

DESCRIPTION

TITLE OF INVENTION: COMPOSITION FOR SUPPRESSING OR
AMELIORATING COGNITIVE FUNCTION DECLINE

5

TECHNICAL FIELD

[0001]

The present invention relates to, for example, a
composition for reducing a decline in cognitive function or
10 improving cognitive function.

BACKGROUND ART

[0002]

Regardless of generations, there is a desire to
15 improve cognitive functions such as memory function.
Recently, a decline in aging-related cognitive function has
been a problem in countries as Japan where the elderly
ratio of the population is high, and a search has been made
for a component that can reduce a decline in cognitive
20 function or improve cognitive function through daily intake
of the component as a food or beverage, or the like.

[0003]

For example, Patent Literature 1 discloses an agent
for reducing a decline in cognitive function and/or
25 improving cognitive function, which contains Cyclo(Gly-
Pro). According to the disclosure, when the agent for
reducing a decline in cognitive function and/or improving
cognitive function is orally ingested by a human, the agent
can reduce a decline in functions such as attention,
30 concentration, verbal skills, and
visuospatial/constructional skills and/or can improve these
functions.

CITATION LIST

35 - Patent Literature

[0004]

Patent Literature 1: JP 2020-196686 A

SUMMARY OF INVENTION

5 - Technical Problem

[0005]

As described above, searches have been made to find a component for reducing a decline in cognitive function or improving cognitive function. As disclosed in Patent
10 Literature 1, there has been a demand for another component capable of reducing a decline in cognitive function or improving cognitive function.

[0006]

The present invention was made in view of the current
15 situation described above and aims to provide a composition for reducing a decline in cognitive function or improving cognitive function.

- Solution to Problem

20 [0007]

As a result of extensive studies on the above issue, the present inventors found that cyclo-leucyl-glutamate (Cyclo(Leu-Glu)), which is a cyclic dipeptide, is effective in reducing a decline in cognitive function or improving
25 cognitive function.

[0008]

Specifically, although not limited thereto, the present invention relates to, for example, the following composition for reducing a decline in cognitive function or
30 improving cognitive function.

(1) A composition for reducing a decline in cognitive function or improving cognitive function, containing Cyclo(Leu-Glu) or a salt thereof as an active ingredient.

(2) The composition according to (1) above, wherein
35 the composition reduces at least one of amyloid- β

production or amyloid- β accumulation.

(3) The composition according to (1) or (2) above, wherein the composition reduces at least one of amyloid- β production or amyloid- β accumulation by inhibiting β -secretase.

(4) The composition according to any one of (1) to (3) above, wherein the composition is for oral use.

(5) The composition according to any one of (1) to (4) above, wherein the composition is a food or beverage or a pharmaceutical product.

(6) The composition according to any one of (1) to (5) above, wherein the composition is labeled with one or more function claims selected from the group consisting of "enhancing cognitive function", "reducing a decline in cognitive function", "maintaining good cognitive function", "improving memory", "reducing a decline in memory", "maintaining good memory", "improving accuracy of memory", "preventing memory disorders", "ameliorating memory disorders", "maintaining memory that is one domain of cognitive function", "function suitable for those who are concerned about a decline in memory", "improving accuracy of memory and/or correctness of judgement that is part of cognitive function", "improving memory retention or consolidation", "sustaining cognitive enhancement", "improving executive function", "promoting attention and concentration", "improving learning ability", "maintaining or improving orientation", "delaying an aging-related decline in cognitive function", "enhancing short-term and long-term memory", "promoting verbal and visuospatial memory", and "maintaining or improving logical thinking".

(7) Use of Cyclo(Leu-Glu) or a salt thereof in production of a composition for reducing a decline in cognitive function or improving cognitive function.

(8) Use of Cyclo(Leu-Glu) or a salt thereof for reducing a decline in cognitive function or improving

cognitive function.

- Advantageous Effects of Invention

[0009]

5 The present invention can provide a composition for
reducing a decline in cognitive function or improving
cognitive function. The composition of the present
invention can be used as a food or beverage, a
pharmaceutical product, or the like for reducing a decline
10 in cognitive function or improving cognitive function.

BRIEF DESCRIPTION OF DRAWINGS

[0010]

FIG. 1 is a graph showing β -secretase (BACE)
15 inhibitory activity of a group to which no test compound is
added (Control), Cyclo(Leu-Ala) (Comparative Example 1),
and (Cyclo(Leu-Glu) (Examples 1 and 2).

