Figure 4 A, B). Pituitary and hypothalamic GHSR mRNA expression did not differ between the control and treatment groups (Figure 4 C). Somatostatin mRNA expression in the

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hypothalamus was markedly increased in the treatment group compare to in the control group (Figure 4 D). In addition, somatostatin receptor-2 mRNA expression in the pituitary gland was decreased in the treatment group compare to in the control group (Figure 4 E).

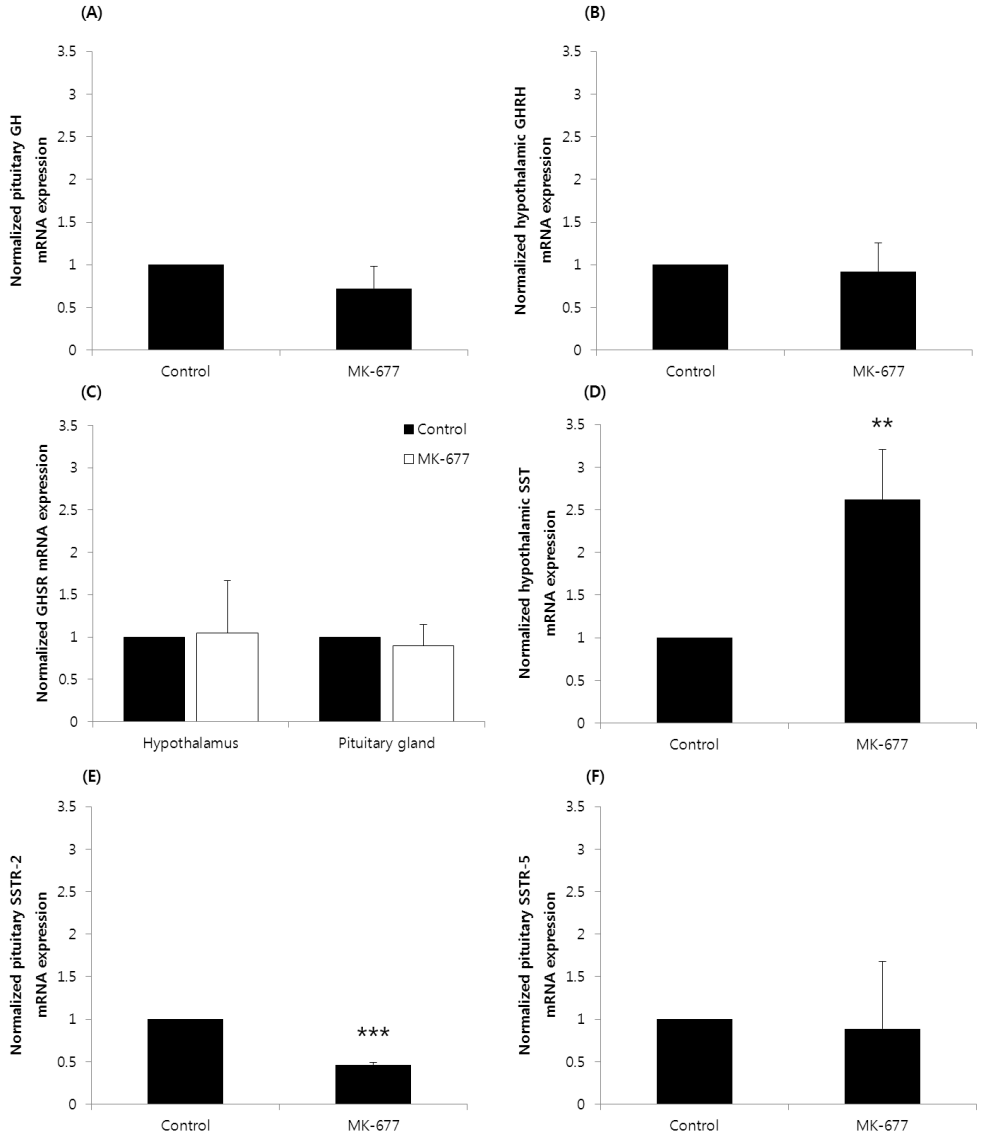

Figure 4. Effect of MK-677 on expression of GH, GHRH, GHS receptor (GHSR), somatostatin (SST), somatostatin receptor-2 (SSTR-2) and somatostatin receptor-5 (SSTR-5) mRNA in hypothalamus or pituitary gland. (A) Pituitary GH mRNA level, (B) hypothalamic GHRH mRNA level, (C) hypothalamic and pituitary GHSR mRNA level, (D) hypothalamic somatostatin mRNA level, (E) pituitary somatostatin receptor-2 mRNA level, (F) Pituitary somatostatin receptor-5 mRNA level. n=4/treatment.** P <0.01, *** P <0.001.

