AGENT FOR REGULATING MELATONIN SECRETION, AND METHOD FOR REGULATING MELATONIN SECRETION

Technical Field

[0001]

The present invention relates to an agent for regulating melatonin secretion containing ornithine or a salt thereof, a method for regulating melatonin secretion, ornithine or a salt thereof for use in regulation of melatonin secretion, and use of ornithine or a salt thereof for the manufacture of an agent for regulating melatonin secretion.

Background Art

[0002]

In mostly the United States, L-ornithine has been used as a food material for enhancing muscle synthesis or for increasing basal metabolism to prevent obesity. In Europe, L-ornithine is used in the form of L-ornithine-L-aspartate as a medicament for ameliorating liver damage.

[0003]

Ornithine is also known to have other effects, including improvement of waking performance (Patent Document 1), improvement of oversensitiveness to cold (Patent Document 2), and promotion of eating activity and/or digestive activity (Patent Document 3). However, it is not known that ingestion of ornithine or a salt thereof advances the timing of melatonin secretion increase.

[0004]

Melatonin is a hormone secreted from the pineal gland of the brain. This hormone is suppressed by daylight, and the secretion increases as darkness occurs. Melatonin secretion regulates the circadian rhythm through receptors found in the suprachiasmatic nucleus, and promotes natural sleepiness through regulation of the hypothermic effect or nerve and endocrine functions.

[0005]

Night-time light suppresses melatonin secretion, and disrupts the circadian rhythm, or causes sleep disorder due to a disrupted circadian rhythm. Melatonin secretion decreases with age, and is involved in sleep disorders in older adults.

[0006]

It is therefore expected that regulation of in vivo melatonin concentration or melatonin receptor activity, either endogenously or exogenously, would improve circadian rhythm sleep disorders, for example, such as jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, and non-24-hour sleep-wake disorder (Non-Patent Documents 1 and 2, and Patent Document 4), and age-related sleep disorders, for example, such as wake after sleep onset, and insomnia (Non-Patent Document 3).

[0007]

In fact, melatonin preparations or melatonin receptor agonist preparations have been clinically used for these purposes. Melatonin is also commercially available as a dietary supplement in the United States.

Related Art

Patent Document

[0008]

Patent Document 1: JP-A-2006-342148

Patent Document 2: JP-A-2007-119348

Patent Document 3: WO2013/129642

Patent Document 4: JP-A-2003-335691

Non-Patent Document

[0009]

Non-Patent Document 1: Sleep Medicine, 2004, Vol. 5, p. 523-532

Non-Patent Document 2: Sleep Medicine Reviews, 2007, Vol. 11, p. 485-496

Non-Patent Document 3: Experimental Gerontology, 2005, Vol. 40, p. 911-925

Disclosure of Invention

Problems to Be Solved by the Invention

[0010]

However, exogenously ingested melatonin preparations have possible side effects, and the safety has not been established. There accordingly is a need for a method that regulates in vivo melatonin secretion.

[0011]

It is accordingly an object of the present invention to provide a method for regulating in vivo melatonin secretion, specifically a melatonin secretion regulator capable of advancing the timing of melatonin secretion increase.

Means for Solving the Problems

[0012]

The present inventors found that the foregoing problems can be solved with an agent containing ornithine or a salt thereof as an active ingredient, and completed the present invention on the basis of this finding. Specifically, the present invention is concerned with the following (1) to (16).

(1) An agent for regulating melatonin secretion comprising ornithine or a salt thereof as an active ingredient.

(2) The agent for regulating melatonin secretion described in (1), wherein the agent for regulating melatonin secretion is a therapeutic agent for circadian rhythm sleep disorder and/or age-related sleep disorder.

(3) The agent for regulating melatonin secretion described in (2), wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

(4) The agent for regulating melatonin secretion described in (2), wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

(5) A method for regulating melatonin secretion comprising a process for administering an effective amount of ornithine or a salt thereof to a subject in need thereof.

