Claims

1. A controlled-release neuroprotective formulation capable of delivering a neuroprotective polypeptide to at least a portion of a central nervous system (CNS) of a subject, comprising 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 GLP-1 or 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.

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

3. The controlled-release neuroprotective formulation of claim 1, wherein the controlled-release formulation further comprises a biodegradable polymer with a specific viscosity, and a coating material.

4. The controlled-release neuroprotective formulation of claim 1, 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 that coats the core.

5. The controlled-release neuroprotective formulation of claim 2, wherein the long acting formulation comprises a depot formulation for sustained release of the neuroprotective polypeptide.

6. The controlled-release neuroprotective formulation of claim 2, wherein the long acting formulation comprises a composition for sustained release of the neuroprotective polypeptide.

7. The controlled-release neuroprotective formulation of claim 3, 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 from the polymer group, a copolymer of a polymer selected from the polymer group and polyethyleneglycol (PEG), or a polymer-sugar complex where a sugar is coupled with a polymer selected from the polymer group or a copolymer comprising a polymer of the polymer group.

8. The controlled-release neuroprotective formulation of claim 1, 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.

9. The controlled-release neuroprotective formulation of claim 1, wherein 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 X_1-Z_1, (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;

X_1 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;

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, and Xaa26 are Ala; and

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

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

11. The controlled-release neuroprotective formulation of claim 1, capable of alleviating at least one symptom of at least one CNS-related condition in the subject.