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(54) Title: METHODS OF TREATING OBESITY WITH COMBINATION THERAPEUTICS

(57) Abstract: Compositions and methods of treating obesity or obesity-related condition, including reducing body weight, improving diabetic parameters, metabolic syndrome. liver steatosis, and/or hypertension with a combination of CNTF or a CNTF-related molecule and a second agent which is a therapeutic molecule useful in the treatment of obesity, type II diabetes, or other obesity-related conditions.

Methods of Treating Obesity with Combination Therapeutics

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to therapeutic combinations which include a CNTF-related polypeptide useful for the treatment of obesity and obesity related diseases or disorders.

Statement of Related Art

[0002] Ciliary neurotrophic factor (CNTF) is a protein that is required for the survival of embryonic chick ciliary ganglion neurons *in vitro* (Manthorpe et al.,1980, J. Neurochem. 34:69-75). Over the past decade, a number of biological effects have been ascribed to CNTF in addition to its ability to support the survival of ciliary ganglion neurons. CNTF has been cloned and synthesized in bacterial expression systems (Masiakowski et al. 1991 J. Neurosci. 57:1003-1012 and WO 91/04316).

[0003] U.S. 6,472,178 and 6,565,869 describe modified ciliary neurotrophic factor (CNTF) molecules useful for treatment of a number of diseases, including neurological diseases, obesity, and diabetes. Human CNTF is shown in SEQ ID NO:1. Variants of human CNTF are shown as follows: hCNTF (Q63R) SEQ ID NO:2; Axokine™("Ax-15"; hCNTF C17A Q63R Δ15) (SEQ ID NO:3 or SEQ ID NO:4); Ax-13 (hCNTF C17A Q63R Δ13) (SEQ ID NO:5); hCNTFΔ13 (SEQ ID NO:6); hCNTF Q63RΔ13 (SEQ ID NO:7); hCNTF C17AΔ13 (SEQ ID NO:8).

SUMMARY OF THE INVENTION

[0004] The invention provides combinations of CNTF or a CNTF-related molecule and at least one agent useful in the treatment of obesity or an obesity-related condition, wherein the combination composition is useful for the treatment of obesity or an obesity-related condition.

[0005] In a first aspect, the invention features a pharmaceutical composition, comprising a CNTF molecule or a modified CNTF molecule in combination with at least one second agent, and a pharmaceutically acceptable carrier, wherein the second agent is a therapeutic molecule useful in the treatment of obesity.

[0006] In specific embodiments, the CNTF or CNTF-related molecule is human CNTF (SEQ ID NO:1), hCNTF (Q63R) (SEQ ID NO:2); Axokine™("Ax-15"; hCNTF C17A Q63R Δ15) (SEQ ID NO:3 or SEQ ID NO:4); Ax-13 (hCNTF C17A Q63R Δ13)

(SEQ ID NO:5); hCNTFΔ13 (SEQ ID NO:6); hCNTF Q63RΔ13 (SEQ ID NO:7); hCNTF C17AΔ13 (SEQ ID NO:8).

[0007] In specific embodiments, the second agent used in combination with a CNTF or CNTF-related molecule is one or more of sulfonylurea, biguanide metformin (e.g., Glucophage™, Bristol-Myers Squibb), and metformin variants, phentermine (Sigma), alpha-glucosidase inhibitors (e.g., Glucobay™, Precose™, Bayer), a thiazolidinedione such as troglitazone (Rezulin™, Warner-Lambert), rosiglitazone (Avandia™, SmithKline Beecham), pioglitazone (Actos™, Takeda/Lilly), repaglintide (NovoNorm™, Prandin™, Novo Nordisk), a small molecule such as MCC-555 (Mitsubishi), Targretin™ (Ligand Pharmaceuticals), bromocriptine (Ergoset™, Ergo Science), $5HT_{2c}$ receptor agonists (Cerebrus™, Roche), sibutramine, (Meridia™, Knoll), orlistat (Xenical™, Roche), leptin pathway therapeutics (metreleptin, Amgen), ghrelin antagonists, neuropeptide receptor antagonists, thermogenesis pathway therapeutics, $PPAR\gamma$ antagonists, aminoguanidine, AGE inhibitors, pimagedine, ALT-711 (Amgen), symlin (Pramlintide™, Exendin-4™, GLP-1, Amylin), HNF-4 modulators (Lingand Pharmaceuticals), MC4-R receptor modulators and other GPCRs (Millenium), small molecule MC4-R agonists, UCP modulators, and rimonabant (Acomplia™, Sanofi-Aventis) and other endocannabinoid receptor antagonists, bupropion (Wellbutrin™, Zyban™, Sanofi-Aventis), miglitol (Glyset™, Bayer), zonisamide (Zonegran™, Dainippon) and other calcium channel antagonists, topirqamate (Topamax™, Johnson & Johnson), bombesin, ATL 962 (Alizyme), AOD9604 (Metabolic), GW181771 and other CCK-A agonists (GSK), P57 (Phytopharm), PYY3-36 (Nastech Pharmaceuticals), AC 162352 (Amylin), SLV319 (Solvay), T71 (Tularik), ADP356 (Arena Pharmaceuticals), beta-3 AR agonists (L796568, Merck).

