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Impaired secretion of growth hormone-releasing hormone, growth hormone and IGF-I in elderly men

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Abstract. The GHRH test and L-dopa test were performed in 12 normal young men (24.1±1.1 years) and 12 normal elderly men (77.8±1.4 years) to investigate age-related changes in secretion of GHRH, GH and IGF-I. The basal plasma levels of GHRH and GH were not significantly different in young and elderly men, but the basal plasma level of IGF-I was higher in the young men (159.0±11.7 vs 86.7±11.6 μg/l). The area under the curve for plasma GH in the GHRH test was less in the elderly group (35.1±5.9 vs 11.2±2.1 $\mu g \cdot h^{-1} \cdot l^{-1}$, $p<0.001$). The AUCs for the plasma GHRH and GH responses in the L-dopa test in young and elderly men were 32.0±2.7 vs 20.3±1.8 $ng \cdot h^{-1} \cdot l^{-1}$ ($p<0.001$), and 21.8±4.6 vs 5.4±1.1 $\mu g \cdot h^{-1} \cdot l^{-1}$ ($p<0.01$), respectively, indicating decreased releases of GHRH and GH in the elderly. Correlations between the AUCs for plasma GHRH and GH responses in L-dopa were found in both groups, but the ratio of the AUCs for GH/GHRH was lower in the elderly group. The elderly group showed a significant correlation between the basal plasma IGF-I level and the AUCs for plasma GH in the GHRH and L-dopa tests. These results suggest that elderly men have a decreased reserve of hypothalamic GHRH, resulting in secondarily impaired GH release, which may lead to a lower level of IGF-I than in young men.

The age-related change in GH secretion in men is still controversial: the basal GH concentrations in elderly men have been reported to be either unchanged (1) or decreased (2). However, spontaneous 24-h secretion of GH in human subjects is reported to decrease with age (2,3). With regard to the plasma GH response to exogenous GHRH in the elderly, Shibasaki et al. (4) and Lang et al. (5) reported a marked decrease in men older than 40 years, but Pavlov et al. (6) observed no age-related decrease in the GH response to GHRH even in subjects in their eighties.

The development of a radioimmunoassay for plasma GHRH enabled us to evaluate hypothalamic-pituitary function by measuring plasma GHRH and GH in normal subjects and patients with various endocrine disorders (7). We have reported an increase in plasma GHRH after oral administration of L-dopa followed by GH release (8). These findings were confirmed by others (9-11).

In the present study, we compared the function of the GHRH-GH axis in young and elderly men by measuring the plasma GH response to GHRH and the plasma GHRH and GH responses to L-dopa, in addition to the basal plasma IGF-I level.

Subjects and Methods

Subjects and protocols

The subjects studied consisted of 12 young and 12 elderly males with no obesity or endocrine disorder (Table 1). The study was approved by the Human Subjects Protection Committee, School of Medicine, University of Tokushima, and informed consent was obtained from all subjects participating in the study.

Tests were performed on subjects in bed after overnight fasting. At least 30 min before the start of each test, a 21-gauge indwelling needle was inserted into the antecubital vein and blood samples were taken serially through a cannula before and after administration of GHRH or L-dopa.

Table 1.
Age, body mass index (BMI), area under the curve (AUC) for plasma GHRH and GH in the L-dopa test, AUC for plasma GH in the GHRH test, and basal plasma IGF-I levels in young and elderly men.

	Case No.	Age (years)	BMI (kg/m^2)	L-dopa test		GHRH test	basal IGF-I
				GHRH ($ng \cdot h^{-1} \cdot l^{-1}$)	GH ($\mu g \cdot h^{-1} \cdot l^{-1}$)	GH ($\mu g \cdot h^{-1} \cdot l^{-1}$)	($\mu g/l$)
Young	1	25	24.3	37.2	22.7	61.1	211.5
	2	24	17.9	41.2	21.2	41.8	191.0
	3	31	21.0	29.4	18.5	25.0	186.5
	4	23	22.3	34.7	31.5	17.4	165.7
	5	24	17.9	39.7	12.0	25.2	175.7
	6	27	22.5	31.0	18.1	49.4	159.7
	7	21	23.7	25.9	33.1	55.1	170.2
	8	20	17.8	53.5	57.0	68.9	145.3
	9	20	16.8	21.7	8.9	37.7	127.5
	10	23	18.0	22.9	9.3	9.5	100.5
	11	21	21.6	25.5	16.1	15.5	78.7
	12	30	21.1	21.3	13.1	14.7	195.7
	Mean	24.1	20.4	32.0	21.8	35.1	159.0
	±SEM	1.1	1.5	2.7	4.6	5.9	11.7
Elderly	1	74	20.1	14.6	7.2	19.7	101.8
	2	81	18.6	22.4	7.8	14.9	49.3
	3	77	23.8	28.2	11.0	12.8	91.1
	4	78	19.7	12.3	1.4	9.2	83.1
	5	79	23.2	25.3	1.7	4.2	34.4
	6	70	20.4	20.4	4.0	13.7	112.8
	7	84	20.0	26.3	9.6	15.3	130.5
	8	81	21.0	20.7	3.0	2.2	75.6
	9	80	20.3	10.9	1.6	0.8	46.9
	10	73	19.4	15.2	0.9	17.4	56.3
	11	85	22.5	19.5	5.2	2.8	85.1
	12	71	19.6	27.7	10.5	21.1	172.9
	Mean	77.8	20.7	20.3	5.4	11.2	86.7
	±SEM	1.4	0.9	1.8	1.1	2.1	11.6

GHRH and L-dopa tests

A synthetic preparation of GHRH(1-44)NH_2 (100 µg, Sumitomo Pharmaceutical Co, Ltd, Osaka, Japan), which is a registered drug for hormonal examination, were administered iv. Blood samples were obtained serially 0, 15, 30, 45, 60, 90 and 120 min after GHRH administration, and the plasma concentrations of GH were measured.

A dose of 500 mg of L-dopa was administered orally, and serial blood samples were obtained 0, 30, 60, 90 and 120 min later for measuring the plasma concentrations of GHRH and GH.

Radioimmunoassays of plasma GHRH, GH and IGF-I

GHRH was extracted from plasma as described previously (7,11). Briefly, 3.5 ml of plasma was mixed with 7 ml of cold acetic acid-acetone solution (3:100, vol/vol) and centrifuged. The supernatant was extracted twice with 20 ml of petroleum ether, and the ether layer was carefully removed. Remaining acetone was eliminated by evaporation, and the aqueous portion was lyophilized. The residue was dissolved in assay buffer and subjected to RIA for GHRH.

Synthetic GHRH(1-44)NH_2 (generously provided by Dr A. Felix, Hoffman-La Roche Inc, Nutley, NJ) was labelled with ^{125}I by the chloramine-T method and the iodinated product was purified on a 1 × 10 cm carboxymethyl cellulose column (CM 23, Whatman, Maidstone, England). The anti-GHRH serum (RAS-8061, Peninsula Lab, San Carlos, CA; lot No. 004118) used in this study did not cross-react with relevant neuropeptides and rec-