European Journal of Pharmacology 800 (2017) 9–15

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

The involvement of spinal release of histamine on nociceptive behaviors induced by intrathecally administered spermine

Hirokazu Mizoguchi[a], Chizuko Watanabe[a], Takafumi Hayashi[b], Yoko Iwata[a], Hiroyuki Watanabe[c], Soh Katsuyama[d], Kengo Hamamura[e], Tsukasa Sakurada[e], Hiroshi Ohtsu[f], Kazuhiko Yanai[g], Shinobu Sakurada[a,*]

[a] Department of Physiology and Anatomy, Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan
[b] Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan
[c] Department of Pharmaceutical Biosciences, Division of Biological Research on Drug Dependence, Uppsala University, Husargatan 3, Uppsala 751 24, Sweden
[d] Center for Experiential Pharmacy Practice, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan
[e] First Department of Pharmacology, Daiichi College of Pharmaceutical Sciences, 22-1 Tamagawa-cho, Minami-ku, Fukuoka 815-8511, Japan
[f] Department of Quantum Science and Energy Engineering, Graduate School of Engineering, Tohoku University, 6-6-01-2 Aobayama, Aoba-ku, Sendai, 980-8579, Japan
[g] Department of Pharmacology, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan

ARTICLE INFO

Keywords:
Spermine
Histamine
Release
NMDA receptor
Nociception
Spinal cord

ABSTRACT

The involvement of spinal release of histamine on nociceptive behaviors induced by spermine was examined in mice. Intrathecal spermine produced dose-dependent nociceptive behaviors, consisting of scratching, biting and licking. The nociceptive behaviors induced by spermine at 0.02 amol and 10 pmol were markedly suppressed by i.t. pretreatment with antiserum against histamine and were abolished in histidine decarboxylase-deficient mice. In histamine H_1 receptor-deficient mice, the nociceptive behaviors induced by spermine were completely abolished after treatment with 0.02 amol of spermine and significantly suppressed after treatment with 10 pmol of spermine. The i.t. pretreatment with takykinin NK_1 receptor antagonists eliminated the nociceptive behaviors induced by 0.02 amol of spermine, but did not affect the nociceptive behaviors induced by 10 pmol of spermine. On the other hand, the nociceptive behaviors induced by spermine at both 0.02 amol and 10 pmol were suppressed by i.t. pretreatment with antagonists for the NMDA receptor polyamine-binding site. The present results suggest that the nociceptive behaviors induced by i.t. administration of spermine are mediated through the spinal release of histamine and are elicited via activation of NMDA receptors.

1. Introduction

The polyamines spermine, spermidine and putrescine are endogenous aliphatic amines that are widely distributed (Gilad and Gilad, 1992). Since they have a polycationic structure, they electrically bind to negatively charged cellular molecules, including nucleic acids, acidic lipids and proteins (Ahern et al., 2006; Scott et al., 1993). Therefore, polyamines are considered to be closely involved with cellular functions (Ekegren et al., 2004; Gilad and Gilad, 1992; Scott et al., 1993; Tanabe et al., 2004). Polyamines are mainly synthesized from ornithine by ornithine decarboxylase, spermidine synthase and spermine synthase (Gilad and Gilad, 1992; Laube et al., 2002; Silva et al., 2011; Wolff et al., 2003). Putrescine is formed from ornithine by ornithine decarboxylase, and then, putrescine is converted to spermidine and spermidine is converted to spermine by spermidine synthase and spermine synthase, respectively. Polyamine synthesis has been observed in both neurons and glial cells in the central nervous system (Bernstein and Müller, 1999; Ekegren et al., 2004; Laube 2002). Immunoreactivity for spermine/spermidine was detected in both neurons and glial cells in most regions in the central nervous system (Laube, 2002). Immunoreactivity for ornithine decarboxylase was detected in neurons and glial cells in the brains under several pathophysiological conditions (Bernstein and Müller, 1999). The physiological functions of polyamines in the central nervous system

* Corresponding author.
E-mail address: s-sakura@tohoku-mpu.ac.jp (S. Sakurada).

http://dx.doi.org/10.1016/j.ejphar.2017.01.031
Received 27 August 2016; Received in revised form 6 January 2017; Accepted 24 January 2017
Available online 26 January 2017

are considered to include the control of neuronal excitability involved in the variable physiological responses related to pathophysiological conditions (Gilad and Gilad, 1992).

In the neurons and glial cells of the central nervous system, the molecular target for polyamines is considered to be the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor is a hetero-tetramer consisting of 7 NMDA receptor subunits (NR1, NR2A-D and NR3A-B) that form a Ca^{2+}/Na^{+} channel (Dingledine et al., 1999). The NR1 subunit is an essential subunit for NMDA receptors and is ubiquitously distributed in the central nervous system (Nagy et al., 2004). It contains a polyamine-binding site, through which endogenous polyamines positively modulate the functions of the NMDA receptors (Dingledine et al., 1999). On the other hand, the NR2A-D subunits contain binding sites for the endogenous ligand glutamate, and the activation of the glutamate-binding site opens the Ca^{2+}/Na^{+} channel and results in neural excitation. This response plays an important role in pain transmission in the spinal cord (Dickenson et al., 1997). Glutamate is contained in and released from primary afferent nerves (Ueda et al., 1994) and binds to NMDA receptors on the cell body of the second order neuron for pain transmission.

