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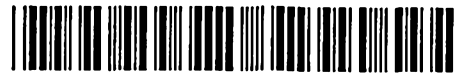
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(54) Title: PREVENTIVE/REMEDY FOR FREQUENT URINATION AND URINARY INCONTINENCE (54) 発明の名称 頻尿および尿失禁の予防・治療剤 (57) Abstract A novel preventive/remedy for frequent urination and urinary incontinence, containing as the active ingredient a β_3 -adrenergic stimulating agent having a potent effect of relaxing human vesical smooth muscles.		

ABSTRACT

The present invention relates to a novel drug for the prevention or treatment of pollakiuria and urinary

5 incontinence which comprises as an active ingredient a β_3 -adrenoceptor stimulating agent, which exerts potent relaxing effects on human bladder smooth muscle.

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DESCRIPTION

DRUG FOR THE PREVENTION OR TREATMENT OF POLLAKIURIA AND URINARY INCONTINENCE

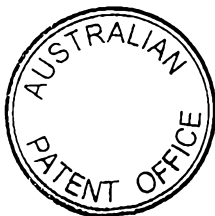
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Technical Field

The present invention relates to a drug for the prevention
or treatment of pollakiuria and urinary incontinence which
comprises as an active ingredient a β_3 -adrenoceptor stimulating
10 agent.

Background Art

At present, anticholinergic agents have been mainly used
for pollakiuria and urinary incontinence which are diseases
15 related to bladder functions. However, it was indicated that
anticholinergic agents have the problem of side effects such
as dry mouth, constipation and mydriasis. Moreover, it was
reported that they are unsatisfactory in effect for the
treatment of pollakiuria and urinary incontinence of the aged.
20 Clenbuterol, one of β_2 -adrenoceptor stimulating agents, has
been used for stress incontinence. On the other hand, it was
not reported that clenbuterol is effective in pollakiuria and
urge incontinence. Thus, agents hitherto used for the
treatment of pollakiuria and urinary incontinence are not
25 satisfactory clinically. Therefore, drugs of different type



which act effectively on bladder smooth muscle have been greatly desired.

Accordingly, to develop drugs which act more effectively on human bladder smooth muscle, earlier elucidation of the distribution of some receptors in human bladder smooth muscle has been expected.

It is known that there are three subtypes of β -adrenoceptor, which have been classified as β_1 , β_2 and β_3 .

Each β -adrenoceptor subtype is distributed in specified organs.

For example, β_1 -adrenoceptor is mainly present in the heart and its stimulation enhances the function of the heart. β_2 -

Adrenoceptor is mainly present in the trachea, peripheral blood vessels and the uterus, and smooth muscle of these organs is relaxed by the stimulation of this receptor.

Recently, it has been reported that β_3 -adrenoceptor is present in the digestive tract, adipocytes and so on. The stimulation of β_3 -adrenoceptor leads to the relaxation of gastrointestinal smooth muscle, lipolysis and energy expenditure in adypose tissues.

In general, the distribution of each receptor subtype in organs or tissues is decided depending upon a kind of a species, and there is a difference between each species. For example, it was reported that β_2 -adrenoceptor is dominant as β -adrenoceptors in the bladder of rats and rabbits (The



Autonomic Nervous System, Vol.26, pp.380-387 (1989); The
Journal of Urology, Vol.139, pp.844-848 (1988) etc.). Up to
the present, it has been similarly thought that β_2 -adrenoceptor
is mainly present in the human bladder (The Journal of
5 Urology, Vol.139, pp.844-848 (1988)).

Disclosure of Invention

The present invention relates to a drug for the prevention
or treatment of pollakiuria and urinary incontinence which
10 comprises as an active ingredient a β_3 -adrenoceptor
stimulating agent.

The present invention relates to a method for the
prevention or treatment of pollakiuria and urinary
incontinence which comprises administering a β_3 -adrenoceptor
15 stimulating agent.

