THE USE OF DES-ASPARTATE-ANGIOTENSIN I AS AN AGENT FOR THE TREATMENT AND PREVENTION OF GLOMERULOSCLEROSIS AND RENAL FAILURE

FIELD OF THE INVENTION

The present invention relates generally to a method for the treatment and/or prophylaxis of renal-related disorders. More particularly, the present invention contemplates a method for the treatment and/or prophylaxis of glomerulosclerosis and/or end stage renal failure and/or related conditions. The method of the present invention is preferably practised by the administration of a derivative of angiotensin I. Generally, but not exclusively, the angiotensin I derivative exhibits anti-angiotensin II properties. In a preferred embodiment, the angiotensin I is des-Aspartate-angiotensin I or a derivative, homologue or analogue thereof. The present invention further contemplates compositions for use in the treatment and/or prophylaxis of renal-related disorders such as but not limited to glomerulosclerosis and/or end stage renal failure.

BACKGROUND OF THE INVENTION

Renal failure and other renal related conditions contribute to significant morbidity and mortality in patients affected by such conditions. There is a need, therefore, to develop more efficacious pharmaceutical molecules useful in the treatment of renal conditions.

des-Aspartate angiotensin I (des-Asp-angiotensin I) is a nonapeptide produced from a decapeptide by the action of an aminopeptidase. The nonapeptide is produced from angiotensin I by enzymatic NH_2-terminal degradation (1). des-Asp-angiotensin I is a substrate for plasma and pulmonary angiotensin converting enzyme (2). Furthermore, des-Asp-angiotensin I acts on a specific indomethacin-sensitive subtype of angiotensin receptor (3) and to antagonize the pressor (4) and hypertrophic (5) actions of angiotensin II. Angiotensin II is a key mediator of glomerulosclerosis in progressive kidney diseases (6-8). In work leading up to the present invention, the inventors determined that the anti-angiotensin II properties of des-Asp-angiotensin I can be exploited in the treatment and/or prophylaxis of renal-related disorders.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

One aspect of the present invention contemplates a method for the treatment and/or prophylaxis of a renal-related disorder, said method comprising administering to a subject an effective amount of a derivative of angiotensin I for a time and under conditions sufficient for the onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated.

Another aspect of the present invention provides a method for the treatment and/or prophylaxis of a renal-related disorder, said method comprising administering to a subject an angiotensin II-inhibiting effective amount of a derivative of angiotensin I for a time and under conditions sufficient for the onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated.

Yet another aspect of the present invention is directed to a method for the treatment and/or prophylaxis of a renal-related disorder, said method comprising administering to a subject an effective amount of des-Asp-angiotensin I or a derivative, homologue or analogue thereof for a time and under conditions sufficient for the onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated.

Still a further aspect of the present invention provides a composition for use in the treatment and/or prophylaxis of renal-related disorders, said composition comprising a derivative of angiotensin I and a pharmaceutically acceptable carrier and/or diluent.

In yet another aspect, the invention provides a method for the treatment and/or prophylaxis of a renal-related disorder selected from the group consisting of focal or segmental glomerulosclerosis, oligomeganephronia, membranous nephropathy, minimal change nephritis, proliferative glomerulonephritis, analgesic nephropathy, diabetes mellitus, unilateral nephrectomy, cortical necrosis, unilateral renal agenesis and end stage renal failure, said method comprising administering to a subject in need thereof an effective amount of a derivative of angiotensin I for a time and under conditions sufficient for the

onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated, said derivative of angiotensin I inhibiting one or more activities of angiotensin II.

In yet another aspect , the invention provides a kit for the prophylaxis or treatment of a renal-related disorder comprising: a container suitable for storing a pharmaceutical preparation; an effective amount of des-Asp-angiotensin I or a derivative, homologue or analogue thereof in said container, said derivative, homologue or analogue inhibiting one or more activities of angiotensin II; and instructions associated with said container giving instructions for the use of said des-Asp-angiotensin I or a derivative, homologue or analogue thereof for the prophylaxis or treatment of a renal-related disorder selected from the group consisting of focal or segmental glomerulosclerosis, oligomeganephronia, membranous nephropathy, minimal change nephritis, proliferative glomerulonephritis, analgesic nephropathy, diabetes mellitus, unilateral nephrectomy, cortical necrosis, unilateral renal agenesis and end stage renal failure.

