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原　　著

Inhibin-like Immunoreactivity Produced by the Adrenal Gland is Circulating in Vivo

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Abstract To clarify the contribution of the inhibin-like immunoreactivity (inhibin-LI) produced by adrenal glands to the total circulating levels of inhibin-LI, we measured serum inhibin-LI in normal and hypogonadal subjects under ACTH-loading or dexamethasone-loading condition. The mean basal concentration of inhibin-LI in the peripheral serum of the hypogonadal cases was 3.6±1.3 IU/ml (mean±SD, n=5), which corresponded to 19.5±5.8% of that of normal controls matched for age and sex. The low levels of inhibin-LI in hypogonadal subjects (n=7) rose significantly (3.6±1.1 vs 8.1±1.7 IU/ml, $p<0.001$) after the administration of synthetic $^{1-24}$ACTH (40 units / day intramuscular injection) for 2 days, while the levels of serum inhibin-LI were not increased in two cases of Addison's disease with hypogonadism after the administration of ACTH. After the oral administration of a low dose of dexamethasone (1 mg) the serum inhibin-LI level in normal subjects (eight males and eight females) decreased significantly (male, 16.2± 3.3 vs 14.5±4.1 IU/ml; female, 12.9±6.3 vs 10.8±5.6 IU/ml; $p<0.01$ each) without significant change in the levels of serum gonadotropin (LH and FSH) and those of gonadal steroid (testosterone or estradiol). These results indicate that a small, but significant amount of inhibin-LI is secreted from the adrenal gland and circulating in vivo, and that the proportion of adrenal-derived inhibin-LI is much higher in patients with hypogonadism.

Key words: inhibin, adrenal, in vivo

Introduction

The inhibins, which are heterodimeric glycoproteins isolated from the gonads[4)] suppress the secretion of FSH from the pituitary gland[1)4)33)]. The level of inhibin-like immunoreactivity (inhibin-LI) in human serum has been estimated by radioimmunoassay (RIA)[2)3)11)14)18)21)31)] and these in vivo studies support the concept that most part of circulating inhibin-LI originates from gonads. However, the presence of in-

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hibins or inhibin-like proteins in extragonadal tissues such as placenta, pituitary gland and adrenal glands has been recently revealed[5)22)33)]. In human, the expression of mRNAs encoding the inhibin subunits (α, β A and β B) has been shown in fetal adrenal gland[28)30)], furthermore, an ACTH-dependent expression of inhibin α-subunit mRNA[30)] and the secretion of inhibin-LI have been reported by us and others[10)28)]. Recently, we have demonstrated that human adrenocortical tumors and normal adrenal glands produce and secrete inhibin-LI into peripheral blood[24)], however, there is little information on the extent of the contribution of inhibin-LI of adrenal origin to the level of total circulating inhibin-LI. Accordingly, we evaluated, in the present study, the contribution of the adrenal glands to the circulating level of inhibin-LI by compairing the the serum inhibin-LI levels between normal and hypogonadal subjects under the stimulation and suppression of adrenal cortex.

Materials and Methods

Measurement of serum inhibin-LI levels in normal men and women

To determine chronological changes in inhibin-LI levels in peripheral venous blood, we obtained 100 serum samples from normal men aged 20-69 years and 80 serum samples from women aged 20-69 years. Samples from the women were collected without regard to their menstural cycle. All samples were collected in the morning, and none of the samples showed any abnormalities in screening tests for metabolic, endocrine and cardiovascular diseases.

ACTH loading test

Studies were conducted in four cases of hypogonadotropic hypogonadism with conserved adrenal function, aged 20-43 years (two males and two females, mean age, 35.8±10.6 years old), two cases with postmenopausal hypogonadal state (55 and 63 year-old females), one case with premature ovarian failure (31 year-old female), two cases of Addison's disease with hypogonadism (55 year-old female and 18 year-old male) and three normal men aged 30-32 years (mean age 31.0±1.0 y.o.). Profiles of these nine hypogonadal subjects are shown in Table 1. One mg (40 units) of synthetic $^{1-24}$ adrenocorticotrophic hormone ($^{1-24}$ACTH) (Cortrosyn-Z; N.V. Organon Co. Ltd., Netherlands) was intramuscularly injected every 24 hours at 9: 00 am for 2 days to the three normal men and the nine hypogonadal subjects. Samples of peripheral venous serum were obtained daily for three days at 9: 00 am, before the daily injection of $^{1-24}$ACTH. All the samples were stored at −20°C until the assay for inhibin-LI and others.

