Life Sciences 99 (2014) 7–13

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

(Poly)peptide-based therapy for diabetes mellitus: Insulins versus incretins

Aljoša Bavec *

Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 30 September 2013
Accepted 26 December 2013

Keywords:
Insulin analogues
Incretins
Peptide drugs
Glucagon like peptide-1 mimetics
Diabetes

ABSTRACT

Insulin therapy remains the standard of care for achieving and maintaining adequate glycemic control, especially in hospitalized patients with critical and noncritical illnesses. Insulin therapy is more effective against elevated fasting glycaemia but less in the reduction of postprandial hyperglycaemia. It is associated with a high incidence of hypoglycemia and weight gain. Contrary, GLP-1 mimetic therapy improves postprandial glycaemia without the hypoglycaemia and weight gain associated with aggressive insulin therapy. Moreover, it has the potential to reduce cardiovascular related morbidity. However, its increased immunogenicity and severe gastrointestinal adverse effects present a huge burden on patients. Thus, a right combination of basal insulin which has lowering effect on fasting plasma glucose and GLP-1 mimetic with its lowering effect on postprandial plasma glucose with minimal gastrointestinal adverse effects, seems the right therapy choice from a clinical point of view for some diabetic patients. In this article, we discuss the pros and cons of the use of insulin analogues and GLP-1 mimetics that are associated with the treatment of type 2 diabetes.

Contents

Introduction

Diabetes afflicts an estimated 347 million people worldwide (Danaei et al., 2011), of whom the majority have type 2 diabetes, and the World Health Organization has predicted that diabetes will be the 7th leading cause of death in 2030 (Anon, 2011). It results from insulin resistance in peripheral tissues and impaired insulin secretion. Insulin resistance is a consequence of obesity, physically inactive lifestyles and aging. Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type 2 diabetes mellitus (Anon, 2011). People in the very early stages of type 2 diabetes with mild or no symptoms may decrease their chances of developing the disease with oral anti-diabetic drugs, including sulfonylurea derivatives or meglitinides to stimulate insulin release (Doyle and Egan, 2003); biguanides (metformin) to reduce insulin resistance,

* Tel.: +386 1 543 76 59; fax: +386 1 543 76 41.
E-mail address: aljosa.bavec@mf.uni-lj.si.

0024-3205/$ – see front matter
http://dx.doi.org/10.1016/j.lfs.2013.12.210

suppress glucose production by the liver and increase uptake of glucose by the periphery, including skeletal muscle (Matthaei et al., 2000); thiazolidinediones to decrease insulin resistance in fat and muscle (Matthaei et al., 2000); alpha-glucosidase inhibitors to slow the digestion of starch and sucrose in the small intestine (Stumvoll et al., 2005); dipeptidyl peptidase 4 (DPP-4) inhibitors to increase incretin levels (Raz et al., 2006; Drucker, 2007); and sodium-glucose transport protein 2 (SGLT2) inhibitors to prevent glucose reabsorption in the kidney (Yale et al., 2013). However, monotherapy is frequently defeated with these oral antidiabetic drugs (Kahn et al., 2006), thus the combination (Heine et al., 2005) of glucagone-like peptide-1 (GLP-1) mimetic therapy (Cvetković and Plosker, 2007; Nauck et al., 2013) and/or insulin therapy (Padwal et al., 2005) is therefore often necessary as diabetes becomes more aggressive.

(Poly)peptide drugs based on insulin are already considered as a mainstay of this treatment (Umpierrez and Korytkowski, 2013). But also other peptides such as GLP-1 receptor agonists, or amylin analogues (e.g. pramlintide) help as an adjunct to insulin therapy (Schwartz and DeFronzo, 2013; Singh-Franco et al., 2011). Moreover, the American Diabetes Association/European Association for the study of diabetes consensus algorithm currently recommends that a basal insulin with a GLP-1 mimetic is appropriate for patients failing lifestyle changes and metformin therapy (Perfetti, 2011).

There is strong pro et contra debate about incretin-based therapy for the care of hospitalized patients with type 2 diabetes among experts at the moment (Umpierrez and Korytkowski, 2013; Schwartz and DeFronzo, 2013). Thus, in this minireview, we focus on pros and cons of both therapies with insulin analogues and GLP-1 mimetics (Table 1). We introduce the group of insulin analogues and compare them with incretin hormones, especially with GLP-1 and its analogues that are associated with the treatment of type 2 diabetes. Finally, we discuss the evidence for a novel pharmacological target, mono-ADP-ribosyltransferase (ART), its ART peptide inhibitors and their potential role as drugs in treatment of type 2 diabetes.

