

GHRELIN SECRETION PROMOTER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001]

- 5 The present patent application claims priority based on Japanese Patent Application No. 2014-130143 filed on June 25, 2014, the entire disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

10 [0002]

 The present invention relates to a novel ghrelin secretion promoter.

BACKGROUND ART

[0003]

- 15 Loss of appetite in humans includes cases where it is due to diseases and cases where it is not due to diseases. Especially, loss of appetite which is not due to diseases, for example in the case of older people, is caused by social factors such as separation from and loss of spouse and mandatory
- 20 retirement, and by physical factors such as reduction in amount of exercise due to aging and reduction in masticatory strength due to use of artificial teeth and the like, that are concerned to lead to undernutritional condition and decrease in resistance in their body.

25 [0004]

- Known neuropeptides which enhance appetite are, for example, neuropeptide Y (NPY), orexins, motilin, melanin-concentrating hormone (MCH) and agouti-related protein (AGRP). Also, substances which suppress appetite are,
- 30 for example, α -melanocyte-stimulating hormone (α -MSH), corticotropin-releasing factor (CRF), cocain- and

amphetamine-regulated transcript (CART) and cholecystokinin (CCK). These peptides are involved in the physiological mechanism which controls the gastrointestinal motility, and are considered to affect energy homeostasis.

5 [0005]

Ghrelin is known as one of other peptides which enhance appetite. Ghrelin is a peptide hormone of 28 residues discovered from the human stomach as an endogenous ligand for a growth hormone secretagogue receptor (GHSR). Ghrelin
10 includes two main molecular forms: active (acyl) ghrelin and inactive (desacyl) ghrelin. Active ghrelin has a structural feature that the third serine is modified (acylated) by octanoic acid. This modification is essential for development of the activity of ghrelin. Active ghrelin has the growth hormone (GH)
15 secretomotor action, and is expected to provide muscle synthesis and antiaging via the GH secretory action and also expected to be utilized in the treatment of dwarfism. Also, ghrelin is a sole endogenous eating promoter, and is expected to be utilized in the treatment of eating disorder (anorexia) via
20 the eating enhancement action. Additionally, ghrelin has been found, from nonclinical and clinical researches in recent years, to provide various effects.

Specially, ghrelin exhibits effects of fat accumulation promotion, insulin secretion suppression and suppression of the
25 function of brown fat tissues, concerning the energy metabolism regulating function; effects of enterokinesis promotion, gastric acid secretion and pancreatic exocrine secretion enhancement, concerning the digestive system; and effects of sympathetic nervous system suppression, vasodilatation, increase in force of
30 heart contraction and protection of cardiac muscle cells, concerning the circulatory system. Attempts to clinically apply these various physiological effects have already been started, and there have been conducted clinical trials of administering ghrelin to patients after prosthetic replacement arthroplasty,

after digestive cancer operation, with eating disorder, with functional dyspepsia, with cancer cachexia, with chronic heart failure cachexia, with chronic renal failure cachexia and with chronic obstructive pulmonary disease (COPD).

5 [0006]

Active ghrelin is rapidly octanoic acid-removed in the blood and becomes inactive desacyl ghrelin. Such ghrelin occupies 90% or more of the whole ghrelin in the circulating plasma, and reflects the total secretory ability and metabolic state. Inactive ghrelin has no action of inducing growth hormone secretion promotion, and, conversely, antagonizes ghrelin to suppress eating behavior, or, with respect to enterokinesis, to suppress gastric motility in a fasting period. Therefore, it can be said that active ghrelin is more effective when active ghrelin /inactive ghrelin level is higher.

[0007]

Patent Document 1 reveals the appetite regulating action of ghrelin and the mechanism thereof, and describes the development of a novel therapeutic agent for undernitrional symptom disorders through the use thereof and also the development of a novel therapeutic agent for eating abnormality or metabolism abnormality through the use of an agonist or antagonist for ghrelin.

[0008]

25 For example, Patent Document 2 describes that intake of a specific steroid saponin such as dioscin promotes ghrelin secretion in ghrelin secretory cells isolated from the rat stomach.

[0009]

30 On the other hand, in Patent Document 1, it is necessary to synthesize a peptide having the same amino acid sequence

as that of human ghrelin when ghrelin and its derivative are added. Also, it is necessary to suppress the decomposition of the hydrophobic modified structure of ghrelin to stabilize ghrelins, as described in Patent Document 3, in order to apply it to pharmaceutical formulations.

[0010]

Also, in Patent Document 2, it is necessary to purify a specific steroid saponin, such as dioscin, which promotes ghrelin secretion again.

10 [0011]

Thus, it is necessary to forcibly give (administer) ghrelin or a known substance which secretes ghrelin to humans with loss of appetite in order to secrete in the body, and there are also physical and/or psychological barriers when they take ghrelin or such a substance. Under such a technical situation, a novel technical means which can effectively promote the secretion of ghrelin in the body can be said to be demanded.

Prior Art Documents

Patent Documents

20 [0012]

Patent Document 1: JP 2010-006823 A

Patent Document 2: JP 2013-227309 A

Patent Document 3: WO 2003/006349

SUMMARY OF INVENTION

25 [0013]

One object of the present invention is to provide a novel ghrelin secretion promoter. Also, one object of the present invention is to provide a novel, safe and side effect-free ghrelin secretion promoter which can exert the action of secreting ghrelin which is present in human bodies, without synthesis

and/or separation and purification of a compound and in an easily ingestible form.

[0014]

5 The present inventors have obtained the following finding, as a result of intensive studies in light of the above problems. Specifically, the present inventors have found that the secretion of ghrelin in the body can be promoted by intake (administration) of a composition comprising specific ingredients including a protein, a lipid and a saccharide.

10 [0015]

Namely, the present invention is as follows.

[1] A ghrelin secretion promoter comprising a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid, as a lipid; and a saccharide.

15 [2] The ghrelin secretion promoter according to item [1], comprising a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid-containing fat, a phospholipid and an oleic acid-containing fat, as lipids; and isomaltulose as a saccharide.

20 [3] The ghrelin secretion promoter according to item [1] or [2], wherein the protein hydrolysate is a protein hydrolysate made of a raw material selected from casein, a milk protein concentrate (MPC), a whey protein concentrate (WPC), a whey protein isolate (WPI), α -lactoalbumin, β -lactoglobulin and
25 lactoferrin.

[4] The ghrelin secretion promoter according to any one of items [1] to [3], wherein the protein hydrolysate is a whey protein hydrolysate.

