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(54) **DERIVATIVES OF GLP-1 ANALOGS**

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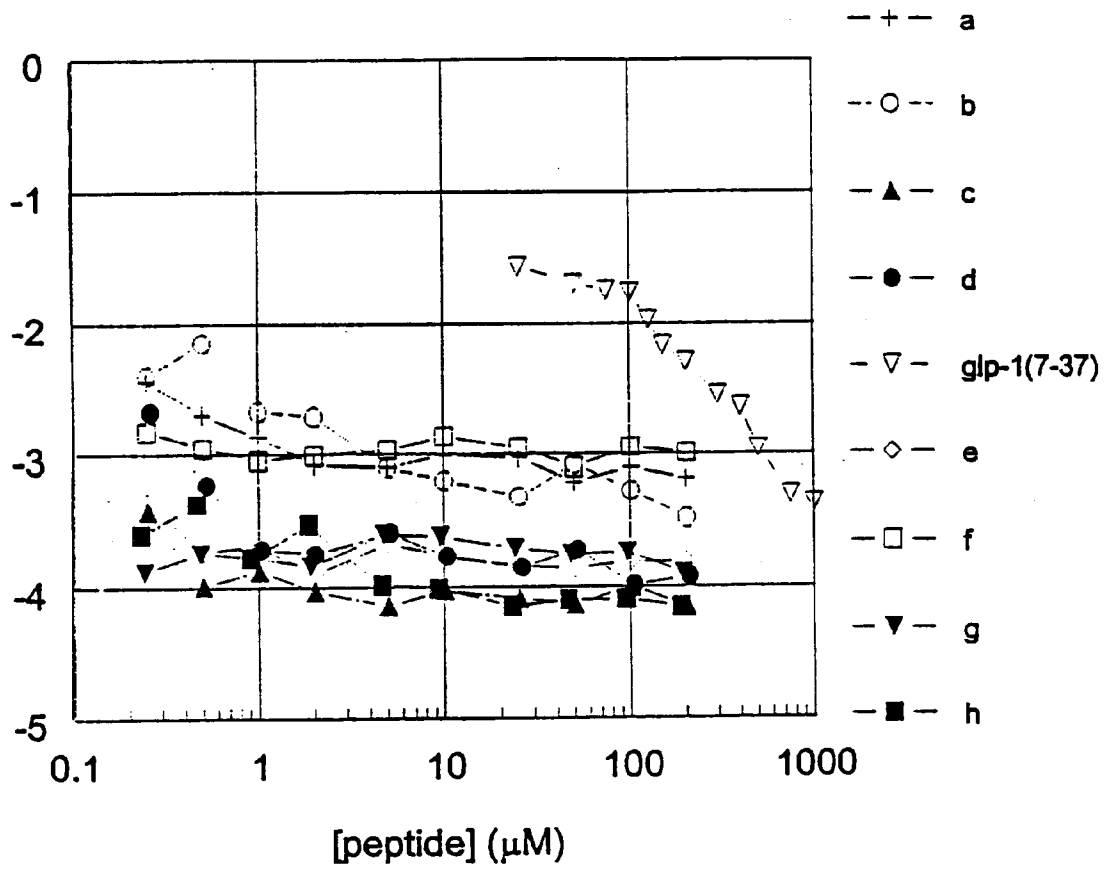
(57) **ABSTRACT**

The present invention relates to GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods of making an using same. The GLP-1 derivatives of the present invention have a protracted profile of action.

40 Claims, 1 Drawing Sheet

Fig. 1



DERIVATIVES OF GLP-1 ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Ser. No. 09/038,432 filed Mar. 11, 1998, now abandoned which is a continuation-in-part of Ser. No. 08/918,810 filed Aug. 26, 1997 now abandoned and of PCT application serial no. PCT/DK97/00340 filed Aug. 22, 1997, and claims priority of U.S. provisional application Ser. Nos. 60/035,904, 60/036,226, 60/036,255, 60/082,478, 60/082,480, 60/082,802, and 60/084,357 filed Jan. 24, 1997, Jan. 25, 1997, Jan. 24, 1997, Apr. 21, 1998, Apr. 21, 1998, Apr. 23, 1998, and May 5, 1998, respectively, and of Danish application serial nos. 0931/96, 1259/96, 1470/96, 0263/98, 0264/98, 0268/98, 0272/98, 0274/98, 0508/98, and 0509/98 filed Aug. 30, 1996, Nov. 8, 1996, Dec. 20, 1996, Feb. 27, 1998, Feb. 27, 1998, Feb. 27, 1998, Feb. 27, 1998, Feb. 27, 1998, Apr. 8, 1998, and Apr. 8, 1998, respectively, the contents of each of which is fully incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments and/or analogues thereof which have a protracted profile of action and to methods of making and using them.

