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Lessons from Laron Syndrome on the Role of IGF-I on Carbohydrate Metabolism

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Abstract

Laron syndrome (LS) is a rare form of dwarfism caused by defects in the growth hormone receptor causing congenital IGF-I deficiency. The effects of the IGF-I deficiency and its administration on the carbohydrate metabolism was studied in a cohort of 75 patients with LS. IGF-I deficiency in young children is accompanied by hypoglycemia, but progressive obesity leads to insulin resistance and glucose intolerance. Administration of endogenous IGF-I causes hypoglycemia independent of insulin.

Keywords: Laron Syndrome, IGF-I, Hypoglycemia, Diabetes, Carbohydrate Metabolism

Introduction

Laron Syndrome (LS) (OHIM #262500:ICD-10: primary growth hormone insensitivity) is a rare fully penetrant autosomal recessive type of dwarfism caused by exon deletion or mutations of the growth hormone receptor (GH-R) gene [1]. The majority of the mutations are in the extracellular domain of the receptor and few are in the trans membranal or intracellular domain. So far over 70 mutations have been described including 2 in an intron region [2,3]. Only subjects homozygous for the defect are affected. The molecular defects of the GH-R are associated with a high GH serum growth hormone (GH) and low to undetectable serum IGF-I (insulin-like growth factor I) [4,5] i.e., a congenital IGF-I deficiency.

First described in 1966 [6] in Yemenite Jewish families. Its characteristics are dwarfism, below normal head circumference, underdeveloped facial bones, obesity, and delayed puberty; in summary features resembling congenital GH deficiency [7].

In this manuscript the aspects on the changes in the carbohydrate metabolism in Laron syndrome are reviewed.

Subjects

We had the opportunity to study the physiology, patho-physiology of IGF-I in 75 untreated LS patients and the pharmacological effects of IGF-I in treated LS patients [8].

Methods

Determination of blood glucose and insulin and IGF-I after an overnight fast, glucose tolerance test, the glucose/insulin ratio, and the glucose and insulin response after an intravenous bolus of IGF-I.

Results and Discussion

The carbohydrate metabolism is mainly regulated by the glucose and insulin secretion.

As the chemical structure of insulin and IGF-I bear great resemblance. The availability of patients with IGF-I deficiency and sufficiency made it possible to study their metabolic interaction.

Both IGF-I and insulin are pleiotropic hormones with multiple roles in regulating vital metabolic and developmental processes [9].

Whereas insulin is mainly involved in metabolic activities (e.g., control of sugar levels), IGF-I is mainly a protein anabolic and growth factor. However, there are overlapping activities due to the great similarity between the molecular structure of IGF-I and that of proinsulin and between the genomic organization

of the insulin and IGF-I receptors despite that the genes reside on different chromosomes, (that of insulin on chromosome 11 and that of IGF-I on chromosome 12). The highest similarity (84%) between both molecules is found in the tyrosine kinase domain of the β subunit of the receptors. [10].

The study of untreated and subsequently IGF-I treated patients enabled us to study the interaction between these two hormones.

Patients with LS are born slightly obese. Due to the congenital IGF-I deficiency and lack of Growth hormone activity, have hypoglycemia and insulin sensitivity [1,11]. Untreated patients develop progressive obesity [12,13] leading to a decrease in the insulin/glucose ratio [14] hyperinsulinemia, glucose intolerance [15] and eventually Type 2 diabetes mellitus [16].

Further information on the effects of IGF-I treatment on carbohydrate metabolism was obtained once biosynthetic IGF-I became available [17] and when treatment of LS patients with IGF-I was initiated in 1987.

Intravenous IGF-I infusion resulted in a rapid decrease of blood glucose concomitantly with a reduction in serum insulin [18] (Table 1).

Table 1: Glucose and insulin response to an IV injection of IGF-I (75 µg/kg) to 7 untreated adult patients with Laron Syndrome (m ± SD) from Laron et al [19].

	Glucose mg/dl	Insulin µU/ml
Time (min.)		
0	77.4 ± 3.6	5.75 ± 0.8
5	64.2 ± 3.6	4.58 ± 0.7
15	43.2 ± 5.4	2.56 ± 0.4
30	35.7 ± 3.6	2.33 ± 0.2
60	46.0 ± 5.3	2.17 ± 0.3
120	49.1 ± 3.5	2.62 ± 0.7
180	128.6 ± 7.2	16.6 ± 3.6

This finding denoted that IGF-I has a hypoglycemic effect independent from insulin. We assume that it is caused by IGF-I stimulation of hypothalamic somatostatin [19].

Long-term IGF-I treatment of children with Laron syndrome increased adiposity and with-it insulin resistance [20].

The insulin suppressing activity of IGF-I was tried in the treatment of postprandial hyperinsulinemia [21,22] Type 2 diabetes and the metabolic syndrome [23,24].

Conclusion

Despite the similarity in structure between IGF-I and insulin IGF-I, they affects the carbohydrate metabolism also in an insulin independent way.

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