Drugs of the Future 2005, 30(2): 124-127

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.02.880891

Pralmorelin

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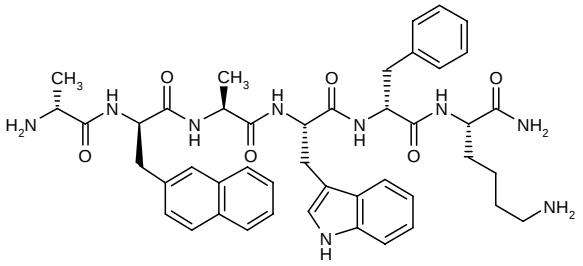
Diagnosis and Treatment of Growth Hormone Deficiency
Growth Hormone Secretagogue

Growth Hormone-Releasing Peptide 2
GHRP-2
GPA-748
KP-102
WAY-GPA-748

D-Alanyl-D-(2-naphthyl)alanyl-alanyl-tryptophyl-D-phenylalanyl-lysinamide



$C_{45}H_{55}N_9O_6$
Mol wt: 817.9971

CAS: 158861-67-7

CAS: 158827-34-0 (as dihydrochloride)

EN: 195636

Abstract

Growth hormone (GH) deficiency results in growth retardation. In addition to growth hormone-releasing hormone (GHRH), ghrelin has also been identfied as a potent stimulant of GH. The search for GH-releasing peptides and GH secretagogues resulted in the discovery of pralmorelin, a small synthetic peptide that mimics the action of ghrelin. In rats, pralmorelin was more potent in inducing the release of GH than GHRH, and it was also less sensitive to the inhibitory effects of somatostatin than GHRH. Body weight gain and increased food intake were observed in rats administered pralmorelin. In clinical studies, pralmorelin has been administered to children with short stature. Pralmorelin has also been evaluated in patients with prolonged critical illness, in which a characteristic wasting syndrome results from the suppressed pulsatile release of pituitary hormones. Pralmorelin synchronized the release of these hormones, and in combination with infusions of thyrotropin-releasing hormone (TRH) and GHRH, resulted in beneficial metabolic effects in these patients.

Introduction

Growth hormone (GH), or somatotropin, is vital for the control of growth and metabolism. GH deficiency can result from either a deficiency in the production of the hormone or in the target cell's response to the hormone, and results in growth retardation or dwarfism. GH release is stimulated by growth hormone-releasing hormone (GHRH) and also by a peptide hormone secreted from the stomach, known as ghrelin. Somatostatin inhibits GH release in response to GHRH and other stimulatory factors (1-3).

There are also alterations in the somatotropic index during the course of critical illness. Hyposomatotropism may be a factor in the pathogenesis of the wasting syndrome characteristic of the chronic phase of critically ill patients (4).

Research into GH-releasing peptides and GH secretagogues resulted in the development of a class of small synthetic peptides that mimic the action of ghrelin (5). One of these, pralmorelin (KP-102, GPA-748, GHRP-2), is a potent GH secretagogue in development as a diagnostic agent for growth hormone deficiency and for the treatment of pituitary disorders and GH deficiency. The potential of pralmorelin to enhance the recovery of patients with protracted critical illness has also been evaluated.

Pharmacological Actions

The pharmacological effects of pralmorelin have been evaluated *in vitro* and *in vivo*. *In vitro*, pralmorelin concentration-dependently increased the release of GH from

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cultured rat primary anterior pituitary cells. The potency of pralmorelin was less than that of GHRH. The GH-releasing activity of pralmorelin was also investigated in conscious, freely moving rats. Pralmorelin at doses of 10, 100 or 1000 μg/kg, increased plasma GH concentrations (C_{max} and AUC) significantly more than in the saline control group and a group administered GHRH. *In vivo*, therefore, the potency of pralmorelin was greater than that of GHRH. Under conditions of pentobarbital anesthesia whereby endogenous somatostatin secretion is decreased, the GH-releasing potency of both pralmorelin and GHRH was very similar. Furthermore, only pralmorelin was associated with GH release in conscious dogs. These findings indicate that pralmorelin is less sensitive to the inhibitory effect of somatostatin than GHRH. Other experiments in hypophysectomized rats and median eminence-lesioned rats indicated that the GH-releasing effect of pralmorelin involves a direct effect on the anterior pituitary and requires endogenous GHRH release (6).