The present invention relates to a use of a β_3 -adrenoceptor
stimulating agent for the manufacture of a drug for the
prevention or treatment of pollakiuria and urinary
incontinence.

20 Furthermore, the present invention relates to a use of a
 β_3 -adrenoceptor stimulating agent as a drug for the prevention
or treatment of pollakiuria and urinary incontinence.

Brief Description of Drawings



Figure 1 illustrates the effect of each drug on the resting tension of isolated human bladder smooth muscle. The axis of the ordinates shows the bladder tension (%) after the drug treatment by each drug. The bladder tension before the treatment is indicated as 100 %, and the tension after the treatment by 10^{-5} M of forskolin which produces maximal relaxation of the bladder is indicated as 0 %. The axis of the abscissas shows concentration (M) of used drugs. The symbols -○- and -●- show isoproterenol and CGP-12,177A hydrochloride, respectively.

Figure 2 illustrates the relaxing effect of isoproterenol on the resting tension of isolated human bladder smooth muscle and influence of some β -adrenoceptor blocking agents on the relaxing effect induced by isoproterenol. The axis of the ordinates shows the bladder tension (%) after the treatment by each drug. The bladder tension before the drug treatment is indicated as 100 %, and the tension after the treatment by 10^{-5} M of forskolin which produces maximal relaxation of the bladder is indicated as 0 %. The axis of the abscissas shows concentration (M) of isoproterenol. The symbols -○-, -△-, -□- and -●- show isoproterenol alone, 100 nM metoprolol tartrate + isoproterenol, 100 nM ICI-118,551 hydrochloride + isoproterenol and 1 μ M bupranolol + isoproterenol, respectively.



Best Mode for Carrying Out the Invention

The inventors of the present invention studied extensively drug effects on the human bladder to elucidate the β -adrenoceptor or subtypes distributed in the human bladder. As a result,
5 it was found surprisingly that β_3 -adrenoceptor is mainly present in human bladder smooth muscle, thereby accomplishing the present invention.

Accordingly, the present inventors carried out the following experiments on the human bladder using isoproterenol

10 as a nonselective β -adrenoceptor stimulant, CGP-12,177A

hydrochloride [chemical name: $(\pm)$ -4-[3-[(1,1-dimethylethyl)-amino]-2-hydroxypropoxy]-1,3-dihydro-2H-benzimidazol-2-on hydrochloride] as a selective β_3 -adrenoceptor partial

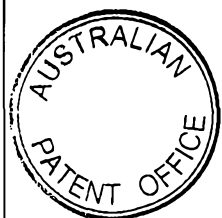
stimulant with β_1 - and β_2 -adrenoceptors blocking activities

15 (Molecular Pharmacology, Vol.44, pp.1094-1104 (1993)),

metoprolol tartrate [chemical name: $(\pm)$ -1-isopropylamino-3-[p-(β -methoxyethyl)phenoxy]-2-propanol (+)-tartrate] as a selective β_1 -adrenoceptor blocker, ICI-118,551 hydrochloride

[chemical name: $(\pm)$ -1-[(2,3-dihydro-7-methyl-1H-inden-4-yl)-oxy]-3-[(1-methylethyl)amino]-2-butanol hydrochloride] as a

20 selective β_2 -adrenoceptor blocker and bupranolol [chemical name: 1-(2-chloro-5-methylphenoxy)-3-[(1,1-dimethylethyl)-amino]-2-propanol] as a nonselective β -adrenoceptor blocker and



found new fact that β_3 -adrenoceptor is dominant in human bladder smooth muscle.

The effects of these drugs on the resting tension of human bladder smooth muscle were investigated. It was found
5 that CGP-12,177A hydrochloride, a selective β_3 -adrenoceptor partial stimulant, produced apparent relaxation of bladder smooth muscle. This result indicates that β_3 -adrenoceptor is present in human bladder.

