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Young et al.

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(54) **METHODS OF TREATMENT USING
EXENDIN PEPTIDES OR GLP-1 PEPTIDES**

7,153,825 B2 12/2006 Young et al.
7,442,680 B2 10/2008 Young et al.
7,928,065 B2* 4/2011 Young et al. 514/6.7

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FOREIGN PATENT DOCUMENTS

W● W●9805351 2/1998
W● W●9907404 2/1999

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OTHER PUBLICATIONS

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 541 days.

This patent is subject to a terminal dis-
claimer.

Barragan at al., Interactions of Exendin-(9-39) with the effects of
glucagon-like peptide-1-(7-36) amide and of Exendin-4 on arterial
blood pressure and heart rate in rats, *Regulatory Peptides* 67:63-68
(1996).

Bhaysar et al., Inhibition of gastric emptying and of food intake
appear to be independently controlled in rodents, *Soc. Neurosci.*
Abstr. 21:460 (Abstract 188.8) (1995).

D'Alessio et al., Elimination of the Action of Glucagon-like Peptide
1 Causes an Impairment of Glucose Tolerance after Nutrient Inges-
tion by Healthy Baboons, *J. Clin. Invest.* 97(1):133-138 (1996).

Edwards et al., Cardiovascular and Pancreatic Endocrine Responses
to Glucagon-Like Peptide-1(7-36)Amide in the Conscious Calf, *Exp.*
Physiol. 82:709-716 (1997).

Eissele at al., Rat Gastric Somatostatin and Gastrin Release: Interac-
tions of Exendin-4 and Truncated Glucagon-Like Peptide-1 (GLP-1)
Amide, *Life Sci.* 55(8):629-634 (1994).

Eng et al., Purification and Structure of Exendin-3, a New Pancreatic
Secretagogue Isolated from *Heloderma horridum* Venom, *J. Biol.*
Chem. 265(33):20259-20262 (1990).

Eng et al., Isolation and Characterization of Exendin-4, an Exendin-3
Analogue, from *Heloderma suspectum* Venom, *J. Biol. Chem.*,
267(11):7402-7405 (1992).

Fehmann et al., Stable Expression of the Rat GLP-1(7-36)-Amide,
●xynomodulin, Exendin-4, and Exendin (9-39), *Peptides*,
15(3):453-456 (1994).

Ferguson et al., Cell-Surface Anchoring of Proteins via
Glycosylphosphatidylinositol Structures, *Annu. Rev. Biochem.*
57:285-320 (1988).

(Continued)

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USPC **514/11.7**; 514/15.4; 514/15.7; 514/16.4

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,424,286 A 6/1995 Eng
5,512,549 A 4/1996 Chen et al.
5,545,618 A 8/1996 Buckley et al.
5,574,008 A 11/1996 Johnson et al.
5,846,937 A 12/1998 Drucker
5,955,488 A 9/1999 Chang

(57) **ABSTRACT**

Methods for increasing urine flow are disclosed, comprising
administration of an effective amount of GLP-1, an exendin,
or an exendin or GLP-1 agonist. Methods for increasing urinary
sodium excretion and decreasing urinary potassium concen-
tration are also disclosed. The methods are useful for
treating conditions or disorders associated with toxic hyper-
volemia, such as renal failure, congestive heart failure, neph-
rotic syndrome, cirrhosis, pulmonary edema, and hyperten-
sion. The present invention also relates to methods for
inducing an inotropic response comprising administration of
an effective amount of GLP-1, an exendin, or an exendin or
GLP-1 agonist. These methods are useful for treating condi-
tions or disorders that can be alleviated by an increase in
cardiac contractility such as congestive heart failure. Pharma-
ceutical compositions for use in the methods of the invention
are also disclosed.

(56)

