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Growth Hormone Response in Man to L-692,429, a Novel Nonpeptide Mimic of Growth Hormone-Releasing Peptide-6

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ABSTRACT

L-692,429, a substituted benzolactam, is a novel nonpeptide mimic of the GH secretagogue, GH-releasing peptide-6. The safety and GH secretory activity of L-692,429 (0.001–1.0 mg/kg, iv) were investigated in 24 healthy nonobese young (18–26 yr old) male volunteers who demonstrated a GH response of 7 μg/L or more after 1 μg/kg, iv, GH-releasing hormone [GH-releasing hormone-(1–29)NH_2]. L-692,429 was administered as a 15-min iv infusion in an incremental dose, double blind, placebo-controlled, alternating panel fashion to 3 panels of 8 subjects each. Dose-dependent GH secretion was observed with a threshold dose of 0.05 mg/kg (4 of 6 subjects responded with peak GH >7 μg/L), and 0.2 mg/kg produced a response in all 14 subjects tested (mean ± SE peak GH, 41.0 ± 6.3 μg/L). The maximum dose of 1.0 mg/kg L-692,429 resulted in a pronounced GH response (peak GH, 82.5 ± 14.9 μg/L; n = 8). The GH peak was seen 30–45 min after initiation of the infusion. Small transient increases in cortisol and PRL were observed (increases in cortisol averaged 182.1 ± 33.1 nmol/L and peak PRL was 21 ± 2.6 μg/L after 1.0 mg/kg L-692,429, respectively), whereas no significant changes occurred in LH, FSH, TSH, insulin, or glucose concentrations. Plasma pharmacokinetic analysis revealed dose-related increases in plasma concentrations of L-692,429 and a half-life of 3.8 ± 0.2 (±SE) h, a plasma clearance of 214 ± 67 mL/min, and a steady state volume of distribution of 14.2 ± 4.8 L. Facial flushing or a warm sensation were reported in 4 subjects, primarily at dose levels of 0.2 mg/kg L-692,429 or more, but no other clinical or laboratory adverse experiences appeared related to drug treatment. L-692,429, synthesized as a specific nonpeptide mimic of GH-releasing peptide-6, is thus a well tolerated, highly effective, and selective GH secretagogue in man. (*J Clin Endocrinol Metab* **77:** 1393–1397, 1993)

THE SYNTHESIS and investigation of nonpeptide antagonists of peptide hormone receptors have accelerated since the demonstration of selective, high affinity, nonpeptide antagonists of cholecystokinin (1, 2). Such antagonists have subsequently been reported, for example, for the receptors of substance-P (NK_1 receptor) (3) and angiotensin-II (4). These receptor antagonists are useful as probes for revealing the physiological role of their respective hormonal agonists in animals and humans (2, 5, 6) and may yield therapeutic advances.

However, other than the synthetic and semisynthetic agonists that act at the receptors for the endogenous opioid peptides (7), specific, high affinity, nonpeptide mimics of peptide agonists have not been reported thus far. The present study reveals the biological activity in man of L-692,429, a substituted benzolactam (8), which is functionally indistinguishable *in vitro* (9–11) and in animals (11, 12) from the GH secretagogue GH-releasing peptide (GHRP-6; His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) (13–23).

GHRP-6 has been demonstrated to be a potent, reasonably selective, GH secretagogue in all species tested (13–15), including humans (17–23). Marked increases in GH concentrations were evident in young men over the iv dose range of 0.1–1.0 μg/kg, without effects on LH, FSH, TSH, insulin, or glucose concentrations.

GHRP-6 acts synergistically with GH-releasing hormone (GHRH) to release GH in cultured rat pituicytes (16) and in humans (18). Several additional lines of evidence indicate that GHRP-6 acts via receptors and signaling mechanisms distinct from those of GHRH (16, 24–28). GHRP-6 does not increase cAMP alone, but does act synergistically with GHRH to increase cAMP. Peptide antagonists have been synthesized that specifically block the activity of either GHRH or GHRP-6, but not the other, and each peptide rapidly causes homologous, but not heterologous, desensitization.

