STATEMENTS OF INVENTION

1. A method for delivering a neuroprotective polypeptide to at least a portion of a central nervous system (CNS) of a subject, the method comprising:

administering to the systemic blood circulation of the subject a therapeutically effective amount of the neuroprotective polypeptide by a controlled-release formulation or a device providing a sustained release of the neuroprotective polypeptide, wherein the neuroprotective polypeptide includes at least one neuroprotective polypeptide selected from the group consisting of GLP-1, exendin-4, or 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 or sustained release of the neuroprotective polypeptide 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 method according to claim 1, wherein the controlled-release formulation is a long acting formulation of the neuroprotective polypeptide.

3. The method according to claim 1 or 2, wherein the controlled-release formulation further comprises a biodegradable polymer with a specific viscosity, and a coating material so that bioavailability and sustained release of an effective amount of the neuroprotective polypeptide is effectuated for a sufficient period.

4. The method of according to any of claims 1-3, 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 method according to claim 2, wherein the long acting formulation comprises a depot formulation for sustained release of the neuroprotective polypeptide.

6. The method according to claim 2 or 3, wherein the long acting formulation comprises a composition for sustained release of the neuroprotective polypeptide.

7. A method of treating a subject with a central nervous system (CNS)-related disease or reducing at least one symptom of a CNS-related disease in a subject in need thereof, the method comprising:

administering to the systemic blood circulation of the subject a therapeutically effective amount of a neuroprotective polypeptide by a controlled-release formulation or a device providing a sustained release of the neuroprotective polypeptide, wherein the neuroprotective polypeptide includes at least one neuroprotective polypeptide selected from the group consisting of GLP-1, exendin-4, or 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 or the sustained release of the neuroprotective polypeptide enhances the delivery 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 polypeptide.

8. The method according to claim 7, wherein the controlled-release formulation is a long acting formulation of the neuroprotective polypeptide.

9. The method according to claim 7 or 8, wherein the controlled-release formulation further comprises a biodegradable polymer with a specific viscosity and coating materials, having bioavailability and sustained release of the neuroprotective polypeptide in an effective concentration for a certain period.

10. The method according to any of claims 7-9, 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.

11. The method according to claim 8, wherein the long acting formulation comprises a depot formulation for sustained release of the neuroprotective polypeptide.

12. The method according to claim 8, wherein the long acting formulation comprises a composition for sustained release of the neuroprotective polypeptide.

13. The method according to any of claims 3, 4, 9, or 10, 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.

14. The method according to any of claims 1-13, wherein administering the controlled-release neuroprotective formulation comprises injecting the controlled-release neuroprotective formulation to the subject.

15. The method according to claim 14, wherein injecting the controlled-release formulation to the subject is a subcutaneous injection.

16. The method according to any of claim 1-15, wherein the controlled-release formulation is administered a subsequent time about 7 to about 21 days (e.g., once every about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, or about 21 days) after the previous administration.

17. The method according to any of claims 1-13, wherein the device provides the sustained release of the controlled-release formulation.

18. The method of any of claim 1, 8, or 17, wherein the device is a pump (e.g., a pump, a mini-pump, an osmotic pump, an osmotic delivery device, an infusion pump, an intravenous administration device, a peristaltic pump, a miniature infusion pump, or the like).

19. The method of any of claims 1, 8, 17, or 18, wherein the neuroprotective polypeptide is administered by the device at a rate of about 1 pM/kg/min to about 30 pM/kg/min (e.g., about 3 pM/kg/min to about 17.5 pM/kg/min).

20. The method according to any of claims 1-19, wherein administering the neuroprotective polypeptide to the systemic blood circulation alleviates at least one symptom of at least one CNS-related condition in the subject.

21. The method according to claim 20, wherein the CNS-related condition is selected from the group consisting of Parkinson's disease (PD), traumatic brain injury (TBI), multiple sclerosis, drug addiction, alcohol addiction, neurodegenerative conditions, inflammation of a brain, Alzheimer's disease (AD), multiple system atrophy, Huntington's disease, chronic traumatic encephalopathy (CTE)motor neuron diseases (e.g., amyotrophic lateral sclerosis, spinal cord injury, spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA)), vascular dementia, dementia with Lewy bodies (DLB), mixed dementia, frontotemporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, or a combination thereof.

22. The method according to any of claim 1-21, wherein administering the controlled release formulation or providing the sustained release of the neuroprotective polypeptide by a device results in a steady-state plasma concentration of the neuroprotective polypeptide that is in a range of about 50 to about 4500 pg/mL.

23. The method according to any of claims 1-22, wherein administering the controlled-release formulation or providing the sustained release of the neuroprotective polypeptide by a device results in a cumulative increase in the neuroprotective polypeptide concentration in at least one of the cerebrospinal fluid (CSF), the brain, or a combination thereof.

24. The method according to any of claims 1-23, wherein the neuroprotective polypeptide concentration in the CSF is within the range of about 10 to about 400 pg/mL.

25. The method according to any of claims 1-24, wherein the ratio of the steady-state polypeptide concentration in the CFS to the plasma is in the range of about 0.1% to about 5%.

26. The method of according to any of claims 1-25, wherein the exendin-4 analogue is represented by Chemical Formula I or its pharmaceutically acceptable salt:

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, or N-alkylalanine, Xaa39 is Ser, or Tyr (e.g. Ser), 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.

27. The method according to any of claims 1-25, wherein the exendin-4 analogue is represented by Chemical Formula II or their 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, 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.

28. The method according to any of claims 1-25, wherein the neuroprotective polypeptide is selected from the group consisting of SEQ ID NOS: 1-55.

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.