(6) The method for regulating melatonin secretion described in (5), wherein the method is a treatment method of circadian rhythm sleep disorder, and/or age-related sleep disorder.

(7) The method for regulating melatonin secretion described in (6), wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

(8) The method for regulating melatonin secretion described in (6), wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

(9) Ornithine or a salt thereof for use in regulation of melatonin secretion.

(10) The ornithine or a salt thereof described in (9), wherein the regulation of melatonin secretion is a treatment of circadian rhythm sleep disorder, and/or age-related sleep disorder.

(11) The ornithine or a salt thereof described in (10), wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

(12) The ornithine or a salt thereof described in (10), wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

(13) Use of ornithine or a salt thereof for the manufacture of an agent for regulating melatonin secretion.

(14) The use described in (13), wherein the agent for regulating melatonin secretion is a therapeutic agent for circadian rhythm sleep disorder, and/or age-related sleep disorder.

(15) The use described in (14), wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

(16) The use described in (14), wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

Effects of the Invention

[0013]

The present invention can provide an agent for regulating melatonin secretion containing ornithine or a salt thereof. With the L-ornithine or a salt thereof contained as an active ingredient, the agent for regulating melatonin secretion or the method for regulating melatonin of the present invention can advance the timing of melatonin secretion increase during night time.

Brief Description of the Drawings

[0014]

FIG. 1 is a graph representing time (hours) after the start of a light period on the horizontal axis, and plasma melatonin concentration (pg/mL) on the vertical axis. Solid circle (•) represents a distilled water administered group (control group), blank square ( ) represents an L-ornithine hydrochloride1,000 mg/kg administered group, and blank triangle (Δ) represents an L-ornithine hydrochloride 3,000 mg/kg administered group. The difference from the distilled water administered group at hour 12 was considered significant for $p < 0.001$ (***) in the distilled water administered group, $p < 0.05$ (#) or $p < 0.01$ (##) in the L-ornithine hydrochloride 1,000 mg/kg administered group, and $p < 0.05$

(+) in the L-ornithine hydrochloride 3,000 mg/kg administered group in a Dunnett's multiple comparison test.

Embodiments for Carrying Out the Invention

[0015]

The present invention includes an agent for regulating melatonin secretion containing ornithine or a salt thereof as an active ingredient.

[0016]

The ornithine used in the present invention may be L-ornithine or D-ornithine. However, preferred for use in the present invention is L-ornithine. L-ornithine is preferred because ornithine is present in L-form in the body.

[0017]

Ornithine may be obtained, for example, through chemical synthesis or fermentation. It is also possible to use commercially available ornithine products.

[0018]

Chemical synthesis of L-ornithine may be performed by using, for example, the method described in Coll. Czechoslov. Chem. Commun., 24, 1993 (1959). The methods described in, for example, JP-A-53-24096 and JP-A-61-119194 may be used for production of L-ornithine through fermentation. L-ornithine and D-ornithine may be purchased from Sigma-Aldrich or other manufacturers.

[0019]

The salt of ornithine may be, for example, an acid addition salt, a metal salt, an ammonium salt, an organic amine addition salt, or an amino acid addition salt.

[0020]

Examples of the acid addition salt include inorganic acid salts such as hydrochlorides, sulfates, nitrates, and phosphates, and organic acid salts such as acetates, maleates, fumarates, citrates, malates, lactates, α-ketoglutarate, gluconates, and caprylates.

[0021]

Examples of the metal salt include alkali metal salts such as sodium salts, and potassium salts; alkali-earth metal salts such as magnesium salts, and calcium salts; aluminum salts; and zinc salts.

[0022]

Examples of the ammonium salt include salts of ammonium, and tetramethylammonium.

[0023]

Examples of the organic amine addition salt include salts of morpholine, and piperidine.

[0024]

Examples of the amino acid addition salt include salts of glycine, phenylalanine, lysine, aspartic acid, and glutamic acid.

