MOLECULAR METABOLISM

“100 Years of progress in understanding insulin, its mechanism of action, and its roles in disease and diabetes therapy”

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The year 2021 marks the 100th year of the discovery of insulin, one of the most important discoveries in the history of medical science—in terms of its lasting impact on hundreds of millions of people worldwide and in the development of medical science. This special issue of Molecular Metabolism takes us through the journey over this remarkable century and highlights several aspects of this discovery and its impact — both in diabetes and medical science — in a much broader way.

The journey begins with the history of the discovery of insulin by Banting, Best, Collip, and McLeod. In his article, Flier [1] not only reviews the events that led to this discovery, but also demonstrates how insulin is served as a pacesetter for many advances in modern biomedical sciences. Thus, insulin was the first protein sequenced, one of the first mammalian DNAs cloned, the first hormone for which the 3-dimensional structure was determined by x-ray crystallography, and the target of the first radioimmunoassay —all advances, in addition to the discovery of insulin itself, where the scientists and their study were recognized by a Nobel Prize. Insulin was also the stimulus for many other key advances which changed the concepts of modern biology, including the following discoveries: prehormone and prehormone processing, insulin receptor and its regulation in disease, insulin receptor tyrosine kinase, and unraveling of the molecular mechanism of insulin action. The latter topic, including the roles of insulin receptor substrates and PI 3-kinase, is reviewed in detail in the article by White and Kahn [2], along with the important relationship between insulin and insulin-like growth factors reviewed in the article by LeRoith et al. [3]. Like the insulin molecule itself, how the structure of insulin and IGF-1 receptors change following ligand binding has now been elucidated using a single particle cryo-electron microscopy coupled with x-ray crystallography. This provides even more insight into the nature of this important biological process [reviewed by Lawrence [4]].

Insulin has also been the subject of continuous improvement through pharmacological development [reviewed by Weiss et al. [5]]. However, over the past century, there have been many important advances in insulin therapy, including the development of intermediate- and long-acting insulins, the ability to produce human insulin and insulin analogs with improved properties using recombinant DNA technology, and the ability to deliver insulin by using programable pumps—the newest of which can also adjust infusion rates based on blood glucose, i.e., serve as an artificial pancreas. Innovation continues in this area toward the development of “smart insulins”, i.e., insulins that can change their bioavailability or activity depending on the level of glucose, orally absorbable insulin, and insulins that may preferentially act on different tissues of the body.

The second half of this special issue deals with the many roles of insulin and insulin action in disease. While mutations in the insulin molecule are relatively rare, they have taught us a lot about the nature of the insulin and proinsulin molecules, along with proinsulin processing to insulin [refer the article by Stoy et al. [6]]. Insulin is also the primary autoantigen in type 1 diabetes. Insulin autoantibodies are the first to appear in early-onset type 1 diabetes and the only antibodies to an antigen that is beta-cell specific. This is the dark side of the insulin molecule; but, ongoing studies are now delineating the structural features of insulin involved in the immune response, and this may serve as a guide to new ways to prevent or delay the disease [reviewed by Harrison [7]].

Insulin resistance is central to type 2 diabetes, obesity, and metabolic syndrome. It is driven by both intrinsic (genetic) factors and extrinsic factors, including many circulating and cellular metabolites. One class of metabolites involved in this process are the branched-chain amino acids [refer to the article by White et al. [8]]. Insulin resistance is also a central component of cardiovascular disease, both in patients with obesity and/or type 2 diabetes, and the population at large [reviewed by Fu et al. [9]]. One of the newest concepts in insulin resistance is that the brain is an insulin-sensitive tissue and that insulin resistance in the brain may be a part of Alzheimer’s and other neurodegenerative disease pathogenesis — which have an important role in the control of metabolism [refer to the article by Milstein and Ferris [10]].

From these articles, it is clear that the discovery of insulin was not only a major landmark in the treatment of diabetes, but it has also been a major stimulus to important contemporary research in areas stretching from diabetes and obesity to neurodegeneration. In addition, it continues to be at the forefront of contemporary research. Thus, the discovery of insulin and all that resulted from it stands out as one of the greatest accomplishments of biomedical research over the past century.

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