

Claims

1. A polypeptide comprising the amino acid sequence of
 TX₁LETX₂X₃X₄GX₅X₆X₇PX₈TIRVX₉Q (SEQ ID NO: 1)
 5 wherein
 X₁ is H, H-3Me or PyA-4;
 X₂ is T, S, D or E;
 X₃ is F, F-2-Br, F-2-Cl or F-3-F;
 X₄ is W, Nal, or absent;
 10 X₅ is D or *N*-Me-D;
 X₆ is G, A or P;
 X₇ is E or D;
 X₈ is K or *N*-Me-K; and
 X₉ is T or *N*-Me-T;
 15 or a pharmaceutically acceptable salt thereof.
2. The polypeptide according to claim 1, wherein the polypeptide comprises or
 consists of the amino acid sequence TX₁LETX₂X₃X₄GX₅X₆X₇PX₈TIRVX₉QpGX₁₀
 (SEQ ID NO: 2)
 20 wherein
 X₁ is H, H-3Me or PyA-4;
 X₂ is T, S, D or E;
 X₃ is F, F-2-Br, F-2-Cl or F-3-F;
 X₄ is W, Nal, or absent;
 25 X₅ is D or *N*-Me-D;
 X₆ is G, A or P;
 X₇ is E or D;
 X₈ is K or *N*-Me-K;
 X₉ is T or *N*-Me-T; and
 30 X₁₀ is C, Q or E;
 or a pharmaceutically acceptable salt thereof.
3. The polypeptide according to claim 1, wherein the polypeptide comprises or
 consists of the amino acid sequence TX₁LETX₂X₃GX₅X₆X₇PX₈TIRVX₉Q (SEQ
 35 ID NO: 3)

wherein

X₁ is H, H-3Me or PyA-4;

X₂ is T, S, D or E;

X₃ is F, F-2-Br, F-2-Cl or F-3-F;

5 X₅ is D or *N*-Me-D;

X₆ is G, A or P;

X₇ is E or D;

X₈ is K or *N*-Me-K; and

X₉ is T or *N*-Me-T;

10 or a pharmaceutically acceptable salt thereof.

4. The polypeptide according to claim 1, wherein the polypeptide comprises or consists of the amino acid sequence TX₁LETX₂X₃GX₅X₆X₇PX₈TIRVX₉QpGX₁₀ (SEQ ID NO: 4)

15 wherein

X₁ is H, H-3Me or PyA-4;

X₂ is T, S, D or E;

X₃ is F, F-2-Br, F-2-Cl or F-3-F;

X₅ is D or *N*-Me-D;

20 X₆ is G, A or P;

X₇ is E or D;

X₈ is K or *N*-Me-K;

X₉ is T or *N*-Me-T; and

X₁₀ is C, Q or E;

25 or a pharmaceutically acceptable salt thereof.

5. The polypeptide according to claim 1, wherein the polypeptide comprises or consists of the amino acid sequence TX₁LETTFX₄GX₅X₆X₇PX₈TIRVX₉QpGX₁₀ (SEQ ID NO: 5)

30 wherein

X₁ is H, H-3Me or PyA-4;

X₄ is W, Nal, or absent;

X₅ is D or *N*-Me-D;

X₆ is G, A or P;

35 X₇ is E or D;

X₈ is K or *N*-Me-K;
 X₉ is T or *N*-Me-T; and
 X₁₀ is C, Q or E;
 or a pharmaceutically acceptable salt thereof.

5

6. The polypeptide according to claim 1, wherein the polypeptide comprises or consists of the amino acid sequence TX₁LETTFGX₅X₆X₇PX₈TIRVX₉QpGX₁₀ (SEQ ID NO: 6)

wherein

10

X₁ is H, H-3Me or PyA-4;

X₅ is D or *N*-Me-D;

X₆ is G, A or P;

X₇ is E or D;

X₈ is K or *N*-Me-K;

15

X₉ is T or *N*-Me-T; and

X₁₀ is C, Q or E;

or a pharmaceutically acceptable salt thereof.

7. The polypeptide according to claim 1, wherein the polypeptide comprises or consists of the amino acid sequence TX₁LETTFX₄GDGX₇PX₈TIRVX₉Q (SEQ ID NO: 7), wherein

20

X₁ is H, or PyA-4;

X₄ is W or Nal;

X₇ is E or D;

25

X₈ is K or *N*-Me-K; and

X₉ is T or *N*-Me-T;

or a pharmaceutically acceptable salt thereof.