[0025]

Preferred for use as salts of ornithine are hydrochlorides, citrates, malates, α-ketoglutarate, and aspartates. However, the ornithine salts may be used with other salts, or may be used in a combination of two or more, as appropriate.

[0026]

As used herein, "agent for regulating melatonin secretion" is an agent that, when ingested, advances the timing of daily melatonin secretion increase as compared to when it is not ingested.

[0027]

The agent for regulating melatonin secretion of the present invention may appropriately contain additives as may be suited for the intended applications, in addition to ornithine or a salt thereof.

[0028]

The agent for regulating melatonin secretion of the present invention may be directly administered in the form of ornithine or a salt thereof. It is, however, typically preferable to provide the agent for regulating melatonin secretion in the form of various preparations.

[0029]

Such preparations contain ornithine or a salt thereof as an active ingredient, and may contain any other active ingredient. The preparations are produced by mixing the active ingredient with one or more pharmaceutically acceptable carriers, using any method well known in the field of pharmacology.

[0030]

Preferably, the preparation is administered in a route that is believed to be most effective for the regulation of melatonin secretion. The preparation may be administered orally, or parenterally through, for example, intravenous, intraperitoneal, or subcutaneous administration. The preferred route is oral administration.

[0031]

The dosage form may be oral or parenteral. Examples of the oral dosage form include tablets, powders, granules, pills, suspensions, emulsions, infusions or decoctions, capsule formulations, syrups, liquids, elixirs, extracts, tinctures, and fluid extracts. The parenteral dosage form may be, for example, an injection, a drop, a cream, or a suppository. Preferred is an oral dosage form.

[0032]

Liquid preparations, for example, such as syrups, suited for oral administration may be prepared with various additives, including, for example, water, sugars (e.g., sucrose, sorbitol, and fructose), glycols (e,g, polyethylene glycol, and propylene glycol), oils (e.g., sesame oil, olive oil, and soybean oil), antiseptics (e.g., p-hydroxybenzoic acid esters), para-oxybenzoic acid derivatives (e.g., methyl para-oxybenzoate), preservatives (e.g., sodium benzoate), and flavors (e.g., a strawberry flavor, and peppermint).

[0033]

For example, tablets, powders, and granules suited for oral administration may be prepared with various additives, including, for example, sugars (e.g., lactose, sucrose, glucose, sucrose, mannitol, and sorbitol), starch (e.g, potato, wheat, and corn), inorganic materials (e.g, calcium carbonate, calcium sulfate, sodium bicarbonate, and sodium chloride), excipients such as plant powders (e.g., microcrystalline cellulose, powdered glycyrrhiza, and powdered gentian), disintegrants (e.g., starch, agar, a gelatin powder, microcrystalline cellulose, carmellose sodium, carmellose calcium, calcium carbonate, sodium bicarbonate, and sodium alginate), lubricants (e.g., magnesium stearate, talc, hydrogenated vegetable oil, macrogol, and silicone oil), binders (e.g., polyvinyl alcohol, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, carmellose, gelatin, and a starch paste), surfactants (e.g., fatty acid esters), and plasticizers (e.g., glycerine).

[0034]

Preparations suited for oral administration may contain various additives, including, for example, common food and beverage additives, such as sweeteners, colors, preservatives, thickening agents, antioxidants, color fixatives, bleaching agents, anti-fungal agents, gum bases, bittering agents, enzymes, brightening agents, acidulants, flavor enhancers, emulsifiers, toughening agents, processing aids, flavoring ingredients, and spice extracts.

[0035]

Preparations suited for oral administration may be used either directly, or as food or drinks, for example, food with health claims, functional food products, dietary

supplement products, and food for specified health uses, intended for regulation of melatonin secretion. Such food products may be in the form of, for example, a powdered food, a food sheet, a bottled food, a canned food, a retort food, a capsule food, a tablet food, a liquid food, or a drinkable preparation.

