Claims

1. Use of a neuroprotective polypeptide formulation in the manufacture of a controlled-release neuroprotective formulation for treating a central nervous system (CNS)-related disease or reducing at least one symptom of a CNS-related disease in a subject, wherein the controlled-release neuroprotective formulation comprises a therapeutically effective amount of the neuroprotective polypeptide comprising at least one polypeptide selected from the group consisting of GLP-1, exendin-4, and a therapeutically effective exendin-4 analogue, wherein the neuroprotective polypeptide binds to and activates a receptor that binds at least one of GLP-1, exendin-4, or a combination thereof; and wherein the controlled-release neuroprotective formulation enhances the delivery and/or uptake of the neuroprotective polypeptide across a blood-brain barrier (BBB) of the subject to at least a portion of the central nervous system (CNS) relative to a rapid release formulation of the neuroprotective peptide;

wherein the CNS-related disease is Parkinson's disease (PD) or traumatic brain injury (TBI);

wherein the controlled-release neuroprotective formulation comprises a controlled-release microsphere that includes a core with the neuroprotective polypeptide and a biodegradable polymer; and a coating layer comprising coating materials that coats the core;

wherein the biodegradable polymer is selected from the group consisting of polylactide (PLA), polyglycolide (PGA), poly(lactide-co-glycolide) (PLGA), polyorthoester, polyanhydride, polyhydroxybutyric acid, polycaprolactone, and polyalkylcarbonate, a copolymer or a simple mixture of two or more selected the polymer group, a copolymer of the polymer and polyethylenglycol (PEG), or a polymer-sugar complex where a sugar is coupled with the polymer or the copolymer;

wherein the coating material is one or more selected from the group consisting of basic amino acids, polypeptides, and organic nitrogen compounds, wherein the basic amino acid is one or more selected from the group consisting of arginine, lysine, and histidine; wherein the polypeptide is a polypeptide comprising one or more basic amino acids selected from the group consisting of arginine, lysine, and histidine and having 2 to 10 amino acids, in which the whole amino acids in the polypeptide include more basic amino acids than acidic amino acids; and wherein the organic nitrogen compound is one or more selected from the group consisting of creatine, creatinine, and urea;

wherein the exendin-4 analogue is represented by Chemical Formula I or its pharmaceutically acceptable salts:

Xaa1 Xaa2 Xaa3 Xaa4 Xaa5 Xaa6 Xaa7 Xaa8 Xaa9 Xaa10 Xaa11 Xaa12 Xaa13 Xaa14 Xaa15 Xaa16 Xaa17 Ala Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 Xaa25 Xaa26 Xaa27 Xaa28-Z_1, (Chemical Formula I)

wherein:

Xaa1 is His, Arg, Tyr, Ala, Norval, Val, Norleu, or 4-imidazopropionyl;

Xaa2 is Ser, Gly, Ala, or Thr;

Xaa3 is Ala, Asp, or Glu;

Xaa4 is Ala, Norval, Val, Norleu, or Gly;

Xaa5 is Ala or Thr;

Xaa6 is Ala, Phe, Tyr, or naphthylalanine;

Xaa7 is Thr or Ser;

Xaa8 is Ala, Ser, or Thr;

Xaa9 is Ala, Norval, Val, Norleu, Asp, or Glu;

Xaa10 is Ala, Leu, Ile, Val, pentylglycine, or Met;

Xaa11 is Ala or Ser;

Xaa12 is Ala or Lys;

Xaa13 is Ala or Gln;

Xaa14 is Ala, Leu, Ile, pentylglycine, Val, or Met;

Xaa15 is Ala or Glu;

Xaa16 is Ala or Glu;

Xaa17 is Ala or Glu;

Xaa19 is Ala or Val;

Xaa20 is Ala, or Arg;

Xaa21 is Ala, Leu, or Lys-NHε-R, wherein R is Lys, Arg, or a C1-C10 straight chain or branched alkanoyl;

Xaa22 is Ala, Phe, Tyr, or naphthylalanine;

Xaa23 is Ile, Val, Leu, pentylglycine, tert-butylglycine, or Met;

Xaa24 is Ala, Glu, or Asp;

Xaa25 is Ala, Trp, Phe, Tyr, or naphthylalanine;

Xaa26 is Ala or Leu;

Xaa27 is Ala or Lys;

Xaa28 is Ala or Asn; and

Z_1 is --OH, --NH_2, Gly-Z_2, Gly Gly-Z_2, Gly Gly Xaa31-Z_2, Gly Gly Xaa31 Ser-Z_2, Gly Gly Xaa31 Ser Ser-Z_2, Gly Gly Xaa31 Ser Ser Gly-Z_2, Gly Gly Xaa31 Ser Ser Gly Ala-Z_2, Gly Gly Xaa31 Ser Ser Gly Ala Xaa36-Z_2, Gly Gly Xaa31 Ser Ser Gly Ala Xaa36 Xaa37-Z_2, Gly Gly Xaa31 Ser Ser Gly Ala Xaa36 Xaa37 Xaa38-Z_2, or Gly Gly Xaa31 Ser Ser Gly Ala Xaa36 Xaa37 Xaa38 Xaa39-Z_2,

