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DISCLOSURE OF THE INVENTION

PROBLEM TO BE SOLVED BY THE INVENTION

[0016] An object of the present invention is to provide a method for screening for a prophylactic or therapeutic agent for tauopathy capable of blocking the propagation of tau-mediated neurodegeneration.

Summary

In one aspect, there is provided a method for screening for a prophylactic or therapeutic agent for tauopathy, comprising the following steps (1) to (3):

- (1) contacting neurons having a mutant MAPT gene with a test substance;
- (2) measuring any one index selected from the group consisting of the following (a) to (e) in the neurons:
 - (a) the amount of a tau oligomer in a culture supernatant,
 - (b) the amount of an intracellular tau oligomer,
 - (c) the frequency of depolarization,
 - (d) an intracellular calcium ion concentration, and
 - (e) the number of living cells; and
- (3) selecting the test substance as a prophylactic or therapeutic agent for tauopathy when the value of (a), (b), (c), or (d) measured in the step (2) after the contact with the test substance in the step (1) is lower than the value obtained without the contact with the test

substance in the step (1), and/or when the value of (e) measured in the step (2) after the contact with the test substance in the step (1) is higher than the value obtained without the contact with the test substance in the step (1).

In another aspect, there is provided a method for screening for a prophylactic or therapeutic agent for tauopathy, comprising the following steps (1) to (4):

(1) contacting first neurons having a mutant MAPT gene with a test substance, followed by culture;

(2) contacting the culture supernatant of the first neurons obtained in the step (1) with second neurons;

(3) measuring any one index selected from the group consisting of the following (a) to (d) in the second neurons obtained in the step (2):

- (a) the amount of an intracellular tau oligomer,
- (b) the frequency of depolarization,
- (c) an intracellular calcium ion concentration, and
- (d) the number of living cells; and

(4) selecting the test substance as a prophylactic or therapeutic agent for tauopathy when the value of (a), (b), or (c) measured in the step (3) after the contact of the first neurons with the test substance in the step (1) is lower than the value obtained without the contact of the first neurons with the test substance in the step (1), and/or when the value of (d) measured in the step (3) after the contact of the first neurons with the test substance in the step (1) is higher than the value obtained without the contact of the first neurons with the test substance in the step (1).

In another aspect, there is provided a method for screening for a prophylactic or therapeutic agent for tauopathy, comprising the following steps (1) to (4):

(1) contacting a culture supernatant of first neurons having a mutant MAPT gene with second neurons;

(2) further contacting the second neurons with a test substance;

(3) measuring any one index selected from the group consisting of the following (a) to (d) in the second neurons obtained in the step (2):

- (a) the amount of an intracellular tau oligomer,
- (b) the frequency of depolarization,
- (c) an intracellular calcium ion concentration, and
- (d) the number of living cells; and

(4) selecting the test substance as a prophylactic or therapeutic agent for tauopathy when the value of (a), (b), or (c) measured in the step (3) after the contact of the second neurons with the test substance in the step (2) is lower than the value obtained without the contact of the second neurons with the test substance in the step (2), and/or when the value of (d) measured in the step (3) after the contact of the second neurons with the test substance in the step (2) is higher than the value obtained without the contact of the second neurons with the test substance in the step (2).

In a further aspect, there is provided a method for screening for a prophylactic or therapeutic agent for tauopathy, comprising the following steps (1) to (4):

- (1) contacting a tau oligomer with neurons;
- (2) further contacting the neurons with a test substance;
- (3) measuring any one index selected from the group consisting of the following (a) to (d) in the neurons obtained in the step (2):

- (a) the amount of an intracellular tau oligomer,
- (b) the frequency of depolarization,
- (c) an intracellular calcium ion concentration, and
- (d) the number of living cells; and

(4) selecting the test substance as a prophylactic or therapeutic agent for tauopathy when the value of (a), (b), or (c) measured in the step (3) after the contact with the test substance in the step (2) is lower than the value obtained without the contact with the test substance in the step (2), and/or when the value of (d) measured in the step (3) after the contact with the test

substance in the step (2) is higher than the value obtained without the contact with the test substance in the step (2).

In yet another aspect, there is provided a culture supernatant of neurons having a mutant MAPT gene.

In a further aspect, there is provided a tau oligomer isolated from a culture supernatant according to the present invention.

In a further aspect, there is provided a screening kit for a prophylactic or therapeutic agent for tauopathy, comprising a culture supernatant of neurons having a mutant MAPT gene, a tau oligomer isolated from the supernatant, or an artificial tau oligomer.

MEANS TO SOLVE THE PROBLEM

[0017] In order to solve the problems of the conventional techniques, the present inventors have prepared induced pluripotent stem cells from mouse and human cells having a mutant MAPT gene and allowed the induced pluripotent stem cells to differentiate into neurons by the expression of a foreign neurogenin 2 gene. These neurons have been found to be excellent tauopathy cell models that spontaneously exhibit typical pathological conditions of tauopathy, such as tau hyperphosphorylation and oligomerization, and decrease in synaptic density, and cause cell death.

[0018] The present inventors have further found that in the tauopathy model cells, both of a spontaneous firing rate and a firing rate are increased, and these cells secrete a tau oligomer into a medium in a manner dependent on neural activity. Furthermore, the secreted tau oligomer has been found to specifically bind to lipid raft on the cell membranes of normal neurons and increase the excitability of the normal neurons to induce tauopathy-like cell