30 [5] The ghrelin secretion promoter according to any one of items [1] to [4], wherein the amount of the protein hydrolysate to be incorporated ranges from 0.5 g to 3 g per 100 ml.

[6] The ghrelin secretion promoter according to any one

of items [1] to [5], wherein the fermented milk protein is derived from a substance obtained by discharging whey from fermented milk.

5 [7] The ghrelin secretion promoter according to any one of items [1] to [6], wherein the fermented milk protein is derived from fermented milk obtained by fermenting skimmed milk with *Lactobacillus Bulgaricus* or *Streptococcus Thermophilus*, or a combination thereof.

10 [8] The ghrelin secretion promoter according to any one of items [1] to [7], wherein the fermented milk protein is derived from fresh cheese.

[9] The ghrelin secretion promoter according to any one of items [1] to [8], wherein the amount of the fermented milk protein to be incorporated ranges from 0.5 g to 6 g per 100 ml.

15 [10] The ghrelin secretion promoter according to any one of items [1] to [9], wherein the protein hydrolysate is obtained by hydrolyzing a whey protein isolate (WPI) with an endo-type protease derived from *Bacillus licheniformus* and hydrolyzing the resultant hydrolysate with swine pancreas-derived trypsin.

20 [11] The ghrelin secretion promoter according to any one of items [1] to [10], wherein the molecular cutoff of the protein hydrolysate is 10,000 or less.

[12] The ghrelin secretion promoter according to any one of items [1] to [11], wherein the amount of the saccharide to be incorporated ranges from 1 g to 15 g per 100 ml.

[13] The ghrelin secretion promoter according to any one of items [1] to [12], wherein the amount of the oleic acid to be incorporated in the lipid is 25% by weight or more of the whole fatty acid.

30 [14] The ghrelin secretion promoter according to any one of items [1] to [13], wherein the amount of the medium-chain fatty acid to be incorporated ranges from 0.01 g to 4 g per 100 ml.

35 [15] The ghrelin secretion promoter according to any one of items [1] to [14], wherein the heat quantity thereof ranges from 50 kcal to 150 kcal per 100 ml.

[16] The ghrelin secretion promoter according to any one of items [8] to [15], wherein the fresh cheese is quark.

[17] The ghrelin secretion promoter according to any one of items [2] to [16], wherein the phospholipid is milk
5 phospholipid.

[18] The ghrelin secretion promoter according to any one of items [2] to [17], wherein the amount of the phospholipid to be incorporated ranges from 0.01 g to 0.5 g per 100 ml.

[19] The ghrelin secretion promoter according to any one
10 of items [1] to [18], wherein the medium-chain fatty acid is a medium-chain fatty acid having 8 to 14 carbon atoms.

[20] The ghrelin secretion promoter according to any one of items [1] to [19] for eating enhancement, fat accumulation promotion, insulin secretion suppression, suppression of the
15 function of brown fat tissues, enterokinesis promotion, gastric acid secretion enhancement, pancreatic exocrine secretion enhancement, sympathetic nervous system suppression, vasodilatation, increase in force of heart contraction or protection of cardiac muscle cells.

20 [0016]

The ghrelin secretion promoter of the present invention uses constituent ingredients which have been orally taken for a long term, i.e., a protein, a lipid and a saccharide, and further comprises a fermented milk protein as an essential ingredient,
25 and thus can provide refreshingness derived from fermented milk. Thus, the ghrelin secretion promoter of the present invention can be easily taken (administered) with safe and less risk of side effects. Further, the ghrelin secretion promoter of the present invention can be prepared without synthesis and/or
30 separation and purification of a chemical compound. Further, according to the ghrelin secretion promoter of the present invention, ghrelin is secreted in the body, thereby making it possible to provide the effect of improving various symptoms. Examples of such an effect include: concerning the
35 eating/energy metabolism adjusting function, actions of eating

enhancement, fat accumulation promotion, insulin secretion suppression, and suppression of the function of brown fat tissues; concerning the digestive system, actions of enterokinesis promotion, gastric acid secretion enhancement, and pancreatic exocrine secretion enhancement; concerning the circulatory system, actions of sympathetic nervous system suppression, vasodilatation, increase in force of heart contraction, and protection of cardiac muscle cells.

DETAILED DESCRIPTION OF THE INVENTION

10 [0017]

The protein hydrolysate of the present invention can be provided as a composition comprising: a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid as a lipid; and a saccharide, as described above. Also, according to a preferred embodiment of the present invention, the ghrelin secretion promoter comprises: a protein hydrolysate and a fermented milk protein as proteins; a medium-chain fatty acid-containing fat, a phospholipid and an oleic acid-containing fat as lipids; and isomaltulose as a saccharide.

20 [0018]

For the protein hydrolysate of the present invention, there can be used milk-derived raw materials such as casein, whey protein (milk protein concentrate (MPC), whey protein concentrate (WPC), whey protein isolate (WPI), α -lactoalbumin and β -lactoglobulin), a milk protein concentrate (MPC) and lactoferrin. Even protein raw materials derived from substances other than milk can be used without particular limitation, so long as the effect of the present invention can be obtained. The above raw materials for the protein hydrolysate may be changed in terms of its functional properties (in addition to physical properties such as solubility, viscosity, gelation, heat stability and emulsion stability, physiological properties and the like), for example, by modifying an amino acid residue according to need. The above raw materials for the protein

hydrolysate are subjected to hydrolyzation treatment with an enzyme or the like to be fractionated into a predetermined molecular weight or less according to need, and thus can also be used as the protein hydrolysate of the present invention. A commercial protein hydrolysate can be used so long as a similar effect to that of the present invention can be obtained.

[0019]

For example, when a whey protein, which is one form of the raw material for the protein hydrolysate of the present invention, is hydrolyzed with an enzyme, usable enzymes include purified products of other known enzymes which hydrolysate proteins, such as plant-derived proteases (e.g., papain, bromelain and actinidine) and microorganism-derived proteases; crude purified products including these enzymes; and crushed bacterial products including these enzymes, without limited to commonly used enzymes, i.e., pepsin, trypsin and chymotrypsin.

[0020]

For example, a method for preparing a whey protein hydrolysate, which is one embodiment of the protein hydrolysate of the present invention, comprises the following steps (1) to (5).

(1) A whey protein isolate (WPI) comprising about 90% by weight of a protein as dry matter was dissolved in water so that 8% by weight of the protein was contained.

(2) The resultant WPI solution was heated at 85°C for 2 minutes for denaturation of the whey protein. The pH of the whey protein solution at this time was 7.5.