BACKGROUND OF THE INVENTION

Peptides are widely used in medical practice, and since they can be produced by recombinant DNA technology it can be expected that their importance will increase also in the years to come. When native peptides or analogues thereof are used in therapy it is generally found that they have a high clearance. A high clearance of a therapeutic agent is inconvenient in cases where it is desired to maintain a high blood level thereof over a prolonged period of time since repeated administrations will then be necessary. Examples of peptides which have a high clearance are: ACTH, corticotropin-releasing factor, angiotensin, calcitonin, insulin, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin-like growth factor-2, gastric inhibitory peptide, growth hormone-releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostain, somatotropin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods and analogues thereof, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminase, adenosine deaminase and ribonuclease. In some cases it is possible to influence the release profile of peptides by applying suitable pharmaceutical compositions, but this approach has various shortcomings and is not generally applicable.

The hormones regulating insulin secretion belong to the so-called enteroinsular axis, designating a group of hormones, released from the gastrointestinal mucosa in response to the presence and absorption of nutrients in the gut, which promote an early and potentiated release of insulin. The enhancing effect on insulin secretion, the so-called incretin effect, is probably essential for a normal glucose tolerance. Many of the gastrointestinal hormones, including gastrin and secretin (choleystokinin is not insulinotropic in man), are insulinotropic, but the only physiologically important ones, those that are responsible for the incretin effect, are the glucose-dependent insulinotropic

polypeptide, GIP, and glucagon-like peptide-1 (GLP-1). Because of its insulinotropic effect, GIP, isolated in 1973 (1) immediately attracted considerable interest among diabetologist. However, numerous investigations carried out during the following years clearly indicated that a defective secretion of GIP was not involved in the pathogenesis of insulin dependent diabetes mellitus (IDDM) or non insulin-dependent diabetes mellitus (NIDDM)(2). Furthermore, as an insulinotropic hormone, GIP was found to be almost ineffective in NIDDM (2). The other incretin hormone, GLP-1 is the most potent insulinotropic substance known (3). Unlike GIP, it is surprisingly effective in stimulating insulin secretion in NIDDM patients. In addition, and in contrast to the other insulinotropic hormones (perhaps with the exception of secretin) it also potently inhibits glucagon secretion. Because of these actions it has pronounced blood glucose lowering effects particularly in patients with NIDDM.

GLP-1, a product of the proglucagon (4), is one of the youngest members of the secretin-VIP family of peptides, but is already established as an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism (5). The glucagon gene is processed differently in the pancreas and in the intestine. In the pancreas (9), the processing leads to the formation and parallel secretion of 1) glucagon itself, occupying positions 33–61 of proglucagon (PG); 2) an N-terminal peptide of 30 amino acids (PG (1–30)) often called glicentin-related pancreatic peptide, GRPP (10, 11); 3) a hexapeptide corresponding to PG (64–69); and, finally, the so-called major proglucagon fragment (PG (72–158)), in which the two glucagon-like sequences are buried (9). Glucagon seems to be the only biologically active product. In contrast, in the intestinal mucosa, it is glucagon that is buried in a larger molecule, while the two glucagon-like peptides are formed separately (8). The following products are formed and secreted in parallel: 1) glicentin, corresponding to PG (1–69), with the glucagon sequence occupying residues Nos. 33–61 (12); 2) GLP-1(7–36)amide (PG(78–107)amide (13), not as originally believed PG (72–107)amide or 108, which is inactive). Small amounts of C-terminally glycine-extended but equally bioactive GLP-1(7–37), (PG (78–108)) are also formed (14); 3) intervening peptide-2(PG (111–112)amide) (15); and 4) GLP-2 (PG(126–158))(15, 16). A fraction of glicentin is claved further into GRPP (PG (1–30)) and oxyntomodulin (PG (33–69)) (17, 18). Of these peptides, GLP-1, has the most conspicuous biological activities.

