Non-islet cell hypoglycemia

D. LeRoith
Chief Diabetes Branch, NIDDK, Bethesda MD 20892, USA.
e-mail: derek@helix.nih.gov

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NICTH is a fairly uncommon disorder but has been well characterized and the molecular mechanisms involved have given insights into the IGF system, both normal and abnormal. NICTH has brought together the molecular biologists and endocrinologists in a classic cross cultural coordination to study the disorder from all angles and to further understand the disorder.

Key words: Hypoglycemia, Non-islet cell tumor, IGF-2.

INTRODUCTION

Hypoglycemia in adults maybe classified primarily as fasting or reactive. The major causes of fasting hypoglycemia as shown in table 1, include drug-induced, insulinomas and hypoglycemia in association with non-islet tumors (NICTH). This brief review will discuss the role of insulin-like growth factors (particularly IGF-2) in this syndrome. The review will discuss the IGF system, expression of IGF-2 by cancer cells, the potential mechanisms whereby IGF-2 may affect cancer cell proliferation and how IGF-2 causes hypoglycemia in the clinical setting. Diagnostic criteria have been established for the syndrome and certain therapeutic modalities are important for the clinician to consider and will be presented.

THE INSULIN-LIKE GROWTH FACTOR SYSTEM

The IGF system comprises ligands (insulin, IGF-1 and IGF-2), receptors (insulin receptor, IR and the IGF-I receptor, IGF-IR as well as a non-enzymatic IGF-2 receptor also known as the mannose-6-phosphate receptor) (fig. 1) [13], Insulin is produced by the pancreas, circulates free with a very short half-life and interacts with the insulin receptor to affect glucose, fat and protein metabolism primarily on liver, fat and muscle cells. The IGFs, are expressed by many tissues, circulate bound to 6
well-described IGF-binding proteins (IGFBPs 1-6) and interact with the IGF-IR on most cells to affect proliferative, differentiative and anti-apoptotic functions. The six IGFBPs all bind the very high circulating levels of IGFs prolonging the half life to hours rather than minutes in the case of insulin, deliver the IGFs to the peripheral tissues and regulate the interaction of the IGFs and the IGF-IR. Most of the IGFs circulate bound to a ternary complex comprising IGFs, IGFBP-3 and an acid-labile subunit (ALS). IGF-I, IGFBP-3 and ALS are all regulated by growth hormone, such that when GH levels are increased IGF-I, IGFBP-3 and ALS levels rise. IGFs on the other hand, regulate the secretion of GH by negative feedback suppression.

The insulin and IGF-I receptors are a subclass of tyrosine kinase receptors, that are activated following ligand binding which results in autophosphorylation of the receptor [16]. The receptors are synthesized and are expressed on the surface of the cell as oligomers bound together by disulfide bridges. The ligands bind to the extracellular surface on the alpha subunit and the tyrosine kinase domain is on the cytoplasmic portion of the beta subunit. Insulin binds to the IR with very high affinity and with lower affinity to the IGF-IR, whereas IGF-1 and IGF-2 interact with the IGF-IR with high affinity and less so with the IR [16]. More recently, evidence has been presented that the hybrid receptors may be expressed on certain cells. These hybrids are formed during the normal post-translational processing of the IR and IGF-IR and comprise one half IGF-IR and one half IR [12]. The IR: IGF-IR hybrids are detectable in tissues and cells that express both receptors, and thus would not be found to any significant degree in say liver and fat that express predominantly the IR, but are detectable in muscle which expresses significant amounts of both receptors [16]. As best as can be determined, they interact with IGF-I with high affinity and with lower affinity with insulin. In addition, there are splicing variants of the insulin receptor with the exclusion (IR-A) or inclusion (IR-B) of an in-frame exon 11, adding 11 aminoacids to the receptor (fig. 2). IR-A receptor has been detected during fetal development, in epithelial and mesenchymal tumors [8, 11, 17, 19] and reacts with IGF-2 (not IGF-1) with very high affinity [7, 10, 15]. It is believed that this sub-type of the insulin receptor may explain the effects of IGF-2 on cell proliferation under certain conditions. IR-B is the predominant form that is expressed by normal adult tissues that are major targets for the metabolic effects of insulin (adipose tissue, liver and muscle).

Table 1
Major causes of adult hypoglycemia.

<table>
<thead>
<tr>
<th>Fasting</th>
<th>Drug induced: Insulin and sulfonylureas (diabetics on medication or factitious usage)</th>
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<tbody>
<tr>
<td>Insulinomas</td>
<td></td>
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<tr>
<td>Non-islet cell tumors</td>
<td></td>
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<tr>
<td>Endocrinopathies (pituitary or adrenal failure)</td>
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</tr>
</tbody>
</table>

**Figure 1:** The IGF system is comprised of ligands, binding proteins and receptors (primarily the insulin and IGF-I receptors, both tyrosine kinase receptors).