L-692,429 ([3(*R*)-amino-3-methyl-*N*-(2,3,4,5-tetrahydro-2-oxo-1)-(2′-(1H-tetrazol-5-yl)-(1,1′-biphenyl)4-yl][*methyl*-1H-1-benzazepin-3yl]butanamide, mono(hydrochloride), dihydrate) was synthesized to mimic the effects of GHRP-6 (9–12). Except for somewhat lower potency (EC_{50} for GH release, 60 *vs.* 10 nmol/L for GHRP-6 in isolated rat pituicytes) (10), L-692,429 and GHRP-6 have been functionally indistinguishable in preclinical investigations (9–12). There may be advantages to a small organic molecule that could effectively reproduce the actions of this peptide agonist. The present study was undertaken to assess the safety, tolerability, and GH secretory activity of L-692,429 in young nonobese healthy male volunteers.

Subjects and Methods

Study subjects

Male volunteers (age range, 18–26 yr) were recruited by means of local advertisements and provided written informed consent. The pro-

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tocol was approved by the Institutional Review Board of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. All subjects were in good general health, based on medical history, physical examination, and routine clinical laboratory testing.

Each subject (n = 30) first underwent a screening test for GH response to GHRH [1 μg/kg iv bolus; GHRH-(1–29)NH_2, GEREF] in the early morning after an overnight fast. Only subjects with a peak GH response of 7 μg/L or more were admitted to the study (n = 24). These subjects were required to be within 15% of ideal body weight based on the Metropolitan Life Insurance Co. tables [body mass index, 21.8 ± 3.3 (± SD) kg/m^2].

Study design

Participants were divided into three panels (A–C) of eight subjects each. L-692,429 was administered in an incremental dose, alternating panel, double blind, placebo-controlled fashion. Dosing was performed in the early morning (~0800–0900 h) after a fast from all food and liquid except water since the previous midnight. Panel A received 0, 0.001, 0.005, 0.02, and 0.1 mg/kg; panel B received 0, 0.002, 0.01, 0.05, and 0.2 mg/kg; and panel C received 0, 0.2, 0.5, and 1.0 mg/kg. On any given treatment day, six of eight subjects received active drug, and two received saline placebo iv over 15 min.

Outcome variables

Serum was collected at 10 and 0 min before treatment for hormone assays, and the results were averaged to yield baseline values. Blood was collected at intervals over the 4 h after treatment for determination of GH and at selected dose levels (0.1, 0.2, and 1.0 mg/kg L-692,429) for assay of LH, FSH, TSH, PRL, cortisol, insulin, and glucose concentrations. In six subjects treated with 1.0 mg/kg L-692,429, serum samples were available for insulin-like growth factor-I (IGF-I) determination immediately before treatment and 24 h after treatment.

Plasma samples were also collected at specified time points from selected treatment periods for measurement of L-692,429 concentration by high pressure liquid chromatography with fluorescence detection after a solid phase extraction using a cyanopropyl cartridge (29). The assay was linear over the 0.5–50 ng/mL concentration range. The limit of reliable detection was 0.5 ng/mL, and variability (coefficient of variation) was, at most, 6.6% (>0.5–50 ng/mL). The plasma area under the concentration *vs.* time curve for 0–4 h (AUC_{0-4h}) was calculated using the modified trapezoidal method (30). The terminal half-life was calculated as the quotient of the ln(2) and the terminal elimination rate constant. The elimination rate constant was estimated by regression of the terminal log linear concentration time points. The steady state volume of distribution was estimated according to previously reported methods (31).

Subject safety was monitored by clinical observation, including frequent assessment of vital signs. Routine clinical hematology and chemistries, urinalysis, and electrocardiograms were obtained before and 24 h posttreatment and again 5–7 days after the study.