[0008] Preferred embodiments of the invention are those wherein the administration of the combination composition of the invention is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, epidural, and oral routes.

[0009] In a second aspect, the invention features a method of treating or reducing obesity, or an obesity-related condition, comprising administering a combination of CNTF or a CNTF-related molecule in combination with at least one second agent to a subject suffering from obesity or an obesity-related condition.

[0010] In specific embodiments, the obesity or obesity-related condition treated is a reduction in body weight, improvement in diabetic parameters such as fasting glucose and insulin levels, oral glucose tolerance, triglycerides and non-esterified

free fatty acids, type II diabetes, and liver steatosis, and hypertension. Generally, the combined therapeutics are useful for treatment of metabolic syndrome.

[0011] In a third aspect, the invention features the use of a combination of a ciliary neurotrophic factor (CNTF) or CNTF-related molecule and a second agent in the preparation of a medicament for the treatment of obesity or an obesity-related condition. The CNTF or CNTF-related molecule is human CNTF (SEQ ID NO:1), hCNTF (Q63R) (SEQ ID NO:2); Axokine™("Ax-15"; hCNTF C17A Q63R Δ15) (SEQ ID NO:3 or SEQ ID NO:4); Ax-13 (hCNTF C17A Q63R Δ13) (SEQ ID NO:5); hCNTFΔ13 (SEQ ID NO:6); hCNTF Q63RΔ13 (SEQ ID NO:7); or hCNTF C17AΔ13 (SEQ ID NO:8). The second agent is sulfonylurea, biguanide metformin and metformin variants, alpha-glucosidase inhibitors, a thiazolidinedione, rosiglitazone, pioglitazone, repaglintide, a small molecule, bromocriptine, an $5HT_{2c}$ receptor agonist, sibutramine, orlistat, a leptin pathway therapeutic, a ghrelin antagonist, a neuropeptide receptor antagonist, a thermogenesis pathway therapeutic, a PPARγ antagonist, aminoguanidine, an AGE inhibitor, pimagedine, ALT-711, symlin, a HNF-4 modulator, a MC4-R receptor modulator, a GPCR, small molecule MC4-R agonist, a UCP modulator, rimonabant, an endocannabinoid receptor antagonist, bupropion, miglitol, zonisamide, a calcium channel antagonist, topirqamate, bombesin, ATL 962, AOD9604, GW181771, a CCK-A agonist, P57, PYY3-36,, AC 162352, SLV319, T71, ADP356, or a beta-3 AR agonist.

[0012] In a fourth aspect, the invention features the use of CNTF or a CNTF-related molecule in the manufacture of a medicament for the treatment of obesity or an obesity related condition by co-administration with a second therapeutic agent.

[0013] Other objects and advantages will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0014] Fig. 1 is a graph of the change in body weight as a percentage of weight at Day 0 from Day 0 to Day 21 food intake (24 hours) over time (Days -1 to 21) for diet-induced obese (DIO) mice treated with 0.9% NaCl (4 μl/g, intraperitoneal (IP) injection) and placebo (4 μl/g subcutaneous (SC) injection; Group A: Control = X); Axokine™ (0.03 mg/kg, SC; Group B =♦); phentermine (10.0 mg/kg, IP; Group C =□); Axokine™ (0.03 mg/kg, SC) and phentermine (10.0 mg/kg, IP; Group D = ■); and pair fed to group B =◊).

[0015] Fig 2 is a graph of 24 h food intake monitored for the duration of the study for the DIO mice treated as described in the legend of Fig. 1.

