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(57) **Abrégé/Abstract:**

The invention refers to the use O-(3-piperidino-2-hydroxy-1- propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the prevention of abnormal body weight gain or reduction of overweight or obesity.



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(54) Title: REDUCTION OF OVERWEIGHT OR OBESITY

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Reduction of overweight or obesity

Field of the invention

The invention refers to pharmaceutical composition suitable for the prevention of abnormal body weight gain or reduction of overweight or obesity.

Background of the invention

Overweight and obesity represent the most prevalent nutritional problem in the developed countries. According to the estimations of World Health Organization, more than 300 million adults are obese worldwide. In general, energy intake exceeding the energy expenditures for a longer time results in abnormal body weight gain leading, at first, to overweight, later, obesity. In case of adults, overweight is characterized by a body mass index of 25-30 kg/m², while a body mass index of above 30 kg/m² indicates obesity.

Food intake and energy expenditure are normally matched over time. The biological system that controls energy homeostasis evolved, principally, to protect against weight loss during times of limited nutrient availability rather than weight gain during periods of food excess. Inherent biological defense against weight gain such as that conveyed by an elevated plasma level remained relatively undeveloped. [Leibel R.L.: The role of leptin in the control of body weight, *Nutr. Rev.*, 60, S15-S19, discussion: S68-S87; Flier J.S., Clinical review 94: What's in a name? In search of leptin's physiologic role. *J. Clin. Endocrinol. Metab.*, 83, 1407-1413, (1998); Berthoud

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H.R.: Mind versus metabolism in the control of food intake and energy balance, *Physiol. Behav.*, 81, 781-793 (2004).] Therefore, once adaptive gene variants are implicated in weight gain when they are expressed in individuals living in an obesogenic environment e.g. one that is characterized by ready availability of highly palatable, energy-rich foods and by minimal demand for physical activity. In the same way, insufficient or defective adiposity feedback signaling by hormones such as leptin can contribute to common forms of obesity. Thus, weight gain under certain nutrient load that is compensated in normal individuals can be referred to as pathological or abnormal body weight gain.

Overweight and obesity themselves are associated with hypertension and abnormal metabolic changes such as insulin resistance and dyslipidemia which are risk factors for diabetes. Obesity (particularly abdominal obesity), insulin resistance and dyslipidemia are major features of „pre-diabetes” (metabolic syndrome) that leads to type 2 diabetes mellitus. Diabetes is accompanied by increased mortality due to a greater risk of cardiovascular disease. Thus, it can be stated that obesity predisposes to diseases of high risk such as type 2 diabetes mellitus, cardiovascular diseases, osteoarthritis, formation of gall stones and various malignant diseases.

The aim of the invention is to provide a pharmaceutical composition suitable for the prevention of abnormal body weight gain or reduction of overweight or obesity.

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O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime) (abbreviated as BGP-15) was patented in 1976 as a new compound useful in the treatment of diabetic angiopathy, a complication of diabetes resulting in the damage of blood vessels. The basic patent is, among others, US-P No. 4,187,220.

US-P No. 6,306,878 refers to a method for the protection of the mitochondrial genome and/or mitochondrion from damage leading to myopathies and neurodegenerative diseases which comprises administering an effective non-toxic dose to a patient susceptible to such damage of an amidoximic acid derivative including BGP-15. A preferred myopathy is cardiomyopathy. Neurodegenerative diseases include Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

US-P No. 6,458,371 refers to a composition comprising 0.1-30 % of a hydroximic acid derivative including BGP-15 as the active ingredient and a carrier that is in the form of a cream, lotion, foam or spray. The composition is suitable for reducing the incidence of photodamage by radiation with UV-B.

US-P No. 6,884,424 refers to a method for preventing actinic keratosis by applying a hydroximic acid derivative including BGP-15 to the affected skin surface.

US-P No. 6,451,851 refers to a method of treating a patient suffering from a viral infection comprising administering to the patient a pharmaceutically effective amount of a known

antivirally active agent together with a hydroximic acid derivative including BGP-15.

US-P No. 6,440,998 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising cisplatin or carboplatin and a hydroximic acid derivative including BGP-15. US-P No. 6,656,955 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising paclitaxel or docetaxel and a hydroximic acid derivative including BGP-15. US-P No. 6,720,337 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising oxaliplatin and a hydroximic acid derivative including BGP-15. US-P No. 6,838,469 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising pyrimidine derivatives and BGP-15.