Being secreted in parallel with glicentin/enteroglucagon, it follows that the many studies of enteroglucagon secretion (6, 7) to some extent also apply to GLP-1 secretion, but GLP-1 is metabolised more quickly with a plasma half-life in humans of 2 min (19). Carbohydrate or fat-rich meals stimulate **(20)**, presumably as a result of direct interaction of yet unabsorbed nutrients with the microvilli of the open-type L-cells of the gut mucosa. Endocrine or neural mechanisms promoting GLP-1 secretion may exist but have not yet been demonstrated in humans.

The incretin function of GLP-1 (29–31) has been clearly illustrated in experiments with the GLP-1 receptor antagonist, exendin 9–39, which dramatically reduces the incretin effect elicited by oral glucose in rats **(21, 22)**. The hormone interacts directly with the β-cells via the GLP-1 receptor **(23)** which belongs to the glucagon/VIP/calcitonin family of G-protein-coupled- 7-transmembrane spanning

receptors. The importance of the GLP-1 receptor in regulating insulin secretion was illustrated in recent experiments in which a targeted disruption of the GLP-1 receptor gene was carried out in mice. Animals homozygous for the disruption had greatly deteriorated glucose tolerance and fasting hyperglycaemia, and even heterozygous animals were glucose intolerant (**24**). The signal transduction mechanism (**25**) primarily involves activation of adenylate cyclase, but elevations of intracellular Ca^{2+} are also essential (**25**, **26**). The action of the hormone is best described as a potentiation of glucose stimulated insulin release (**25**), but the mechanism that couples glucose and GLP-1 stimulation is not known. It may involve a calcium-induced calcium release (**26**, **27**). As already mentioned, the insulinotropic action of GLP-1 is preserved in diabetic β-cells. The relation of the latter to its ability to convey "glucose competance" to isolated insulin-secreting cells (**26**, **28**), which respond poorly to glucose or GLP-1 alone, but fully to a combination of the two, is also not known. Equally importantly, however, the hormone also potently inhibits glucagon secretion (**29**). The mechanism is not known, but seems to be paracrine, via neighbouring insulin or somatostatin cells (**25**). Also the glucagonostatic action is glucose-dependent, so that the inhibitory effect decreases as blood glucose decreases. Because of this dual effect, if the plasma GLP-1 concentrations increase either by increased secretion or by exogenous infusion the molar ratio of insulin to glucagon in the blood that reaches the liver via the portal circulation is greatly increased, whereby hepatic glucose production decreases (**30**). As a result blood glucose concentrations decrease. Because of the glucose dependency of the insulinotropic and glucagonostatic actions, the glucose lowering effect is self-limiting, and the hormone, therefore, does not cause hypoglycaemia regardless of dose (**31**). The effects are preserved in patients with diabetes mellitus (**32**), in whom infusions off slightly supraphysiological doses of GLP-1 may completely normalise blood glucose values in spite of poor metabolic control and secondary failure to sulphonylurea (**33**). The importance of the glucagonostatic effect is illustrated by the finding that GLP-1 also lowers blood glucose in type-1 diabetic patients without residual β-cell secretory capacity (**34**).

In addition to its effects on the pancreatic islets, GLP-1 has powerful actions on the gastrointestinal tract. Infused in physiological amounts GLP-1 potently inhibits pentagastrin-induced as well as meal-induced gastric acid secretion (**35**, **36**). It also inhibits gastric emptying rate and pancreatic enzyme secretion (**36**). Similar inhibitory effects on gastric and pancreatic secretion and motility may be elicited in humans upon perfusion of the ileum with carbohydrate- or lipid-containing solutions (**37**, **38**). Concomitantly, GLP-1 secretion is greatly stimulated, and it has been speculated that GLP-1 may be at least partly responsible for this so-called "ileal-brake" effect (**38**). In fact, recent studies suggest that, physiologically, the ileal-brake effects of GLP-1 may be more important than its effects on the pancreatic islets. Thus, in dose response studies GLP-1 influences gastric emptying rate at infusion rates at least as low as those required to influence islet secretion (**39**).