The effects of pralmorelin on GH release were also investigated in monosodium glutamate-treated (growth-retarded) rats under pentobarbital anesthesia, in halothane-anesthetized rats with lesions in the bilateral hypothalamic arcuate nuclei (ARC) and in normal rats. Although plasma GH levels were significantly lower in the growth-retarded rats compared to normal rats after administration of pralmorelin (100 μg/kg i.v.), GH release was significantly increased in the growth-retarded rats administered pralmorelin compared to normal rats treated with saline. The GH release response to i.v. pralmorelin in rats with ARC lesions was also lower than in normal rats. Dose-related GH release was observed after the peptide was injected into the ARC in normal rats and intracerebroventricular (i.c.v.) administration produced a similar effect on GH release, supporting a direct central action for the drug (7).

In urethane-anesthetized rats, the stimulation of GH release by pralmorelin was found to be dependent upon the presence of GHRH. Also, the synergistic effect seen in combination with GHRH was suggested to be due to somatostatin antagonism (8).

Studies in hypophysectomized rats administered pralmorelin systemically demonstrated selective induction of c-*fos* expression in the ventromedial and ventrolateral regions of the ARC. Although the distribution of c-*fos*-expressing cells overlapped that of GHRH mRNA-containing neurons, but not somatostatin-containing neurons, only about one-fifth to one-fourth of the c-*fos* mRNA-containing neurons were GHRH neurons, while the rest were unidentified. These findings indicated that pralmorelin activates GHRH neurons and other unidentified cells in the ARC via a central effect to stimulate the release of GH (9).

Intracerebroventricular, but not systemic, administration of picomolar doses of pralmorelin or human GHRH to freely moving rats significantly increased food intake. The effect of GHRH, but not that of pralmorelin, was abolished by i.c.v. pretreatment with a GHRH antagonist. Moreover, combination of pralmorelin and GHRH significantly increased food intake compared to either treatment alone (10). A 6-day i.c.v. infusion of pralmorelin to both non-stressed and intermittently stressed rats also resulted in significantly increased food intake and body weight (11). However, the results from another study indicated that the stimulation of food intake by pralmorelin in rats was modified by fasting, restraint stress and i.c.v. somatostatin (12).

Toxicity

The general pharmacological effects of pralmorelin were investigated in mice, rats, guinea pigs, rabbits and beagle dogs. The effects of pralmorelin on the central nervous system, autonomic nervous system, smooth muscle, respiratory, cardiovascular and digestive systems and renal function were investigated *in vitro* and *in vivo*. Pralmorelin had no clinically significant effect on the central nervous, cardiovascular or respiratory systems at pharmacologically active doses. A small, transient increase in motility and contraction of isolated ileal segments was observed at high drug concentrations. Effects on the digestive system, renal function and blood were negligible. The results indicated that pralmorelin had no serious general pharmacological effects in these experimental animals (13).

Pharmacokinetics and Metabolism

The pharmacokinetics and pharmacodynamics of pralmorelin were evaluated in a phase I study in children with short stature who were undergoing evaluation for GH deficiency. A single i.v. dose (1 μg/kg) was administered to 10 children aged 4-12 years. Pharmacodynamic analysis indicated a linear and predictable drug concentration-*versus*-effect relationship. The mean EC_{50} was 1.09 ng/ml, representing the serum pralmorelin concentration associated with a 50% response as measured by the post-treatment increase in serum GH concentrations, and was significantly less than the C_{max} (7.4 ng/ml). Pharmacokinetics were best described by a biexponential function and were similar to those previously reported in healthy adult volunteers (14).

Clinical Studies

Pralmorelin was administered in an open-label, dose-escalating study to 6 prepubertal children with GH deficiency and growth failure. Doses of 0.3, 1.0 and 3.0 μg/kg/day were administered subcutaneously in successive 2-month periods. In the fourth 2-month period, pralmorelin 3.0 μg/kg/day was adminiistered concomitantly with 3.0 μg/kg/day GHRH. After each 2-month treatment period, GH increased acutely and dose-dependently in response to pralmorelin. However, the acute rise in GH concentration persisted for less than 2 h, and there was no effect on episodic GH concentrations later in the night. Growth velocities were higher during the 6 months of treatment than during the baseline or follow-up periods

(mean 5.3 cm/year *vs.* 3.0 and 3.3 cm/year, respectively). The treatment was well tolerated (15).