8. The polypeptide according to any of the preceding claims, wherein said polypeptide is cyclic.

30

9. The polypeptide according to any of the preceding claims, wherein said polypeptide is back-bone cyclized.

35

10. The polypeptide according to any of the preceding claims, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of:
- 5 THLETTFWGDGE (SEQ ID NO: 8),
 THLETTFWGDGD (SEQ ID NO: 9),
 THLETTF(Nal)GDGE (SEQ ID NO: 10), and
 T(PyA-4)LETTFWGDGE (SEQ ID NO: 11).
- 10 11. The polypeptide according to any one of the preceding claims, wherein the polypeptide is a cyclic polypeptide comprising or consisting of the amino acid sequence TX₁LETTFX₄GDGEPKTIRVTQpGX₁₀ (SEQ ID NO: 13) wherein
- 15 X₁ is H or H-3Me;
 X₄ is W or absent;
 X₁₀ is C, Q or E;
 or a pharmaceutically acceptable salt thereof.
- 20 12. The polypeptide according to any one of the preceding claims, wherein the polypeptide is a cyclic polypeptide comprising or consisting of an amino acid sequence selected from THLETTFWGDGEPKTIRVTQ (SEQ ID NO: 419), THLETTFGDGEPKTIRVTQ (SEQ ID NO: 420), TH(3-Me)LETTFWGDGEPKTIRVTQ (SEQ ID NO: 421) and TH(3-Me)LETTFGDGEPKTIRVTQ (SEQ ID NO: 422).
- 25 13. The polypeptide according to any of the preceding claims, wherein the polypeptide comprises at least 20 amino acid residues, such as at least 21 amino acid residues, such as at least 22 amino acid residues, such as at least 23 amino acid residues, such as at least 24 amino acid residues, such as at
- 30 least 25 amino acid residues, such as at least 26 amino acid residues, such as at least 27 amino acid residues, such as at least 28 amino acid residues, such as at least 29 amino acid residues, such as at least 30 amino acid residues, such as at least 31 amino acid residues, such as at least 32 amino acid residues, such as at least 33 amino acid residues, such as at least 34 amino

acid residues, such as at least 35 amino acid residues, such as at least 36 amino acid residues, such as at least 37 amino acid residues.

- 5 14. The polypeptide according to any of the preceding claims, wherein the polypeptide comprises no more than 50 amino acid residues, such as no more than 45 amino acid residues, such as no more than 40 amino acid residues, such as no more than 35 amino acid residues, such as no more than 30 amino acid residues, such as no more than 29 amino acid residues, such as no more than 28 amino acid residues, such as no more than 27 amino acid residues, such as no more than 26 amino acid residues, such as no more than 25 amino acid residues, such as no more than 24 amino acid residues, such as no more than 23 amino acid residues, such as no more than 22 amino acid residues, such as no more than 21 amino acid residues, such as no more than 20 amino acid residues.
- 15 15. The polypeptide according to any one of the preceding claims, wherein the polypeptide binds to PSD-95-PDZ2 with a K_d of less than 100 μM , such as less than 75 μM , such as less than 50 μM , such as less than 25 μM , such as less than 20 μM , such as less than 15 μM , such as less than 10 μM , such as less than 5 μM , such as less than 4 μM , such as less than 3 μM , such as less than 2 μM , such as less than 1 μM .
- 20 16. The polypeptide according to any one of the preceding claims, wherein the compound has a K_i value for inhibiting binding of nNOS to PDZ2 domain of PSD-95 of less than 100 μM , such as less than 75 μM , such as less than 50 μM , such as less than 10 μM , such as less than 5 μM , such as less than 2.5 μM , such as less than 1 μM .
- 25 17. The polypeptide according to any one of the preceding claims, wherein the polypeptide is further conjugated to a moiety selected from the group consisting of PEG, monosaccharides, fluorophores, chromophores, radioactive compounds, and cell-penetrating peptides.
- 30 18. The polypeptide according to any one of the preceding claims, wherein the polypeptide is further modified by glycosylation, PEGylation, amidation, esterification, acylation, acetylation and/or alkylation.
- 35

19. The polypeptide according to any one of claims 1, 8, 9, or 13 to 18, wherein the polypeptide comprises or consist of an amino acid sequence selected from the group consisting of SEQ ID NO: 14 to 136 and SEQ ID NO: 139 to 433.
- 5
20. The polypeptide according to any of the preceding claims, wherein the polypeptide is cyclo-(THLETTFWGDGE**EP**KTIRVTQpG(E α)) (SEQ ID NO: 423), cyclo-(THLETTFGDGE**EP**KTIRVTQpG(E α)) (SEQ ID NO: 424), cyclo-(**TH(3-Me)**LETTFWGDGE**EP**KTIRVTQpG(E α)) (SEQ ID NO: 425), cyclo-(**TH(3-Me)**LETTFGDGE**EP**KTIRVTQpG(E α)) (SEQ ID NO: 426), cyclo-(THLETTFWGDGE**EP**KTIRVTQpG(Q α)) (SEQ ID NO: 14), cyclo-(THLETTFGDGE**EP**KTIRVTQpG(Q α)) (SEQ ID NO: 15), cyclo-(**TH(3-Me)**LETTFWGDGE**EP**KTIRVTQpG(Q α)) (SEQ ID NO: 16), or cyclo-(**TH(3-Me)**LETTFGDGE**EP**KTIRVTQpG(Q α)) (SEQ ID NO: 17).
- 10
- 15
21. Use of the polypeptide according to any one of claims 1 to 20 for the manufacture of a medicament for the treatment and/or prevention of an excitotoxicity-related disease and/or neuropathic pain in a subject.
- 20
22. The use according to claim 21, wherein wherein the excitotoxic-related disease is selected from:
- a. stroke, such as ischemic stroke;
 - b. ischemic or traumatic injury of the CNS, such as spinal cord injury and traumatic brain injury;
 - 25 c. epilepsy; and
 - d. a neurodegenerative disease of the CNS, such as Alzheimer's disease, Huntington's disease or Parkinson's disease.
- 30
23. A kit of parts comprising at least two separate unit dosage forms (A) and (B), wherein
- (A) comprises the polypeptide according to any one of claims 1 to 20, and
 - (B) comprises a thrombolytic agent.