Insulin-based therapies for type 2 diabetes

Insulin is a 51 amino acid 5.8 kDa protein synthesized by pancreatic islet β-cells. Because it has only 51 amino acids, and most of biotechnological companies today are capable to synthesize peptides up to 75 amino acids in length, this fact can be used to refer the monomeric insulin to peptide or polypeptide. However, insulin molecules in solution exist in dynamic equilibrium as monomers, dimers, tetramers, hexamers and higher-order protein aggregates, but only monomers and dimers are biologically active molecules (McAulay and Frier, 2003). Insulin monomer is composed of two chains, A and B, which are bonded by two disulfide bridges. This structurally simple molecule is responsible for many physiological effects in humans, including glucose uptake by the liver, muscle and adipose tissue, increased glycogen synthesis and esterification of fatty acids, decreased proteolysis, lipolysis and gluconeogenesis… In 1922 insulin was already used as a treatment of type 1 diabetes. Since then, insulin has traversed a long path from animal to biosynthetic human and insulin analogue formulations and now is considered as a second line of defense after metformin for treatment of type 2 diabetes. The advances from animal to human preparations such as regular insulin (Humulin R) had obvious advantages, mostly reducing the incidence of antibody formation and thus increasing therapeutic effect. Before the invention of insulin analogues, the leading method of delaying absorption through stabilization of insulin hexamers was by adding zinc (in Lente series) and/or protamine (in NPH insulin also known as Humulin N) in insulin preparations (Heller et al., 2007). Insulin analogues were developed in order to modify the pharmacokinetics, such as absorption, distribution, metabolism and elimination of a drug, to better mimic insulin endogenous secretion without altering immunogenicity. In addition, variability between subjects or within the same individual in pharmacological response of human insulin preparations presents severe problem, especially when it leads to unpredictable side effects with hypoglycaemia and hyperglycaemia (Evans et al., 2011). All these limitations of human insulin preparations have driven the development of insulin analogues. By site-directed mutagenesis and recombinant technology, the insulin molecule has been modified to either shorten or prolong duration of its action. Thus, insulin analogues can be divided into two categories, short-acting and long-acting, according to their pharmacokinetic profiles.

Short-acting insulin analogues

Modifications to the human insulin molecule have focused on B chain, away from receptor binding surface of chain A, in order to reduce the rate of self-association into hexamers, thus obtaining faster absorption of monomers and higher peak serum level when injected into the subcutaneous tissue (Huang et al., 2007; Brange et al., 1988). Insulin lispro (Humalog) was the first short-acting analogue available for clinical use, formed by switching lysine and proline at positions B28 and B29 (Brems et al., 1992). Insulin aspart (Novolog) is formed by substituting proline with aspartic acid in position B28. Both insulin analogues have similar pharmacokinetic and pharmacodynamic properties (Plank et al., 2002). Insulin glulisine (Apidra) is formed by substituting asparagine for aspartic acid at position B3 and lysine for glutamic acid at position B29 and unlike lispro and aspart, does not contain zinc. Absorption profile of short-acting analogues over time should rise to a peak very quickly, in approximately one half of the time than that of injected human insulin. Peak is always higher to that of injected human insulin and duration of action is shorter (Howey et al., 1994; Heinemann et al., 1998; Becker and Frick, 2008). Insulin lispro, aspart and glulisine bind to the insulin receptor with similar binding affinity in comparison to that of native human insulin (Kurtzhals et al., 2000; Hennige et al., 2005).

Long-acting insulin analogues

Insulin glargine (Lantus) is recombinant human insulin analogue obtained by changing asparagine at position A21 in the A chain with glycine and adding two arginines to the C terminus of B chain at positions B31 and B32. The arginine amino acids shift the isoelectric point of the molecule from a pH of 5.4 to 6.7, making it less soluble at physiological pH. In more neutral pH environment, such as subcutaneous tissue, it precipitates and forms a depot of microcrystals that slowly release insulin, giving a long duration of action of 18 to 24 h, with a more or less peakless absorption profile (Hompesch et al., 2009). It has similar receptor binding affinity to that of native human insulin (Kurtzhals et al., 2000). Insulin detemir (Levemir) is not a real insulin analogue but rather a derivative, where threonine at position B30 is removed and C14 fatty acid is covalently bonded to lysine at B29. Fatty acid side chain not only allows self-association of detemir monomers into hexamers, but also reversible binding of insulin detemir to albumin. After subcutaneous injection, both, binding to albumin and formation of hexamers on the one hand prolong the duration of action and also reduce the availability of free insulin detemir (Kurtzhals, 2007). Insulin detemir binding affinity to insulin receptor is reduced as compared to human insulin (Kurtzhals et al., 2000). Insulin degludec (Tresiba) retains the insulin detemir amino acid sequence with the exception of adding a 16-carbon di-carboxylic fatty acid side chain attached to lysine in position B29 of the insulin B chain via a glutamic acid linker (Kurtzhals, 2007). The addition of this specific di-carboxylic fatty acid via the glutamic acid spacer is what enables degludec to form soluble and stable multi-hexamer long chains when injected into subcutaneous tissue. These slowly disassemble with the diffusion of zinc to release a slow, stable and continuous delivery of degludec monomers into the circulation. The process is remarkably smooth, without a significant peak, but rather with a flat profile, producing a stable glucose-lowering effect. Like insulin detemir, degludec binds to albumin. This adds little to its duration of action, but is likely to buffer the