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(54) THE USE OF INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM FOR THE TREATMENT OF HYPOXIA OR IMPAIRED METABOLIC FUNCTION

VERWENDUNG VON HEMMERN DES RENIN-ANGIOTENSIN SYSTEMS ZUR BEHANDLUNG VON HYPOXIE ODER VERRINGERTEM STOFFWECHSEL

UTILISATION D'INHIBITEURS DU SYSTEME RENINE-ANGIOTENSINE POU LE TRAITEMENT DE L'HYPOXIE OU DE LA DIMUNITION DE LA FONCTION METABOLIQUE

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DescriptionField of the Invention

[0001] This invention relates to the use of inhibitors of the renin-angiotensin system.

Background of the Invention

[0002] Wasting diseases may be categorised into generalised and localised wasting diseases. To deal first with generalised wasting, many disease processes can lead to aggressive generalised weight loss through either the inability to consume sufficient nutrients and energy sources, through their loss from the body (either enterally or in the form of cellular matter), or through an inability to absorb them. Other diseases are associated with marked weight loss quite out of proportion to any reduction in nutrient absorption or increase in nutrient loss. Such weight loss may have a metabolic origin. Severe cardiac failure as well as renal, hepatic and malignant disease processes are all associated with such inappropriate weight loss. Some neurological diseases, such as Parkinson's disease and syndrome are similarly related, as are conditions associated with inflammatory processes, such as severe sepsis or septic shock and autoimmune and connective tissue disorders. This weight loss may at best be disabling and at worst associated with an increased mortality. Current treatment and preventative strategies largely focus on nutritional support.

[0003] In localised wasting, disuse of any given muscle group (for instance due to musculoskeletal or neurological injury) may lead to wasting in the affected territory. There are currently no available treatments which are routinely used to slow or limit such wasting, nor which have been shown to accelerate the reversal of such wasting with appropriate exercise or after the cessation of the initiating disease state.

[0004] Current strategies for the promotion of trainability and fitness have largely focused on alterations in training pattern. More recently, nutritional supplementation has been suggested using the manipulation of scale and nature of intake of carbohydrates, fats, vitamins and amino acids. The addition of other substrates, such as creatine derivatives, have also been used. Most such interventions are either currently unproven, or have been shown to have no or only modest influence. Endocrinological interventions have been attempted, including the use of androgens and other steroid hormones. The use of insulin or of growth hormone may also have a role. However, these treatments may be associated with an unacceptable side-effect profile and also suffer from the disadvantage that they have to be parenterally administered (usually by intramuscular injection). Pharmacological manipulations are not currently available.

[0005] The possibility of improving cardiovascular, and other organ, function is known in connection with

the phenomenon of "preconditioning". The exposure of an organ - most notably the heart - to a brief period of reduced blood flow or oxygen supply has been shown to provide protection against a second more severe similar event which might otherwise prove lethal to cells or the organ itself. Much research is currently being undertaken in an effort to identify pharmacological agents which might mimic this process. None is available for routine clinical practice.

[0006] The renin-angiotensin system (RAS) and its components may be described as follows. Briefly, cells of the renal juxta-glomerular apparatus produce the aspartyl protease renin which acts on the alpha-2 globulin angiotensinogen (synthesised in the liver) to generate angiotensin I (AI). This non-pressor decapeptide is converted to angiotensin II (ATII) by contact with the peptidyldipeptidase angiotensin-converting enzyme (ACE) (reviewed in (1)). ATII stimulates the release of aldosterone, and is also a potent vasoconstrictor. The renin-angiotensin system is therefore important in the maintenance and control of blood pressure as well as the regulation of salt and water metabolism. Renin, angiotensinogen and ACE have also been identified in cardiovascular tissues including the heart (2) and blood vessels, as has mRNA for components of this system such as angiotensinogen (3-5). Receptors for angiotensin II have been found on vascular smooth muscle cells (6). Within tissues, the RAS may therefore have a local paracrine function (reviewed in (7, 8)), and the expression of the different components can be altered by pathophysiological stimuli such as sodium restriction (5). Kinetic studies suggest that much of the circulating angiotensin I and II is derived from the both renal and non-renal tissues (9-11).

[0007] ACE is a zinc metallo-protease which catalyses conversion of the inactive decapeptide ATI to the active octapeptide ATII thorough the hydrolytic cleavage of dipeptides from the carboxyl terminus His-Leu dipeptide. It also catalyses inactivation of bradykinin (a patent vasodilator) by two sequential dipeptide hydrolytic steps; in this context, ACE is also known as kininase II.