DESCRIPTION OF EMBODIMENTS

20 [0011]

The composition of the present invention for reducing
a decline in cognitive function or improving cognitive
function contains Cyclo(Leu-Glu) or a salt thereof. The
composition of the present invention for reducing a decline
25 in cognitive function or improving cognitive function
contains Cyclo(Leu-Glu) or a salt thereof as an active
ingredient. Herein, the composition of the present
invention for reducing a decline in cognitive function or
improving cognitive function is sometimes referred to as
30 "the composition of the present invention". The
composition of the present invention is used to reduce a
decline in cognitive function or improve cognitive
function.

[0012]

35 Cyclo(Leu-Glu) (cyclo-leucyl-glutamate) for use in

the present invention is a cyclic dipeptide having a structure in which leucine is condensed with glutamic acid.

Herein, the term "cyclic dipeptide" refers to a compound containing amino acids as a structural unit and
5 having a diketopiperazine structure generated by dehydration condensation of an amino group of an amino acid at an N-terminal and a carboxyl group at a C-terminal. Herein, the description order of amino acids in a cyclic dipeptide is not limited as long as the amino acid
10 structure is the same. For example, Cyclo(Leu-Glu) and Cyclo(Glu-Leu) (cyclo-glutamyl-leucine/cyclo-glutamate-leucine) represent the same cyclic dipeptide.

[0013]

The salt of Cyclo(Leu-Glu) is not limited as long as
15 it is a pharmacologically or dietary acceptable salt, and it may be an acid salt or a basic salt. Examples of the acid salt include inorganic acid salts such as hydrochloride, sulfate, nitrate, and phosphate; and organic acid salt such as acetate, citrate, maleate, malate,
20 oxalate, lactate, succinate, fumarate, and propionate. Examples of the basic salt include alkali metal salts such as sodium salt and potassium salt, and alkaline earth metal salts such as calcium salt and magnesium salt. A salt of a cyclic dipeptide can be easily prepared by a person skilled
25 in the art by any method known in the relevant field.

[0014]

The source and production method of Cyclo(Leu-Glu) and a salt thereof are not limited. Cyclo(Leu-Glu) or a salt thereof can be produced by a known method. Cyclo(Leu-
30 Glu) and a salt thereof may be one that is naturally derived or artificially synthesized. It may be produced by the enzyme method or microbial fermentation method. It may be synthesized by dehydration and cyclization of linear dipeptides. For example, a product of a heat-treated
35 peptide, which is rich in cyclic dipeptides such as

Cyclo(Leu-Glu), can be obtained by heating a protein hydrolysate such as a collagen hydrolysate.

A protein hydrolysate or a heat-treated product thereof containing Cyclo(Leu-Glu) or a salt may be used to
5 add Cyclo(Leu-Glu) or a salt thereof to a composition. Alternatively, a concentrate, a dry powder, or a purified product of a protein hydrolysate or a heat-treated product thereof containing Cyclo(Leu-Glu) or a salt thereof may be used to add Cyclo(Leu-Glu) or a salt thereof to a
10 composition. For example, the composition of the present invention may contain a protein hydrolysate or a heat-treated product thereof, and Cyclo(Leu-Glu) or a salt thereof may be a part of the protein hydrolysate or the heat-treated product thereof. Cyclo(Leu-Glu) and a salt
15 thereof may be a commercial product.

[0015]

As shown in Examples (described later), Cyclo(Leu-Glu) has β -secretase inhibitory action. β -Secretase is an enzyme involved in amyloid- β (A β) production.

20 Amyloid- β is a peptide that is sometimes also referred to as "amyloid- β protein", "amyloid- β peptide", or " β -amyloid". Amyloid- β is a peptide usually consisting of about 40 amino acids. Examples thereof include amyloid- β_{1-42} and amyloid- β_{1-40} . Amyloid- β in the unassociated form is
25 sometimes referred to as "amyloid- β monomer". Amyloid- β that has aggregated into oligomers or fibrils exhibits neuronal cytotoxicity. Aggregated amyloid- β is not discharged from the brain but accumulates therein, which is considered to trigger onset of Alzheimer's disease
30 (Alzheimer's dementia). Thus, reducing amyloid- β production or amyloid- β accumulation is useful for preventing Alzheimer's disease or suppressing the progression of the disease and is useful for reducing a decline in cognitive function or improving cognitive
35 function.

[0016]

Amyloid- β is produced from amyloid- β precursor protein (APP) by two-step cleavage with β -secretase and γ -secretase. β -Secretase is a rate-determining enzyme for amyloid- β production, and its cleavage regulates the amount of total amyloid- β production. Thus, inhibiting β -secretase can reduce amyloid- β production and can reduce amyloid- β accumulation.