Furthermore, the effects of isoproterenol alone and
10 isoproterenol combined with some β -adrenoceptor blockers were compared in a similar experiment using human bladder smooth muscle. It was confirmed that the relaxing effect of isoproterenol on bladder smooth muscle is not blocked at all by metoprolol tartrate, a selective β_1 -adrenoceptor blocker,
15 or ICI-118,551 hydrochloride, a selective β_2 -adrenoceptor blocker. However, it was confirmed that the above relaxing effect is blocked by bupranolol, a nonselective β -adrenoceptor blocker. This result indicates clearly that β_3 -adrenoceptor is mainly present in the human bladder.

20 Thus, it was confirmed that β_3 -adrenoceptor is mainly present in the human bladder. Accordingly, it was found that drugs having a stimulating effect on β_3 -adrenoceptor can provide clinically satisfactory relaxation of the bladder, which cannot be attained using the drugs hitherto used, and



are extremely useful as a new type of agents for the prevention or treatment of bladder diseases such as pollakiuria and urinary incontinence.

The present invention relates to a drug for the prevention
5 or treatment of pollakiuria and urinary incontinence which comprises as an active ingredient a β_3 -adrenoceptor stimulating agent at least. In the present invention, for example, urge incontinence and stress incontinence can be illustrated as urinary incontinence.

10 The drugs having stimulating effects on β_3 -adrenoceptor of the present invention have efficient relaxing effects on the bladder and enhance accumulation of urine by enlarging bladder volume. Therefore, specially, the drugs are effective in pollakiuria and urinary incontinence associated
15 with bladder functional disease. Preferably, in order to act more efficiently and effectively, drugs having highly selective stimulating effects on β_3 -adrenoceptor are desirable. Furthermore, drugs having high organ specificity for the bladder or having high affinity for β_3 -adrenoceptor
20 in the bladder are more preferable as agents for the prevention and treatment of pollakiuria and urinary incontinence because β_3 -adrenoceptor is also present in the digestive tract and adipocytes. In addition, it was reported that β_2 -adrenoceptor is present in the external



urethrosphincter and that the stimulation of this receptor leads to the contraction of the external urethrosphincter and is closely related to keeping the function in urine accumulation. Therefore, drugs having stimulating effects on both β_2 - and β_3 -adrenoceptors are more effective in stress incontinence associated with external urethrosphincter functional disease.

The EC_{50} values for stimulating β_3 -adrenoceptor can be measured by investigating the relaxing effects on ferret bladder smooth muscle according to the following method. For example, the EC_{50} value of CGP-12,177A hydrochloride was 8.1×10^{-8} (M).

Drugs having markedly weakened β_1 -adrenoceptor stimulating effects (stimulating effects on heart function) are preferred in order to reduce burdens on the heart and so as not to induce side effects such as tachycardia.

EXAMPLES

The contents of the present invention are described further in detail with reference to the following Examples. However, the present invention is not limited thereto.

Measurement of the contractile force of human bladder smooth muscle strips



(1) Smooth muscle preparations

Human bladders were obtained from patients undergoing cystectomy and were carefully dissected free from the surrounding fat and mucosa. Preparations were prepared by cutting the bladder smooth muscle longitudinally into about 1.5 cm in length and about 3 mm in width and used.

(2) Experimental conditions

Buffer solution; the Krebs-Henseleit solution: NaCl (118 mM), KCl (4.7 mM), CaCl_2 (2.5 mM), NaHCO_3 (25.0 mM), MgSO_4 (1.2 mM), KH_2PO_4 (1.2 mM) and glucose (11.1 mM)

An initial tension of about 1 g was set and the effects of drugs on the resting tension were evaluated.

Conditions for measurement; The bathing solution was maintained at 37 °C and gassed with a mixture of 95 % O_2 and 5 % CO_2 .

Drug Treatment; The drug was cumulatively added every about 5 minutes.

