A PHARMACEUTICAL PREPARATION COMPRISING AN ANGIOTENSIN II TYPE 2 RECEPTOR AGONIST, AND USE THEREOF

Technical field of the invention

The present invention relates to a pharmaceutical preparation comprising an angiotensin II type 2 receptor agonist, as well as to a method for prophylaxis and treatment of disorders of the alimentary tract, such as dyspepsia, irritable bowel syndrome and multiple organ failure.

Background art

Functional disorders of the gastrointestinal tract are very common and are characterised by the absence of signs of organic disease, such as peptic ulcers or ulcerative colitis. The symptomatology may be due to an organic disease, such as peptic ulcer disease, or, more commonly, may be without any known origin, i.e. absence of organic pathology in the gut as evidenced by various diagnostic procedures. In clinical routine the symptom-syndrome is commonly divided into two groups: "dyspepsia" ("non-ulcer dyspepsia", "functional dyspepsia", "non organic dyspepsia") or "irritable bowel syndrome", depending on whether the symptoms appear to be elicited from the upper or lower part of the gut, respectively. Furthermore, on the individual basis, there may be a considerable overlap between these two groups of symptoms.

Dyspepsia and irritable bowel syndrome are two of the most frequent health conditions encountered in the general population. Epidemiological studies have reported prevalence rates of 25-30% annually if restricted to those who have recurrent abdominal symptoms.

The exact mechanisms behind functionally related complaints from the gastrointestinal tract are today unknown. It is believed that they depend on dyscoordination of the functional state in various segments along the gut

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axis and/or an increased sensitivity of the sensory systems mediating the perceptions. It has become evident in the art that subjective symptoms are integrated responses to changes in gut subfunctions; i.e. the balance between the digestive processes per se and mucosaprotective barrier functions (protective secretions, motility and immunological host defence systems).

One well-known group of dyspeptic symptoms is "acid-related". The definition of acid-related dyspepsia is that there occurs a symptom-relief when stomach acidity is lowered by use of antacids or antisecretagogues. A prerequisite for acid-related dyspeptic symptoms is that luminal acid gets access to the superficial mucosal cells where the sensory receptors are located. This is not the case during normal conditions, as a continuos transport of fluid and bicarbonate provides a neutral compartment at the mucosal surface. This important acid neutralisation on the mucosal surface is dependent on alkaline volume secretion and mixing transport of the luminal contents by co-ordinated intestinal wall movements. If the surface neutralisation process is down-regulated, e.g. by certain stress conditions or drugs (e.g. non-steriodal antiinflammatory drugs), mucosal acidification may occur allowing for perception of abdominal discomfort either due to direct activation of mucosal acid-receptors, or indirectly by changed wall motility registered by nociceptors in the muscle layers of the gut.

Dyspepsia due to peptic ulcers can be cured by intake or antacids and inhibitors of gastric acid secretion. Ulcer-like dyspeptic symptoms without known organic cause are usually sensitive to similar treatment. As mentioned, acid related dyspepsia is defined by the symptom-relief in association with the intake of neutralising agents or inhibition of gastric acid production by use of proton pump inhibitors or histamine type 2 receptor antagonists. However, the former principle is shortlasting and neutralising drugs must thus be administered repeat-

edly during the day. The latter drugs have disadvantages of being expensive and exert a great impact on the gut physiology as the anacid gastric conditions increase the risk for intestinal and/or systemic infections. Prokinetic drugs, such as cisapride, modulating gut wall motility; anticholineric compounds inhibiting acid secretion and wall contractions; as well as prostglandine-analogues for preservation of mucosal integrity; are other principles that are utilised for dyspeptic symptoms and IBS, usually with low efficacy and high frequency of side effects. It follows that therapeutic regimens for treatment of functional disorders of the gut are largely lacking and those available are impaired by serious disadvantages.

Another condition in which the intestinal mucosaprotective functions are disturbed is multiple organ failure, MOF. Severe physical stress on the organism (life-threatening critical illness due to e.g. burn injuries or mechanical multitrauma) elicits a vasoregulatory response associated with down-regulation of the functional state of non-vital organs, preferentially the mesenteric organs. Distorted mucosa-protective functions are associated with acid-dependent gastric erosions and bleedings ("haemorrhaged stress-gastritis") and enables gut pathogens to cross the intestinal mucous and penetrate the mucosal epithelium to eventually spread to systemic compartments via lymphatic and blood vessels. The latter may have severe consequences as the microbial translocation elicits a systemic inflammatory response which, together with the initially compromised systemic circulation, leads to functional failure of various distant organs, e.g. kidney, heart, lungs, and haemostasis. Such a sequential development of devastating sequels is defined as multiple organ failure (MOF).