PCT Patent Application published under No. WO 00/07580 disclosed experimental data for the antidiabetic effect of BGP-15 in the treatment of type 1 diabetes mellitus. It is to be noted that type 1 diabetes mellitus is an autoimmune disease occurring at young age, while type 2 diabetes mellitus is a metabolic disease occurring at higher age.

PCT Application published under No. WO 03/007951 refers to a pharmaceutical combination of hydroximic acid derivatives including BGP-15 and an antidiabetic or anti-hyperlipidemic active agent for the prevention or treatment of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above,

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namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium and/or female endocrinic disorders based on androgenic preponderance. In the description, laboratory data indicate that BGP-15 enhances, synergistically, the effect of the known antidiabetic agent metformin and troglitazone, respectively. The laboratory data also show that BGP-15 in itself enhances the insulin sensitivity (thus, reduces the insulin resistance) in both normal and hyper-cholesterolemic animals relative to the control.

PCT Application published under No. WO 2005/122678 refers to the use of BGP-15 in a pharmaceutical composition having prokinetic effect (i.e. induces activity in the stomach and intestines). Prokinetic effect includes possible treatment of reflux esophagitis, gastroparesis, influencing bile flow from the gall bladder etc.

PCT Application published under No. WO 2005/123049 refers to the use of BGP-15 for mitochondrial genesis i.e. to increase the number of mitochondria in the cells resulting in a roborating effect.

PCT Application published under No. WO 2006/079910 refers to the use of BGP-15 for the treatment of lesions in the oral cavity, especially periodontal disease.

Summary of the invention

It has been found that O-(3-piperidino-2-hydroxypropyl)-nicotinic amidoxime or a pharmaceutically suitable acid addition salt thereof can be used for the prevention or reduction of overweight or obesity.

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Thus, the invention provides the use of O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the preparation of a pharmaceutical composition suitable for the prevention of abnormal body weight gain or reduction of overweight or obesity.

Description of preferred embodiments

BGP-15 can be prepared by the process described in e.g. US-P No. 4,187,220.

A pharmaceutically suitable acid addition salt is a salt formed with an inorganic acid such as hydrochloric acid, sulfuric acid etc. or with an organic acid such as acetic acid, lactic acid, tartaric acid etc. A preferred acid addition salt of O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime is the dihydrochloride thereof.

According to the invention, a non-toxic dose of BGP-15 or a pharmaceutically suitable acid addition salt thereof is administered in the form of a pharmaceutical composition. This non-toxic dose of BGP-15 prevents, effectively, the abnormal body weight gain or reduces overweight or obesity. In general, the daily dose for an adult person of about 70 kg body weight is 5 mg to 1000 mg of BGP 15 (as dihydrochloride), suitably 50-500 mg of BGP-15.

According to a preferred embodiment of the invention, the pharmaceutical composition is used for the reduction or treatment of a body mass index of 25-30 kg/m².

According to a further preferred embodiment of the invention, the pharmaceutical composition is used for the reduction or treatment of a body mass index of above 30 kg/m².

BGP-15 or a pharmaceutically suitable acid addition salt thereof is administered in form of a conventional pharmaceutical composition containing the active agent and, optionally, one or more pharmaceutically acceptable carrier(s). The pharmaceutical composition may include any dosage form suitable for peroral, parenteral or rectal administration or for local treatment, and can be solid or liquid.

The solid pharmaceutical compositions suitable for peroral administration may be powders, capsules, tablets, film-coated tablets, microcapsules etc., and can comprise binding agents such as gelatine, sorbitol, poly(vinylpyrrolidone) etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tableting such as magnesium stearate, talc, poly(ethylene glycol), silica etc.; wetting agents such as sodium laurylsulfate etc. as the carrier. Capsules may contain the pure active agent without any carrier, other dosage forms contain, in addition to the active agent, one or more carrier(s).

The liquid pharmaceutical compositions suitable for peroral administration may be solutions, suspensions or emulsions and can comprise e.g. suspending agents such as gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as water, oils, glycerol,

propylene glycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc. as the carrier.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions of the active ingredients, in general. The sterile solution may contain, in addition to the active agent, pH control agents and osmolarity control agents, preservatives, surfactants etc.

Dosage forms listed above as well as other dosage forms are known *per se*, see e.g. Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co., Easton, USA (1990).

