New Therapies for the Treatment of Type 2 Diabetes: Challenges and Opportunities

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The pathogenesis of type 2 diabetes (T2DM) involves a set of three primary defects: insulin resistance, insulin secretory dysfunction, and hepatic glucose overproduction. These defects are the principal targets of both current and future therapy. Currently available classes of oral antihyperglycemic agents include biquanides (hepatic glucose production), PPARγ agonists (insulin resistance), sulfonyureas /meglitinides (insulin secretion), and DPP-4 inhibitors (insulin secretion/hepatic glucose output). These agents are used either in monotherapy or, increasingly, in combinations to lower glucose levels. Injectable therapies, typically used after failure of oral therapies, include insulin analogs and GLP-1 agonists. Despite the availability of a range of agents for the treatment of T2DM, there remain critical unmet medical needs, including increased efficacy in monotherapy and/or combination, improved durability, excellent safety/tolerability, and/or simultaneous control of glucose and comorbidities. Therapies that have the potential for a cardiovascular benefit are a particularly high priority. Several new approaches for the treatment of T2DM are currently being explored in clinical studies: oral approaches include SGLT2 inhibitors and glucokinase activators. New insulin analogs and a number of GLP-1 agonist peptides are also in clinical development. The limitations of existing therapies, and the potential of new classes for the treatment of this disorder, will be discussed.