Evaluation of the drug effects; The drug-induced relaxation was evaluated. The tension before the drug treatment is indicated as 100 %, and the tension after treatment with 10^{-5} M forskolin which produces maximal bladder relaxation is indicated as 0 %.

Example 1



According to the method described above, the bladder relaxing effects of the following drugs were measured using human bladder smooth muscle.

Drugs used: 1. isoproterenol and 2. CGP-12,177A

5 hydrochloride

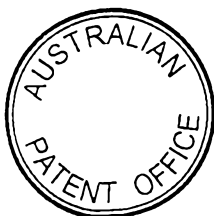
The results are indicated in Figure 1.: CGP-12,177A hydrochloride, a selective β_3 -adrenoceptor partial stimulant, as well as isoproterenol, a non-selective β -adrenoceptor stimulant, also showed apparent relaxing effects on bladder
10 smooth muscle. These results indicate that the β_3 -adrenoceptor is concerned in the relaxation of human bladder smooth muscle.

Example 2

According to the method described above, the interaction
15 between a β -adrenoceptor stimulant and a β -adrenoceptor blocker was evaluated in human bladder smooth muscle using the following drugs.

Drugs used: 1. isoproterenol, 2. metoprolol tartrate, 3. ICI-118,551 hydrochloride and 4. bupranolol

20 The results are indicated in Figure 2.: The pre-treatment with metoprolol tartrate (100 nM), a selective β_1 -adrenoceptor blocker, or ICI-118,551 hydrochloride (100 nM), a selective β_2 -adrenoceptor blocker, did not attenuate the isoproterenol-induced bladder relaxation at all. On the other hand, the



isoproterenol-induced bladder relaxation was apparently weakened by the pre-treatment of bupranolol ($1 \mu\text{M}$), a non-selective β -adrenoceptor blocker. To judge from these findings, it is also demonstrated that the relaxation of human bladder smooth muscle is hardly mediated via β_1 - and β_2 -adrenoceptors but is mainly mediated via β_3 -adrenoceptor.

Example 3

Experiment for measuring the β_3 -adrenoceptor stimulating effect

(The effects of the drugs on the resting tension in the isolated bladders of ferrets)

The bladders of ferrets were isolated and bladder smooth muscle preparations (about 10 mm in length and about 2 mm in width) were prepared. The experiment was conducted according to the Magnus method. The preparations with a tension of 1 g were suspended in the Krebs-Henseleit solution maintained at 37°C and gassed with a mixture of 95 % O_2 and 5 % CO_2 . The resting tension of bladder was introduced isometrically via a pressure transducer and recorded on a rectigraph. The drug was added cumulatively to the Magnus bath every about 5 minutes. The drug efficacy of the drug was evaluated as 50 % relaxing concentration (i.e., EC_{50} value). The tension before the drug treatment was indicated as 100 %, and the tension after the treatment by 10^{-5} M of forskolin which produces



maximal relaxation of the bladder is indicated as 0 %.

Example 4

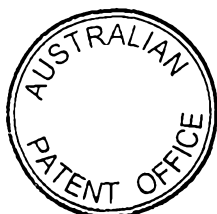
Experiment for measuring the β_2 -adrenoceptor stimulating effect

5 (The effects of the drugs on the spontaneous contractions of the isolated pregnant rat myometrium)

The uteri of pregnant SD rats (pregnancy day 21) were isolated and longitudinal preparations (about 15 mm in length and about 5 mm in width) free from the basal plate were prepared. The experiment was conducted according to the Magnus method. The preparations with a tension of 1 g were suspended in the Locke-Ringer solution maintained at 37 °C and gassed with a mixture of 95 % O₂ and 5 % CO₂. The spontaneous contraction of uterus was introduced isometrically via a pressure transducer and recorded on a rectigraph. The drug was added cumulatively to the Magnus bath every 5 minutes. The drug efficacy was evaluated as 50 % inhibitory drug concentration (i.e., EC₅₀ value) by comparing the sum of uterine contraction during 5 minutes before the addition of the drug with the that during 5 minutes after the addition of the drug.