All hormone assays were performed by Nichols Institute (San Juan Capistrano, CA). GH was assayed by the double antibody RIA method (32, 33) using WHO-1 International Reference Preparation (66/217) as the standard. The limit of assay sensitivity was reported to be 0.5 μg/L. Intra- and interassay variabilities were 8.9% and 10.7% at 1.9 μg/L and 3.3% and 6.2% at 15.8 μg/L, respectively. Samples with GH concentrations greater than 50 μg/L were diluted as appropriate with human serum and reassayed. All samples from a given treatment period for any subject were run as a single batch. All other hormone assays were performed by RIA according to established methods at Nichols Institute. IGF-I measurements were made on extracted serum from six subjects treated with the maximum dose of L-692,429.

Statistical methods

GH and other hormones. Peak concentration (C_{max}) and AUC_{0-4h} were computed for GH, PRL, LH, glucose, and insulin. Peak concentrations and cortisol, FSH, and TSH AUCs were computed on the basis of change from pretreatment baseline because there were significant differences in these baseline values for the same subjects in different periods. These variables for all hormones and glucose were analyzed using analysis of variance (ANOVA) appropriate for a rising dose, alternating panel design, which included the factors panel, subject within panel, and dose within panel. For GH data only, a linear contrast with active dose levels on the log scale was used to test for possible dose-dependent relationships within each panel. Within each panel, *t* tests were used to make pairwise comparisons of mean responses to the L-692,429 dose and the placebo. The standard ANOVA assumptions of common variance and normality were tested with Hartley's Fmax test and the Shapiro-Wilk test, respectively.

Plasma concentrations of L-692,429. Correlations of C_{max} for L-692,429 and L-692,429 AUC_{0-4h} with peak GH and AUC_{0-4h} for GH were computed. First, ANOVA was used to adjust individual determinations of C_{max} and AUC_{0-4h} for L-692,429, as well as peak and AUC_{0-4h} for GH for the panel and subject within panel effects. The correlations of mean C_{max} and L-692,429 AUC_{0-4h} residuals with the mean peak GH and AUC_{GH} residual, respectively, were computed to verify that, on the average, increases in peak GH and AUC_{GH} were dependent upon increases in plasma L-692,429 concentrations caused by increases in dose. Also, residuals from the ANOVA model with the factors panel, subject within panel, and dose within panel for peak GH and AUC_{GH} were correlated with residuals from the same model for C_{max} and L-692,429 AUC_{0-4h}. A positive association between the residuals of peak GH with C_{max} and AUC_{GH} and L-692,429 AUC_{0-4h} would indicate that the GH secretory response of a subject to independent administrations of the same dose was related to the plasma concentration after administration.

Results

GH

The peak GH concentration and AUC_{0-4h} for GH after doses equal to or greater than 0.02 mg/kg L-692,429, placebo, and GHRH (1 μg/kg) are presented in Table 1. The time course of the GH response to L-692,429 is illustrated for panel C in Fig. 1. A similar time course for the GH response to L-692,429 was evident at the lower doses as well (data not shown). The peak GH response was evident within 15–30 min after completion of the infusion. Dose-dependent stimulation of GH secretion was present from the apparent threshold dose of 0.05 mg/kg (four of six subjects responding, with a response defined as a peak GH ≥7 μg/L) up to 1.0 mg/kg, with no apparent plateau response reached over the dose range investigated. All subjects given doses of 0.2 mg/kg L-692,429 or more demonstrated peak GH values greater than 10 μg/L.

TABLE 1. GH response to L-692,429 and GHRH

Dose	n[a]	GH peak (μg/L)[b]	GH AUC (μg/min·L)[b]
L-692,429 (mg/kg)			
0.00	24	2.0 ± 0.5	283 ± 41
0.02	6	2.4 ± 1.3	280 ± 79
0.05	6	9.0 ± 3.0[c]	564 ± 235[d]
0.10	6	10.3 ± 6.0[c]	685 ± 281[c]
0.20	14	39.9 ± 6.3[c,e]	2595 ± 493[c,e]
0.50	8	60.8 ± 7.3[c]	4189 ± 523[c]
1.00	8	82.5 ± 14.9[c,f]	6786 ± 1410[c,f]
GHRH (μg/kg)			
1.00	24	24.1 ± 5.9[c]	1134 ± 189[c]

The peak and integrated (AUC_{0-4h}) GH response to L-692,429, placebo, and GHRH are shown.