[0008] The presence of renin-angiotensin system (RAS) components in many animal species (such as locusts and elasmobranchs) suggests that they must have some other role than that of a conventional circulating RAS. This function must be fundamental and important in order to have been phylogenetically conserved over many millions of years. In fact, complete renin-angiotensin systems are now thought to exist within many human (and animal) tissues: physiologically-responsive gene expression of RAS components within these tissues, local generation of ATII, the presence of ATII receptors and the demonstration that these receptors are physiologically active have all been shown. Thus, angiotensinogen messenger RNA (mRNA) is identified in renal, neural and vascular tissues, and local synthesis may strongly influence its concentration in interstitial fluid (10). Renin mRNA (12) and product (13)

is found in cultured mammalian vascular smooth muscle cells and throughout the vessel wall (13), and in rat ileum, brain, adrenal, spleen, lung, thymus and ovaries. Liver renin gene expression is physiologically responsive, being increased 3-fold by sodium deprivation or captopril administration (14).

[0009] Non-renin angiotensinogenases may also exist in tissues. A neutral aspartyl protease with renin-like activity has been demonstrated in canine brain (15, 16). Some (e.g. tonin, elastase, cathepsin G and tissue plasminogen activator) can cleave ATII directly from angiotensinogen (16).

[0010] ACE expression occurs at high level in vascular endothelium, but also in the small intestinal epithelium, the epididymis (17) and brain (15). Tissue-specific/age-related ACE gene transcription occurs in renal tissue (where there is very high proximal tubular epithelial expression), and in cardiovascular, hepatic and pulmonary tissues (18).

[0011] Such local systems may be paracrine in nature: receptors for ATII are classically described as existing on cell surfaces, allowing transduction of the effects of endocrine and paracrine ATII. However, true autocrine systems (intracellular production and actions) may also exist. ATII receptors may also exist on the cell nuclei. Specific binding sites for ATII exist on cellular chromatin which may regulate gene transcription (19, 20).

[0012] There are many marketed or investigation-stage agents which inhibit RAS activity, and many of them fall into two broad classes: the inhibitors of angiotensin-converting enzyme, whose approved names generally end in "-pril" or in the case of active metabolites "-prilat", and antagonists at angiotensin receptors (more specifically, currently, the AT₁ receptor), whose approved names generally end in "-sartan". Also potentially of increasing importance may be a class of drugs known as neutral endopeptidase inhibitors, some of which will also have an ACE-inhibitory effect or the potential to reduce RAS activity.

[0013] Brink *et al.* (21) suggested that angiotensin II may have a metabolic effect in rats (*in vivo* experimental work) which is independent of its effects on blood pressure.

[0014] There is evidence that angiotensinogen gene expression is differentially modulated in fat tissue in obese rats when compared to their equivalent lean strain (22).

[0015] ACE inhibition increases rabbit hind leg oxygen consumption at high work loads, but not at lower workloads (23).

[0016] ACE inhibitor (ACEI) increases insulin-dependent glucose uptake into the skeletal muscle of an obese rat strain which exhibits relative insulin-resistance (24), and this may be kinin-dependent (25). Glucose transporter levels were elevated in this study, as they were sustained by AT₁ receptor antagonism in the diabetic rat heart (26).

[0017] ATII increases rat hind limb O₂ usage and twitch tension (27). This paper concludes that the effects might have been due to effects on blood flow or neurotransmission and not to a direct metabolic effect.

[0018] In heart failure in dogs, fatigue-resistant fibres are conserved by ACE inhibitor therapy (28). In rats, capillary density is maintained, and collagen volume reduced (29, 30).

[0019] Kinases (such as ACE) have been shown to exist in the cell membranes of human skeletal muscle (31). Thus, skeletal muscle RAS may exist (32).

[0020] *In vitro*, ACE inhibitors cause an increase in myocardial oxygen utilisation. Whether this was due to increased or reduced efficiency was unclear (33). This work related to myocardial muscle extracts. This effect may be due to reduced kinin breakdown, and thus increased kinin levels, despite the fact that angiotensin II may modulate (and increase) kinin release (34).

[0021] Other publications suggest an effect of ACE inhibitors or of angiotensin II on muscle performance or metabolism, but all of these have concluded that the effects are mediated by alterations in nutritive blood flow (35, 36).

[0022] In human forearm, kinins increase blood flow and glucose uptake, although again a direct effect of RAS, or an effect on performance, was not detailed (37).