In yet another aspect, the invention provides use of des-Asp-angiotensin I or a derivative, homologue or analogue thereof, in the manufacture of a medicament for use in the prevention or treatment of a renal-related disorder selected from the group consisting of focal or segmental glomerulosclerosis, oligomeganephronia, membranous nephropathy, minimal change nephritis, proliferative glomerulonephritis, analgesic nephropathy, diabetes mellitus, unilateral nephrectomy, cortical necrosis, unilateral renal agenesis and end stage renal failure.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the determination that a derivative of angiotensin I prevents or otherwise attenuates or ameliorates the effects of glomerulosclerosis and the accompanying proteinuria in experimentally-induced

nephropathic rats. Animal models for studying renal disease are well accepted in the art (9). In accordance with the present invention, the effect of des-Asp-angiotensin I on the proteinuria in rats which had undergone sub-total nephrectomy was determined. It was surprisingly discovered that des-Asp-angiotensin was capable of preventing or otherwise ameliorating the effects of renal-related disorders.

Accordingly, one aspect of the present invention provides a method for the prophylaxis and/or treatment of a renal-related disorder, said method comprising administering to a subject an effective amount of a derivative of angiotensin I.

More particularly, the present invention contemplates a method for the treatment and/or prophylaxis of a renal-related disorder, said method comprising administering to a subject an effective amount of a derivative of angiotensin I for a time and under conditions sufficient for the onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated.

The term renal-related disorder is used herein in its broadest sense and includes focal and segmental glomerulosclerosis, oligomeganephronia, membranous nephropathy, minimal change nephritis, proliferative glomerulonephritis, analgesic nephropathy, diabetes mellitus, unilateral nephrectomy, cortical necrosis, unilateral renal agenesis and end stage renal failure. Preferably, the renal-related disorder is glomerulosclerosis and/or end stage renal failure.

A derivative of des-Asp-angiotensin I includes any mutant, fragment, part or portion of angiotensin I or des-Asp-angiotensin I including molecules comprising single or multiple amino acid substitutions, deletions and/or additions to angiotensin I or to des-Asp-angiotensin I. Generally, the derivative of angiotensin I inhibits, reduces or otherwise interferes with the activity or functioning of angiotensin II.

According to this embodiment, there is provided a method for the treatment and/or prophylaxis of a renal-related disorder, said method comprising administering to a subject an angiotensin II-inhibiting effective amount of a derivative of angiotensin I for a time and under conditions sufficient for the onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated.

The preferred derivative in accordance with the present invention is des-Asp-angiotensin I or a derivative, homologue or analogue thereof. Reference to a homologue or an analogue includes a mimotope or peptide or analogue mimetic. Such derivatives, homologues and analogues may function in place of des-Asp-angiotensin I or its equivalent or they may act as an agonist thereof or, when necessary, an antagonist thereof.

As stated above, a derivative includes single or multiple amino acid substitutions, additions and/or deletions to des-Asp-angiotensin I.

Amino acid insertional derivatives of des-Asp-angiotensin I include amino and/or carboxyl terminal fusions as well as intra-sequence insertions of single or multiple amino acids. Insertional amino acid sequence variants are those in which one or more amino acid residues are introduced into a predetermined site in the des-Asp-angiotensin I although random insertion is also possible with suitable screening of the resulting product. Deletional variants are characterized by the removal of one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one residue in the sequence has been removed and a different residue inserted in its place.