(3) Hydrolysis of the whey protein solution after the heat treatment was carried out by adding 2.4L (Novozymes) of alkalase, as an endo-type protease derived from *Bacillus licheniformus*, in an amount of 2% by weight based on the

weight of the whey protein, and causing a reaction at 55°C for 3 hours.

(4) Next, PTN6.0S (Novozymes), as a swine-derived trypsin, was added in an amount of 3% by weight based on the weight of the whey protein, and a reaction was caused at 55°C for 3 hours. When the reaction was finished, the reaction liquid showed a pH of 7.

(5) The resultant reaction liquid was centrifuged at 20,000 × g for 10 minutes, and the supernatant having passed through the UF film (Millipore) having a molecular cutoff of 10,000 was defined as a whey protein hydrolysate.

[0021]

The amount of the protein hydrolysate of the present invention to be incorporated can appropriately be adjusted, for example, depending on the contents of the other ingredients (such as a fermented milk protein as a protein, a medium-chain fatty acid-containing fat, a phospholipid, and an oleic acid-containing fat as lipids, and isomaltulose as a saccharide); pathological condition, disease state, age or body weight of a subject of intake; and/or intended use. For example, a suitable example of the amount of the protein hydrolysate to be incorporated is 0.5-3 g, 0.75-2.8 g, 1-2.5 g, 1.25-2.25 g, 1.5-2.25 g, 1.75-2.25 g, 1.6-2.25 g or 1.6-2.1 g per 100 ml of the agent. Such an amount of the protein hydrolysate to be incorporated is especially preferred when the protein hydrolysate is a whey protein hydrolysate.

[0022]

As the derivation of the fermented milk protein according to the present invention, so-called fermented milk (all products obtained by fermenting liquid milk prepared from one or a combination of two or more of milk raw materials such as livestock milk including cow milk, buffalo milk, goat milk, sheep

milk and horse milk and/or partially skimmed milk, skimmed milk, reconstituted whole milk, reconstituted skimmed milk and reconstituted partially skimmed milk thereof, butter and cream, with a starter such as lactic acid bacteria) can be used. More specifically, as the raw material for the fermented milk protein according to the present invention, products obtained by fermenting milk, for example, with lactic acid bacteria and/or bifidobacteria, such as yogurt and cheese, can be used.

Examples of one form of the fermented milk protein according to the present invention can include natural cheese obtained by discharging (reducing) whey from fermented milk, which is unmaturred fresh cheese (quark, mascarpone, cream cheese and the like). Also, *Lactobacillus bulgaricus*, *Streptococcus thermophiles* and the like can be mainly used as starters for producing fermented milk, but, without limitation to these, lactic acid bacteria and bifidobacteria such as *Streptococcus lactis*, *Streptococcus cremoris*, *Streptococcus diacetylactis*, *Enterococcus faecium*, *Enterococcus fecalis*, *Lactobacillus casei*, *Lactobacillus helveticus*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus murinus*, *Lactobacillus reuteri*, *Lactobacillus brevis*, *Lactobacillus gasseri*, *Bifidobacterium longum*, *Bifidobacterium bifidum* and *Bifidobacterium breve* can also be used. Additionally, microorganisms, such as bacteria of the genus *Propionibacterium*, used in the production of fermented milk, can also be used in combination. The fermented milk protein according to the present invention may be prepared by using any fermented milk, but preferably is derived from quark or fermented milk obtained by fermenting skimmed milk with *Lactobacillus Bulgaricus*, *Streptococcus Thermophilus* or a combination thereof, and more preferably is derived from fermented milk obtained by fermenting skimmed milk with *Lactobacillus Bulgaricus* and *Streptococcus Thermophilus*.

[0023]

A common method for preparing the fermented milk protein according to the present invention involves, firstly, sterilizing skimmed milk and inoculating the sterilized skimmed milk with a starter of lactic acid bacteria (*Lactobacillus*
5 *bulgaricus* or *Streptococcus thermophilus*) in an amount of 0.5-5% (w/w) for fermentation thereof. When the pH of the solution reaches about 4.6, curds are formed. Then, whey is centrifuged with a separator, if desired, and thereafter the obtained curds are cooled. The fermented milk protein
10 according to the present invention can have a formulation of: the total solid content of 17-19% (w/w); a protein of 11-13% (w/w); a fat of less than 1% (w/w), a carbohydrate of 2-8% (w/w); and lactose of less than 2% (w/w), as one example. Additionally, those obtained by coagulation with rennet are also
15 encompassed in the fermented milk protein according to the present invention. Also, those obtained by adding a culture solution mixture of lactis and cremoris bacteria belonging to the genus *Lactococcus* and bacterial species of the genus *Leuconostoc* to skimmed milk for culture thereof and removing
20 whey are also encompassed in the fermented milk protein according to the present invention. Also, those obtained by cutting, with a cutter, curds obtained in a similar manner as in the above method, and then separating whey while warming the solution are also encompassed in the fermented milk protein
25 according to the present invention. The above preparation method is suitably used also in the Examples of the present invention.

[0024]

The amount of the fermented milk protein of the present
30 invention to be incorporated can be appropriately adjusted, for example, depending on the contents of the other ingredients (such as a protein hydrate as a protein, a medium-chain fatty acid-containing fat, a phospholipid, and an oleic acid-containing fat as lipids, and isomaltulose as a saccharide); pathological
35 condition, disease state, age or body weight of a subject of

intake; and/or intended use. A suitable example of the amount of the fermented milk protein to be incorporated is 0.5-6 g, 1-5 g, 1.5-4.5 g, 2-4 g, 2.5-3.5 g or 2.75-3.25 g per 100 ml of the agent. Such an amount of the fermented milk protein to be
5 incorporated is especially preferred when the fermented milk protein is derived from quark or fermented milk obtained by fermenting skimmed milk with *Lactobacillus Bulgaricus*, *Streptococcus Thermophilus* or a combination thereof.

[0025]

10 As the raw material for the phospholipid according to the present invention, one or more known raw materials for phospholipids such as milk phospholipid, soybean-derived lecithin and egg-yolk lecithin can be used.

The phospholipid according to the present invention can
15 be fractionated and purified from a raw material from which the phospholipid is derived, such as milk, soybean and egg. Also, commercial phospholipid-containing raw materials can be used so long as the effect of the present invention can be obtained.