Xaa31, Xaa36, Xaa37, and Xaa38 are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine, and N-alkylalanine, Xaa39 is Ser, or Tyr, and

Z_2 is --OH, or --NH_2,

provided that:

no more than three of Xaa3, Xaa4, Xaa5, Xaa6, Xaa8, Xaa9, Xaa10, Xaa11, Xaa12, Xaa13, Xaa14, Xaa15, Xaa16, Xaa17, Xaa19, Xaa20, Xaa21, Xaa24, Xaa25, Xaa26, Xaa27, and Xaa28 are Ala; and

when Xaa1 is His, Arg, or Tyr, at least one of Xaa3, Xaa4, and Xaa9 is Ala; or

the exendin-4 analogue is represented by Chemical Formula II or its pharmaceutically acceptable salts:

Xaa1 Xaa2 Xaa3 Xaa4 Xaa5 Xaa6 Xaa7 Xaa8 Xaa9 Xaa10 Xaa11 Xaa12 Xaa13 Xaa14 Xaa15 Xaa16 Xaa17 Ala Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 Xaa25 Xaa26 X1-Z1, (Chemical Formula II)

wherein:

Xaa1 is His, Arg, Tyr, Ala, Norval, Val, Norleu, or 4-imidazopropionyl;

Xaa2 is Ser, Gly, Ala, or Thr;

Xaa3 is Ala, Asp, or Glu;

Xaa4 is Ala, Norval, Val, Norleu, or Gly;

Xaa5 is Ala or Thr;

Xaa6 is Ala, Phe, Tyr, or naphthylalanine;

Xaa7 is Thr or Ser;

Xaa8 is Ala, Ser, or Thr;

Xaa9 is Ala, Norval, Val, Norleu, Asp, or Glu;

Xaa10 is Ala, Leu, Ile, Val, pentylglycine, or Met;

Xaa11 is Ala or Ser;

Xaa12 is Ala or Lys;

Xaa13 is Ala or Gln;

Xaa14 is Ala, Leu, Ile, pentylglycine, Val, or Met;

Xaa15 is Ala or Glu;

Xaa16 is Ala or Glu;

Xaa17 is Ala or Glu;

Xaa19 is Ala or Val;

Xaa20 is Ala, or Arg;

Xaa21 is Ala, Leu, or Lys-NHε-R, wherein R is Lys, Arg, or a C1-C10 straight chain or branched alkanoyl, or cycloalleyl-alkanoyl;

Xaa22 is Phe, Tyr, or naphthylalanine;

Xaa23 is Ile, Val, Leu, pentylglycine, tert-butylglycine, or Met;

Xaa24 is Ala, Glu, or Asp;

Xaa25 is Ala, Trp, Phe, Tyr, or naphthylalanine;

Xaa26 is Ala or Leu;

X1 is Lys Asn, Asn Lys, Lys-NHε-R Asn, Asn Lys-NHε-R, Lys-NHε-R Ala, Ala Lys-NHε-R, wherein R is Lys, Arg, a C1-C10 straight chain or branched alkanoyl, or cycloalkylalkanoyl;

Z1 is --OH, --NH2, Gly-Z2, Gly Gly-Z2, Gly Gly Xaa31-Z2, Gly Gly Xaa31 Ser-Z2, Gly Gly Xaa31 Ser Ser-Z2, Gly Gly Xaa31 Ser Ser Gly-Z2, Gly Gly Xaa31 Ser Ser Gly Ala-Z2, Gly Gly Xaa31 Ser Ser Gly Ala Xaa36-Z2, Gly Gly Xaa31 Ser Ser Gly Ala Xaa36 Xaa37-Z2, Gly Gly Xaa31 Ser Ser Gly Ala Xaa36 Xaa37 Xaa38-Z2, or Gly Gly Xaa31 Ser Ser Gly Ala Xaa36 Xaa37 Xaa38 Xaa39-Z2,

Xaa31, Xaa36, Xaa37, and Xaa38 are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine, and N-alkylalanine, Xaa39 is Ser, or Tyr, and

Z2 is --OH, or --NH2,

provided that:

no more than three of Xaa3, Xaa4, Xaa5, Xaa6, Xaa8, Xaa9, Xaa10, Xaa11, Xaa12, Xaa13, Xaa14, Xaa15, Xaa16, Xaa17, Xaa19, Xaa20, Xaa21, Xaa24, Xaa25, and Xaa26 are Ala; and

when Xaa1 is His, Arg, Tyr or 4-imidazopropionyl, at least one of Xaa3, Xaa4, and Xaa9 is Ala.

2. The use of claim 1, wherein the controlled-release formulation is a long acting formulation of the neuroprotective polypeptide.

3. The use of claim 2, wherein the long acting formulation comprises a depot formulation for sustained release of the neuroprotective polypeptide.

4. The use of claim 2, wherein the long acting formulation comprises a composition for sustained release of the neuroprotective polypeptide.

5. The use of claim 1, wherein the neuroprotective polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-55.

6. The use of any one of claims 1-5, wherein the biodegradable polymer has a specific viscosity of 0.1 to 0.6 dL/g.