Secretion of Anterior Pituitary Hormones in Patients with Insulin-Dependent Diabetes Mellitus and Polyglandular Autoimmune Syndrome

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We extracted gammaglobulins from the serum of 10 patients with insulin-dependent diabetes mellitus (IDDM) to investigate their effect on anterior pituitary hormone secretion using cultures of rat anterior pituitary cells. Three of the 10 patients also had the polyglandular autoimmune syndrome (PGA) type III with an isolated failure of anterior pituitary hormone secretion. The gammaglobulin from each of the 3 patients with PGA and an isolated failure of secretion of adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH) or gonadotropin inhibited the secretion of ACTH, TSH or gonadotropin in cultures of rat anterior pituitary cells. The gammaglobulins obtained from the other 7 patients with IDDM also showed an inhibitory or stimulatory effect on anterior pituitary hormone secretion *in vitro*. We postulate that some patients with IDDM, especially those with other endocrine autoimmune diseases, may have substances in their gammaglobulin fraction that can affect the secretion of anterior pituitary hormones. (Internal Medicine 35: 686–692, 1996)

Key words: isolated anterior pituitary hormone deficiency, endocrine autoimmune diseases, gammaglobulin

Introduction

The polyglandular autoimmune syndrome (PGA) was described by Neufeld et al in 1980 (1) as an autoimmune disease that involves multiorgan failure. Insulin-dependent diabetes mellitus (IDDM), autoimmune thyroid disease (AITD), and autoimmune hypophysitis are included in this syndrome. Autoimmune hypophysitis was first reported in 1962 by Goudie and Pinkerton as a disease that shows lymphocytic infiltration of the anterior pituitary (2). Patients with autoimmune hypophysitis show a wide range of pituitary functions including normal function, panhypopituitarism, partial hypopituitarism and specific isolated pituitary hormone deficiency (3–5). While patients with both IDDM and autoimmune hypophysitis are rare, antipituitary antibodies have been detected by using immunofluorescence techniques in certain patients with IDDM (6–8), which suggests a broader involvement of the endocrine system in IDDM (7). In addition, reports of IDDM with an isolated failure of anterior pituitary hormone secretion suggest the existence of an autoimmune disorder of the anterior pituitary (8, 9).

We studied 10 patients with IDDM, three of whom had the

PGA type III with a specific failure of anterior pituitary hormone secretion. A rat anterior pituitary cell line was used to evaluate anterior pituitary hormone secretion as affected by the gammaglobulins isolated from the sera of the 10 patients.

Subjects

The clinical profiles of the 10 Japanese patients who participated in this study are summarized in Table 1. There were 4 males and 6 females, aged 21 to 71 years (average age, 39.3 years). Cases 1–4 had been diagnosed as IDDM with AITD. Chronic thyroiditis was present in cases 1–3, and Graves' disease was present in case 4. Cases 5–10 had been diagnosed as IDDM without AITD. All 4 patients with the PGA type III syndrome had antiglutamic acid decarboxylase (GAD) antibody, positive tests for microsome hemoagglutinin (MCHA), and human leukocyte antigen (HLA) DR4. Immunofluorescence testing using At-T 20 cells showed that case 1 possessed antipituitary antibody as well.

In these patients, serum HbA_{1c} levels ranged from 7.3–10.2%. Thyroid function was normal in the 6 patients with IDDM without AITD, except for two patients (cases 9 and 10)

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Table 1. Clinical Data on Patients with IDDM