[0026]

20 Milk phospholipid is preferred as the phospholipid according to the present invention. Milk phospholipid (referred to also as milk lecithin) is composed of sphingomyelin (SM), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS) and
25 lysophosphatidylcholine (LPC), and is localized only in milk fat globule membranes (MFGM). The ingredient formulation of the MFGM phospholipid fraction is described, for example, in Dairy Technique, Bulletin of Japan Dairy Technical Association, Vol. 50: pp. 58-91, 2000.

30 [0027]

The amount of the phospholipid of the present invention to be incorporated can appropriately be adjusted, for example,

depending on the contents of the other ingredients (such as a protein hydrolysate and a fermented milk protein as proteins, a medium-chain fatty acid-containing fat and an oleic acid-containing fat as lipids, and isomaltulose as a saccharide);
5 pathological condition, disease state, age or body weight of a subject of intake; and/or intended use. A suitable example of the amount of the phospholipid to be incorporated is 0.01-0.5 g, 0.025-0.4 g, 0.05-0.3 g, 0.06-0.2 g, 0.075-0.2 g, 0.07-0.15 g, 0.07-0.12 g, 0.07-0.1 g, 0.08-0.15 g, 0.08-0.12 g or 0.08-0.1 g
10 per 100 ml of the agent. Such an amount of the phospholipid to be incorporated is especially preferred when the phospholipid is milk phospholipid.

[0028]

Raw materials for the other oils/fats of the present
15 invention are not limited in terms of derivation or kind, so long as the effect of the present invention is not inhibited. For example, the standards for intake of a lipid as defined by the Ministry of Health, Labour and Welfare and the actual intake of a lipid can be compared to adjust the amount of a saturated
20 fatty acid (e.g., palmitic acid or stearic acid), a monovalent unsaturated fatty acid (e.g., oleic acid) or a polyvalent unsaturated fatty acid (e.g., linoleic acid or linolenic acid) to be incorporated. Among others, the increase in proportion of a monovalent unsaturated fatty acid in all fatty acids is also
25 preferred, since it is difficult, in our country, to increase an intake of the monovalent unsaturated fatty acid only by meals. Therefore, for example, oleic acid, which is a monovalent unsaturated fatty acid, can be incorporated in the composition of the present invention. Examples of a lipid source containing
30 a large amount of oleic acid include high oleic sunflower oil having a high oleic acid content, rapeseed oil, olive oil, high oleic acid safflower oil, soybean oil, corn oil and palm oil. Also, examples of the oleic acid-containing lipid source include a nutrient-adjusted fat (NOF CORPORATION). A mixture of
35 sunflower oil, rapeseed oil and olive oil can also be used.

[0029]

The content of the oleic acid in the oleic acid-containing fat of the present invention is not especially limited, so long as the effect of the present invention is not inhibited, and is
5 preferably 30% by weight or more, more preferably 40% by weight or more, more preferably 50% by weight or more.

[0030]

Also, the proportion and amount of the oleic acid to be incorporated in the agent of the present invention can
10 appropriately be adjusted, for example, depending on the contents of the other ingredients (such as a protein hydrolysate and a fermented milk protein as proteins, a medium-chain fatty acid-containing fat and a phospholipid as lipids, and isomaltulose as a saccharide); pathological condition, disease
15 state, age or body weight of a subject of intake; and/or intended use.

[0031]

A suitable example of the proportion of the oleic acid to be incorporated with respect to the whole fatty acid (the whole
20 fatty acid formulation) in the agent of the present invention is 25% by weight or more, 25-95% by weight, 25-90% by weight, 25-80% by weight, 25-70% by weight, 30-70% by weight, 30-60% by weight, 30-50% by weight or 35-45% by weight. The wording "whole fatty acid" used in the present invention
25 means the total amount of the free fatty acids and lipid-constituting fatty acids contained in the agent of the present invention.

[0032]

Also, a suitable example of the amount of the oleic acid
30 to be incorporated is 0.5-8 g, 0.7-7 g, 0.8-6 g, 1-5 g, 1-3 g, 1-2.2 g, 1.2-4 g, 1.4-3 g or 1.6-2 g per 100 ml of the agent. Such an amount of the oleic acid to be incorporated is especially

preferred when the oleic acid-containing fat is high oleic sunflower oil having a high oleic acid content.

[0033]

Also, examples of the medium-chain fatty acid-containing fat according to the present invention include commercial oil mixtures (commercial medium-chain fatty acid oils) containing a medium-chain fatty acid triglyceride. Further, as the medium-chain fatty acid according to the present invention, medium-chain fatty acids (preferably, medium-chain saturated fatty acids) having 8-14 carbon atoms can be used, and preferable examples thereof include caprylic acid, capric acid or lauric acid.

[0034]

The content of the medium-chain fatty acid in the medium-chain fatty acid-containing fat according to the present invention is not especially limited, so long as the effect of the present invention is not inhibited, and is preferably 50% by weight or more, more preferably 70% by weight or more, more preferably 90% by weight or more, more preferably 100% by weight.

[0035]

The proportion and amount of the medium-chain fatty acid in the agent of the present invention can appropriately be adjusted, for example, depending on the contents of the other ingredients (such as a protein hydrolysate and a fermented milk protein as proteins, a phospholipid and an oleic acid-containing fat as lipids, and isomaltulose as a saccharide); pathological condition, disease state, age or body weight of a subject of intake; and/or intended use.

30 [0036]

A suitable example of the proportion of the medium-chain fatty acid to be incorporated with respect to the whole fatty acid in the agent of the present invention is 5% by weight or more, 5-95% by weight, 10-90% by weight, 15-80% by weight, 15-70% by weight, 20-70% by weight, 20-60% by weight, 20-40% by weight or 20-30% by weight.

[0037]

Also, a suitable example of the amount of the medium-chain fatty acid to be incorporated is 0.01-4 g, 0.02-3 g, 0.05-2 g, 0.08-1.5 g, 0.1-1.2 g, 0.2-1 g, 0.4-0.8 g or 0.4-0.7 g per 100 ml of the agent.

[0038]

Preferably, the agent of the present invention further comprises, as a lipid, a polyvalent unsaturated fatty acid-containing fat. As the polyvalent unsaturated fatty acid of the present invention, there can be used a polyvalent unsaturated fatty acid having 18-24 carbon atoms and a degree of unsaturation of 2-8, preferably a polyvalent unsaturated fatty acid having 18-22 carbon atoms and a degree of unsaturation of 2-8, more preferably a polyvalent unsaturated fatty acid having 18-22 carbon atoms and a degree of unsaturation of 2-6. Known fatty acids such as linoleic acid, linolenic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and arachidonic acid can be used. For example, commercial refined fish oils containing the above fatty acid including DHA and EPA can be used as raw materials for the polyvalent unsaturated fatty acid.

