pharmaceutical compositions suitable for commercial use. Native glucagon is neither soluble, nor stable in the physiological pH range and thus must be manufactured as a dry product that requires reconstitution and immediate use. The glucagon analogs described herein have enhanced physical properties that render them superior for use in current medicinal settings where the native hormone is currently employed. These compounds can be used in accordance with one embodiment to prepare pre-formulated solutions ready for injection to treat hypoglycemia. Alternatively, the glucagon agonists can be co-administered with insulin to buffer the effects of insulin to allow for a more stable maintenance of blood glucose levels. In addition, other beneficial uses of compositions comprising the modified glucagon peptides disclosed herein are described in detail below.

SUMMARY

One ~~embodiment of the invention~~example provides glucagon peptides that retain glucagon receptor activity and exhibit improved solubility relative to the native glucagon peptide (SEQ ID NO: 1). Native glucagon exhibits poor solubility in aqueous solution, particularly at physiological pH, with a tendency to aggregate and precipitate over time. In contrast, the glucagon peptides ~~of one embodiment of the invention~~disclosed herein exhibit at least 2-fold, 5-fold, or even higher solubility compared to native glucagon at a pH between 6 and 8, for example, at pH 7 after 24 hours at 25°C.

Thus, in a first aspect, the present invention refers to a glucagon peptide with improved solubility relative to native glucagon (SEQ ID NO: 1), that is an analog of SEQ ID NO: 1 comprising (a) one, two, or three charged amino acid(s) C-terminal to the amino acid at position 27 of the glucagon peptide, (b) a Leu or Nle at position 27, and (c) up to 4 additional amino acid modifications relative to SEQ ID NO: 1, wherein the glucagon peptide retains improved solubility and glucagon activity.

In a second aspect, the present invention refers to a homo dimer comprising two glucagon peptides of the present invention bound to one another through a linker.

In a third aspect, the present invention refers to a glucagon peptide with improved solubility relative to native glucagon (SEQ ID NO: 1) comprising the sequence of SEQ ID NO: 33 or an analog of SEQ ID NO: 33, wherein said analog differs from SEQ ID NO: 33 by one to three amino acid substitutions, said amino acid substitutions located at one or more positions selected from positions 1, 2, 5, 7, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21 and 24 of the analog, with the proviso that said glucagon peptide comprises a charged amino acid at position 28 or 29, or an additional acidic amino acid added to the carboxy terminus of the peptide.

In a fourth aspect, the present invention refers to a pharmaceutical composition comprising the glucagon peptide of the present invention or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

In a fifth aspect, the present invention refers to a solution comprising the glucagon peptide of the present invention or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier; said solution at pH of about 5.5 to about 8.0.

In a sixth aspect, the present invention refers to a kit for administering a glucagon agonist to a patient in need thereof, said kit comprising the solution of the present invention; and a device for administering said composition to a patient.

In one ~~embodiment~~example the glucagon peptides retain at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75% activity, 80% activity, 85% activity, or 90% of the activity of native glucagon. In one ~~embodiment~~example, the glucagon peptides ~~of the present invention~~disclosed herein have potency greater than glucagon. Any of the glucagon peptides ~~of the invention~~disclosed herein may additionally exhibit improved stability and/or reduced degradation, for example, retaining at least 95% of the original peptide after 24 hours at 25°C.

In accordance with one ~~embodiment~~example a glucagon peptide is provided wherein the peptide is modified by amino acid substitutions and/or additions that introduce a charged amino acid into the C-terminal portion of the peptide, and in one ~~embodiment~~example at a position C-terminal to position 27 of SEQ ID NO: 1. Optionally, one, two or three charged amino acids may be introduced within the C-terminal portion, and in one ~~embodiment~~example C-terminal to position 27. In accordance with one ~~embodiment~~example the

native amino acid(s) at positions 28 and/or 29 are substituted with a charged amino acid, and/or one to three charged amino acids are added to the C-terminus of the peptide. In ~~exemplary embodiments~~some examples, one, two or all of the charged amino acids are negatively charged. Additional modifications, e.g. conservative substitutions, may be made to the glucagon peptide that still allow it to retain glucagon activity.