DETAILED DESCRIPTION OF THE INVENTION

[0016] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only the appended claims.

[0017] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0018] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

General Description

[0019] The invention is based in part on observation that administration of the modified CNTF molecule Axokine™ in combination with a second agent results in a far greater improvement in body weight and diabetic parameters such as fasting glucose and insulin levels, oral glucose tolerance, triglycerides and non-esterified free-fatty acids than can be achieved by comparable food restriction or with either agent alone.

Pharmaceutical Compositions

[0020] In one embodiment, the invention provides a pharmaceutical composition comprising CNTF or a modified CNTF molecule and, together or separately, a composition comprising one or more therapeutic agents, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S.

Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0021] The composition of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0022] The amount of the composition of the invention that will be effective for its intended therapeutic use can be determined by standard clinical techniques based on the present description. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. Generally, suitable dosage ranges for intravenous administration are generally about 20-500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0023] For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vivo* data, e.g., animal models, using techniques that are well known in the art. One

having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0024] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. In cases of local administration or selective uptake, the effective local concentration of the compounds may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[0025] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may also be provided in combination with other methods of treating obesity or obesity related conditions, for example, exercise, weight loss, reduction of alcohol intake, or improved control of a condition such as exercise, caloric restriction, etc.

Methods of Administration

[0026] The invention provides methods of treatment comprising administering to a subject an effective amount of a pharmaceutical composition(s) comprising CNTF or modified CNTF in in combination with one or more therapeutic agent(s) useful for treatment of obesity. The active components used in the method of the invention may be administered separately, simultaneously, sequentially, or together. Various delivery systems are known and can be used to administer the composition of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intraocular, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. Administration can be acute or chronic (e.g.

daily, weekly, monthly, etc) or in combination with other agents. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0027] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome, in a controlled release system, or in a pump. In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), by direct injection, or by use of microparticle bombardment, or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0028] A composition useful in practicing the methods of the invention may be a liquid comprising an agent of the invention in solution, in suspension, or both. The term "solution/suspension" refers to a liquid composition where a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix. A liquid composition also includes a gel. The liquid composition may be aqueous or in the form of an ointment.

[0029] An aqueous suspension or solution/suspension useful for practicing the methods of the invention may contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers and water-insoluble polymers such as cross-linked carboxyl-containing polymers. An aqueous suspension or solution/suspension of the present invention is preferably viscous or muco-adhesive, or even more preferably, both viscous or mucoadhesive.

[0030] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0031] The following example is put forth so as to provide those of ordinary skill in

the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Effect of Axokine™ and Phentermine on Body Weight and Food Intake.

[0032] A study was conducted to determine the effect of the combination of phentermine and Axokine™ on body weight and food intake in a mouse model of obesity. 30 DIO (Diet-Induced Obesity; AKR/J mice fed a high fat diet) mice were divided into 5 equal groups (n=6 per group). Four groups were treated daily in the afternoon starting on Day 0 as follows: Group A (control): 0.9% NaCl (4 μl/g, intraperitoneal (IP) injection) and placebo (4 μl/g subcutaneous (SC) injection); Group B: Axokine™ (0.03 mg/kg, SC); Group C: phentermine (10.0 mg/kg, IP); Group D: Axokine™ (0.03 mg/kg, SC) + phentermine (10.0 mg/kg, IP). The sixth group, Group E was pair fed to Group B; each animal in this group received the average amount of food the Axokine™ treated animals consumed the previous day. This treatment paradigm continued until Day 21 (last injection on Day 20). As illustrated in Fig. 1, daily administration of Axokine™ or phentermine resulted in a significant decrease in body weight relative to control animals. After 21 days of treatment, animals receiving Axokine™ lost approximately 19% of their starting body weight; phentermine-treated mice lost about 15%, while control animals had a decrease of 2%. DIO mice receiving daily administration of Axokine™ + phentermine lost approximately 26% of their starting body weight, an amount that was significantly greater than either Axokine™ alone or phentermine alone. Animals who were pair-fed to the Axokine™ group, lost weight at a rate similar to that of the Axokine™ group up to Day 11 of the study. After this time, their weight loss reached a plateau. Despite receiving less food than controls and the same amount as the Axokine™ group, they did not lose any additional weight.