[0023] Losartan (an AT₁ antagonist) improves insulin sensitivity in human skeletal muscle (38).

[0024] Other publications suggest no beneficial effect of ACE inhibition, amongst those with heart failure in muscle energy balance (39). ACE inhibition did not alter perceived work or maximal work capacity of 20 students on a bicycle ergometer (40).

35 Summary of the Invention

[0025] It has now been found that renin-angiotensin systems are implicated in the regulation of cellular metabolic efficiency, in the mechanical efficiency of tissue systems such as cardiac and skeletal muscle, and in the regulation of growth of cardiac and skeletal muscle. This observation leads to the possibility of down-regulating the activity of this system (thus reducing the action of the substance angiotensin II and increasing the activity of kinins) so as to enhance metabolic efficiency and enhance mechanical performance of tissues. Such enhancement allows improved management of diseases involving wasting, consistent with the discovery of a previously unknown effect of RAS-inhibitors, i.e. for the promotion of metabolic function or efficiency.

[0026] Improvement in metabolic function or efficiency may be seen as: improvement of cellular function and survival in the presence of low oxygen supply relative to demand; enhancement of mechanical performance of human skeletal and cardiac muscle; and/or enhancement of nutritional status.

[0027] According to the present invention, a lipophilic inhibitor of the renin-angiotensin system is used for the

manufacture of a medicament for the treatment or prevention of wasting or cachexia or its recurrence, wherein the wasting or cachexia is associated with ageing, hepatic or malignant disease, a chronic or acute inflammatory process, or musculoskeletal or neurological injury.

[0028] Evidence presented below indicates that the effect of RAS inhibitors on mitochondrial function is consistent with the theory presented herein. It also explains the utility of such agents in cardiac problems, but broadens the scope of their utility, e.g. to non-cardiac uses, in brain, liver, kidney etc, and in skeletal muscle. Cells are able to function effectively under conditions of reduced oxygen availability, and/or to utilise oxygen more efficiently.

[0029] Inhibitors of RAS have been given to subjects having raised blood pressure, and it may be that this will have provided effects associated with the present invention. An aspect of the present invention is the realisation that such agents are useful when the subject has normal blood pressure, and that the effects are independent of any effect on blood pressure. The invention is of value where undue reduction in blood pressure does not occur, or is not a problem.

Description of the Invention

[0030] The invention may be utilised to affect any RAS. Amongst other tissues, local tissue renin-angiotensin systems have been suggested in the brain, blood vessel wall, heart, intestine, liver and kidney.

[0031] Having described the various components of the RAS above, it will be apparent that the system can be inhibited at various points. In principle, it is expected that any sufficiently non-toxic compound which is bioavailable and active to inhibit the RAS system at any suitable point can be used in the invention. This invention contemplates the administration of all such agents (either singly or in combination with each other and/or with other classes of pharmacological agents), and also of pro-drugs which are converted *in vivo* to an active agent which inhibits RAS activity. Note that RAS inhibition need not be total inhibition; rather, sufficient inhibition to be beneficial in the invention is all that is required. In practice, it is preferred at the present state of knowledge to use in the practice of the invention any of the known RAS inhibitors which are either on the market or under investigation for their antihypertensive effects.

[0032] Many inhibitors of the renin-angiotensin system are licensed or under investigation for use in humans in the United Kingdom and are compounds whose use is preferred in the practice of the invention. They include the ACE-inhibitors Quinapril, Captopril, Lisinopril, Perindopril, Trandolapril, Enalapril, Moexipril, Fosinopril, Ramipril, Cilazapril, Imidapril, Spirapril, Temocapril, Benazepril, Alacepril, Ceronapril, Cilazapril, Delapril, Enalaprilat and Moveltipril. Suitable angiotensin II-inhibitors include Losartan, Valsartan, Irbesartan, Candesartan, Eprosartan, Tasosartan and Telmisartan.

[0033] The specific compounds listed may be useful in accordance with the invention in their free form, for example as the free acid or base as the case may be, and they may be useful as acid addition salts, esters, N-oxides or other derivatives as appropriate. The use of

5 suitable pro-drugs (whether themselves active or inactive) and the use of active metabolites of RAS inhibitors are also within the scope of the invention. For example, alacepril is a pro-drug for captopril, and enalaprilat is an 10 active metabolite of enalapril.

[0034] Although ACE inhibitors and angiotensin II-receptor antagonists are presently the most widely developed classes of drugs suitable for use in the present invention, the invention is by no means limited to their use.

