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VIEWPOINT

Insulin Secretion and Action and Diabetes Mellitus

Insulin is generally recognized as the most important short-term anabolic hormone in mammalian organisms. As a consequence, studies have been carried out to understand both the secretion of insulin from the beta cells and the mechanisms of insulin action in target tissues. Moreover in non-insulin dependent diabetes (adult onset diabetes, type II diabetes) there are defects in both insulin action and insulin secretion. Since this disease affects about 5% of the general population, and more than half the population of certain minorities such as certain Native American Indian tribes, it was the purpose of this Prospect to have leading investigators in the field present their opinions as to future directions in the areas of both insulin secretion and insulin action.

After insulin, the second "player" clearly identified as being important in insulin signaling is, of course, the insulin receptor. The $\alpha_2\beta_2$ structure of the insulin receptor has been elucidated and studies are being performed to determine where on the external surface of the receptor insulin binds. In a Prospect published in this issue, Cecil Yip reviews evidence from several groups suggesting that insulin recognition/binding site is in the 2nd and 3rd exon of the receptor α subunit. How this binding/recognition site interacts with the rest of the molecule awaits elucidation of insulin receptor structure by crystallography or other means. Very interesting studies have suggested that hybrids (heterodimers) occur between mutant and normal insulin receptors, and between the insulin receptor and the closely related IGF-1 receptor. These studies have major implications in receptor signaling reviewed here by Frattali et al., and by Steve Jacobs to be published in a Prospect future issue. In addition, hybrid insulin receptor heterodimers consisting of one kinase-deficient half and one half with normal kinase activity, when combined, exhibit no insulin-stimulated kinase activity. This dominant negative phenotype is almost certain to account for the in vivo insulin resistance in patients having one normal and one mutant insulin receptor allele. These patients are extremely rare, however, and receptor kinase defects do not seem to account for a large proportion of type II diabetes.

The general mechanism of insulin action is not well understood. One series of studies, consistent with the results just described, suggests that stimulation of insulin receptor tyrosine kinase leads to signal transmission mediated through covalent modification of cellular proteins by tyrosine phosphorylation. The Prospect by Richard Roth et al. reviews strengths and weaknesses of this hypothesis. Based on the prevalence and importance of such activity in nature, and the general finding that abolishing such activity by site directed mutagenesis also abolished biological function, it seems evident that tyrosine kinase activity should be obligatory for insulin action. On the other hand, certain data inconsistent with this idea (see below), as well as the failure of anyone so far to describe a biochemical pathway for the insulin receptor (or any other tyrosine kinase) action that must include a tyrosine phosphorylated substrate, has led to considerable frustration with this hypothesis. Another line of investigation has suggested that interaction of insulin with its receptor, in the presence of ATP, leads to conformational changes in insulin receptor, and that these conformational changes facilitate interactions of noncovalent receptors with various effector systems. It is likely that both types of mechanisms play a role in insulin signaling.

Another important area of investigation on regulation stems from the very recent observation that tyrosine specific phosphatases play a role in inactivating insulin receptors. These phosphatases may be involved in cells of certain patients with NIDDM, although these investigations are in their early stages. The role of tyrosine phosphatases in insulin action is discussed in a Prospect by Barry Goldstein.

There is substantial investigational activity on effects of insulin on regulation of gene transcription activation and glucose transport. Magnuson and Bridges et al., respectively, describe here their dissection of the genes for glucokinase and glyceraldehyde dehydrogenase where DNA sequences interacting with trans acting

factors have been at least partially elucidated. In the current issue, Klip and Marette, and separately, Barbara Kahn, review recent studies in vivo and in vitro regulation of the insulin responsive glucose transporter. Glucose transporters are members of a gene family including at least six members. One transporter, Glut 4, is acutely and chronically regulated by insulin in two key insulin responsive tissues, muscle and fat. Based on the initial reports of the decreased Glut 4 expression concomitant with hyperglycemia and insulin resistance in a rodent model of diabetes, it was thought that diminished Glut 4 expression might explain much or at least some of human type II diabetes. However, Kahn concludes that more recent data on both rodents and humans do not support this notion. It seems likely nevertheless, as is the case for insulin receptor, that there will be rare forms of insulin resistance involving mutations in Glut 4 that compromise its function. For the majority of type II diabetics, it is probable that other defects, presumably the products of as yet unidentified genes, underlie this complex disease.

As a possible means toward identifying these genetic components of type II diabetes mellitus, one key human model may be the Pima Indians. This highly genetically homogenous tribe of Paleo Indians has a very high prevelance ($>50\%$) of non-insulin dependent diabetes mellitus. These individuals therefore present an important human model of obesity-induced non-insulin dependent diabetes mellitus. In their Prospects Bogardus and Lillioja review the features of these individuals, their genetic makeup, and prospects they present for future research are discussed.

Finally, in the area of insulin secretion two recent developments are the subject of intensive investigation. First, high concentrations of glucose have been shown to desensitize the beta cell both in vivo and in vitro. These data are reviewed in Prospects by Paul Robertson and Grodsky and Bolaffi who propose possible mechanisms for glucose-induced desensitization. Second, certain ion channels in the beta cell are major regulatory systems for stimulus responsive insulin secretion. Sulfonylureas, agents used clinically in non-insulin dependent diabetes to augment insulin secretion, appear to act by regulating these channels as discussed in a Prospect by Chris Boyd.

Thus, "Prospects" in this and future issues of the *Journal of Cellular Biochemistry* review current molecular and cellular biology that underlie key regulatory components of insulin secretion and action. We believe these Prospects will provide a basis and a stimulus for further studies aimed at solving major problems in cell biology and human disease. Such studies will most likely require the identification of novel genes by a variety of modern genetic techniques.

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