Claims

1. A method for producing a cell mass comprising pituitary tissue, comprising the following steps (1) and (2):
(1) a first step of dispersing pluripotent stem cells into single cells and suspension-culturing the dispersed pluripotent stem cells for about 12 hr to 48 hr to form a cell aggregate in the presence of a non-canonical Wnt signal transduction pathway inhibiting substance,
(2) a second step of suspension-culturing the aggregate obtained in the first step in the presence of a BMP signal transduction pathway activating substance and a Sonic hedgehog signal transduction pathway activating substance, thereby obtaining a cell mass comprising pituitary tissue.

2. A method for producing a cell mass comprising pituitary tissue, comprising the following steps (a), (1) and (2):
(a) step a of culturing pluripotent stem cells in the absence of feeder cells and in a medium containing 1) a TGFβ family signal transduction pathway inhibiting substance and/or a Sonic hedgehog signal transduction pathway activating substance, and 2) a factor for maintaining an undifferentiated state,
(1) a first step of dispersing pluripotent stem cells into single cells and suspension-culturing the dispersed pluripotent stem cells, which were cultured in step a, for about 12 hr to 48 hr to form a cell aggregate in the presence of a non-canonical Wnt signal transduction pathway inhibiting substance,
(2) a second step of suspension-culturing the aggregate obtained in the first step in the presence of a BMP signal transduction pathway activating substance and a Sonic hedgehog signal transduction pathway activating substance, thereby obtaining a cell mass comprising pituitary tissue.

3. A method for producing a cell mass comprising pituitary tissue, comprising the following steps (1), (2-1) and (2-2):
(1) a first step of dispersing pluripotent stem cells into single cells and suspension-culturing the dispersed pluripotent stem cells for about 12 hr to 48 hr to form a cell aggregate in the presence of a non-canonical Wnt signal transduction pathway inhibiting substance,
(2-1) a second step (1) of suspension-culturing the aggregate obtained in the first step in the presence of a BMP signal transduction pathway activating substance and a Sonic hedgehog signal transduction pathway activating substance,
(2-2) a second step (2) of suspension-culturing the aggregate suspension-cultured in the second step (1) in the presence of a BMP signal transduction pathway inhibiting substance, thereby obtaining a cell mass comprising pituitary tissue.

4. A method for producing a cell mass comprising pituitary tissue, comprising the following steps (a), (1), (2-1) and (2-2):
(a) step a of culturing pluripotent stem cells in the absence of feeder cells and in a medium containing 1) a TGFβ family signal transduction pathway inhibiting substance and/or a Sonic hedgehog signal transduction pathway activating substance, and 2) a factor for maintaining an undifferentiated state,
(1) a first step of dispersing pluripotent stem cells into single cells and suspension-culturing the dispersed pluripotent stem cells, which were cultured in step a, for about 12 hr to 48 hr to form a cell aggregate in the presence of a non-canonical Wnt signal transduction pathway inhibiting substance,
(2-1) a second step (1) of suspension-culturing the aggregate obtained in the first step in the presence of a

BMP signal transduction pathway activating substance and a Sonic hedgehog signal transduction pathway activating substance,
(2-2) a second step (2) of suspension-culturing the aggregate suspension-cultured in the second step (1) in the presence of a BMP signal transduction pathway inhibiting substance, thereby obtaining a cell mass comprising pituitary tissue.

5. The production method according to any one of claims 1 to 4, wherein the non-canonical Wnt signal transduction pathway inhibiting substance is a PORCN inhibitor.

6. The production method according to claim 5, wherein the PORCN inhibitor is at least one kind of compound selected from the group consisting of IWP-2, IWP-3, IWP-4, IWP-L6, IWP-12, LGK-974, ETC-159, GNF-6231 and Wnt-C59.

7. The production method according to any one of claims 1 to 6, wherein the suspension culturing in the steps (1), (2), (2-1) and (2-2) is performed in the further presence of a TGFβ signal transduction pathway inhibiting substance.

