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(54) Title: GLUCAGON–LIKE PEPTIDE–1 ANALOGS

(57) Abstract

The invention provides extended–action GLP–1 based peptides and compositions that are useful for treating diabetes and minimize the risk of hypoglycemia.

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GLUCAGON-LIKE PEPTIDE-1 ANALOGS

Field of Invention

The present invention relates to protein chemistry as applied to pharmaceutical research and development. The invention provides novel peptides and compositions that are useful for treating diabetes.

Background of the Invention

The World Health Organization estimates that there may be as many of 100 million patients with type II diabetes worldwide, although only 23 million have been diagnosed and are receiving therapy. Type II diabetes (non-insulin dependent diabetes mellitus - NIDDM) is characterized by a resistance to insulin action in peripheral tissues such as muscle, adipose and liver and by a progressive failure in the ability of the islet β-cell to secrete insulin. Because current therapeutics do not halt the progression of β-cell failure, virtually all NIDDM patients eventually require insulin to control blood glucose levels. The most commonly described therapeutics for such patients are the sulfonylureas, so called oral agents, that stimulate insulin secretion. Each year, 10-20% of the patients on sulfonylureas fail to maintain acceptable blood glucose levels and switch to insulin therapy.

Insulin however, is a difficult drug for patients to self-administer for several reasons. First, insulin has a narrow therapeutic index. This leads to poor control of blood glucose levels since most patients and physicians prefer elevated glucose levels to the risk of hypoglycemia and coma. Second, proper insulin dosing is complicated. The insulin dose that a diabetic patient should administer is dependent on the amount of food consumed, the time between meals, the amount of physical exercise, and the prevailing blood glucose level which requires blood glucose monitoring to determine. The general diabetic population is

ill-equipped to correlate these factors to the proper insulin dose. Third, as a parenteral product, insulin is inconvenient to administer. Alternative delivery methods are made even more difficult by the narrow therapeutic index for insulin. Thus, many diabetic patients lack good control of blood glucose.

The Diabetes Control and Complication Trial definitively established for Type I diabetics that disease complications (retinopathy, neuropathy and nephropathy) are directly correlated to blood glucose control. A clinical trial is currently underway in the UK to determine if this link also holds true to Type II diabetes. A positive result is reasonable to anticipate, and with it will come a desire for agents that improve the ability for the patient with diabetes to control blood glucose levels tightly. In addition, a standard of care for diabetes is being developed by the US government in coordination with care-givers and the pharmaceutical industry. Thus, there is clearly a need for agents that truly are able to tightly control blood glucose levels in the normal range.

Glucagon-like peptide-1 (GLP-1) was first identified in 1987 as a incretin hormone, a peptide secreted by the gut upon ingestion of food. GLP-1 is secreted by the L-cells of the intestine after being proteolytically processed from the 160 amino acid precursor protein, preproglucagon. Cleavage of preproglucagon first yields GLP-1, a 37 amino acid peptide, GLP-1(1-37)OH, that is poorly active. A subsequent cleavage at the 7-position yields biologically active GLP-1(7-37)OH. Approximately 80% of the GLP-1(7-37)OH that is synthesized is amidated at the C-terminal after removal of the terminal glycine residue in the L-cells. The biological effects and metabolic turnover of the free acid GLP-1(7-37)OH , and the amide, GLP-1 (7-36)NH_2, are indistinguishable.

GLP-1 is known to stimulate insulin secretion (insulinotropic action) causing glucose uptake by cells which decreases serum glucose levels (*see*, e g., Mojsov, S.,

Int. J. Peptide Protein Research, 40:333-343 (1992)). Numerous GLP-1 analogs demonstrating insulinotropic action are known in the art. These variants and analogs include, for example, GLP-1(7-36), Gln^9-GLP-1(7-37), D-Gln^9-GLP-1(7-37), acetyl-Lys^9-GLP-1(7-37), Thr^{16}-Lys^{18}-GLP-1(7-37), and Lys^{18}-GLP-1(7-37). Derivatives of GLP-1 include, for example, acid addition salts, carboxylate salts, lower alkyl esters, and amides (*see*, e.g., WO91/11457 (1991); EP 0 733,644 (1996); and US Patent No: 5,512,549 (1996)). It has also been demonstrated that the N-terminal histidine residue (His 7) is very important to insulinotropic activity of GLP-1 (Suzuki, S., *et al. Diabetes Res.; Clinical Practice* 5 (Supp. 1):S30 (1988).

Multiple authors have demonstrated the nexus between laboratory experimentation and mammalian, particularly human, insulinotropic responses to exogenous administration of GLP-1, particularly GLP-1 (7-36)NH_2 and GLP-1 (7-37) [see, e.g., Nauck, M.A., *et al.*, *Diabetologia*, 36:741-744 (1993); Gutniak, M., *et al.*, *New England J. of Medicine*, 326(20):1316-1322 (1992); Nauck, M.A., *et al.*, *J. Clin. Invest.*, 91:301-307 (1993); and Thorens, B., *et al.*, *Diabetes*, 42:1219-1225 (1993)].

GLP-1 based peptides hold great promise as alternatives to insulin therapy for patients with diabetes who have failed on sulfonylureas. GLP-1 has been studied intensively by academic investigators, and this research has established the following for patients with type II diabetes who have failed on sulfonylureas:

1) GLP-1 stimulates insulin secretion, but only during periods of hyperglycemia. The safety of GLP-1 compared to insulin is enhanced by this property of GLP-1 and by the observation that the amount of insulin secreted is proportional to the magnitude of the hyperglycemia. In addition, GLP-1 therapy will result in pancreatic release of insulin and first-pass insulin action at the liver. This results in lower circulating levels of insulin in the periphery compared to subcutaneous insulin injections. 2)

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