15 Other inhibitors of the RAS system include renin inhibitors and neutral endopeptidase inhibitors: ACE inhibitors may work through both a reduction in ATII formation and through a reduction in kinin metabolism. Other agents may also inhibit kinin degradation, and as such

20 have similarly beneficial effects. These classes of drugs include inhibitors of neutral endopeptidases, some of which also of ACE-inhibitory properties. The invention thus contemplates the use of all kininase-inhibitors and kinin receptor antagonists (such as bradykinin).

[0035] In many circumstances, it may be that a combination of the tissue/metabolic effects of such antagonists to the RAS with their systemic effects (e.g. reduced blood pressure, reduced cardiac preload or afterload and vasodilatation) and other combined effects (e.g. 30 ventricular remodelling) may be of value. Such circumstances might be in the treatment of patients with hypertension, peripheral vascular disease, cardiac failure or cardiac hypertrophy.

[0036] In normotensive subjects, or in hypotensive individuals (either through the effect of other drugs, through natural phenotype, or through disease states such as sepsis or septic shock) any further reduction in blood pressure or other systemic effects of RAS antagonists might be disadvantageous. Under such circumstances, the use of lipophilic, or even highly lipophilic,

40 agents may have advantages in enabling tissue-RAS inhibition to be achieved without effect on systemic blood pressure. That this can be done in animals has been shown by many groups. Indeed, even in a profoundly 45 hypertensive animal model, 5 µg/kg/day of ramipril administered to rats had no effect on systolic blood pressure. This technique of using very low doses of a lipophilic ACE inhibitor has also been applied to humans: a low dose of ramipril could produce significant biological 50 effect without any recordable effect on systemic blood pressure (41).

[0037] The invention contemplates the use of compounds which are essentially non-lipophilic, or only moderately lipophilic, but which have been rendered 55 more lipophilic either chemically, such as by appropriate derivatisation, or physically, such as by formulation with lipophilic carriers or delivery systems.

[0038] Compounds having activities as described

above are useful, in accordance with the invention, for promoting metabolic function or efficiency and hence improved biochemical and mechanical function. This may be achieved through a variety of mechanisms (above) which may include:

- improved blood supply (and hence substrate supply);
- increased substrate uptake (e.g. of glucose or oxygen); and/or
- improved cellular efficiency in the use of these substrates (e.g. achieving the same mechanical or biochemical work for the use of less oxygen or metabolic substrates).

[0039] The first two examples may be regarded as improved metabolic function, and the third may be regarded as improved metabolic efficiency.

[0040] Generally speaking, a RAS inhibitor may be administered at any effective but tolerated dose, and the optimum dose and regimen can be established without undue difficulty by essentially conventional trial work. Some general guidance follows, but ultimately the appropriate dosage and regimen of each drug for the various conditions within the ambit of the invention will be within the control of the clinician or physician. In general, compounds useful in the invention may be given by oral therapy (by mouth) or enteric therapy (administration through nasogastric, nasoenteric or other enteric feeding tubes) or parenterally, such as intravenously, for example by the addition of compound(s) to bags of parenteral nutrition.

Generalised wasting: It has been discussed that many disease processes, including severe cardiac, renal, hepatic and malignant disease, respiratory disease, AIDS, and chronic or acute inflammatory processes such as severe sepsis (or septic shock) and autoimmune and connective tissue disorders, can lead to a generalised weight loss through a metabolic mechanism. The present invention enables the prevention or treatment of such conditions with the RAS inhibiting agents as described above. It is anticipated that low doses of such agents (e.g. $\leq 1.25\text{mg}$ of ramipril) may be effective. In principle, however, a similar strategy to that used in the treatment of heart failure would seem most likely to be used, namely a steady increase in dosage to a maximum tolerated. The major limiting factors in treatment may be:

- a. The development of cough in some individuals treated with an ACE inhibitor, although switch to another agent or class of agent might be possible; and/or
- b. A significant fall in blood pressure. At doses of 2.5mg ramipril (or equivalent of other agents), a first-dose fall in blood pressure occurs with the same frequency as is seen with placebo in trials of treatment of acute myocardial infarction, suggest-

ing that in many this sort of dose would be safe.

[0041] Appropriate doses for critically-vasodilated patients (such as those with septic shock) would be established following appropriate protocols known to those skilled in the art and/or by titration to an individual patient..

5 Localised wasting: Dosage of the RAS inhibitor may be at the maximum tolerated dose, as in the published 10 range for each agent for use in treating heart failure or hypertension. Low doses (such as 1.25mg ramipril) may allow benefit without any significant hypotensive effect, as discussed above.

