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(54) Title: METHODS FOR RELIEVING NEUROPATHIC PAIN BY MODULATING ALPHA1G T-TYPE CALCIUM CHANNELS AND MICE LACKING ALPHA 1G T-TYPE CALCIUM CHANNELS

(57) Abstract: The present invention relates to a novel use of a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel as an animal model for the study of neuropathic diseases, more precisely, a novel use of a transgenic mouse having resistance against neuropathic pain as an animal model for the development of a therapeutic agent and a treatment method for human neuropathic diseases. The transgenic mouse deficient in $\alpha 1G$ T-type calcium channel having resistance against neuropathic pain, provided by the present invention, can be effectively used for the development of a therapeutic agent and a treatment method for human neuropathic diseases.

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METHODS FOR RELIEVING NEUROPATHIC PAIN BY
MODULATING ALPHA 1G-T TYPE CALCIUM CHANNELS
AND MICE LACKING ALPHA 1G T-TYPE CALCIUM
CHANNELS

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Technical Field

The present invention relates to a novel use of a mouse lacking $\alpha 1G$ T-type calcium channel as a model for the development of a therapeutic agent and a method for treating of neuropathic disease. More particularly, the present invention relates to a novel use of a transgenic mouse having resistance against stimulus such as neurophathic pain as a model for the development of a therapeutic agent and a method for treating of neuropathic disease.

Background Art

Voltage dependent calcium channel increases calcium content in cells by the activation of neurons (Tsien, R. W., *Annu. Rev. Physiol.* 45, 341-358, 1983), and is divided into high-voltage dependent channel and low-voltage dependent channel (Tsien, R. W. et al., *Trends Neurosci.* 18, 52-54, 1995). As a representative low-voltage dependent calcium channel found in human, T-type calcium channel is divided into three classes by genotype for alpha subunit, which are

Cav3.1 ($\alpha 1G$), 3.2 ($\alpha 1H$) and 3.3 ($\alpha 1I$) (Perez-Reyes, E., *Physiol. Rev.* 83, 117-161, 2003). $\alpha 1G$ calcium channel is involved in the generation of multiple burst firings of neurons in thalamic nucleus, and
5 major pathological functions of the channel have been recently disclosed (Kim, D. et al., *Science* 302, 117-119, 2003; Kim, D. et al., *Neuron* 31, 35-45, 2001).

The pronociceptive role of T-type calcium channel among signal transduction process of pains has
10 been a major target of study on the development of a therapeutic agent for pain relief (Carbone, E. & Lux, H. D., *Nature* 310, 501-2, 1984; Todorovic, S. M. et al., *Neuron* 31, 75-85, 2001; Todorovic, S. M. et al., *Brain Res.* 951, 336-40, 2002; Ikeda, H. et al.,
15 *Science* 299, 1237-40, 2003; Heinke, B., et al., *Eur. J. Neurosci.* 19, 103-11, 2004).

However, according to a recent report, thalamus has an antinociceptive function, meaning that it hinders pain signal transduction by $\alpha 1G$ T-type
20 calcium channel, and in fact, the changed firing pattern of thalamocortical neuron affects the thalamocortical mechanism of inhibiting response to a pain, resulting in hyperalgesia against abdominal pain (Kim, D. et al., *Science* 302, 117-119, 2003).

25 The change of plasticity in synapse between pain reactive afferent and spinal dorsal horn neuron such as spinal cord causes over-activation of central

nerve, resulting in pathogenesis of neuropathic pain
(Mayer, D. J. et al., *Proc. Natl. Acad. Sci. U.S.A.* 96,
7731-6, 1999; Woolf, C. J. & Salter, M. W., *Science*
288, 1765-9, 2000; Hunt, S. P. & Mantyh, P. W., *Nat.*
5 *Rev. Neurosci.* 2, 83-91, 2002).

Recently, Ikeda and his colleagues proposed that
T-type calcium channel might induce long-term
potentiation (LTP) in synapse (Ikeda, H. et al.,
Science 299, 1237-40, 2003). That is, T-type calcium
10 channel might be involved in the generation and
maintenance of neuropathic pain. Blockade of spinal
T-type calcium channel by ethosuximide inhibits
neuronal response of horn (Matthews, E. A. & Dickenson,
A. H., *Eur. J. Pharmacol.* 415, 141-9, 2001), and the
15 systemic administration of mibefradil or ethosuximide
can effectively reverse ethological signal of
neuropathic pain (Dogrul, A. et al., *Pain* 105, 159-68,
2003).

