



(51) International Patent Classification:

A61K 38/18 (2006.01)

(21) International Application Number:

PCT/US2018/047183

(22) International Filing Date:

21 August 2018 (21.08.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/549,743 24 August 2017 (24.08.2017) US

(71) Applicant: OHIO UNIVERSITY [US/US]; 340 W. State Street, Athens, OH 45701 (US).

(72) Inventor: LIST, Edward, O.; Ohio University, 340 W. State Street, Athens, OH 45701 (US).

(74) Agent: MARTINEAU, Catherine, B.; MacMillan, Sobanski & Todd, LLC, One Maritime Plaza, 5th Floor, 720 Water Street, Toledo, OH 43604 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: METHODS OF TREATMENTS USING GROWTH HORMONE VARIANTS AND COMPOSITIONS THEREFOR

(57) Abstract: Methods of treatments using growth hormone variants and compositions therefor are described.



WO 2019/040406 A2

TITLE

**METHODS OF TREATMENTS USING
GROWTH HORMONE VARIANTS AND COMPOSITIONS THEREFOR**

Inventor: Edward O. List

RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application Ser. No. 62/549,743 filed under 35 U.S.C. § 111(b) on August 24, 2017, the disclosure of which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with no government support. The government has no rights in this invention.

SEQUENCE LISTING

[0003] The instant application contains a Sequence Listing which has been submitted via EFS-web and is hereby incorporated by reference in its entirety. The ASCII copy, created on August 16, 2018, is named 3834_59501-US-PCT-OU-18003_SL.txt, and is 5,497 bytes in size.

BACKGROUND OF THE INVENTION

[0004] Growth Hormone (GH) - shown in SEQ ID NO:1 is commonly used to for several indications including treatment of GH deficiency. Unfortunately, the current form of human GH that is prescribed for patients possesses several activities that are considered detrimental to health. For example, human GH has been found to bind to not only the GH receptor but also bind to prolactin receptor. Unfortunately prolactin receptor activation has been shown to stimulate growth of certain types of cancers, including pancreatic, breast, prostate and bone cancers.

[0005] In addition, human GH is well known to possess anti-insulin (also called diabetogenic, i.e. "promotes diabetes") activity. Despite its ability to improve body composition, growth hormone has also been described as a diabetogenic agent with the ability to inhibit the action of insulin. Thus, one concern about use of growth hormone is the possibility of developing or worsening existing insulin resistance.

[0006] Non-alcoholic fatty liver disease (NAFLD) is an increasingly prevalent disease with little to no current treatment options.

[0007] Now described herein are methods of treatment with a variant of GH that is far superior at reversing NAFLD than standard human GH. It would be desirable to develop a GH that does not have these drawbacks or the harmful diabetogenic and cancer promoting effects.

SUMMARY OF THE INVENTION

[0008] Described herein is GH-V-20K peptide and variants thereof, where the GH-V-20K peptide has the amino acid sequence SEQ ID NO: 3. In certain embodiments, the variant has at least 60-90% sequence identity to such amino acid sequence.

[0009] In certain embodiments, the peptides are formulated into therapeutic compositions which can further include pharmaceutically acceptable excipients, diluents, adjuvants, and/or carriers.

[0010] Further provided is a method of treating a subject with a condition caused by GH deficiency in a manner that does not result in diabetogenic activity, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof, to reduce diabetogenic activity in the subject. In certain embodiments, the variant has at least 60-90% sequence identity to such amino acid sequence/s.

[0011] Further provided is a method of treating a subject with a condition caused by GH deficiency in a manner that does not stimulate prolactin activity, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof, to reduce prolactin activity in the subject. In certain embodiments, the variant has at least 60-90% sequence identity to such amino acid sequence/s.

[0012] Further provided is a method of enhancing the ability to reverse non-alcoholic fatty liver disease in a subject, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof, to enhancing the ability to reverse non-alcoholic fatty liver disease in the subject. In certain embodiments, the variant has at least 60-90% sequence identity to such amino acid sequence/s.

