INTRODUCTION

Although the regulation of plasma glucose is a dominant response associated with insulin action, glucose homeostasis depends on the integration of insulin signals in many tissues and cells—hepatocytes, muscle, adipose, hypothalamic neurons, pancreatic β-cells, and others (1-7). Understanding how insulin action is coordinated and modulated in these tissues by heterologous signaling cascades is a challenging scientific question of clinical importance.

Unlike classical feedback regulation—illustrated by corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) for cortisol, or gonadotrophin-releasing hormone and gonadotrophins for sex steroids—a well-defined linear feedback mechanism controlling insulin action has never emerged. By contrast, tissue-specific insulin responses are attenuated by circulating nutrients—glucose, amino acids, free fatty acids, and ketones—and proinflammatory cytokines produced in excess during chronic physiologic and inflammatory stress (8). Even compensatory hyperinsulinemia exacerbates the insulin resistance and promotes a cohort of systemic disorders—includ-
ing dyslipidemia, hypertension, cardiovascular disease, and female infertility (9,10). Many laboratories including ours are using mouse genetics to reveal how dysregulated insulin signals in specific tissues can lead to systemic insulin resistance and β-cell failure that progresses to type 2 diabetes (11–14). Understanding the effects of tissue-specific insulin resistance is revealing the principal targets responsible for metabolic disease and its progression to diabetes (15).

THE MAMMALIAN INSULIN/IGF1 RECEPTOR TYROSINE KINASES

The mammalian insulin signaling system includes three well-defined ligands—insulin, insulin-like growth factor-1 (IGF1), and insulin-like growth factor-2 (IGF2)—that regulate the activity of the canonical insulin receptor (IR), the IGF1 receptor (IGF1R), and the IR-related receptor (IRR); however, IRR appears to have a limited role in testicular development that is revealed only upon deletion of both the IR and the IGF1R (16). Thus, central and peripheral insulin and IGF actions are mediated entirely by the IR and IGF1R (Fig. 14.1).

![Figure 14.1](image-url)

**Figure 14.1.** The insulin/insulin-like growth factor family. The insulin/IGF family consists of three hormones: insulin, insulin-like growth factor-1 (IGF1), and insulin-like growth factor-2 (IGF2). These peptide ligands bind as indicated in the figure to five distinct receptor isoforms that generate cytoplasmic signals: two insulin receptor isoforms, IRa and IRb; the insulin-like growth factor receptor, IGF1r; and two hybrid receptors, IRa::IGF1r and IRb::IGF1r. IGF2 also binds to the mannose-6-phosphate receptor, which mediates its endocytosis and degradation. The insulin receptor is the primary target for insulin throughout development and life. The IGF1 receptor is the primary target for IGF1. IGF2 binds to the insulin receptor primarily during embryonic development, and binds the IGF1 receptor throughout life. IGF2 also binds to the mannose-6-phosphate receptor, which targets the IGF2 for degradation instead of signaling. Activation of the insulin receptor or the IGF1 receptor mediate signals primarily via the cytoplasmic proteins IRS1 and IRS2, which mediate somatic cell growth and metabolism.