20 Thus, the present inventors induced spinal nerve
ligation (SNL) in mice lacking the gene above, and
then investigated the response of the transgenic mice
for various abnormal pains caused by such nerve injury
in order to investigate the role of $\alpha 1G$ T-type
25 calcium channel in pain reactivity and pathological
pain.

As a result, it was observed that normal response for general pain and for other stimuli such as physical stimulus, low temperature and high temperature was significantly decreased in the transgenic (knock-out) mice lacking $\alpha 1G$ T-type calcium channel, and so the present inventors completed this invention by confirming that pain caused by nerve injury could be relieved by regulating $\alpha 1G$ T-type calcium channel.

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Disclosure

Summary of the Invention

It is an object of the present invention to provide a use of a mouse deficient in $\alpha 1G$ T-type calcium channel as a model for the development of a therapeutic agent and a method for treatment of neuropathic diseases, and a method for relieving pains caused by nerve injury by regulating $\alpha 1G$ T-type calcium channel.

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Detailed Description of the Invention

In order to achieve the above object, the present invention provides a method for using the transgenic mouse deficient in $\alpha 1G$ T-type calcium channel as an animal model for the study on the development of a therapeutic agent and a method for

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treatment of neuropathic diseases.

The present invention also provides a method for relieving neuropathic pain caused by nerve injury by inhibiting $\alpha 1G$ gene encoding a pore forming subunit of $\alpha 1G$ T-type calcium channel.

The present invention further provides a screening method for $\alpha 1G$ T-type calcium channel inhibitor by using a cell line expressing $\alpha 1G$ T-type calcium channel.

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Hereinafter, the present invention is described in detail.

The present invention provides a method for using a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel as an animal model for the development of a therapeutic agent and a method for treatment of neuropathic diseases.

The present inventors prepared a transgenic mouse whose genotype is $\alpha 1G$ -/- by using a fertilized egg (Korean Collection for Type Cultures, Korea Research Institute of Bioscience and Biotechnology, Accession No : KCTC 10086BP) having $\alpha 1G$ +/- genotype of T-type calcium channel. Particularly, a fertilized egg whose genotype is $\alpha 1G$ +/- was transplanted in a surrogate mouse to prepare a heterozygote mouse whose genotype is $\alpha 1G$ +/- . Then, the heterozygote transgenic female and male mice were mated to prepare a

homozygote mouse whose genotype is $\alpha 1G^{-/-}$.

T-type calcium channel is sub-divided into $\alpha 1G$, $\alpha 1H$ and $\alpha 1I$ according to the pore forming subunit. In the present invention, among those three sub-types, $\alpha 1G$ protein, a constituent of $\alpha 1G$ T-type calcium channel, was inhibited to prepare a transgenic mouse having $\alpha 1G^{-/-}$ genotype, and then spinal nerve ligation (SNL) was induced therein for the experiments on response against neuropathic pain caused by nerve injury.

As a result, neuropathic pain caused by nerve injury induced by spinal nerve ligation was significantly decreased in the transgenic mouse deficient in $\alpha 1G$ T-type calcium channel, comparing to a wild type mouse (see Fig. 1 and Fig. 2).

Therefore, the transgenic mouse deficient in $\alpha 1G$ T-type calcium channel, in which neuropathic pain was induced, can be used as an animal model for the development of a therapeutic agent and a treatment method for neuropathic diseases.

The present invention also provides a method for relieving neuropathic pain by suppressing a gene encoding a pore forming subunit of $\alpha 1G$ T-type calcium channel.

The present inventors performed experiments on pain response against various stimuli after inducing

spinal nerve ligation in $\alpha 1G$ gene knock-out mouse. As a result, the response against neuropathic pain after spinal nerve ligation was remarkably decreased in the transgenic mouse deficient in $\alpha 1G$ T-type calcium channel. The result indicates that neuropathic pain can be relieved by suppressing $\alpha 1G$ gene in a wild-type individual. That is, the transmission of pain can be hindered by regulating $\alpha 1G$ T-type calcium channel by suppressing the function of $\alpha 1G$ gene, resulting in relieving neuropathic pain.

The present invention further provides a screening method for an $\alpha 1G$ inhibitor by using a cell line expressing $\alpha 1G$ T-type calcium channel.

