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Kasuga M, Karisson F A & Kahn C R. Insulin stimulates the phosphorylation of the 95,000 dalton subunit of its own receptor. *Science* **215**:185-7, 1982.
[Diabetes Branch. National Institute of Arthritis. Diabetes, and Digestive and Kidney Diseases, Bethesda. MD]

Cultured lymphocytes and hepatoma cells were labeled with [^{32}P]orthophosphate, and the insulin receptor subunits identified by immunoprecipitation and SDS gel electrophoresis. In both cell types insulin rapidly stimulated the phosphorylation of the (3 subunit of the insulin receptor. Phosphorylation was dose-dependent and occurred on both tyrosine and serine residues. Thus tyrosine phosphorylation is an early event in insulin action. [The *SCI*® indicates that this paper has been cited in more than 765 publications.]

Identification of the Insulin Receptor Tyrosine Kinase Activity

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In part because of the important role of insulin in human physiology and the pathophysiology of diabetes, studies of the mechanism of insulin action have captured the attention of investigators for over 70 years. Although insulin was among the first peptide hormones isolated and the insulin receptor was among the first receptors characterized, the molecular mechanism of signal transduction through this receptor was initially elusive. In the 1970s, the prevailing model of peptide hormone signal transduction for all hormones (including insulin) was based on the paradigm established for hormones acting via generation of cAMP. In this model, the receptor interacted with a separate membrane protein or effector system, presumably an enzyme, to generate a soluble second intracellular messenger of hormone action. However, no second messenger could be found for insulin.

In 1979, a second model of hormone action was defined by the observation that the receptor for the peptide growth factor EGF possessed intrinsic enzymatic activity as a tyrosine protein kinase. We had actually considered a similar possibility for the insulin receptor as early as 1976, but our initial attempts to demonstrate receptor phosphorylation were all negative. Stimulated by the EGF receptor work, however, Masato Kasuga, Anders Karisson, and I decided to repeat the phosphorylation studies, but this time with more persistence. Again the initial attempts were negative, but by switching from membrane- bound to solubilized receptors, eventually we were successful. The initial publication (cited above) appeared in the January 8 issue of *Science,* and before the end of the year at least three other groups had publications confirming and extending our results.

With increased application of ceil and molecular biological techniques, the family of receptor tyrosine kinases or receptors linked to tyrosine kinases has now grown and includes over a dozen members.[1] Aside from insulin, however, the other receptors have growth factors as ligands. Exactly how these tyrosine kinases actually produce their intracellular events was initially unclear. Another decade has passed and only now is the picture beginning to become clear. In the case of insulin, the receptor kinase phosphorylates a high molecular weight intracellular substrate called IRS-1 on multiple tyrosine residues.[2,3] IRS-1 then noncovalently interacts with and stimulates other proteins and enzymes which contain SH2 (src homology 2) domains.[4,5] As with other components of the insulin action cascade, the receptor tyrosine kinase activity and IRS-1 are regulated in diabetes and other states of altered glucose metabolism.[6]

A number of critical questions remain, however. For example, how these events are linked to insulin action in glucose transport is still unknown. Where is the exact defect which causes insulin resistance in Type II diabetes? How and where do the signaling pathways for different biological events diverge? No doubt a decade from now these questions will be answered, and this expanded fundamental knowledge about insulin action will open horizons to new approaches to the treatment and prevention of diabetes mellitus.

1. **Ullrich A & Schlessinger J.** Signal transduction by receptors with tyrosine kinase activity. *Cell* 61:203-12, 1990. (Cited 995 times.)
2. **White M F, Maron R & Kahn C R.** Insulin rapidly stimulates tyrosine phosphorylation of a Mr 185,000 protein in intact cells. *Nature* 318:183-6, 1985. (Cited 275 times.)
3. **Sun X J. Rothenberg P. Kahn C R. Backer J M, Araki E, Wilden** P A, Cahill D A, Goldstein B J & White M F. The structure of the insulin receptor substrate IRS-1 defines a unique signal transduction protein. *Nature* 352:73-7. 1991.
4. **Backer J M. Schroeder G. Kahn C R.** Myers **M G, Jr., Wilden P A, Cahill D A & White M F.** Insulin stimulation of phosphatidylinositol 3-kinase activity maps to insulin receptor regions required for endogenous substrate phosphorylation. *J. Biol. Chem.* 267:1367-74. 1992.
5. **Myers M G, Jr. & White M F.** The new elements of insulin signaling: insulin receptor substrate-I and proteins with SH2 domains. *Diabetes* 42(5):643-50. May 1993.
6. **Saad M J A, Araki E. Miralpeix M, Rothenberg P L, White M F & Kahn C R.** Regulation of insulin receptor substrate 1 in liver and muscle of animal models of insulin resistance. *J. Clin. Invest.* 90:1839-49. 1992.

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