R^3 and R^4 are the same or different and each represents a hydrogen atom or alkyl,

R^5 is a hydrogen atom,

Y is N,

A is NR^6, and R^6 is alkyl,

D is alkylene,

E is a single bond,

G is O, and

Q is carboxy or a group represented by formula (4), and R^7 is amino, monoalkylamino, dialkylamino, or hydroxy; or any of groups 1) to 4) below:

[0023]

1) alkyl,

2) aryl,

3) aryloxy, and

4) a heterocyclic group,

optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro.

[0024]

Specifically, for example, the compound A and 2-{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropylamino]butyloxy}acetic acid (which is hereinafter referred to as "—compound B") are preferable.

[0025]

(1) A 5 or 6-membered aromatic ring group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom, and a sulfur atom or its benzene fused ring, wherein when the ring-constituting atoms are nitrogen or sulfur atoms, the nitrogen or sulfur atoms may form an oxide. Examples thereof can include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-indolyl, 2-furanyl, 3-furanyl, 3-benzofuranyl, 2-thienyl, 3-thienyl, 3-benzothienyl, 1,3-oxazole-2-yl, 4-isoxazolyl, 2-thiazolyl, 5-thiazolyl, 2-benzothiazolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl, 1H-1,2,——4-triazole-1-yl, 1H-tetrazole-5-yl, 2H-tetrazole-5-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-pyrazolyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-pyrazinyl, and 1,3,5-triazine-2-yl.

(2) A 4 to 8-membered saturated ring group or its benzene fused ring group containing the same or different 1 to 4 nitrogen, oxygen, or sulfur atoms as ring-constituting atoms, wherein when the ring-constituting atoms are nitrogen or sulfur atoms, the nitrogen or sulfur atoms may form an oxide. Examples thereof can include piperidino, piperazinyl, 3-methylpiperazine-1-yl, homopiperazinyl, morpholino, thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, and 2-tetrahydrofuranyl.

[0037]

The heterocyclic derivative (1) can be synthesized by the method described in Patent Literature 1 (International Publication No. WO 02/088084).

[0038]

The heterocyclic derivative (1) can be used as a medicine as a free base or acid, but can also be used in the form of a pharmaceutically acceptable salt by a known method.

[0039]

Examples of the "salt" when the heterocyclic derivative (1) exhibits basicity include salts of inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrofluoric acid, or hydrobromic acid, or salts of organic acids such as acetic acid, tartaric acid, lactic acid, citric acid, fumaric acid, maleic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, or camphorsulfonic acid.

[0040]

Examples of the "salt" when the heterocyclic derivative (1) exhibits ~~acidic~~ acidity can include alkali metal salts such as sodium salt and potassium salt, or alkaline earth metal salts such as calcium salt.

[0041]

Geometric isomers (Z-form and E-form) are present for the heterocyclic derivative (1), and each of the geometric isomers and mixtures thereof are included in the heterocyclic derivative (1). Further, those having an asymmetric carbon are present for the heterocyclic

derivative (1), and the optical isomers and their racemates are also included in the heterocyclic derivative (1). Optical isomers ~~are~~ can be produced by optical resolution according to a known method from the racemate obtained as described above by utilizing basicity thereof and using optically active acids (such as tartaric acid, dibenzoyl tartaric acid, mandelic acid, and 10-camphorsulfonic acid), or can be produced by using an optically active compound prepared in advance as a raw material.

[0042]

The therapeutic agent for gait disturbance according to the present invention can be used, for example, for improving the walking distance and the walking time of a patient.

[0043]

According to one aspect of the present invention, examples of the improvement in the walking distance and the walking time of a patient include the improvement in maximal and/or painless walking time and/or distance.

[0044]

According to one aspect of the present invention, the patient is, for example, a patient with ischemic disease, preferably peripheral arterial disease, further preferably ~~chronic arterial occlusive disease, or~~ a patient with chronic arterial occlusive disease, or arteriosclerosis obliterans, further preferably a patient with arteriosclerosis obliterans.

[0045]

A non-toxic salt or salt solution can be added to make the injection isotonic. Stabilizers, preservatives, emulsifiers and the like can also be added.

[0063]

Suppositories can be prepared by dissolving or suspending the heterocyclic derivative (1) in water-soluble or insoluble solids having a low melting point, such as polyethylene glycol, cocoa butter, semi-synthetic fats and oils [e.g., WITEPSOL—®], higher esters (e.g., palmitate myristyl ester) or a mixture thereof.

[0064]

The dose of the therapeutic agent for gait disturbance according to the present invention varies depending on the patient's condition such as body weight and age, the administration route, the severity of symptoms, and the like, but in general, the amount of the heterocyclic derivative (1) for adults is suitably within the range of 0.001 mg to 100 mg per day, more preferably within the range of 0.01 mg to 10 mg. Depending on the case, less than this dose may be sufficient, and conversely, more than this dose may be required. In addition, it can be administered once to several times a day or at intervals of one to several days.