Where the des-Asp-angiotensin I is derivatized by amino acid substitution, the amino acids are generally replaced by other amino acids having like properties, such as hydrophobicity, hydrophilicity, electronegativity, bulky side chains and the like. Amino acid substitutions are typically of single residues. Amino acid insertions will usually be in the order of about 1-6 amino acid residues and deletions will range from about 1-6 residues. Preferably, deletions or insertions are made in adjacent pairs, i.e. a deletion of two residues or insertion of two residues.

Homologues include functionally, structurally or stereochemically similar polypeptides from, for example, other sources such as for livestock animals, laboratory test animals or primates. The similar peptides may also be homologues of des-Asp-angiotensin I.

Analogues and mimetics include molecules which contain non-naturally occurring amino acids as well as molecules which do not contain amino acids but nevertheless behave functionally the same as the des-Asp-angiotensin I. Analogues contemplated herein include modifications to side chains, incorporation of unnatural amino acids and/or their derivatives

during peptide synthesis and the use of crosslinkers and other methods which impose conformational constraints on the peptide molecule or their analogues.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids.

Crosslinkers can be used, for example, to stabilize 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety.

All these types of modifications may be important to stabilize the subject des-Asp-angiotensin I. This may be important if used, for example, in the manufacture of a vaccine or therapeutic composition or in detection assays. Examples of unnatural amino acids contemplated by the present invention are presented in Table 1.

TABLE 1

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α-aminobutyric acid	Abu	L-N-methylalanine	Nmala
α-amino-α-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
aminocyclopropane-carboxylate	Cpro	L-N-methylasparagine	Nmasn
		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-carboxylate	Norb	L-N-methylglutamine	Nmgln
		L-N-methylglutamic acid	Nmglu
cyclohexylalanine	Chexa	L-N-methylhistidine	Nmhis

	cyclopentylalanine	Cpen	L-N-methylisolleucine	Nmile
	D-alanine	Dal	L-N-methylleucine	Nmleu
	D-arginine	Darg	L-N-methyllysine	Nmlys
	D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
5	D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
	D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
	D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
	D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
	D-isoleucine	Dile	L-N-methylproline	Nmpro
10	D-leucine	Dleu	L-N-methylserine	Nmser
	D-lysine	Dlys	L-N-methylthreonine	Nmthr
	D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
	D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
	D-phenylalanine	Dphe	L-N-methylvaline	Nmval
15	D-proline	Dpro	L-N-methylethylglycine	Nmetg
	D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
	D-threonine	Dthr	L-norleucine	Nle
	D-tryptophan	Dtrp	L-norvaline	Nva
	D-tyrosine	Dtyr	α-methyl-aminoisobutyrate	Maib
20	D-valine	Dval	α-methyl-α-aminobutyrate	Mgabu
	D-α-methylalanine	Dmala	α-methylcyclohexylalanine	Mchexa
	D-α-methylarginine	Dmarg	α-methylcylcopentylalanine	Mcpen
	D-α -methylasparagine	Dmasn	α-methyl-α-napthylalanine	Manap
	D-α-methylaspartate	Dmasp	α-methylpenicillamine	Mpen
25	D-α -methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D-α-methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D-α-methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
	D-α -methylisoleucine	Dmile	N-amino-α-methylbutyrate	Nmaabu
	D-α-methylleucine	Dmleu	α-napthylalanine	Anap
30	D-α-methyllysine	Dmlys	N-benzylglycine	Nphe
	D-α-methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln

	D-α-methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
	D-α-methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
	D-α-methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
	D-α-methylserine	Dmser	N-cyclobutylglycine	Ncbut
5	D-α-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D-α-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D-α-methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
	D-α-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
10	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
15	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl))glycine	Nser
	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl))glycine	Nhis
	D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
	D-N-methyllysine	Dnmlys	N-methyl-α-aminobutyrate	Nmgabu
20	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
25	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyla-napthylalanine	Nmanap
	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	α-aminobutyric acid	Gabu	N-(*p*-hydroxyphenyl)glycine	Nhtyr
30	L-*t*-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
	L-ethylglycine	Etg	penicillamine	Pen