[0039]

The proportion and amount of the polyvalent unsaturated fatty acid to be incorporated can appropriately be adjusted, for example, depending on the contents of the other ingredients (such as a protein hydrolysate and a fermented milk protein as

proteins, a medium-chain fatty acid-containing fat, a phospholipid, and an oleic acid-containing fat as lipids, and isomaltulose as a saccharide); pathological condition, disease state, age or body weight of a subject of intake; and/or
5 intended use.

[0040]

A suitable example of the proportion of the polyvalent unsaturated fatty acid to be incorporated with respect to the whole fatty acid in the agent of the present invention is 25% by
10 weight or more, 25-90% by weight, 25-80% by weight, 25-70% by weight, 30-70% by weight or 30-60% by weight. Also, another suitable example of the proportion of the polyvalent unsaturated fatty acid to be incorporated is 10% by weight or more, 10-70% by weight, 10-60% by weight, 10-50% by weight,
15 10-40% by weight, 10-30% by weight, 15-30% by weight or 15-20% by weight.

[0041]

Also, a suitable example of the amount of the polyvalent unsaturated fatty acid to be incorporated is 0.01-5 g, 0.02-4 g,
20 0.05-3 g, 0.08-2 g, 0.1-1 g, 0.15-2 g, 0.2-1 g, 0.15-0.5 g, 0.2-1 g, 0.3-0.8 g, 0.4-0.6 g or 0.18-0.3 g per 100 ml of the agent. Such an amount of the polyvalent unsaturated fatty acid to be incorporated is especially preferred when the raw material therefor is refined fish oil.

25 [0042]

Since the medium-chain fatty acid and polyvalent unsaturated fatty acid as described above have a specific flavor or the like, it is generally difficult, especially for inappetent humans, to directly take such a fatty acid. However, the agent
30 of the present invention essentially comprises a fermented milk protein, and thus humans can also perceive refreshingness derived from fermented milk. Therefore, the claimed agent is

easy to take even when comprising necessary amounts of the medium-chain fatty acid and polyvalent unsaturated fatty acid.

[0043]

Also, the agent of the present invention preferably
5 further comprises, as a lipid, a long-chain saturated fatty acid. As the long-chain saturated fatty acid according to the present invention, there can be used a saturated fatty acid having 16-24 carbon atoms, preferably a saturated fatty acid having 16-22 carbon atoms, more preferably a saturated fatty acid having
10 16-20 carbon atoms, even more preferably a saturated fatty acid having 16-18 carbon atoms. Specific examples of such a long-chain saturated fatty acid include known fatty acids such as palmitic acid and stearic acid.

[0044]

15 A suitable example of the proportion of the long-chain saturated fatty acid with respect to the whole fatty acid in the agent of the present invention is 15% by weight or more, 15-95% by weight, 15-90% by weight, 15-80% by weight, 15-70% by weight, 15-50% by weight, 15-30% by weight or
20 15-25% by weight.

[0045]

Also, a suitable example of the amount of the long-chain saturated fatty acid to be incorporated is 0.01-5 g, 0.1-1 g, 0.15-0.8 g, 0.18-0.7 g or 0.35-0.6 g per 100 ml of the agent.

25 [0046]

Preferably, isomaltulose is mainly used as the raw material for the saccharide of the present invention. In place of, or together with isomaltulose, sugar alcohols (sorbitol, xylitol and maltitol) can also be used. For example, in the case
30 of isomaltulose, these raw materials can be commercial

isomaltulose raw materials such as commercial isomaltulose syrup, reconstituted isomaltulose and isomaltulose starch syrup.

[0047]

5 The amount of the saccharide (preferably isomaltulose) of the present invention to be incorporated can appropriately be adjusted, for example, depending on the contents of the other ingredients (such as a protein hydrolysate and a fermented milk protein as proteins, and a medium-chain fatty acid-containing fat, a phospholipid, and an oleic acid-containing fat as lipids);
10 pathological condition, disease state, age or body weight of a subject of intake; and/or intended use.. A suitable example of the amount of the saccharide to be incorporated in the agent of the present invention is 1-15 g, 1.5-12 g, 2-10 g, 3-9 g, 4-8 g or 5-7 g per 100 ml of the agent.

15 [0048]

In addition to isomaltulose, known saccharides can be incorporated as a raw material for the saccharide of the present invention, for the purpose of nutritional design and improvement in palatability. Also, known dietary fibers can be
20 incorporated for the purpose of nutritional design and health seeking. Further, known saccharides such as dextrans may be incorporated for the purpose of nutritional design and improvement in palatability.

[0049]

25 The weight ratio between the protein and the lipid, in the agent of the present invention, is preferably 0.3:1-3:1, more preferably 1.4:1-2:1.

[0050]

30 The weight ratio between the protein and the saccharide, in the agent of the present invention, is preferably 1:2-1:20, more preferably 1:2-1:4.

[0051]

The weight ratio between the lipid and the saccharide, in the agent of the present invention, is preferably 1:3-1:7, more preferably 1:4-1:6.

5 [0052]

Further, the agent of the present invention can arbitrarily be adjusted, in terms of heat quantity, by appropriately adding a protein, a lipid and a saccharide. For example, a suitable example of the heat quantity of the agent according to the
10 present invention is 50-150 kcal, 60-140 kcal, 70-130 kcal, 80-120 kcal or 90-110 kcal per 100 ml of the agent.

[0053]

In the agent of the present invention, the energy percentages (heat quantities) of the protein, lipid and
15 saccharide to the whole agent are not especially limited, so long as the effect of the present invention is not inhibited, and may be set almost in conformity to the sixth revised Japanese dietary allowances, and, for example, can be designed so that the energy percentage of the protein to the whole agent is
20 15-25%; that the energy percentage of the lipid thereto is 20-30%; and that the energy percentage of the saccharide thereto is 45-65%.

[0054]

In addition to the above protein, lipid, saccharide and
25 dietary fibers, water and known raw materials which can be given (administered) to humans can be incorporated in the agent of the present invention. For example, from the viewpoint of suppressing side effects, food raw materials and food additives which have been used in foods for a long term
30 can be incorporated. Also, the agent of the present invention may be used in any forms, e.g., liquid, solid, powdery, gel and any other forms. Further, the agent of the present invention

can be prepared by a known method for producing a nutrient composition.

[0055]

Also, the agent of the present invention is preferably
5 composed of forms of a single oral intake unit. The amounts of the ingredients contained in the single oral intake unit of the present invention can be determined, for example, based on the amounts of the respective ingredients to be incorporated as defined above.

