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ORIGINAL ARTICLE

Changes in median eminence of fatty acid–binding protein 3 in a mouse model of pain

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Abstract

Aims: Fatty acid–binding protein (FABP) regulates polyunsaturated fatty acid (PUFA) intracellular trafficking and signal transduction. Our previous studies demonstrated that the alteration of PUFA in the hypothalamus is involved in pain process. However, how FABP subtypes change during pain remain unclear. Here, we examined the expression changes and localization in the hypothalamic FABP subtype in postoperative pain model mice.

Methods: Paw incision–induced postoperative methods were adopted as a pain model in male ddY mice. Mechanical allodynia was examined using the von Frey test. The analysis of several FABPs mRNA was measured by real-time PCR, and cellular localization of its protein level was measured by immunofluorescent study.

Results: Postoperative pain mouse elicited mechanical allodynia on Day 2 after paw incision, and mRNA expression of FABP3 increased significantly in the hypothalamus in the postoperative pain mouse model compared to that in control mice. FABP3 protein expressed in the median eminence and the arcuate nucleus, and colocalized with Iba-1, which is a microglial cell marker. Its protein level significantly increased in the median eminence on Day 2 after incision and returned to the control level on Day 4 after incision.

Conclusions: Our findings indicate that FABP3 in the median eminence may change in pain stimuli and may represent a molecular link controlling pain.

KEYWORDS
fatty acid, fatty acid–binding protein 3, median eminence, postoperative pain

1 | INTRODUCTION

Our previous study showed the alteration of polyunsaturated fatty acids (PUFA) including docosahexaenoic acid (DHA) in the hypothalamus area of postoperative pain[1] and complete Freund's adjuvant model mice.[2] We speculate that the changes of hypothalamic fatty acids, which caused by pain stimuli, may involve in pain control because these changes are dependent on pain behavior. Recently, there are several evidences that the elevated dietary n-6 PUFA such as linoleic acid and arachidonic acid affects nociceptive thresholds,[3-5] whereas n-3 PUFA such as DHA attenuates pain.[6-9] We also found that mice-fed n-3 PUFA-deficient diet decreased pain threshold against mechanical stimuli,[10] suggesting that the alteration of fatty acids composition may affect pain.

The hypothalamus is well known as a brain region responsive to noxious stimuli.[11-13] Some cell type of neuron in the hypothalamus

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can be activated to suppress pain-related behavior.[14,15] On the other hand, this region is one of the first brain area, which primarily senses nutrient signals including PUFA[16,17] from the periphery via the systemic circulation.[18-20] Therefore, the changes of hypothalamic fatty acids, which caused during pain, may alter pain sensitivity. However, it is unclear how alteration of fatty acids in the brain is affected pain behavior, and its mechanism remains unknown.

Fatty acid–binding proteins (FABP), which are known as cellular chaperones of PUFA, are involved in gene transcription, signal transduction, and intracellular trafficking of PUFA.[21] Of FABP subtypes, FABP3, FABP5, and FABP7 are expressed in the mammalian central nervous system such as neurons and glial cells in the brain.[22-24] These three subtypes of FABP are involved in the regulation of composition and cellular localization of PUFA in the brain. Here, we were interested in determining whether three subtypes of hypothalamic FABP are involved in pain process.

In the present study, we tested the changes of hypothalamic FABP subtype in postoperative pain model mice and also evaluated the cellular localization of FABP in the hypothalamus.

2 | METHODS

2.1 | Animals

Animal experiments were performed according to the Animals in Research: Reporting In Vivo Experiments guidelines, as detailed previously. Male ddY mice (n = 101, 5-7 weeks of age) were purchased from Japan SLC, Inc. The mice were kept in cages at 23-24°C with a 12-hours light/dark cycle (lights on from 8 AM to 8 PM), with food and water available ad libitum. All the behavioral tests were performed by researchers who were blinded to the surgeries and genotype.

2.2 | Mouse model of postoperative pain

Incision from heel to toe in plantar was made in the mouse, as detailed previously by Pogatzli et al.[25] In brief, the mice were anesthetized with three types of mixed anesthesia containing medetomidine (0.75 mg/kg), midazolam (4 mg/kg), and butorphanol (5 mg/kg). After antiseptic preparation of the right hind paw, a 1-cm longitudinal incision was made through the skin and fascia of the plantar foot. The underlying muscle was elevated with curved forceps, leaving the muscle origin and insertion intact. Control mice without incision were anesthetized with three types of mixed anesthesia alone. After surgery, atipamezole (0.75 mg/kg) was administered in mice.

