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Miniperspectives: Advances in Type 2 Diabetes Therapy

Novel "Second-Generation" Approaches for the Control of Type 2 Diabetes

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Numerous reports have documented the sharply increasing incidence of type 2 diabetes in the industrialized Western world. Recent estimates project that the number of patients diagnosed with type 2 diabetes will more than double to 300 million before 2025. Once found in primarily in middle-aged adults (hence the terminology "adult onset" diabetes), the disease is now being observed with increasing frequency in young children and adolescents. This group of patients has been reported to suffer from an increased risk of cardiovascular disease, similar to that observed in adults. Clearly type 2 diabetes is a serious chronic disease, a major health risk, and a major cause of blindness, kidney failure, amputation, and cardiovascular disease.

Current treatment approaches for type 2 diabetes include diet, exercise, and a variety of pharmacologic agents including insulin, biguanides, sulfonylureas, and thiazolidinediones (TZDs). These agents act by different mechanisms to attempt to normalize blood glucose levels and avoid the well-recognized, serious complications of diabetes that affect the kidneys, cardiovascular, ophthalmic, and nervous systems. These sequelae are directly related to the substantially increased morbidity and mortality associated with the disease. Adverse effects of these "first-generation" therapies include hypoglycemia, weight gain, and edema. Each of these can be serious, and none of the mechanisms by which these compounds act offer the potential to preserve the function of insulin-producing β-cells in the pancreas and thereby attempt to preserve endogenous glucose homeostasis and endocrine function. In many cases, monotherapy gradually fails to improve blood glucose control, and combination therapy is employed. The long-term success of this treatment paradigm varies substantially and can often be further complicated by other medications taken to help control blood pressure and to lower plasma cholesterol. Thus, there is an urgent need for novel therapeutic approaches for blood sugar control that can complement existing agents, offer new choices and combinations to physicians and patients, and possibly attempt to preserve normal endocrine responses to food intake.

The Miniperspectives that make up this series focus clearly on this issue and provide excellent surveys of some of the most active areas of diabetes research: PPARα/γ receptor agonists, GLP-1 analogues, dipeptidyl peptidase 4 (DPP4) and protein tyrosine phosphatase 1B (PTP1B) inhibitors. The following Miniperspective, written by Jay S. Skyler of the University of Miami, succinctly summarizes the serious nature of type 2 diabetes and the status and effectiveness of currently available treatments and identifies desirable characteristics of new agents.

Several pharmaceutical companies have PPARα/γ agonists in advanced stages of clinical evaluation, and Brad R. Henke of GlaxoSmithKline (an organization recognized as a leader in the field of orphan nuclear receptor research) reviews the contributions these nuclear hormone receptors play in diabetes, recent advances in the design of new agents with a range of activity at each receptor, and X-ray crystallographic information useful in the development of ligand design. The issues facing development of dual-acting agonists include a determination of the appropriate balance between α and γ

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activity and how to model this in animals and then effectively to translate this information in human use.

GLP-1 is an incretin hormone that is the most potent stimulator of endogenous insulin release known. In addition, GLP-1 is known to have beneficial effects on β-cell function, can restore insulin sensitivity, and can reduce gastric emptying and food intake, all without inducing hypoglycemia. This combination of favorable activity is tempered by the rapid metabolic degradation of the peptide. One approach to make use of the GLP-1 axis for blood sugar control is outlined by Lotte Bjerre Knudsen of Novo Nordisk, who details work being undertaken at her company to develop a metabolically stable, fatty acid modified GLP-1 analogue, liraglutide, presently in phase III trials, and exendin-4, a GLP-1 analogue, also in late-stage clinical evaluation by Eli Lilly and Amylin. Preliminary clinical evidence suggests that these compounds are safe and effective treatments for the reduction of blood sugar in type 2 diabetic patients. The primary drawback to GLP-1-based therapy is mechanism-based nausea due to delayed gastric emptying. This appears to be manageable in small-scale trials but must be carefully evaluated in larger patient populations.

An alternative approach to enhance GLP-1 activity is to inhibit its degradation by the enzyme dipeptidyl peptidase 4 (DPP4), a nonclassical serine protease. Several DPP4 inhibitors are in phase III evaluation, and Ann E. Weber of Merck Research Laboratories describes the variety of structures known to be effective DPP4 inhibitors and summarizes the early-stage clinical results that have been released by Novartis, which indicate that DPP4 inhibitors effectively and safely lower blood glucose in diabetic patients. A key question facing researchers in this field is the potential effect in humans of inhibition of DPP4 function on other systems, such as the immune system, and its role as a cellular adhesion molecule. Like dual PPAR agonists, these questions will be addressed in large-scale clinical trials. An additional benefit associated with both of these GLP-1-based therapies is weight loss, which may contribute to their ultimate clinical effectiveness and stands in contrast to the weight gain associated with both insulin and TZD use.

The final Miniperspective written by Rob Hooft van Huijsduijnen et al. of Serono Pharmaceutical Research Institute addresses a very new and exciting but challenging target, the enzyme protein tyrosine phosphatase 1B (PTP1B). This enzyme, whose potential role in the treatment of diabetes, was discovered by analysis of mice lacking the PTP1B gene in 1999. PTP1B knockout mice have increased ability to clear glucose in a glucose tolerance test, have decreased plasma insulin levels, and are resistant to weight gain when placed on a high-fat diet. The challenge facing medicinal chemists is the development and optimization of cell-permeable, selective inhibitors of PTP1B with sufficient potency to have a beneficial physiological effect. The degree of phosphatase selectivity needed to achieve a measurable effect on blood glucose while minimizing off-target effects remains to be determined. The highly charged polyanionic nature of the active site, which is very similar in phosphatase enzymes, is a primary contributor to the hurdles medicinal chemists in the field currently face. Antisense inhibition of PTP1B has shown sufficient promise in animal studies such that clinical evaluation is now underway.

David J. Triggle, the Perspective Editor for the *Journal of Medicinal Chemistry*, conceived the idea for this timely set of Miniperspectives following a session sponsored by the Division of Medicinal Chemistry at the 224th National Meeting of the American Chemical Society in New Orleans in the spring of 2003. He encouraged me to identify topics reflecting the state of the art in the field and authors who could speak authoritatively on the subject, and as readers will discover, the contributors have done an outstanding job, and we thank them for their manuscripts.

Biography

David P. Rotella earned a Ph.D. in Medicinal Chemistry at The Ohio State University under the direction of Donald T. Witiak. After postdoctoral studies at Pennsylvania State University in Ken Feldman's laboratory, he held a faculty position at the University of Mississippi School of Pharmacy for 4 years before moving to Cephalon. At Cephalon, he led the group that discovered CEP1347, a kinase inhibitor in clinical trials for Parkinson's disease. At Bristol-Myers Squibb, his team was the first to publish on PDE5 inhibitors more potent and selective than sildenafil. Currently, he is a senior group leader at Lexicon Pharmaceuticals in Princeton, NJ, where he is responsible for a drug discovery program in obesity. He has published over 20 peer-reviewed papers, is a co-inventor on six patents, and has written several invited reviews.

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