Review

MOLECULAR METABOLISM

GLP-1 receptor agonists in the treatment of type 2 diabetes — state-of-the-art

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ABSTRACT

Background: GLP-1 receptor agonists (GLP-1 RAs) with exenatide b.i.d. first approved to treat type 2 diabetes in 2005 have been further developed to yield effective compounds/preparations that have overcome the original problem of rapid elimination (short half-life), initially necessitating short intervals between injections (twice daily for exenatide b.i.d.).

Scope of review: To summarize current knowledge about GLP-1 receptor agonist.

Major conclusions: At present, GLP-1 RAs are injected twice daily (exenatide b.i.d.), once daily (lixisenatide and liraglutide), or once weekly (exenatide once weekly, dulaglutide, albiglutide, and semaglutide). A daily oral preparation of semaglutide, which has demonstrated clinical effectiveness close to the once-weekly subcutaneous preparation, was recently approved. All GLP-1 RAs share common mechanisms of action: augmentation of hyperglycemia-induced insulin secretion, suppression of glucagon secretion at hyper- or euglycemia, deceleration of gastric emptying preventing large post-meal glycemic increments, and a reduction in calorie intake and body weight. Short-acting agents (exenatide b.i.d., lixisenatide) have reduced effectiveness on overnight and fasting plasma glucose, but maintain their effect on gastric emptying during long-term treatment. Long-acting GLP-1 RAs (liraglutide, once-weekly exenatide, dulaglutide, albiglutide, and semaglutide) have more profound effects on overnight and fasting plasma glucose and HbA_{1c}, both on a background of oral glucose-lowering agents and in combination with basal insulin. Effects on gastric emptying decrease over time (tachyphylaxis). Given a similar, if not superior, effectiveness for HbA_{1c} reduction with additional weight reduction and no intrinsic risk of hypoglycemic episodes, GLP-1RAs are recommended as the preferred first injectable glucose-lowering therapy for type 2 diabetes, even before insulin treatment. However, GLP-1 RAs can be combined with (basal) insulin in either free- or fixed-dose preparations. More recently developed agents, in particular semaglutide, are characterized by greater efficacy with respect to lowering plasma glucose as well as body weight. Since 2016, several cardiovascular (CV) outcome studies have shown that GLP-1 RAs can effectively prevent CV events such as acute myocardial infarction or stroke and associated mortality. Therefore, guidelines particularly recommend treatment with GLP-1 RAs in patients with pre-existing atherosclerotic vascular disease (for example, previous CV events). The evidence of similar effects in lower-risk subjects is not quite as strong. Since sodium/glucose cotransporter-2 (SGLT-2) inhibitor treatment reduces CV events as well (with the effect mainly driven by a reduction in heart failure complications), the individual risk of ischemic or heart failure complications should guide the choice of treatment. GLP-1 RAs may also help prevent renal complications of type 2 diabetes. Other active research areas in the field of GLP-1 RAs are the definition of subgroups within the type 2 diabetes population who particularly benefit from treatment with GLP-1 RAs. These include pharmacogenomic approaches and the characterization of non-responders. Novel indications for GLP-1 RAs outside type 2 diabetes, such as type 1 diabetes, neurodegenerative diseases, and psoriasis, are being explored. Thus, within 15 years of their initial introduction, GLP-1 RAs have become a well-established class of glucose-lowering agents that has the potential for further development and growing impact for treating type 2 diabetes and potentially other diseases.

Keywords Glucagon-like peptide-1 receptor agonists; Exenatide; Lixisenatide; Liraglutide; Dulaglutide; Albiglutide; Semaglutide; Type 2 diabetes; Cardiovascular disease; Body weight

1. DEVELOPMENT OF GLP-1 RAS

The identification of gut-derived glucagon-like peptide-1 (GLP-1), putatively belonging to the family of incretin hormones (i.e. gastrointestinal hormones released after nutrient intake with the ability to glucose-dependently augment insulin secretory responses during periods characterized by hyperglycemia) triggered the development of GLP-1 receptor agonists (GLP-1 RAs). The groups around Jens Holst (Copenhagen, Denmark) [1] and Joel Habener (Boston, MA, USA) [2] were the first to correctly identify "truncated" GLP-1 (GLP-1 [7—36 amide], the amidated form [1], or GLP-1 [7—37], the glycine-extended form [2]), as the product(s) of proglucagon translational processing in mammalian gut mucosa (L cells) as published in 1987. Based on the proglucagon nucleotide sequence, prior assumptions regarding processing enzymes led to an erroneous GLP-1 sequence longer by 6 N-terminal amino acid residues [3]. However, "truncated" GLP-1 was

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