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Section 29(1)
Regulation 3.1(2)

650048

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

We APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.

of John B. Gorsiraweg 6, Curaçao, Netherland Antilles

being the Applicant and Nominated Person, in respect of Application No. 84305/91 entitled Treatment of Obesity with an Alpha-2-Adrenergic Agonist and a Growth Hormone Releasing Peptide state the following:

Convention priority is claimed from the following basic application referred to in the declaration under Article 8 of the PCT:

Basic Applicant	Application Number	Application Date	Country	Country Code
Jesus D. Mugica	580,686	10 Sep 1990	USA	US

Jesus Devesa Mugica is the actual inventor of the invention.

The nominated person is the assignee of the invention from the inventor by virtue of a deed of assignment dated 30 August 1990.

The basic application was the first application made in a Convention country in respect of the invention the subject of this request.

DATED this 21st day of July 1992

APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.
By their Patent Attorney

GRIFFITH HACK & CO

438/21783C

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 650048

(54) Title
TREATMENT OF OBESITY WITH AN ALPHA-2-ADRENERGIC AGONIST AND A GROWTH HORMONE RELEASING PEPTIDE

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(71) Applicant(s)
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(72) Inventor(s)
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(57) Claim

1. The use of an alpha-2-adrenergic agonist in a medicament for treating obesity in a patient, such use comprising the administration to the patient of the medicament simultaneously, separately or sequentially with a growth hormone releasing hormone to induce growth hormone secretion in said patient.

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(54) Title: TREATMENT OF OBESITY WITH AN ALPHA-2-ADRENERGIC AGONIST AND A GROWTH HORMONE RELEASING PEPTIDE

(57) Abstract

Obese patients may be effectively treated by cojointly administering an alpha-2-adrenergic agonist, such as clonidine, and a growth hormone releasing peptide, such as GHRH, to restore or substantially enhance growth hormone release in such patients.

TREATMENT OF OBESITY WITH AN ALPHA-2-ADRENERGIC AGONIST AND A GROWTH HORMONE RELEASING PEPTIDE

Background of the Invention

This invention relates to the treatment of obesity with an alpha-2-adrenergic agonist and a growth hormone releasing peptide to induce growth hormone secretion in a patient with this condition.

It is generally known that obese patients have impaired growth hormone (GH) release, both in basal conditions and in response to a number of stimuli, including growth hormone releasing hormone (GHRH, also identified as GRF) (1,2,3,4). This has been postulated to be the result of a hypothalamic disorder (3), leading to a chronic state of somatostatin hypersecretion (5).

It is also known that administering to a normal patient an agent that interferes with the hypothalamic release of somatostatin will enhance growth hormone release. This effect has been shown for clonidine, an alpha-2-adrenergic agonist, and pyridostigmine, a cholinergic agonist, although the mechanism of action is different for each drug (6). Likewise, galanin has been shown to potentiate GHRH induced GH secretion in normal subjects (7) via the cholinergic pathways (8). It has also been recently shown that treatment of obese patients with the cholinergic agonist pyridostigmine will moderately restore the growth hormone responsiveness to GHRH administration, although to a substantially lesser degree than in normal subjects (5,11). While it has been shown that treatment of normal children and adults with clonidine and GHRH has resulted in significantly enhanced growth hormone levels (9,10), it was not known whether such treatment could be extended to obese patients given the lack of response by such patients to most other known treatments.

Summary of the Invention

It has now been discovered that obese patients may be effectively treated by cojointly administering an alpha-2-adrenergic agonist, such as

clonidine, and a growth hormone releasing peptide, such as GHRH, to restore or substantially enhance growth hormone release in such patients.

Detailed Description of the Invention

While obese patients, and particularly obese children, have exhibited an impaired GH response which heretofore could not be restored with therapies shown to be effective in enhancing GH response in normal patients and short stature patients, a unique and effective treatment has now been found. This treatment involves administering cojointly to the obese patient an effective amount of an alpha-2-adrenergic agonist and a growth hormone releasing peptide.

The alpha-2-adrenergic agonist may be any of those which produce a post-synaptic stimulation of the alpha-2-adrenergic pathway so as to inhibit somatostatin release by the hypothalamus into the hypothalamic-pituitary portal system. Alpha-2-adrenergic agonists which may be utilized include clonidine (2-(2,6-dichloroanilino)-2-imidazoline), guanfacine, guanabenz, guanclofine, guanoxabenz (US 4,910,215), and medetomidine (US 4,910,214). Clonidine is preferred. The dosage is adjusted in accordance with the needs of the patient and the result desired. Typically, clonidine is administered orally at a dosage of about 100 to about 300 ug/m^2, preferably about 150 ug/m^2. It is preferably administered from 0 to about 120 minutes, most preferably about 60 minutes, prior to administering the growth hormone releasing peptide.