[0033] In terms of 24h food intake (Fig. 2), all treatment groups had a decrease in food intake over the first 2 days of the study (Day 0 to Day 2) relative to their pre-study intake (Day -1). After the second day of the study, control animals resumed

their typical eating pattern, consuming approximately 4 g of food a day. Animals who received Axokine™ or were pair-fed, maintained this decreased food intake of about 2.75 g per day until Day 12 when they began to consume more food (3.5 g at the end of the study).

[0034] Phentermine treated mice also had decreased food intake relative to control but the overall pattern was more variable. As expected, the combination of Axokine™ and phentermine also resulted in a decreased food consumption that was noticeably different than either compound alone, starting around Day 9 of the study. Taken together, the results of the study demonstrate that the combination of Axokine™ and phentermine can cause a greater degree of weight loss than either agent by itself and this is due in part to a reduction in food intake.

Example 2. Effect of Axokine™ and Rimonabant on Food Intake and Weight Loss.

[0035] Rimonabant (SR-141716 or N- piperidine-5-(4-chlorophenyl)-1-(2,4-dichloropheyl)-4-methylpyrazole-3-carbozamide) is a CB1 receptor antagonist. A study is conducted of the effect of Axokine™ alone, rimonabant alone, or Axokine™+rimonabant on food intake and weight loss on 25 DIO (Akr/J) mice as described in Example 1. The mice are divided into 5 equal groups treated as follows: Group A (n=5) control (200 μl PBS subcutaneous); Group B (n=5): 0.03 mg/kg Axokine™ (subcutaneous injection); Group C (n=5) 1.0-10.0 mg/kg rimonabant (intraperitoneal injection); Group D (n=5) 0.03 mg/kg Axokine™ (subcutaneous injection) + 1.0 mg/kg rimonabant (intraperitoneal injection); Group E (n=5) pair fed to Group B + 200 μl PBS (subcutaneous injection). Food intake and body weight are measured daily over the 21 day treatment period. Terminal serum chemistry analyis (22 point analysis) is conducted at the end of the treatment period.

We claim:

1. Use of a combination of a ciliary neurotrophic factor (CNTF) or CNTF-related molecule and a second agent in the preparation of a medicament for the treatment of obesity or an obesity-related condition.

2. The use of claim 1, wherein the CNTF or CNTF-related molecule is human CNTF (SEQ ID NO:1), hCNTF (Q63R) (SEQ ID NO:2); Axokine™("Ax-15"; hCNTF C17A Q63R Δ15) (SEQ ID NO:3 or SEQ ID NO:4); Ax-13 (hCNTF C17A Q63R Δ13) (SEQ ID NO:5); hCNTFΔ13 (SEQ ID NO:6); hCNTF Q63RΔ13 (SEQ ID NO:7); or hCNTF C17AΔ13 (SEQ ID NO:8).

3. The use of claims 1 or 2, wherein the second agent is sulfonylurea, biguanide metformin and metformin variants, alpha-glucosidase inhibitors, a thiazolidinedione, rosiglitazone, pioglitazone, repaglintide, a small molecule, bromocriptine, an $5HT_{2c}$ receptor agonist, sibutramine, orlistat, a leptin pathway therapeutic, a ghrelin antagonist, a neuropeptide receptor antagonist, a thermogenesis pathway therapeutic, a PPARγ antagonist, aminoguanidine, an AGE inhibitor, pimagedine, ALT-711, symlin, a HNF-4 modulator, a MC4-R receptor modulator, a GPCR, small molecule MC4-R agonist, a UCP modulator, rimonabant, an endocannabinoid receptor antagonist, bupropion, miglitol, zonisamide, a calcium channel antagonist, topirqamate, bombesin, ATL 962, AOD9604, GW181771, a CCK-A agonist, P57, PYY3-36,, AC 162352, SLV319, T71, ADP356, or a beta-3 AR agonist.

4. The use of any of claims 1 to 3, wherein administration is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, epidural, and/or oral.

5. The use of claim 4, wherein administration is to a human subject suffering from obesity or an obesity related condition.

6. The use of claim 6, wherein the obesity or obesity-related condition treated results in a loss of body weight or improvement in diabetic parameters, metabolic syndrome, liver steatosis and/or hypertension.

The method of claim 6, wherein the diabetic parameter is one or more of fasting glucose and insulin levels, oral glucose tolerance, triglycerides and non-esterified free-fatty acids, and type II diabetes.

