cleavage. It would further be desirable to provide OXM analogs that are capable of acting as dual GLP-1 receptor/glucagon receptor agonists.

BRIEF SUMMARY OF THE DISCLOSURE~~INVENTION~~

The present disclosure~~invention~~ provides oxyntomodulin (OXM, glucagon-37) peptide analogs, which have been modified to be resistant to cleavage and inactivation by dipeptidyl peptidase IV (DPP-IV) and to increase *in vivo* half-life of the peptide analog while enabling the peptide analog to act as a dual GLP-1/glucagon receptor (GCGR) agonist, and the use of such peptide analogs for treatment of metabolic disorders such as diabetes and obesity. In particular, the analogs disclosed herein reduce food intake and body weight, increase metabolic rate, mediate glucose-dependent insulin secretion (GDIS) from pancreatic islets and improve glucose tolerance, thereby providing a treatment option for individuals afflicted with a metabolic disorder such as metabolic syndrome, obesity, diabetes, metabolic syndrome X, hyperglycemia, impaired fasting glucose, dyslipidemia, atherosclerosis, and other prediabetic states.

Therefore, the present disclosure~~invention~~ provides a peptide comprising the amino acid sequence of a human oxyntomodulin (OXM) shown in SEQ ID NO:1 wherein the second amino acid from the N-terminus is substituted with an amino acid that renders the peptide resistant to cleavage and inactivation by dipeptidyl peptidase IV the peptide includes a lipid or cholesterol moiety covalently linked to the peptide; the peptide optionally includes one to three amino acid substitutions in addition to the substitution at position 2; and the peptide optionally includes a protecting group that, if present, is joined to the C-terminal carboxy group of the peptide; wherein the peptide is capable of acting as a dual GLP-1 receptor and glucagon receptor agonist and has a serum half-life greater than the serum half-life of the human OXM, and pharmaceutically acceptable salts thereof. In further aspects, the amino acid substituted for the second amino acid from the N-terminus is selected from the group consisting of D-serine and α-aminoisobutyric acid.

Further provided is a peptide comprising the amino acid sequence of a human oxyntomodulin (OXM) shown in SEQ ID NO:1 wherein the second amino acid from the N-terminus is substituted with an amino acid selected from the group consisting of D-serine and α-aminoisobutyric acid; the C-terminus of the peptide includes a cysteine residue in which the thiol group of the cysteine residue is covalently linked to a cholesterol moiety by a hydrophilic linker; the peptide optionally includes one to three amino acid substitutions in addition to the substitution at position 2; and the peptide optionally includes a protecting group that, if present, is joined to the C-terminal carboxy group of the peptide; wherein the peptide acts as a dual GLP-1 receptor and glucagon receptor agonist and has a serum half-life greater than the serum half-life of the human OXM, and pharmaceutically acceptable salts thereof.

by a spacer comprising one or more gamma glutamic acid residues, or (iii) a lipid moiety, wherein M is covalently linked to C-terminal or internal amino acid of P by a spacer comprising one or more gamma-glutamic acid residues; and Z_2 is an optionally present protecting group that, if present, is joined to the C-terminal carboxy group; and pharmaceutically acceptable salts thereof, wherein the peptide analog or salt thereof has a pI of less than 6.0 and is a dual GLP-1 receptor agonist and glucagon receptor agonist. In particular aspects, peptide analogs have a pI between 4 and 6, or a pI of about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, or 5.9, or a pI of about 5.4 to 5.5.

In one aspect, there is provided a peptide analog comprising the structure

$$Z_1\text{-}P\text{-}M\text{-}Z_2$$

wherein P is a peptide having the amino acid sequence

$HX_1QGTFTSDX_2SX_3YLDX_4X_5X_6AX_7DFVQWLX_8NTKX_9X_{10}$ (SEQ ID NO:110)

wherein X_1 is a D-serine, α-aminoisobutyric acid (aib), 1-Amino-1-cyclobutane carboxylic acid (Acb) residue, 1-Amino-1-cyclohexane carboxylic acid (Acx); alpha-aminobutyric acid(Abu); D- alpha-aminobutyric acid (D-Abu); Aminovaleric acid Nva); beta-cyclopropyl-alanine (Cpa); propargylglycine (Prg); Allylglycine (Alg); 2-Amino-2-cyclohexyl-propanoic acid (2-Cha); D-tertbutylglycine (D-tbg); Vinylglycine (Vg); 1-Amino-1-cyclopropane carboxylic acid (Acp); or 1-Amino-1-cyclopentane carboxylic acid (Acpe) residue;

