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(54) Title: GLP-1 ANALOGS USEFUL FOR DIABETES TREATMENT

(57) Abstract

The invention provides effective analogs of the active GLP-1 peptides, 7-34, 7-35, 7-36, and 7-37, which have improved characteristics for treatment of diabetes Type II. These analogs have amino acid substitutions at positions 7-10 and/or are truncated at the C-terminus and/or contain various other amino acid substitutions in the basic peptide. The analogs may either have an enhanced capacity to stimulate insulin production as compared to glucagon or may exhibit enhanced stability in plasma as compared to GLP-1 (7-37) or both. Either of these properties will enhance the potency of the analog as a therapeutic. Analogs having D-amino acid substitutions in the 7 and 8 positions and/or N-alkylated or N-acylated amino acids in the 7 position are particularly resistant to degradation *in vivo*.

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GLP-1 ANALOGS USEFUL FOR DIABETES TREATMENT

This is a continuation-in-part of U.S. Application Serial No. 468,736, filed 24 January 1990.

Technical Field

The invention relates to the field of improved pharmaceutical compositions. Specifically, the invention concerns analogs of the glucagon-like peptide I fragment 7-36 or 7-37 with improved pharmacological properties.

Background Art

Glucose metabolism is regulated by a number of peptide hormones, including insulin, glucagon, and gastric inhibitory peptide (GIP). The complex mechanism by which these peptide hormones regulate this metabolism and the manner in which they affect each other is at least partially elucidated. For example, glucagon binds to receptors on the surface of the pancreatic beta cells which produce insulin, and stimulates insulin secretion. Glucagon-like peptide I has been suggested to stimulate insulin secretion but this has not been confirmed.

Several of these hormones originate from a mammalian glucagon precursor "proglucagon" which is a 180 amino acid peptide. Proteolysis and processing of this peptide results in a number of these protein hormones; the results of the processing depend on the origin of the cells in which this occurs. For example, in the pig and rat pancreas, proglucagon is processed to form glucagon and glicentin-related pancreatic peptide, a large peptide

which contains both GLP-1 and GLP-2 sequences. In porcine small intestine, the secreted products are the 69 amino acid glucagon-containing peptide glicentin and the two glucagon-like sequences, GLP-1 and GLP-2 as separate peptides.

In any event, however, the overall sequence of proglucagon contains the 29 amino acid sequence of glucagon, the 36 or 37 amino acid sequence of GLP-1 and the 34 amino acid sequence of GLP-2, separated by amino acid spacer sequences.

Early attempts to assign a pattern of activity to GLP-1 gave ambiguous results, and it was subsequently concluded that truncated forms of this peptide are biologically active. Mojsov, S., et al. J Clin Invest (1987) 79:616-619 disclose that only the 31 amino acid peptide GLP-1 (7-37) strongly stimulates the release of insulin from pancreas; although both the truncated and full length 37 amino acid form had earlier been found in pancreas and intestine. It has been demonstrated that GLP-1 (7-36), possibly with the carboxy terminus amidated, is also a potent mediator of insulin release. (See, e.g., Holst, J.J., et al. FEBS Letters (1987) 211:169-174).

The invention described below concerns analogs of these truncated forms of GLP-1, which have desirable combinations of characteristics as they relate to potency in potentiating glucose-induced insulin secretion and glucose-induced inhibition of glucagon secretion and to circulating half-life. The physiological effects of the truncated forms in potentiating glucose-induced insulin secretion have been shown as described above by Holst, J.J., et al. and Mojsov, S., et al. (supra). The activity of the truncated hormones in inhibiting glucagon release has been shown by Orskov, C., et al. Endocrinol

(1988) 123:2009-2013; Suzuki, S., et al. Diabetes Research: Clinical Practice (1988) 5(Supp. 1):S30. The circulating half-life of these truncated forms is short--approximately four minutes as shown by Kreymann et al. The Lancet (December 5, 1987) 1300-1303. The modified forms of these truncated GLP-1 peptides provide the opportunity to optimize these properties.

There is some literature relating to the study of degradation of peptide hormones in the liver and in plasma and the half-life of such hormones in vivo generally. An early paper by McDonald, J.K. et al., J Biol Chem (1969) 244:6199-6208 showed that a dipeptidase was responsible for the degradation of glucagon in rat liver. Studies on the growth hormone releasing factor, a member of the general glucagon, GLP-1, GLP-2 family, was shown to be rapidly degraded in plasma in vitro and also in vivo by a dipeptidase, (Frohman, L.A. et al., J Clin Invest (1986) 78:906-913). Murphy, W.A. et al., in Peptide Research (1988) 1:36-41, showed that some but not all alkylated growth hormone releasing factor peptides had higher potency in vivo. In particular, for example, the triisopropylated GRF-29 was found to be 106 times more active than GRF-29 itself. On the other hand, GRF-29 which was in methylated at the N-terminus was only 40% as potent as the parent. It was also shown that substitution of D-Ala position 2 of this hormone enhanced its potency. It was, of course, not certain to what effect on properties the enhancement of potency could be attributed.

Others have attempted some modifications of GLP-1 (7-37). It has been shown that deletion of the histidine residue at position 7 greatly diminishes the activity of the hormone (Suzuki, S., et al. (supra); Hendrick, G.K., et al. Abstract: Endocrine Society

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