GLP-1 seems to have an effect on food intake. Intraventricular administration of GLP-1 profoundly inhibits food intake in rats (**40**, **42**). This effect seems to be highly specific. Thus, N-terminally extended GLP-1 (PG 72–107) amide is inactive and appropriate doses of the GLP-1 antagonist, exendin 9–39, abolish the effects of GLP-1 (**41**). Acute, peripheral administration of GLP-1 does not inhibit food intake acutely in rats (**41**, **42**). However, it remains possible that GLP-1 secreted from the intestinal L-cells may also act as a satiety signal.

Not only the insulinotropic effects but also the effects of GLP-1 on the gastrointestinal tract are preserved in diabetic patients (**43**), and may help curtailing meal-induced glucose excursions, but, more importantly, may also influence food intake. Administered intravenously, continuously for one week, GLP-1 at 4 ng/kg/min has been demonstrated to dramatically improve glycaemic control in NIDDM patients without significant side effects (**44**). The peptide is fully active after subcutaneous administration (**45**), but is rapidly degraded mainly due to degradation by dipeptidyl peptidase IV-like enzymes (**46**, **47**).

The amino acid sequence of GLP-1 is given i.a. by Schmidt et al. (*Diabetologia* 28 704–707 (1985). Human GLP-1 is a 37 amino acid residue peptide originating from preproglucagon which is synthesised, i.a. in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to GLP-1 (7–36)amide, GLP-1 (7–37) and GLP-2 occurs mainly in the L-cells. Although the interesting pharmacological properties of GLP-1 (7–37) and analogues thereof have attracted much attention in recent years only little is known about the structure of these molecules. The secondary structure of GLP-1 in micelles have been described by Thorton et al. (*Biochemistry* 33 3532–3539 (1994)), but in normal solution, GLP-1 is considered a very flexible molecule. Surprisingly, we found that derivatisation of this relatively small and very flexible molecule resulted in compounds whose plasma profile were highly protracted and still had retained activity.

GLP-1 and analogues of GLP-1 and fragments thereof are useful i.a. in the treatment of Type 1 and Type 2 diabetes and obesity.

WO 87/06941 discloses GLP-1 fragments, including GLP-1 (7–37), and functional derivatives thereof and to their use as an insulinotropic agent.

WO 90/11296 discloses GLP-1 fragments, including GLP-1 (7–36), and functional derivatives thereof which have an insulinotropic activity which exceeds the insulinotropic activity of GLP-1 (1–36) or GLP-1 (1–37) and to their use as insulinotropic agents.

The amino acid sequence of GLP-1 (7–36) and GLP-1 (7–37) is (SEQ ID NO:1):

```
 7   8   9  10  11  12  13  14  15  16  17     (I)
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-

18  19  20  21  22  23  24  25  26  27  28
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-

29  30  31  32  33  34  35  36
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X
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wherein X is H_2 for GLP-1 (7–36) and X is Gly for GLP-1 (7–37).

WO 91/11457 discloses analogues of the active GLP-1 peptides 7–34, 7–35, 7–36, and 7–37 which can also be useful as GLP-1 moieties.

EP 0708179-A2 (Eli Lilly & Co.) discloses GLP-1 analogues and derivatives that include an N-terminal imidazole group and optionally an unbranched C_6–C_{10} acyl group in attached to the lysine residue in position 34.

EP 0699686-A2 (Eli Lilly & Co.) discloses certain N-terminal truncated fragments of GLP-1 that are reported to be biologically active.

Unfortunately, the high clearance limits the usefulness of these compounds. Thus there still is a need for improvements in this field.

Accordingly, it is an object of the present invention to provide derivatives of GLP-1 and analogues thereof which have a protracted profile of action relative to GLP-1 (7–37).

It is a further object of the invention to provide derivatives of GLP-1 and analogues thereof which have a lower clearance than GLP-1 (7–37).

It is a further object of the invention to provide a pharmaceutical composition with improved solubility and stability.

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