Extreme Insulin Resistance

Introduction

In 1954, Donohue and Uchida described the first reported patients with leprechaunism. The symptoms reported were retardation in intrauterine and postnatal growth, generalized lipodystrophy, and facial abnormalities such as thickened lips and skin, creating a gnome-like appearance. During then 1970's, additional clinical symptoms were added to this syndrome. These include severe insulin resistance, hyperinsulinemia, abnormal glucose homeostasis, myocardial hypertrophy, gonadotropin-independent early onset of puberty, enlarged breasts and clitoris in females, and histological changes in the pancreas and ovaries. This condition affects approximately one in four million live births, and often causes death within the first year of life.

The severe insulin resistance can be caused by defective insulin-receptors which either cannot bind insulin, or have a defective intracellular domain and cannot initiate a signal transduction pathway. The following shows an insulin-binding profile from one normal individual (control) and two patients with leprechaunism:

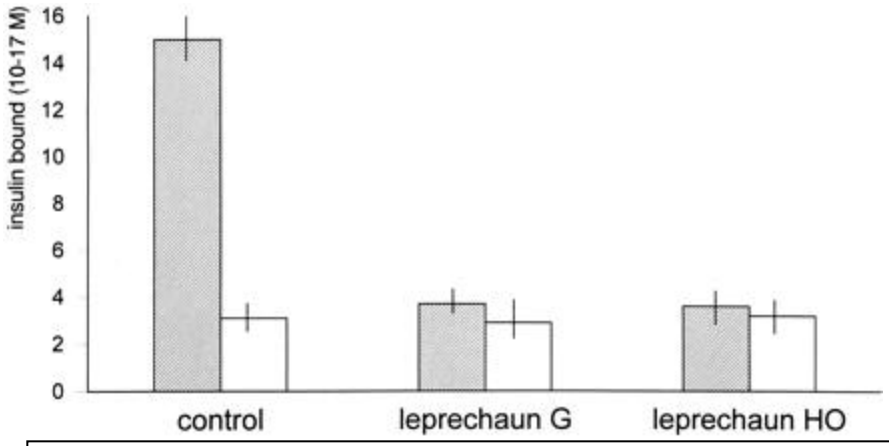

Figure 1: Insulin-binding profile for normal individuals and individuals with leprechaunism (Hart et al, 1996).

The Problem

A six-month old Japanese girl was admitted to the hospital for testing because of her abnormal glucose metabolism. Her body size was very small for her age, and she also had other symptoms such as low-set ears and prominent eyes, decreased subcutaneous fat, and an enlarged clitoris. The following are her oral glucose tolerance and insulin tolerance test results:

Table 1A. Oral glucose tolerance test

Time (min)	0	30	60	90	120	180
Blood glucose (mg/dL)	45	141	182	200	125	49
IRI (μU/mL)	185	1920	1902	2490	2220	1120

Table 1B. Insulin tolerance test (0.1 U/kg insulin)

Time (min)	Blood glucose (mg/dL)
-30	68
-15	47
0	51
15	44
30	45
60	48

Tables 1A and 1B: Oral glucose tolerance test and insulin tolerance test of the patient. Glucose tolerance test was performed with a standard oral glucose ingestion (1.75 g/kg; A), and insulin tolerance test was performed with IV injection of insulin (0.1 U/kg; B) (Nakae et al, 1998).

The following is a profile of insulin binding to insulin receptors in lymphocytes of the patient and a healthy individual (control).

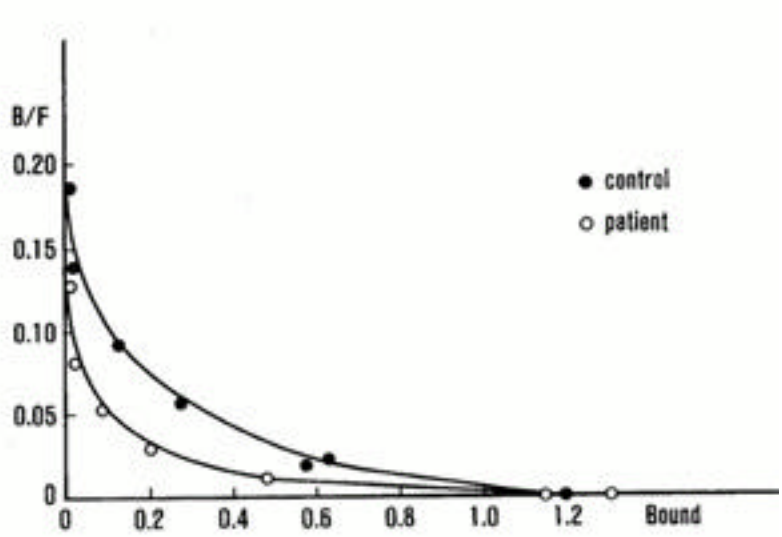

Figure 2. Insulin binding to insulin receptors in lymphocytes. Insulin binding affinity of insulin receptor expressed in control and patient's lymphocytes. Insulin binding was 15.8% in the control subject and 11.4% in the patient, and the K_d values estimated from the plot was 0.45 nM in the control subject and 0.36 nM in the patient (Takahashi et al. 1997).