The growth hormone releasing peptide which may be utilized includes those peptides which stimulate a GH response at the GHRH level, i.e. stimulate the pituitary somatotropes. Such peptides include GHRH itself in its various known active forms such as GRF 1-44, GRF 1-40, GRF 1-37 and GRF 1-29. GHRH is typically administered by injection (i.v. or s.c.), and may be advantageously delivered in a pulsatile manner (e.g. by infusion pump). The dosage is typically about 1 ug/kg if administered by i.v. bolus, or about 10 ug/kg s.c.. Obviously, the dosage and frequency of administration can be adjusted to meet the needs of the particular patient under treatment and the desired objective.

Other growth hormone releasing peptides which can be effectively utilized are those short chain peptides (4-11 amino acids, preferably 5-7

amino acids) which have been recently found to stimulate a GH response similar to GHRH. These peptides include, but are not limited to those active peptides which are disclosed in US 4,223,019, US 4,223,020, US 4,223,021, US 4,224,316, US 4,226,857, US 4,228,155, US 4,228,156, US 4,228,157, US 4,228,158, US 4,410,512, US 4,410,513, US 4,411,890, US 4,839,344, US 4,880,777, US 4,880,778, WO 89/07110, WO 89/07111 and WO 89/10933. Of the peptides disclosed in the above-identified patents, especially preferred are peptides of the formula:

AA_1-His-AA_3-Ala-Trp-D-Phe-Lys-NH_2

wherein AA_1 is H or Ala and AA_3 is D-Trp or D-β-Nal, as well as analogs and derivatives thereof with similar activity.

Example

Eight prepubertal obese children (boys), aged 10 to 12.4 years, all in good general health and taking no medication, participated in the study with informed consent (parent and child). All had height within normal percentiles for chronological age. Bone age was advanced 6-24 months in all but one patient and weight was above the 100th percentile for chronological age in all cases. The children were tested six times at random intervals ranging from 7 to 10 days, each patient serving as his own control. Studies commenced at 0900h after an overnight fast and bed rest and thirty minutes after the insertion of a nontrombogenic catheter for blood withdrawal in a forearm vein. The study consisted of administering clonidine (Catapresan, Boehringer Ingelheim, Spain) orally at 150 micrograms/m^2 at time 0 followed by administering GHRH (GRF 1-29, Serono, Spain) as an intravenous bolus at 1 microgram/kg at time 60 minutes. The control experiments consisted of administering on separate occasions either clonidine at time 0 or GHRH at time 60 minutes. Blood samples for GH assays (RIA, BioMerieux, France) were taken at 15 minute intervals for two hours. The mean intra-assay coefficient of variation was 5.9, 4.6 and 3.9% at mean GH concentrations of 1.5, 8 and 24 micrograms/L respectively. To avoid inter-assay variations, all samples from a subject were run in the same assay.

Baseline plasma GH levels were not different in the 6 study days. Oral clonidine administration did not produce any significant plasma GH increase

except for one patient who showed a maximal GH value of 6.5 ug/L at time 105 min. The mean amplitude of maximal GH plasma levels following clonidine challenge was 2.9 ± 0.8 ug/L.

GHRH administration produced a slight but significant increase in plasma GH. The mean peak plasma GH level was 9.6 ± 2 ug/L, a value significantly higher than after clonidine challenge, which peak appeared 45 minutes after administration. This GH response to GHRH in obese children is significantly less than the mean GH peak of 17.1 ± 4.3 ug/L found in a control group of short children diagnosed as having constitutional growth delay. It is also significantly less than the reported GHRH-induced GH response in normal children and adolescents of 25.8 ± 5.6 ug/L (9). This confirms previous reports of impaired GHRH-induced GH response in obese children.

Pretreatment with clonidine led to a clear and substantial GH response to GHRH with a peak value of 27.5 ± 4.3 ug/L, significantly higher than any other study in obese children. Moreover, GH peaked earlier, 30 minutes after administering GHRH.

To confirm the uniqueness of the alpha-2-adrenergic agonist in achieving substantially enhanced GH response in obese patients versus another known GH potentiator which operates via a different mechanism (somatostatin inhibition via activation of cholinergic pathway), comparative experiments were performed with galanin (Bachem, Switzerland). Galanin (Gal) was administered alone, with clonidine (Clo) and with GHRH by infusion as a saline solution at 50 pmol/kg/min through a Millex-GY (0.22 um, Millipore) filter at time 55 to 120 minutes in all experiments. Also, for comparison purposes a similar group of short stature children diagnosed as having constitutional growth delay (CGD) were administered GHRH, galanin plus GHRH, and clonidine plus GHRH (previous study) by the same procedure.