[0042] As far as formulation and administration are 15 concerned, it is expected that the various drugs useful in the invention could be administered in the same formulations as currently exist. New formulations might be developed with the express intent of being able to exert a predominantly tissue-effect without significant systemic hypotensive effects, in the same way as has been described for low-dose ramipril, or for local tissue delivery or for intravenous or intra-arterial administration. Currently, there has been an emphasis on the oral administration of most of these agents. However, formulations 20 to allow systemic parenteral administration may enhance the ability to treat the critically ill, or those undergoing interventions leading to vascular occlusion or low blood flow rates as indicated above. Additionally, new formulations (for example, for local delivery, as already mentioned) may become available.

[0043] Administration of the active agent may be by 25 any suitable route. As is conventional for ACE inhibitors at least oral administration may be preferred, especially for the purposes of achieving a prophylactic or preventative effect. In certain circumstances, especially when a more immediate effect is required, intravenous administration may be preferred. Suitable formulations for intravenous administration will be evident to those skilled in the art.

[0044] In the above discussion, indicative doses have 30 been given, by way of example only, as optimal doses may be established experimentally and/or clinically. It should be noted that useful doses in accordance with the invention may be below optimal anti-hypertensive doses or even below effective anti-hypertensive doses.

[0045] The optimum frequency of dosage and duration of treatment may also be established experimentally and/or clinically. Again by way of example, oral ramipril may be given once daily for an appropriate period of 35 time. Frequencies of dosage for other compounds useful in the invention will vary, and will depend on, among other things, the pharmacokinetics of the compound in question. **[deletion(s)]**

[0046] The invention may be used in the treatment of 40 subjects exhibiting severe cachexia, as has been observed in cases of TB, HIV, pleural effusion, meningitis, hepatitis, perforated stomach ulcer, liver cirrhosis, cellulitis, hepatoma, sickle cell anemia, appendicitis, si-

nusitis, dysphagia, abcess, pneumonia, chronic diarrhoea, encephalopathy and bone fracture.

[0047] The following Example illustrates the invention and the evidence on which it is based.

Example

[0048] This Example demonstrates that ACE inhibitors increase the mitochondrial membrane potential of cardiomyocytes. It is based on observation of the potential difference ($\Delta\Psi_m$) across the inner mitochondrial membrane that is generated by the extrusion of protons to the outside of the mitochondrion during the transport of electrons from electron-carrying coenzymes to molecular oxygen. Part of the energy stored in $\Delta\Psi_m$ is utilised to support the synthesis of most of the ATP derived from aerobic metabolism. Thus, $\Delta\Psi_m$ is an indicator of the energisation state of the mitochondrion, and also of the efficiency of oxygen utilisation to generate chemical energy. To investigate whether some of the therapeutic properties of ACE inhibitors could be accounted for by an increase in $\Delta\Psi_m$, this parameter was examined in rat cardiomyocytes, following pre-treatment with the ACE inhibitor lisinopril.

[0049] More particularly, cardiomyocytes were isolated from new-born Sprague-Dawley rats hearts and maintained in 30 mm tissue culture dishes in the presence of DMEM supplemented with 1% foetal calf serum at 37°C in a humidified 5% CO₂ atmosphere. For experiments, cultures were treated with 1 μ M lisinopril or with an equivalent amount of vehicle for various lengths of time, before analysis of $\Delta\Psi_m$.

[0050] To measure $\Delta\Psi_m$, the mitochondrial-specific probes rhodamine 123 (Rh123) and 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolocarbocyanine iodide (JC-1) were used. Cells were incubated for 15 min with 2.5 μ M Rh123 or for 10 min with 10 μ g/ml JC-1 (Molecular Probes) in fresh culture medium, at 37°C and 5% CO₂. The cells were then washed twice with cold PBS, resuspended by trypsinisation and stored in the dark at 4°C until the time of analysis (usually within 30 min). Flow cytometry was performed on a FACScan instrument. Data were acquired and analysed using Lysis II software (Becton Dickinson).

Results:

[0051] Cationic lipophilic fluorochromes such as Rh123 serve as reporter molecules to monitor mitochondrial activity. These dyes accumulate in the mitochondrial matrix in accordance with the Nernst equation. When used in combination with flow cytometry, they are effective probes to estimate changes of $\Delta\Psi_m$ in intact cells. As shown in Figure 1, pre-treatment of cardiomyocytes with 1 μ M lisinopril for 36 hours caused an increase in Rh123 fluorescence of about 30%, indicating that ACE inhibition induced an increase in $\Delta\Psi_m$.