It was proved in the present invention that neuropathic pain could be relieved by suppressing $\alpha 1G$ gene. Therefore, any substance that is able to suppress $\alpha 1G$ gene can be used as a pain reliever for the treatment of neuropathic diseases. For the screening of such neuropathic pain reliever, it is important to investigate the activity of inhibiting $\alpha 1G$ T-type calcium channel of a target substance by using a cell line expressing $\alpha 1G$, which might provide an important clue for the development of a therapeutic agent for neuropathic diseases.

T-type calcium channel is a LVA calcium channel, meaning it is activated under low voltage. Membrane

potential of most cells expressing T-type calcium channel is not hyperpolarized enough to activate the T-type calcium channel. Thus, it is necessary to express potassium channel, which contributes greatly to the formation of membrane potential, together with $\alpha 1G$ T-type calcium channel in a cell line, in order to activate $\alpha 1G$ calcium channel with keeping membrane potential stable by lowering the membrane potential a little toward hyperpolarization.

The present inventors have previously deposited a cell line expressing $\alpha 1G$ T-type calcium channel together with potassium channel to activate $\alpha 1G$ T-type calcium channel (Accession No: KCTC 10519BP), which enables the screening of an inhibitor for the activation of $\alpha 1G$ T-type calcium channel.

Particularly, the method for the screening of an inhibitor suppressing the activity of $\alpha 1G$ T-type calcium channel includes following steps:

i) Culturing a cell line expressing $\alpha 1G$;
ii) Treating an inhibitor candidate for the suppression of the activity of $\alpha 1G$ T-type calcium channel at different concentrations to the cells cultured in the above step i); and

iii) Measuring calcium current in the cell line treated with the above inhibitor candidate of ii).

At first, a cell line expressing $\alpha 1G$ was cultured, and then an inhibitor candidate was treated

to the cell culture solution at different concentrations. The inhibition of electric current by $\alpha 1G$ T-type calcium channel was measured at each concentrations using voltage-clamp method (Dillon G. H. et al., Mol. Pharmacol. 1993, Bodding M., J. Biol. Chem. 2004). Based on the measurement, a substance inhibiting most effectively the activity of $\alpha 1G$ T-type calcium channel and the concentration thereof were determined.

The inhibitor of the activity of $\alpha 1G$ T-type calcium channel, confirmed by the screening above, is a prospective candidate for a therapeutic agent for neuropathic diseases.

Brief Description of Drawings

Fig. 1A is a graph showing that spontaneous pain resulted from nerve injury in a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel was significantly decreased after each 14 and 21 days from the inducement of the nerve injury, comparing to a control group:

● : Wild-type, ○ : $\alpha 1G$ -/-.

Fig. 1B is a graph showing that mechanical allodynia caused by nerve injury was remarkably decreased in a transgenic mouse deficient in $\alpha 1G$ T-type calcium on day 1, day 7 and day 21 after the

nerve injury was induced, comparing to a control group:

● : Wild-type, ○ : $\alpha 1G^{-/-}$.

5 Fig. 1C is a graph showing that cold allodynia (15°C) caused by nerve injury was significantly decreased on day 21 after the nerve injury was induced in a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel, comparing to a control group:

10 ● : Wild-type, ○ : $\alpha 1G^{-/-}$.

Fig. 2A is a graph showing that thermal hyperalgesia (infrared strength 30) caused by nerve injury was significantly decreased in a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel on day 1, day 14 and day 21 after the inducement of the nerve injury, comparing to a control group:

● : Wild-type, ○ : $\alpha 1G^{-/-}$.

20 Fig. 2B is a graph showing that thermal hyperalgesia (infrared strength 60) caused by nerve injury was significantly decreased in a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel on day 14 and day 21 after the inducement of the nerve injury, comparing to a control group:

● : Wild-type, ○ : $\alpha 1G^{-/-}$.

Preferred Embodiments of the Invention

Practical and presently preferred embodiments of the present invention are illustrative as shown in the following Examples.

