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Insulin Glulisine

Treatment of Type 1 and Type 2 Diabetes

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1964
HMR-1964

[Lys^{B3},Glu^{B29}]-insulin (human)
[3B-L-lysine,29B-L-glutamic acid]insulin (human)

CAS: 207748-29-6
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Abstract

Diabetes mellitus is a group of diseases that requires long-term drug therapy to limit and manage complications and to prevent premature death. Insulin is the standard treatment for type 1 diabetes and is required in nearly half of all patients suffering from type 2 diabetes. Currently available insulin preparations are slowly absorbed from subcutaneous tissue and are therefore unable to mimic the endogenous patterns of insulin secretion and normoglycemia cannot be achieved. Thus, the search for novel insulin molecules continues. Modifications of the insulin molecule using DNA recombinant technology has resulted in the discovery of several insulin analogs. However, some of these analogs with a modified carboxy terminal of the B chain of insulin have an altered affinity for the insulin-like growth factor-I receptor, resulting in increased signaling. Therefore, long-term use of insulin analogs may lead to enhanced mitogenic activity, a potentially serious safety concern. Insulin glulisine is a novel, rapid-acting insulin analog which has mitogenic potential identical to regular human insulin. It has a more rapid onset and shorter duration of action than the native molecule and also has the unique property of preferentially activating the insulin receptor substrate-2 signaling pathway which plays a crucial role in pancreatic β-cell growth and survival. Insulin glulisine was selected for further development as a treatment for type 1 and type 2 diabetes to be used in combination with long-acting insulin or basal insulin analogues.

Introduction

Diabetes mellitus is a group of diseases characterized by hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion and/or action. Diabetes is classified according to 4 subtypes: type 1 diabetes which accounts for 5-10% of all cases, type 2 diabetes which accounts for over 90% of all reported cases, gestational diabetes occurring in 2-8% of all pregnancies, and other types, including drug-induced diabetes and diabetes secondary to infection or illness which accounts for only 1-2% of all cases. Diabetes develops when the pancreas does not produce sufficient quantities of endogenous insulin (*i.e.*, type 1 diabetes) or when the body is unable to effectively use the insulin it produces (*i.e.*, insulin resistance or type 2 diabetes). According to the National Institute of Diabetes and Digestive and Kidney Diseases, 17 million Americans have diabetes and another 16 million suffer from impaired glucose tolerance, including insulin resistance syndrome. In 2000, the World Health Organization reported that there were 154.4 million diabetics worldwide and has predicted that by the year 2005, there will be almost 300 million people suffering from the disease (1-4).

Diabetes is a chronic syndrome requiring long-term drug therapy to limit and manage complications and to prevent premature death. Insulin is the gold standard of therapy for type 1 diabetes and is required in nearly half of all patients suffering from type 2 diabetes. The purpose of insulin therapy is to tightly control blood glucose levels and decrease progression of long-term complications. However, currently available insulin preparations are unable to mimic the patterns of endogenous insulin secretion and normoglycemia cannot be achieved. This can be caused by slow absorption from subcutaneous tissue due to a slow dissociation rate of hexameric insulin complexes into monomers at the injection site. Thus, the search for novel insulin molecules with altered pharmacodynamic and pharmacokinetic profiles continues (1, 5-8).

L.A. Sorbera, P.A. Leeson. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Recombinant DNA technology is an attractive method used in the search for new insulin molecules and several novel insulin analogues and derivatives have been discovered and are currently under active development for the treatment of diabetes. For example, modifications of the carboxy terminal B26-B30 region of the B chain of insulin (*e.g.*, substitution of amino acids with charge residues at association sites) yields insulin analogs with decreased self-association and no alterations in insulin receptor recognition (7, 9). However, although modification in the B10 and B26-B30 regions of the insulin molecule does not affect affinity for the insulin receptor, it alters affinity for the insulin-like growth factor (IGF)-I receptor, thereby increasing signaling. Therefore, long-term use of insulin analogues may lead to enhanced mitogenic activity in several cell systems and this safety concern must be taken into account when searching for novel insulin molecules (10-12).

Insulin glulisine ([Lys^{B3},Glu^{B29}]-insulin (human); HMR-1964] is a novel, rapid-acting insulin analogue which has mitogenic potential identical to regular human insulin but a more rapid onset and shorter duration of action than the native molecule. Moreover, insulin glulisine has the unique property of preferentially activating the insulin receptor substrate (IRS)-2 signaling pathway which plays a crucial role in pancreatic β-cell growth and survival and its dysfunction has been linked to the pathophysiology of type 2 diabetes. Insulin glulisine was selected for further development as a treatment for type 1 and type 2 diabetes to be used in combination with long-acting insulin or basal insulin analogues (1, 13-16).