[0017]

The composition of the present invention is useful for reducing amyloid- β production and/or amyloid- β accumulation. In one embodiment, the composition of the present invention can be used to reduce amyloid- β production and/or amyloid- β accumulation by inhibiting β -secretase. In one embodiment, the composition of the present invention can be used to reduce a decline in cognitive function or improve cognitive function by reducing amyloid- β production and/or amyloid- β accumulation.

The amyloid- β in the present invention includes amyloid- β in the unassociated form and amyloid- β forming an aggregate such as an oligomer. The aggregate may be, for example, a soluble aggregate (amyloid- β oligomer) in which two or more (e.g., 2 to 50) amyloid- β monomers are aggregated.

[0018]

In the present invention, the cognitive function refers to the brain function such as memory function, matching function, integration function, executive function, attention (attention function), and concentration.

In the present invention, the expression "reducing a decline in cognitive function" encompasses maintaining cognitive function, delaying the progression of a decline in cognitive function, stopping a decline in cognitive

function, and the like. The expression "improving cognitive function" encompasses reducing cognitive dysfunction (e.g., alleviating (moderating) the degree of cognitive dysfunction), recovering cognitive function, enhancing cognitive function, and the like. The expression "cognitive dysfunction" refers to partial or entire loss of the cognitive function. The expression "reducing a decline in cognitive function or improving cognitive function" encompasses reducing a decline in partial cognitive function or improving partial cognitive function. The expression "recovering" encompasses at least partial recovering.

[0019]

Examples of causes of the decline in cognitive function or the cognitive dysfunction include aging; neurodegenerative diseases such as Alzheimer's disease, Pick's disease, and diffuse Lewy body disease; brain diseases such as cerebral infarction, cerebral hemorrhage, chronic subdural hematoma, brain tumor, encephalitis, and normal pressure hydrocephalus; and Creutzfeldt-Jakob disease.

In one embodiment, the composition containing Cyclo(Leu-Glu) or a salt thereof is suitably used to reduce a decline in cognitive function due to Alzheimer's disease and/or to reduce cognitive dysfunction due to Alzheimer's disease. The aging-related cognitive dysfunction may be aging-related cognitive dysfunction among middle-aged and older people. The middle-aged and older people include the elderly.

[0020]

In one embodiment, the composition containing Cyclo(Leu-Glu) or a salt thereof is suitably used to reduce a decline in cognitive function or improving cognitive function, the cognitive function being at least one selected from the group consisting of memory function,

executive function, attention, and concentration. The composition of the present invention can be used, for example, to reduce a decline in cognitive function due to Alzheimer's disease, the cognitive function being at least one selected from the group consisting of memory function, executive function, attention, and concentration, or to improve the cognitive function described above which has declined due to Alzheimer's disease.

[0021]

10 The memory function is a function for retaining past events and reliving the past events for use at a later time. The memory function is classified into, for example, verbal memory function, nonverbal memory function, visuospatial memory function, gist memory function, and
15 working memory function.

[0022]

 The executive function is a function for formulating and carrying out plans to achieve goals and is a crucial function for people to behave socially, independently, and
20 creatively. The executive function compares various kinds of information such as visual, auditory, and olfactory information to past events and coordinates the information in the frontal lobe.

[0023]

25 The attention is a function for selecting information from a large amount of information. It is a selective processing function for selectively processing necessary information by not assigning processing resources to unnecessary information in order to effectively use limited
30 processing resources in the brain.

 The concentration is a function that allows investing mental effort and focusing effectively on the task at hand while ignoring distractions.

 In one embodiment, the composition of the present
35 invention can be suitably used to reduce a decline in

memory function or improve memory function and can be more suitably used to reduce a decline in functions such as verbal memory function, nonverbal memory function, visuospatial memory function, gist memory function, and
5 working memory function, or to improve these functions.
[0024]

In one embodiment, the composition of the present invention can be used, for example, to prevent or ameliorate a condition or disease that exhibits a decline
10 in cognitive function and/or a condition or disease associated with amyloid- β accumulation in the brain. Examples of such a condition or disease include Alzheimer's disease (including Alzheimer's dementia) and mild cognitive impairment.

15 The composition of the present invention can be used to prevent or ameliorate the condition or disease and can be suitably used to prevent the condition or disease.

Herein, the expression "to prevent a condition or disease" encompasses preventing the onset, delaying the
20 onset, reducing the incidence rate, reducing the onset risk, and the like. The expression "to ameliorate a condition or disease" encompasses helping a subject recover from a condition or disease, alleviating a symptom of a condition or disease, favorably changing a symptom of a
25 condition or disease, delaying or preventing the progress of a condition or disease, and the like.