The effects of pralmorelin were evaluated in 15 children aged 5-14 years with short stature. The drug was administered intranasally at doses of 5-15 μg/kg twice daily for 3 months, then 3 times daily. The children were treated for a total period of 6 months, with 6 children continuing for a total of 18-24 months. The growth rate increased significantly in most children, from a mean of 3.7 cm/year pretreatment to 6.1 cm/year at 6 months and 6.0 cm/year at 18-24 months. GH-binding protein concentrations also increased significantly, from 439 pmol/l at baseline to 688 pmol/l after 6 months. These changes were correlated with the increase in growth velocity at 6 months. The modest increase in growth rate observed in this study was not associated with any clinically significant changes in routine laboratory parameters (16).

The effects of oral pralmorelin on appetite and body weight have also been evaluated. Pralmorelin 900 μg/kg b.i.d. was administered for 12 months to 10 prepubertal children with GH deficiency. Seven children reported a significant increase in appetite during the first 6 months of the study. Although there was a tendency for body mass index (BMI) to increase during the study, no statistically or clinically significant effect was seen (17).

The GH secretory response to an acute dose of 2 μg/kg pralmorelin was compared in 11 patients with GH deficiency due to a mutation of the GHRH receptor gene and 8 normal volunteers. The basal and stimulated levels of GH were significantly reduced in subjects with the mutation, whereas basal and stimulated levels of prolactin and cortisol were similar in both groups. The presence of a reduced but detectable GH response indicated that there was at least a partial direct action of pralmorelin on somatotroph cells *in vivo* (18).

An assessment of serum concentrations of GH, thyrotropin and prolactin in patients with prolonged critical illness showed that infusion of pralmorelin (1 μg/kg/h for 21 h) synchronized the release of these hormones from the anterior pituitary. This synchronizing effect was not observed following infusion of either GHRH or thyrotropin-releasing hormone (TRH) (19).

Another study in 33 men with prolonged critical illness showed that the combined administration of pralmorelin, TRH and GHRH resulted in beneficial metabolic effects which were not observed following infusion of pralmorelin alone. A 5-day infusion of pralmorelin with TRH to 14 critically ill patients also demonstrated reactivation of GH and TRH, with a shift towards anabolic metabolism. These and other studies demonstrated the beneficial effects of pralmorelin on the metabolic condition of patients with protracted critical illness (20-22).

Pralmorelin was launched in Japan just recently as a diagnostic agent for growth hormone deficiency and is undergoing phase II clinical evaluation for the treatment of short stature (23).

Source

Kaken Pharmaceutical Co., Ltd. (JP).

References

1. Devesa, J., Lima, L., Tresguerres, J.A.F. *Neuroendocrine control of growth hormone secretion in human.* Trends Endocrinol Metab 1992, 3: 175-83.

2. de Boer, H., Block, G.-J., Van der Veen, E.A. *Clinical aspects of growth hormone deficiency in adults.* Endocr Rev 1995, 16: 63-86.

3. Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., Kangawa, K. *Ghrelin is a growth-hormone-releasing acylated peptide from stomach.* Nature 1999, 402: 656-60.

4. Van den Berghe, G. *Growth hormone secretagogues in critical illness.* Horm Res 1999, 51(Suppl. 3): 21-8.

5. Huang, P., Loew, G.H., Funamizu, H. et al. *Rational design, discovery, and synthesis of a novel series of potent growth hormone secretagogues.* J Med Chem 2001, 44: 4082-91.

6. Doi, N., Hirotani, C., Ukai, K. et al. *Pharmacological characteristics of KP-102 (GHRP-2), a potent growth hormone-releasing peptide.* Arzneim-Forsch Drug Res 2004, 54: 857-67.

7. Nakagawa, T., Ukai, K., Ohyama, T., Koida, M., Okamura, H. *Effects of the synthesized growth hormone releasing peptide, KP-102, on growth hormone release in sodium glutamate monohydrate-treated low growth rats.* Life Sci 1996, 59: 705-12.