In accordance with one ~~exemplary embodiment~~example the glucagon peptide comprises an amino acid sequence of SEQ ID NO: 11, or an analog thereof that contains 1 to 3 further amino acid modifications relative to native glucagon, or a glucagon agonist analog thereof. SEQ ID NO: 11 represents a modified glucagon peptide wherein the asparagine residue at position 28 of the native protein has been substituted with an aspartic acid. In another ~~exemplary embodiment~~example the glucagon peptide comprises an amino acid sequence of SEQ ID NO: 38, wherein the asparagine residue at position 28 of the native protein has been substituted with glutamic acid. Other ~~exemplary embodiments~~examples include glucagon peptides of SEQ ID NOS: 24, 25, 26, 33, 35, 36 and 37.

The solubility of any of the foregoing compounds can be further improved by attaching a hydrophilic moiety to the peptide. In one ~~embodiment~~example the hydrophilic moiety is a polyethylene glycol chain or other water soluble polymer that is covalently linked to the side chain of an amino acid residue at position 16, 17, 21 or 24 of said glucagon peptide. The polyethylene glycol chain in accordance with one ~~embodiment~~example has a molecular weight selected from the range of about 500 to about 40,000 Daltons. The present invention further encompasses pharmaceutically acceptable salts of said glucagon agonists.

In other ~~exemplary embodiments~~examples, any of the foregoing compounds can be further modified to alter its pharmaceutical properties by the addition of a second peptide to the carboxy terminus of the glucagon peptide. In one ~~embodiment~~example a glucagon peptide is covalently bound through a peptide bond to a second peptide, wherein the second peptide comprises a sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.

In yet further ~~exemplary embodiments~~examples, any of the foregoing compounds can be further modified to improve stability by modifying the amino acid at position 15 of SEQ ID NO: 1 to reduce degradation of the peptide over time, especially in acidic or alkaline buffers.

In accordance with one ~~embodiment~~example a pharmaceutical composition is provided comprising any of the novel glucagon peptides disclosed herein, preferably at a purity level of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, and a pharmaceutically acceptable diluent, carrier or excipient. Such compositions may contain a glucagon peptide at a concentration of at least 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, 5 mg/ml, or higher. In one ~~embodiment~~example the pharmaceutical compositions comprise aqueous solutions that are sterilized and optionally stored within various containers. In other ~~embodiments~~examples the pharmaceutical compositions comprise a lyophilized powder. The pharmaceutical compositions can be further packaged as part of a kit that includes a disposable device for administering the composition to a patient. The containers or kits may be labeled for storage at ambient room temperature or at refrigerated temperature.

In accordance with one ~~embodiment~~example a method of rapidly increasing glucose level or treating hypoglycemia using a pre-formulated aqueous composition is provided. The method comprises the step of administering an effective amount of an aqueous solution comprising a novel modified glucagon peptide of the present disclosure. In another ~~embodiment~~example a method is provided for inducing the temporary paralysis of the intestinal tract. The method comprises the step of administering one or more of the glucagon peptides disclosed herein to a patient in need thereof.

In yet another ~~embodiment~~example a method of reducing weight gain or inducing weight loss is provided, which involves administering an effective amount of an aqueous solution comprising a glucagon peptide of the invention. In further ~~embodiments~~examples, methods of treating diabetes involving co-administering insulin and a glucagon peptide of the invention are provided.

Exemplary glucagon peptides are selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 33, wherein amino acid 29 of the glucagon peptide is bound to a second peptide through a peptide bond, and said second peptide comprises the sequence of SEQ ID NO: 20, SEQ ID NO: 21 or SEQ ID NO: 22. In one ~~embodiment~~example the glucagon peptide is pegylated. In one ~~embodiment~~example the method comprises the step of administering a peptide comprising the sequence of SEQ ID NO: 24, SEQ ID NO: 25,