Oral dexamethasone loading test

A low dose (1 mg) of dexamethasone (Decadron; Banyu Co. Ltd., Japan) was orally administered at 23: 00 pm to eight normal men aged 29-53 years (mean age, 36.6±3.6 years old) and eight normal women aged 25-33 years (mean age, 28.4±3.1 years old), and the samples of their peripheral venous serum were obtained 10 hours after the administration. For a high-dose dexamethasone loading test, 8 mg of dexamethasone was orally administered to five normal men aged 29-50 years (mean age, 36.6±4.2 years old) and five normal women aged 26-36 years (mean age, 31.4±3.7 years old) at 23: 00 pm on the next day of the day for 1 mg dexamethasone administration, and their serum samples were obtained 10 hours later. All the samples were stored at −20°C until the assay.

Table 1 Profiles of the subjects with hypogonadism

Case	Age (years old)	Sex	Diagnosis	E2 (pg/ml)	T (ng/dl)	LH (mIU/ml)	FSH (mIU/ml)
1	31	female	premature ovarian failure	<10.0	n.d.	21.9	63.1
2	39	female	panhypopituitarusm	11.3	n.d.	0.7	4.8
3	43	female	postoperative panhypopituitarism	<10.0	n.d.	0.1	0.1
4	55	female	postmenopausal state	<10.0	n.d.	27.7	69.2
5	63	female	postmenopausal atate	<10.0	n.d.	23.7	56.7
6	20	male	hypogonadotrophic hypogonadism	n.d.	10.1	0.8	5.9
7	41	male	postoperative panhypopituitarism	n.d.	<10.0	0.1	2.1
8[a)]	55	female	Addison's disease with postmenopausal state	18.4	n.d.	35.2	60.5
9[b)]	18	male	Congenital adrenal hypoplasia with hypogonadotropic hypogonadism	n.d.	<10.0	0.7	6.1

[a)]serum contents of cortisol<1.0 μg/dl, ACTH 378 pg/ml ; [b)]serum contents of cortisol 1.55 μg/dl, ACTH 4420 pg/ml E2, serum contents of estradiol ; T, serum contents of testosterone ; n.d., not determined

Radioimmunoassay

Serum inhibin-LI levels were measured by a double-antibody radioimmunoassay (RIA) using a minor modification of the method reported previously[10)11)22)24)32)]. The antiserum (TNDH-1) obtained against partially purified 32-Kd inhibin from bovine follicular fluid (bFF) showed no cross-reactivities with [Tyr^{30}] inhibin-α-(1-30), activin, or transforming growth factor-β, but had 50% cross binding with bovine inhibin-α monomer[11)16)23)24)]. ^{125}I-labeled bFF 32-Kd inhibin was prepared by the chloramine-T method[11)]. Human recombinant inhibin B was used as a standard[10)24)], the potency of which was defined in terms of its in vivo inhibin bioactivity and was calibrated against the WHO/NIH inhibin standard 86/690[4)]. A mixture of sera from post-menopausal women with suppressed adrenocortical functions who were receiving long-term treatment with the synthetic glucocorticoids (GSAS-serum) was employed as free serum for the inhibin-LI assay (GSAS-assay). A mixture of sera from post-menopausal women with conserved adrenal function (GSAN-serum) was also employed as free serum for the inhibin-LI assay (GSAN-assay). The lowest detection level for these assay was 1.6 IU/ml, with an ED50 of about 10.8 IU/ml.

A serum internal standard was used to calibrate inter-assay variation. Intra- and inter-assay coefficients of variation were 4.5% (n=10) and 5.2% (n=5), respectively.

To compare the serum inhibin-LI contents measured with these two inhibin-LI radioimmunoassay system, the contents of serum inhibin-LI in peripheral venous blood of twelve control subjects (six men and six women aged 20-65 years, mean age, 36.1±11.4 years old) were measured with GSAS-assay and with GSAN-assay, and the data in each subjects obtained by these two assays were compared each other.

Serum levels of cortisol, testosterone, estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH) were measured with commercially available RIA kits (cortisol : cortisol RIA kit, Daiichi Radioisotope Institute, Tokyo, Japan, testosterone : testosterone ^{125}I-kit, C.I.S-Diagnostics Co. Ltd., Tokyo, Japan, estradiol : estradiol coat-RIA kit, C.I.S.-Diag-

nostics Co. Ltd., Tokyo, Japan, LH : SPAC-S LH kit, Daiichi Radioisotope Institute, Tokyo, Japan, FSH : SPAC-S FSH kit, Daiichi Radioisotope Institute, Tokyo, Japan).

Statistics

Age-dependent changes in serum inhibin-LI levels in adult men and women were evaluated by One-way ANOVA, followed by Fisher's method of protected least significant difference (Fisher's PLSD). Changes in the levels of serum inhibin-LI in hypogonadal cases after the injection of ACTH were evaluated by Two-way ANOVA, followed by Fisher's PLSD. Changes in the levels of serum cortisol, inhibin-LI and testosterone in normal men after the injection of ACTH were evaluated by Two group t-test : paired. Changes in the levels of serum cortisol, inhibin-LI, LH, FSH, testosterone or estradiol in normal men and women after the administration of dexamethasone were evaluated by Two group t-test : paired. A level of $p<0.05$ was accepted as statistically significant.