Patient No.	Diagnosis	Age, sex	BMI	Duration of IDDM (year)	Duration of AITD (year)	HbA _{1c} (%)	T ₃ (ng/dl) TSH (μIU/ml)	ICA ICSA GAD-antibody (U/ml)	PCA PCSA	TGHA MCHA	HLA
1	IDDM Chronic thyroiditis ACTH deficiency	48, F	18.4	15	8	7.3	76 6.15	(-) (-) 4.9	(-) (+)	×100 ×6,400	A24 (9), A26 (10), BW61 (40), B39 (16), CW3, CW7, DR4, DRW13
2	IDDM Chronic thyroiditis TSH secretion failure	38, M	21.5	15	0.5	8.3	67 <0.05	(-) (-) 51.3	(-) (-)	×400 ×800	A11, A26 (10), BW54 (W22), BW61 (40), CW1, CW3, DR4, DRW8
3	IDDM Chronic thyroiditis Gonadotropin secretion failure	32, F	21	12	0.3	9.2	48 5.55	(+) (-) 2391	(-) (-)	×100 ×100	A2, A31 (19), B62 (15), B48, DR4, DR9
4	IDDM Graves' disease	22, F	23.7	3	5	9.2	122 0.68	(+) (±) 91.8	(-) (+)	<×100 ×1,600	A11, A24 (9), BW54 (W22), BW61 (40), CW1, CW3, DR4
5	IDDM	45, F	17.2	2	N/A	7.3	91 1.55	(-) (-) <4	(-) (-)	<×100 ×200	A11, BW54 (W22), CW1, DR4, DR9
6	IDDM	71, F	16	1	N/A	9	95 1.07	(-) (-) <4	(-) (-)	<×100 <×100	A2, A31 (W19), BW48, CW7, DR4, DRW12 (5)
7	IDDM	32, M	18.2	5	N/A	7.8	115 2.38	(-) (-) <4	(-) (-)	<×100 <×100	A2, AW33 (W19), B35, B44 (12), CW3, DR2, DRW6
8	IDDM	62, M	18.3	<1	N/A	7.6	122 0.46	(-) (-) <4	N.D.	<×100 <×100	BW54 (W22), CW1, DR9
9	IDDM	22, M	16.2	<1	N/A	10.2	72 1.5	(-) (-) 6	N.D.	<×100 <×100	A2, B54 (22), B61 (40) CW1, CW3, DR6, DR8
10	IDDM	21, F	23.8	7	N/A	10.2	72 1.5	(+) (-) 7.8	N.D.	<×100 <×100	A11, A24 (9) B54 (22), B7 CW1, CW7, DR4, DR1

AITD: Autoimmune thyroid disease, ICA: Islet cell antibody, MCHA: Microsome hemoagglutinin test, TGHA: Thyroglobulin hemoagglutinin test, BMI: Body mass index, ICSA: Islet cell surface antibody, PCA: Pituitary cell antibodies, GAD: Antiglutamic acid decarboxylase, IDDM: Insulin-dependent diabetes mellitus, PCSA: Pituitary cell surface antibodies, N.D.: not determined, N/A: not available.

who exhibited the low T₃ syndrome. Case 1, who had chronic thyroiditis, was receiving supplemental thyroid hormone for hypothyroidism, and case 4, who had Graves' disease, was receiving thiamazole, and had normal serum levels of thyroid hormone. Case 2 showed secondary and case 3 showed primary hypothyroidism. Neither was receiving supplemental thyroid hormone. Details of the clinical course of cases 1–3 were reported previously (10).

Methods

Pituitary function tests

A combined anterior pituitary function test, consisting of an intravenous injection of corticotropin-releasing hormone (CRH) 100 μg (Mitsubishi Kasei Co., Tokyo, Japan), growth hormone-releasing hormone (GRH) 100 μg (Sumitomo Pharmaceutical Co., Osaka, Japan), thyrotropin-releasing hormone (TRH) 500 μg (Tanabe Pharmaceutical Co., Osaka, Japan) and luteinizing hormone-releasing hormone (LH-RH) 100 μg (Tanabe Phar-

maceutical Co., Osaka, Japan), was performed in all 10 patients to evaluate their pituitary function. Blood samples were collected before, and at 15, 30, 60, and 90 minutes after the hormone injection. Plasma or serum levels of adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH), thyroid stimulating hormone (TSH), prolactin (PRL), luteinizing hormone (LH), and follicle stimulating hormone (FSH) were measured with commercially available kits. The ACTH II IRMA kit was obtained from Mitsubishi Petrochemicals, Tokyo, Japan; the AMEREY CORTISOL kit was purchased from Amersham, Tokyo, Japan; the HGH kit was from Eiken Chemical, Tokyo, Japan; and the TSH RIA BEAD II and PROLACTIN RIA BEAD kits were purchased from Dainabot, Tokyo, Japan. Results of this combined anterior pituitary function test performed in 11 healthy volunteers (average age, 34 years) were used to determine the normal ranges. The normal ranges of ACTH and cortisol were determined by using the data from the CRH research group (11). The peaks and increments of the pituitary hormone responses were considered to be normal if they were between -1.5 SD and $+2$ SD of the values obtained from the healthy volunteers.