[0036]

Dosage forms, for example, such as injections, suited for parenteral administration preferably contain a sterile aqueous agent containing ornithine or a salt thereof, isotonic to the blood of a recipient. For example, in the case of injections, a solution for injections is prepared with a carrier, which may be, for example, a salt solution, a glucose solution, or a mixture of a salt solution and a glucose solution.

[0037]

One or more additional components selected from various additives, including the antiseptics, preservatives, flavors, excipients, disintegrants, lubricants, binders, surfactants, and plasticizers exemplified above for the oral dosage forms also may be added to parenteral dosage forms such as above.

[0038]

The concentration of the ornithine or a salt thereof in the agent for regulating melatonin secretion of the present invention is appropriately selected according to, for example, the type of preparation, or the effects expected from the administration of the preparation. Typically, the ornithine or a salt thereof is preferably 0.1 to 100 weight%, more preferably 0.5 to 80 weight%, particularly preferably1 to 70 weight%.

[0039]

When the agent for regulating melatonin secretion of the present invention is administered to humans, the dose and the frequency of administration depend on factors such as the dosage form, and the age or body weight of the subject of administration. Typically, the agent for regulating melatonin secretion is administered once to several times a day in preferably 50 mg to 30 g, more preferably 100 mg to 10 g, particularly preferably 200 mg to 3g per day for adults in terms of an amount of ornithine or a salt thereof.

[0040]

The human to be administered with the agent for regulating melatonin secretion of the present invention may be, for example, an individual who is aware of abnormal melatonin secretion such as delayed melatonin secretion, an individual who is not aware of abnormal melatonin secretion, but having a lifestyle that may lead to abnormal melatonin

secretion, or an individual of an age with a reasonably anticipated risk of abnormal melatonin secretion.

[0041]

The subject of administration is preferably a human individual who is aware of abnormal melatonin secretion, specifically an individual with circadian rhythm sleep disorder, and/or age-related sleep disorder. Examples of such human individuals with circadian rhythm sleep disorder include individuals with symptoms of, for example, jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

[0042]

Examples of human individuals with age-related sleep disorder include individuals with, for example, wake after sleep onset, or insomnia. Human individuals with age-related sleep disorder may be individuals with the age of preferably 51 or more, more preferably 61 or more, further preferably 71 or more.

[0043]

The timing of administration of the agent for regulating melatonin secretion of the present invention is not particularly limited, and may be any time between morning and afternoon in humans. The duration of administration is not particularly limited. Typically, 1 day to 1 year is preferable, and 1 week to 3 months is more preferable.

[0044]

The dose and the frequency of administration of the agent for regulating melatonin secretion of the present invention in non-human animals depend on factors such as the dosage form, and the age and the type of animal. Typically, the agent for regulating melatonin secretion is administered once to several times a day in preferably 1 to 5,000 mg, more preferably 2 to 4,000 mg, particularly preferably 4 to 3,000 mg per kg body weight per day in terms of an amount of ornithine or a salt thereof.

[0045]

The duration of administration is not particularly limited. Typically, 1 day to 1 year is preferred, and 1 week to 3 months is more preferred.

[0046]

Circadian rhythm sleep disorder, and/or age-related sleep disorder can be prevented or ameliorated by administering or feeding the agent for regulating melatonin secretion of the present invention. The circadian rhythm sleep disorder may be, for example, jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or

non-24-hour sleep-wake disorder. The age-related sleep disorder may be, for example, wake after sleep onset, or insomnia.

[0047]

The present invention also includes a method for regulating melatonin secretion that includes administering an effective amount of ornithine or a salt thereof to a subject in need thereof. As used herein, "method for regulating melatonin secretion" means a method that advances the timing of daily melatonin secretion increase.

[0048]

The dose and the frequency of administration of an effective amount of ornithine or a salt thereof in humans depend on factors such as the dosage form, and the age and body weight of the subject of administration. Typically, an effective amount of ornithine or a salt thereof for subjects in need thereof is preferably 50 mg to 30 g, more preferably 100 mg to 10 g, particularly preferably 200 mg to 3 g per day for adults in terms of an amount of ornithine or a salt thereof, and the ornithine or a salt thereof is administered once to several times a day in such an effective amount.