Industrial Applicability

A drug comprising as an active ingredient a β_3 -adrenoceptor



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stimulating agent of the present invention exerts potent relaxing effects on human bladder smooth muscle, and is suitable as a drug for the prevention or treatment of pollakiuria and urinary incontinence.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A β_3 -adrenoceptor stimulating agent for the prevention or treatment of pollakiuria and urinary incontinence.
2. An agent as claimed in claim 1 which has a selective β_3 -adrenoceptor stimulating effect for the prevention or treatment of pollakiuria and urinary incontinence associated with bladder functional disease.
3. An agent as claimed in claim 1 which has stimulating effects on both β_3 - and β_2 -adrenoceptor for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease.
4. An agent as claimed in claim 3 in combination with a β_2 -adrenoceptor stimulating agent for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease.
5. A composition for the prevention or treatment of pollakiuria and urinary incontinence which includes as an active ingredient a β_3 -adrenoceptor stimulating agent, and a pharmaceutically acceptable carrier or diluent.
6. A composition as claimed in claim 5 for the prevention or treatment of pollakiuria and urinary incontinence associated with bladder functional disease which includes as an active ingredient a selective β_3 -adrenoceptor stimulating agent, and a pharmaceutically acceptable carrier or diluent.
7. A composition as claimed in claim 5 for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease which includes as an active ingredient an agent having stimulating effects on both β_3 - and β_2 -adrenoceptor, and a pharmaceutically acceptable carrier or diluent.
8. A composition as claimed in claim 7 for the



prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease which includes as an active ingredient the β_3 -adrenoceptor stimulating agent in combination with a β_2 -adrenoceptor stimulating agent, and a pharmaceutically acceptable carrier or diluent.

9. A use of a β_3 -adrenoceptor stimulating agent in the manufacture of a medicament used for the prevention or treatment of pollakiuria and urinary incontinence in a patient in need thereof.

10. A use as claimed in claim 9 of a selective β_3 -adrenoceptor stimulating agent in the manufacture of a medicament used for the prevention or treatment or pollakiuria and urinary incontinence associated with bladder functional disease in a patient in need thereof.

11. A use as claimed in claim 9 of an agent having stimulating effects on both β_3 - and β_2 -adrenoceptor in the manufacture of a medicament used for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease in a patient in need thereof.

12. A use as claimed in claim 9 of an agent being a combination of a β_3 -adrenoceptor stimulating agent with a β_2 -adrenoceptor stimulating agent for the manufacture of a medicament used for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease in a patient in need thereof.

13. A use of a β_3 -adrenoceptor stimulating agent in the manufacture of a medicament for the prevention or treatment of pollakiuria and urinary incontinence in a patient suffering therefrom including the step of incorporating the β_3 -adrenoceptor stimulating agent into a pharmaceutically acceptable carrier or diluent to form the medicament.

14. A use as claimed in claim 13 of a selective β_3 -adrenoceptor stimulating agent in the manufacture of a



medicament for the prevention or treatment of pollakiuria and urinary incontinence associated with bladder functional disease in a patient suffering therefrom including the step of incorporating the selective β_3 -adrenoceptor stimulating agent into a pharmaceutically acceptable carrier or diluent to form the medicament.

15. A use of an agent having stimulating effects on both β_2 - and β_3 -adrenoceptor in the manufacture of a medicament for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease in a patient suffering therefrom including the step of incorporating the agent into a pharmaceutically acceptable carrier or diluent to form the medicament.

16. A use of a combination of a β_2 -adrenoceptor stimulating agent with a β_3 -adrenoceptor stimulating agent in the manufacture of a medicament for the prevention or treatment of pollakiuria and urinary incontinence associated with external urethrosphincter functional disease in the person suffering therefrom including the step of incorporating the agents into a pharmaceutically acceptable carrier or diluent to form the medicament.