[0013] Further provided is a method of treating growth hormone deficiency in a subject, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof, to treat a growth hormone deficiency in the subject. In certain embodiments, the variant has at least 60-90% sequence identity to such amino acid sequence/s.

[0014] Further provided is a use of a synthetic peptide to treat a subject with a condition caused by GH deficiency in a manner that does not result in diabetogenic activity, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof. In certain embodiments, the variant has at least 90% sequence identity to such amino acid sequence/s.

[0015] Further provided is a use of a synthetic peptide to reduce prolactin activity in a subject, the method comprising administering to a subject an effective amount of a composition

comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof, to reduce prolactin activity in the subject. In certain embodiments, the variant has at least 90% sequence identity to such amino acid sequence/s.

[0016] Further provided is a use of a synthetic peptide to enhance the ability to reverse non-alcoholic fatty liver disease in a subject, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof, to enhancing the ability to reverse non-alcoholic fatty liver disease in the subject. In certain embodiments, the variant has at least 90% sequence identity to such amino acid sequence/s.

[0017] Further provided is a use of a synthetic peptide to treat a growth hormone deficiency in a subject, the method comprising administering to a subject an effective amount of a composition comprising at least one of the amino acid sequences having SEQ ID NO:3 (GH-V-20K), or variants thereof. In certain embodiments, the variant has at least 90% sequence identity to such amino acid sequence/s.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The patent or application file may contain one or more drawings executed in color and/or one or more photographs. Copies of this patent or patent application publication with color drawing(s) and/or photograph(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fees.

[0019] **FIG. 1:** Glucose disposal rate in response to insulin in mice treated with saline (blue), standard human GH (red), or GH-V-20K variant (green). Mice treated with human GH had a significantly impaired response to insulin treatment compared to GH variant. Data are represented by mean $\pm$ SEM. Differences are considered significant at $p=0.05$. $p<0.001$.

[0020] **FIG. 2:** Endogenous mouse prolactin levels in serum. Mice receiving standard human GH (shown in red) had significantly decreased levels of prolactin demonstrating the prolactin binding activity of human GH. In contrast, mice receiving the GH-V-20K variant (green) showed no change in prolactin demonstrating that the GH variant lacks prolactin activity in vivo.

[0021] **FIG. 3:** Triglyceride content of liver. Mice receiving GH-V-20K variant (shown in green) had significantly decreased levels of triglyceride. In contrast, mice receiving standard human GH (red) showed no change in triglyceride compared to controls (blue).

[0022] **FIG. 4:** Circulating IGF-1 levels in mice treated with saline (blue), standard human GH (red), or GH variant (green). GH variant produces IGF-1. Data are represented by mean $\pm$ SEM. Differences are considered significant at $p=0.05$. **** = $p<0.0001$.

[0023] **FIG. 5:** Amino acid sequences for GH-N-22K [SEQ ID NO:1]; GH-V-22K [SEQ ID NO:2]; and, GH-V-20K [SEQ ID NO:3].

DETAILED DESCRIPTION OF THE INVENTION

[0024] Throughout this disclosure, various publications, patents, and published patent specifications are referenced by an identifying citation. The disclosures of these publications, patents, and published patent specifications are hereby incorporated by reference into the present disclosure in their entirety to more fully describe the state of the art to which this invention pertains.

[0025] The term “peptide/s” is used herein to encompass the peptide GH-V-20K having SEQ ID NO:3, as well as variants and derivatives of these sequences which share the activity of the peptide having SEQ ID NO:3, and the amino acid sequence of SEQ ID NO:3 with one or more tags or labels, such as a fluorescent tag.