Questions

(1) What is a glucose tolerance test? Are the patient's results abnormal? What do these results show?

(2) The patient shows a different insulin-binding profile than a normal individual. What do these results imply? What problems can this cause for the patient?

(3) Leprechaunism is caused by a genetic mutation. Where is this mutation located, and what kind of mutation is it? What is the primary effect of this mutation?

(4) What are some possible treatments for this disorder?

Commentary

Leprechaunism is a metabolic disorder similar to diabetes mellitus, but it is much more severe. Two of the tests used to indicate insulin resistance are a glucose-tolerance test and an insulin-tolerance test. In a glucose tolerance test, a fasting plasma glucose test is performed. Then, the patient is fed about 75 grams of glucose, and blood samples are taken over a three-hour period to measure the glucose levels. In a normal individual, glucose levels will rise quickly and then fall quickly back to normal levels. In an individual with diabetes or other form of insulin resistance, such as leprechaunism, the glucose levels will rise quickly, but will fall back down very slowly. This patient's results show that she does have a severe insulin resistance. Her blood glucose levels do not go back to normal until three hours after she is given the glucose. Because it takes so long for her glucose levels to drop, this indicates that her body cannot get the signal that her blood contains a lot of glucose, and this glucose needs to be pulled out and converted to glycogen for storage.

The insulin-binding profile shown for this patient illustrates the cause of her insulin resistance. Her insulin receptors have a lower Kd for insulin than normal. Her receptors have a higher affinity for the insulin, but since they are faulty, they just hang on to the insulin and don't send a signal that insulin is bound. She also has a lower percentage of insulin bound than normal. She will never be able to have as much insulin bound to receptors as a normal individual would, so it is more difficult for insulin to send the signal that there is plenty of glucose in the blood. For this reason, her body will always "think" it is hungry and in need of glucose for energy.

In 1985, the human insulin receptor was cloned, which makes it easy to find exact mutations in defective receptors. There are many different mutations in the insulin receptor gene that result in leprechaunism. A few examples of these mutations include a substitution of methionine for isoleucine at codon 119 in exon 2; missense mutations at codon 1153 in the tyrosine kinase domain substituting either an isoleucine or threonine for methionine; and replacement of a 13-base pair sequence in exon 13 by a 5-base pair sequence, resulting in a net 8-base pair deletion which shifts the open reading frame and results in premature termination. Each of these mutations cause production of genes which code for defective receptors which either cannot bind insulin or cannot initiate a signal transduction pathway.

Leprechaunism is a disorder with varying degrees of severity. There is no known effective therapy for patients with severe insulin resistance, and these patients usually die within the first year of life. Patients such as the one described in this case study can survive with the administration of various substances. Patients are given injections of recombinant human insulin-like growth factor I (rhIGF-I) which improves glucose metabolism by mimicking insulin's effects on glucose metabolism, but it binds to different receptors which are functional. Although this does appear to be working, it is a fairly new treatment, and little is known about it's long-term effects. Patients are also given injections of growth factors to counteract the retardation of growth that accompanies leprechaunism. Because this disorder also effects the metabolism of fat and causes very low levels of subcutaneous fat, patients are also often given injections of subcutaneous fat. In the future, it is possible that this will be a target for gene therapy. Through recombinant DNA techniques, the patients could be given the genes that code for functional insulin receptors. This would greatly reduce all the symptoms and problems this disease causes.

Bibiography

Hart, Leen M. et al. "An insulin receptor mutant (Asp^{707} → Ala), involved in leprechaunism, is processed and transported to the cell surface but unable to bind insulin. *Journal of Biological Chemistry* 1996 271: 18719-18724.

Nakae, Jun et al. "Long-term effect of recombinant human insulin-like growth factor I on metabolic and growth control in a patient with leprechaunism." *Journal of Clinical Endocrinology and Metabolism* 1998 83: 542-549.

Takahashi, Yoshihiko et al. "Roles of insulin receptor substrate-1 and Shc on insulin-like growth factor I receptor signaling in early passages of cultured human fibroblasts." *Endocrinology* 1997 138: 741-750.