Extraction of gammaglobulin

Five ml of serum prepared from each patient and control subject (healthy volunteer) was diluted in the same volume of 0.01 M phosphate-buffered saline (PBS). Then, 10 ml of saturated ammonium sulfate was added to the diluted serum, mixed for 30 minutes, and centrifuged at 10,000 rpm for 20 minutes at 16°C . The supernatant was decanted and a small amount of PBS was added to dissolve the pellet. The dissolved pellet was placed in a dialysis membrane (Seamless Cellulose Tubing, 8×32 mm, Union Carbide Co., Chicago, IL, USA) and dialyzed against PBS for 24 hours with gentle agitation at 4°C . The residual gammaglobulin was subsequently lyophilized.

Anterior pituitary cell culture

Male Wistar rats, weighing 200–240g, were decapitated and the anterior pituitary glands were immediately removed. The glands were minced into small pieces and placed in a Hanks-HEPES buffer (pH 7.4, GIBCO Laboratories, Grand Island, N. Y., USA) containing 0.03% collagenase and 0.1% bovine serum albumin (BSA, Sigma Chemical Co., St. Louis, MO, USA). Samples were then agitated in a 37°C water bath for 20–30 minutes. After incubation, the dispersed cells were washed three times with an appropriate volume of Dulbecco's Modified Eagle Medium (DMEM, GIBCO), containing 10% horse serum, 3% fetal calf serum, 1% nonessential amino acids, fungizone, penicillin, and streptomycin (GIBCO). The cells were resuspended in the same medium and approximately $2-4 \times 10^4$ cells/1.5 ml medium were placed in sterile Petri dishes (Falcon 35×10 mm). The cells were cultured at 37°C for 3–4 days in an atmosphere of 95% O_2 /5% CO_2 saturated with water vapor.

After 4 days in culture, cells were washed twice with fresh serum-free DMEM. The gammaglobulins from the patients and control subjects, resuspended in the DMEM, were added to the

cultured cells (final concentration, 2.5 mg/ml) with or without CRH (10 ng/ml) (Peptide Institute, Inc., Osaka, Japan) and incubated at 37°C for 3–4 hours. Then, media were collected and stored at -30°C until hormone assays. Data were obtained from 3 independent experiments.

Hormone assays

Concentrations of rat TSH, PRL, and LH in the medium were measured with kits provided by National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) (Bethesda, MD, USA). The ACTH concentration in the medium was measured by using an immunoradiometric assay kit (ACTH II IRMA kit). LH was measured only in cases 3 and 9, since insufficient amounts of media precluded this analysis in the remaining cases.

Detection of anti-CRH receptor binding antibody in immunoglobulins

Male Wistar rats (200–240 g) were used. Rat pituitary membrane preparations were prepared as previously described (12). Briefly, 100 μl of the rat pituitary membrane suspension was added to a 1.5 ml polypropylene microtube containing 100 μl ^{125}I -ovine CRH (final concentration, 100 pM, New England Nuclear Research Products, Boston, MA, USA), 100 μl incubation buffer (PBS with 0.1% BSA), and extracted gammaglobulin (final concentration, 2.5 mg/ml). Nonspecific binding was determined in the presence of 300 nM rat/human CRH. The reaction was allowed to proceed for 2 hours at room temperature after which the pituitary membranes were separated from the incubation medium by centrifugation in a TOMY microfuge (Tokyo, Japan) for 5 minutes at 12,000 g at room temperature. The resulting pellet was washed with 1 ml Dulbecco's PBS (GIBCO) containing 0.01% Triton X-100, pH 7.4, and re-centrifuged for 5 minutes at 12,000 g. The final supernatant was aspirated and the radioactivity in the pellet was measured in a gamma scintillation counter (Aloka, Tokyo, Japan) at 80% efficiency.