Results

Inhibin-LI contents in peripheral venous blood of twelve cases (six male and six female, aged 25 to 63 years) were measured with GSAS-, and GSAN-assay, and the data obtained from these two assay were compared with each other. As shown in Fig. 1, significantly larger contents of inhibin-LI in the peripheral venous blood were noted by the GSAS-assay than those by GSAN-assay ($p<0.001$). This finding indicated that the GSAN-serum contained small but comparatively larger amount of inhibin-LI than did the GSAS-serum. With this knowledge, we employed the GSAS-assay for the following measurement of serum inhibin-LI contents in normal and hypogonadal subjects.

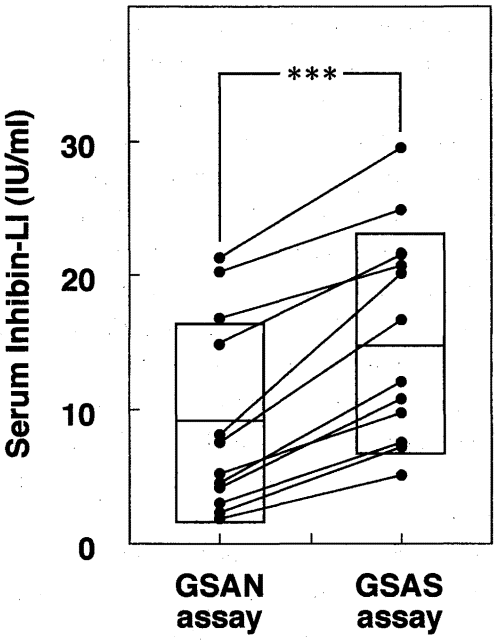

Fig. 1 Comparison of serum inhibin-LI contents measured with different two inhibin-LI radioimmunoassay system. The contents of serum inhibin-LI in peripheral venous blood of twelve control subjects (six men and six women aged 20-65 years, mean age, 36.1±11.4 years old) were measured with GSAS-assay (inhibin-LI radioimmunoassay using a mixture of sera from postmenopausal women with suppressed adrenocortical functions as inhibin-free serum) and with GSAN-assay (inhibin-LI radioimmunoassay using a mixture of sera from postmenopausal women with conserved adrenocortical functions as free serum), and the data of each subjects obtained by these two assays were compared with each other.

Open boxes represent mean ± S.D. (n=12) of inhibin-LI levels for the cases in each assay. ***$p<0.001$, paired T-test.

Inhibin-LI concentrations in peripheral venous blood of various ages were measured in normal adult men (Fig. 2A) and women (Fig. 2B). The highest level of serum inhibin-LI was found in men aged 20 to 29 years. There was a gradual, but significant, age-dependent decrease ($p<0.01$). A significant decrease of serum inhibin-LI level was found in women aged of 50 to 69 years, as compared with that in women aged 20 to 29 years, 30 to 39 years and 40 to 49 years. There were no significant differences in inhibin-LI levels within groups of women aged 20 to 29, 30 to 39 and 40 to 49 years.

The basal levels of inhibin-LI in peripheral venous blood of hypogonadal patients (three female and two male cases, aged 20 to 43 years.), who were chronologically within the fertile period, were then compared with those of age- and sex-matched controls. As shown in Table 2, basal inhibin-LI levels in the five cases with hypogonadism were, on average, 19.5% of those in the controls. When synthetic $^{1-24}$ ACTH (1 mg/day) was injected intramuscularly to those five patients with hypogonadism and to two postmenopausal women, their low levels of serum inhibin-LI were increased significantly one day after the injection of 1 mg $^{1-24}$ACTH, and further increased by the second injection of ACTH (Fig. 3A). However, no increase in the levels of circulating inhibin-LI by the administration of ACTH was observed in two cases of Addison's disease with hypogonadism (Fig. 3B). A significant decrease in the levels of inhibin-LI (Fig. 4B) and of testosterone (Fig. 4C), with a concomitant increase in the levels of serum cortisol (Fig. 4A), was observed in the normal control men two day after the injection of ACTH.