The pharmaceutical composition contains dosage unit, in general. The daily dose can be administered in one or more portions. The actual dosage depends on many factors and is determined by the doctor.

The pharmaceutical composition is prepared by admixing the active ingredient to one or more carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known *per se*. Useful methods are known from the literature, e.g. Remington's Pharmaceutical Sciences mentioned above.

The effect of BGP-15 on the body weight gain was examined in the tests of the following Examples.

Example 1**Effect of BGP-15 on the body weight gain induced by olanzapine or clozapine**

Since it is known that certain antipsychotics induce overweight and later obesity in the treated patients [Ruetsch O. et al., L'Encéphale, 31, 507-16 (2005)], rats treated with olanzapine [2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]-benzodiazepine] or mice treated with olanzapine or clozapine [8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo-[b,e][1,4]diazepine] were used as the experimental system for the determination of the effect of BGP-15 on abnormal weight gain.

A. Experimental induction of overweight with olanzapine and comparison with oral antidiabetics

Groups of female Wistar rats were treated with vehicle (control group) and the agents to be tested for 28 days. Each group consisted of 6 animals fed with normal laboratory chow and tap water *ad libitum*. The agents to be tested were administered twice daily, at 8 h and 18 h, perorally. The antipsychotic olanzapine was administered in a dose of 1 mg/kg to induce body weight gain. BGP-15 was administered in a dose of 10 mg/kg, alone and together with olanzapine. The oral antidiabetics metformin (100 mg/kg) and rosiglitazone (3 mg/kg) were employed as reference compounds, alone and together with olanzapine. The average starting weight of the

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animals was 171 g. The weights of the animals at the end of the test on the 28th day are listed in Table 1.

Table 1

Treatment	Body weight (average in the group) in g
Control	255
Olanzapine, 1 mg/kg	330
BGP-15 dihydrochloride, 10 mg/kg	242
Metformin, 100 mg/kg	266
Rosiglitazone, 3 mg/kg	284
Olanzapine 1 mg/kg + BGP-15 dihydrochloride 10 mg/kg	262
Olanzapine 1 mg/kg + metformin 100 mg/kg	331
Olanzapine 1 mg/kg + rosiglitazone 3 mg/kg	359

The weight gain of the control group relative to the starting weight during the test period of 28 days can be considered as normal in case of rats. Olanzapine produced high average weight relative to the control group. Treatment with BGP-15 alone reduced the average weight relative to the control group, while treatment with metformin and rosiglitazone, respectively, produced somewhat higher average weight relative to the control group. In the group treated with both olanzapine and BGP-15 dihydrochloride, a very high reduction of the body

weight was experienced and nearly the value that characterized the healthy animals (control group) was obtained. Treatment with metformin did not reduce, while treatment with rosiglitazone even increased the weight gain induced by olanzapine in the experimental model.

B. Experimental induction of overweight with olanzapine or clozapine

Groups of female NMRI mice were treated with vehicle (control group) and the agents to be tested for 15 days, perorally. Each group consisted of 10 animals fed with normal laboratory chow and tap water *ad libitum*. Treatments were performed between 5 and 6 pm, shortly before the dark phase, the primary feeding period of the day. Olanzapine was administered in a dose of 0.5 mg/kg, while clozapine was administered in a dose of 1 mg/kg to induce body weight gain. BGP-15 was administered in a dose of 10 mg/kg, alone and together with olanzapine and clozapine, respectively. Weight of the animals were recorded twice weekly and the increase of the body weight of the animals between the first and 15th days are given in Table 2.

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Table 2

Treatment	Body weight increase (average in the group) in g
Control	2.98
Olanzapine, 0.5 mg/kg	3.5
Clozapine, 1 mg/kg	4.11
BGP-15 dihydrochloride, 10 mg/kg	2.85
Olanzapine, 0.5 mg/kg + BGP-15 dihydrochloride, 10 mg/kg	2.33
Clozapine, 1 mg/kg + BGP-15 dihydrochloride, 10 mg/kg	2.19

BGP-15 alone could lower the body weight gain by about 4.4 % relative to the control. However, in the groups of the experimental model, BGP-15 could reduce the body weight change relative to the control group by 22 % and 26.5 %, respectively.