8. Use of CNTF or a CNTF-related molecule in the manufacture of a medicament for the treatment of obesity or an obesity related condition by co-administration with a second therapeutic agent.

9. The method of claim 8, wherein the CNTF or CNTF-related molecule is human CNTF (SEQ ID NO:1), hCNTF (Q63R) (SEQ ID NO:2); Axokine™("Ax-15"; hCNTF C17A Q63R Δ15) (SEQ ID NO:3 or SEQ ID NO:4); Ax-13 (hCNTF C17A Q63R Δ13) (SEQ ID NO:5); hCNTFΔ13 (SEQ ID NO:6); hCNTF Q63RΔ13 (SEQ ID NO:7); or hCNTF C17AΔ13 (SEQ ID NO:8).

10. The use of claims 8 or 9, wherein the second agent is sulfonylurea, biguanide metformin and metformin variants, alpha-glucosidase inhibitors, a thiazolidinedione, rosiglitazone, pioglitazone, repaglintide, a small molecule, bromocriptine, an $5HT_{2c}$ receptor agonist, sibutramine, orlistat, a leptin pathway therapeutic, a ghrelin antagonist, a neuropeptide receptor antagonist, a thermogenesis pathway therapeutic, a PPARγ antagonist, aminoguanidine, an AGE inhibitor, pimagedine, ALT-711, symlin, a HNF-4 modulator, a MC4-R receptor modulator, a GPCR, small molecule MC4-R agonist, a UCP modulator, rimonabant, an endocannabinoid receptor antagonist, bupropion, miglitol, zonisamide, a calcium channel antagonist, topirqamate, bombesin, ATL 962, AOD9604, GW181771, a CCK-A agonist, P57, PYY3-36,, AC 162352, SLV319, T71, ADP356; or a beta-3 AR agonist.