When a low dose of dexamethasone (1 mg) was orally administered to the eight normal control men and the eight normal control women, a significant decrease in the levels of

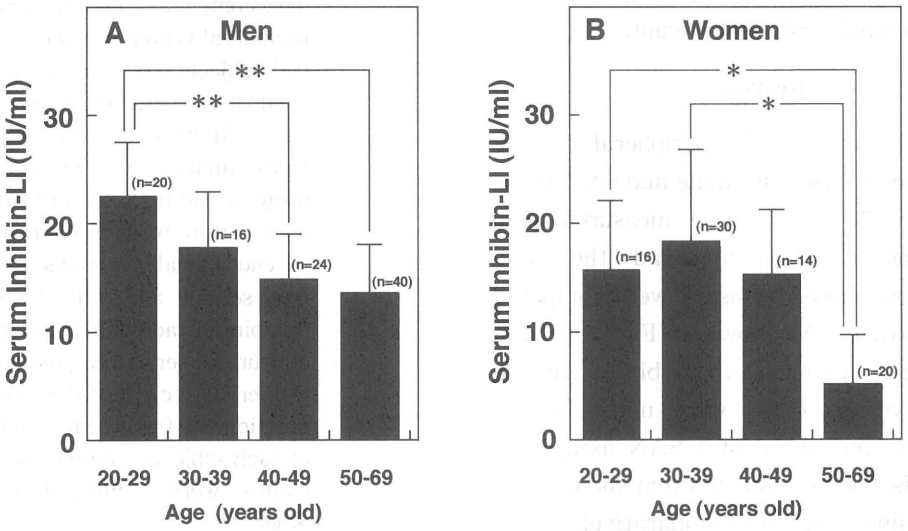

Fig. 2 Age-dependent changes in peripheral serum concentrations of inhibin-LI in normal adult men (A) and women (B). Values are expressed as mean ± S.D. for each decade in subjects aged from 20 to 69 years. Numbers in paretheses indicate the number of subjects evalueted. *$p<0.05$, **$p<0.01$, one-way ANOVA followed by Fisher's method of protected least significant difference (Fisher's PLSD).

Table 2 Serum inhibin-LI levels in hypogonadal cases within fertile period

Case[a)]	Age (years old)	Sex	Serum inhibin-LI (IU/ml)	% of inhibin-LI in age- and sex-matched control subjects[b)]
1	31	female	4.8	26.2
2	39	female	2.2	12.1
3	43	female	3.6	22.9
6	20	male	4.8	21.3
7	41	male	2.2	14.9
Mean ± S.D.				19.5±5.8

[a)]numbers of cases correspond to those in Table 1

[b)]percent values are calculated based on the inhibin-LI levels in control subjects shown in Fig. 2

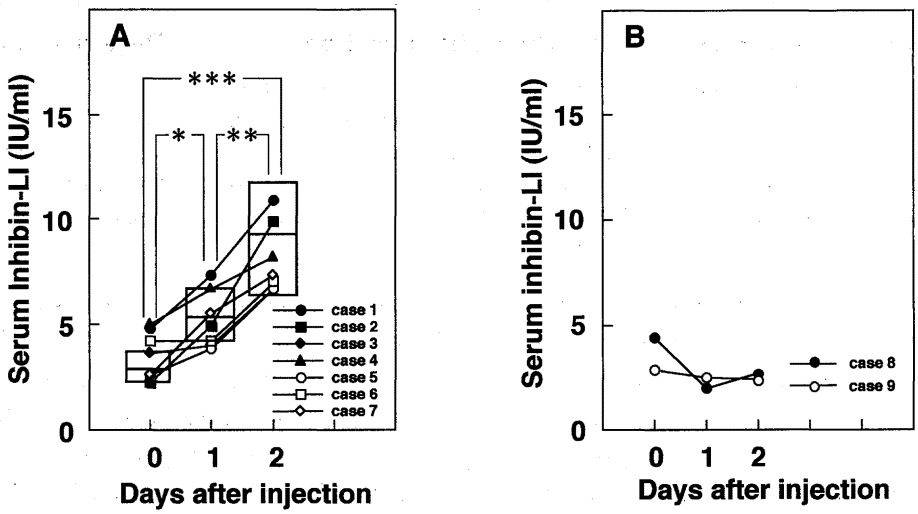

Fig. 3 Effect of ACTH administration on inhibin-LI concentrations in peripheral venous blood of hypogonadal patients and post menopausal women. Synthetic $^{1-24}$ACTH was intramuscularly injected and samples were obtained as described in Materials and Methods. Numbers correspond to those shown in Table 1. Time-dependent increase of serum inhibin-LI levels in the hypogonadal cases with conserved adrenal function (case 1-7 in Table 1) was observed (day 0, 3.6±1.1 IU/ml ; day 1, 5.2±1.4 IU/ml ; day 2, 8.1±1.7 IU/ml) (A). On the other hand, no increase of serum inhibin-LI was observed in two hypogonadal patients with adrenal insufficiency (case 8, 9 in Table 1) (B). Open boxes represent mean ± S.D. of inhibin-LI levels for the cases analyzed on the designated day. *$p<0.05$, **$p<0.01$, ***$p<0.001$, two-way ANOVA followed by Fisher's PLSD.

