Introduction to Biological and Small Molecule Drug Research and Development: Chapter 6. Therapies for type 2 diabetes: modulating the incretin pathway ... peptidase inhibitors or peptide mimetics

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The increasing global prevalence of type 2 diabetes represents a significant burden of disease for afflicted patients and for health care systems. In the developed world poorly controlled diabetes is the leading cause of non-traumatic amputation, blindness and end-stage renal disease requiring dialysis and kidney transplant. Additionally, diabetes represents a significant risk factor for the development of cardiovascular disease with its associated morbidity and premature death. Currently available glucose lowering drugs used to treat type 2 diabetes do not impede progression of the disease. Therefore, as the disease progresses these agents rapidly lose efficacy, first as monotherapy and then in combination, resulting in poorly controlled disease. Clearly, there is a significant need for novel glucose lowering drugs for type 2 diabetes that will deliver sustained efficacy over several years by impeding disease progression. Such agents would reduce the risk of developing the microvascular complications of diabetes that ultimately result in amputation, blindness and kidney transplant. Novel glucose lowering drugs should ideally also exhibit a positive impact on the increased cardiovascular risk associated with diabetes. The incretin-based therapies first entered the market in the mid 2000’s and were heralded for their potential to impede progression of type 2 diabetes and to reduce cardiovascular risk. Through mimicking the actions of the gut incretin hormone GLP-1, these drugs had been shown to lower blood glucose in clinical trials by potentiating glucose stimulated insulin secretion from pancreatic β-cells. Moreover, data from preclinical rodent disease models and isolated human pancreatic islets suggested that these novel agents could preserve pancreatic β-cell function and thus impede disease progression. Further preclinical and clinical data supported the notion that these drugs could also aid blood glucose control by suppressing glucagon secretion, slowing gastric emptying and by suppressing appetite. The incretin-based drugs have potential to reduce cardiovascular risk through their ability to reduce body weight, blood pressure and atherogenic blood lipids. This chapter will review the incretin-based therapies and consider what impact these new drugs have made to date in the pharmacotherapy of type 2 diabetes. The incretin-based therapies are of particular relevance to this book as this class of drugs is composed of two sub-classes, injectable peptide drugs and oral small molecule drugs. The similarities and differences between these small molecule and peptide drugs are described.

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