[0025]

Alzheimer's disease and mild cognitive impairment are known to cause a decline in cognitive function. Examples
30 of symptoms of the decline in cognitive function caused by Alzheimer's disease and mild cognitive impairment include a decline in memory, memory disorders (forgetfulness), aphasia (inability to formulate words), apraxia, agnosia (e.g., getting lost in a familiar place), decline in
35 orientation (ability to correctly recognize one's

situation, such as a place, time, and people's names), decline in verbal and non-verbal learning abilities, a decline in auditory and visual processing, a decline in executive function, executive dysfunction (an inability to
5 formulate and carry out plans), a decline in concentration, a decline in attention, a decline in judgement, a decline in spatial awareness, a decline in cognitive flexibility, and a decline in information processing speed. The composition of the present invention can be used, for
10 example, to prevent or ameliorate the above symptoms.
[0026]

The composition of the present invention is applicable for therapeutic use (medical use) and non-therapeutic use (non-medical use). The term "non-
15 therapeutic" is a concept that does not include medical activities, i.e., a concept that does not include methods of surgery, therapy, or diagnosis of humans.

The composition of the present invention for reducing a decline in cognitive function or improving cognitive
20 function can be provided in the form of an agent, but it is not limited thereto. The agent can be directly provided as a composition or can be provided as a composition containing the agent.

In one embodiment, the composition of the present
25 invention for reducing a decline in cognitive function or improving cognitive function can also be referred to as an agent for reducing a decline in cognitive function or improving cognitive function.
[0027]

30 The composition of the present invention may be for oral use or parenteral use. Preferably, the composition of the present invention is a composition for oral use. The composition of the present invention can be provided, for example, in the form of a food or beverage, a
35 pharmaceutical product, a quasi-pharmaceutical product,

feed, or the like. Preferably, the composition is provided in the form of a food or beverage or a pharmaceutical product. The composition of the present invention can also be used by being added to a food or beverage, a
5 pharmaceutical product, a quasi-pharmaceutical product, feed, or the like. The composition of the present invention may be in any form, such as solid (e.g., powder, granule, tablet, etc.), liquid, or paste.

[0028]

10 The composition of the present invention contains Cyclo(Leu-Glu) or a salt thereof and may further contain various types of additives, which are accepted as additives to foods or beverages, pharmaceutical products, and the like, such as diluents, acidulants, antioxidants,
15 stabilizers, preservatives, flavoring or masking agents, emulsifiers, pigments, seasonings, pH adjusters, and nutrient enhancers.

[0029]

For example, when the composition of the present
20 invention is provided as a food or beverage, a component usable in a food or beverage (e.g., a food material or an optional food additive) can be added to Cyclo(Leu-Glu) or a salt thereof to provide various types of foods or beverages. Non-limiting examples of the food or beverage
25 include general foods and beverages, health foods, foods with function claims, foods for specified health uses, dietary supplements, and foods and beverages for the sick. The health foods, the foods with function claims, the foods for specified health uses, the dietary supplements, and the
30 like can be used, for example, in various forms of preparations such as liquids, fine granules, tablets, granules, powders, capsules, chewable tablets, dry syrups, and liquid foods.

[0030]

35 When the composition of the present invention is

provided as a pharmaceutical or quasi-pharmaceutical product, a pharmacologically acceptable carrier, an optional additive, or the like can be added to Cyclo(Leu-Glu) or a salt thereof to provide various dosage forms of pharmaceutical or quasi-pharmaceutical products. Such a carrier, additive, or the like may be any pharmacologically acceptable one that can be used in pharmaceutical products or quasi-pharmaceutical products. Examples thereof include excipients, binders, disintegrants, lubricants, antioxidants, and colorants. One or more of these can be used. The form of administration (ingestion) of the pharmaceutical product or the quasi-pharmaceutical product may be oral or parenteral (e.g., transdermal, transmucosal, enteral, or injection) administration. When the composition of the present invention is provided as a pharmaceutical or quasi-pharmaceutical product, a pharmaceutical product for oral administration or a quasi-pharmaceutical product for oral administration is preferred. Examples of dosage forms for oral administration include liquids, tablets, powders, fine granules, granules, sugar-coated tablets, capsules, suspensions, emulsions, and chewable tablets. Examples of dosage forms for parenteral administration include injections, intravenous agents, ointments, lotions, adhesive skin patches, suppositories, nasal agents, and transpulmonary agents (inhalants). The pharmaceutical product may be for non-human animals.

[0031]

When the composition of the present invention is provided as feed, Cyclo(Leu-Glu) or a salt thereof may be simply added to feed. The feed includes feed additives. Examples of the feed include livestock feed for animals such as cows, pigs, chickens, sheep, and horses; feed for small animals such as rabbits, rats, and mice; and pet food for animals such as dogs, cats, and birds.

