

[0012]

[8] A method of preventing or treating dementia selected from diabetic dementia and vascular dementia, which comprises administration of an effective dose of a RGMa inhibiting substance to a mammal in need of treatment.

[9] The preventive or therapeutic method according to [8], wherein the RGMa inhibiting substance is an anti-RGMa neutralizing antibody.

[10] Use of a RGMa inhibiting substance in manufacture of an agent for preventing or treating dementia selected from diabetic dementia and vascular dementia.

[11] The use according to [10], wherein the RGMa inhibiting substance is an anti-RGMa neutralizing antibody.

[0012a]

In one aspect, provided herein is a use of a preventive or therapeutic agent in manufacture of an agent for preventing or treating diabetic dementia or vascular dementia, wherein the preventive or therapeutic agent comprises an anti-RGMa neutralizing antibody or an antigen-binding fragment thereof.

Effects of Invention

[0013]

According to the present invention, a RGMa inhibiting substance, in particular, an anti-RGMa neutralizing antibody, is useful as an agent for preventing or treating dementia selected from diabetic dementia and vascular dementia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Fig. 1 is a graph showing the Discrimination Index (DI) values obtained from the anti-RGMa neutralizing antibody(may be simply referred to as anti-RGMa antibody)-administered group and the isotype control antibody-administered group at 4 weeks after the onset of pathological conditions of diabetes (DM), respectively, as well as the DI value of healthy mice.

Fig. 2 is a graph showing the numbers of doublecortin positive cells upon administration of the anti-RGMA neutralizing antibody or the control antibody to non-diabetic (non-DM) mice or diabetic (DM) mice. The numbers of doublecortin positive cells were normalized by the area of the hippocampal dentate gyrus.

Fig. 3 is a graph showing the Discrimination Index (DI) values obtained respectively from the anti-RGMA neutralizing antibody-administered group and the isotype control antibody-administered group of chronic cerebral hypoperfusion model, as well as the DI value obtained from the isotype control antibody-administered group of

CLAIMS

1. Use of a preventive or therapeutic agent in manufacture of an agent for preventing or treating diabetic dementia or vascular dementia, wherein the preventive or therapeutic agent comprises an anti-RGMa neutralizing antibody or an antigen-binding fragment thereof.
2. The use according to claim 1, wherein the anti-RGMa neutralizing antibody is a humanized antibody.
3. The use according to claim 1 or 2, wherein the anti-RGMa neutralizing antibody is an antibody that recognizes an amino acid sequence selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39.
4. The use according to any one of claims 1 to 3, wherein the anti-RGMa neutralizing antibody is an antibody selected from the group consisting of:
 - (a) an anti-RGMa neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 5, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 6, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 7, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 8, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 9, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 10;
 - (b) an anti-RGMa neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 11, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 12, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 13, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 14, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 15, and an HCDR3 comprising an amino acid sequence comprising SFG;
 - (c) an anti-RGMa neutralizing antibody comprising a light chain variable region

comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 17, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 18, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 19, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 20, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 21, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 22;

(d) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 23, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 24, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 25, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 26, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 27, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 28;

(e) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 31, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(f) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 35, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(g) an anti-RGMA neutralizing antibody comprising a light chain variable region

comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 40, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(h) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 41, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(i) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 42, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(j) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 43, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(k) an anti-RGMA neutralizing antibody comprising a light chain variable region

comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 44, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34; and

(l) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 45, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34.

5. The use according to any one of claims 1 to 4, wherein the anti-RGMA neutralizing antibody is an antibody represented by the following (a):

(a) an anti-RGMA neutralizing antibody comprising a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 5, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 6, and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 7, and a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 8, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 9, and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 10.