[0065]

For example, for adults, the dose can be started by oral administration of 0.1 mg or 0.2 mg of the heterocyclic derivative (1) twice a day after meals.

of ~~a~~ compound A in the 0.5 w/v% methylcellulose aqueous solution.

(b) Beraprost sodium

The 0.5 w/v% methylcellulose aqueous solution was added to beraprost sodium, to prepare a 1.0 mg/mL aqueous solution of beraprost sodium in the 0.5 w/v% methylcellulose aqueous solution.

(c) Cilostazol

The 0.5 w/v% methylcellulose aqueous solution was added to cilostazol, to prepare a 150 or 50 mg/mL suspension of cilostazol.

[0069]

(3) Test method

Urethane (Wako Pure Chemical Industries, Ltd.) was dissolved in saline (Otsuka Pharmaceutical Factory, Inc.) to prepare a solution of 0.3 g/mL. The urethane saline solution was subcutaneously administered to rats at 4 mL per 1 kg of body weight (1.2 g/kg) to anesthetize them. When the effect of anesthesia was insufficient, the dose was appropriately increased by increments of about 10% of the initial dose. Male Wistar rats aged 9 to 10 weeks were used as rats.

[0070]

The abdomen of the rat was incised to expose the duodenum, and drugs were injected 2 to 3 mm downstream from the vicinity of the gastric-duodenal boundary using a 26G injection needle and syringe. The compound A and

minutes due to the administration 60 minutes before induction. In the 1 mg/kg-administered group of beraprost sodium, the vascular occlusion time was significantly prolonged to about 43 minutes due to the administration 30 minutes before induction. In the 0.3 mg/kg-administered group of beraprost sodium, the vascular occlusion time was not prolonged, and further a reduction in blood pressure (25%) was observed over time. Neither dose of cilostazol prolonged the occlusion time.

[0074]

Experimental Example 2: Gait improvement in rat ischemic gait disturbance model

(1) Test method

Wistar rats (male, 7 week-old) (available from CHARLES RIVER LABORATORIES JAPAN, INC.) were subjected to gait training using a treadmill (MK-680, available from Muromachi Kikai Co., Ltd.) for three consecutive days--6 days before surgery, 5 days before surgery, and 4 days before surgery. On the day before surgery, the pre-value of the walking distance was measured, the animals were divided into groups, and sham surgery or iliac artery ligation surgery described in i) below was performed.

[0075]

After the surgery, for the sham surgery group and the control group, a 0.5 w/v% methylcellulose aqueous solution was used, whereas for the drug-administered group, a suspension containing the compound A at 0.6

mg/mL (medium: 0.5 w/v% methylcellulose aqueous solution) was used to repeatedly orally administer the compound A (3 mg/kg) twice a day for 9 days from one day after the surgery—.

[0076]

Walking time was measured 3 days, 7 days and 10 days after the surgery. Based on the measured walking time, the walking distance was calculated.

[0077]

i) Method of iliac artery ligation surgery

Rats were anesthetized by intraperitoneal administration of 50 mg/kg pentobarbital sodium (Somnopentyl—®, Schering-Plough Animal Health). When anesthesia was insufficient, Somnopentyl—® was additionally administered in increments of 0.02 to 0.03 mL (amount of pentobarbital sodium: 1.3 to 1.9 mg). Under anesthesia, the abdomen was incised along the midline, and the left and right common iliac arteries were exposed. Sutures (Nescosture Silk Blade No. 4, Alfresa Pharma) were applied to the common iliac arteries on both sides, and their central sides were ligated one by one using ligation clips (Weck Hemoclip, small, Teleflex Medical). Furthermore, the left and right iliac arteries were ligated one by one with sutures. After the ligation, the peritoneum and muscle layer of the midline laparotomy were sutured with sutures, and the skin was sutured. An appropriate amount of terramycin ointment

(containing oxytetracycline hydrochloride and polymyxin B sulfate, Pfizer Limited.) was applied to the sutured part. Bixillin® S for injection (ampicillin sodium 50 mg strength, cloxacillin sodium 50 mg strength, Meiji Seika Pharma Co., Ltd) was dissolved in 1 mL of physiological saline (Otsuka Saline Injection, Otsuka Pharmaceutical Factory, Inc.), and 0.1 mL of this solution was intramuscularly injected into the thigh. In the sham-operated group, both common iliac arteries were similarly exposed, sutured, but not ligated, and the abdomen was closed after the sutures were removed. The ligation of the iliac artery was performed by the data manager and this information was not disclosed to the gait tester until the study was completed.

[0078]

ii) Walking time measurement method

The speed of the treadmill belt was increased from 15 m/min to 35 m/min by increments of 5 m/min in each 3 minutes, and the time the rat got on the electrical stimulation plate at the rear end of the belt was recorded as the dropout ~~shedding~~ time. The walking time was defined as the time until falling off five times. The gait test was conducted by two persons in charge of the gait test. At the same time when the treadmill was started, the start button of a stopwatch (S058, Seiko S-yard) provided for each of the five lanes was pressed, and the dropout ~~shedding~~ time was recorded as a split time.