17. A method of treating a person suffering from pollakiuria and/or urinary incontinence including administering an effective amount of a β_3 -adrenoceptor stimulating agent.

18. A method as claimed in claim 17 of treating a person suffering from pollakiuria and/or urinary incontinence associated with bladder functional disease including administering an effective amount of a selective β_3 -adrenoceptor stimulating agent.

19. A method as claimed in claim 17 of treating a person suffering from pollakiuria and/or urinary incontinence associated with external urethrosphincter functional disease including administering an effective amount of an agent having stimulating effects on both β_3 - and β_2 - adrenoceptor.



20. A method as claimed in claim 17 of treating a person suffering from pollakiuria and/or urinary incontinence associated with external urethrosphincter functional disease including administering an effective
5 amount of a β_3 -adrenoceptor stimulating agent and a β_2 -adrenoceptor stimulating agent.

21. A composition including a β_3 -adrenoceptor stimulating agent, or a β_3 -adrenoceptor stimulating agent and a β_2 -adrenoceptor stimulating agent substantially as
10 herein described with reference to the accompanying examples.

22. A method of using a β_3 -adrenoceptor stimulating agent, or a β_3 -adrenoceptor stimulating agent and a β_2 -adrenoceptor stimulating agent substantially as herein
15 described with reference to the accompanying examples.

Dated this 19th day of January 2001

KISSEI PHARMACEUTICALS CO. LTD

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Trade Mark Attorneys of Australia



Figure 1

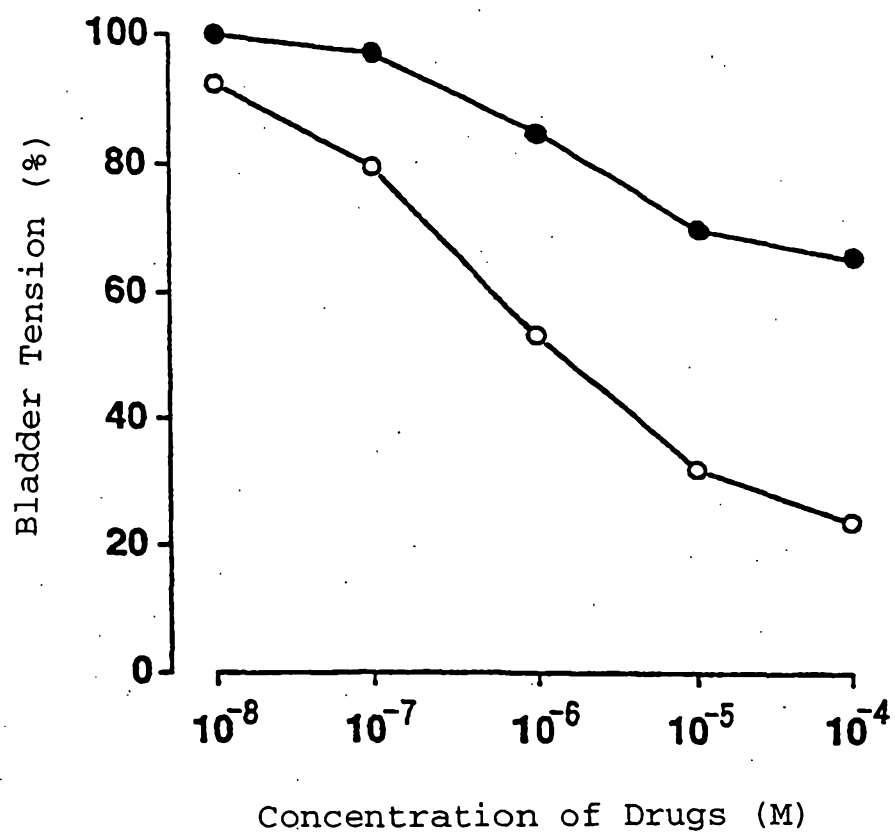


Figure 2