References Cited

OTHER PUBLICATIONS

- Göke et al., Exendin-4 is a High Potency Agonist and Truncated Exenin-(9-39)-amide an Antagonist at the Glucagon-like Peptide 1-(7-36)-amide Receptor of Insulin-secreting β Cells, *J. Biol. Chem.* 268(26):19650-19655 (1993).
- Knudsen et al., Potent Derivatives of Glucagon-like Peptide-1 with Pharmacokinetic Properties Suitable for Once Daily Administration, *J. Med. Chem.* 43:1664-1669 (2000).
- Kolligs et al., Reduction of the Incretin Effect in Rats by the Glucagon-Like Peptide 1 Receptor Antagonist Exendin (9-39) Amide, *Diabetes* 44:16-19 (1995).
- Malhotra et al., Exendin-4, a new peptide from *Heloderma suspectum* venom, potentiates cholecystokinin-induced amylase release from rat pancreatic acini, *Regulatory Peptides* 41:149-156 (1992).
- Montrose-Rafizadeh et al., Structure-Function Analysis of Exendin-4 / GLP-1 analogs, *Diabetes* 45(Suppl. 2):152A (1996).
- Halloran et al., Glucagon-Like Peptide-1 (7-36)-NH₂: a physiological inhibitor of gastric acid secretion in man, *J. Endocrinology* 126:169-173 (1990).
- Ørskov et al., Biological Effects and Metabolic Rates of Glucagon-like Peptide-1 7-36 Amide and Glucagonlike Peptide-1 7-37 in Healthy Subjects are Indistinguishable, *Diabetes* 42:658-661 (1993).
- Raufman et al., Exendin-3, a Novel Peptide from *Heloderma horridum* Venom, Interacts with Vasoactive Intestinal Peptide Receptors and a Newly Described Receptor on Dispersed Acini from Guinea Pig Pancreas, *J. Biol. Chem.*, 266(5):2897-2902 (1991).
- Raufman et al., Truncated Glucagon-Like Peptide-1 Interacts with Exendin Receptors in Dispersed Acini from Guinea Pig Pancreas, *J. Biol. Chem.* 267(30):21432-21437 (1992).
- Schepp et al., Exendin-4 and Exendin-(9-39)NH₂: Agonist and Antagonist, Respectively, at the Rat Parietal Cell Receptor for Glucagon-Like Peptide-1-(7-36)NH₂, *Eur. J. Pharm.* 269:183-191 (1994).
- Schinzel et al., The Phosphate Recognition Site of *Escherichia coli* Maltodextrin Phosphorylase, *FEBS Letters* 286:125-128 (1991).
- Schjoldager et al., GLP-1 (Glucagon-like Peptide 1) and Truncated GLP-1, Fragments of Human Proglucagon, Inhibit Gastric Acid Secretion in Humans, *Digestive Disease and Sciences* 34(5):703-708 (1989).
- Singh et al., Use of ¹²⁵I-[Y³⁹]Exendin-4 to characterize receptors on dispersed pancreatic acini and gastric chief cells from guinea pig, *Regulatory Peptides* 53:47-59 (1994).
- Tang-Christensen et al., Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats, *Am. J. Physiol.* 271:R848-R856 (1996).
- Thorens et al., Expression cloning of the Pancreatic β Cell Receptor for the gluco-incretin hormone glucagon-like peptide 1, *Proc. Natl. Acad. Sci. USA* 88:8641-8645 (1992).
- Thorens et al., Cloning and Functional Expression of the Human Islet GLP-1 Receptor, *Diabetes* 42:1678-1682 (1993).
- Turton et al., A Role for Glucagon-like peptide-1 in the central regulation of feeding, *Nature* 379:69-72 (1996).
- Wang et al., Glucagon-like Peptide-1 is a Physiological incretin in Rat, *J. Clin. Invest.* 95:417-421 (1995).
- Wettergren et al., Truncated GLP-1 (Proglucagon 78-107-Amide) Inhibits Gastric and Pancreatic Functions in Man, *Digestive Diseases and Sciences* 38(4):665-673 (1993).
- Whims et al., Gastric emptying, Glucose Responses, and Insulin Secretion after a Liquid Test Meal: Effects of Exogenous Glucagon-Like Peptide-1 (GLP-1-(7-36)Amide) in Type 2 (Noninsulin-Dependent) Diabetic Patients, *J. Clin. Endocrinol Metab.* 81(1):327-332 (1996).
- Young et al., Preclinical Pharmacology of Pramlintide in the Rat: Comparisons with Human and Rat Amylin, *Drug Development Research* 37:231-248 (1996).