[0032]

For example, when the composition of the present invention is provided as a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product,
5 feed, or the like, the composition can be produced by any common method using Cyclo(Leu-Glu) or a salt thereof.

[0033]

In one embodiment, the composition of the present invention is preferably a liquid composition, more
10 preferably a beverage. The beverage may be a functional beverage. The beverage may be in any form, and it may be a beverage in a sealed container. The container of the beverage in a sealed container is not limited. The container may be in any form and made of any material. For
15 example, any of the following commonly used containers can be used: metal containers such as aluminum cans and steel cans; resin containers such as plastic bottles; paper containers such as drink cartons; glass containers such as glass bottles; and wooden containers such as barrels. Any
20 of these containers is filled with the beverage and sealed, whereby the beverage in a sealed container can be obtained.

[0034]

The amount of Cyclo(Leu-Glu) or a salt thereof in the composition of the present invention is not limited and can
25 be set according to the form of the composition or the like.

In one embodiment, the amount of Cyclo(Leu-Glu) or a salt thereof in the composition of the present invention may be, for example, 0.000001 wt% or more, preferably
30 0.00001 wt% or more, more preferably 0.0001 wt% or more, still more preferably 0.001 wt% or more, particularly preferably 0.01 wt% or more, and is preferably 50 wt% or less. In one embodiment, the amount of Cyclo(Leu-Glu) or a salt thereof may be, for example, 0.000001 to 25 wt%,
35 preferably 0.00001 to 10 wt%, more preferably 0.0001 to 5

wt%, still more preferably 0.001 to 5 wt%, particularly preferably 0.01 to 1 wt% in the composition of the present invention.

Cyclo(Leu-Glu) or a salt thereof can be quantified by
5 a known method using liquid chromatography-mass spectrometry (LC/MS), for example.

[0035]

Preferably, the composition of the present invention is orally ingested (orally administered). The
10 administration amount (intake) of the composition of the present invention is not limited. The administration amount of the composition of the present invention is not limited as long as it is an amount that achieves the effect of reducing a decline in cognitive function or improving
15 cognitive function. The administration amount may be suitably set according to the administration form, administration method, body weight of a subject, and the like. Preferably the administration amount of the composition of the present invention is an amount that
20 achieves the β -secretase inhibitory effect. Preferably, the administration amount of the composition of the present invention is an amount that achieves the effect of reducing amyloid- β production and/or amyloid- β accumulation.

[0036]

25 In one embodiment, when the composition of the present invention is ingested by or administered to a human (adult) as a subject, the administration amount in terms of the administration amount of Cyclo(Leu-Glu) per day is preferably 0.001 mg or more, more preferably 0.01 mg or
30 more, still more preferably 0.1 mg or more, and is preferably 5000 mg or less, more preferably 1000 mg or less, still more preferably 100 mg or less. In one embodiment, when the composition of the present invention is ingested by or administered to a human (adult), the
35 administration amount of Cyclo(Leu-Glu) or a salt thereof

in terms of Cyclo(Leu-Glu) per day is preferably 0.001 to 5000 mg, more preferably 0.01 to 1000 mg, still more preferably 0.1 to 100 mg.

Preferably, the above amount is ingested or
5 administered in one or more portions per day, for example, one to several portions (e.g., two to three portions) per day. In one embodiment, preferably, the above amount of Cyclo(Leu-Glu) or a salt thereof is orally ingested or administered. In the case of a human (adult), preferably,
10 the above amount of Cyclo(Leu-Glu) or a salt thereof is ingested or administered per 60 kg body weight per day. In one embodiment, the composition of the present invention may be an oral composition for allowing the above amount of Cyclo(Leu-Glu) or a salt thereof to be ingested by or
15 administered to a human per 60 kg body weight per day.
[0037]

Preferably, the composition of the present invention is continuously ingested or administered. Continuous ingestion or administration of Cyclo(Leu-Glu) or a salt
20 thereof is expected to enhance the effects. In one embodiment, the composition of the present invention is continuously ingested or administered preferably for at least one week, more preferably for at least four weeks, still more preferably for at least eight weeks.

25 Cyclo(Leu-Glu) or a salt thereof can be ingested as a food or beverage or the like. For example, long-term ingestion is considered to be low risk in terms of safety.
[0038]

The composition of the present invention may be
30 ingested by or administered to any subject (administration subject). The administration subject is preferably a human or non-human mammal, more preferably a human.

