Symposium on Receptor Diseases*

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(1) Hormone-Receptor Diseases Concept and Nation-Wide Survey in Japan

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I. Introduction.

It has been generally accepted that hormones bind receptors in target organs as the first step and then exert their actions through a sequence of complex biochemical events. Abnormalities at any steps of these events lead to the disturbances in hormone actions, "peripheral unresponsiveness to hormones". These disorders can be divided into two groups: one is the receptor defect and the other is the post-receptor defect. "Hormone-receptor diseases" correspond in general to the receptor defect and can be defined as disorders caused by abnormalities in hormone receptors and not in the steps following the hormone-receptor interaction. This article deals with the definition and classification of hormone-receptor diseases and then describes results of a survey in Japan on certain hormone-receptor diseases.

2. Definition and classification of hormone-receptor diseases.

"Hormone-receptor diseases" can be defined as disorders caused by abnormalities in the number, affinity and specificity of hormone receptors. In a wide sense, they also imply disorders possibly resulted from the receptor defect, but having the possibility of post-receptor defects as well. The receptor diseases exhibit usually, but not necessarily, clinical manifestations of unresponsiveness to hormones. For example, Graves' disease, which is considered to be caused by antibodies to TSH receptors, shows signs of hyperfunction.

Table 1 shows a list of hormone-receptor diseases. The first group includes congenital defect in either the number or affinity of hormone receptors. The second group comprises acquired abnormalities in hormone receptors. The first subgroup includes diseases caused by receptor antibodies. Insulin resistance type B resulted from destruction of insulin receptors by

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Table 1. Classification of hormone-receptor diseases

1. Congenital receptor defect
Testicular feminization syndrome or other androgen insensitivity
Refetoff's syndrome
Insulin resistance (Type A)
2. Acquired receptor defect
A. Disorders due to anti-receptor antibodies
Insulin resistance (Type B)
Graves' disease
B. Disorders due to down regulation of receptors
Obesity
Bartter's syndrome (?)
C. Receptor abnormalities in neoplasm
3. Possible receptor defect (postreceptor defect cannot be ruled out)
Pseudohypoparathyroidism
Nephrogenic diabetes insipidus
Congenital adrenocortical unresponsiveness to ACTH
Congenital unresponsiveness to TSH
Laron type dwarfism
Unresponsiveness to gonadotropin
Pseudohypoadosteronism
Vitamin D-resistant rickets

insulin-receptor antibodies is an example of this group. The second subgroup is the receptor abnormality induced by the regulatory mechanism of hormone receptors. Excess of a hormone usually results in a decrease in the number of its receptors (down regulation) and insensitivity to the hormone. Insulin resistance in obesity is caused at least in part by a decrease of hormone receptors induced by hyperinsulinemia. The third subgroup is the abnormality in specificity of hormone receptors seen in neoplasms. The third group includes a variety of diseases possibly caused by receptor abnormalities, although further studies should determine whether these are receptor defects or post-receptor defects.

3. Survey of certain hormone-receptor diseases in Japan.

1) Methods

Five diseases, testicular feminization syndrome, pseudohypoparathyroidism, nephrogenic diabetes insipidus, Bartter's syndrome and congenital adrenocortical unresponsiveness to ACTH, were selected for the nation-wide survey in their prevalence and clinical features. The first inquiry was sent to all hospitals in Japan with beds more than 200, in order to know the approximate number of the diseases in a period of 1967-1976. The detailed survey was done based on the results of the first survey, by sending the form of inquiry. Details of results are published elsewhere¹⁾.

2) Prevalence of the diseases

Table 2 shows results of the first and second survey and estimated numbers of the patients. The first column represents the number of patients collected from the first inquiry and the second column the number of patients corrected by the recovery rate. The third column shows the number of patients collected in the second survey and the fourth one the number of definite cases. The fifth column shows estimated number of patients based on an assumption that definite cases are equally distributed in non-responding hospitals.

3) Clinical and biochemical features of testicular feminization syndrome (TFS)

In the second survey, 73 cases of TFS were collected. Signs of partial virilization,

Table 2. Prevalence of hormone-receptor diseases in Japan, estimated from results of nation-wide survey.

	First Survey		Second Survey		Estimated
	Nr. of Patients	Corrected Nr.	Nr. of Patients	Definite Case	Nr. of Patients
Testicular Feminization Syndrome	185	448	83	73	394
Pseudohypoparathyroidism	108	256	78	69	220
Nephrogenic Diabetes Insipidus	128	312	81	75	288
Bartter's Syndrome	66	164	61	34	93
Congenital Unresponsiveness to ACTH	14	33	9	5	18

See text for the explanation of each column

such as clitoral enlargement, labial fusion and hypospadias, that suggest the incomplete form of TFS, were observed in 23% of the cases. However, deepening of the voice, acne and masculine habitus were seen in 11%, 10% and 10%, respectively. Pubic and axillary hairs were absent in 70% and vagina was normal in length in only 30%. Uterus was absent in all cases and tuba in 92%. None of the cases had seminal vesicles, whereas 84% of them had epididymis, suggesting the difference in sensitivity to androgens. Testes were found in the inguinal region in 65%, in the labia in 8% and in the abdomen in 27%. Plasma testosterone levels were within normal limit in 93% and high in 7%, whereas plasma LH and FSH levels were elevated in 93% and 79%, respectively. Karyotyping revealed XY in 99% and mosaicism in 1%. Familial occurrence of the disease was observed in 28 siblings from 8 families. Within a family, the concordance was observed in the grade of virilization and the site of testes present. Dihydrotestosterone receptors in fibroblasts were negative in 2 cases tested.