Detection of anti-CRH antibody in immunoglobulins

Anti-CRH antibody in each patient's serum gammaglobulin fraction was quantitated by using a CRH RIA system. [^{125}I -Tyr]-rat CRH (New England Nuclear Research Products) (20,000 cpm) was added to a mixture of 300 μl CRH incubation buffer (0.1 M phosphate buffer containing 0.14 M NaCl, 0.1% bovine serum albumin, 0.05% Tween 20, 0.01% NaN_3 ; pH 7.4) and 100 μl CRH incubation buffer containing the gammaglobulin extracted from each patient (cases 1–10) or the controls (final concentration, 2.5 mg/ml and 500 $\mu\text{g}/\text{ml}$, respectively). To check for non-specific binding, 2 $\mu\text{g}/\text{ml}$ CRH was added to the mixture. The mixture was incubated for 48 hours at 4°C . One ml of 20% polyethylene glycol and 100 μl of 1% human gammaglobulin (Sigma) were then added to the mixture and centrifuged at 3,000 rpm for 20 minutes. After discarding the supernatant, the radioactivity in the pellet was measured with a gamma scintillation counter.

Statistical analysis

Data are expressed as mean $\pm$ SEM. Statistical evaluations utilized one-way ANOVA followed by Duncan's new multiple range test or Sheffe's F-test. A level of $p < 0.05$ was accepted as statistically significant.

Results

Combined anterior pituitary function tests in 10 patients with IDDM demonstrated an isolated deficiency of ACTH secretion, an isolated failure of TSH secretion, and an isolated failure of gonadotropin secretion in cases 1, 2, and 3, respectively (10). In cases 2 and 3, TRH (500 μ g/day) and LH-RH (400 μ g/day) were successively administered for 1 week, respectively. However, the patients' serum TSH or gonadotropin did not respond to such treatment, thus confirming the diagnosis. Baseline serum levels of LH were normal in cases 1 and 2. Case 1, a female, showed a hyperresponse of LH to LH-RH, suggesting that she was post-menopausal. Case 2 showed a normal response to LH-RH. The other 7 patients showed no failure of pituitary hormone secretion. However, exaggerated responses of GH, PRL, and TSH in 6, 5 and 5 cases, respectively.

Effects of patients' gammaglobulin on *in vitro* secretion of ACTH, TSH, LH, and PRL

The serum gammaglobulins from case 1, who suffered from IDDM, chronic thyroiditis, and isolated ACTH deficiency, and those from case 7, who suffered from IDDM alone, significantly inhibited the CRH-induced secretion of ACTH in rat anterior pituitary cell cultures as compared with gammaglobulins from the control subjects (Fig. 1). The serum gammaglobulins from case 4 who had both IDDM and Graves' disease significantly stimulated basal ACTH secretion compared with gammaglobulins from the control subjects (Fig. 1). The serum gammaglobulins extracted from case 1 and those from case 2,

who suffered from IDDM, chronic thyroiditis, and an isolated failure of TSH secretion, significantly inhibited the basal secretion of TSH in rat anterior pituitary cell cultures compared with the gammaglobulins from the control subjects (Fig. 2). The serum gammaglobulins from case 3, who suffered from IDDM, chronic thyroiditis, and an isolated failure of gonadotropin secretion, significantly inhibited the basal secretion of LH in rat anterior pituitary cell cultures compared with the gammaglobulins from the control subjects (Fig. 3). The serum gammaglobulins from cases 1, 2, and 5 significantly stimulated basal PRL secretion as compared with the gammaglobulins from control subjects (Fig. 4).

The addition of gammaglobulins did not affect the viability of the pituitary cells because the baseline hormone levels in the cultured pituitary cells after the experiments were almost unchanged compared with the baseline hormone levels before the experiments.