The treatment of multiple organ failure is very costly and results in long term treatments at intensive care units. Therapeutic efforts in MOF treatment today

are mainly aimed at lifesustaining treatments, such as administration of antibiotics, volume expansion and respiratory assistance. As a key-event in the development of MOF is a mucosal barrier dysfunction and it follows that therapeutic strategies that support mucosaprotective functions of the gut may improve or prevent the condition.

The renin-angiotensin system is a regulatory axis, which primarily is involved in circulation homeostasis but has also large impact on gut functions. One important factor in the renin-angiotensin system is angiotensin II. Angiotensin II is a polypeptide, more specifically an octapeptide, occurring in the sera of mammals, including humans. It is a hormone released when the mammal is subjected to stress, and it has a vasoconstrictive and thus blood pressure-raising effect. It also stimulates the secretion of aldosterone from the adrenal glands, which contributes to the blood pressure-raising effect. It is produced in the renin-angiotensin-aldosterone system by conversion of angiotensin I under the influence of the angiotensin-converting enzyme, ACE.

Although the existence of angiotensin II receptor subtypes has been suspected for some time, definite evidence for angiotensin II receptor heterogeneity has been obtained only with the recently introduced non-peptide angiotensin II receptor antagonists, exemplified with the prototypic compounds DuP 753 (losartan) and PD 123177. The sites having high affinity for DuP 753 are designated as site 1 - angiotensin II type 1 receptors - and those having high affinity for PD 123177 as site 2 - angiotensin II type 2 receptors. The function of angiotensin II type 2 receptors has been unidentified in spite of numerous investigations.

Activation of angiotensin II-type 2 receptors are involved in the reduction of mesenteric blood flow and the decreased mucosaprotective functional state during various stress conditions. Thus, one possible way to pre-

vent dyspeptic symptoms and MOF is to block the formation of angiotensin II. This may be done by administration of angiotensin converting enzyme inhibitors (ACE-inhibitors), i.e. compounds that block the formation of angiotensin II. This method has for example been shown to improve mesenteric oxygenation during severe shock.

The use of ACE-inhibitors for treatment of gut disorders is, however, hampered by the fact that they are acting as non-specific enzyme inhibitors, resulting in accumulation of several vasoactive peptides, e.g. bradykinin, substance P, and endogenous opoids. This may lead to instable blood pressure regulation as well as an increased risk for allergic manifestations and upper airway irritation. Another way to prevent MOF is to block the angiotensin II type 1 receptors. This is known from the patent application PCT/SE96/00602 (claiming priority from the Swedish patent application No. 9501881-8), wherein the use of angiotensin II type 1 receptor antagonists for treatment and prophylaxis of MOF is described. The effect of these agonists is a pharmacological specific blockade of angiotensin II type 1 receptors resulting in an increase of gastrointestinal tissue oxygenation in turn reinforcing the mucosal barrier function in the upper gastrointestinal tract.

Summary of the invention

The object of the invention is to provide a pharmaceutical preparation as well as a method for treatment of condition affecting the alimentary tract, such as dyspepsia, irritable bowel syndrome or multiple organ failure.

The invention is based on a new, until now unknown functional role for a subclass of angiotensin II receptors. Selective stimulation of angiotensin II type 2 receptors has been found to elicit a profound activation of gastroduodenal mucosal alkaline secretion and gut motility, effects which lead to a strengthening of the intestinal mucous membrane, thus counteracting conditions of

the alimentary tract, such as dyspepsia, irritable bowel syndrome or by multiple organ failure.

Thus, the present invention relates to a pharmaceutical preparation comprising at least one angiotensin II type 2 receptor agonist or a physiologically acceptable salt thereof.

The invention also relates to use of an angiotensin II type 2 receptor agonist or a physiologically acceptable salt thereof for the manufacture of a medicament for treatment and/or prophylaxis of a disorder of the alimentary tract, such as dyspepsia, or of multiple organ failure.