[0052] JC-1 is a more reliable and sensitive fluores-

cent probe for assessing changes in $\Delta\Psi_m$. At low concentrations, JC-1 exists mainly in a monomeric form which is characterised by the emission of green fluorescence. Upon accumulation in the mitochondrial matrix

5 JC-1 forms J-aggregates in proportion to the magnitude of $\Delta\Psi_m$. These aggregates are characterised by the emission of red fluorescence. Thus, an increase in the red to green fluorescence ratio indicates an increase in $\Delta\Psi_m$. Figure 2 shows that treatment of rat cardiomyocytes with 1 μ M lisinopril for various lengths of time caused a progressive increase in red fluorescence (•) with a corresponding decrease in green fluorescence (○). Thus, the ratio of red to green fluorescence (□) increased as the time of incubation with lisinopril progressed.

10 **[0053]** These experiments demonstrate that treatment with ACE inhibitors increases $\Delta\Psi_m$. This indicates that ACE inhibitors may protect against ischaemic situations and/or improve mechanical/biosynthetic performance by increasing the efficiency of energy transduction in the mitochondrion.

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6. The use as claimed in claim 2, wherein the ACE inhibitor is imidapril.
7. The use as claimed in claim 1, wherein the inhibitor of the renin-angiotensin system is an angiotensin receptor antagonist.
8. The use as claimed in claim 7, wherein the angiotensin receptor antagonist is an AT₁ receptor antagonist.
9. The use as claimed in claim 8, wherein the AT₁ receptor antagonist is selected from losartan, valsartan, irbesartan, candesartan, eprosartan, tasosartan and telmisartan.
10. The use as claimed in claim 8, wherein the AT₁ receptor antagonist is selected from losartan, valsartan and irbesartan.
15. The use as claimed in claim 1, wherein the inhibitor of the renin-angiotensin system is a neutral endopeptidase-inhibitor.
20. The use as claimed in claim 1, wherein the inhibitor of the renin-angiotensin system is a renin-inhibitor.
25. The use as claimed in claim 1, wherein the inhibitor of the renin-angiotensin system is an inhibitor of kinin degradation.
30. The use as claimed in claim 1, wherein the inhibitor of the renin-angiotensin system is a kininase-inhibitor.
35. The use as claimed in any preceding claim, wherein the wasting or cachexia is associated with an inflammatory process selected from sepsis, septic shock, autoimmune disorders and connective tissue disorders.

Claims

1. The use of a lipophilic inhibitor of the renin-angiotensin system for the manufacture of a medicament for the treatment or prevention of wasting or cachexia or its recurrence, wherein the wasting or cachexia is associated with ageing, hepatic or malignant disease, a chronic or acute inflammatory process, or musculoskeletal or neurological injury.
2. The use as claimed in claim 1, wherein the inhibitor of the renin-angiotensin system is an inhibitor of angiotensin-converting enzyme ("ACE").
3. The use as claimed in claim 2, wherein the ACE inhibitor is selected from quinapril, captopril, perindopril, trandolapril, enalapril, moexipril, fosinopril, ramipril, cilazapril, lisinopril, imidapril, spirapril, temocapril, benazepril, alacepril, ceronapril, delapril, moveltipril and trandolapril.
4. The use as claimed in claim 2, wherein the ACE inhibitor is selected from quinapril, captopril, perindopril, trandolapril, enalapril, moexipril, fosinopril, ramipril, cilazapril and lisinopril.
5. The use as claimed in claim 2, wherein the ACE inhibitor is ramipril.

Patentansprüche

1. Verwendung eines lipophilen Inhibitors des Renin-Angiotensin-Systems zur Herstellung eines Arzneimittels zur Behandlung oder Verhütung von Kräfteverfall oder Kachexie oder dessen bzw. deren Wiederauftreten, wobei der Kräfteverfall oder die Kachexie mit Alterung, einer hepatischen oder malignen Erkrankung, einem chronischen oder akuten entzündlichen Prozess oder einer Knochenskelett und Muskulatur betreffenden oder neurologischen Verletzung oder Schädigung verbunden ist.
2. Verwendung nach Anspruch 1, wobei der Inhibitor des Renin-Angiotensin-Systems ein Inhibitor des Angiotensin-Converting-Enzyms ("ACE") ist.