10 [0056]

Further, the agent of the present invention is preferably provided in a package form of a single oral intake unit. Examples of the unit package form per single oral intake include forms such that a constant amount is defined by using a pack, a
15 container or the like, and those surfaces may show the ingredients of the single oral intake and the intended use. Suitable examples of such a unit package form include supplements and pharmaceutical formulations.

[0057]

20 The promoter of the present invention is continuously taken and thus can be expected to exert the effect more. Suitable examples of the planning of intake of the agent of the present invention include a daily intake of 200 ml or more, a daily intake of 400 ml or more, a daily intake of 600 ml or more,
25 a daily intake of 800 ml or more, a daily intake of 1000 ml or more, a daily intake of 1200 ml or more, a daily intake of 1600 ml or more, or a daily intake of 2000 ml or more, in the case of humans having a body weight 60 kg; and also a period of 1 weeks or more, a period of 2 weeks or more, a period of 3
30 weeks or more, a period of 4 weeks or more, a period of 6 weeks or more, a period of 8 weeks or more, a period of 12 weeks or more, or a period of 24 weeks or more, in the case of

humans having a body weight 60 kg. Further, continuous intake is preferably defined as once a week, twice a week, three times a week, four times a week, five times a week, six times a week, or seven times a week.

5 [0058]

According to another embodiment of the present invention, there is provided a ghrelin secretion promoting method comprising giving an effective amount of a composition comprising: a protein hydrolysate and a fermented milk protein,
10 as proteins; a medium-chain fatty acid, as a lipid; and a saccharide to a subject in need thereof. Also, according to a preferred embodiment of the present invention, the above composition comprises: a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid-containing
15 fat, a phospholipid and an oleic acid-containing fat, as lipids; and isomaltulose as a saccharide. According to a preferred embodiment of the present invention, the above composition further comprises, as a lipid, a polyvalent unsaturated fatty acid. According to another preferred embodiment of the present
20 invention, the above ghrelin secretion promoting method is used for eating enhancement, fat accumulation promotion, insulin secretion suppression, suppression of the function of brown fat tissues, enterokinesis promotion, gastric acid secretion enhancement, pancreatic exocrine secretion enhancement,
25 sympathetic nervous system suppression, vasodilatation, increase in force of heart contraction or protection of cardiac muscle cells. Further, according to another preferred embodiment of the present invention, the above ghrelin secretion promoting method is a method for eating
30 enhancement, fat accumulation promotion, insulin secretion suppression, suppression of the function of brown fat tissues, enterokinesis promotion, gastric acid secretion enhancement, pancreatic exocrine secretion enhancement, sympathetic nervous system suppression, vasodilatation, increase in force of
35 heart contraction or protection of cardiac muscle cells.

[0059]

According to another preferred embodiment of the present invention, the above ghrelin secretion promoting method is defined as a method for treating a subject.

- 5 According to still another embodiment, the above ghrelin secretion promoting method is defined as a non-therapeutic method except medical activities. Incidentally, the "treatment" of the present invention includes not only treatment of established pathological conditions-symptoms, but also
- 10 prevention of pathological conditions-symptoms which may be established in the future. Also, the "effective amount " can be determined in accordance with the planning of intake of the ghrelin secretion promoter.

[0060]

- 15 The composition (agent) used for ghrelin secretion promotion in the method of the present invention can preferably be orally taken. According to a preferred embodiment, the above composition can be taken with meals.

[0061]

- 20 According to one embodiment of the present invention, there is provided use of a composition comprising a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid, as a lipid; and a saccharide, in the production of a ghrelin secretion promoter. Further, according
- 25 to another embodiment, there is provided use of a composition comprising a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid, as a lipid; and a saccharide, for a ghrelin secretion promoter. According to still another embodiment, there is provided a composition
- 30 comprising a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid, as a lipid; and a saccharide, for ghrelin secretion promotion. Also, according to a preferred embodiment of the present invention, all of the

above compositions comprise a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid-containing fat, a phospholipid and an oleic acid-containing fat, as lipids; and isomaltulose as a saccharide. Further,
5 according to a more preferred embodiment of the present invention, any of the above compositions further comprises, as a lipid, a polyvalent unsaturated fatty acid.

[0062]

The subject is not especially limited, so long as the effect
10 of the present invention is not inhibited, and is preferably a mammal, more preferably a human.

EXAMPLES

[0063]

Hereinafter, the present invention will be described in
15 more detail by way of Examples, but the present invention is not limited thereby. Incidentally, the symbol "%" means % by weight in the following Examples, unless otherwise noted. Also, the units and measurement methods described herein are in
20 accordance with the regulations in the Japanese Industrial Standards (JIS).

[0064]

(Test Example 1)

Twenty four (24) 7-week-old male C57BL/6 mice (Japan SLC, Inc.) were divided into 3 groups each including 8 mice.
25 Specifically, these groups were: a group of mice to which a preliminarily prepared powder of the ghrelin secretion promoter according to the present invention was administered (ghrelin secretion promoter group); a group of mice to which a control nutrient composition powder was administered (control group);
30 and a group of mice to which a standard animal chow (CRF-1) powder was administered (CRF-1 group).

The nutritive formulations of the ghrelin secretion promoter according to the present invention and of the control nutrient composition are as indicated in Table 1. The amounts of raw materials for protein, saccharide and lipid to be incorporated are as indicated in Table 2. Incidentally, the content of an oleic acid contained in the ghrelin secretion promoter in the tables was 39% in the fatty acid formulation.

[0065]

[Table 1]

		Unit (per 100 ml)	Control nutrient composition	Ghrelin secretion promoter
General formulation	Protein	g	4	5
	Lipid	g	2.8	2.8
	Carbohydrate	g	15.5	14.5
	Saccharide	g	14.5	13.3
	Dietary fiber	g	1	1.2
	Ash	g	0.7	0.6
	Energy	kcal	100	100
Vitamin	Vitamin A	μgRE	60	60
	β Carotene	μg	-	180
	Vitamin D	μg	0.5	0.75
	Vitamin E	mgα-TE	3	5
	Vitamin K	μg	5	3.4
	Vitamin B1	mg	0.15	0.25
	Vitamin B2	mg	0.2	0.3
	Niacin	mgNE	2.4	4
	Vitamin B6	mg	0.3	0.3
	Folic acid	μg	50	50
	Vitamin B12	μg	0.6	0.6
	Biotin	μg	15	7.5
	Pantothenic acid	mg	0.6	1.2
	Vitamin C	mg	16	50
	Choline	mg	1.7	9.2
Mineral	Sodium	mg	110	70
	Calcium	mg	60	80
	Iron	mg	1	1
	Phosphorus	mg	60	70
	Magnesium	mg	20	20
	Potassium	mg	100	80
	Copper	mg	0.08	0.05

