Claims

1. A method for producing a nonhuman primate animal model of cerebral infarction, comprising administering endothelin to basal ganglia and thalamic region of a nonhuman primate, and thereby inducing basal ganglia damage, thalamus damage, and internal capsule damage.

2. The method according to claim 1, wherein endothelin is administered to one or two or more nerve nuclei selected from the group consisting of putamen, caudate nucleus, globus pallidus, ventral lateral nucleus of thalamus, and ventral posterior nucleus of thalamus in the basal ganglia and thalamic region.

3. The method according to claim 1 or 2, wherein endothelin is administered to at least three nerve nuclei selected from the group consisting of putamen, caudate nucleus, globus pallidus, ventral lateral nucleus of thalamus, and ventral posterior nucleus of thalamus in the basal ganglia and thalamic region.

4. The method according to any one of claims 1 to 3, wherein endothelin is administered to at least four nerve nuclei selected from the group consisting of putamen, caudate nucleus, globus pallidus, ventral lateral nucleus of thalamus, and ventral posterior nucleus of thalamus in the basal ganglia and thalamic region.

5. The method according to any one of claims 1 to 4, wherein endothelin is administered to all of five nerve nuclei of the group consisting of putamen, caudate nucleus, globus pallidus, ventral lateral nucleus of thalamus, and ventral posterior nucleus of thalamus in the basal ganglia and thalamic region.

6. The method according to any one of claims 1 to 5, wherein the cerebral infarction is cerebral infarction at a subacute to chronic stage.

7. The method according to any one of claims 1 to 6, wherein the cerebral infarction is cerebral infarction at a chronic stage.

8. The method according to any one of claims 1 to 7, wherein the cerebral infarction is penetrating branch infarction.

9. The method according to any one of claims 1 to 7, wherein the cerebral infarction is cerebral infarction having brain damage in a penetrating branch territory.

10. The method according to claim 8 or 9, wherein the penetrating branch infarction, or the cerebral infarction having brain damage in a penetrating branch territory is cerebral infarction at a subacute to chronic stage.

11. The method according to claim 8 or 9, wherein the penetrating branch infarction, or the cerebral infarction having brain damage in a penetrating branch territory is cerebral infarction at a chronic stage.

12. The method according to any one of claims 2 to 11, comprising determining an administration site so as to target said nerve nuclei, and administering endothelin to the administration site.

13. A method for producing a nonhuman primate animal model of cerebral infarction, comprising administering endothelin to basal ganglia and thalamic region of a nonhuman primate, and thereby inducing basal ganglia damage, thalamus damage, and internal capsule damage, wherein the method comprises the steps of:
(a) determining administration sites so as to target at least four nerve nuclei selected from the group consisting of putamen, caudate nucleus, globus pallidus, ventral lateral nucleus of thalamus, and ventral posterior nucleus of thalamus in the basal ganglia and thalamic region;

and

(b) administering endothelin to the administration sites.

14. A method for producing a nonhuman primate animal model of cerebral infarction, comprising administering endothelin to basal ganglia and thalamic region of a nonhuman primate, and thereby inducing basal ganglia damage, thalamus damage, and internal capsule damage, wherein the method comprises the steps of:

(a) determining administration sites so as to target all of five nerve nuclei of the group consisting of putamen, caudate nucleus, globus pallidus, ventral lateral nucleus of thalamus, and ventral posterior nucleus of thalamus in the basal ganglia and thalamic region; and

(b) administering endothelin to the administration sites.

15. The method according to claim 13 or 14, wherein the administration sites are at least three sites.

16. The method according to any one of claims 1 to 15, wherein the nonhuman primate is a cynomolgus macaque.

17. The method according to any one of claims 1 to 16, wherein a dose of endothelin per administration site is at least 10 μg.

18. The method according to any one of claims 1 to 17, wherein the endothelin is endothelin-1.

19. A nonhuman primate animal model of cerebral infarction, which has basal ganglia damage, thalamus damage, and internal capsule damage, wherein the nonhuman primate animal model is produced by a method according to any one of claims 1 to 18.