3. Verwendung nach Anspruch 2, wobei der ACE-Inhibitor aus Quinapril, Captopril, Perindopril, Trandolapril, Enalapril, Moexipril, Fosinopril, Ramipril, Cilazapril, Lisinopril, Imidapril, Spirapril, Temocapril, Benazepril, Alacepril, Ceronapril, Delapril, Moveltipril und Trandolapril ausgewählt wird.
4. Verwendung nach Anspruch 2, wobei der ACE-Inhibitor aus Quinapril, Captopril, Perindopril, Trandolapril, Enalapril, Moexipril, Fosinopril, Ramipril, Cilazapril und Lisinopril ausgewählt wird.
5. Verwendung nach Anspruch 2, wobei der ACE-Inhibitor Ramipril ist.
6. Verwendung nach Anspruch 2, wobei der ACE-Inhibitor Imidapril ist.
7. Verwendung nach Anspruch 1, wobei der Inhibitor des Renin-Angiotensin-Systems ein Angiotensin-Rezeptor-Antagonist ist.
8. Verwendung nach Anspruch 7, wobei der Angiotensin-Rezeptor-Antagonist ein AT₁-Rezeptor-Antagonist ist.
9. Verwendung nach Anspruch 8, wobei der AT₁-Rezeptor-Antagonist aus Losartan, Valsartan, Irbesartan, Candesartan, Eprosartan, Tasosartan und Telmisartan ausgewählt wird.
10. Verwendung nach Anspruch 8, wobei der AT₁-Rezeptor-Antagonist aus Losartan, Valsartan und Irbesartan ausgewählt wird.
11. Verwendung nach Anspruch 1, wobei der Inhibitor des Renin-Angiotensin-Systems ein neutraler Endopeptidase-Inhibitor ist.
12. Verwendung nach Anspruch 1, wobei der Inhibitor des Renin-Angiotensin-Systems ein Renin-Inhibitor ist.
13. Verwendung nach Anspruch 1, wobei der Inhibitor des Renin-Angiotensin-Systems ein Inhibitor des Kinin-Abbaus ist.
14. Verwendung nach Anspruch 1, wobei der Inhibitor des Renin-Angiotensin-Systems ein Kininase-Inhibitor ist.
15. Verwendung nach einem der vorangegangenen Ansprüche, wobei der Kräfteverfall oder die Kachexie mit einem entzündlichen Prozess, ausgewählt aus Sepsis, septischem Schock, Autoimmunerkrankungen und Bindegewebserkrankungen, verbunden ist.

Revendications

1. Utilisation d'un inhibiteur lipophylique du système rénine- angiotensine pour la fabrication d'un médicament pour le traitement ou la prévention de l'amaigrissement ou de la cachexie, ou sa récurrence, dans lequel l'amaigrissement ou la cachexie est associé au vieillissement, à une maladie hépatique ou maligne, à un processus inflammatoire chronique ou aigue, ou à un dommage musculo-squeletique ou neurologique.
5. Utilisation selon la revendication 1, dans laquelle l'inhibiteur du système rénine-angiotensine est un inhibiteur de l'enzyme de conversion de l'angiotensine ("ACE").
10. Utilisation selon la revendication 2 dans laquelle l'inhibiteur ACE est sélectionné parmi le quinapril, le captopril, le perindopril, le trandolapril, l'énalapril, le moexipril, le fosinopril, le ramipril, le cilazapril, le lisinopril, le imidapril, le spirapril, le temocapril, le benazepril, l'alacepril, le ceronapril, le delapril, le moveltipril et le trandolapril.
15. Utilisation selon la revendication 2 dans laquelle l'inhibiteur ACE est sélectionné parmi le quinapril, le captopril, le perindopril, le trandolapril, l'énalapril, le moexipril, le fosinopril, le ramipril, le cilazapril et le lisinopril.
20. Utilisation selon la revendication 2 dans laquelle l'inhibiteur ACE est sélectionné parmi le quinapril, le captopril, le perindopril, le trandolapril, l'énalapril, le moexipril, le fosinopril, le ramipril, le cilazapril et le lisinopril.
25. Utilisation selon la revendication 2 dans laquelle l'inhibiteur ACE est le ramipril.
30. Utilisation selon la revendication 2 dans lequel l'inhibiteur ACE est l'imidapril.
35. Utilisation selon la revendication 1, dans laquelle l'inhibiteur du système rénine-angiotensine est un antagoniste du récepteur de l'angiotensine.
40. Utilisation selon la revendication 7, dans lequel l'antagoniste du récepteur d'angiotensine est un antagoniste de récepteur AT₁.
45. Utilisation selon la revendication 8 dans lequel l'antagoniste de récepteur AT₁ est sélectionné parmi le losartan, le valsartan, l'irbesartan, le candesartan, l'éprosartan, le tasosartan et la temisartan.
50. Utilisation selon la revendication 8 dans lequel l'antagoniste de récepteur AT₁ est sélectionné parmi le losartan, le valsartan, l'irbesartan.
55. Utilisation selon la revendication 1 dans laquelle l'inhibiteur du système rénine-angiotensine est un inhibiteur d'endopeptidase neutre.