8. Sawada, H., Sugihara, H., Onose, H., Minami, S., Shibasaki, T., Wakabayashi, I. *Effect of D-Ala-D-β Nal-Ala-Trp-D-Phe-Lys-NH_2 (KP-102) on GH secretion in urethane-anesthetized rats.* Regul Pept 1994, 53: 195-201.

9. Kamegai, J., Hasegawa, O., Minami, S., Sugihara, H., Wakabayashi, I. *The growth hormone-releasing peptide KP-102 induces c-fos expression in the arcuate nucleus.* Mol Brain Res 1996, 39: 153-9.

10. Okada, K., Ishii, S., Minami, S., Sugihara, H., Shibasaki, T., Wakabayashi, I. *Intracerebroventricular administration of the growth hormone-releasing peptide KP-102 increases food intake in free-feeding rats.* Endocrinology 1996, 137: 5155-8.

11. Kuriyama, H., Hotta, M., Wakabayashi, I., Shibasaki, T. *A 6-day intracerebroventricular infusion of the growth hormone-releasing peptide KP-102 stimulates food intake in both non-stressed and intermittently-stressed rats.* Neurosci Lett 2000, 282: 109-12.

12. Shibasaki, T., Yamauchi, N., Takeuchi, K., Ishii, S., Sugihara, H., Wakabayashi, I. *The growth hormone secretagogue KP-102-induced stimulation of food intake is modified by fasting, restraint stress, and somatostatin in rats.* Neurosci Lett 1998, 255: 9-12.

13. Furuta, S., Shimada, O., Doi, N., Ukai, K., Nakagawa, T., Watanabe, J., Imaizumi, M. *General pharmacology of KP-102 (GHRP-2), a potent growth hormone-releasing peptide.* Arzneim-Forsch Drug Res 2004, 54: 868-80.

14. Pihoker, C., Kearns, G.L., French, D., Bowers, C.Y. *Pharmacokinetics and pharmacodynamics of growth hormone-releasing peptide-2: A phase I study in children.* J Clin Endocrinol Metab 1998, 83: 1168-72.

15. Mericq, V., Cassorla, F., Salazar, T., Avila, A., Iñiguez, G., Bowers, C.Y., Merriam, G. *Effects of eight months treatment with graded doses of a growth hormone (GH) releasing peptide in GH-deficient children.* J Clin Endocrinol Metab 1998, 83: 2355-60.

16. Pihoker, C., Badger, T.M., Reynolds, G.A., Bowers, C.Y. *Treatment effects of intranasal growth hormone releasing peptide-2 in children with short stature.* J Endocrinol 1997, 155: 79-86.

17. Mericq, V., Cassorla, F., Bowers, C.Y., Avila, A., Gonen, B., Merriam, G.R. *Changes in appetite and body weight in response to long-term oral administration of the ghrelin agonist GHRP-2 in growth hormone deficient children.* J Pediatr Endocrinol Metab 2003, 16: 981-5.

18. Gondo, R.G., Aguiar-Oliveira, H., Hayashida, Y. et al. *Effects of acute administration of GHRP-2 in subjects with growth hormone deficiency due to mutation of the GHRH receptor gene.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1999.

19. Van den Berghe, G., Wouters, P., Bowers, C.Y., de Zegher, F., Bouillon, R., Veldhuis, J.D. *Growth hormone-releasing peptide-2 infusion synchronizes growth hormone, thyrotrophin and prolactin release in prolonged critical illness.* Eur J Endocrinol 1999, 140: 17-22.

20. Van den Berghe, G., Baxter, R.C., Bowers, C.Y., Iranmanesh, A., Veldhu *combined administration of GH relea TRH and GnRH to men with prolon superior endocrine and metabolic effe with GHRP-2 alone.* Clin Endocrinol 2

21.Van den Berghe, G., Wouters, P., Baxter, R.C., Veldhuis, J.D., Bow *Reactivation of pituitary hormone improvement by infusion of growth h and thyrotropin-releasing hormone i critical illness*. J Clin Endocrinol Metal

22. Van den Berghe, G., Wouters, P., Bouillon, R., Bowers, C.Y. *Leptin leve ness: Effects of growth hormone secre releasing hormone.* J Clin Endocrinol

23. *Kaken launches GHRP K* DailyDrugNews.com (Daily Essentials