Insulin signaling pathways The insulin signaling pathways provide an excellent example of the "recognition –> hormone release –> signal generation –> effects" paradigm outlined in Figure 42–1. Insulin is released into the bloodstream from pancreatic ?–cells in response to hyperglycemia. Binding of insulin to a target cell–specific plasma membrane heterotetrameric insulin receptor (IR) results in a cascade of intracellular events. First, the intrinsic tyrosine kinase activity of the insulin receptor is activated, and marks the initial event. Receptor activation results in increased tyrosine phosphorylation (conversion of specific Y residues –> Y–P) within the receptor. One or more of the insulin receptor substrate (IRS) molecules (IRS 1–4) then bind to the tyrosine–phosphorylated receptor and themselves are specifically tyrosine phosphorylated. IRS proteins interact with the activated IR via N–terminal PH (pleckstrin homology) and PTB (phosphotyrosine binding) domains. IR–docked IRS proteins are tyrosine phosphorylated and the resulting Y–P–tyrosines form the docking sites of multiple downstream signaling proteins (ie, PI–3 kinase, GRB2, and mTOR). GRB2 and PI3K bind to IRS P–Y residues via their SH2 (Src Homology) domains. Binding to IRS–Y–P residues leads to activation of the activity of many intracellular signaling molecules such as GTPases, protein kinases, and lipid kinases, all of which play key roles in central anabolic actions of insulin. The two best described pathways are shown. In detail, phosphorylation of an IRS molecule (probably IRS–2) results in docking and activation of the lipid kinase PI–3 kinase. PI–3 kinase+ generates novel lipid products that act as "second messenger" molecules.(aPKC, atypical protein kinase C; GRB2, growth factor receptor binding protein 2; IGFBP, insulin–like growth factor binding protein; IRS 1–4, insulin receptor substrate isoforms 1–4; MAP kinase, mitogen–activated protein kinase; MEK, MAP kinase kinase and ERK kinase; mSOS, mammalian son of sevenless; mTOR, mammalian target of rapamycin; p70S6K, p70 ribosomal protein S6 kinase; PDK1, phosphoinositide–dependent kinase; PI–3 kinase, phosphatidylinositol 3–kinase; PKB, protein kinase B; PTEN, phosphatase and tensin homolog deleted on chromosome 10; SGK, serum and glucocorticoid–regulated kinase.)Next, phosphorylation of IRS (probably IRS–1) results in docking of GRB2/mSOS and activation of the small GTPase, p21Ras, which initiates a protein kinase cascade that activates Raf–1, MEK, and the p42/44 MAP kinase isoforms.These, in turn, activate PDK1 and then a variety of downstream signaling molecules, including protein kinase B (PKB/AKT), SGK, and aPKC.These enzymes such as the phosphatase PTEN dephosphorylate the product of the PI–3 kinase reaction, thereby antagonizing the pathway and terminating the signal.Activation or inhibition of their activity is not only mediated by activating phosphoprotein phosphatases and reducing intracellular cAMP levels.The mTOR pathway provides another means by which activated p70S6K and other kinases are involved in nutrient signaling as well as in insulin action.Each of these cascades may influence different biological processes, as shown (protein translocation, protein/enzyme activity, gene transcription, cell growth).An alternative pathway involves the activation of p70S6K and perhaps several other yet unidentified kinases.These protein kinases are important in the regulation of proliferation and differentiation of many cell types.