20. A method for producing a nonhuman primate animal model of cerebral infarction at a

subacute to chronic stage, comprising administering endothelin to a cynomolgus macaque, and thereby inducing basal ganglia damage, thalamus damage, and internal capsule damage, wherein endothelin administration sites include the following:
administration sites respectively positioned at (i) B: 1 to 3 mm, L: 7 to 9 mm, and D: 18 to 20 mm, (ii) B: 4 to 6 mm, L: 7 to 9 mm, and D: 18 to 20 mm, and (iii) B: 8 to 12 mm, L: 4 to 13 mm, and D: 12 to 20 mm from Bregma as a base point.

21. The method according to claim 20, wherein the endothelin administration sites include any one of the following (1) to (3):
(1) administration sites respectively positioned at (i) B: 1 to 3 mm, L: 7 to 9 mm, and D: 18 to 20 mm, (ii) B: 4 to 6 mm, L: 7 to 9 mm, and D: 18 to 20 mm, (iii) B: 8 to 10 mm, L: 4 to 6 mm, and D: 12 to 14 mm, and (iv) B: 8 to 10 mm, L: 11 to 13 mm, and D: 14 to 16 mm from Bregma as a base point;
(2) administration sites respectively positioned at (i) B: 1 to 3 mm, L: 7 to 9 mm, and D: 18 to 20 mm, (ii) B: 4 to 6 mm, L: 7 to 9 mm, and D: 18 to 20 mm, and (iii) B: 8 to 10 mm, L: 7 to 9 mm, and D: 18 to 20 mm from Bregma as a base point; and
(3) administration sites respectively positioned at (i) B: 1 to 3 mm, L: 7 to 9 mm, and D: 18 to 20 mm, (ii) B: 4 to 6 mm, L: 7 to 9 mm, and D: 18 to 20 mm, and (iii) B: 10 to 12 mm, L: 7 to 9 mm, and D: 18 to 20 mm from Bregma as a base point.

22. The method according to claim 20 or 21, wherein the endothelin administration sites include any one of the following (1) to (3):
(1) administration sites respectively positioned at (i) B: 2 mm, L: 8 mm, and D: 19 mm, (ii) B: 5 mm, L: 8 mm, and D: 19 mm, (iii) B: 9 mm, L: 5 mm, and D: 13 mm, and (iv) B: 9 mm, L: 12 mm, and D: 15 mm from Bregma as a base point;
(2) administration sites respectively positioned at (i) B: 2 mm, L: 8 mm, and D: 19 mm, (ii) B: 5 mm, L: 8 mm, and D: 19 mm, and (iii) B: 9 mm, L: 8 mm, and D: 19 mm from Bregma as a base point; and
(3) administration sites respectively positioned at (i) B: 2 mm, L: 8 mm, and D: 19 mm, (ii) B:

5 mm, L: 8 mm, and D: 19 mm, and (iii) B: 11 mm, L: 8 mm, and D: 19 mm from Bregma as a base point.

23. The method according to any one of claims 20 to 22, wherein the endothelin administration sites include the following administration sites:
administration sites respectively positioned at (i) B: 2 mm, L: 8 mm, and D: 19 mm, (ii) B: 5 mm, L: 8 mm, and D: 19 mm, (iii) B: 9 mm, L: 5 mm, and D: 13 mm, and (iv) B: 9 mm, L: 12 mm, and D: 15 mm from Bregma as a base point.

24. The method according to any one of claims 20 to 23, wherein the endothelin administration sites are the following administration sites:
administration sites respectively positioned at (i) B: 2 mm, L: 8 mm, and D: 19 mm, (ii) B: 5 mm, L: 8 mm, and D: 19 mm, (iii) B: 9 mm, L: 5 mm, and D: 13 mm, and (iv) B: 9 mm, L: 12 mm, and D: 15 mm from Bregma as a base point.

25. The method according to any one of claims 20 to 24, wherein the cerebral infarction is cerebral infarction at a chronic stage.

26. The method according to any one of claims 20 to 25, wherein the cerebral infarction is penetrating branch infarction, or cerebral infarction having brain damage in a penetrating branch territory.

27. The method according to any one of claims 20 to 26, wherein a dose of endothelin per administration site is at least 10 μg.