In one embodiment, examples of the administration subject of the composition of the present invention include
35 a subject needing or wanting to reduce a decline in

cognitive function or improve cognitive function, a subject needing or wanting to reduce amyloid- β production and/or amyloid- β accumulation, and a subject needing or wanting to prevent or ameliorate a condition or disease associated with amyloid- β accumulation. In one embodiment, examples of the administration subject include a subject needing or wanting to prevent or ameliorate a decline in memory function and a subject with a decline in memory function. The decline in cognitive function may be a decline in cognitive function due to amyloid- β accumulation, an aging-related decline in cognitive function, or the like. In one embodiment, the administration subject in the present invention may be a middle-aged or older person. The expression "middle-aged and older people" encompasses the elderly. The middle-aged and older people may be those who are 40 years old and older, for example. In one embodiment, the elderly are preferred subjects among the middle-aged and older people. The elderly may be people who are 60 years old and older or 65 years old and older, for example. In one embodiment, the administration subject in the composition of the present invention may be a healthy person. For example, the composition can also be used on a healthy person for purposes such as preventing a condition or disease that is likely to be prevented or ameliorated by reducing a decline in cognitive function or improving cognitive function, reducing amyloid- β production and/or amyloid- β accumulation in the brain, preventing amyloid- β accumulation in the brain, and preventing Alzheimer's disease or mild cognitive impairment.

[0039]

The composition of the present invention may be labeled as having an action that reduces a decline in cognitive function or improves cognitive function. Alternatively, the composition may be labeled as having a function based on reduction of decline in cognitive

function or improvement of cognitive function or based on reduction of amyloid- β production and/or amyloid- β accumulation. Such a label is also referred to as a function claim. The label is not limited. Examples of the label include "enhancing cognitive function", "reducing a decline in cognitive function", "maintaining good cognitive function", "improving memory", "reducing a decline in memory", "maintaining good memory", "improving accuracy of memory", "preventing memory disorders", "ameliorating memory disorders", "maintaining memory that is one domain of cognitive function", "function suitable for those who are concerned about a decline in memory", "improving accuracy of memory and/or correctness of judgement that is part of cognitive function", "improving memory retention or consolidation", "sustaining cognitive enhancement", "improving executive function", "promoting attention and concentration", "improving learning ability", "maintaining or improving orientation", "delaying an aging-related decline in cognitive function", "enhancing short-term and long-term memory", "promoting verbal and visuospatial memory", and "maintaining or improving logical thinking", as well as labels or function claims considered to be equated to these labels.

In one embodiment of the present invention, preferably, the composition of the present invention is a food or beverage labeled with one or more function claims described above. The label may be indicating use of the composition for obtaining any of the above functions. One or more of these labels may be directly attached to the composition or may be attached to a container or a package of the composition.

[0040]

Cyclo(Leu-Glu) or a salt thereof is also useful as an active ingredient for reducing amyloid- β production and/or amyloid- β accumulation. The present invention also

encompasses a composition for reducing amyloid- β production and/or amyloid- β accumulation, containing Cyclo(Leu-Glu) or a salt thereof as an active ingredient. In one embodiment, the composition for reducing amyloid- β production and/or amyloid- β accumulation can also be referred to as an agent for reducing amyloid- β production and/or amyloid- β accumulation. Cyclo(Leu-Glu) or a salt thereof is useful, for example, for preventing or ameliorating a condition or disease associated with or resulting from amyloid- β accumulation in the brain. Examples of such a condition or disease include Alzheimer's disease (including Alzheimer's dementia) and mild cognitive impairment.

[0041]

Cyclo(Leu-Glu) or a salt thereof is also useful as an active ingredient for inhibiting β -secretase. The present invention also encompasses a composition for inhibiting β -secretase, containing Cyclo(Leu-Glu) or a salt thereof. The composition for inhibiting β -secretase can also be referred to as a β -secretase inhibitor.

Preferred embodiments, preferred administration amounts, preferred administration subjects, and the like of the composition for reducing amyloid- β production and/or amyloid- β accumulation and the composition for inhibiting β -secretase are the same as those of the composition for reducing a decline in cognitive function or improving cognitive function.

[0042]

The present invention also encompasses the following methods and uses:

a method of reducing a decline in cognitive function or improving cognitive function, the method including administering Cyclo(Leu-Glu) or a salt thereof;

a method of reducing amyloid- β production and/or amyloid- β accumulation, the method including administering Cyclo(Leu-Glu) or a salt thereof;

a method of inhibiting β -secretase, the method including administering Cyclo(Leu-Glu) or a salt thereof; use of Cyclo(Leu-Glu) or a salt thereof for reducing a decline in cognitive function or improving cognitive function;

use of Cyclo(Leu-Glu) or a salt thereof for reducing amyloid- β production and/or amyloid- β accumulation; and use of Cyclo(Leu-Glu) or a salt thereof for inhibiting β -secretase.