	Iodine	µg	15	9.7
	Manganese	mg	0.23	0.175
	Selenium	µg	3.5	5
	Zinc	mg	0.8	1
	Chromium	µg	3	2.96
	Molybdenum	µg	2.5	2.5
	Chlorine	mg	140	80
Energy Balance	Protein	%	16	20
	Lipid	%	25	25
	Saccharide	%	59	55

[0066]

[Table 2]

Nutritive formulation	Control nutrient composition		Ghrelin secretion promoter	
Ingredient	Raw material	g/100 ml	Raw material	g/100 ml
Protein	Sodium Caseinates	4	Whey protein hydrolysate	2
	Milk protein		Fermented milk protein	3
Lipid	Edible oil	2.8	Edible oil	1.91
			Milk phospholipid	0.09
			Medium-chain triglycerides	0.6
			Refined fish oil	0.2
Saccharide	Dextrin	14.5	Dextrin	7.2
	Sucrose		isomaltulose	6.2
	Dietary fiber	1	Dietary fiber	1.5

5 [0067]

All the respective groups were allowed to freely take a feed for two weeks, and thereafter subjected to blood sampling from the abdominal vena cava. Blood was sampled into a tube containing a protease inhibitor Pefabloc SC (Sigma) in an amount of 1/100 of the blood amount, and then admixed by slight tapping. This was centrifuged at 7000 rpm and 4°C for 2 minutes for separation of plasma. 1N HCl was added to the

resultant plasma in an amount of 1/10 of the plasma amount to prepare plasma for measuring the ghrelin concentration.

As the ghrelin concentration, the concentration of acyl ghrelin as active ghrelin was measured. The concentration of acyl ghrelin in plasma was measured by an ELISA kit (SCETI: Active Ghrelin ELISA kit). Blood plasma was diluted 5 times with an assay buffer for measurement, and the measured value was corrected by the dilution magnification to calculate the acyl ghrelin concentration.

10 [0068]

As a result, the acyl ghrelin concentration was 82.8 ± 37.7 (fmol/ml) for the ghrelin secretion promoter group, 46.9 ± 12.0 (fmol/ml) for the control group and 38.0 ± 18.9 (fmol/ml) for the CRF-1 group, respectively. In view of the above, the ghrelin secretion promoter group showed a significant increase in the concentration of activated ghrelin (acyl ghrelin) in the blood, as compared with the control group and CRF-1 group.

[0069]

Incidentally, the whey protein decomposition product in Table 1 was prepared in accordance with the above procedures (1) to (5). Also, indigestible dextrin was used as the dietary fibers.

[0070]

Table 3 indicates the formulation of all the fatty acids in the agent indicated in Table 1.

[0071]

[Table 3]

Fatty acid formulation	Content (%)
Medium-chain fatty acid	21
Palmitic acid	16

Stearic acid	3
Oleic acid	39
Linoleic acid	12
α -linolenic acid	4
EPC	1.2
DHA	0.8
Other fatty acids	3

[0072]

Table 4 indicates an example formulation of the milk phospholipid in Table 1.

5 [Table 4]

Phospholipid	Content (%)
Phosphatidylcholine	24.2
Phosphatidylethanolamine	20.4
Sphingomyelin	17.1

[0073]

Table 5 indicates the amounts of the oleic acid, medium-chain fatty acid and polyvalent fatty acid in the agent
10 indicated in Table 1.

[Table 5]

Ghrelin secretion promoter	
Fatty acid formulation	g/100 ml
Medium-chain fatty acid	0.53
Palmitic acid	0.40
Stearic acid	0.08

Oleic acid	0.98
Linoleic acid	0.30
α -linolenic acid	0.10
EPC	0.03
DHA	0.02
Other fatty acids	0.08

[0074]

(Test Example 2)

Forty (40) 9-week-old male C57BL/6 mice (Japan SLC, Inc.) were divided into 4 groups each including 10 mice. Specifically, a test was conducted on a group of mice to which the preliminarily prepared powder of the ghrelin secretion promoter according to the present invention, as described in Test Example 1, was administered (ghrelin secretion promoter group); a group of mice to which the control nutrient composition powder, as described in Test Example 1, was administered (control group); a group of mice to which a powder of a purified diet AIN93G was administered (AIN93G group); and a group of mice to which a powder of the purified diet AIN93G and a medium chain triglycerides added thereto was administered (AIN93G+MCT group). The amount per energy of the medium chain triglycerides to be incorporated in AIN93G+MCT was defined as identical with that in the ghrelin secretion promoter of the present invention. Also, the amounts of the vitamins and minerals in the ghrelin secretion promoter, AIN93G and AIN93G+MCT were defined as equivalent to each other. Also, the control nutrient composition and ghrelin secretion promoter used in this Test Example are identical with those indicated in Tables 1 and 2.

[0075]

The formulations of AIN93G and AIN93G+MCT were as indicated below (Tables 6 and 7).

[Table 6]

		Unit per 100 kcal	Ghrelin secretion promoter	AIN93G	AIN93G+ MCT
General formulation	Protein	g	5	5	5
	Lipid	g	2.8	1.8	1.8
	Carbohydrate	g	14.5	18.4	18.4
	Saccharide	g	13.3	17	17
	Dietary fiber	g	1.2	1.3	1.3
	Energy	kcal	100	100	100

[0076]

5 [Table 7]

Nutrient formulation	Ghrelin secretion promoter		AIN93G		AIN93G+MCT	
Ingredient	Raw material	g/100 kcal	Raw material	g/100 kcal	Raw material	g/100 kcal
Protein	Whey protein hydrolysate	2	Casein	5	Casein	5
	Fermented milk protein	3	L-cystine		L-cystine	
Lipid	Edible oil	1.91	Soybean oil	1.8	Soybean oil	1.2
	Milk phospholipid	0.09				
	Medium-chain triglycerides	0.6			Medium-chain triglycerides	0.6
	Refined fish oil	0.2				
Carbohydrate	Dextrin	7.2	Corn starch	17	Corn starch	17
	isomaltulose	6.2	Sucrose		Sucrose	
	Dietary fiber	1.2	Dietary	1.3	Dietary fiber	1.3

			fiber			
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[0077]

All the respective groups were allowed to freely take a feed for two weeks (fasted overnight), and thereafter subjected to blood sampling from the abdominal vena cava. Blood was sampled into a tube containing a protease inhibitor Pefabloc SC (Sigma) in an amount of 1/100 of the blood amount, and then admixed by slight tapping. This was centrifuged at 7000 rpm and 4°C for 2 minutes for separation of plasma. 1N HCl was added to the resultant plasma in an amount of 1/10 of the plasma amount to prepare plasma for measuring the ghrelin concentration.