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I V. DISCUSSION

Secretion of GH in the pituitary gland is regulated by GHRH and somatostatin in the hypothalamus. GHRH stimulates the release of GH through the GHRH receptor, whereas somatostatin represses the release of GH through the somatostatin receptor.[15] In 1977, new synthetic peptides, with GH-releasing ability, were discovered.[16] These new compounds are enkephalin analogs, which have weak GH-releasing activity *in vitro* and are inactive *in vivo*. Subsequently, additional more potent GHRPs were developed by chemical modifications.[17] GHRPs have no sequential homology with GHRH and are more effective for inducing GH release even at the same dose of GHRH.[18] Many studies found that GHRPs have GH releasing activity in several species via their own receptors known as the GHS receptor, not the GHRH receptor.[19] GHRPs have several effective routes by intravenous, subcutaneous, intranasal and oral administration. Recently, to overcome the limit of low oral bioavailability, peptide-mimicking and non-peptidyl GHS, which can be administered orally, were developed. [4,5,20] SM-130686, an orally active non-peptidyl GHS, was developed and was confirmed to have GH-releasing activity. In rats, SM-130686 enhanced GH secretion and body weight gain.[20] Another non-peptidyl GHS, ibutamorenmesylate (MK-677), was reported to stimulate the release of GH, and showed an oral bioavailability of more than 60%.[4,18] Oral administration of MK-677 also elevates GH level, as well as IGF-I and cortisol level in dogs,[6]and this stimulatory effect is dependent on the presence of an intact pituitary.[7] In humans, daily oral administration of MK-677 in healthy elderly adults,[8]GH-deficient adults,[9] or GH-deficient children[10] increases serum GH, IGF-I, and IGFBP-3 concentrations, suggesting that these GHSs are potential treatments for growth disorders. However, repeated administration of GHRP has been reported to desensitize the stimulatory effect on GH secretion and there have been no studies of the growth promoting effect after long-term use, limiting clinical application.[21]

In our study, oral administration of 4 mg/kg of MK-677 increased the peak concentrations of serum

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GH by 1.8-fold compared to basal level and GH AUC was significantly increased, suggesting that oral administration of MK-677 has GH-releasing activity. However, the growth promoting effect assessed by measuring the body weight, body length, width of tibia growth plate, and serum level of IGF-I was not observed after oral administration of 4 mg/kg of MK-677 for 6 weeks. The desensitization phenomenon of GHRP has been reported previously.[22-26] In an animal study using transgenic growth-retarded rats, infusion of GHRP-6 for 7 days produced a dose-dependent increase in body weight gain, and accelerated of skeletal growth.[26] However, this growth promoting effect was observed only in the group infused with GHRP-6 at 3-h pulses. Continuous infusion of GHRP-6 was only effective in accelerating growth for the first 2 days of infusion, suggesting that the growth response with continuous infusion is transient because of desensitization. In normal female rats, continuous infusion of GHRP has been reported to induce tachyphlaxis after an initial increase in growth velocity, suggesting that continuous infusion of GHRP induce desensitization.[27] Repeated administration of hexarelin at 120-min intervals decreased the magnitude of the GH response in healthy adult males.[25] In our study, oral administration of MK-677 did not stimulate GH secretion after treatment for 6 weeks, suggesting that the initial GH stimulatory effect of MK-677 was abolished in animals treated with MK-677 for 6 weeks.