their serum inhibin-LI was observed 10 hours after the administration ($p<0.01$) (Fig. 5B and Fig. 5G) with no significant change in the levels of serum LH, FSH, and testosterone or estradiol (Fig. 5C, 5D, 5E, 5H, 5I and 5J). When a high dose of dexamethasone (8 mg) was administered to the five normal control men and the five normal control women 24 hours after the administration of the low dose of dexamethasone, a profound decrease in the levels of

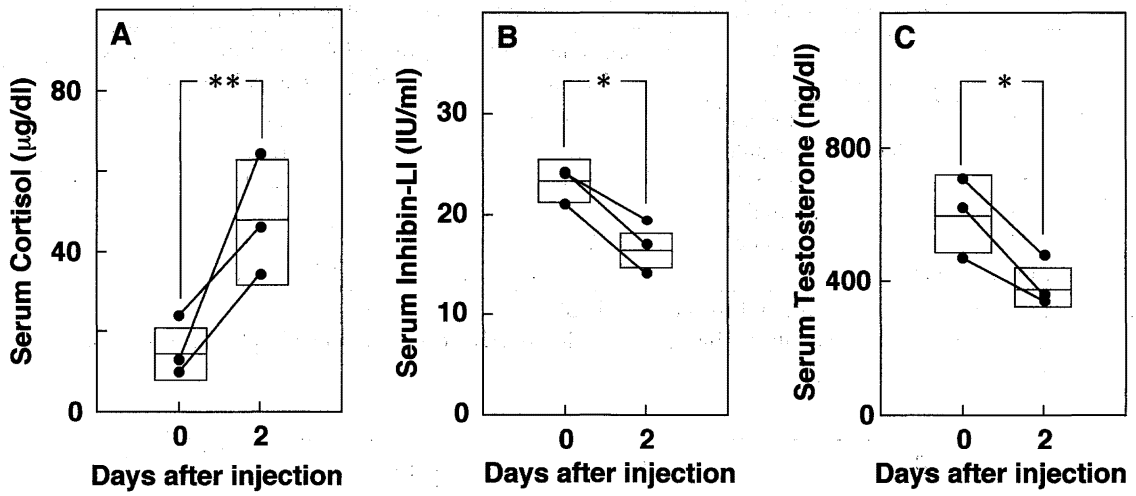

Fig. 4 Effects of ACTH administration on peripheral serum concentrations of cortisol (A), inhibin-LI (B) and testosterone (C) in normal control men. In contrast to the increase in the level of cortisol (15.7±7.4 vs 48.3±15.0 mg/d/, $p<0.01$), decreases of inhibin-LI level (23.1±8.8 vs 16.3±1.9 IU/ml, $p<0.05$) and that of testosterone (600±121 vs 393±76 ng/dl, $p<0.05$) were noted 2 days after the administration. The values are expressed as mean ± S.D. (n=3). *$p<0.05$, **$p<0.01$, paired T-test.

serum inhibin-LI was noted 10 hours after the treatment (Fig. 6B and Fig. 6G), along with a significant decrease in the level of serum testosterone in the control men (Fig. 6C) and that of serum estradiol in the control women (Fig. 6H). No significant change, again, in the levels of serum LH (Fig. 6D and Fig. 6I) or serum FSH (Fig. 6E and Fig. 6J) was observed in the same treatment.

Discussion

The synthesis and the secretion of inhibin-LI in adrenal glands have been demonstrated by the observations that the addition of ACTH induces the expression of mRNA of inhibin α-subunit[5)30)] and the secretion of inhibin-LI[10)24)28)] in primary cultured human adrenocortical cells. However, there is little evidence for the contribution of inhibin-LI of adrenal origin to the levels of circulating inhibin-LI.

To determine the proportion of the inhibin-LI derived from extragonadal sources to the total circulating inhibin-LI, we measured inhibin-LI levels in peripheral serum obtained from postmenopausal women, from patients with premature ovarian failure, and from patients with hypogonadotropic hypogonadism, in whom the amount of inhibin-LI of gonadal origin would be negligible[2)14)16)23)].