[0026] Thus, in some embodiments, a peptide has an amino acid sequence consisting of SEQ ID NO:3. In other embodiments, the peptide is a variant that has an amino acid sequence where one or more of the amino acids in SEQ ID NO:3 has been substituted with another amino acid, but the peptide nonetheless has the ability to increase GH levels in a subject while minimizing or eliminating the possibility of the subject developing insulin resistance or increased prolactin activity, which can result in diabetes or certain cancers, respectively. Further, the peptide is able to reverse non-alcoholic fatty liver disease and to stimulate IGF-1.

[0027] Modifications to the amino acid sequences can be introduced by, for example, mutagenesis or protein synthesis. Such modifications include, for example, deletions from, insertions into, and/or substitutions within the amino acid sequence. Any combination of deletion, insertion, and substitution can be made to arrive at the final amino acid construct of the variant, provided that the final construct possesses the desired biological activity. Accordingly, in some embodiments, the variants have at least 90% sequence identity to the amino acid sequences. Reference to a “% sequence identity” with respect to a reference polypeptide is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity.

[0028] The term “variant” refers to a protein derived from the native protein by deletion (so-called truncation) or addition of one or more amino acids to the N-terminal and/or C-terminal end of the native protein; deletion or addition of one or more amino acids at one or more sites in the native protein; substitution of one or more amino acids at one or more sites in the native protein; or synthetically-produced polypeptides having such an amino acid sequence. Variant proteins encompassed by the present disclosure are biologically active, meaning they continue to possess the desired biological activity of the native protein. Such variants may result from, for example, genetic polymorphism or from human manipulation. Biologically active variants of a native the protein of the present disclosure have at least about 75%, 80%, 85%, preferably at least about 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, or more preferably at least about 98% or 99% sequence identity to the amino acid sequence for the native protein. Sequence identity can be determined by sequence alignment programs described elsewhere using default parameters. A biologically active variant of a protein of the present disclosure may differ from that protein by as few as 1-15 amino acid residues, as few as 1-10, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue.

[0029] The term “therapeutic” refers to a generic term that includes both diagnosis and treatment. It will be appreciated that in these methods the “therapy” may be any therapy for treating a disease including, but not limited to, pharmaceutical compositions, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods described herein may be used to evaluate a patient or subject before, during and after therapy, for example, to evaluate the reduction in disease state.

[0030] The term “adjunctive therapy” refers to a treatment used in combination with a primary treatment to improve the effects of the primary treatment.

[0031] The term “clinical outcome” refers to the health status of a patient following treatment for a disease or disorder or in the absence of treatment. Clinical outcomes include, but are not limited to, an increase in the length of time until death, a decrease in the length of time until death, an increase in the chance of survival, an increase in the risk of death, survival, disease-free survival, chronic disease, metastasis, advanced or aggressive disease, disease recurrence, death, and favorable or poor response to therapy.

[0032] The term “subject” includes human and non-human animals. The preferred subject for treatment is a human. “Patient,” “individual” and “subject” are used interchangeably herein.

[0033] The terms “preventing, treating or ameliorating a disease” generally refer to: “Preventing” a disease refers to inhibiting the full development of a disease. “Treating” refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. “Ameliorating” refers to the reduction in the number or severity of signs or symptoms of a disease.

[0034] The terms “comprising, comprises and comprised of,” as used herein, are synonymous with “including”, “includes” or “containing”, “contains”, and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps. The terms “comprising”, “comprises” and “comprised of” also include the term “consisting of”.

[0035] The term “about,” as used herein, when referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, is meant to encompass variations of +/- 10% or less, preferably +/- 5% or less, more preferably +/- 1% or less, and still more preferably +/- 0.1% or less of and from the specified value, insofar such variations are appropriate to perform in the disclosed invention. It is to be understood that the value to which the modifier “about” refers is itself also specifically, and preferably, disclosed.

[0036] The term “and/or,” when used in a list of two or more items, means that any one of the listed items can be employed by itself or any combination of two or more of the listed items can be employed. For example, if a list is described as comprising group A, B, and/or C, the list can comprise A alone; B alone; C alone; A and B in combination; A and C in combination, B and C in combination; or A, B, and C in combination.