Furthermore, the invention relates to a method for treatment and/or prevention of an affection selected from the group consisting of disorders of the alimentary tract, such as dyspepsia, irritable bowel syndrome and/or multiple organ failure in a patient, characterised in that an effective amount of at least one angiotensin II type 2 receptor agonist or a pharmaceutically acceptable salt thereof is administered to the patient.

According to another aspect of the present invention, there is provided a pharmaceutical preparation comprising at least one non-selective angiotensin II type 2 receptor agonist or a physiologically acceptable salt thereof and at least one angiotensin II type 1 receptor antagonist.

According to yet another aspect of the present invention, there is provided the use of an angiotensin II type 2 receptor agonist or a physiologically acceptable salt thereof for the manufacture of a medicament for treatment and/or prophylaxis of a functional disorders of the gastrointestinal tract, said agonist being either a selective angiotensin II type 2 receptor agonist or a non-selective angiotensin II type 2 receptor agonist, provided that when it is a non-selective angiotensin II type 2 receptor agonist it is used in combination with a angiotensin II type 1 receptor antagonist.

The characterising features or the invention will be evident from the following description and the appended claims.

Detailed description of the invention

The term "angiotensin II type 2 receptor agonist" used herein relates to any compound binding specifically to, and thus stimulating, angiotensin II type 2 receptors.

The term "patient" used herein relates to all kinds of mammals, including humans, in need of treatment and/or prophylaxis according to the invention.

Thus, according to the present invention an angiotensin II type 2 receptor agonist or a pharmaceutically acceptable salt thereof. The agonist used according to the invention may be any substance, derived from natural sources or from synthesis by chemical and/or genetic en-

gineering methods, functioning as an angiotensin II type 2 receptor agonist. The agonist may be either a peptide or a peptide mimetic with high selectivity for the angiotensin II type 2 receptor.

Examples of peptides functioning as angiotensin II type 2 receptor agonist and thus suitable for use according to the present invention are p-aminophenylalanine^6-angiotensin II or N-α-nicotinoyl-Tyr-(N-α-CBZ-Arg)-Lys-His-Pro-Ile-OH.

When p-aminophenylalanine^6-angiotensin II is used, it is preferably administered to the patient directly into the blood. This peptid has a short length of life and will therefore only have an effect for a limited time. This enables an easy control of the effects.

However, since many peptides, including p-aminophenylalanine^6-angiotensin II, are difficult to use directly as drugs due to problems such as poor solubility, poor gastrointestinal absorption and short biological half-times, it may be advantageously to use a peptide mimetic. A peptide mimetic may contain elements that enforce steric constraints of a peptide and a peptide mimetic may retain some peptidic character. A peptide mimetic may alternatively be lacking peptidic fragments and consist of an organic molecule. A peptide mimetic can be an organic molecule comprising biaryl, arylheteroaryl, or biheteroaryl fragments that can be attached to a nitrogen containing monocyclic or bicyclic heterocycle by a one, two or three atom linker. A selective angiotensin II type 2 receptor agonist may be an analogue of the non-selective angiotensin II type 2 receptor ligand 5,7-dimethyl-2-ethyl-3-[[4-[2(n-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]-imidazo[4,5-b]-pyridine

It is preferable to use a selective angiotensin II type 2 agonist. However, it is also possible to use non-selective angiotensin II type 2 agonists. In order to block the negative effects that these non-selective ago-

nists may cause due to their influence on the angiotensin II type 1 receptor, it is suitable to combine them with a angiotensin II type 1 receptor antagonist in order to block the angiotensin II type 1 receptor. Several angiotensin II type 1 receptor antagonists are known in the art; examples of suitable substances are e.g. described in the patent application PCT/SE96/00602 (claiming priority from the Swedish patent application No. 9501881-8).

The pharmaceutical preparations according to the invention may be any kind of conventionally used preparations. Besides the angiotensin II type 2 receptor agonist, the pharmaceutical preparations according to the invention may comprise other substances such as e.g. physiologically acceptable additives, such as a solvent, an adjuvant, a carrier and/or a suitable preservative. Preferably, the pharmaceutical preparations according to the invention have the form of solutions for injection, but they may also be e.g. solutions, suspensions, tablets or capsules intended for oral, sublingual or rectal administration.

The pharmaceutical preparations according to the invention are particularly useful for prophylaxis and/or treatment of multiple organ failure, dyspepsia and other disorders affecting the alimentary tract.

