Insulin-Like Growth Factor Physiology

What we have Learned from Human Studies

Jeff M.P. Holly, PhD*, Claire M. Perks, PhD

KEYWORDS

- Insulin-like growth factor I • Insulin-like growth factor II
- Insulin-like growth factor binding protein • Insulin-like growth factor receptors

KEY POINTS

- Although very similar to insulin and its receptor; the modus operandi of the insulin-like growth factors (IGFs) within the body is very different from that of the traditional peptide hormone.
- In the tissues the IGFs are important regulators of cell survival, growth, metabolism, and differentiated function; the complex system of interacting proteins may confer some specificity to these actions.
- The IGFs play an important role in metabolic regulation. Many of the major health issues that are increasingly common in our societies relate to the energy imbalance associated with a modern lifestyle and the consequent metabolic disturbance.

BACKGROUND

The insulin-like growth factors (IGF-I and IGF-II) were originally described in the late 1950s as skeletal growth factors that were produced in the liver in response to pituitary growth hormone (GH) and appeared to mediate the effects on whole-body somatic growth, and hence were called somatomedins.[1] The IGFs were independently discovered as "insulin-like" activity that was present in serum and could not be blocked by very specific insulin antibodies, which was termed nonsuppressible insulin-like activity.[2] When these peptides were subsequently characterized structurally[3] it was realized that they shared considerable homology with proinsulin and hence were given their present names. Accumulating evidence indicated that in addition to production in the liver, both IGF-I and IGF-II were produced in most, if not all, tissues. It also became clear that in addition to their metabolic and growth-promoting actions, the IGFs were also able to regulate cell survival, adhesion, motility, differentiation, and

School of Clinical Sciences, University of Bristol, IGFs & Metabolic Endocrinology Group, Learning & Research Building, 2nd Floor, Southmead Hospital, Bristol BS10 5NB, UK
* Corresponding author.
E-mail address: Jeff.holly@bristol.ac.uk

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most differentiated cell functions. With their ubiquitous presence and pluripotential actions, the IGFs have been purported to play important roles in a wide variety of human abnormalities, many of which are the topic of the other articles in this issue. This article concentrates on studies that have indicated how the IGF system operates and its role in normal human physiology, and focuses on aspects that are different from those revealed in animal models or have yet to be examined in such experimental models.

SYSTEMIC MODUS OPERANDI

The growth factors IGF-I and IGF-II share a high degree of homology with proinsulin, and their actions on cells are mediated by a classic transmembrane tyrosine kinase cell-surface receptor that is also remarkably similar to the insulin receptor, particularly in the tyrosine kinase domain. These receptors each exist as dimers within the cell surface, and they are so similar that in cells where both are expressed there is substantial heterodimerization, forming hybrid IGF-I/insulin receptors. These hybrids appear to act more like IGF-I receptors in vitro, but their physiologic role in vivo is poorly understood. All of these receptors share considerable overlap in their intracellular signaling capability.[4] There is also an IGF-II receptor, a single large transmembrane protein that is completely unrelated to the IGF-I and insulin receptors. The IGF-II receptor does not appear to act as a traditional signaling receptor in response to IGF-II binding. In relation to IGF function it is thought to act as a clearance receptor for IGF-II, because disruption of gene expression in mice resulted in elevated IGF-II levels and overgrowth. These receptors therefore appear to provide an additional safeguard to control the amount of IGF-II to which a cell is exposed in addition to all of the IGF-binding proteins (IGFBPs) that will control both IGF-I and IGF-II. These receptors, however, are clearly multifunctional. Their most well characterized role is as mannose-6-phosphate receptors involved in the targeting of lysosomal enzymes to the lysosomes within the cell. However, they also bind latent transforming growth factor β and enable its activation on the cell surface, and also bind to retinoids, urokinase receptors, and many other proteins. The potential functional consequences of interactions between IGF-II and all the other possible ligands of the IGF-II receptor are far from clear.[5]

Despite the remarkable similarities between the IGFs and insulin and their signaling receptors, they have evolved in mammals to operate in a very different way as communication systems within the body. Insulin expression is very restricted, principally just to the β cells of the pancreatic islets. It is stored there in secretory granules within the cells and secreted via the regulated secretory pathway from these cells in response to stimuli, primarily glucose fluctuations. Regulated secretion from the pancreas is therefore the primary determinant of insulin activity throughout the body. By contrast, the IGFs are expressed widely and in many cell types in tissues throughout the body. Furthermore, like most other cytokines, the IGFs are not stored within secretory granules within cells but are secreted as they are produced, via the constitutive secretory pathway. Insulin therefore acts in a classic endocrine manner; it is secreted from the pancreas into the circulation and is carried around the body until it encounters a cell receptor in a target tissue. By contrast, when the IGFs are secreted they then immediately associate with soluble high-affinity binding proteins, the IGFBPs, which are present in excess. The IGFBPs sequester the IGFs and considerably slow their clearance; enabling very high concentrations of IGFs to accumulate. In the circulation 2 of the IGFBPs, IGFBP-3 and IGFBP-5, are bound to a further large glycoprotein, the acid-labile subunit (ALS) that is present in excess. This ternary