[0037] ***General Description***

[0038] Described herein is a variant of GH, GH-V-20K, which is 20kDa placental human GH variant that has three separate improved activities compared to standard human GH: 1) a human growth hormone that lacks prolactin activity in vivo; 2) a human growth hormone that has reduced anti-insulin (diabetogenic) activity by measuring insulin activity in vivo (as opposed to insulin levels); 3) a human growth hormone that is able to reverse fatty liver disease; and, 4) a human growth hormone that is able to stimulate IGF-1.

[0039] ***EXAMPLES***

[0040] Certain embodiments of the present invention are defined in the Examples herein. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

[0041] ***Methods***

[0042] Mice were treated with saline, standard human GH, or GH-V-20K variant. Mice were then treated for 6 days with saline to serve as controls, standard human GH, or the GH-V-20K 20kDa placental human GH variant at similar doses (15 ug GH variant/gram body weight/day), to compare the GH variant to human GH.

[0043] ***Example 1- Reducing Diabetogenic Activity***

[0044] Insulin tolerance tests were performed on the 3rd or 4th day of treatment results of the insulin tolerance tests are shown in **FIG. 1** and demonstrate that treatment with standard hGH decreases insulin's ability to remove glucose from circulation, while mice treated with GH variant had much less impairment to insulin's activity.

[0045] These experiments also demonstrate a reduced anti-insulin (diabetogenic) effect by measuring insulin activity in vivo for the first time for this GH-V-20K variant (as opposed to insulin levels).

[0046] ***Example 2 – Effects on Prolactin Activity***

[0047] At the end of 6 days of treatment, the mice were euthanized and tissues collected (including liver and serum). Serum samples were used to measure endogenous mouse prolactin levels (shown in **FIG. 2**), which is a biological readout of prolactin activity in vivo since prolactin has a negative feedback loop (i.e., high prolactin activity will shut down endogenous prolactin

production, while low prolactin activity will lead to increased prolactin production).

[0048] These experiments demonstrate the lack of prolactin receptor binding activity in vivo for this GH-V-20K variant.

[0049] ***Example 3 - Reversing Non-alcoholic Fatty Liver Disease***

[0050] Liver samples collected at dissection were analyzed for triglyceride content using liver triglyceride assays. Results of these assays (shown in **FIG. 3**) show that the livers of mice treated with GH-V-20K variant (green) contained significantly less triglyceride than mice treated with standard human GH (red).

[0051] Further, these experiments demonstrate the ability of the GH-V-20K variant to reverse fatty liver disease.

[0052] ***Example 4 – Treating Growth Hormone Disorders***

[0053] Most of the growth promoting activities of GH (including those that stimulate longitudinal bone growth) are via GH stimulated production of IGF-1 in various tissues. A clinical readout of GH action is circulating levels of IGF-1. (i.e., the higher the levels of circulating IGF-1 the better GH treatment is working).

[0054] **FIG. 4** shows circulating IGF-1 levels in mice treated with saline (blue), standard human GH (red), or GH-V-20K variant (green). The GH-V-20K variant produced IGF-1. Data are represented by mean +/- SEM. Differences are considered significant at $p=0.05$. **** = $p<0.0001$.

[0055] Still further uses includes treatments where standard human GH is useful, such as for growth hormone deficiency and/or idiopathic short stature.

[0056] The use of the GH variant (GH-V-20K) is safer to use than GH-N since the GH-V-20K variant still retains the ability to stimulate IGF-1 and longitudinal body growth, without the undesirable side effects known to be caused by GH-N.

[0057] ***Example 5 – Other Treatments***

[0058] Other uses include the treatment for obesity to improve body composition, increasing lean mass and decreasing fat mass without the dangers of stimulating prolactin sensitive cancers, or blocking insulin action using the GH-V-20K variant.