X_2 is a tyrosine (Y) or lysine (K) residue;

X_3 is serine (S) or lysine (K) residue;

X_4 is serine (S), α-aminoisobutyric acid (aib), or glutamic acid (E) residue;

X_5 is an arginine (R) or glutamic acid (E) residue;

X_6 is an arginine (R) or alanine (A) residue;

X_7 is a glutamine (Q) or lysine (K) residue;

X_8 is a methionine (M), norleucine (Nle), methionine sulfoxide (m), or O-methyl-L-homoserine (o) residue;

X_9 is a gamma glutamic acid (γGlu) residue;

X_{10} is a gamma glutamic acid (γGlu) residue or absent;

Z_1 is an optionally present protecting group that, if present, is joined to the *N*-terminal amino group,

M is (i) a cysteine residue covalently linked to a cholesterol moiety by a hydrophilic linker, (ii) a lysine residue covalently linked to a lipid moiety by a spacer comprising one or more gamma glutamic acid residues, or (iii) a lipid moiety, wherein M is covalently linked to C-

terminal or internal amino acid of P by a spacer comprising one or more gamma-glutamic acid residues; and

Z_2 is an optionally present protecting group that, if present, is joined to the C-terminal carboxy group; and pharmaceutically acceptable salts thereof

In further aspects of the peptide analog, M is a cysteine residue covalently linked to a cholesterol moiety with a hydrophilic linker and the cysteine residue is linked to the C-terminus of P. In further embodiments, the hydrophilic linker is an ethoxy polymer that includes one to twenty-four ethoxy units, which in particular aspects can include for example, four ethoxy units.

In further aspects, M is a lysine residue covalently linked to a lipid moiety by a spacer comprising one or more gamma glutamic acid residues and the lysine residue is linked to the C-terminus of P or M is a lysine residue covalently linked to a lipid moiety by a spacer comprising one or more gamma glutamic acid residues and the lysine residue is at position X_2 or X_7 of P. In particular aspects, the lipid moiety is a palmitoyl, myristoyl, or stearoyl moiety.

In particular aspects, the peptide analog is OXM317 (SEQ ID NO:60); OXM318 (SEQ ID NO:61); OXM319 (SEQ ID NO:62); OXM323 (SEQ ID NO:64); OXM327 (SEQ ID NO:66); or OXM329 (SEQ ID NO:67). In further aspects, the peptide analog is OXM345 (SEQ ID NO:69); OXM355 (SEQ ID NO:70); OXM357 (SEQ ID NO:71); OXM359 (SEQ ID NO:72); OXM361 (SEQ ID NO:73); OXM373 (SEQ ID NO:74); OXM374 (SEQ ID NO:75); OXM380 (SEQ ID NO:76); OXM381 (SEQ ID NO:77); OXM383 (SEQ ID NO:78); OXM388 (SEQ ID NO:79); OXM392 (SEQ ID NO:80); OXM395 (SEQ ID NO:81); OXM398 (SEQ ID NO:82); OXM399 (SEQ ID NO:83); OXM400 (SEQ ID NO:84); OXM401 (SEQ ID NO:85); OXM404 (SEQ ID NO:86); OXM406 (SEQ ID NO:87); OXM407 (SEQ ID NO:88); OXM408 (SEQ ID NO:89); OXM410 (SEQ ID NO:91); OXM411 (SEQ ID NO:92); OXM412 (SEQ ID NO:93); OXM414 (SEQ ID NO:95); OXM415 (SEQ ID NO:96); OXM416 (SEQ ID NO:97; OXM417 (SEQ ID NO:98); OXM418 (SEQ ID NO:99; OXM419 (SEQ ID NO:100; OXM420 (SEQ ID NO:101); or OXM421 (SEQ ID NO:102).

Further provided is the use of any one of the aforementioned peptides and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of a metabolic disorder.

Definitions