L-homophenylalanine	Hphe	L-α-methylalanine	Mala
L- -methylarginine	Marg	L-α-methylasparagine	Masn
L- -methylaspartate	Masp	L-α-methyl-*t*-butylglycine	Mtbug
L- -methylcysteine	Mcys	L-methylethylglycine	Metg
L- -methylglutamine	Mgln	L-α-methylglutamate	Mglu
L- -methylhistidine	Mhis	L-α-methylhomophenylalanine	Mhphe
L- -methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
L- -methylleucine	Mleu	L-α-methyllysine	Mlys
L- -methylmethionine	Mmet	L-α-methylnorleucine	Mnle
L- -methylnorvaline	Mnva	L-α-methylornithine	Morn
L- -methylphenylalanine	Mphe	L-α-methylproline	Mpro
L- -methylserine	Mser	L-α-methylthreonine	Mthr
L- -methyltryptophan	Mtrp	L-α-methyltyrosine	Mtyr
L- -methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane	Nmbc		

The present invention further contemplates chemical equivalents of the des-Asp-angiotensin I. Chemical equivalents may not necessarily be derived from the subject des-Asp-angiotensin I itself but may share certain conformational or functional similarities. Alternatively, chemical equivalents may be specifically designed to mimic certain physiochemical properties of the des-Asp-angiotensin I. Chemical equivalents may be chemically synthesized or may be detected following, for example, natural product screening. Preferably, a chemical equivalent is a functional equivalent.

As mentioned above, included within the scope of the present invention are functionally-equivalent variants of des-Asp-angiotensin I and their fragments and precursors. "Functionally-equivalent" is used herein to define peptides or polypeptides related to or derived from the angiotensin I or its derivative such as des-Asp-angiotensin I where the

amino acid sequence has been modified by single or multiple amino acid substitutions, addition and/or deletion and also sequences where the amino acids have been chemically modified, including by deglycosylation or glycosylation, but which nonetheless retain anti-angiotensin II activity.

Reference herein to the des-Asp-angiotensin I of the present invention should be read as including reference to all forms of this molecule including, by way of example, isoforms, monomeric, dimeric and multimeric forms and peptide fragments of the des-Asp-angiotensin I as well as homologues and functional equivalents thereof. Other functionally equivalent derivatives or homologues of angiotensin I are also encompassed by this term.

The amino acid variants referred to above may readily be made using peptide synthetic techniques well known in the art, such as solid phase peptide synthesis and the like, or by recombinant DNA manipulations. Techniques for making substitution mutations at predetermined sites in DNA having known or partially known sequence are well known and include, for example, M13 mutagenesis. The manipulation of DNA sequence to produce variant proteins which manifest as substitutional, insertional or deletional variants are conveniently described, for example, in Sambrook *et al.* (10).

Accordingly, another aspect of the present invention provides a method for the treatment and/or prophylaxis of a renal-related disorder, said method comprising administering to a subject an effective amount of des-Asp-angiotensin I or a derivative, homologue or analogue thereof for a time and under conditions sufficient for the onset of the renal-related disorder to be prevented, inhibited or delayed or the symptoms of the renal-related disorder to be ameliorated.

Yet a further aspect of the present invention contemplates the use of a derivative of angiotensin I in the manufacture of a medicament in the treatment and/or prophylaxis of renal-related disorders.

The present invention further provides a composition for use in the treatment and/or prophylaxis of renal-related disorders, said composition comprising a derivative of angiotensin I and a pharmaceutically acceptable carrier and/or diluent.

Preferably, the derivative of angiotensin I inhibits angiotensin II activity or all or part of the

effects of angiotensin II.

Most preferably, the derivative is des-Asp-angiotensin I or a derivative, homologue or analogue thereof.

Preferably, the renal-related disorder is glomerulosclerosis and/or end stage renal failure.

