RECENT PROGRESS IN HORMONE RESEARCH, VOL. 48

The Insulin Receptor and Its Substrate: Molecular Determinants of Early Events in Insulin Action

C. RONALD KAHN, MORRIS F. WHITE, STEVEN E. SHOELSON, JONATHAN M. BACKER, EIICHI ARAKI, BENTLEY CHEATHAM, PETER CSERMELY, FRANCO FOLLI, BARRY J. GOLDSTEIN, PEDRO HUERTAS, PAUL L. ROTHENBERG, MARIO J. A. SAAD, KENNETH SIDDLE, XIAO-JIAN SUN, PETER A. WILDEN, KAZUNORI YAMADA, AND STACY A. KAHN

Research Division, Joslin Diabetes Center, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts 02215

Insulin is a potent metabolic and growth-promoting hormone that has pleiotropic effects at the level of the cell and within the intact organism. Insulin acts on cells to stimulate glucose, protein, and lipid metabolism, as well as RNA and DNA synthesis, by modifying the activity of a variety of enzymes and transport processes. The glucoregulatory effects of insulin at a whole body level are predominantly exerted by insulin action on liver, fat, and muscle. In liver, insulin stimulates glucose incorporation into glycogen and inhibits the production of glucose by glycogenolysis and gluconeogenesis. In muscle and fat, insulin stimulates glucose uptake, storage, and metabolism. In addition to these more classical effects, insulin also stimulates glucose metabolism in many other tissues that play little or no role in overall glucose homeostasis. In these nonclassical target tissues, insulin also often acts as a growth factor and in some manner modifies or augments the function of other regulators of metabolism of these cells.

Since the discovery of insulin over 70 years ago, considerable research has been devoted to attempting to understand the molecular mechanism of insulin action. The importance of understanding insulin action has been pointed out by its complex physiologic effects, as well as by the fact that altered insulin action, i.e., insulin resistance, plays important roles in the pathogenesis of many disorders, including obesity, diabetes mellitus, hypertension, and the glucose intolerance associated with many endocrine diseases (Caro *et al.*, 1986, 1987; DeFronzo, 1988; Reaven, 1988; Reddy and Kahn, 1988; Moller and Flier, 1991). It is only with the recent characterization of the insulin receptor as a tyrosine kinase (Kasuga *et al.*, 1982b; Shia and Pilch, 1983; Petruzzelli *et al.*, 1984) and identification of some of