[0049]

The human to be administered with ornithine or a salt thereof may be, for example, an individual who is aware of abnormal melatonin secretion such as delayed melatonin secretion, an individual who is not aware of abnormal melatonin secretion, but having a lifestyle that may lead to abnormal melatonin secretion, or an individual of an age with a reasonably anticipated risk of abnormal melatonin secretion.

[0050]

The subject of administration is preferably a human individual who is aware of abnormal melatonin secretion, specifically an individual with circadian rhythm sleep disorder, and/or age-related sleep disorder. Examples of such human individuals with circadian rhythm sleep disorder include individuals with symptoms of, for example, jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

[0051]

Examples of human individuals with age-related sleep disorder include individuals with, for example, wake after sleep onset, or insomnia. Human individuals with age-related sleep disorder may be individuals with the age of preferably 51 or more, more preferably 61 or more, further preferably 71 or more.

[0052]

The timing of administration of ornithine or a salt thereof is not particularly limited, and may be any time between morning and afternoon in humans. The duration of administration is not particularly limited. Typically, 1 day to 1 year is preferable, and 1 week to 3 months is more preferable.

[0053]

The dose and the frequency of administration of an effective amount of ornithine or a salt thereof in non-human animals depend on factors such as the dosage form, and the age and the type of animal. Typically, an effective amount of ornithine or a salt thereof for non-human animals is preferably 1 to 5,000 mg, more preferably 2 to 4,000 mg, particularly preferably 4 to 3,000 mg per kg body weight per day in terms of an amount of ornithine or a salt thereof, and the ornithine or a salt thereof is administered once to several times a day in such an effective amount.

[0054]

The duration of administration is not particularly limited. Typically, 1 day to 1 year is preferred, and 1 week to 3 months is more preferred.

[0055]

Circadian rhythm sleep disorder, and/or age-related sleep disorder can be prevented or ameliorated by administering or feeding an effective amount of ornithine or a salt thereof. The circadian rhythm sleep disorder may be, for example, jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder. The age-related sleep disorder may be, for example, wake after sleep onset, or insomnia.

[0056]

The method for regulating melatonin secretion of the present invention may prepare melatonin secretion by administering an effective amount of ornithine or a salt thereof to a subject as the "agent for regulating melatonin secretion."

[0057]

The present invention also includes use of ornithine or a salt thereof for the manufacture of the agent for regulating melatonin secretion.

[0058]

When producing the agent for regulating melatonin secretion with ornithine or a salt thereof, the agent for regulating melatonin secretion contains ornithine or a salt thereof as an active ingredient, and may additionally contain any other active ingredient, such as above. When produced as a preparation, the active ingredients are mixed with one or

more pharmaceutically acceptable carriers, and prepared into the product using any method well known in the field of pharmacology.

[0059]

While the present invention has been described in detail and with reference to a certain embodiment of the invention, it will be apparent to a skilled person that various changes and modifications may be made thereto without departing from the spirit and scope of the invention. This patent application is based on Japanese patent application No. 2014-072675 filed March 31, 2014, the entire contents of which are hereby incorporated by reference.

Examples

[0060]

Examples and Production Examples are described below. However, the following Examples and Production Examples are not intended to limit the present invention.

[0061]

[Example 1]

CBA/N mice (male, 7 weeks of age, average body weight 20 to 30 g) were used for testing. The animals were placed under the lighting conditions with a light-dark cycle consisting of 12 hours of a light period and 12 hours of a dark period. The mice were maintained in a cage in groups of four with free access to water and food at a room temperature of 25 ± 1°C. A solution or distilled water for administration to each group was prepared according to the following procedures 1) to 3).

[0062]

1) Solution for 1,000mg/kg administered group

L-ornithine hydrochloride of a weight to be dosed in 1,000 mg/kg body weight was dissolved in 10 mL of distilled water per kg of the subject mouse to produce a solution for 1,000 mg/kg administered group.

