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[Summary]

[Technical Problem]

[0014]

An object of the present disclosure is to provide a nonhuman primate animal model of cerebral infarction that can be used in the screening for or evaluation of a therapeutic agent for cerebral infarction, particularly, a therapeutic agent for cerebral infarction at a subacute to chronic stage, penetrating branch infarction, or cerebral infarction having brain damage in a penetrating branch territory; and a method for producing the animal model. Another object of the present disclosure is to provide a therapeutic agent or a treatment method for penetrating branch infarction, or cerebral infarction having brain damage in a penetrating branch territory.

[Solution to Problem]

[0015]

The present inventors have conducted diligent studies to attain the objects described above and consequently found that: basal ganglia damage and thalamus damage as well as internal capsule damage can be induced by administering endothelin to basal ganglia and thalamic region of a nonhuman primate; the resulting nonhuman primate having basal ganglia damage, thalamus damage, and internal capsule damage is capable of serving as a nonhuman primate animal model of cerebral infarction; and the nonhuman primate animal model of

cerebral infarction is particularly useful as a nonhuman primate animal model of cerebral infarction at a subacute to chronic stage, penetrating branch infarction, or cerebral infarction having brain damage in a penetrating branch territory (Example 1). The present inventors have also found using the nonhuman primate animal model that NeuroD1 is effective as a therapeutic agent for penetrating branch infarction, or cerebral infarction having brain damage in a penetrating branch territory (Example 2 to Example 5, Example 11, and Example 12). The present disclosure has been completed on the basis of these findings.

[0016]

Specifically, the present disclosure provides the following.

[0017]

[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 [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 [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 of [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 of [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

[133] The polynucleotide for use according to [98], wherein the lipid nanoparticle comprises di(heptadecan-9-yl) 8,8'-{[1-(2-hydroxyethyl)piperidin-4-yl]azanediyl}di(octanoate) or a salt thereof as a cationic lipid.

[134] The polynucleotide for use according to [98], wherein the lipid nanoparticle comprises bis(2-nonylundecyl) 7,7'-[({[1-(N,N-dimethylglycyl)piperidin-4-yl]oxy}carbonyl)azanediyl]di(heptanoate) or a salt thereof as a cationic lipid.

[135] The polynucleotide for use according to [133] or [134], wherein the lipid nanoparticle further comprises DSPC, cholesterol, and DMG-PEG2000.

[136] Use according to [122], wherein the lipid nanoparticle comprises di(heptadecan-9-yl) 8,8'-{[1-(2-hydroxyethyl)piperidin-4-yl]azanediyl}di(octanoate) or a salt thereof as a cationic lipid.

[137] Use according to [122], wherein the lipid nanoparticle comprises bis(2-nonylundecyl) 7,7'-[({[1-(N,N-dimethylglycyl)piperidin-4-yl]oxy}carbonyl)azanediyl]di(heptanoate) or a salt thereof as a cationic lipid.

[138] Use according to [136] or [137], wherein the lipid nanoparticle further comprises DSPC, cholesterol, and DMG-PEG2000.

[0017a]

In one aspect, the present disclosure provides 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.

[0017b]

In another aspect, the present disclosure provides 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.

[0017c]

In another aspect, the present disclosure provides 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.

[0017d]

In another aspect, the present disclosure provides 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 as described herein.

[0017e]

In another aspect, the present disclosure provides 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.

[0017f]

In another aspect, the present disclosure provides a cynomolgus macaque model of cerebral infarction at a subacute to chronic stage, produced by a method as described herein.

[0017g]

In another aspect, the present disclosure provides 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 as described herein.

[0017h]

In another aspect, the present disclosure provides 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.

[0017i]

In another aspect, the present disclosure provides 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.

[0018]

The present specification encompasses the contents disclosed in Japanese Patent Applications No. 2022-106308, 2022-211994, and 2023-041345, of which the present application claims priority.

[Advantageous Effects of Invention]

[0019]

According to the present invention, a nonhuman primate animal model of cerebral infarction having basal ganglia damage, thalamus damage, and internal capsule damage can be produced. This nonhuman primate animal model of cerebral infarction is particularly useful as a nonhuman primate animal model of cerebral infarction at a subacute to chronic stage, penetrating branch infarction, or cerebral infarction having brain damage in a penetrating branch territory. The present invention can also provide a therapeutic agent, a pharmaceutical composition for treatment, or a treatment method particularly useful in the treatment of