8. The production method according to any one of claims 1 to 7, wherein at least one step selected from the group consisting of the steps (1), (2), (2-1) and (2-2) is performed in the presence of an FGF signal transduction pathway activating substance.

9. The production method according to any one of claims 1 to 8, wherein at least one step selected from the group consisting of the steps (1), (2), (2-1) and (2-2) is performed in the presence of a Wnt signal transduction pathway activating substance.

10. The production method according to any one of claims 1

to 9, wherein the suspension culturing in at least one step selected from the group consisting of the steps (1), (2), (2-1) and (2-2) is performed in the further presence of a Notch signal inhibitor.

11. The production method according to any one of claims 1 to 10, wherein the suspension culturing in at least one step selected from the group consisting of the steps (1), (2), (2-1) and (2-2) is performed in the further presence of dexamethasone.

12. The production method according to any one of claims 1 to 11, wherein the cell mass comprising pituitary tissue comprises 1) nonneural epithelium, 2) neuroepithelium, and 3) mesenchymal cells,

wherein the cell mass has an outside covered by the nonneural epithelium, ventral diencephalon or hypothalamus-like neuroepithelial tissue having a ventricle-like structure in the inside, and cranial mesenchymal cell present between the nonneural epithelium and the neuroepithelium, and

wherein a part of the outer nonneural epithelium is pituitary placode.

13. A method for producing a pituitary tissue, comprising the following steps (1) - (3):
(1) a first step of dispersing pluripotent stem cells into single cells and suspension-culturing the dispersed pluripotent stem cells for about 12 hr to 48 hr to form a cell aggregate in the presence of a non-canonical Wnt signal transduction pathway inhibiting substance,
(2) a second step of suspension-culturing the aggregate obtained in the first step in the presence of a BMP signal transduction pathway activating substance and a Sonic hedgehog signal transduction pathway activating substance, thereby obtaining a cell mass comprising pituitary tissue,

(3) a third step of collecting pituitary tissue from the cell mass obtained in the second step.

14. A method for producing a pituitary tissue, comprising the following steps (1), (2-1), (2-2) and (3):
(1) a first step of dispersing pluripotent stem cells into single cells and suspension-culturing the dispersed pluripotent stem cells for about 12 hr to 48 hr to form a cell aggregate in the presence of a non-canonical Wnt signal transduction pathway inhibiting substance,
(2-1) a second step (1) of suspension-culturing the aggregate obtained in the first step in the presence of a BMP signal transduction pathway activating substance and a Sonic hedgehog signal transduction pathway activating substance,
(2-2) a second step (2) of suspension-culturing the aggregate suspension-cultured in the second step (1) in the presence of a BMP signal transduction pathway inhibiting substance, thereby obtaining a cell mass comprising pituitary tissue,
(3) a third step of collecting pituitary tissue from the cell mass obtained in the second step (2).

15. A pituitary tissue obtained by the production method according to claim 13 or 14.

16. A cell mass comprising 1) neural cells or neural tissue, 2) pituitary tissue and 3) mesenchymal cells.

17. A cell mass comprising 1) neural cells or neural tissue, 2) pituitary tissue and 4) neural crest cells and neural crest-derived cells.

18. A therapeutic drug for a disease due to a disorder of pituitary gland, comprising a cell mass produced by the method according to any one of claims 1 to 12 or a pituitary

tissue produced by the method according to claim 13 or 14.

19. A cell mass according to claim 16, wherein the cell mass comprises 1) nonneural epithelium, 2) neuroepithelium and 3) mesenchymal cells,

wherein the cell mass has an outside covered by the nonneural epithelium, ventral diencephalon or hypothalamus-like neuroepithelial tissue having a ventricle-like structure in the inside, and cranial mesenchymal cell present between the nonneural epithelium and the neuroepithelium, and

wherein a part of the outer nonneural epithelium is pituitary placode.