[0063]

2) Solution for 3,000 mg/kg administered group

L-ornithine hydrochloride of a weight to be dosed in 3,000 mg/kg body weight was dissolved in 10 mL of distilled water per kg of the subject mouse to produce a solution for 3,000 mg/kg administered group.

[0064]

3) Distilled water for control group

Ten milliliters of distilled water per kg of the subject mouse was collected for a control group. After 22 hours from the start of a light period, the solutions or distilled water prepared in 1) to 3) were each forcibly administered to the group through the mouth with an oral sonde. Because the animals were in the dark period at the time of administration, the solutions or distilled water were administered under dark red light of 1 lux or less. The same oral administration procedure was repeated daily over the course of 7 days. On the day after the oral administration in day 7, the blood collected at hour 12, 14, 16, 18, 20, and 22 after the start of a light period (n = 3 to 4 for each collection in each group) was centrifuged at 3,000 rpm for 10 min while being cooled at 4°C, and the plasma was collected. The plasma melatonin concentration was then measured by radioimmunoassay using tritium-labeled melatonin.

[0065]

FIG. 1 shows a graph representing plasma melatonin concentration. The results are given as mean values ± standard error. For statistical procedures, Dunnett's multiple comparison test was used, and the results were presented as significant differences from the base level of the control group taken at hour 12 after the start of a light period. As shown in FIG. 1, the melatonin concentration showed a significant increase after hour 20 from the start of a light period in control mice administered with distilled water (***: $p < 0.001$).

[0066]

In mice administered with L-ornithine (1,000 or 3,000 mg/kg body weight), the melatonin concentration started to increase after hour 16 from the start of a light period, and had significant values after hour 18 (+ and #: $p < 0.05$, ##: $p < 0.01$).

[0067]

These results showed that administration of L-ornithine advances the timing of night-time melatonin secretion.

[0068]

[Production Example 1] Production of Ornithine-Containing Tablet

10.0 g of Ornithine hydrochloride (trade name: L-ornithine hydrochloride, manufactured by Kyowa Hakko Bio, Co., Ltd.), 90.0 g of lactose, 2.0 g of dry corn starch, 1.8 g of talc, and 0.2 g of magnesium stearate were uniformly mixed, and the mixture was punched with a single-press tableting machine to obtain a tablet measuring 5 mm in diameter, and 15 mg in weight.

[0069]

[Production Example 2] Production of Ornithine-Containing Granule

The tablet obtained in Production Example 1 was pulverized, granulated, and sieved to obtain 20-50 mesh granules.

[0070]

[Production Example 3] Production of Ornithine-Containing Drinkable Preparation

5.0 g of L-Ornithine hydrochloride, 1.0 g of sodium benzoate, 10.0 g of fructose, a flavoring ingredient (an appropriate amount), a dye (an appropriate amount), and purified water (an appropriate amount) were uniformly mixed, stirred, and dissolved. Purified water was added to the mixture to make the total amount 1,000 mL, and an ornithine-containing drinkable preparation was produced. The appropriate amounts of flavoring ingredient and dye are amounts commonly used for the production of drinks, and the appropriate amount of purified water is an amount needed to make the total amount 1,000 mL with the other components.

[0071]

[Production Example 4] Production of Ornithine-Containing Tablet

136.2 k g of Ornithine hydrochloride (trade name: L-ornithine hydrochloride, manufactured by Kyowa Hakko Bio, Co., Ltd.), 36.0 kg of microcrystalline cellulose (trade name: Avicel FD101, manufactured by Asahi Kasei Chemicals Corporation), 6.6 kg of sucrose fatty acid ester (trade name: DK Ester F-20W, manufactured by Dai-Ichi Kogyo Seiyaku Co., Ltd.), 1.2 kg of calcium phosphate (trade name: tricalcium phosphate, manufactured by Taihei Chemical Industrial Co., Ltd.), and 20.0 kg of β-cyclodextrin (trade name: Celdex B-100, manufactured by Nihon Shokuhin Kako Co., Ltd.) were mixed with one another using a conical blender (CB-1200 blender, manufactured by Nikkan). The mixture was compression molded under the pressure of 10 kN with a rotary compression molding machine (VIRGO524SS1AY, manufactured by Kikusui Seisakusho Ltd.) to produce a tablet measuring 8 mm in diameter, and 250 mg in weight.

