Tissue resistance to insulin is a clinically significant phenomenon that predisposes an individual to numerous health risks beyond the well-established role it plays in the pathogenesis of type 2 diabetes mellitus (T2D). Quantification of whole-body insulin resistance in humans typically involves determining the ability of insulin to stimulate glucose uptake into muscle. The hyperinsulinemic, euglycemic clamp procedure provides a measurement of muscle insulin sensitivity, as this tissue accounts for 75% of glucose disposal under these conditions (1). The decrement in glucose disposal in an insulin-resistant state such as obesity is entirely due to reduced muscle glucose uptake (1). However, insulin resistance can occur in any insulin target tissue, and will produce a phenotype distinct for the biological characteristics of that tissue (2).

As in vivo determination of insulin sensitivity of an individual is reflective of muscle glucose disposal, this chapter will focus on the studies of insulin signaling in this tissue. In humans, insulin-stimulated muscle glucose disposal varies widely across the normal population, and the insulin-resistant state represents individuals in the lower end of a normal distribution, rather than a discrete condition. In vivo, muscle insulin sensitivity is regulated on a long-term basis by factors such as obesity, and is altered in a more rapid manner by changes in dietary habits and physical activity (3). Though more difficult to quantify, there is evidence for genetic or intrinsic differences in muscle insulin sensitivity as well (4). In any individual, therefore, the degree of insulin sensitivity is determined by numerous factors, both genetic and environmental. Despite advances in the understanding of cellular alterations that can inhibit the biological response to
insulin, the challenge remains to determine the mechanisms contributing significantly to insulin resistance in an individual who is subject to this range of physiological factors.

**INSULIN SIGNALING PATHWAY**

As the components of the intracellular signaling pathway of insulin action have been elucidated over the past 15 years, the potential sites for cellular modulation of insulin responsiveness have increased dramatically. As described recently, the insulin signaling system (Fig. 15.1) consists of a complex integrated network of second messenger proteins (5). The divergence of insulin signaling into separate pathways that regulate distinct biological effects has been well described. However, it has also been long recognized that each of these second messenger pathways are also employed in mediating the intracellular effects of a variety of other hormones. The extent to which activities of these separate pathways interrelate to produce a specific and coordinated cellular response to insulin is only recently being appreciated (5).

![Insulin signaling pathway diagram](image)

**Figure 15.1.** The insulin signaling pathway. The binding of insulin to its receptor leads to autophosphorylation of the β-subunits and the tyrosine phosphorylation of insulin receptor substrates (IRS) and other signaling intermediates such as Shc. Phosphorylated IRS proteins serve as docking proteins for other second messengers. Binding of the SH2 domains of PI 3-kinase (PI3K) to phosphorytrosines on IRS-1 activates this enzyme, thus increasing the intracellular concentration of phosphatidylinositol phospholipids. This in turn activates phosphatidylinositol phosphate-dependent kinase-1 (PDK-1), which subsequently activates AKT/PKB. The net effect of this pathway is to produce a translocation of the glucose transporter (GLUT4) from cytoplasmic vesicles to the cell membrane to facilitate glucose transport. Insulin stimulation of proliferation and protein synthesis can also be mediated by this pathway, although the Ras/Raf pathway is more closely associated with the mitogenic effects of insulin. (Reproduced with permission from Youngren JE. Regulation of insulin receptor function. Cell Mol Life Sci 2007; 64(7–8): 873–91.)