Figure 2. Effects of gammaglobulins extracted from the sera of cases 1–10, on baseline TSH release by rat pituitary cell cultures. Data are expressed as mean $\pm$ SEM. Numbers in the columns indicate case number. ***Significant alterations at $p < 0.05$ and $p < 0.01$ when compared to normal subjects, respectively.

Figure 1. Effects of gammaglobulins, extracted from the sera of cases 1–7, 9, and 10, on the baseline (–CRH) and the CRH-induced (+CRH, 10 μ g/ml) release of ACTH by rat pituitary cell cultures. Data are expressed as mean $\pm$ SEM and are representative of at least two experiments. Numbers in the columns indicate case number. *Significant alterations at $p < 0.05$ when compared to normal subjects.

Figure 3. Effects of gammaglobulins extracted from the sera of cases 3 and 9, on baseline LH release by rat pituitary cell cultures. Data are expressed as mean±SEM. Numbers in the columns indicate case number. *Significant alterations at $p<0.05$ when compared to normal subjects.

Figure 4. Effects of gammaglobulins extracted from the sera of cases 1–10, on baseline PRL release by rat pituitary cell cultures. Data are expressed as mean±SEM and are representative of at least two experiments. Numbers in the columns indicate case number. ***Significant alterations at $p<0.05$ and $p<0.01$ when compared to normal subjects, respectively.

Analysis of anti-CRH receptor binding antibody

Only 10–12% of the total ^{125}I -ovine CRH added was bound to rat pituitary cell membrane preparations in the presence of gammaglobulins from patients and controls. Gammaglobulins from all 10 patients, including cases 1, 4, and 7, whose gammaglobulins showed an inhibitory or stimulatory effect on ACTH secretion neither inhibited nor stimulated the binding of ^{125}I -ovine CRH to the cell membrane preparations as compared with gammaglobulins from the control subjects (data not shown).

Analysis of anti-CRH antibody activity

Gammaglobulins from cases 3 and 8 (final concentration, 2.5 mg/ml) showed slight [^{125}I -Tyr]-CRH binding activity, (3% and 2.4%, respectively). These results slightly exceeded the mean+2SD (1.91%) observed in control subjects (Table 2).

Table 2. [^{125}I -Tyr]-CRH Binding (%)

Patient	Gammaglobulin	
	2.5 mg/ml	0.5 mg/ml
1	1.3	0.2
2	0	0.3
3	3.0 ⁺	0.8
4	0.8	0
5	1.8	1.3
6	0.8	1.0
7	0	0.7
8	2.4 ⁺	1.1
9	1.3	1.2
10	0	0
Controls	0.75±0.58	1.0±0.59*

*Mean±SD, ⁺>Mean+2SD

Gammaglobulins from the remaining 8 patients showed no significant anti-CRH antibody activity.

Discussion

Gammaglobulins extracted from the sera of 3 patients with PGA type III (IDDM + AITD) and an isolated failure of pituitary hormone, inhibited the secretion of ACTH, TSH, and gonadotropin, in our rat anterior pituitary cell culture system. Gammaglobulins from some other IDDM patients also showed either inhibitory or stimulatory effects on anterior pituitary hormone secretion.

Involvement of an autoimmune disorder in the dysfunction of the anterior pituitary has been suspected in IDDM. Mirakian et al detected anti-pituitary antibodies in some IDDM patients by using immunofluorescence (7). Additional reports have described patients with IDDM and an ACTH deficiency, Hashimoto's thyroiditis and idiopathic hypoparathyroidism (PGA), and patients with IDDM combined with a gonadotropin deficiency (8, 9). These reports suggest that an autoimmune disorder contributes to the pathogenesis of anterior pituitary dysfunction. With respect to ACTH deficiency, pituitary autoimmunity has been suggested as a primary cause in some cases (12–16). This was corroborated by Richtsmeier et al who described a patient with ACTH deficiency and lymphoid hypophysitis who exhibited a selective loss of corticotropin-secreting cells (4).