[0072]

[Production Example 5] Production of Ornithine-Containing Enteric Capsule

A mixture obtained after mixing and agitating 20 kg of the mixture prepared in Production Example 4 and 0.2 kg of silicon dioxide was fed to a capsule charger, and charged into 20,000 gelatin #2 hard capsules to obtain hard capsules. The surface of each hard capsule was coated with a zein solution using a Hi-Coater, Model HCT-48

(manufactured by Freund) to obtain 20,000 enteric capsules containing ornithine hydrochloride.

[0073]

[Production Example 6] Production of Ornithine-Containing Enteric Tablet

The surface of the tablets prepared in Production Example 4 were coated with a shellac solution with a Hi-Coater, Model HCT-48 (manufactured by Freund) to produce enteric tablets.

[0074]

[Production Example 7] Production of Ornithine-Containing Drinkable Preparation

1.28 kg of Ornithine hydrochloride (trade name: L-ornithine hydrochloride, manufactured by Kyowa Hakko Bio, Co., Ltd.), 3 kg of erythritol (manufactured by Nikken Chemical Laboratory), 0.05 kg of citric acid (manufactured by Kyowa Hi Foods), 3 kg of artificial sweetener, and 0.06 kg of a flavoring ingredient were stirred and dissolved in 50 L of water at a liquid temperature of 70°C. After adjusting the pH to 3.3 with citric acid, and solution was sterilized by plate sterilization, and charged into a bottle. The content was then pasteurized to obtain a drinkable preparation.

Claims

[Claim 1]

An agent for regulating melatonin secretion comprising ornithine or a salt thereof as an active ingredient.

[Claim 2]

The agent for regulating melatonin secretion according to claim 1, wherein the agent is a therapeutic agent for circadian rhythm sleep disorder and/or age-related sleep disorder.

[Claim 3]

The agent for regulating melatonin secretion according to claim 2, wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

[Claim 4]

The agent for regulating melatonin secretion according to claim 2, wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

[Claim 5]

A method for regulating melatonin secretion comprising a process for administering an effective amount of ornithine or a salt thereof to a subject in need thereof.

[Claim 6]

The method for regulating melatonin secretion according to claim 5, wherein the method is a treatment method of circadian rhythm sleep disorder, and/or age-related sleep disorder.

[Claim 7]

The method for regulating melatonin secretion according to claim 6, wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

[Claim 8]

The method for regulating melatonin secretion according to claim 6, wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

[Claim 9]

Ornithine or a salt thereof for use in regulation of melatonin secretion.

[Claim 10]

The ornithine or a salt thereof according to claim 9, wherein the regulation of melatonin secretion is a treatment of circadian rhythm sleep disorder, and/or age-related sleep disorder.

[Claim 11]

The ornithine or a salt thereof according to claim 10, wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

[Claim 12]

The ornithine or a salt thereof according to claim 10, wherein the age-related sleep disorder is wake after sleep onset, or insomnia.

[Claim 13]

Use of ornithine or a salt thereof for the manufacture of an agent for regulating melatonin secretion.

[Claim 14]

The use according to claim 13, wherein the agent for regulating melatonin secretion is a therapeutic agent for circadian rhythm sleep disorder, and/or age-related sleep disorder.

[Claim 15]

The use according to claim 14, wherein the circadian rhythm sleep disorder is jet lag syndrome, shift work sleep disorder, delayed sleep-phase syndrome, or non-24-hour sleep-wake disorder.

[Claim 16]

The use according to claim 14, wherein the age-related sleep disorder is wake after sleep onset, or insomnia.