5 However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

10 <Example 1> Preparation and maintenance of α 1G-/- transgenic mouse

<1-1> Preparation of α 1G-/- transgenic mouse

The present inventors prepared a transgenic mouse whose genotype is α 1G-/- by using a fertilized
15 egg (Korean Collection for Type Cultures, Korea Research Institute of Bioscience and Biotechnology, Accession No: KCTC 10086BP) whose genotype is α 1G+/- of T-type calcium channel. Particularly, a fertilized egg whose genotype is α 1G+/- was transplanted in a
20 surrogate mother mouse to prepare a heterozygote mouse whose genotype is α 1G+/- . A female and a male heterozygote mouse were mated to prepare a homozygote mouse whose genotype is α 1G-/- .

25 <1-2> Maintenance of animals

The transgenic mouse was raised under 12 hour of light and 12 hour of dark cycle, during which water and food were supplied without limitation. The light cycle was started at 6 am. All the behavioral experiments including animal protection and pain tests were conducted by following ethical guidelines proposed by Korea Institute of Science and Technology and Institutional Animal Care and Use Committee affiliated with International association for the Study of Pain.

<Example 2> Preparation of surgical operation for nerve injury induced mouse: spinal nerve ligation (SNL)

A test animal was anesthetized by gas mixture of oxygen and enflurane (2% for inducement, and 0-5% for maintenance), followed by surgical operation. L5 spinal nerve was ligated by following the method of Kim and Chung (1992). Briefly, spine ranging from L4 to S2 was open and L6 vertebral transverse process was eliminated. L5 spinal nerve was tightly ligated by using 6-0 silk threads under dissecting microscope. After complete stanching, the wound was sutured.

<Example 3> Analysis of response against stimulus

<3-1> Spontaneous pain test

In order to investigate spontaneous pain, behavioral evaluation method for spontaneous pain that was modified from formalin test system (Dubuisson, 5 1977) was used. A test animal was given a free hand in a transparent plastic cylinder (6 cm in diameter x 16 cm in height) with the top opened. The animal was let adapt to the circumstance for 20 minutes before observation was start. During three-minute 10 observation, cumulative time that the animal was up in the air was recorded. However, the time that the animal lifted up its feet during movement or for back to its place was not measured. An average score for two times experiments was calculated.

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<3-2> Von Frey filament test

In order to quantify the mechanical sensitivity of paw, up/down method was used to measure withdrawal threshold of paw against von Frey filament (Chaplan, 20 1994). In each test, a test animal was put on the metal mesh floor in a transparent plastic chamber (9.5 x 5.5 x 5 cm³). 50% withdrawal threshold was measured by using a set of von Frey filament (0.02, 0.07, 0.16, 0.4, 1, 2, 4, 6 g, Stoelting, Wood Dale, IL, USA). 25 The active paw lift for the adaptation to von Frey was regarded as withdrawal response. The first stimulus

was 0.4 g filament. If there was a withdrawal response, the next weak filament was given, but if there was not a withdrawal response, the next strong filament was given. 50% threshold interpolation was performed by the method of Dixon (1980).

<3-3> Tail clip test

A strong mechanical stimulus was given to the tail by using an alligator clip (Fine Science Tools Inc., North Vancouver, Canada). The latent time to response (shaking and biting) was investigated.

<3-4> Paw withdrawal test

The present inventors measured hind-paw withdrawal latency by modified Hargreaves' method. The test was performed at low (IR 30) and high (IR 60) intensities. Cut-off time was set to 15 seconds to prevent tissue damage. Thermal stimulus was given to each paw 4 - 5 times at 5 - 10 minutes interval, and the average time for lifting up the paw was measured.

<3-5> Tail flick test

Cut-off time was also set to 15 seconds for the tail flick test to minimize tissue damage. The test was performed at high (IR 50) intensity. Thermal stimulus caused by radiant heat was given to the tail

5 times and then the average latent time was calculated. At least 10 minute-intermission was permitted between each trial.

5 <3-6> Hot plate test

A mouse was adapted on the metal floor in a transparent test box (15 x 15 x 25 cm³) for one hour. Then, the mouse was transferred into a box which was pre-heated to 52.5°C in a thermal control bath. The
10 latent time to the first licking or jumping was measured.

<3-7> Cold sensitivity test

In order to quantify the cold sensitivity of
15 paws, a drop of cold water (15°C) was dropped onto the paw and then sudden shrink of the paw was measured. The mouse was put on the metal mesh floor in a transparent plastic chamber, and then had the sole of its hind-paw contacted cold water. To do so, a drop
20 of cold water was formed by using a small polyethylene tube fragment connected to a syringe. The drop of cold water was given to each hind-paw five times (at 5 minutes interval). The frequency of paw withdrawal was calculated as percentage (%) (Frequency of paw
25 withdrawal/total trial number x 100).