According to the present invention it is thus possible to treat and/or prevent disorders of the alimentary tract or gastrointestinal disorders. Examples of such disorders include xerostomia, gastro-oesophageal reflux disease, oesophagitis, gastritis, gastroparesis, gastroduodenal ulcer disease, non ulcer dyspepsia, hyperacidity, pancreatitis, disorders of the biliary tract, coeliacia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, irritable bowel disease, colic, dysphagia, obesitas, vomiting, nausea, indigestion and Sjögren's syndrome.

The invention will be further explained in the following examples. These examples are only intended to il-

lustrate the invention and should in no way be considered to limit the scope of the invention.

Example 1

In this in-vivo example, the angiotensin II type 2 receptor agonist p-aminophenylalanine^{6}-angiotensin II, a peptide obtained from SIGMA (Product No. A1811), was used. This agonist was administered intravenously to a chloralose-anesthetized rat prepared for in-situ titration of duodenal mucosal alkaline secretion (the methodological is described by Flemström et al in Am. J. Physiol. 1982, 243: G348). It was found that increasing infusion rates of the compound stimulated markedly the mucosal alkalinisation in a dose-dependent fashion, which is illustrated in the table below.

In order to further illustrate the receptor specificity of the agonist, it was also administered in the presence of an specific angiotensin II type 2 reeeptor antagonist (PD123319, 200 µg/kg intravenously), without any obvious side effects on global parameters such as mean arterial pressure. The mucosal alkalinisation was then counteracted. This is also illustrated in table 1 below, in the right column.

The values given in the table represent group-means (± standard error) of the secretory level obtained after 30 min infusion.

Table 1

Dose of agonist µg/(kg·h)	Mucosal alkaline secretion µEq/(cm intestine · h)	
	Rat treated with the agonist (n=5)	Rat treated with the agonist in presence of an antagonist (n=5)
0	12 ± 1	11 ± 1,5
0,75	11 ± 1	12 ± 2
2,5	19 ± 3	12 ± 2
7,5	25 ± 4	14 ± 2,5
25	25 ± 3	18 ± 4

Example 2

In this in-vivo example, the selective angiotensin II type 2 receptor agonist CGP 42112A (N-α-nicotinyl-Tyr-(N-α-CZB-Arg)Lys-His-Pro-Ile-OH), a peptide obtained from NEOSYSTEM S.A., France (product number SC431, was used. This agonist was administered intravenously to chloralose-anaesthetised rats prepared for in-situ titration as described in Example 1.

It was found that a single dose of CGP 42112A (0.1 µg/kg x min) increased the duodenal mucosal bicarbonate secretion as shown in table 2 below. Co-administration of the specific angiotensin II type 1 receptor antagonist losartan (10 mg/kg intravenously) did not affect the stimulatory response, as shown in the table below.

In order to further illustrate the receptor specificity of the agonist, CGP 42112A was also administered together with a specific angiotensin II type 2 receptor antagonist PD123319 (200 µg/kg intravenously). The duodenal mucosal alkaline secretion was then effectively blocked. This is also shown in table 2.

Table 2

Dose of agonist (µg/kg x min)	Increase in duodenal mucosal alkaline secretion (% increase compared to baseline)		
	Rats treated with agonist alone	Rats pre-treated with losartan	Rats pre-treated with PD123319
0.1	58	55	3

Example 3

In this in-vivo example, the endogenous ligand of angiotensin II receptors, Angiotensin II, obtained from SIGMA, was used. This agonist was administered intravenously to chloralose-anaesthetised rats prepared for in-situ titration as described in Example 1.

It was found that angiotensin II given alone did not increase the duodenal mucosal alkaline secretion, as shown in table 3 below.

After pre-treatment with the specific angiotensin II type 1 receptor antagonist losartan (10 mg/kg intravenously), angiotensin II infusion stimulated duodenal mucosal alkaline secretion, as evident from the table.

Co-administration of the specific angiotensin II type 2 receptor antagonist PD 123319 (200 µg/kg intravenously) effectively counteracted the stimulatory response, also evident from the table.

Table 3

Dose of agonist (µg/kg x h)	Increase in duodenal mucosal alkaline secretion (% increase compared to baseline)		
	Rats treated with agonist alone	Rats pre-treated with losartan	Rats pre-treated with PD123319
0.25	0	23	6
0.75	0	92	8

Example 4

In this in-vivo example, the non-selective angiotensin II receptor agonist L-162,312, a non-peptidergic compound, was used. This agonist was administered intravenously to chloralose-anaesthetised rats (n=6) prepared for in-situ titration as described in Example 1.

