

## Insulin signalling

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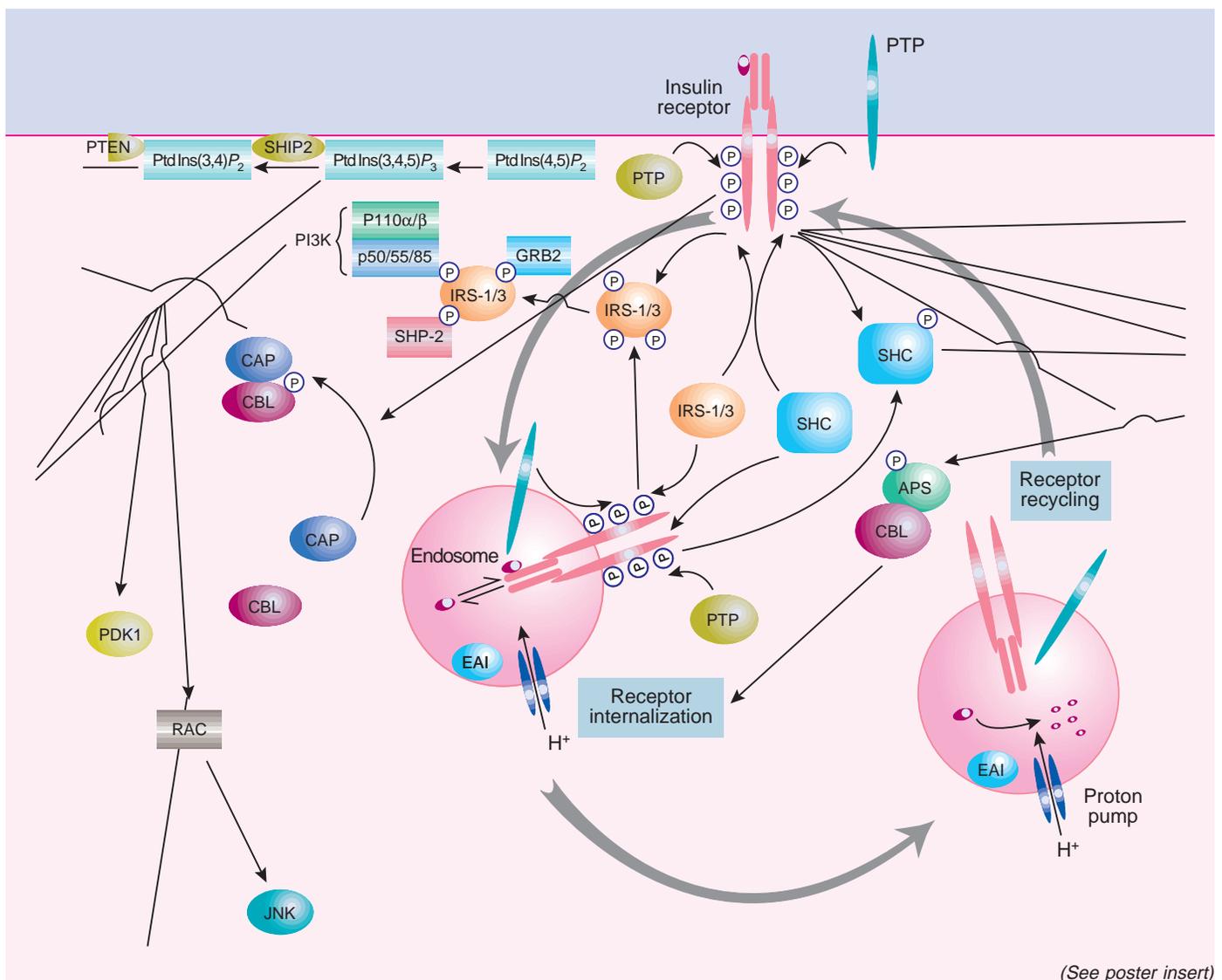
Insulin binding to its receptor results in receptor autophosphorylation on tyrosine residues and the tyrosine phosphorylation of insulin receptor substrates (IRS-1, IRS-2 and IRS-3) by the insulin receptor tyrosine kinase. This allows association of IRSs with the regulatory subunit of phosphoinositide 3-kinase (PI3K) through its SRC homology 2 (SH2) domains. Once activated, the catalytic subunit phosphorylates phosphoinositides at the 3' position of the inositol ring or proteins at serine residues. PI3K activates

PtdIns(3,4)P<sub>2</sub> / PtdIns(3,4,5)P<sub>3</sub>-dependent kinase 1 (PDK1), which activates PKB/Akt, a serine kinase. PKB in turn deactivates glycogen synthase kinase 3 (GSK-3), leading to activation of glycogen synthase and thus glycogen synthesis. Activation of PKB also results in the translocation of GLUT-4 vesicles from their intracellular pool to the plasma membrane, where they allow uptake of glucose into the cell. PKB also leads to mTOR-mediated activation of protein synthesis by PHAS/elf4 and p70<sup>s6k</sup>.

Other signal transduction proteins interact with IRS molecules, including GRB2 and SHP2, a protein-tyrosine phosphatase (PTP) containing SH2 domains. GRB2, an adaptor protein, contains an SH3 domain, which allows

constitutive association with the guanine nucleotide exchange factor mSOS and is part of the cascade including RAS, RAF and MEK that leads to activation of mitogen-activated protein kinase (MAPK) and mitogenic responses in the form of gene transcription stimulated by FOS and ELK1. SHC is another substrate of the insulin receptor; it exists in three isoforms, of 46 kDa, 52 kDa and 66 kDa and contains SH2 and phosphotyrosine binding (PTB) domains. When tyrosine phosphorylated, SHC associates with GRB2 and can thus activate the RAS/MAPK pathway independently of IRS-1.

Signal transduction by the insulin receptor is not limited to its activation at the cell surface. The activated ligand-receptor complex, initially at the cell



surface, is internalised into endosomes, and this process is dependent on tyrosine autophosphorylation. Endocytosis of activated receptors has the dual effect of concentrating receptors within endosomes and allowing the insulin receptor tyrosine kinase to phosphorylate substrates that are spatially distinct from those accessible at the plasma membrane. Acidification of the endosomal lumen, due to the presence of proton pumps, results in dissociation of insulin from its receptor. (The endosome constitutes the major site of insulin degradation by the endosomal acidic insulinase (EAI).) This loss of the

ligand-receptor complex attenuates any further insulin-driven receptor re-phosphorylation events and leads to receptor dephosphorylation by extralumenal endosomally associated PTPs.

The lifetime of a ligand-receptor complex within the endosomal compartment may be an important factor influencing the types of response produced by a particular receptor. Insulin, which has a relatively short endosomal residence, elicits primarily acute metabolic effects, whereas EGF and IGF-I, which have longer endosomal residences, elicit mitogenic responses.

These differences in biological responses could reflect differences in activation of intracellular signalling molecules at specific cellular locations. Thus differences in ligand residency, along with differences in the intrinsic activity of receptors, could contribute to different downstream responses.

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