As a result, spontaneous pain response (Fig. 1A), mechanical allodynia (Fig. 1B), cold allodynia (Fig. 1C) and thermal hyperalgesia (Fig. 2) were all observed in both mutant mice having $\alpha 1G^{+/+}$ and $\alpha 1G^{-/-}$,
5 in which spinal nerve ligation (SNL) was induced (Friedman repeated measures analysis of variance with post-hoc test by Dunnett's method, $*p < 0.05$). However, neuropathic pain response was significantly decreased in a transgenic mouse having $\alpha 1G^{-/-}$ genotype,
10 comparing to a wild-type mouse.

As shown in Fig. 1A, a transgenic mouse having $\alpha 1G^{-/-}$ genotype had shorter continuance of paw withdrawal than a mouse having $\alpha 1G^{+/+}$ genotype, which was proved through spontaneous pain response (Mann-Whitney rank sum test, $*p < 0.05$ 및 $**p < 0.01$). In addition, mechanical and cold allodynia was also reduced in the $\alpha 1G^{-/-}$ mouse (Fig. 1B and Fig. 1C, Mann-Whitney rank sum test, $**p < 0.01$), and further thermal hyperalgesia was also greatly decreased in the
20 mouse (Fig. 2A and Fig. 2B, Mann-Whitney rank sum test, $**p < 0.01$ and $***p < 0.001$).

Industrial Applicability

As explained hereinbefore, the present invention
25 relates to a use of a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel having resistance against pain caused by nerve injury as an animal model for the

study of human neuripathic pain related diseases. The animal model provided by the present invention can be effectively used for the development of a therapeutic agent and a treatment method for human neuropathic diseases.

Those skilled in the art will appreciate that the conceptions and specific embodiments disclosed in the foregoing description may be readily utilized as a basis for modifying or designing other embodiments for carrying out the same purposes of the present invention. Those skilled in the art will also appreciate that such equivalent embodiments do not depart from the spirit and scope of the invention as set forth in the appended claims.

What is claimed is:

1. A method for use of a transgenic mouse deficient in $\alpha 1G$ T-type calcium channel as an animal model for the study of human neuripathic pain related diseases.

2. The method as set forth in claim 1, wherein the mouse is spinal-nerve-ligated (SNL).

3. A method for relieving neuropathic pain by suppressing $\alpha 1G$ gene coding a pore forming subunit of T-type calcium channel.

4. A method for screening of an inhibitor suppressing the activity of $\alpha 1G$ T-type calcium channel by using a cell line expressing $\alpha 1G$ T-type calcium channel.

5. The method as set forth in claim 4, wherein the cell line is deposited as KCTC 10519BP.

6. The method as set forth in claim 4 or claim 5, wherein the method includes following steps:

- i) culturing a cell line expressing $\alpha 1G$;
- ii) treating an inhibitor candidate for the suppression of the activity of $\alpha 1G$ T-type calcium channel at different concentrations to the cells