The gammaglobulins extracted from the sera of cases 1 and 7 in the present study inhibited the CRH-induced secretion of ACTH in rat anterior pituitary cell cultures. This suggests an autoimmune mechanism impairing ACTH-secreting cells, which may be partly responsible for the development of the ACTH deficiency seen in case 1. Meanwhile Scherbaum et al detected autoantibodies to ACTH-producing cells in the serum of a patient with Cushing's disease, which suggests the existence of

an ACTH-stimulating antibody (17). In the present study, gammaglobulins from case 4, a patient with Graves' disease, stimulated basal ACTH secretion in our cell culture system. Thus, inhibitory and stimulatory autoimmune mechanisms may be involved in the anterior pituitary function of patients with IDDM.

We also investigated the site of action of the gammaglobulins isolated from these patients. In our CRH receptor binding assay system, the gammaglobulins studied neither inhibited nor stimulated the binding of CRH to the membrane preparations vs. controls. Except for a small amount in cases 3 and 8, no anti-CRH antibody activity was detected. Sauter et al reported a case of ACTH deficiency in which antipituitary antibody was detected by immunofluorescence (18). Those authors postulated that the autoantigen could be a cell-specific glandular factor that is involved in the posttranslational processing of proopiomelanocortin (POMC) or in the secretion of ACTH (18). Thus, the site of gammaglobulin action in the ACTH-producing cells of cases 1, 4, and 7 may be within the cytosol of the pituitary cells. Plasma levels of ACTH and the responses to the combined pituitary hormone tests were normal in cases 5 and 7, who had active gammaglobulins. The discrepancy between the *in vitro* and *in vivo* findings may be explained by other factors that affect pituitary function, and which overcome the effect of gammaglobulins *in vivo*. Gammaglobulins from case 1 significantly inhibited basal TSH secretion, whereas the TSH response to the combined pituitary hormone tests was enhanced. It is possible that the hypothyroidism in case 1 overwhelmed the inhibitory effect of gammaglobulins on TSH secretion.

With respect to the isolated deficiencies of gonadotropin and TSH, several reports suggest that an autoimmune disorder occurs in only one type of pituitary hormone-producing cell (9, 19–22). Pouplard observed that the sera of patients with an isolated deficiency of FSH-LH and TSH caused specific immunofluorescent staining on FSH-LH-producing cells as well as on TSH-producing cells of the guinea pig pituitary (20). The author also postulated pituitary autoimmunity as the initiator of this pituitary dysfunction. The gammaglobulins isolated from case 2 with an isolated failure of TSH inhibited the secretion of TSH *in vitro*, and those from case 3 with an isolated failure of gonadotropin inhibited the secretion of LH, which suggests that autoimmune mechanisms are exerted on each type of pituitary cell to cause a specific, isolated failure in pituitary hormone secretion.

The role of prolactin in humoral and cell-mediated autoimmune reactions (23–27) and in endocrine autoimmune diseases associated with hyperprolactinemia (28–30) has been discussed. Bottazzo et al reported the existence of autoantibodies to prolactin secreting cells in some patients with the PGA syndrome (31). Serum PRL levels are reportedly elevated in some patients with autoimmune hypophysitis as well (31–35). The presence of a PRL-stimulating antibody or the compression of the pituitary stalk by swelling may be responsible for the PRL elevation (23, 33–35). Case 5 in the present study showed a hyperresponse of PRL in the combined tests of pituitary

hormone function. Gammaglobulins from cases 1, 2, and 5 stimulated basal PRL secretion *in vitro* suggestive of a stimulatory effect on the PRL secreting cells. These data also suggest a possible relationship between PRL and endocrine autoimmunity. The differing effects of gammaglobulins on TSH, LH, and PRL indicate that different antibodies may act independently on each hormone-producing cell (20).

In summary, the present data suggest that some patients with IDDM, especially those with other endocrine autoimmune diseases, may possess substances in the gammaglobulin fraction that affect the secretion of specific hormones of the anterior pituitary and might be antibodies to the anterior pituitary.

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