Each method may be a therapeutic or non-therapeutic method. Each use may be a therapeutic or non-therapeutic use.

[0043]

Administration of Cyclo(Leu-Glu) or a salt thereof can reduce a decline in cognitive function or improve cognitive function. This can prevent or ameliorate, for example, a decline in memory, forgetfulness, aphasia, apraxia, agnosia, executive dysfunction, a decline in concentration, a decline in attention, a decline in judgement, a decline in spatial awareness, a decline in cognitive flexibility, a decline in executive function, and a decline in information processing speed. In one embodiment, Cyclo(Leu-Glu) or a salt thereof is suitably used to reduce a decline in memory function (memory) or improving memory function (memory).

[0044]

In one embodiment, Cyclo(Leu-Glu) or a salt thereof can be used to reduce amyloid- β production and/or amyloid- β accumulation by inhibiting β -secretase. For example, amyloid- β production and/or amyloid- β accumulation can be reduced by inhibiting β -secretase, which in turn can reduce a decline in cognitive function or improve cognitive function. In one embodiment, Cyclo(Leu-Glu) or a salt thereof can be used to reduce a decline in cognitive function or improve cognitive function associated with

amyloid- β accumulation by inhibiting β -secretase.

[0045]

In the above methods and uses, preferably, Cyclo(Leu-Glu) or a salt thereof is ingested by or administered to a
5 subject at least once a day, for example, once to several times (for example, two or three times) per day. The above uses are preferably for humans or non-human mammals, more preferably for humans.

In one embodiment, Cyclo(Leu-Glu) or a salt thereof
10 can be used to prevent or ameliorate a condition or disease associated with amyloid- β accumulation by inhibiting β -secretase. The present invention also encompasses a method of preventing or ameliorating a condition or disease associated with amyloid- β accumulation, the method
15 including administering Cyclo(Leu-Glu) or a salt thereof.

[0046]

In the above methods and uses, Cyclo(Leu-Glu) or a salt thereof may be used in an amount (effective amount) that achieves the effect of reducing a decline in cognitive
20 function or improving cognitive function. Preferably, the effective amount is an amount that can achieve the effect of reducing amyloid- β production and/or amyloid- β accumulation. More preferably, the effective amount is also an amount that can achieve the β -secretase inhibitory
25 effect. Preferred administration amount, administration method, administration subject, and the like of Cyclo(Leu-Glu) or a salt thereof are the same as those of the composition of the present invention described above. Cyclo(Leu-Glu) or a salt thereof may be ingested or
30 administered as it is, or it may be ingested or administered in the form of a composition containing Cyclo(Leu-Glu) or a salt thereof. For example, the composition of the present invention may be ingested or administered.

35 [0047]

Cyclo(Leu-Glu) or a salt thereof can be used to produce a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like for use in reducing a decline in cognitive function or improving
5 cognitive function. Cyclo(Leu-Glu) or a salt thereof can be used to produce a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like for use in reducing amyloid- β production and/or amyloid- β accumulation. In one embodiment, the present invention
10 also encompasses use of Cyclo(Leu-Glu) or a salt thereof in production of a composition for reducing a decline in cognitive function or improving cognitive function. In one embodiment, the present invention also encompasses use of Cyclo(Leu-Glu) or a salt thereof in production of a
15 composition for reducing amyloid- β production and/or amyloid- β accumulation. The present invention also encompasses use of Cyclo(Leu-Glu) or a salt thereof in production of a composition for inhibiting β -secretase.

Cyclo(Leu-Glu) or a salt thereof can be used to
20 produce a composition for preventing or ameliorating a condition or disease associated with amyloid- β accumulation.

[0048]

The numerical range defined by the lower limit and
25 the upper limit herein, i.e., "the lower limit to the upper limit", includes the lower limit and the upper limit. For example, the range defined by "1 to 2" means 1 or more and 2 or less, with 1 and 2 being inclusive. Herein, the range may be any combination of any upper limit and any lower
30 limit.

EXAMPLES

[0049]

The following describes the present invention in
35 further detail below with reference to Examples, which are

not intended to limit the scope of the present invention.

[0050]

<Examples 1 and 2 and Comparative Example 1>
(Evaluation of compound having β -secretase inhibitory
5 activity)

Materials and methods

β -Secretase inhibitory activity of test compounds was
examined. Cyclo-leucyl-alanine (Cyclo(Leu-Ala)) was used
as a test compound in Comparative Example 1. Cyclo-leucyl-
10 glutamate (Cyclo(Leu-Glu)) was used as a test compound in
Examples 1 and 2. Cyclo(Leu-Ala) was purchased from
Bachem. Cyclo(Leu-Glu) was purchased from Peptide
Institute, Inc.