Example 2

Effect of BGP-15 on the body weight gain induced by risperidone in rats

The experiments were carried out in eight-week-old female Wistar rats. Each test group consisted of 10 animals fed with normal laboratory chow and tap water *ad libitum*. The animals were treated with vehicle (control group) and the compounds to be tested for 21 days. In this experimental system, the

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antipsychotic risperidone [3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one] was injected subcutaneously once daily in doses of 0.005 and 0.05 mg/kg, respectively to induce body weight gain. BGP-15 dihydrochloride was administered in a dose of 20 mg/kg, perorally, once daily, alone and together with risperidone.

The average starting weight of the animals was 195 g. The weights of the animals at the end of the test on the 21th day are listed in Table 3

Table 3

Treatment	Body weight gain in g
Control	27
BGP-15 dihydrochloride 20 mg/kg p.o.	22.7
Risperidone 0.005 mg/kg s.c.	39.7
Risperidone 0.05 mg/kg s.c.	41
Risperidone 0.005 mg/kg s.c. + BGP-15 dihydrochloride 20 mg/kg p.o.	25.8
Risperidone 0.05 mg/kg s.c. + BGP-15 dihydrochloride 20 mg/kg p.o.	28.7

Both doses of the antipsychotic drug risperidone caused increased body weight gain relative to the control group. BGP-15 alone reduced body weight gain somewhat. However, in

both groups of the experimental model, BGP-15 could reduce the body weight change caused by the addition of risperidone.

Example 3

Effect of BGP-15 on the body weight of mice that are genetically susceptible to obesity

The ob/ob mouse represents a genetic model of obesity, where the mutation of leptin gene, one of the most important satiety hormone, causes the disease. The leptin-deficiency causes both reduced metabolic rate and increased food intake. These mice show a rapid weight gain, the 6 weeks old animals have an average body weight of about 30 g, while the wild type mice at that age have only about 20 g of body weight.

In the test, 6 weeks old, male ob/ob mice were treated orally with 15 mg/kg daily dose of BGP-15 dihydrochloride for 15 days. The weight of the animals was measured weekly. The body weights of the control and BGP-15 treated animals after 15 days treatment are shown in Table 3.

Table 3

Treatment	Body weight gain in g
Control (vehicle)	8.73 ± 0.76
BGP-15 dihydrochloride, 15 mg/kg	6.35 ± 0.17

As Table 3 indicates, BGP-15 dihydrochloride caused a rather significant reduction in body weight gain in ob/ob mouse model of obesity since the body weight gain of the test group was lower by 27 % than that of the control group.

Example 4**Effect of BGP-15 on the body weight gain induced by high fat diet in mice**

Test groups of female NMRI mice obtained palatable food that contained 50 % fat. In one of the test groups, mice were treated, perorally, with a dose of 20 mg/kg of BGP-15 dihydrochloride, daily. The animals of the control group were fed with conventional mouse food with low fat content. In a further group of mice fed with conventional mouse food, the animals were treated, perorally, with 20 mg/kg of BGP-15 dihydrochloride, daily. The weight of the animals were evaluated weekly for two weeks and body weight changes were calculated. At the beginning of the study, the average weight of the animals was about 26 g. The average body weight gains on the 8th and 15th day of the experiment are shown in Table 4.

Table 4

Treatment	Body weight gain in g	
	on day 8	on day 15
Control (conventional diet)	1.97	2.47
BGP-15 dihydrochloride 20 mg/kg p.o. (conventional diet)	2.01	2.48
Palatable high fat diet	3.65	5.37
Palatable high fat diet + BGP-15 dihydrochloride 20 mg/kg p.o.	2.48	2.67

From Table 4 it can be seen that palatable high fat diet resulted in a very high body weight gain relative to the control group, however, BGP-15 treatment almost completely blocked the effect of high fat diet. BGP-15 treatment alone had no significant effect on body weight gain in case of conventional diet.

In the Examples it was shown that obesity developed in different experimental models could be effectively reduced by treatment with BGP-15.

Claims:

1. Use of O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the preparation of a pharmaceutical composition suitable for the prevention of abnormal body weight gain or reduction of overweight or obesity.
2. A use of Claim 1 in which O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime dihydrochloride is employed.
3. A use of Claim 1 or 2 in which the pharmaceutical composition is used for the reduction of a body mass index of 25-30 kg/m².
4. A use of Claim 1 or 2 in which the pharmaceutical composition is used for the reduction of a body mass index of above 30 kg/m².