2.3 | von Frey test

As described previously,[1] mechanical allodynia was tested with von Frey filaments (NeuroScience Inc.). The mice were placed on a 5 × 5-mm wire-mesh grid floor that was covered with a foil-wrapped cup to avoid visual stimulation and allowed to adapt for 1 hour before the von Frey test. The von Frey filament (0.16 g and 0.4 g) was then applied to the middle of the plantar surface of the hind paw. The withdrawal responses following the hind paw stimulation were measured 10 times, and the mechanical allodynia, which was defined as an increase in the number of withdrawal responses to the stimulation, was compared.

TABLE 1 Primer sequences employed in this study

FABP3	Forward	5′-CATGAAGTCACTCGGTGTGG-3′
	Reverse	3′-TGCCATGAGTGAGAGTCAGG-5′
FABP5	Forward	5′-TGTCATGAACAATGCCACCT-3′
	Reverse	3′-CTGGCAGCTAACTCCTGTCC-5′
FABP7	Forward	5′-CAAGAACACAGAGATCAATTTCCA-3′
	Reverse	3′-CATCCAACCGAACCACAGA-5′
GAPDH	Forward	5′-AACTTTGGCATTGTGGAAGG-3′
	Reverse	3′-GGATGCAGGGATGATGTTCT-5′

2.4 | Real-time PCR

Total RNA was extracted from each brain tissue using the RNeasy mini kit (Qiagen), according to the manufacturer's instructions. RNA was quantified spectrophotometrically at 260 nm using a NanoDrop Lite Spectrophotometer (Thermo Fisher Scientific Inc.) and stored at −80°C. Reverse transcription was performed using the Primescript RT reagent kit according to the manufacturer's instructions (Takara Bio, Inc.). Amplification was performed using the LightCycler 96 system (Roche) with SYBR green PCR master mix (Roche). Forward and reverse primers (500 nmol each) were used in 20-μL reactions containing 2 μL of template DNA. The primers used for gene expression analyses are shown in Table 1. Quantitative real-time PCR (qRT-PCR) was carried out with an initial activation at 95°C for 5 minutes followed by 40 cycles of amplification at 95°C for 10 seconds, 60°C or 57°C for 20 seconds, and 72°C for 20 seconds. Fluorescence was measured once per cycle after the elongation step, as recommended by the manufacturer. Relative mRNA levels were determined according to the $2^{-\Delta\Delta Ct}$ method, in which all ΔCt values were normalized to the expression levels of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The PCR products were visualized as single bands on agarose gel stained with ethidium bromide.

2.5 | Double immunofluorescence study

Immunohistochemical analysis was performed according to methods described previously.[14] Brain tissue sections include the third ventricle of hypothalamus area, were incubated in 4% paraformaldehyde solution, washed three time with phosphate-buffered saline (PBS) containing 0.1% Tween-20 (PBST) at 5-minutes intervals, and

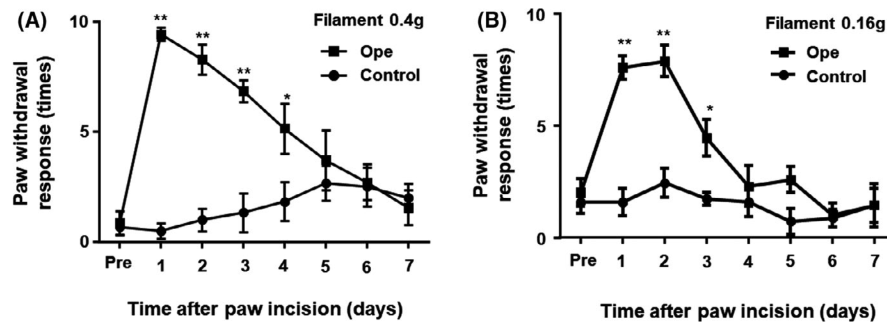

FIGURE 1 Time course of mechanical allodynia in the postoperative pain mouse model. Ope and Control indicate the postoperative pain mouse model and the normal mouse without incision, respectively. Mechanical allodynia was evaluated by the von Frey test using 0.4 g (A) and 0.16 g filaments (B). Data are presented as the mean ±standard error of the mean (SEM). (A) Control (n = 6), Ope (n = 7), (B) Control (n = 7), Ope (n = 7), $^{**}P < .01$, $^{*}P < .05$ vs. Control (analyzed by two-way ANOVA with Bonferroni's multiple comparison *post hoc* test)