In each case, a commercial kit "Beta Secretase
15 (BACE1) Activity Assay Kit (Abcam)" was used for evaluation
of β -secretase inhibitory activity. The β -secretase enzyme
activity inhibitory effect was evaluated according to the
method described in the kit.

A sample solution (test compound solution) was mixed
20 with an enzyme solution on a 96-well plate (Corning),
followed by incubation at 37°C for 10 minutes.
Subsequently, a substrate solution was added for reaction
at 37°C for 60 minutes. The fluorescence intensity (RFU)
(Ex/Em = 335 nm/495 nm) of the reaction solution was
25 measured at every five minutes from 0 to 60 minutes after
the start of the reaction, using a microplate reader "Flex
Station 3" (Molecular Devices). The reaction was carried
out with n = 2, and the average fluorescence intensity of
the reaction solution was regarded as the measured value.

30 The concentration (final concentration) of each test
compound in the evaluation was set as shown in Table 1.

[0051]

[Table 1]

	Compound	Concentration ($\mu\text{g/mL}$)
Control	Not added	-
Comparative Example 1	Cyclo(Leu-Ala)	20
Example 1	Cyclo(Leu-Glu)	35.4
Example 2	Cyclo(Leu-Glu)	17.7

[0052]

The enzyme activity was evaluated using Δ fluorescence intensity of the reaction solution (fluorescence intensity at the end of reaction (at minutes 60)) - (fluorescence intensity before the start of reaction (at minutes 0)). The group to which no test compound was added was used as control. The inhibitory activity of each test compound was evaluated relative to the enzyme activity (Δ fluorescence intensity) of control, which was taken as 1.

[0053]

Results

FIG. 1 is a graph showing β -secretase (BACE) inhibitory activity of each test compound.

The results were represented as means $\pm$ standard deviation ($n = 2$). BACE activity shown in FIG. 1 is a value of BACE activity of each test compound (Δ fluorescence intensity of each reaction solution to which the test compound was added) relative to BACE activity of control (Δ fluorescence intensity of control), which was taken as 1.

The inhibitory activity was not observed in cyclo-leucyl-alanine (Cyclo(Leu-Ala)) measured as Comparative Example 1. A reduction in the enzyme activity of β -secretase was observed in cyclo-leucyl-glutamate (Cyclo(Leu-Glu)) (Examples 1 and 2).

The above results show that Cyclo(Leu-Glu), which is a cyclic dipeptide, has β -secretase inhibitory activity.

Cyclo(Leu-Glu) or a salt thereof is considered to be effective in reducing a decline in cognitive function or

improving cognitive function because amyloid- β production and/or amyloid- β accumulation, which causes a decline in cognitive function, can be reduced by inhibiting β -secretase.

CLAIMS

Claim 1. A composition for reducing a decline in cognitive function or improving cognitive function,
5 comprising:

Cyclo(Leu-Glu) or a salt thereof as an active ingredient.

Claim 2. The composition according to claim 1,
10 wherein the composition reduces at least one of amyloid- β production or amyloid- β accumulation.

Claim 3. The composition according to claim 1 or 2,
wherein the composition reduces at least one of
15 amyloid- β production or amyloid- β accumulation by inhibiting β -secretase.

Claim 4. The composition according to claim 1 or 2,
wherein the composition is for oral use.
20

Claim 5. The composition according to claim 1 or 2,
wherein the composition is a food or beverage or a pharmaceutical product.

Claim 6. The composition according to claim 1 or 2,
wherein the composition is labeled with one or more function claims selected from the group consisting of
"enhancing cognitive function", "reducing a decline in cognitive function", "maintaining good cognitive function",
30 "improving memory", "reducing a decline in memory", "maintaining good memory", "improving accuracy of memory", "preventing memory disorders", "ameliorating memory disorders", "maintaining memory that is one domain of cognitive function", "function suitable for those who are
35 concerned about a decline in memory", "improving accuracy

of memory and/or correctness of judgement that is part of cognitive function", "improving memory retention or consolidation", "sustaining cognitive enhancement", "improving executive function", "promoting attention and concentration", "improving learning ability", "maintaining or improving orientation", "delaying an aging-related decline in cognitive function", "enhancing short-term and long-term memory", "promoting verbal and visuospatial memory", and "maintaining or improving logical thinking".

10

Claim 7. Use of Cyclo(Leu-Glu) or a salt thereof in production of a composition for reducing a decline in cognitive function or improving cognitive function.

15

Claim 8. Use of Cyclo(Leu-Glu) or a salt thereof for reducing a decline in cognitive function or improving cognitive function.