4) Clinical and biochemical features of pseudohypoparathyroidism (PHP)

Sixty-nine cases of PHP, 27 males and 42 females, were collected. There were 38 cases of PHP of Drezner's Type I and 6 cases of Type II²⁾, although the remaining 25 cases were unclassified because of the lack of data. The mean ($\pm$ SD) ages of probable onset of the disease were 9.1 ± 6.7 in Type I and 12.4 ± 10.8 in Type 2. There was no difference in frequencies of short stature, round face and short metacarpals, but the frequencies of soft tissue calcification and cataract were higher in Type I than in Type II. The mean ($\pm$ SD) serum calcium concentration in Type I, 6.2 ± 1.2 mg/dl, was lower than that in Type II, 7.3 ± 1.3 mg/dl, whereas the mean phosphorus concentration in Type I, 6.7 ± 2.0 mg/dl, was higher than that in Type II, 5.3 ± 1.6 mg/dl. These results indicate that the grade of hypocalcemia and hyperphosphatemia is

more severe in Type I, coinciding with higher frequency of soft tissue calcification.

Ellsworth-Howard test was repeated after the successful treatment in 21 cases (20 Type I and one Type II). None of the type I patients showed normal response of urinary cyclic AMP to PTH after the treatment, although the response of urinary phosphate was normalized in one and improved in 8. One Type II patient showed normal phosphate response after the treatment. These results suggest that the response of cyclic AMP is unchanged irrespective of treatment in most cases, suggesting the receptor defect as the cause of the disease.

5) Clinical and biochemical features of nephrogenic diabetes insipidus (NDI)

In the second survey, 78 cases of NDI, 67 males and 11 females, were collected. The onset of the disease was below age 1 in 48 cases, but there are 7 cases of adult onset. Familial occurrence of NDI was seen in 32%. The initial symptoms were fever, vomiting, cramp in most of the patients below age 1, whereas they are polydipsia and polyuria in adult-onset cases. Growth retardation became evident after the age of 3 months but was ameliorated after puberty. Serum Na was elevated in 41%, plasma osmotic pressure was high in 26% in random sampling and 41% after dehydration. The effect of treatment with diuretics was excellent in 49% and fair in 39%. The mode of inheritance in familial cases coincided with sex-linked recessive in 25 of 27 families.

3. Conclusion

Hormone-receptor diseases can be defined as disorders caused by congenital or acquired abnormalities in the number, affinity and specificity of hormone receptors, although disorders due to possible receptor defect are tentatively included at present. A nation-wide survey for several receptor diseases was performed in Japan by sending the inquiries. The prevalence of testicular

feminization syndrome, pseudohypoparathyroidism, nephrogenic diabetes insipidus, Bartter's syndrome and congenital adrenocortical unresponsiveness of ACTH were estimated. Their clinical and biochemical features are also discussed.

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(2) Diabetes Caused by Anti-Insulin Receptor Antibody

(i) Clinical Findings and Changes of Titer of Anti-Insulin Receptor Antibodies in a Patient with Severe Insulin Resistant Diabetes Caused by Anti-Insulin Receptor Autoantibodies

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Among patients with extreme insulin resistant diabetes, some patients are found to have syndromes with insulin receptor disorders: Type A with probable primary insulin receptor defect, Type B with circulatory antibodies to the insulin receptor and Type C with postreceptor defect.

We experienced a patient with severe insulin resistant diabetes accompanied by hypergammaglobulinemia and Sjögren's syndrome. In this patient there was a high titer of anti insulin receptor autoantibodies. Immunosuppressive therapy resulted in the disappearance of the antiinsulin receptor antibody titer and the patient concurrently showed complete remission of diabetes.

The patient was a 45-year-old woman, who first noted polyarthralgia in June 1972. One year later, she had erythema of both cheeks that spread over most of her

face, followed by Raynaud's phenomenon which persisted during the winter. In December 1973, she first noted an increase in thirst and polyuria and on April 26, 1974 the patient was admitted to the Okayama University Hospital for study. She was never previously treated with insulin.

The patient was not obese. She had erythema that covered most of her face and telangiectasia on both cheeks. Her parotid glands were enlarged bilaterally. Initial laboratory data showed: 2+ urinary sugar, white blood cell count 3,400/cmm; erythrocyte sedimentation rate 96 mm/h; serum protein 7.4 g/dl with 2.7 g gamma globulin; normal liver function; negative antinuclear antibodies; low serum complement titer; positive rheumatoid factor. An abnormal glucose tolerance test with