The mechanisms of GHRP desensitization after continuous infusion or long-term use have not been fully clarified. Many studies demonstrated that continuous infusion of GHRP did not alter GH stores and GHRH receptor expression in the pituitary gland, or GHRH expression in the hypothalamus.[22,23,26] The most direct and probable mechanism is the down regulation of GHSR in the pituitary gland and hypothalamus after treatment with GHRP. However, previous studies demonstrated that continuous infusion of GHRP-6 did not alter hypothalamic GHSR expression in arcuate and ventromedial nuclei,[28] or even increase arcuate GHSR expression.[26] The results of this study also showed that oral administration of MK-677 for 6 weeks did not alter pituitary GH mRNA and hypothalamic GHRH mRNA expression, or GHSR mRNA expression in the pituitary gland and hypothalamus. Another

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possible mechanism of desensitization induction is increased expression of somatostatin in the periventricular nucleus following continuous infusion of GHRP.[26, 29] In our study, somatostatin mRNA expression in the hypothalamus was markedly increased after treatment with MK-677 for 6 weeks, which inhibits GHRH- and GHS-induced GH secretion. In contrast, somatostatin receptor-2 mRNA expression in the pituitary gland was decreased, which may have resulted from elevated expression of somatostatin in the hypothalamus. Elevated somatostatin expression was reported to inhibit corticotropin releasing factor-induced ACTH secretion.[30] Moreover, GHRP activates the hypothalamo-pituitary-adrenal axis, [31] and elevated glucocorticoids interact with the GH control. Continuous infusion of GHRP-6 suppresses the corticosterone response to bolus injection of GHRP-6.[26] Additional studies investigating the effects of GHRP on hypothalamo-pituitary-adrenal axis, and its interaction with the GH axis, are necessary.

V. CONCLUSION

In conclusion, oral administration of GHS, MK-677 stimulates GH secretion. However, prolonged oral administration for 6 weeks did not promote growth and abolished the GH stimulatory effect of MK-677, which may have resulted from increased expression of somatostatin in the hypothalamus. Further studies are needed to develop a strategy for overcoming the increased expression of somatostatin, thereby leading to growth promotion.

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ABSTRACT(IN KOREAN)

성장호르몬 분비촉진제 경구투여에 의한 흰쥐에서의 신체성장 효과

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성장호르몬 분비촉진제 (growth hormone secretagogues,GHS)는 성장호르몬 분비를 자극하는 효과를 보이므로 성장장애 치료를 위한 대안으로 여겨진다. 성장호르몬은 크기가 큰 펩티드 분자이기에 이는 피하주사 혹은 근육주사로 투여 해야 한다. 하지만 성장호르몬 분비촉진제(growth hormone secretagogues,GHS)는 피하주사, 근육주사, 복강주사 혹은 경구투여로 성장호르몬분비를 촉진 시킬 수 있다. 성장호르몬 분비촉진제 MK-677 의 신체성장 효과를 흰쥐를 통하여 조사하였다. 성장호르몬 분비촉진제, MK-677 4 mg/kg를 경구로 투여하였을 때 성장호르몬 분비가 최대 1.5배 증가하는 것을 확인하였다. 그러나 6주 동안 흰쥐에 4mg/kg의 MK-677와 위약을 경구 투여하였을 때 신장, 체중, 정강이뼈 길이 모두 큰 차이가 없었으며,인슐린양 성장인자-I (insulin-like growth factor I, IGF-I)의 농도에도 차이가 없었다. 6주 동안 MK-677을 투여한 후에는 MK-677의 성장호르몬 분비 자극 효과가 소실되었다. MK-677을 6주 동안 투여한 후에는 뇌하수체의 성장호르몬 mRNA, 시상하부의 성장호르몬방출호르몬 mRNA와 뇌하수체와 시상하부의 성장호르몬 분비촉진제 수용체 mRNA 발현에는 영향을 주지 않았으나, 시상하부의 소마토스타틴 mRNA 발현이 증가되었다.성장호르몬 분비촉진제가 성장장애의 치료에 이용되기 위해서는 장기간 투여 시 나타나는 소미토스타틴 발현의 증가를 조절하는 방안에 대한 연구가 필요하리라 사료된다.

핵심되는말:성장호르몬 분비촉진제, 치료 효과, 성장호르몬, 소마토스타틴