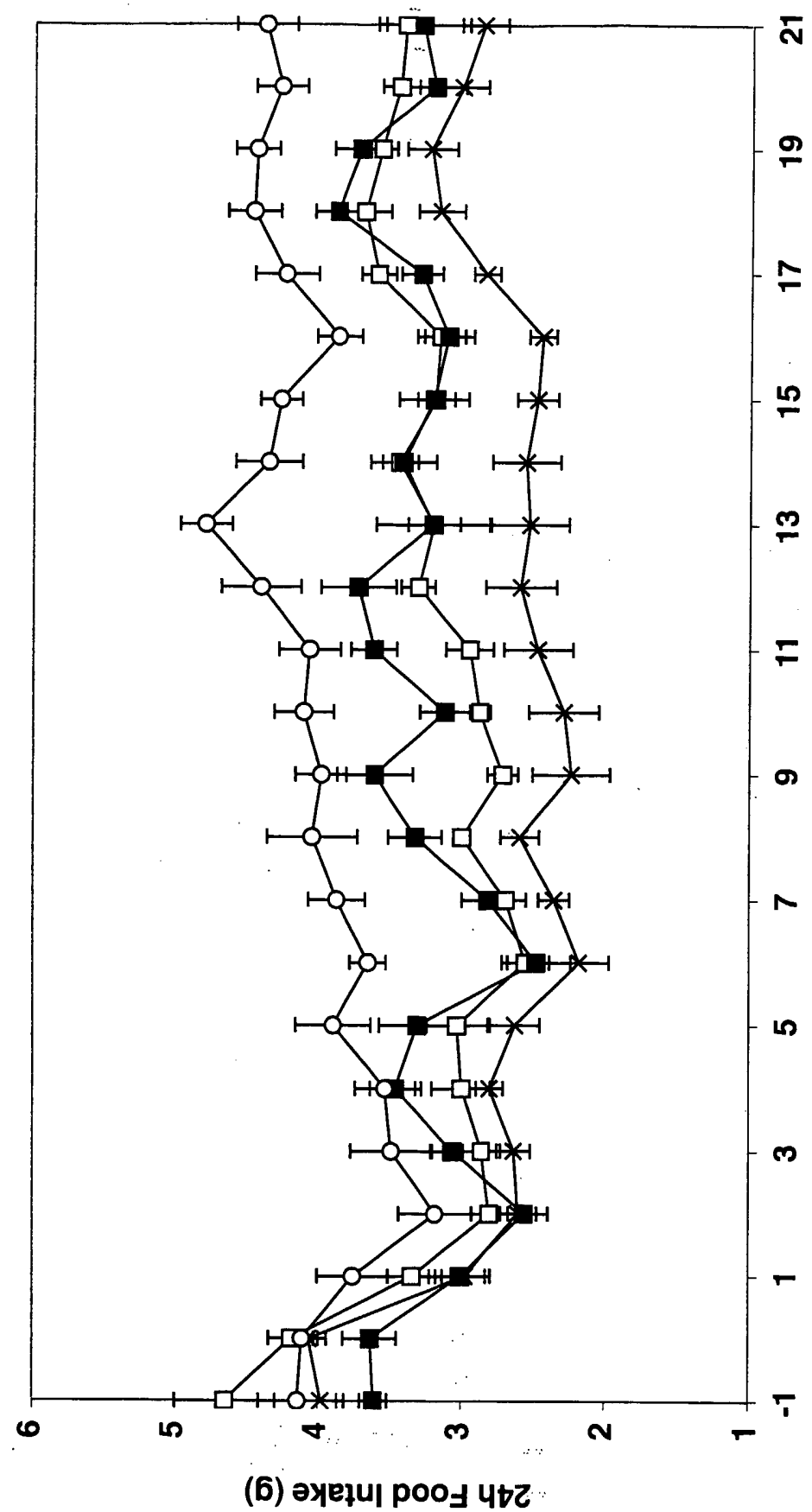

Figure 1

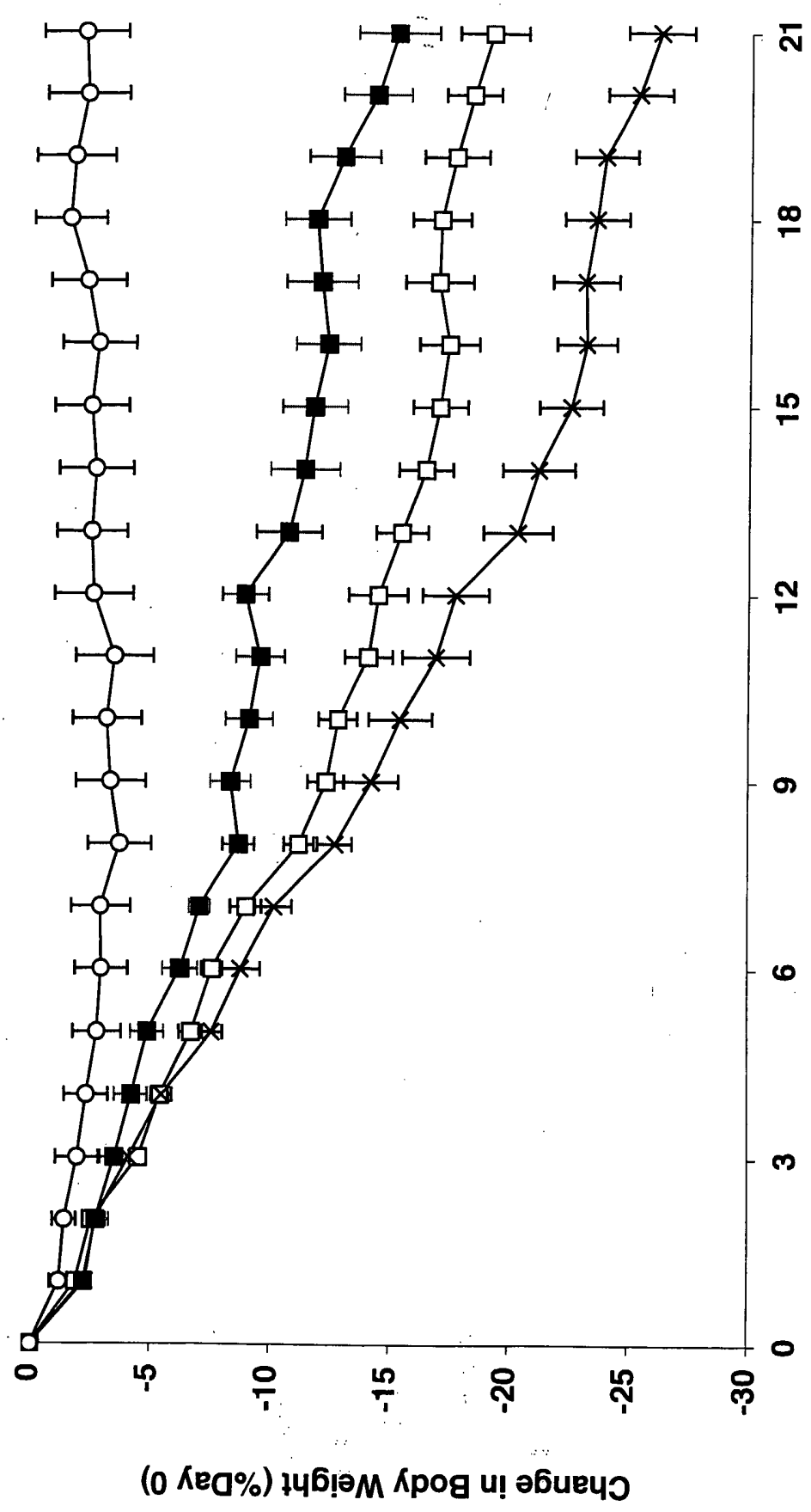

Figure 2

SEQUENCE LISTING

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Tyr Ile Ala Asn Asn Lys Lys Met
195 200