After pre-treatment with the specific angiotensin II type 1 receptor antagonist losartan (10 mg/kg intravenously), L-162,313 infusion (0.3 mg/kg bolus injection i.v., followed by continuos infusion of 0.03 mg/kg x h) increased duodenal mucosal alkaline secretion by 86% compared to baseline.

Co-administration of the specific angiotensin II type 2 receptor antagonist PD 123319 (200 µg/kg intravenously) effectively counteracted the stimulatory response of L-162,313 in losartan pre-treated animals.

CLAIMS

1. A pharmaceutical preparation comprising at least one non-selective angiotensin II type 2 receptor agonist or a physiologically acceptable salt thereof and at least one angiotensin II type 1 receptor antagonist.

2. A pharmaceutical preparation according to claim 1, wherein the agonist is a substance derived from natural sources.

3. A pharmaceutical preparation according to claim 1, wherein the agonist is a synthetic substance.

4. A pharmaceutical preparation according to any one of claims 1 - 5, wherein the agonist is a peptide.

5. A pharmaceutical preparation according to any one of claims 1 - 4, wherein the agonist is a peptide mimetic.

6. A pharmaceutical preparation according to claim 5, wherein the peptide mimetic is an organic molecule structurally related to non-selective angiotensin II type 2 receptor ligands

7. A pharmaceutical preparation according to claim 5 or 6, wherein the peptide mimetic is 5,7-dimethyl-2-ethyl-3-[[4-[2(n-butyloxycarbonyl-sulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]-imidazo[4,5-b]pyridine.

8. A pharmaceutical preparation according to any one of claims 1 – 7, for prophylaxis and/or treatment of a functional disorder of the gastrointestinal tract.

9. A pharmaceutical preparation according to any one of claims 1 - 8, for prophylaxis and/or treatment of functional dyspepsia and irritable bowel syndrome.

10. A pharmaceutical preparation according to any one of claims 1 - 8, for prophylaxis and/or treatment of multiple organ failure.

11. A pharmaceutical preparation according to any one of claims 1 - 10, formulated for oral administration.

12. A pharmaceutical preparation according to any one of claims 1 - 10, formulated for injection.

13. Use of an angiotensin II type 2 receptor agonist or a physiologically acceptable salt thereof for the manufacture of a medicament for treatment and/or prophylaxis of a functional disorders of the gastrointestinal tract, said agonist being either a selective angiotensin II type 2 receptor agonist or a non-

selective angiotensin II type 2 receptor agonist, provided that when it is a non-selective angiotensin II type 2 receptor agonist it is used in combination with a angiotensin II type 1 receptor antagonist.

14. Use according to claim 13, wherein said disorder is functional dyspepsia.

15. Use according to claim 13, wherein said disorder is irritable bowel syndrome.

16. Use according to claim 13, wherein said disorder is multiple organ failure.

17. Use according to any one of the claims 13 - 16, wherein the agonist is a substance derived from natural sources.

18. Use according to any one of the claims 13 - 16, wherein the agonist is a synthetic substance.

19. Use according to any one of claims 13 - 16, wherein the agonist is a selective angiotensin II type 2 receptor agonist.

20. Use according to any one of claims 13 - 18, wherein the agonist is a non-selective angiotensin II type 2 agonist, and said medicament further comprises at least one angiotensin II type 1 receptor antagonist.

21. Use according to any one of claims 13 - 20, wherein the agonist is a peptide.

22. Use according to claim 21, wherein the peptide is p-aminophenyl-alanine^{6}-angiotensin II or N-α-nicotinoyl-Tyr-(N-α-CBZ-Arg)-Lys-His-Pro-Ile-OH.

23. Use according to any one of claims 13 - 20, wherein the agonist is a peptide mimetic.

24. Use according to claim 23, wherein the peptide mimetic is an organic molecule structurally related to non-selective angiotensin II type 2 receptor ligands

25. Use according to claim 23 or 24, wherein the peptide mimetic is 5,7-dimethyl-2-ethyl-3-[[4-[2(n-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]-imidazo[4,5-b]pyridine.

26. Use according to any one of the claims 13 – 25, wherein said medicament is formulated for oral administration.

27. Use according to any one of the claims 13 – 25, wherein said medicament is formulated for injection.