Pharmacological Actions

An *in vitro* study using K6 myoblasts (a rat heart muscle cell line), primary human skeletal muscle cells and adult rat cardiomyocytes which express high levels of IGF-I and marginal levels of insulin receptors, examined the signaling properties of insulin glulisine (0.5 μM). In K6 myoblasts, insulin glulisine exhibited binding properties similar to insulin (2.2 ± 0.1 and 2.8 ± 0.06 fmol/2 x 10^5 cells, respectively). However, internalization (1600 ± 300 *vs.* 2200 ± 200 cpm x 10^2) and degradation (3.0 ± 0.4 *vs.* 6.3 ± 0.5%) were lower for insulin glulisine as compared to human insulin. Insulin glulisine only moderately increased autophosphorylation of the IGF-I receptor in K6 myoblasts and, accordingly, it only marginally activated the Shc/MAPK cascade. Insulin glulisine stimulated DNA synthesis in a manner similar to human insulin. In addition, while only marginally (2-fold) activating tyrosine phosphorylation of IRS-1 in myoblasts and cardiomyocytes, insulin glulisine increased tyrosine phosphorylation of IRS-2 by 20-fold; in human myoblasts, this effect was significantly stronger than that observed for human insulin. Further *in vitro* experiments in rat cardiomyocytes revealed that insulin glulisine preferentially activated IRS-2 with only minor activation of IRS-1. In addition, the agent increased 3-*O*-methyl glucose transport and activated Akt and glycogen synthase kinase-3 (GSK-3) in a manner similar to human insulin. In *in vitro* K6 myoblast cellular proliferation assays, insulin glulisine and human insulin exhibited similar growth promoting activity, consistent with their comparable ability to activate the Shc/MAPK cascade. These results were confirmed *in vivo*, where examination of mammary glands of female rats treated for 12 months with the agent (2 x 20 IU/kg and 2 x 50 IU/kg) or regular human insulin (2 x IU/kg) revealed no significant alterations in cell proliferation. From these results, it was concluded that the mitogenic and metabolic potential of insulin glulisine is the same as that of human insulin. Moreover, the novel insulin analogue preferentially activates the IRS-2 pathway which is involved in β-cell growth and survival (13).

The potential β-cell protective effect of insulin glulisine was confirmed in an *in vitro* study using a rat insulinoma cell line (INS-1) to examine whether the agent mediates enhanced antiapoptotic and cytoprotective effects on β-cells. Insulin glulisine significantly activated IRS-2 (7-fold) in a manner similar to regular human insulin but with no significant effect on IRS-1. In addition, insulin glulisine significantly inhibited cytokine (IL-1β/IFN-γ)- and fatty acid (palmitic acid)-induced apoptosis at the level of caspase 3 activation and nucleosomal release (55-60%). This was in contrast to the 15% less inhibition of apoptosis observed with regular human insulin. In addition, at a dose of 1 nM, regular human insulin and the very short-acting insulins, insulin lispro and insulin aspart (Asp^{B28} insulin) were considerably less effective than insulin glulisine in preventing cytokine- and fatty acid-induced apoptosis (17).

An *in vivo* crossover euglycemic clamp study in normoglycemic dogs compared the pharmacodynamics of insulin glulisine with insulin lispro and regular human insulin (0.3 IU/kg s.c.). When compared to regular human insulin, insulin glulisine and insulin lispro had a significantly faster onset of action (11.34 ± 3.08 and 13.28 ± 5.84 min, respectively, *vs.* 29.07 ± 17.44 min) and an earlier peak and significantly shorter mean time of action (9.59 ± 12.69 and 99.46 ± 12.64 min, respectively, *vs.* 116.04 ± 13.03 min). There were no significant differences between insulin glulisine and insulin lispro (18).

Clinical Studies

A randomized, double-blind, single-dose (0.3 IU/kg s.c.), 3-way crossover study in 16 healthy males (aged 19-30 years; BMI = 21-26 kg/m^2) subjected to euglycemic clamps compared the pharmacodynamic and pharmacokinetic profiles of insulin glulisine with insulin lispro and regular human insulin. The duration of action for insulin glulisine, insulin lispro and regular human insulin were 318, 329 and 385 min, respectively. Absorption of insulin glulisine and insulin lispro was twice as rapid as regular human insulin. C_{max} and t_{max} values (respectively) for insulin glulisine, insulin lispro and regular human insulin were 196 μIU/ml and 56 min, 156 μIU/ml and 50 min and

84 μIU/ml and 99 min, respectively, and $AUC_{0\text{-clamp end}}$ values were 29302, 22116 and 21673 μIU·min/ml, respectively. The mean residence time for both insulin glulisine and insulin lispro were almost half that of regular human insulin (105 and 117 min, respectively, *vs.* 182 min). Total disposal of glucose was similar for all three insulins (19).

A randomized, open-label, 4-way crossover trial in 16 male volunteers (aged 19-28 years; BMI = 21-26 kg/m^2) subjected to a euglycemic clamp procedure compared the pharmacodynamics and pharmacokinetics of insulin glulisine (0.1 IU/kg) administered s.c into femoral, deltoid or abdominal areas or as an i.v. bolus. Similar glucodynamic and pharmacokinetic profiles were obtained for all s.c. routes. The values for median duration of action for femoral, deltoid and abdominal s.c. delivery were 268, 270 and 251 min, respectively (*vs.* 160 min for the i.v. bolus). Absorption, absolute bioavailability and glucose disposal were similar for all routes of s.c administration. However, more rapid insulin delivery was observed after s.c. abdominal injections (t_{max} = 66, 58 and 44 min for femoral, deltoid and abdominal s.c. administration, respectively). The mean residence times for femoral, deltoid and abdominal s.c. delivery and the i.v. bolus were 114, 103, 89 and 12 min, respectively (20).

A marketing authorization application submitted by Aventis for insulin glulisine as a treatment for type 1 and type 2 diabetes was accepted for filing by the European Medicines Evaluation Agency. In addition, an NDA was submitted with the U.S. FDA (21).

Source

Aventis Pharma AG (CH).

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