It has been reported that intrathecal (i.t.) administration of spermine induced nociceptive behaviors, consisting of scratching, biting and licking (Tan-No et al., 2000). However, the mechanism of spermine-induced nociceptive behaviors is not fully understood. We reported the possible interactions among spinal neurotransmitters/neuromodulators, histamine, substance P and polyamines in spinal pain transmission (Sakurada et al., 2003, 2004; Watanabe et al., 2008). Therefore, in the present study, the mechanism of nociceptive behaviors induced by i.t. administration of spermine was investigated, with a focus on the involvement of histamine and NMDA receptors in the mouse spinal cord.

2. Materials and methods

All experiments were performed following the approval of the Ethics Committee for Animal Experiments at Tohoku Medical and Pharmaceutical University and according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Every effort was made to minimize the number of animals and any suffering by the animals used in the following experiments.

2.1. Animals

Male ddY mice (Japan SLC, Hamamatsu, Japan), histidine decarboxylase-deficient mice (supplied by Dr. Ohtsu: Ohtsu et al., 2001), histamine H_1 receptor-deficient mice (supplied by Dr. Yanai: Inoue et al., 1996), histamine H_2 receptor-deficient mice (supplied by Dr. Kobayashi: Kobayashi et al., 2000) and respective wild-type mice weighing 22–25 g were used. The histidine decarboxylase-deficient mice have 129/Sv and CD-1 mixed genetic backgrounds. The histamine H_1 receptor-deficient mice have C57BL/6 and 129/ola mixed genetic backgrounds. The histamine H_2 receptor-deficient mice have C57BL/6 and 129/ola mixed genetic backgrounds and were backcrossed eight times to the C57BL/6 mice. The genotypes of histidine decarboxylase-deficient mice, histamine H_1 receptor-deficient mice, histamine H_2 receptor-deficient mice and wild-type mice, which have the same genetic backgrounds as the respective knockout mice, were identified by the polymerase chain reaction. The animals were housed in a room maintained at 22–23 °C and 50–60% relative humidity with an alternating 12-h light/dark cycle. Food and water were available ad libitum. Mice only were used once.

2.2. Intrathecal injections

I.t. injection was performed following the method described by Hylden and Wilcox (1980) using a 29-gauge stainless-steel needle attached to a 50-μl Hamilton microsyringe. The volume of the i.t. injections was 5 μl.

2.3. Behavioral procedures

The nociceptive behaviors of mice were evaluated according to the methods described in our previous report (Mizoguchi et al., 2011). Approximately 1 h before i.t. injection, mice were adapted to individual plastic cages (22.0×15.0×12.5 cm), which also served as observation chambers. Immediately after i.t. injection of spermine, each mouse was placed in the transparent cage, and the nociceptive behaviors induced by spermine were observed for 30 min at 5 min intervals. The nociceptive behaviors observed included caudally directed biting and licking along with reciprocal hindlimb scratching. The total response times of these nociceptive behaviors were pooled and recorded as a single value for each animal.

2.4. Drugs

The drugs used were spermine tetrahydrochloride (Nacalai Tesque, Kyoto, Japan), arcaine sulfate (Tocris Cookson Ltd., Bristol, UK), agmatine sulfate (Tocris Cookson Ltd.), (5*R*,10*S*)-(+)−5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene-5,10-imine (MK-801) hydrogen maleate (Sigma-Aldrich Chemical Co., St. Louis, MO), D-(-)−2-amino-5-phosphonovaleric acid (D-APV) (Sigma-Aldrich Chemical Co.), 3-((+)−2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) (Sigma-Aldrich Chemical Co.), rabbit antiserum against histamine (Progen Biotechnik GMBH, Heidelberg, German), normal rabbit serum (Vector Laboratories, Burlingame, CA). [Tyr^6,D-Phe^7,D-His^9] substance P-(6–11) (sendide) and [D-Phe^7,D-His^9]substance P-(6–11) were synthesized by solid-phase peptide methodology. (+)-[(2*S*,3*S*)−3-(2-methoxy-benzyl-amino)−2-phenylpiperidine] (CP-99,994) was a gift from Pfizer Pharmaceuticals (New York, NY). These drugs were dissolved or diluted in sterile artificial cerebrospinal fluid (aCSF) containing 126.6 mM NaCl, 2.5 mM KCl, 2.0 mM $MgCl_2$, and 1.3 mM $CaCl_2$.

2.5. Statistical analysis of data

The time spent performing nociceptive behaviors (s) was presented as the mean ± S.E.M for 10 mice. The statistical significance of the differences between groups was assessed with Student's *t*-test and one-way analysis of variance (ANOVA) followed by Bonferroni's test or two-way ANOVA followed by Bonferroni's test.

3. Results

3.1. Involvement of histamine release in spermine-induced nociceptive behaviors

Spermine-induced nociceptive behaviors were observed in mice. Groups of mice were treated with various i.t. doses of spermine (from 0.001 amol to 10 pmol) or aCSF, and nociceptive behaviors were observed for 30 min at 5 min intervals. The i.t. administration of spermine at a dose of 0.001 amol to 1 amol dose-dependently evoked characteristic nociceptive behaviors mainly consisting of vigorous biting and/or licking with a little scratching (Fig. 1). However, at doses over 1 amol, the nociceptive behavior response elicited by spermine was saturated, and no additional increase in nociceptive behaviors was observed with 10 pmol of spermine. The nociceptive behaviors peaked at 5–10 min and disappeared at 25–30 min after the injection (data not shown).

To elucidate the involvement of the spinal release of histamine on spermine-induced nociceptive behaviors, the effect of an antiserum against histamine on spermine-induced nociceptive behaviors was determined. Groups of mice were pretreated with i.t. antiserum against