* cited by examiner

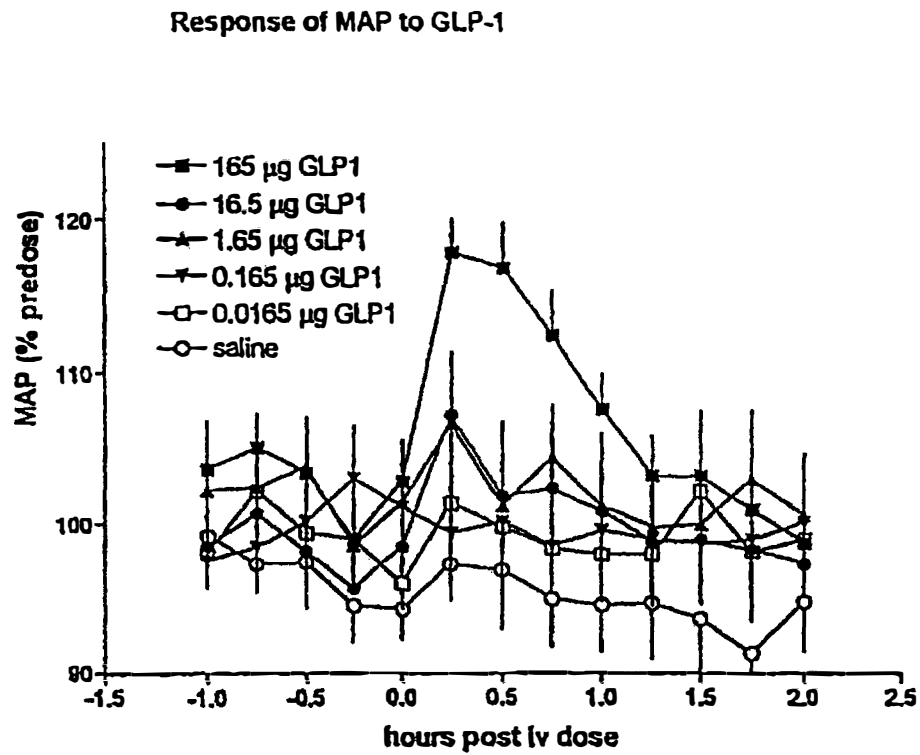


FIGURE 1A

Dose-response curve:
MAP to GLP-1

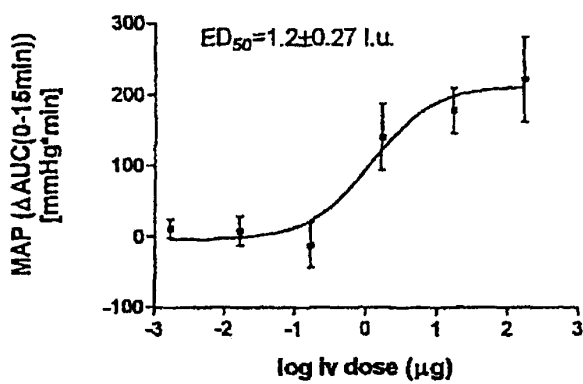


FIGURE 1B

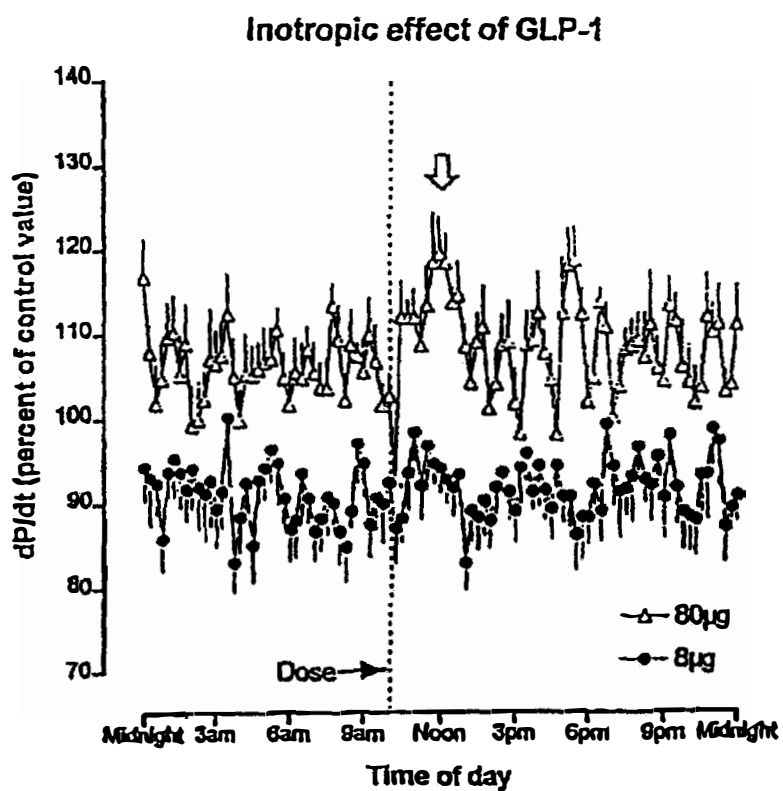


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