The evidence that a serum mixture from postmenopausal women with suppressed adrenocortical functions (GSAS-serum) had a lower content of inhibin-LI than that from postmenopausal women with conserved adrenal function, which was shown in Fig. 1, indicated the existence of circulating inhibin-LI derived from the adrenal gland. By employing this GSAS-serum as free serum for the measurement of serum inhibin-LI, we could detect a small but significant amount of circulating inhibin-LI in hypogonadal subjects. The low levels of inhibin-LI rose approximately two-fold after the administration of synthetic ACTH to them (Fig. 3A). No significant rise in

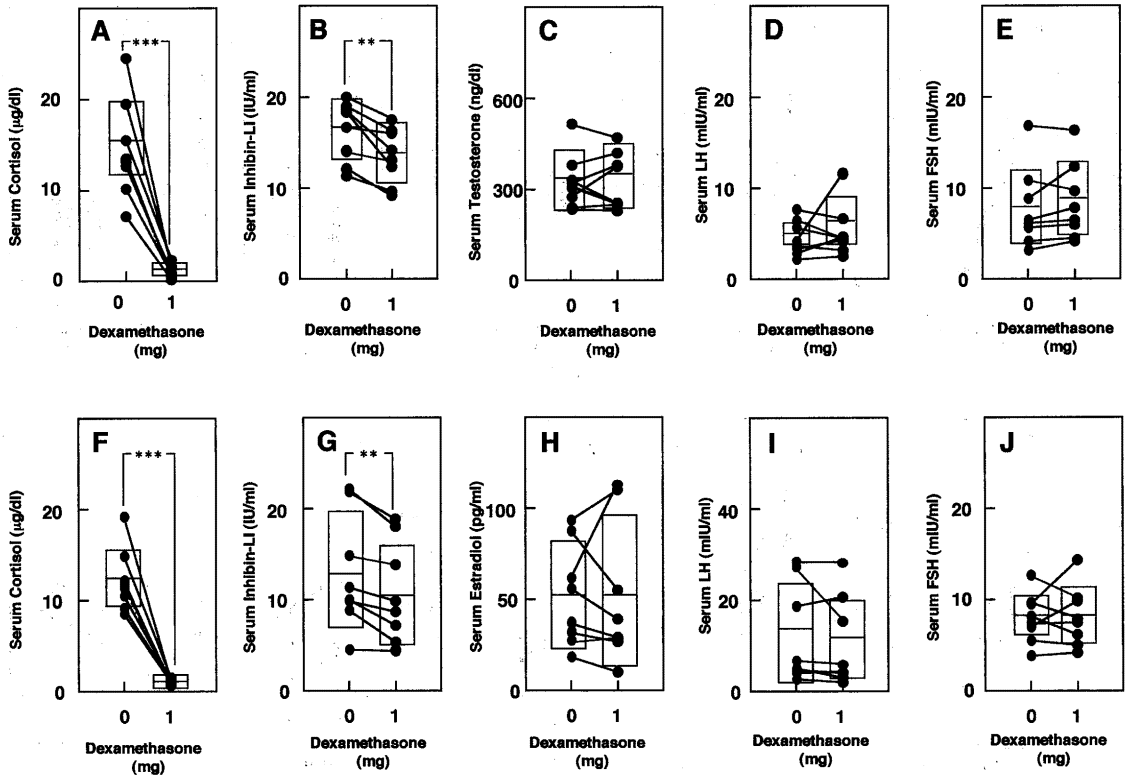

Fig. 5 Effect of low dose dexamethasone (1 mg) administration on peripheral serum concentrations of cortisol (A, F), inhibin-LI (B, G), testosterone (C), estradiol (H), luteinizing hormone (LH) (D, I) and follicle-stimulating hormone (FSH) (E, J) in normal control men (A-E) and women (F-J). Significant decreases in the levels of cortisol ($p<0.001$) and of inhibin-LI ($p<0.01$) were observed 1 day after the administration of a low dose of dexamethasone (1 mg). No significant change was noted in the levels of testosterone, estradiol, LH or FSH after the same treatment. Open boxes represent mean ± S.D. ($n=8$) of the levels of the indicated hormones.

**$p<0.01$ and ***$p<0.001$, paired T-test.

the serum levels of gonadal steroids or gonadotropins was observed in them under the same treatment (data not shown). These observations indicated that the low concentrations of inhibin-LI detected in the hypogonadal subjects contained adrenal-derived inhibin-LI. The contribution of adrenal inhibin-LI to the levels of total circulating inhibin-LI in hypogonadal patients was further evidenced in two cases of Addison's disease with hypogonadism, in whom the levels of circulating inhibin-LI were not increased by the administration of ACTH (Fig. 3B).

A significant decrease ($p<0.01$) in the levels of circulating inhibin-LI was observed in the normal control men and women 10 hr after the oral administration of a low dose of dexamethasone (1 mg) (Fig. 5B, 5G). However, at the same time, there was no significant decrease in the levels of serum testosterone or estradiol (Fig. 5C, 5H). These data also indicated the regulation of circulating inhibin-LI levels by pituito-adrenal axis.

