assessment of neuropathic pain therapeutic agents (draft), 2020, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labor and Welfare, Japan

[Non-Patent Literature 19] The Journal of Japan Society for Clinical Anesthesia, 2009, Vol. 29, No. 1, pp. 35-42

[Non-Patent Literature 20] Clinical Neurology, 2009 Vol. 49, No. 4, pp. 149-157

[Non-Patent Literature 21] Pharmacia, 2012, Vol. 48, No. 8, pp. 761-766

[Summary]

[0028a]

In an aspect of the present disclosure, there is provided a medicament for alleviating human neuropathic pain in a patient, comprising a compound that attenuates the function of the P2X7 receptor.

[0028b]

In another aspect of the present disclosure, there is provided a medicament for alleviating human neuropathic pain, which is to be administered to a patient in which the function of the P2X7 receptor is enhanced.

[0028c]

In a further aspect of the present disclosure, there is provided a compound that attenuates the function of the P2X7 receptor for use in treating human neuropathic pain in a patient, wherein the neuropathic pain is diabetic peripheral neuropathic pain or postoperative pain.

[0028d] In another aspect of the present disclosure, there is provided a use of a compound that attenuates the function of the P2X7 receptor in the manufacture of a medicament for

treating human neuropathic pain in a patient.

[Problems to be solved by Invention]

[0029]

An object of the present invention is to provide a medicament, etc. for alleviating neuropathic pain.

[Means for Solving Problems]

[0030]

One embodiment of the invention is characterized in that a medicament for alleviating (improving or treating) diabetic peripheral neuropathic pain (DPNP), etc., which comprises a compound having a P2X7 receptor inhibitory (or antagonist) activity for attenuating the function of the P2X7 receptor (including the human P2X7 receptor), wherein the compound may be a P2X7 receptor inhibitor (or antagonist), a P2X7 receptor inhibitory (or antagonist) agent, or a P2X7 receptor inhibitory (or antagonist) drug. Another embodiment of a medicament of the present invention is a medicament for alleviating neuropathic pain, which is administered to a patient in which the function of the P2X7 receptor is enhanced.

[0031]

[Document name] CLAIMS

[Claim 1]

A medicament for alleviating human neuropathic pain in a patient, comprising a compound that attenuates the function of the P2X7 receptor.

[Claim 2]

The medicament according to claim 1, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-6-(hydroxymethyl)benzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((R)-1-(2-chloro-4-fluorophenyl)ethyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((3,5-dichloropyridin-2-yl)methyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((R)-1-(2,4-dichlorophenyl)ethyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-

carboxamide;

(5S,8S)-N-(2-chloro-3,4-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-3-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2,4-dichlorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or a pharmaceutically acceptable salt thereof.

[Claim 3]

A medicament for alleviating human neuropathic pain, which is to be administered to a patient in which the function of the P2X7 receptor is enhanced.

[Claim 4]

The medicament according to claim 3, wherein said human neuropathic pain is human diabetic peripheral neuropathic pain (DPNP).

[Claim 5]

The medicament according to any one of claims 1-4, wherein the patient is a patient with the P2X7 receptor gain-of-function type or a patient with the P2X7 receptor unchanged function type.

[Claim 6]

The medicament according to any one of claims 1-4, wherein the patient is a patient with the P2X7 receptor gain-of-function type.

[Claim 7]

The medicament according to claim 1, wherein the

neuropathic pain is diabetic neuropathic pain.

[Claim 8]

The medicament according to claim 1, wherein the neuropathic pain is postoperative pain.

[Claim 9]

The medicament according to claim 1, 7, or 8, wherein the patient is a patient with the P2X7 receptor gain-of-function type or a patient with the P2X7 receptor unchanged function type.

[Claim 10]

The medicament according to claim 1, 7, or 8, wherein the patient is a patient with the P2X7 receptor gain-of-function type.

[Claim 11]

The medicament according to either claim 1 or any one of claims 7-10, wherein the compound that attenuates the function of the P2X7 receptor is: (5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; (5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or (5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide, or a pharmaceutically acceptable salt thereof.

[Claim 12]

The medicament according to either claim 1 or any one of claims 7-10, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-

hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide.

[Claim 13]

A compound that attenuates the function of the P2X7 receptor for use in treating human neuropathic pain in a patient, wherein the neuropathic pain is diabetic peripheral neuropathic pain or postoperative pain.

[Claim 14]

The compound for use according to claim 13, wherein the patient is a patient with the P2X7 receptor gain-of-function type or a patient with the P2X7 receptor unchanged function type.

[Claim 15]

The compound for use according to claim 14, wherein the patient is a patient with the P2X7 receptor gain-of-function type.

[Claim 16]

The compound for use according to any one of claims 13-15, wherein the neuropathic pain is diabetic peripheral neuropathic pain.

[Claim 17]

The compound for use according to any one of claims 13-15, wherein the neuropathic pain is postoperative pain.

[Claim 18]

The compound for use according to any one of claims 13-17, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-6-(hydroxymethyl)benzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((R)-1-(2-chloro-4-fluorophenyl)ethyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((3,5-dichloropyridin-2-yl)methyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((R)-1-(2,4-dichlorophenyl)ethyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-3,4-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-3-fluorobenzyl)-5-fluoro-8-

hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2,4-dichlorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or a pharmaceutically acceptable salt thereof.

[Claim 19]

The compound for use according to any one of claims 13-17 wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide, or a pharmaceutically acceptable salt thereof.

[Claim 20]

The compound for use according to any one of claims 13-17, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-

8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide.

[Claim 21]

Use of a compound that attenuates the function of the P2X7 receptor in the manufacture of a medicament for treating human neuropathic pain in a patient.

[Claim 22]

The use according to claim 21, wherein the neuropathic pain is diabetic peripheral neuropathic pain.

[Claim 23]

The use according to claim 21, wherein the neuropathic pain is postoperative neuropathic pain.

[Claim 24]

The use according to any one of claims 21-23, wherein the patient is a patient with the P2X7 receptor gain-of-function type or a patient with the P2X7 receptor unchanged function type.

[Claim 25]

The use according to any one of claims 21-23, wherein the patient is a patient with the P2X7 receptor gain-of-function type.

[claim 26]

The use according to any one of claims 21-25, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-

carboxamide;

(5S,8S)-N-(2,4-dichloro-6-(hydroxymethyl)benzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((R)-1-(2-chloro-4-fluorophenyl)ethyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((3,5-dichloropyridin-2-yl)methyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-((R)-1-(2,4-dichlorophenyl)ethyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2-chloro-3,4-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-3-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2,4-dichlorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or a pharmaceutically acceptable salt thereof.

[claim 27]

The use according to any one of claims 21-25, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide;

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide, or a pharmaceutically acceptable salt thereof.

[claim 28]

The use according to any one of claims 21-25, wherein the compound that attenuates the function of the P2X7 receptor is:

(5S,8S)-N-(2-chloro-4-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide,

(5S,8S)-N-(2,4-dichloro-6-fluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide; or

(5S,8S)-N-(2-chloro-4,6-difluorobenzyl)-5-fluoro-8-hydroxy-8-(hydroxymethyl)-5,6,7,8-tetrahydroquinoline-5-carboxamide.

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