cultured in the above step i; and

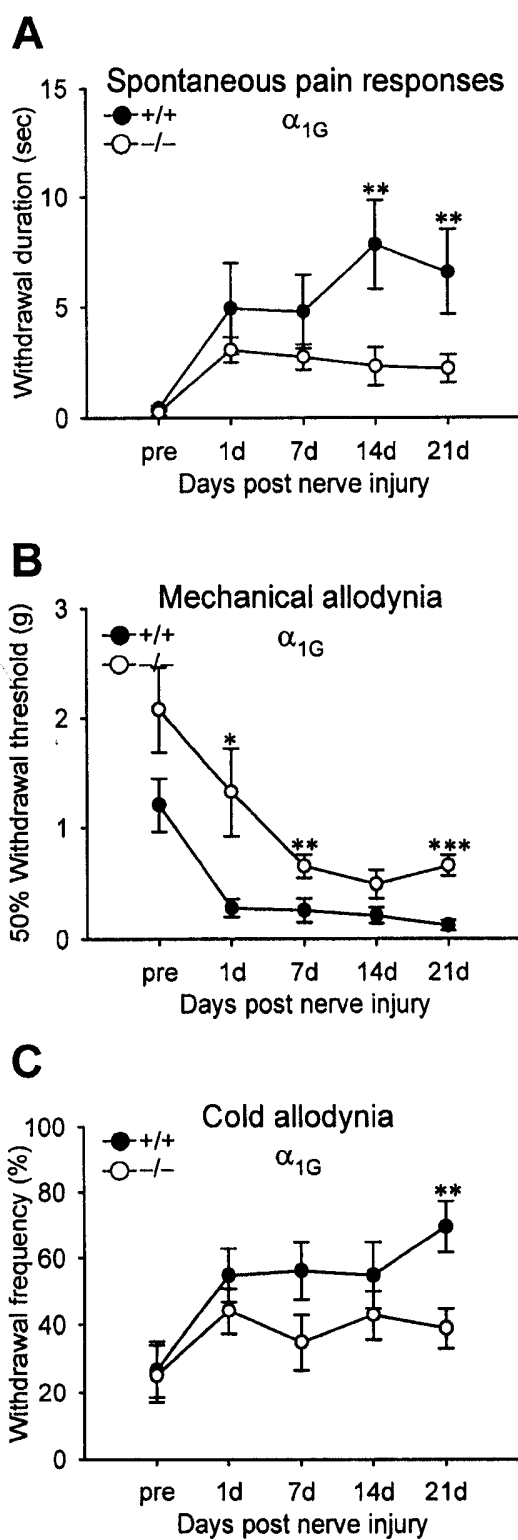
iii) measuring calcium current in the cell line treated with the above inhibitor candidate of ii.

- 5 7. The method as set forth in claim 6, wherein the measurement of calcium current of step iii is performed by voltage-clamp method.

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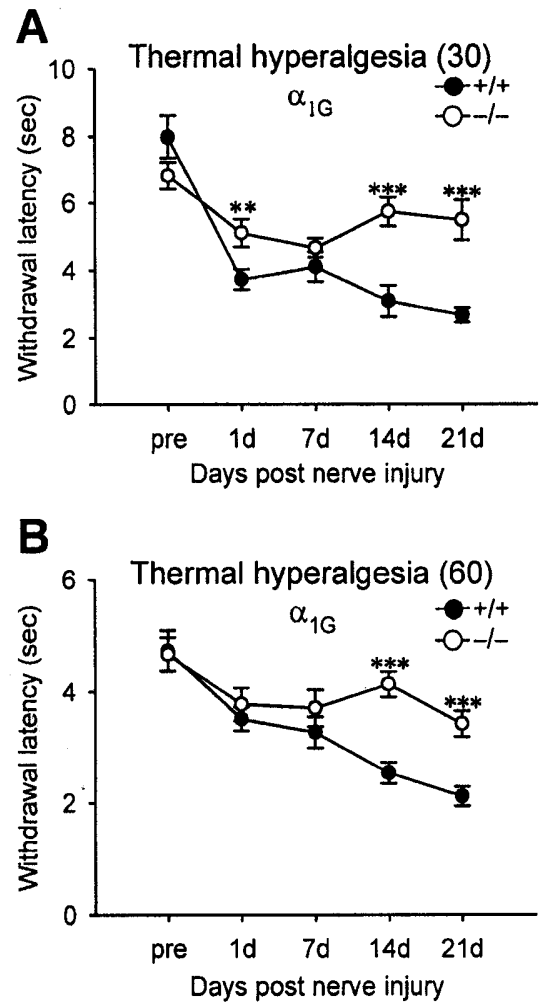
FIGURES

FIG. 1



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FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/003270

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 33/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
GENBANK(STN), CAPLUS(STN), Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Kim D., et al., "Thalamic control of visceral nociception mediated by T-type Ca ²⁺ channels", Science, 2003, Vol.302, No.5642, pp.117-119	1-2, 3
Y	WO 99/28342 A2(SIBIA NEUROSCIENCES,INC.) 10 June 1999 see the abstract	4-7
Y	KR 2003-37081 A(Korea Institutes of Science and Technology) 12 May 2003 see the abstract	1-7
A	US 6,358,706 B1(Ortho-McNeil Pharmaceutical, Inc.) 19 March 2002 see the abstract	1-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search

12 SEPTEMBER 2005 (12.09.2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2004/003270

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WO 99/28342 A2	10.06.1999	AU 199918026 B2 EP 1042468 A2 US 6528630 BA	16.06.1999 11.10.2000 04.03.2003
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