As the ghrelin concentration, the concentration of acyl ghrelin as active ghrelin was measured. The concentration of acyl ghrelin in plasma was measured by an ELISA kit (SCETI: Active Ghrelin ELISA kit).

[0078]

As a result, the acyl ghrelin concentration was 274 ± 172 (fmol/ml) for the ghrelin secretion promoter group, 89 ± 22 (fmol/ml) for the control group, 76 ± 23 (fmol/ml) for the AIN93G group was and 110 ± 56 (fmol/ml) for the AIN93G+MCT group, respectively. Also, the active ghrelin /inactive ghrelin ratio was 0.75 ± 0.14 for the ghrelin secretion promoter group and 0.53 ± 0.16 for the control group, respectively.

Namely, the ghrelin secretion promoter group showed a significant increase in the concentration of active ghrelin (acyl ghrelin) in the blood, as compared with the control group, AIN93G group and AIN93G+MCT group.

[0079]

(Test Example 3)

Two colorectal cancer patients and one malignant lymphoma patient under chemotherapy were made to take the ghrelin secretion promoter. Specifically, the patients were continuously taken 600 mL/day for 3 days before chemotherapy and 200 mL/day for 4 days after chemotherapy in 3-4 courses. The blood active ghrelin concentration and inactive ghrelin concentration before and after intake of the ghrelin secretion promoter were measured to calculate the active ghrelin/inactive ghrelin ratio.

10 [0080]

As a result, the active ghrelin/inactive ghrelin ratio before and after intake of the ghrelin secretion promoter was increased from 0.137 to 0.206 for one colorectal cancer patient, and from 0.116 to 0.272 for another colorectal cancer patient. The malignant lymphoma patient showed an increase from 0.186 to 0.250.

[0081]

The daily average dietary intake (intake calorie) before and after intake of the ghrelin secretion promoter was increased from 1808 kcal to 2304 kcal for one colorectal cancer patient, and from 1242 kcal to 1624 kcal for the malignant lymphoma patient.

CLAIMS

[1] A ghrelin secretion promoter comprising a protein hydrolysate and a fermented milk protein, as proteins; a
5 medium-chain fatty acid, as a lipid; and a saccharide.

[2] The ghrelin secretion promoter according to claim 1, comprising a protein hydrolysate and a fermented milk protein, as proteins; a medium-chain fatty acid-containing fat, a
10 phospholipid and an oleic acid-containing fat, as lipids; and isomaltulose as a saccharide.

[3] The ghrelin secretion promoter according to claim 1 or 2, wherein the protein hydrolysate is a protein hydrolysate made
15 of a raw material selected from casein, a milk protein concentrate (MPC), a whey protein concentrate (WPC), a whey protein isolate (WPI), α -lactoalbumin, β -lactoglobulin and lactoferrin.

[4] The ghrelin secretion promoter according to any one of claims 1 to 3, wherein the protein hydrolysate is a whey protein hydrolysate.

[5] The ghrelin secretion promoter according to any one of
25 claims 1 to 4, wherein the amount of the protein hydrolysate to be incorporated ranges from 0.5 g to 3 g per 100 ml.

[6] The ghrelin secretion promoter according to any one of claims 1 to 5, wherein the fermented milk protein is derived
30 from a substance obtained by discharging whey from fermented milk.

[7] The ghrelin secretion promoter according to any one of claims 1 to 6, wherein the fermented milk protein is derived
35 from fermented milk obtained by fermenting skimmed milk with *Lactobacillus Bulgaricus*, *Streptococcus Thermophilus*, or a

combination thereof.

[8] The ghrelin secretion promoter according to any one of claims 1 to 7, wherein the fermented milk protein is derived
5 from fresh cheese.

[9] The ghrelin secretion promoter according to any one of claims 1 to 8, wherein the amount of the fermented milk protein to be incorporated ranges from 0.5 g to 6 g per 100 ml.
10

[10] The ghrelin secretion promoter according to any one of claims 1 to 9, wherein the protein hydrolysate is obtained by hydrolyzing a whey protein isolate (WPI) with an endo-type protease derived from *Bacillus licheniformis* and hydrolyzing
15 the resultant hydrolysate with swine pancreas-derived trypsin.

[11] The ghrelin secretion promoter according to any one of claims 1 to 10, wherein the molecular cutoff of the protein hydrolysate is 10,000 or less.
20

[12] The ghrelin secretion promoter according to any one of claims 1 to 11, wherein the amount of the saccharide to be incorporated ranges from 1 g to 15 g per 100 ml.

25 [13] The ghrelin secretion promoter according to any one of claims 1 to 12, wherein the amount of the oleic acid to be incorporated in the lipid is 25% by weight or more of the whole fatty acid.

30 [14] The ghrelin secretion promoter according to any one of claims 1 to 13, wherein the amount of the medium-chain fatty acid to be incorporated ranges from 0.01 g to 4 g per 100 ml.

[15] The ghrelin secretion promoter according to any one of
35 claims 1 to 14, wherein the heat quantity thereof ranges from 50 kcal to 150 kcal per 100 ml.

[16] The ghrelin secretion promoter according to any one of claims 8 to 15, wherein the fresh cheese is quark.

- 5 [17] The ghrelin secretion promoter according to any one of claims 2 to 16, wherein the phospholipid is milk phospholipid.

[18] The ghrelin secretion promoter according to any one of claims 2 to 17, wherein the amount of the phospholipid to be
10 incorporated ranges from 0.01 g to 0.5 g per 100 ml.

[19] The ghrelin secretion promoter according to any one of claims 1 to 18, wherein the medium-chain fatty acid is a medium-chain fatty acid having 8 to 14 carbon atoms.

15

[20] The ghrelin secretion promoter according to any one of claims 1 to 19 for eating enhancement, fat accumulation promotion, insulin secretion suppression, suppression of the function of brown fat tissues, enterokinesis promotion, gastric
20 acid secretion enhancement, pancreatic exocrine secretion enhancement, sympathetic nervous system suppression, vasodilatation, increase in force of heart contraction or protection of cardiac muscle cells.