[0059] ***Pharmaceutical Compositions***

[0060] A pharmaceutical composition as described herein may be formulated with any pharmaceutically acceptable excipients, diluents, or carriers. A composition disclosed herein may comprise different types of carriers depending on whether it is to be administered in solid, liquid, or aerosol form, and whether it needs to be sterile for such routes of administration as injection. Compositions disclosed herein can be administered in a suitable manner, including, but not limited to topically (i.e., transdermal), subcutaneously, by localized perfusion bathing target cells directly, via a lavage, in creams, in lipid compositions (e.g., liposomes), formulated as elixirs or solutions for convenient topical administration, formulated as sustained release dosage forms, or by other

method or any combination of the forgoing as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 2003, incorporated herein by reference).

[0061] The compositions provided herein are useful for treating animals, such as humans. A method of treating a human patient according to the present disclosure includes the administration of a composition, as described herein.

[0062] The phrases "pharmaceutical" or "pharmacologically acceptable" refer to molecular entities and compositions that produce no adverse, allergic, or other untoward reaction when administered to an animal, such as, for example, a human. A carrier or diluent may be a solid, semi-solid, or liquid material which serves as a vehicle, excipient, or medium for the active therapeutic substance. Some examples of the diluents or carriers which may be employed in the pharmaceutical compositions of the present disclosure are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol, and propellants such as trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane.

[0063] Solutions of the compositions disclosed herein as free bases or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile solutions or dispersions. In certain cases the form should be sterile and should be fluid to the extent that easy injectability exists. It should be stable under the conditions of manufacture and storage and may optionally be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, a polyol (i.e., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it may be preferable to include isotonic agents, such as, but not limited to, sugars or sodium chloride.

[0064] Pharmaceutical compositions for topical administration may include the compositions formulated for a medicated application such as an ointment, paste, cream, or powder. Ointments include all oleaginous, adsorption, emulsion, and water-soluble based compositions for topical

application, while creams and lotions are those compositions that include an emulsion base only. Topically administered medications may contain a penetration enhancer to facilitate adsorption of the active ingredients through the skin. Suitable penetration enhancers include glycerin, alcohols, alkyl methyl sulfoxides, pyrrolidones and luarocapram. Possible bases for compositions for topical application include polyethylene glycol, lanolin, cold cream, and petrolatum as well as any other suitable absorption, emulsion, or water-soluble ointment base. Topical preparations may also include emulsifiers, gelling agents, and antimicrobial preservatives as necessary to preserve the composition and provide for a homogenous mixture. Transdermal administration of the compositions may also comprise the use of a "patch." For example, the patch may supply one or more compositions at a predetermined rate and in a continuous manner over a fixed period of time.

[0065] It is further envisioned the compositions disclosed herein may be delivered via an aerosol. The term aerosol refers to a colloidal system of finely divided solid or liquid particles dispersed in a liquefied or pressurized gas propellant. The typical aerosol comprises a suspension of active ingredients in liquid propellant or a mixture of liquid propellant and a suitable solvent. Suitable propellants include hydrocarbons and hydrocarbon ethers. Suitable containers can vary according to the pressure requirements of the propellant. Administration of the aerosol can vary according to subject's age, weight, and the severity and response of the symptoms.

[0066] ***Dosage***

[0067] The actual dosage amount of a composition disclosed herein administered to an animal or human patient can be determined by physical and physiological factors such as body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the patient, and the route of administration. Depending upon the dosage and the route of administration, the number of administrations of a preferred dosage and/or an effective amount may vary according to the response of the subject. The compounds of the present disclosure are generally effective over a wide dosage range. The practitioner responsible for administration can, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject.

[0068] Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage can be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations can be contemplated by those preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

[0069] In other non-limiting examples, a dose may also comprise from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body

weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, etc., can be administered, based on the numbers described above. The dosages can depend on many factors, and can in any event be determined by a suitable practitioner. Therefore, the dosages described herein are not intended to be limiting

[0070] In some embodiments, the compositions further include an additional active ingredient. The preparation of a pharmaceutical composition that contains at least one compound or additional active ingredient can be known to those of skill in the art in light of the present disclosure, as exemplified by Remington's Pharmaceutical Sciences, 2003, incorporated herein by reference. Moreover, for animal (e.g., human) administration, it can be understood that preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by the FDA Office of Biological Standards.