The results of all the experiments are summarized in the following Table:

TABLE

Patient Group	Therapy	Mean Peak GH Response (ug/L)
Obese	Clo	2.9 ± 0.8
	Gal	4.1 ± 1.2
	Clo + Gal	5.8 ± 1.4
	GHRH	9.6 ± 2
	Gal + GHRH	12.6 ± 2.6
	Clo + GHRH	27.5 ± 4.3
CGD	GHRH	17.1 ± 4.3
	Gal + GHRH	31.6 ± 4.8
	Clo + GHRH	40.3 ± 3.9 (previous study)

This data is evidence of dysfunction at the level of the central adrenergic pathways involved in GH neuroregulation. This dysfunction is responsible for the impaired GH secretion and the impaired GHRH-induced GH response in obese children and is consistent with the hypothesis that there is a chronic somatostatinergic hypertone in obesity. There also appears to be a GHRH defect in obese patients at the hypothalamic level. The combined treatment with clonidine and GHRH restored and enhanced growth hormone secretion in these patients well beyond any obesity therapy studied heretofore. Such therapy would considerably improve the therapeutic affect of a hypocaloric diet. The superior effect of the alpha-2-adrenergic agonists such as clonidine is believed to result from the direct inhibition of somatostatin, unlike the indirect inhibition that occurs with the cholinergic agonists.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The use of an alpha-2-adrenergic agonist in a medicament for treating obesity in a patient, such use comprising the administration to the patient of the medicament simultaneously, separately or sequentially with a growth hormone releasing hormone to induce growth hormone secretion in said patient.

2. A use as claimed in any one of the preceding claims wherein said alpha-2-adrenergic agonist is clonidine.

3. A use as claimed in any one of the preceding claims wherein said growth hormone releasing hormone is GRF 1-44, GRF 1-40, GRF 1-37 or GRF 1-29.

4. A use as claimed in any one of the claims 1 to 3 wherein said growth hormone releasing hormone is of formula AA_1-His-AA_3-Ala-Trp-D-Phe-Lys-NH_2 wherein AA_1 is H or Ala and AA_3 is D-Trp or D-ß-Nal.

5. A method of inducing growth hormone secretion in an obese patient which comprises administering, simultaneously, separately or sequentially to said patient an effective amount of an alpha-2-adrenergic agonist and a growth hormone releasing hormone.

6. A method of treating obesity which comprises administering to a patient with this condition an alpha-adrenergic agonist simultaneously, separately or sequentially with a growth hormone releasing hormone in an amount effective to induce growth hormone secretion in said patient.

7. The method of claim 6 or 7 wherein said alpha-2-adrenergic agonist is clonidine.

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8. The method of claim 8 wherein said clonidine is administered from 0 to 120 minutes prior to said growth hormone releasing hormone.

9. The method of any one of claims 6 to 9 wherein said growth hormone releasing hormone is GRF 1-44, GRF 1-40, GRF 1-37 or GRF 1-29.

10. The method of any one of claims 6 to 9 wherein said growth hormone releasing hormone as the formula AA_1-His-AA_3-Ala-Trp-D-Phe-Lys-NH_2 wherein AA_1 is H or Ala and AAz_3 is D-Trp or D-ß-Nal.

11. The method of any one of claims 8 to 11 wherein said clonidine is administered in an amount of 100 to 300 micrograms/m^2.

12. The method of claim 12 wherein said clonidine is administered in an amount of 150 micrograms/m^2.

13. The method of any one of claims 6 to 13 wherein said growth hormone releasing hormone is administered in an amount of 1 ug/kg i.v. or 10 ug/kg s.c.

14. The method of any one of claims 6 to 14 which additionally comprises placing said patient on a hypocaloric diet.

15. A method of treating obesity in a patient comprising the administration of an alpha-adrenergic agonist simultaneously, separately or sequentially with a growth hormone releasing hormone substantially as herein described with reference to the Example.

Dated this 24th day of March 1994

APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.

By their Patent Attorneys
GRIFFITH HACK & CO.

AUSTRALIAN 30 MAR 1994 9

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01692

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 37/02 A 61 K 37/43 //(A 61 K 37/43
A 61 K 37:02 A 61 K 31:415)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	Chemical Abstracts, volume 113, no. 3, 16 July 1990 (Columbus, Ohio, US) F. Cordido et al.: "Effect of central cholinergic neurotransmission enhancement by pyridostigmine on the growth hormone secretion elicited by clonidine, arginine, or hypoglycemia in normal and obese subjects", see page 453, abstract 21676s, & J. Clin. Endocrinol. Metab. 1990, 70(5), 1361-70 -----	1-17

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29-11-1991	14. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 18 because they relate to subject matter not required to be searched by this Authority, namely:

see PCT-Rule 39.1(iv).
Although claims 9-17 are directed to a method of treatman of the human/animal body by the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.