According to this aspect of the present invention, an effective amount of the derivative of angiotensin I such as but not limited to des-Asp-angiotensin I or a derivative, homologue or analogue thereof or salt thereof, or a pharmaceutical composition containing the same, as described below, is administered to a subject, such as a human patient, *via* any acceptable method known in the art, either singly or in combination with other pharmaceutical agents such as captopril or other angiotensin converting enzyme inhibitors or angiotensin receptor antagonists. The compound or composition is administered orally, by suppository, or parenterally (e.g. intramuscularly, intravenously, subcutaneously or intradermally), and in the form of either solid or liquid dosage including tablets, suspensions, or solutions, as is discussed in more detail below. The administration may be conducted in single dosage form with continuous therapy or in single dose therapy *ad libitum*.

Useful pharmaceutical carriers for the preparation of the pharmaceutical compositions hereof can be solids, liquids or mixtures thereof; thus, the compositions can take the form of tablets, pills, capsules, powders, enterically coated or other protected formulations, sustained release formulations, erodible formulations, implantable devices or components thereof, microsphere formulations, solutions, suspensions, elixirs, aerosols and the like.

Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic) for injectable solutions. The carrier can be selected from various oils including those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, mineral oil, sesame oil, and the like. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The composition may be subjected to conventional pharmaceutical expedients such as sterilization and may contain conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or

emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulations are described in Martin, ARemington=s Pharmaceutical Sciences, 15th Ed.; Mack Publishing Co., Easton (1975); see, e.g. pp. 1405-1412 and pp 1461-1487. Such compositions will, in general, contain an effective amount of the active compound together with a suitable amount of carrier so as to prepare the proper dosage form for proper administration to the host.

In one preferred embodiment, the therapeutic methods of the present invention are practised when the relief of symptoms is specifically required or perhaps imminent; in another preferred embodiment, the method hereof is effectively practised as a continuous or prophylactic treatment.

In the practice of the therapeutic methods of the invention, the particular dosage of pharmaceutical composition to be administered to the subject will depend on a variety of consideration including the stage of the disease or condition, the severity thereof, the schedule of administration, the age and physical characteristics of the subject, and so forth. Proper dosages may be established using clinical approaches familiar to the medicinal arts.

Although the present invention is particularly exemplified herein in relation to rats, it is understood that the present invention extends to the use of the angiotensin derivatives in any mammal including, but not limited to, humans, mice, rabbits, livestock animals and primates.

The present invention is further described in the following non-limiting Examples.

EXAMPLE 1

Source of Materials

Des-Asp-angiotensin I was obtained from Bachem (Dubendorf, Switzerland). Des-Aspartate-angiotensin I can be prepared by techniques well known in the art. Adult Sprague Dawley rats (SD, 250 - 300 g) were obtained from the Animal Center, National University of Singapore.

EXAMPLE 2

Induction of Glomerulosclerosis and Proteinuria

Five-sixths nephrectomy was carried out as described by Morrison (11). Briefly, each animal was anaesthetized with 7% w/v chloral hydrate (0.4 g/kg, i.p.). An incision was made in the ventral abdominal wall to access the kidneys. Right nephrectomy was performed and the cranial and caudal third of the left kidney were cut off. Tissue adhesive (Histoccryl, B. Braun) was used to seal the cut ends of the left kidney and prevent bleeding. In this way 5/6 of the renal parenchyma was removed. This model results in focal and segmental glomerulosclerosis, resembling renal lesions in humans like oligomeganephronia, membranous nephropathy, minimal change nephritis, proliferative glomerulonephritis, analgesic nephropathy, diabetes mellitus, unilateral nephrectomy, cortical necrosis, and unilateral renal agenesis (9).

