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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 (a) the amount of a tau oligomer in a culture supernatant in the neurons;
- (3) selecting the test substance as a prophylactic or therapeutic agent for tauopathy when the value of (a) 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).

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

What is claimed is:

1. 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 (a) the amount of a tau oligomer in a culture supernatant in the neurons; and

(3) selecting the test substance as a prophylactic or therapeutic agent for tauopathy when the value of (a) 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).

2. The method according to claim 1, wherein the neurons having a mutant MAPT gene have been differentiated by the expression of foreign Neurogenin 2 from pluripotent stem cells having the mutant MAPT gene.

3. The method according to claim 1 or 2, wherein the neurons having a mutant MAPT gene express the mutant MAPT gene under the control of a nervous system-specific promoter.

4. The method according to claim 2 or 3, wherein the pluripotent stem cells having the mutant MAPT gene are induced pluripotent stem cells established from somatic cells of a tauopathy patient.
5. The method according to any one of claims 1 to 4, wherein the mutant MAPT gene is a MAPT gene having one or more mutations at exons 9 to 13 or intron 10.
6. The method according to claim 5, wherein the mutations at exons 9 to 13 are mutations to form mutant tau proteins each having one or more amino acid mutations selected from K257T, I260V, G272V, N297K, K280Δ, L284L, N296N, P301L, P301S, S305N, S305S, V337M, E342V, G389R, and R406W.
7. The method according to claim 5, wherein the mutations at intron 10 are one or more mutations in nucleotides at positions 1 to 20 of the intron 10.