[0071] ***Packaging of the Composition***

[0072] After formulation, the composition is packaged in a manner suitable for delivery and use by an end user. In one embodiment, the composition is placed into an appropriate dispenser and shipped to the end user. Examples of final container may include a pump bottle, squeeze bottle, jar, tube, capsule or vial.

[0073] The compositions and methods described herein can be embodied as parts of a kit or kits. A non-limiting example of such a kit comprises the ingredients for preparing a composition, where the containers may or may not be present in a combined configuration. In certain embodiments, the kits further comprise a means for administering the composition, such as a topical applicator, or a syringe. The kits may further include instructions for using the components of the kit to practice the subject methods. The instructions for practicing the subject methods are generally recorded on a suitable recording medium. For example, the instructions may be present in the kits as a package insert or in the labeling of the container of the kit or components thereof. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, such as a flash drive, CD-ROM, or diskette. In other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, such as via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

[0074] While the invention has been described with reference to various and preferred embodiments, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the essential scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof.

[0075] Certain embodiments of the compositions and methods disclosed herein are defined in the above examples. It should be understood that these examples, while indicating particular embodiments of the invention, are given by way of illustration only. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this disclosure, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the compositions and methods described herein to various usages and conditions. Various changes may be made and equivalents may be substituted for elements thereof without departing from the essential scope of the disclosure. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the disclosure without departing from the essential scope thereof.

[0076] Therefore, it is intended that the invention not be limited to the particular embodiment disclosed herein contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the claims.

CLAIMS

What is claimed is:

1. A method of treating conditions resulting from GH deficiency in a manner that does not stimulate diabetogenic activity in a subject, the method comprising:
administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof.
2. A method of treating conditions resulting from GH deficiency in a manner that does not stimulate prolactin activity in a subject, the method comprising:
administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof.
3. A method of enhancing the ability to reverse non-alcoholic fatty liver disease in a subject, the method comprising:
administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof, to enhancing the ability to reverse non-alcoholic fatty liver disease in the subject.
4. A method of treating a growth hormone deficiency in a subject, the method comprising:
administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof, to treat the growth hormone deficiency in the subject.
5. Use of a synthetic peptide to treat conditions resulting from GH deficiency in a manner that does not stimulate diabetogenic activity in a subject, the use comprising:
administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof.
6. Use of a synthetic peptide to treat conditions resulting from GH deficiency in a manner that does not stimulate prolactin activity in a subject, the use comprising:
administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof.
7. Use of a synthetic peptide to enhance the ability to reverse non-alcoholic fatty liver disease in a subject, the use comprising:

administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof, to enhancing the ability to reverse non-alcoholic fatty liver disease in the subject.

8. Use of a synthetic peptide to treat a growth hormone deficiency in a subject, the use comprising:

administering to a subject an effective amount of a composition comprising at least one of amino acid sequence having SEQ ID NO:3 (GH-V-20K), or variants thereof, to treat the growth hormone deficiency in the subject.