After the administration of a high dose of

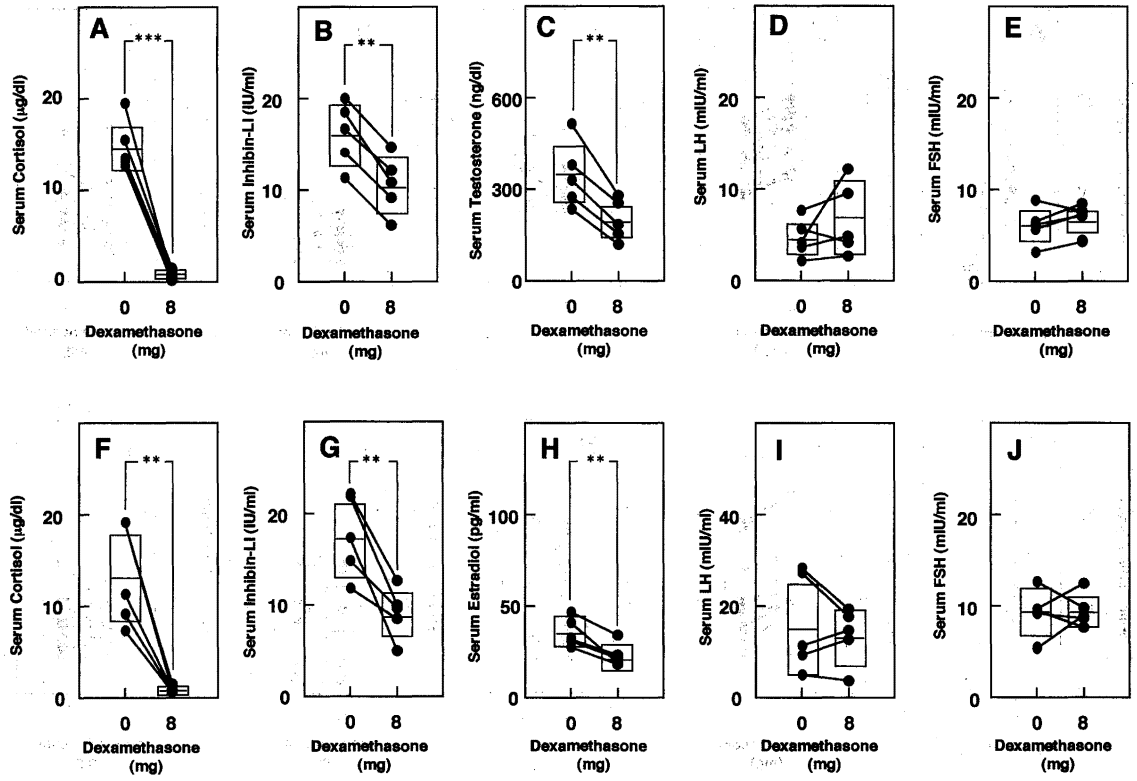

Fig. 6 Effect of high dose dexamethasone (8 mg) administration on peripheral serum concentrations of cortisol (A, F), inhibin-LI (B, G), testosterone (C), estradiol (H), luteinizing hormone (LH) (D, I) and follicle-stimulating hormone (FSH) (E, J) in normal control men (A-E) and women (F-J). Significant decreases in the levels of cortisol (men, $p<0.001$; women, $p<0.01$) and inhibin-LI ($p<0.01$), together with that of testosterone ($p<0.01$) or estradiol ($p<0.01$) were observed 10 hr after the administration of a high dose of dexamethasone (8 mg) on the next day of the day for administration of 1 mg dexamethasone. No significant change was noted in the levels of LH or FSH after the same treatment. Open boxes represent mean ± S.D. ($n=5$) of the levels of the indicated hormones. **$p<0.01$ and ***$p<0.001$, paired T-test.

dexamethasone (8 mg) to the normal control subjects, the levels of circulating inhibin-LI also decreased significantly ($p<0.01$) (Fig. 6B, 6G), with concomitant decrease in that of testosterone ($p<0.01$) (Fig. 6C) or estradiol ($p<0.01$) (Fig. 6H). Since the hypercortisolemic state in patients with Cushing's adrenal adenoma[25] or that under the repeated injection of ACTH[27] or that under the administration of synthetic glucocorticoids[6][7] has been reported to induce the suppression of pituito-gonadal axis at both pituitary and gonadal levels, we suppose that this decrease in the levels of circulating inhibin-LI after the admonistration of a high dose of dexamethasone is due to the decreased secretion of gonadal inhibin-LI in addition to that of adrenal inhibin-LI.

In spite of the fact that the levels of circulating inhibin-LI was singnficantly decreased by the administration of a low dose of dexamethasone, there was no significant rise in the levels of circulating FSH which should be under the

regulation of the inhibin-FSH feedback system (Fig. 5E, 5J). Samely, in a high dose dexamethasone suppression test, no significant rise in the levels of serum FSH or LH was observed (Fig. 6D, 6I, 6E, 6J) in spite of the significant decrease in the levels of serum inhibin-LI, testosterone or estradiol. These findings also indicated the direct inhibitory effect of glucocorticoid on the functions of the pituito-gonadal axis[6)7)25)27)].