[a] Number of subjects tested.

[b] Geometric mean ± geometric between-subject SE.

[c] $P < 0.01$ for within-subject comparison to placebo.

[d] $P < 0.05$ for within-subject comparison to placebo.

[e] $P < 0.05$ *vs.* all doses of 0.1 mg/kg or less.

[f] $P < 0.05$ *vs.* all doses of 0.2 mg/kg or less.

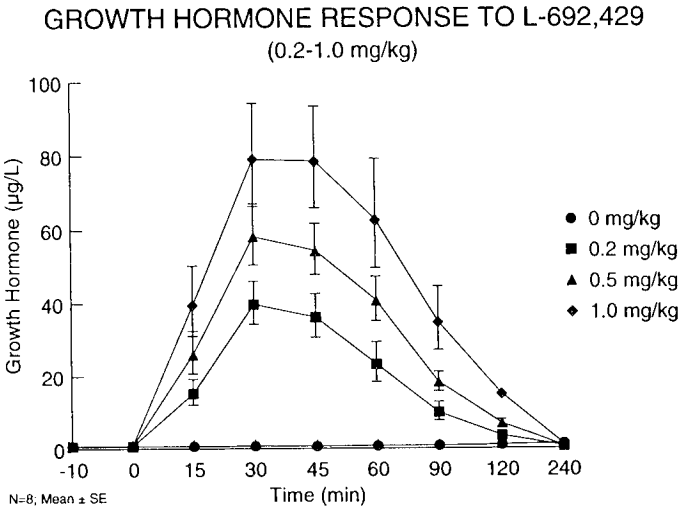

FIG. 1. Time course of the GH response to L-692,429. ●, Placebo; ■, 0.2 mg/kg; ▲, 0.5 mg/kg; ◆, 1.0 mg/kg L-692,429. Values are the geometric mean ± geometric between-subject SE (n = 8).

TABLE 2. PRL and cortisol responses to L-692,429

L-692,429 dose (mg/kg)	n	Peak PRL (µg/L)[a]	PRL AUC_{0-4h} (µg/min·L)[a]	Peak change in cortisol (nmol/L)[b]	AUC_{0-4h} change from baseline in cortisol (µmol/min·dL)[c]
0.0	19	7.4 ± 0.8	757 ± 73	45.0 ± 30.3	1.63 ± 3.40
0.1	6	8.5 ± 1.9	793 ± 167	163.3 ± 79.5	5.79 ± 6.70
0.2	6	21.1 ± 3.3[d]	1,665 ± 208[d]	253.0 ± 72.3[d]	16.17 ± 8.66[d]
1.0	7	21.3 ± 2.6[d]	1,533 ± 212[d]	181.3 ± 32.8[e]	11.62 ± 2.95[e]

[a] Geometric mean ± geometric between-subject SE.
[b] Mean change from predose baseline ± between-subject SE.
[c] Mean AUC using predose average values as baseline ± between subject SE.
[d] $P < 0.01$ for within-subject comparison to their placebo response.
[e] $P < 0.05$ for within-subject comparison to their placebo response.

Cortisol and PRL

There were small transient increases in cortisol and PRL after L-692,429 treatment (Table 2). Although there were significant treatment-related increases in these hormone levels, the dose dependency was less then that for GH, in that maximum effects on PRL and cortisol were evident at 0.2 and 0.1 mg/kg L-692,429, respectively. Both cortisol and PRL concentrations returned to baseline in all subjects by 2 h posttreatment.