12. Utilisation selon la revendication 1 dans laquelle l'inhibiteur du système rénine-angiotensine est un inhibiteur de la rénine.
13. Utilisation selon la revendication 1 dans laquelle l'inhibiteur du système rénine-angiotensine est un inhibiteur de la dégradation de la kinine.
14. Utilisation selon la revendication 1, dans laquelle l'inhibiteur du système rénine-angiotensine est un inhibiteur de la kininase.
15. Utilisation selon n'importe laquelle des revendications précédentes dans laquelle l'amaigrissement ou la cachexie est associé à un processus inflammatoire sélectionné parmi une septie, un choc septique, des affections auto-immunitaires et des affections du tissu conjonctif.

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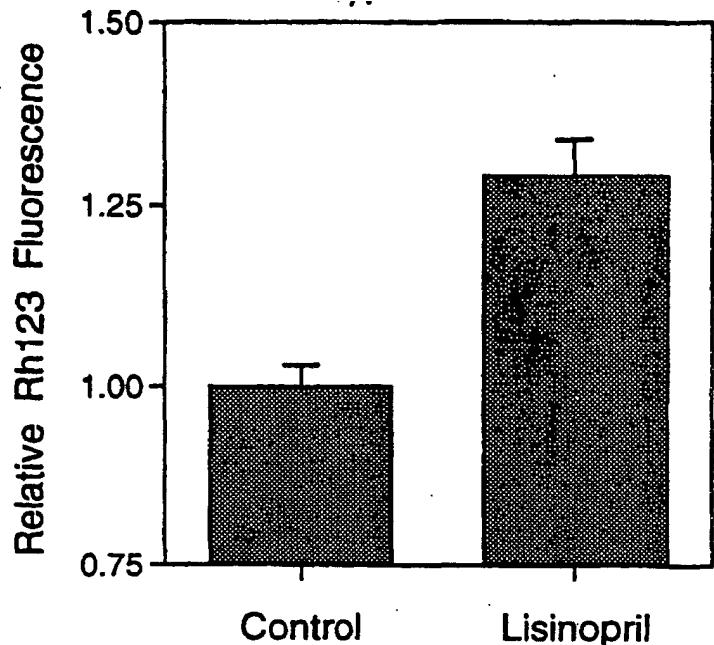


Fig. 1

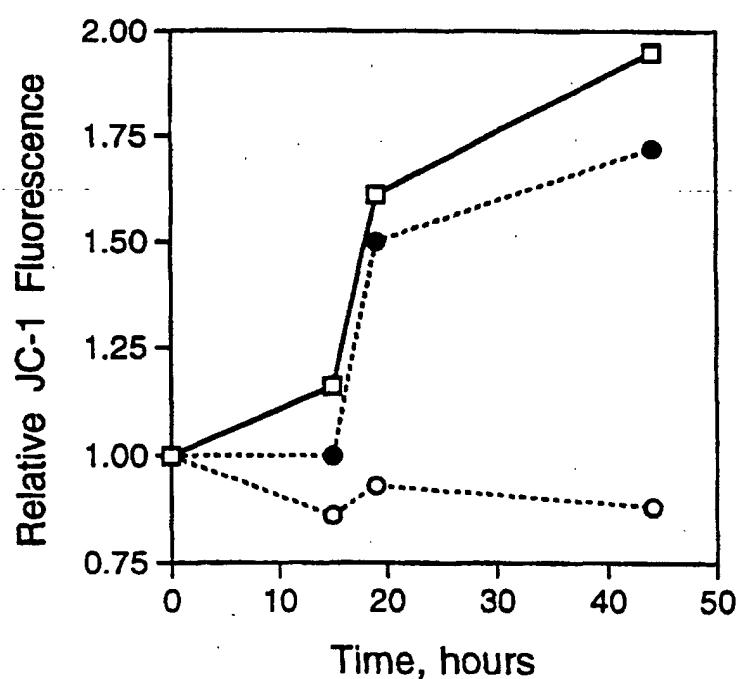


Fig. 2