In contrast to the hypogonadal subjects, administration of ACTH to normal control men reduced the serum concentration of inhibin-LI (Fig. 4B), as well as that of testosterone (Fig. 4C). This paradoxical movement in the levels of circulating inhibin-LI in normal control men may be explained as follows: in normogonadal subjects with ACTH-induced hypercortisolemia, the magnitude of the reduction of gonadal inhibin-LI contents is much greater than that of the increase of adrenal inhibin-LI contents, resulting in a net decrease in the level of total circulating inhibin-LI. However, in the hypogonadal cases, because they don't have large contents of circulating inhibin-LI of gonadal origin, it is suggested that the increase of inhibin-LI from ACTH-stimulated adrenal glands was able to be detected in peripheral blood.

When we compared the serum levels of inhibin-LI in the hypogonadal cases with those of age- and sex-matched controls, the levels of inhibin-LI in the hypogonadal patients were about 20% of those in controls (Table 2). Because these low levels of inhibin-LI in hypogonadal cases are considered to originate still from the gonads with reduced activities in addition from the adrenal glands and other tissues, the extent of the contribution of adrenal inhibin-LI to the total circulating inhibin-LI may be less than 20% in the normal subjects. However, in the hypogonadal conditions such as postmenopausal state, the contribution of adrenal-derived inhibin-LI to the total circulating inhibin-LI seems to be larger than that in normogonadal cases.

The rise in the levels of circulating inhibin-LI in hypogonadal cases after the administration of ACTH, and the decrease in the serum contents of inhibin-LI in normal controls after the oral administration of dexamethasone were also confirmed by the other inhibin-LI assay system (personal communication from Dr. Nishie, Nippon DPC Corporation, Japan). Recently, Kananen K et al.[15)] reported a novel autoregulatory mechanism of extragonadal (adrenal) inhibin α-subunit expression by gonadal inhibin, which may also support our present study.

Until now, special and sensitive two-site enzyme-linked immunosorbent assays for dimeric inhibin A[17)], dimeric inhibin B[8)13)] and pro-αC-containing forms of inhibin[9)] were established and the circulating levels of each forms of inhibin-LIs has been reported. However, the molecular forms of inhibin-LIs originated from the adrenal gland and their pathophysiological roles are still unknown. It may be speculated that the inhibin molecules modulate adrenal function and growth, as reported in the gonadal inhibins and their related molecules[12)19)20)26)29)32)].

In conclusion, the present study demonstrated that a small but significant amount of inhibin-LI is produced in and secreted from adrenal glands under the regulation of the pituito-adrenal axis, and is circulating in vivo.

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(和文抄録)

副腎由来のインヒビン様免疫活性は循環血中に存在する

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卵巣や精巣等の性腺組織で主として産生され，循環血中に分泌されるインヒビンは，性腺外組織の下垂体や副腎等でもその産生分泌が確認されている．

今回われわれは，末梢血中に存在する総インヒビン様免疫活性（total inhibin-LI）中に占める副腎由来の同活性（adrenal inhibin-LI）の割合を確認する目的で，副腎皮質刺激ホルモン（ACTH）又はデキサメサゾン（Dexa）投与下で，健常者および性腺機能低下症症例の末梢血中 total inhibin-LI を測定し，以下の結果を得たので報告する．

測定した性腺機能低下症症例（n=5）の total inhibin-LI は 3.6±1.3 IU/ml であり，これは，健常者対照群（性，年齢を一致）の total inhibin-LI の 19.5±5.8%に相等した．7例の性腺機能低下症症例に，2日間 ACTH（40 unit im）を投与したところ，これらの症例の total inhibin-LI は有意に上昇（3.6±1.1 vs 8.1±1.7，$p<0.001$）した．これに対して，性腺機能低下症に Addison 病（副腎機能不全）を合併した2症例においては，ACTH 負荷による total inhibin-LI の有意な上昇は認められなかった．男女各8名ずつの健常者に対して低用量の Dexa（1 mg/day）を経口投与したところ，その前後で有意な total inhibin-LI の低下（male，16.2±3.3 vs 14.5±4.1；female，12.9±6.3 vs 10.8±5.6 IU/ml；$p<0.01$ each）が認められた．この処置の前後で，血中ゴナドトロピン（LH，FSH）および性ステロイドホルモン（testosterone，estradiol）値の有意な変化は認められなかった．

これらの結果から，副腎由来のインヒビン様免疫活性（adrenal inhibin-LI）が血中に分泌され循環していることが示唆された．また，total inhibin-LI 中に占める adrenal inhibin-LI の割合は，健常者より性腺機能低下症症例の方が高くなる可能性があると考えられた．