**Figure 2:** The insulin receptor has two subtypes, IRA and IRB and IGF-2 may interact with IRA with high affinity.
EXPRESSON OF IGF-2

Whereas, circulating IGF-1 is primarily of liver origin and highly regulated by GH at the promoter level, the expression of IGF-2 in humans is less well characterized. Circulating levels of IGF-2 are not affected by GH or any known factors. At the cellular level the IGF-2 shows a very interesting pattern of regulation [20, 21]. IGF-2 is highly expressed in many common cancers including colorectal cancers [24]. In mice carrying the igf2 transgene, hepatic malignancies develop more commonly, and β-cell oncogenesis is markedly inhibited in igf2 knockout mice [3, 18]. Thus IGF-2 maybe a second "survival" signal for oncogene-induced abnormal cancer cell growth [2]. The mouse igf2 gene is imprinted and essentially expressed only from the paternal allele. In addition, it lies adjacent to the H19 gene on chromosome 7 and their expression is regulated in a reciprocal manner, such that H19 is expressed only from the maternal allele. Alterations in methylation status of the gene affect its expression [21]. Apparently, in cancer cells, there is an alteration in this pattern and many cancer cells express IGF-2 at levels much greater than normal cells. In culture systems these cancer cells can be shown to release IGF-2 which can then in turn stimulate the IGF-IR or the type A insulin receptor and enhance cell proliferation and/or promote cell survival by inhibition of apoptosis. As will be described below the molecular mechanism of non-islet cell tumor hypoglycemia is associated with increased high molecular weight IGF-2 which is released from the tumors and causes hypoglycemia by stimulating the insulin receptor in addition to the IGF-IR.

THE SYNDROME OF NICTH

Hypoglycemia associated with non-islet cell tumors maybe due to extreme cachexia in the more advanced stages of the cancer or due to release of IGF-2 as is the case of a number of mesenchymal tumors found in the thorax, abdomen and pelvis. In the cases where the etiology is due to release of IGF-2 by the tumor, the tumors are not necessarily large nor is there necessarily any signs of metastases. Indeed, removal of the tumor often leads to complete relief of the hypoglycemia [4, 14].

In the work-up of suspected fasting hypoglycemia the universal test is the 72 hour fast (though shorter periods of fasting should induce hypoglycemia in most patients). Once symptomatic hypoglycemia develops, bloods are drawn and the hypoglycemia relieved by appropriate means. Usually, serum insulin, C-peptide and glucose levels give an indication as to the potential cause (table 2).

Hypoglycemia in the face of suppressed insulin and C-peptide levels in the blood strongly points to the possibility of NICTH and should be investigated accordingly with CT scans and MRIs to identify the tumor site. Meanwhile since IGF-2 is the most likely factor involved blood levels of IGF-2 (and IGF-1, which is usually suppressed) should be measured in addition to GH and IGFBP-3 which are also commonly reduced [13].

The IGFs are synthesized as pre-proIGF molecules in a manner similar to pre-proinsulin [14]. During processing the prohormone is cleaved and the final mature circulating form of the IGFs comprises an A and a B chain (like insulin) except that the smaller C-peptide is not cleaved out as with insulin and there is a short D-peptide extension to the B chain. A rather large E peptide is cleaved out of the prohormone molecule. It has been established using gel-filtration sizing chromatography and specific antibodies that a large proportion of the tumor IGF-2 and that found in the circulation is the prohormone; the E-peptide is still intact [14].

It was proposed and then demonstrated experimentally that the larger precursor form of IGF-2 ("big IGF-2") may interact with IGFBP-3 but that the affinity for ALS was reduced and this could result in a molecule that transited the circulation more rapidly (bound to IGFBP-2) and was more available for interactions with cell surface receptors [9].

Whether the interaction with cell surface receptor involved the IGF-IRs, the IR-A receptors or hybrids has not been established, but hypoglycemia is the result.

Using positive emission tomography studies with 18-F glucose, it was further established in patients that the hypoglycemia was not associated with enhanced glucose uptake by the tumor itself, but the major portion of glucose disposal was into skeletal muscle [6]. This could occur via the IR, the IGF-IR or hybrids of the two. Furthermore, hepatic glucose production which should compensate for the lowered blood glucose levels was totally inhibited, suggesting that in this tissue IGF-2 was acting purely through the IR (since no IGF-IRs are expressed by adult liver) (fig. 3).

<table>
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<tr>
<th>Syndrome</th>
<th>Serum Insulin</th>
<th>C-peptide</th>
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<tbody>
<tr>
<td>Drug Induced (Diabetic or factitious)</td>
<td>+++ suppressed</td>
<td></td>
</tr>
<tr>
<td>Insulin secretagogues</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>NICTH</td>
<td>suppressed</td>
<td>suppressed</td>
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MANAGEMENT

Surgical removal of the tumor or reduction in size by radiation or chemotherapy will reduce the circulating levels of “big IGF-2” and cure the hypoglycemia. This effect is apparently due to the return to normal in the proportion of mature processed IGF-2 in he circulation with a reversal of the hormonal changes described above, particularly the ternary complex of IGF-2, IGFBP-3 and ALS. In cases where debulking the tumor is not possible, GH therapy by increasing IGFBP-3 and ALS expression and release into the circulation has been beneficial as has use of corticosteroids and somatostatin.

REFERENCES