After the measurement, the dropout ~~shedding~~ time was recorded in the gait test record. Measurements were performed blinded so that the gait tester could not see which group was which.

[0079]

iii) Gait training method

In order to habituate the rats to walking on the treadmill, gait training was performed 6, 5, or 4 days before the surgery, during which individuals suitable for walking on the treadmill were selected. Individuals who refused to walk during gait training, or individuals who frequently dropped out or turned over were excluded from the subjects of use as individuals who were unsuitable for the gait test on the treadmill.

[0080]

(2) Results

As shown in Figure 1, administration of the compound A significantly improved gait disturbance caused by ischemia caused by ligation of the iliac artery.

[0081]

For the evaluation, the control group was evaluated against the sham surgery group by t-test or Welch test (##: $p < 0.01$). In addition, the drug-administered group was evaluated against the control group by t-test (**: $p < 0.01$).

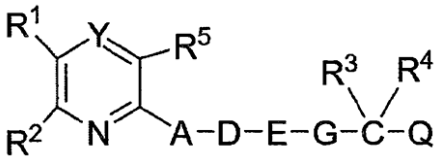
[0082]

Claims

[Claim 1]

A therapeutic agent for gait disturbance in a patient with ischemic disease, comprising a heterocyclic derivative represented by formula (1) below or a pharmaceutically acceptable salt thereof as an active component:

[Chem. 1]



(1)

wherein R^1 and R^2 are the same or different and each represents aryl optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro;

R^3 and R^4 are the same or different and each represents a hydrogen atom or alkyl;

R^5 represents a hydrogen atom, alkyl, or a halogen atom;

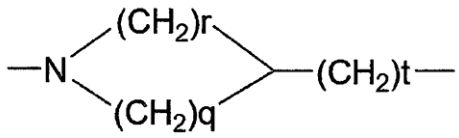
Y represents N or N -> O;

A represents NR^6 and R^6 represents a hydrogen atom, alkyl, alkenyl, or cycloalkyl; and

D represents alkylene or alkenylene optionally substituted with hydroxy, or A and D are combined with each

other to form a divalent group represented by formula (2) below:

[Chem. 2]

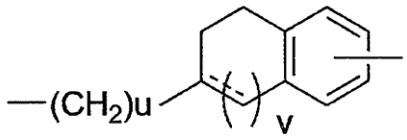


(2)

wherein r represents an integer of 0 to 2, q represents 2 or 3, and t represents an integer of 0 to 4; and

E represents phenylene or a single bond, or D and E are combined with each other to form a divalent group represented by formula (3) below:

[Chem. 3]



(3)

wherein

---- represents a single bond or a double bond,

wherein u represents an integer of 0 to 2; v represents 0 or 1;

G represents O, S, SO, or SO_2; and

Q represents carboxy, alkoxycarbonyl, tetrazolyl, carbamoyl, monoalkylcarbamoyl, dialkylcarbamoyl, or a group represented by formula (4) below:

[Chem. 4]

$$—CONH—SO_2—R^7$$

(4)

wherein R^7 represents amino, monoalkylamino, dialkylamino, or hydroxy; or any of groups 1) to 4) below:

1) alkyl,

2) aryl,

3) aryloxy, and

4) a heterocyclic group,

optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro.

[Claim 2]

The therapeutic agent for gait disturbance according to claim 1, wherein

in the heterocyclic derivative (1), R^1 and R^2 are the same or different and each represents phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, and alkoxy;

R^3 and R^4 are the same or different and each represents a hydrogen atom or alkyl;

R^5 is a hydrogen atom;

Y is N;

A is NR^6, R^6 is alkyl;

D is alkylene;

E is a single bond;

G is O; and

Q is carboxy or a group represented by formula (4), and R^7 is amino, monoalkylamino, dialkylamino, or hydroxy; or any of groups 1) to 4) below:

1) alkyl,

2) aryl,

3) aryloxy, and

4) a heterocyclic group,

optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro.

[Claim 3]

The therapeutic agent for gait disturbance according to claim 1, wherein the patient with ischemic disease is a patient with arteriosclerosis obliterans.

[Claim 4]

The therapeutic agent for gait disturbance according to claim 3, wherein the patient with arteriosclerosis obliterans is a patient classified into at least one selected from Fontaine Classifications I to IV.

[Claim 5]

A therapeutic agent for gait disturbance in a patient with ischemic disease, comprising 2-{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropylamino]butyloxy}acetic acid or 2-{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide, or a pharmaceutically acceptable salt thereof as an active component.

[Claim 6]

The therapeutic agent for gait disturbance according to claim 5, wherein the patient with ischemic disease is a patient with arteriosclerosis obliterans.

[Claim 7]

The therapeutic agent for gait disturbance according to claim 6, wherein the patient with arteriosclerosis obliterans is a patient classified into at least one selected from Fontaine Classifications I to IV.