28. The method according to any one of claims 20 to 27, wherein the endothelin is endothelin-1.

29. A cynomolgus macaque model of cerebral infarction at a subacute to chronic stage,

produced by a method according to any one of claims 20 to 28.

30. A method for screening for a therapeutic agent for cerebral infarction, comprising the step of: determining an effect of a test substance on cerebral infarction that had been administered to the nonhuman primate animal model according to claim 19 or 29.

31. Use of a NeuroD1 protein or a polynucleotide encoding the NeuroD1 protein in the manufacture of a pharmaceutical composition for the treatment of penetrating branch infarction, or cerebral infarction at a subacute to chronic stage.

32. Use of a NeuroD1 protein or a polynucleotide encoding the NeuroD1 protein in the manufacture of a pharmaceutical composition for the treatment of cerebral infarction having brain damage in a penetrating branch territory.

33. The use according to claim 31 or 32, wherein the penetrating branch infarction, or the cerebral infarction having brain damage in a penetrating branch territory is cerebral infarction at a subacute to chronic stage.

34. The use according to any one of claims 31 to 33, wherein the penetrating branch infarction, or the cerebral infarction having brain damage in a penetrating branch territory is cerebral infarction at a chronic stage.

35. The use according to claim 31, wherein the cerebral infarction at a subacute to chronic stage is cerebral infarction at a chronic stage.

36. The use according to any one of claims 31 to 35, wherein the polynucleotide encoding the NeuroD1 protein is a polynucleotide comprising a nucleotide sequence encoding a protein consisting of the amino acid sequence as set forth by SEQ ID NO: 8.

37. The use according to any one of claims 31 to 36, wherein the polynucleotide encoding the NeuroD1 protein comprises a polynucleotide having 70% or higher sequence identity to the nucleotide sequence as set forth by SEQ ID NO: 7 or 10.

38. The use according to any one of claims 31 to 37, wherein the polynucleotide encoding the NeuroD1 protein is a polynucleotide comprising the nucleotide sequence as set forth by SEQ ID NO: 7 or 10.

39. The use according to any one of claims 31 to 38, wherein said polynucleotide is mRNA encoding the NeuroD1 protein.

40. The use according to claim 39, wherein the mRNA encoding the NeuroD1 protein comprises a nucleotide sequence encoding the NeuroD1 protein of positions 44 to 1114 or positions 44 to 1120 of SEQ ID NO: 11 or 13.

41. The use according to claim 39 or 40, wherein the mRNA encoding the NeuroD1 protein comprises 5' UTR and/or 3' UTR.

42. The use according to any one of claims 39 to 41, wherein the mRNA encoding the NeuroD1 protein is mRNA comprising a polynucleotide consisting of the nucleotide sequence of positions 1 to 1231 of SEQ ID NO: 11 or 13.

43. The use according to any one of claims 39 to 42, wherein the mRNA encoding the NeuroD1 protein comprises a polyA sequence.

44. The use according to claim 43, wherein the polyA sequence is 50 to 200 nucleotides in length.

45. The use according to any one of claims 39 to 44, wherein the mRNA encoding the

NeuroD1 protein has a 5' cap structure.

46. The use according to any one of claims 39 to 45, wherein the mRNA encoding the NeuroD1 protein is mRNA containing a modified nucleoside.

47. The use according to claim 46, wherein the modified nucleoside is N1-methylpseudouridine.

48. The use according to claim 47, wherein the mRNA encoding the NeuroD1 protein is a polynucleotide in which some or all uridines are replaced by N1-methylpseudouridine.

49. The use according to any one of claims 39 to 48, wherein the mRNA encoding the NeuroD1 protein is incorporated in a drug delivery system (DDS).

50. The use according to any one of claims 39 to 49, wherein the mRNA encoding the NeuroD1 protein is encapsulated into lipid nanoparticles.

51. The use according to any one of claims 31 to 38, wherein said polynucleotide is DNA.

52. The use according to any one of claims 31 to 38 and 51, wherein said polynucleotide is an expression vector comprising the polynucleotide encoding the NeuroD1 protein.

53. The use according to claim 52, wherein the expression vector is an adeno-associated virus vector, a retrovirus vector, a Sendai virus vector, or a lentivirus vector.

54. The use according to claim 53, wherein the expression vector is an adeno-associated virus vector.