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(12) United States Patent

Young et al.

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

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(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
5,955,480 A	9/1999	Chang

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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

FOREIGN PATENT DOCUMENTS

WO WO98/05351 2/1998 WO WO 99/07404 2/1999

OTHER PUBLICATIONS

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 Ingestion 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: Interactions 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 Secretagoguge 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, Oxyntomodulin, 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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(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 concentration are also disclosed. The methods are useful for treating conditions or disorders associated with toxic hypervolemia, such as renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, and hypertension. 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 conditions or disorders that can be alleviated by an increase in cardiac contractility such as congestive heart failure. Pharmaceutical compositions for use in the methods of the invention are also disclosed.



(56) References Cited

OTHER PUBLICATIONS

Göke et al., Exedin-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 Effecty in Rats by the Glucagon-Like Peptide 1 Receptor Angatonist 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).

O'Halloran et al., Glucagon-Like Peptide-1 (7-36)-NH₂: a physiological inhibitor of gastric acid secretaion in man, *J. Endocrinology* 126:169-173 (1990).

Ørskov et al., Biological Effects and Metabolic Rates of Glucagonlike 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 Patietns, *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



Response of MAP to GLP-1

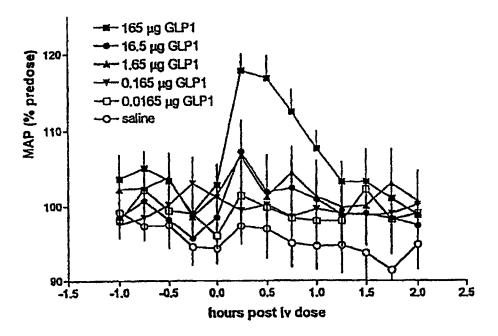


FIGURE 1A

Dose-response curve: MAP to GLP-1

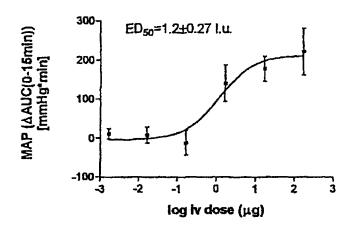


FIGURE 1B

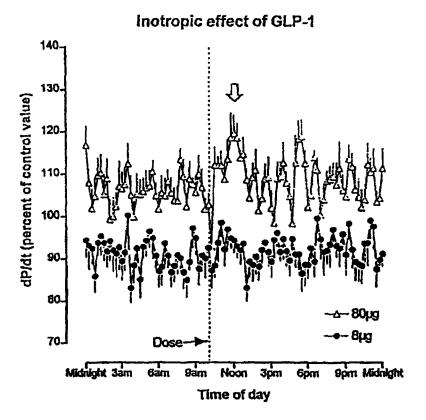


FIGURE 2



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