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<p><b>(54) Title:</b> INOTROPIC AND DIURETIC EFFECTS OF EXENDIN AND GLP-1</p>		
<p><b>(57) Abstract</b></p> <p>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.</p>		

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## DESCRIPTION

### INOTROPIC AND DIURETIC EFFECTS OF EXENDIN AND GLP-1

#### 5 FIELD OF THE INVENTION

The present invention relates to methods for increasing urine flow comprising administration of an effective amount of glucagon-like peptide-1[7-36] amide (abbreviated “GLP-[7-36]NH<sub>2</sub>” or simply “GLP-1”), an exendin, or an exendin or GLP-1 agonist.

10 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.

Pharmaceutical compositions for use in the methods of the invention are also disclosed.

15 The present invention also relates to methods for inducing an inotropic response comprising administration of an effective amount of an exendin, GLP-1, 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.

The following description summarizes information relevant to the present invention. It is not an admission that any of the information provided herein is prior art to  
20 the presently claimed invention, nor that any of the publications specifically or implicitly referenced are prior art to that invention.

#### GLP-1

25 Glucagon-like peptide-1 [7-36] amide (also referred to as GLP-1[7-36]NH<sub>2</sub> or GLP-1) is a product of the proglucagon gene. It is secreted into plasma mainly from the gut and produces a variety of biological effects related to pancreatic and gastrointestinal function. The parent peptide, proglucagon (PG), has numerous cleavage sites that produce other peptide products dependent on the tissue of origin including glucagon (PG[32-62]) and GLP-1[7-36]NH<sub>2</sub> (PG[72-107]) in the pancreas, and GLP-1[7-37] (PG[78-108]) and  
30 GLP-1[7-36]NH<sub>2</sub> (PG [78-107]) in the L cells of the intestine where GLP-1[7-36]NH<sub>2</sub> (78-107 PG) is the major product.

GLP-1[7-36]NH<sub>2</sub>, also known as proglucagon [78-107], or commonly, just GLP-1," as used herein, has an insulinotropic effect, stimulating insulin secretion from pancreatic  $\beta$ -cells; GLP-1 also inhibits glucagon secretion from pancreatic  $\alpha$ -cells (Orskov, et al., Diabetes, 42:658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996).

5 GLP-1 is reported to inhibit gastric emptying (Williams B, et al., J Clin Endocrinol Metab 81 (1): 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid secretion. (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993). A diuretic, antidypsogenic effect of intracerebroventricular administration of GLP-10 1 has been reported, however, this report claims that a peripheral, intraperitoneal injection of GLP-1 did not have this effect. (Tand-Christensen et al., Am. J. Physiol., 271:R848-56, 1996). GLP-1[7-37], which has an additional glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Orskov, et al., Diabetes, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor believed to be responsible 15 for the insulinotropic effect of GLP-1 has been cloned from a  $\beta$ -cell line (Thorens, Proc. Natl. Acad. Sci., USA 89:8641-45, 1992).

Glucagon and glucagon-like peptides have been found to have different cardiovascular effects. Glucagon has been reported to have positive inotropic and chronotropic effects, produce a slight increase in arterial blood pressure in normal 20 individuals, and affect regional blood circulation. GLP-1 has been found to produce a moderate increase in both systolic and diastolic blood pressure, while GLP-2 has no effect on those parameters. GLP-1, administered through the jugular vein, has been reported to induce an increase in systolic and diastolic blood pressure and heart rate. (Reviewed in Barragán, J.M., et al., Regul. Peptides, 67:63-68, 1996).

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### EXENDIN

Exendins are peptides that are found in the venom of the Gila-monster, a lizard endogenous to Arizona, and the Mexican Beaded Lizard. Exendin-3 is present in the venom of *Heloderma horridum*, and exendin-4 is present in the venom of *Heloderma* 30 *suspectum* (Eng, J., et al., J. Biol. Chem., 265:20259-62, 1990; Eng, J., et al., J. Biol. Chem., 267:7402-05, 1992). The exendins have some sequence similarity to several

members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993).

Exendin-4 is a potent agonist at GLP-1 receptors on insulin-secreting TC1 cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide also stimulates somatostatin release and inhibits gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268:19650-55, 1993; Schepp, et al., Eur. J. Pharmacol., 69:183-91, 1994; Eissele, et al., Life Sci., 55:629-34, 1994). Exendin-3 and exendin-4 were found to be GLP-1 agonists in stimulating cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149-56, 1992; Raufman, et al., J. Biol. Chem. 267:21432-37, 1992; Singh, et al., Regul. Pept. 53:47-59, 1994). The use of the insulinotropic activities of exendin-3 and exendin-4 for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Patent No. 5,424,286).

Truncated exendin peptides such as exendin[9-39], a carboxyamidated molecule, and fragments 3-39 through 9-39 have been reported to be potent and selective antagonists of GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993; Raufman, J.P., et al., J. Biol. Chem. 266:2897-902, 1991; Schepp, W., et al., Eur. J. Pharm. 269:183-91, 1994; Montrose-Rafizadeh, et al., Diabetes, 45(Suppl. 2):152A, 1996). Exendin[9-39] blocks endogenous GLP-1 in vivo, resulting in reduced insulin secretion. Wang, et al., J. Clin. Invest., 95:417-21, 1995; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). The receptor apparently responsible for the insulinotropic effect of GLP-1 has been cloned from rat pancreatic islet cells (Thorens, B., Proc. Natl. Acad. Sci. USA 89:8641-8645, 1992). Exendins and exendin[9-39] bind to the cloned GLP-1 receptor (rat pancreatic  $\beta$ -cell GLP-1 receptor: Fehmann HC, et al., Peptides 15 (3): 453-6, 1994; human GLP-1 receptor: Thorens B, et al., Diabetes 42 (11): 1678-82, 1993). In cells transfected with the cloned GLP-1 receptor, exendin-4 is an agonist, i.e., it increases cAMP, while exendin[9-39] is an antagonist, i.e., it blocks the stimulatory actions of exendin-4 and GLP-1. Id.

Exendin[9-39] also acts as an antagonist of the full length exendins, inhibiting stimulation of pancreatic acinar cells by exendin-3 and exendin-4 (Raufman, et al., J. Biol. Chem. 266:2897-902, 1991; Raufman, et al., J. Biol. Chem., 266:21432-37, 1992).

Exendin[9-39] inhibits the stimulation of plasma insulin levels by exendin-4, and inhibits

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