Other hormones

There were no significant changes from baseline or differences from placebo in LH, FSH, TSH, insulin, or glucose concentrations over the 4-h interval after even the maximum (1.0 mg/kg) dose of L-692,429 (data not shown). IGF-I concentrations did not change significantly 24 h after treatment with 1.0 mg/kg L-692,429 (mean change, −23 ng/mL; n = 6; P = NS).

Plasma concentrations of L-692,429

Dose-related increments in plasma concentrations of L-692,429 were detected over the 0.005–1.0 mg/kg dose range. Mean plasma concentrations at the end of the 15-min infusion (C_{max}), the 4-h integrated plasma concentrations (AUC_{0-4h}), and the mean plasma concentration *vs.* time curves for the higher dose levels are provided in Table 3 and Fig. 2, respectively. As expected, there was an association between L-692,429 C_{max} and peak GH response, and AUC_{0-4h} for GH and AUC_{0-4h} for L-692,429. However, after adjusting for panel, subject within panel, and dose within panel effects, the correlation of the GH and L-692,429 plasma concentration variables was not significant. This indicates that for the same dose level, individual subject responses were highly variable.

The plasma half-life of L-692,429 (at 1.0 mg/kg) was 3.8 ± 0.2 (±SD) h, with a plasma clearance of 214 ± 67 mL/min and a steady state volume of distribution of 14.2 ± 4.8 L. Comparing Figs. 1 and 2, it appears that L-692,429 produces a rapid rise in plasma GH concentrations, which then decay despite the continued presence of substantial concentrations of L-692,429 in plasma.

Safety

L-692,429 was well tolerated by these healthy subjects. There were no clinically significant abnormalities noted during frequent monitoring of vital signs or in serial complete blood counts, serum chemistries, urinalyses, or electrocardiograms. Clinical adverse experiences considered possibly or likely drug related included flushing or a warm sensation observed in four subjects. Except in one circumstance at a dose of 0.005 mg/kg, all such instances occurred at L-692,429 levels of 0.2 mg/kg or more and did not occur after placebo administration. Occasional episodes of headache, nausea, or urinary urgency were reported, but had no relation to the L-692,429 dose level.

TABLE 3. Plasma concentrations of L-692,429

Dose of L-692,429 (mg/kg)	n[a]	Cmax (ng/mL)[b]	AUC_{0-4h} (ng/min·mL)[a]
0.005	6	34.7 ± 11.8	1,023 ± 351
0.010	6	74.1 ± 6.0	2,089 ± 673
0.100	6	871.0 ± 137.5	26,915 ± 8,458
0.200	8	1,412.5 ± 255.9	40,738 ± 6,894
0.500	4	3,630.8 ± 503.2	107,152 ± 24,955
1.000	6	6,025.6 ± 1,626.7	177,828 ± 56,693

[a] Number of subjects.
[b] Geometric mean ± geometric between-subject SD.

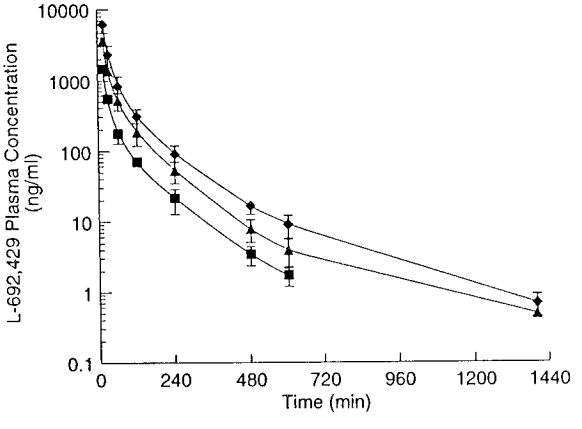

FIG. 2. Plasma concentrations of L-692,429 after iv L-692,429. Values are the mean ± SE (n = 4–8). ■, 0.2 mg/kg; ▲, 0.5 mg/kg; ◆, 1.0 mg/kg L-692,429.