9. The method of any claim herein, wherein the treated subject is a human.

10. The use according to any claim herein, wherein the treated subject is a human.

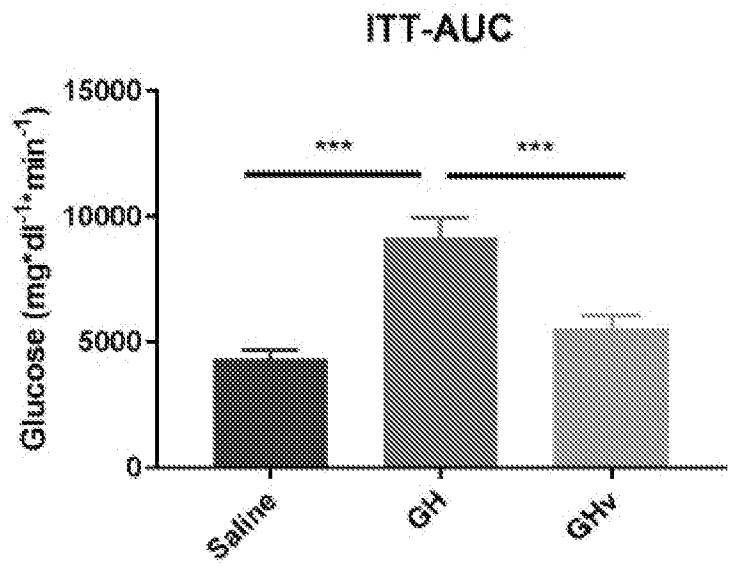


FIG. 1

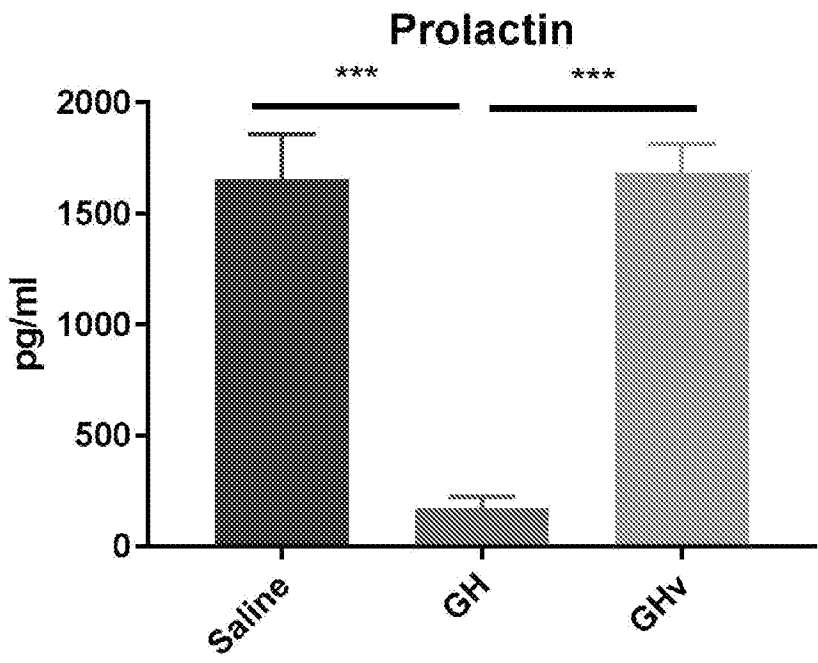


FIG. 2

2/3

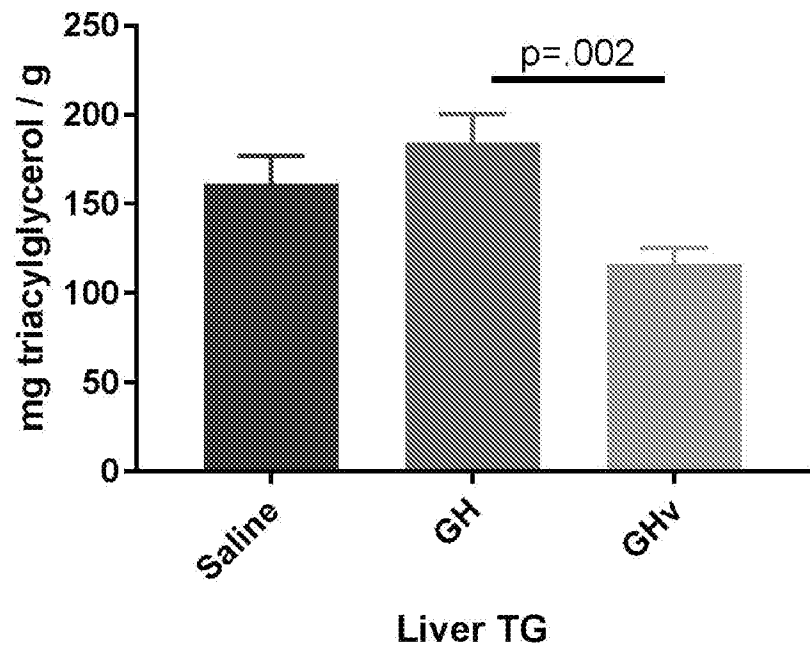


FIG. 3

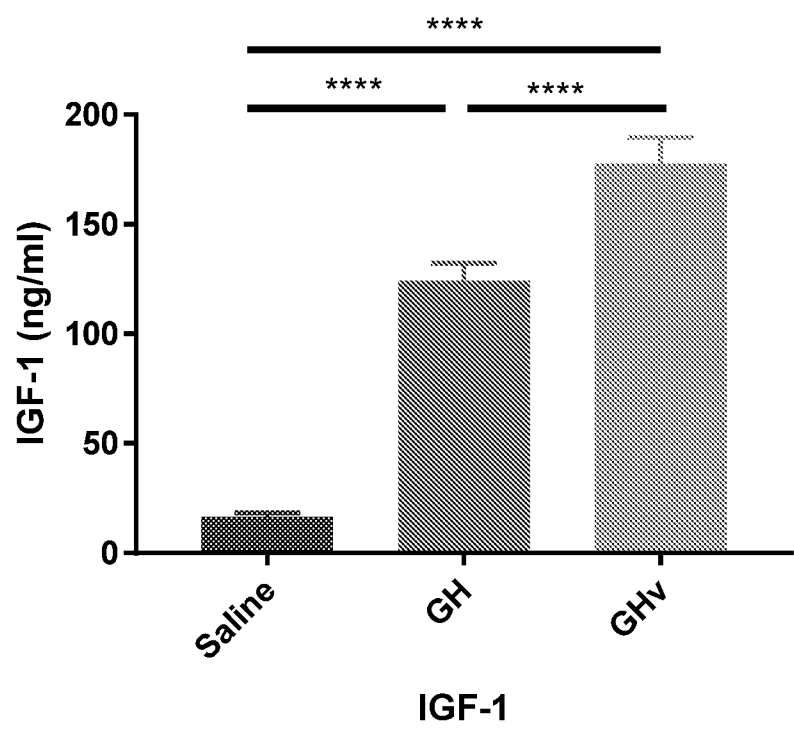


FIG. 4

3/3

GH-N 22K	fptiplsrllf	dnamlrahrl	hqlafdttyqe	feeayipkeq	kysflqnpqt
GH-V 22K	fptiplsrllf	dnamlrahrl	qlafdttyqe	feeayipkeq	kysflqnpqt
GH-V 20K	fptiplsrllf	dnamlrahrl	qlafdttyqe	-----	spqt
	slcfsesipt	psnreettgqk	snlellrlsl	lllgswlepvr	qflrsvfans
	slcfsesipt	psnreettgqk	snlellrlsl	lllgswlepvr	qflrsvfans
	slcfsesipt	psnreettgqk	snlellrlsl	lllgswlepvr	qflrsvfans
	lvygasdsnv	ydlldleeg	iqtlmrlled	gsprtggifk	qtyskfdtns
	lvygasdsnv	ydlldleeg	iqtlmrlled	gsprtggifk	qtyskfdtns
	lvygasdsnv	ydlldleeg	iqtlmrlled	gsprtggifk	qtyskfdtns
	hddallkny	gilycfrkdm	dkvetflriv	qcrsvegscg	f
	hddallkny	gilycfrkdm	dkvetflriv	qcrsvegscg	f
	hddallkny	gilycfrkdm	dkvetflriv	qcrsvegscg	f

FIG. 5