EXAMPLE 3

Measurement of Urine Protein Excretion and Treatment with Des-Asp-Angiotensin I

Following the operation, each animal was placed in a metabolic cage for 24 hours once a week for a duration of 8 weeks. The 24-hour urine output and the concentration of protein in the urine were measured. After the 8th week, the animals were randomly divided into two groups (8 animals per group). Animals in one of the group (the treatment group) were orally administered 762 nmoles/kg/day of des-Asp-angiotensin I dissolved in 0.5 ml of saline via a 1-ml syringe with a blunted needle for a period of 8 weeks. The dose of 762 nmoles/kg/day was calculated based on the maximum effective oral anti-cardiac hypertrophic dose (250 nmole per rat of average weight of 328 g) in the original parent patent. Animals in the other group (the control group) were similarly administered with 0.5 ml of saline. Weekly measurement of 24-hour urine output and the concentration of protein in the urine in these animals were carried out for another 8 weeks. The protocol was designed based on our preliminary observation that urinary excretion of protein in the 5/6 nephrectomized rats commenced to increase above the normal value in 7th to 8th week post nephrectomy. A repeat of the experiment with 12 nephrectomized rats per group was carried out.

To study the effect of des-Asp-angiotensin I on normal rats per se, one group of normal rats

(12 animals) were treated with saline and another 12 normal rats treated with 762 nmoles/kg/day. Their once a week 24-hour urine output and urine protein concentration were similarly measured.

EXAMPLE 4

Effect of des-Asp-angiotensin

The results of the study are summarized in Table 2, Table 3 and Table 4. Data were expressed as mean ± SEM. Significant differences were determined by one way ANOVA and post hoc Newman Kleuf test. The accepted level of significance was $p < 0.05$. Des-Asp-angiotensin I is an effective agent in attenuating the progressive development of proteinuria in ablation nephropathic rats. The anti-proteinuric action is brought about by an oral dose of 762 nmoles/kg/day. At this oral dose, the nonapeptide had no effect on the urinary excretion of protein in normal rats.

TABLE 2

Effects of des-Asp-angiotensin I on proteinuria in rats

Animal Groups	24-hour urinary excretion of protein (mg)	
	Weeks 1-8	Weeks 9-16
Ablation proteinuric rats (control group)	18.7 ± 2.8	37.2 ± 2.3
Ablation proteinuric rats (treatment group)	16.4 ± 1.6	*28.7 ± 2.5

Values were mean ± SEM obtained from 8 individual rats. *Significantly different ($p = 0.024$) from the corresponding value of the control group.

TABLE 3

Effects of des-Asp-angiotensin I on proteinuria in rats

Animal Groups	24-hour urinary excretion of protein (mg)	
	Weeks 1-8	Weeks 9-16
Ablation proteinuric rats (control group)	19.5 ± 1.9	51.7 ± 4.7
Ablation proteinuric rats (treatment group)	19.9 ± 1.5	*39.6 ± 3.3

Values were mean ± SEM obtained from 12 individual rats. *Significantly different ($p = 0.048$) from the corresponding value of the control group.

TABLE 4

Effects of des-Asp-angiotensin I on urinary protein excretion in normal rats

Animal Groups	24-hour urinary excretion of protein (mg)	
	Weeks 1-8	Weeks 9-16
Normal rats (control group)	18.7 ± 1.8	19.9 ± 2.2
Normal rats (treatment group)	16.1 ± 1.7	17.8 ± 1.1

Values were mean ± SEM obtained from 12 individual rats.

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1. Use of des-Asp-angiotensin I or a derivative, homologue or analogue thereof, in the manufacture of a medicament for use in the prevention or treatment of a renal-related disorder selected from the group consisting of focal or segmental glomerulosclerosis, oligomeganephronia, membranous nephropathy, minimal change nephritis, proliferative glomerulonephritis, analgesic nephropathy, diabetes mellitus, unilateral nephrectomy, cortical necrosis, unilateral renal agenesis and end stage renal failure.

2. The use according to Claim 1 wherein said derivative is suitable for being orally administered.

3. The use according to any one of the preceding claims wherein said derivative is suitable for being administered by suppository.

4. The use according to any one of the preceding claims wherein the derivative is suitable for being parenterally administered.

5. The use according to any one of the preceding claims wherein said derivative is in the form of a solid dosage.

6. The use according to any one of the preceding claims wherein said derivative is in the form of a liquid dosage.