<210> 2
<211> 200
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 2
Met Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu
1 5 10 15
Cys Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr
20 25 30
Ala Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile

```
         35                  40                  45
Asn Leu Asp Ser Val Asp Gly Val Pro Val Ala Ser Thr Asp Arg Trp
     50                  55                  60
Ser Glu Met Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr
 65                  70                  75                  80
Arg Thr Phe Gln Gly Met Leu Thr Lys Leu Leu Glu Asp Gln Arg Val
                 85                  90                  95
His Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu
            100                 105                 110
Leu Leu Gln Val Ser Ala Phe Ala Tyr Gln Leu Glu Glu Leu Met Val
        115                 120                 125
Leu Leu Glu Gln Lys Ile Pro Glu Asn Glu Ala Asp Gly Met Pro Ala
    130                 135                 140
Thr Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys
145                 150                 155                 160
Val Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu
                165                 170                 175
Arg Val Ile Ser Ser His Gln Met Gly Ile Ser Ala Leu Glu Ser His
            180                 185                 190
Tyr Gly Ala Lys Asp Lys Gln Met
        195                 200
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<210> 3
<211> 185
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 3

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Met Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu
  1               5                  10                  15
Ala Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr
             20                  25                  30
Ala Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile
         35                  40                  45
Asn Leu Asp Ser Ala Asp Gly Met Pro Val Ala Ser Thr Asp Arg Trp
     50                  55                  60
Ser Glu Leu Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr
 65                  70                  75                  80
Arg Thr Phe His Val Leu Leu Ala Arg Leu Leu Glu Asp Gln Gln Val
                 85                  90                  95
His Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu
            100                 105                 110
Leu Leu Gln Val Ala Ala Phe Ala Tyr Gln Ile Glu Glu Leu Met Ile
        115                 120                 125
Leu Leu Glu Tyr Lys Ile Pro Arg Asn Glu Ala Asp Gly Met Pro Ile
    130                 135                 140
Asn Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys
145                 150                 155                 160
Val Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu
                165                 170                 175
Arg Phe Ile Ser Ser His Gln Thr Gly
            180                 185
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<210> 4
<211> 184
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 4
Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu Ala
1 5 10 15
Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr Ala
20 25 30
Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile Asn
35 40 45
Leu Asp Ser Ala Asp Gly Met Pro Val Ala Ser Thr Asp Arg Trp Ser
50 55 60
Glu Leu Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr Arg
65 70 75 80
Thr Phe His Val Leu Leu Ala Arg Leu Leu Glu Asp Gln Gln Val His
85 90 95
Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu Leu
100 105 110
Leu Gln Val Ala Ala Phe Ala Tyr Gln Ile Glu Glu Leu Met Ile Leu
115 120 125
Leu Glu Tyr Lys Ile Pro Arg Asn Glu Ala Asp Gly Met Pro Ile Asn
130 135 140
Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys Val
145 150 155 160
Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu Arg
165 170 175
Phe Ile Ser Ser His Gln Thr Gly
180

<210> 5
<211> 187
<212> PRT
<213> Homo sapiens

<400> 5
Met Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu
1 5 10 15
Ala Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr
20 25 30
Ala Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile
35 40 45
Asn Leu Asp Ser Ala Asp Gly Met Pro Val Ala Ser Thr Asp Arg Trp
50 55 60
Ser Glu Leu Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr
65 70 75 80
Arg Thr Phe His Val Leu Leu Ala Arg Leu Leu Glu Asp Gln Gln Val
85 90 95
His Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu
100 105 110
Leu Leu Gln Val Ala Ala Phe Ala Tyr Gln Ile Glu Glu Leu Met Ile
115 120 125
Leu Leu Glu Tyr Lys Ile Pro Arg Asn Glu Ala Asp Gly Met Pro Ile
130 135 140
Asn Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys
145 150 155 160
Val Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu
165 170 175
Arg Phe Ile Ser Ser His Gln Thr Gly Ile Pro
180 185

<210> 6

<211> 187
<212> PRT
<213> Homo sapiens

<400> 6
Met Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu
1 5 10 15
Cys Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr
20 25 30
Ala Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile
35 40 45
Asn Leu Asp Ser Ala Asp Gly Met Pro Val Ala Ser Thr Asp Gln Trp
50 55 60
Ser Glu Leu Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr
65 70 75 80
Arg Thr Phe His Val Leu Leu Ala Arg Leu Leu Glu Asp Gln Gln Val
85 90 95
His Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu
100 105 110
Leu Leu Gln Val Ala Ala Phe Ala Tyr Gln Ile Glu Glu Leu Met Ile
115 120 125
Leu Leu Glu Tyr Lys Ile Pro Arg Asn Glu Ala Asp Gly Met Pro Ile
130 135 140
Asn Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys
145 150 155 160
Val Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu
165 170 175
Arg Phe Ile Ser Ser His Gln Thr Gly Ile Pro
180 185

<210> 7
<211> 187
<212> PRT
<213> Homo sapiens

<400> 7
Met Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu
1 5 10 15
Cys Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr
20 25 30
Ala Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile
35 40 45
Asn Leu Asp Ser Ala Asp Gly Met Pro Val Ala Ser Thr Asp Arg Trp
50 55 60
Ser Glu Leu Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr
65 70 75 80
Arg Thr Phe His Val Leu Leu Ala Arg Leu Leu Glu Asp Gln Gln Val
85 90 95
His Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu
100 105 110
Leu Leu Gln Val Ala Ala Phe Ala Tyr Gln Ile Glu Glu Leu Met Ile
115 120 125
Leu Leu Glu Tyr Lys Ile Pro Arg Asn Glu Ala Asp Gly Met Pro Ile
130 135 140
Asn Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys
145 150 155 160
Val Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu
165 170 175
Arg Phe Ile Ser Ser His Gln Thr Gly Ile Pro
180 185

<210> 8
<211> 187
<212> PRT
<213> Homo sapiens

<400> 8

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Met Ala Phe Thr Glu His Ser Pro Leu Thr Pro His Arg Arg Asp Leu
  1               5                  10                  15
Ala Ser Arg Ser Ile Trp Leu Ala Arg Lys Ile Arg Ser Asp Leu Thr
             20                  25                  30
Ala Leu Thr Glu Ser Tyr Val Lys His Gln Gly Leu Asn Lys Asn Ile
         35                  40                  45
Asn Leu Asp Ser Ala Asp Gly Met Pro Val Ala Ser Thr Asp Gln Trp
     50                  55                  60
Ser Glu Leu Thr Glu Ala Glu Arg Leu Gln Glu Asn Leu Gln Ala Tyr
 65                  70                  75                  80
Arg Thr Phe His Val Leu Leu Ala Arg Leu Leu Glu Asp Gln Gln Val
                 85                  90                  95
His Phe Thr Pro Thr Glu Gly Asp Phe His Gln Ala Ile His Thr Leu
            100                 105                 110
Leu Leu Gln Val Ala Ala Phe Ala Tyr Gln Ile Glu Glu Leu Met Ile
        115                 120                 125
Leu Leu Glu Tyr Lys Ile Pro Arg Asn Glu Ala Asp Gly Met Pro Ile
    130                 135                 140
Asn Val Gly Asp Gly Gly Leu Phe Glu Lys Lys Leu Trp Gly Leu Lys
145                 150                 155                 160
Val Leu Gln Glu Leu Ser Gln Trp Thr Val Arg Ser Ile His Asp Leu
                165                 170                 175
Arg Phe Ile Ser Ser His Gln Thr Gly Ile Pro
            180                 185
```