Discussion

L-692,429 was demonstrated to be a highly effective and reasonably selective GH secretagogue in healthy young nonobese males. Dose-dependent increases in circulating GH concentrations were evident over the 0.05–1.0 mg/kg iv dose range. L-692,429 is, thus, the first specifically designed nonpeptide mimic of a peptide agonist that has demonstrable activity in humans. The peptide GHRP-6 shares functional identity with L-692,429 in numerous preclinical assay systems. L-692,429 is specific, having only modest influences on PRL and cortisol levels, without influencing the release of any other anterior pituitary hormones. Furthermore, the magnitude of GH concentrations achieved with the maximum dose of L-692,429 studied (1.0 mg/kg) suggests that it is one of the most active secretagogues available. Thus, L-692,429 could prove therapeutically useful as an alternative to GH or GHRH for the treatment of GH-deficient children or adults.

Although only GH concentrations, and not secretion rates, were measured in this study, it is reasonable to assume that L-692,429 is influencing circulating GH levels by stimulating pituitary secretion. The *in vitro* data clearly demonstrate the direct secretory capacity of L-692,429 (9, 10). Whether there is an additional effect on GH clearance cannot be ascertained from the current data. The shape of the serum GH concentration *vs.* time curves suggests a rapid stimulus to GH secretion followed by a decay consistent with the reported serum half-life for GH of about 20 min (34). The variability of the GH response among individuals for a given dose of L-692,429 may reflect a varying influence of somatostatin. Somatostatin is capable of inhibiting the release of GH in response to L-692,429 in rat pituicytes (10). The lack of a plateau for dose-dependent GH secretion in humans suggests that higher doses of L-692,429 might produce even greater GH release. Higher doses were not investigated in the present study because of limitations imposed by the dose range investigated in the preclinical toxicology assessment.

L-692,429 was studied parenterally to insure bioavailability and permit an unequivocal test of the hypothesis that it would behave in a fashion similar to GHRP-6 in humans. GHRP-6 is active in humans whether it is given iv (17, 18), intranasally (20, 21), or orally (22), although the latter route of administration is only approximately 0.3% as effective as the iv route, presumably due to limited bioavailability.

Like GHRP-6, L-692,429 produced small increases in cortisol and PRL (18). The former appeared to reach a maximum mean increase above baseline of about 181 nmol/L (6.6 μg/dL) at the maximum dose of 1.0 mg/kg L-692,429, with similar increases over the 0.1–1.0 mg/kg dose range. The PRL response was maximal after 0.2 mg/kg L-629,429. This increase in PRL may reflect stimulation of somatomammotrophs by L-692,429, and the increase in cortisol may be the result of an increase in ACTH (12). The increases in both cortisol and PRL were transient and of a magnitude similar to that observed after such physiological stimuli as exercise, mental stress, or sleep (35–37). The absence of effects on any other anterior pituitary hormones indicates the specificity of this compound.

The mechanism of action of GHRP-6 and L-692,429 has not been fully defined, but may involve protein kinase-C (11, 28). The finding that GHRP-6 and L-692,429 produce depolarization of somatotrophs and facilitate an influx of calcium (38–40) suggests that these agents behave as functional antagonists of somatostatin at the level of the pituitary. However, there may also be hypothalamic effects involving GHRH release. The suggestion of specific GHRP-6 receptors at both the pituitary and hypothalamic level would support a multiplicity of actions (24–26). The potency and efficacy of GHRP-6 and L-692,429 also suggest that there may be an endogenous ligand acting through such receptors. Compounds such as L-692,429 may aid in isolating a specific receptor and elucidating an element of control of the GH axis heretofore unexplored.

Development of a small organic molecule with selective GH secretagogue activity could yield a therapeutic alternative to the costly parenteral use of human recombinant GH. The potential utility of a secretagogue in GH-deficient children (41, 42), the frail elderly, (43, 44), cachectic patients, or subjects after surgery or thermal injury has been amply discussed (45–47).

In summary, L-692,429 is a well tolerated GH secretagogue in young normal men, demonstrating the potential for the chemical synthesis of nonpeptide mimics of small peptide hormones with predictable biological activity in man.

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