

Natural occurrence of IgE antibodies to peptide hormones in man

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Abstract. IgE antibodies to peptide hormones or their fragments were investigated using specific radioallergosorbent tests. Ninety-six sera were obtained from otherwise healthy individuals with a positive RAST to at least one common allergen and without previous contact to exogenous hormones. Total serum IgE was normal ($< 300 \text{ ng ml}^{-1}$) in 41 and elevated in 55 sera. Only one serum with normal total IgE had reagins to proinsulin. In sera with elevated total IgE positive tests ($> 8 \times$ background) were observed frequently: hGH 9.1%, GHRH₁₋₄₄ 5.5%, GHRH₁₋₂₉ 12.7%, erythropoietin 10.9%, human calcitonin 14.6%, salmon calcitonin 1.8%, ACTH 5.5%, insulin 14.6%, proinsulin 7.3%, insulin A chain 1.8%, insulin B chain 18.2%, C-peptide 9.1%, and IGF 9.1%.

The data show natural occurrence of reagins to peptide hormones in atopic persons. A risk at exposure to these peptides may exist in about 1% of the general population.

Keywords. IgE antibodies, natural occurrence, peptide hormones, total IgE.

Introduction

Immediate type allergic reactions to insulin have been observed during treatment with the homologous hormone [1,2]. IgE antibodies were identified in these patients, in cases without allergic reactions, and prior to insulin treatment [1,3]. Our untreated diabetic patients with anti-insulin IgE antibodies had also elevated total serum IgE. Persons with elevated total serum IgE are classified atopic [4]. A relationship between atopy and the occurrence of reagins to peptide hormones appeared to be possible.

We have looked for IgE antibodies to peptide hormones in sera from patients prone to allergies. Patients with a positive radioallergosorbent test to at least one of the common allergens were selected. None of them had previous contact with exogenous hormones.

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Patients and methods

Patients

Ninety-six individual sera were obtained from patients with allergic manifestations and with positive radioallergosorbent test (RAST) to any common allergen (50 females, 46 males). Patients with additional diseases, endocrine syndromes, or previous contact with hormones were excluded.

Peptide hormones

The following peptides were generous gifts: Biosynthetic human insulin, proinsulin, and C-peptide (Eli Lilly & Co, Indianapolis, USA); isolated (SSO⁻³) insulin A and B chains (Deutsches Wollforschungsinstitut, Aachen, FRG); biosynthetic human insulin-like growth factor (IGF) and calcitonin (Ciba Geigy, Basel, Switzerland); biosynthetic natural sequence human growth hormone (Serono, Freiburg, FRG); salmon calcitonin (Sandoz AG, Basel, Switzerland); biosynthetic erythropoietin (Boehringer, Mannheim, FRG).

The following peptides were purchased: Human ACTH (Sigma, München, FRG); human growth hormone releasing hormone, sequence GHRH₁₋₄₄ and GHRH₁₋₂₉ (Bissendorf, München, FRG).

Antigen-coated discs

Cellulose discs ($\phi = 6 \text{ mm}$) were made from Whatman No. 54 filter paper (Whatman Ltd., Maidstone, UK), suspended in 50 ml ice water, and activated [5] with 1 g CNBr in 5 ml dimethylformamide (20 min, pH 10–11). Five hundred discs were coated with 1 mg of each antigen in 10 ml of $0.1 \text{ mol l}^{-1} \text{ NaHCO}_3$ overnight. Excess active groups were blocked with 0.3 mol l^{-1} ethanolamine, followed by 2% bovine albumin [5]. Control discs without antigen were also prepared. Determinations of residual antigen in the supernatants showed that the coupling efficiency was $> 80\%$. Insulin, cross-reacting proinsulin, as well as insulin A and B chains, were measured by an insulin RIA (Pharmacia, Freiburg, FRG), and hGH by hGH-MCA (Wellcome, Burghwedel, FRG).

Radioallergosorbent test [5]

Antigen-coated discs were incubated with 50 μ l serum overnight. After washing with 3×2 ml phosphate buffer (0.1 mol l^{-1} , pH 8.0), the discs were incubated with 50 μ l of ^{125}I -labelled horse anti-IgE antibody (Kallestad, Austin, Texas, USA). Four hours later the discs were washed and counted. The background was <100 cpm. Values of >800 cpm were considered positive. Commercial RAST systems use a limit of 500–800 cpm. Total serum IgE was measured with Quanti Clone Kit (Kallestad, Austin, Texas, USA).

Statistics

The χ^2 -test was used. Results are expressed as means $\pm$ SEM.

Results

Ninety-six individual sera from patients with positive RAST to common allergens were investigated. Total serum IgE was normal ($<300 \text{ ng ml}^{-1}$, $138.6 \pm 13.5 \text{ ng ml}^{-1}$) in 41, and elevated ($>300 \text{ ng ml}^{-1}$, $1712.4 \pm 203.4 \text{ ng ml}^{-1}$) in 55 cases. One of the sera with normal serum IgE had specific reagins of more than eight times the background value to proinsulin. IgE antibodies against other peptide hormones were not measured at this level. As shown in Table 1 sera with elevated total IgE concentrations recognized peptide hormones or fragments of hormones more frequently than sera with normal total IgE ($P < 0.001$). Single measurements of up to 17-fold the background were found. Nine sera were positive for one hormone, 12 sera had IgE antibodies against more than one hormone (up to six).

Table 1. Incidence of IgE antibodies to peptide hormones or fragments of hormones in 41 sera with normal total IgE and in 55 sera with elevated total IgE ($>300 \text{ ng ml}^{-1}$)

Hormone	Incidence	
	Normal IgE	Elevated IgE
Human growth hormone	—	9.1%
Human GHRH (1–44)	—	5.5%
Human GHRH (1–29)	—	12.7%
Human erythropoietin	—	10.9%
Human calcitonin	—	14.6%
Salmon calcitonin	—	1.8%
Human ACTH	—	5.5%
Human insulin	—	14.6%
Human proinsulin	2.4%	7.3%
Human insulin A chain	—	1.8%
Human insulin B chain	—	18.2%
Human C-peptide	—	9.1%
Human insulin-like growth factor	—	9.1%

The radioallergosorbent tests were considered positive at more than eight times the background value.

Discussion

The data obtained from this study show that specific IgE antibodies to peptide hormones or their fragments occur naturally in individuals without previous contact to exogenous hormones. A history of an autoimmune process or an inflammation with damage of hormone-producing cells may be discussed as a cause in the case of insulin, but can be ruled out for most other hormones. Reagins to hormones are observed frequently in sera with elevated total IgE. A positive RAST to common allergens alone does not predispose the individual.

The IgE system recognizes hormones stabilized by disulphide bonds (e.g. hGH, insulin or IGF) as well as chain molecules (e.g. ACTH, GHRH_{1–44}). In the case of GHRH the complete 1–44 molecule is less frequently bound than the 1–29 sequence, indicating recognition of the amide group added in position 29.

Persons with elevated total serum IgE constitute about 10% of the general population [6]. An incidence of about 10% of IgE antibodies to single hormones in our atopic population is equivalent to about 1% of the general population.

The natural occurrence of anti-peptide reagins has therapeutical and forensic aspects. Allergic reactions up to fatal events have been observed following initial application of ACTH_{1–39} [7]. Reactions may also occur during the first diagnostic or therapeutic use of other peptides. In addition irritations at the injection site may alter the pharmacokinetics of hormone preparations. Repeated contact with peptides is not a prerequisite for an IgE-mediated allergic reaction in persons with natural reagins.

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