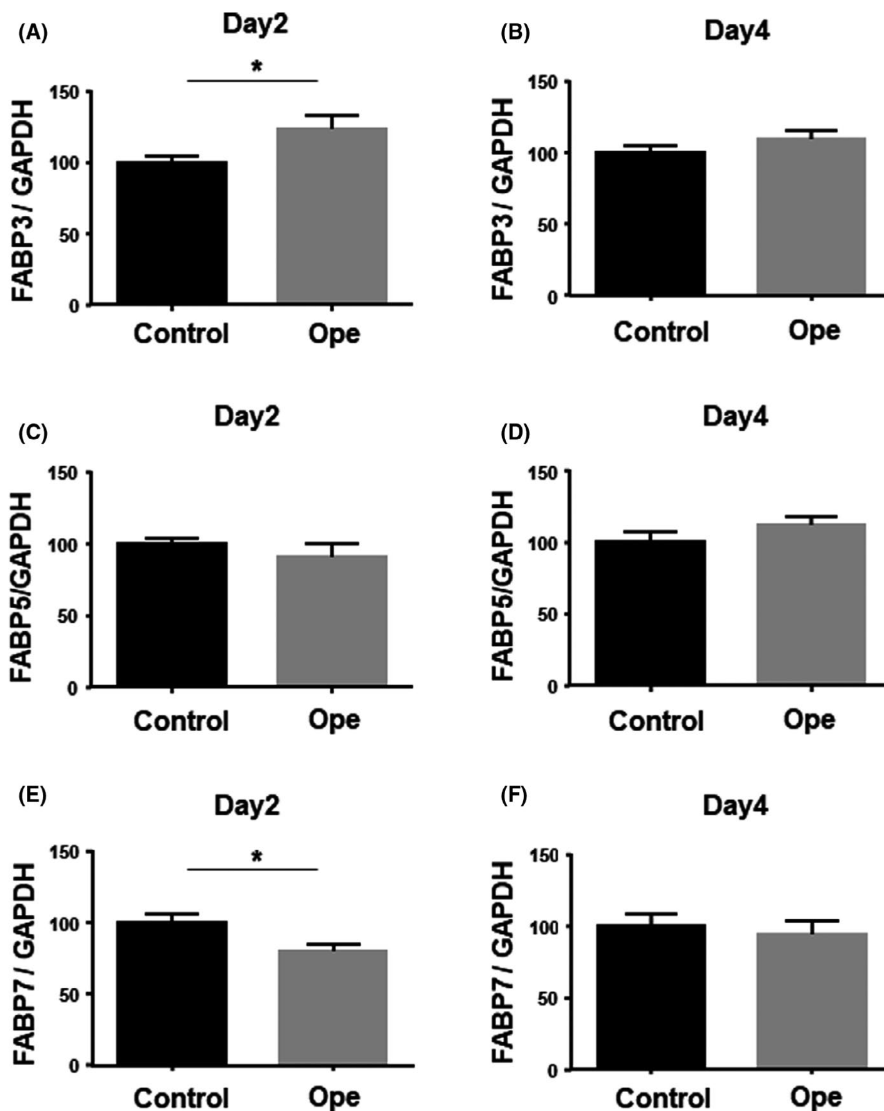

FIGURE 2 Analysis of mRNA expression of FABP3, FABP5, and FABP7 in the hypothalamic tissue from the postoperative pain mouse model. Real-time PCR was employed to determine the mRNA expression levels of FABP. Changes in the mRNA expression of FABP3, FABP5, and FABP7 on days 2 and 4 after paw incision are shown in (A)-(F). Data are presented as the mean ±standard error of the mean (SEM). (A) Control (n = 5), Ope (n = 6), (B) Control (n = 5), Ope (n = 5), (C) Control (n = 5), Ope (n = 6), (D) Control (n = 5), Ope (n = 5), (E) Control (n = 9), Ope (n = 10), (F) Control (n = 6), Ope (n = 6), $^{*}P < .05$ vs. Control (Student's *t*-test)

incubated with blocking buffer (3% bovine serum albumin [BSA] in PBS) for 1 hour at room temperature (RT). The sections were then incubated with specific antibodies against FABP3 (Mouse monoclonal anti-FABP3 antibody, 1:500, HM201, Hycult Biotech), NeuN (Rabbit monoclonal anti-NeuN antibody, 1:1000, EPR12763, Abcam plc), GFAP (Rabbit polyclonal anti-GFAP antibody, 1:1000, ab7260; Abcam plc), and Iba-1 (Rabbit polyclonal anti-Iba-1 antibody, 1:1000, 019-19 741, FUJIFILM Wako Pure Chemical Corporation),

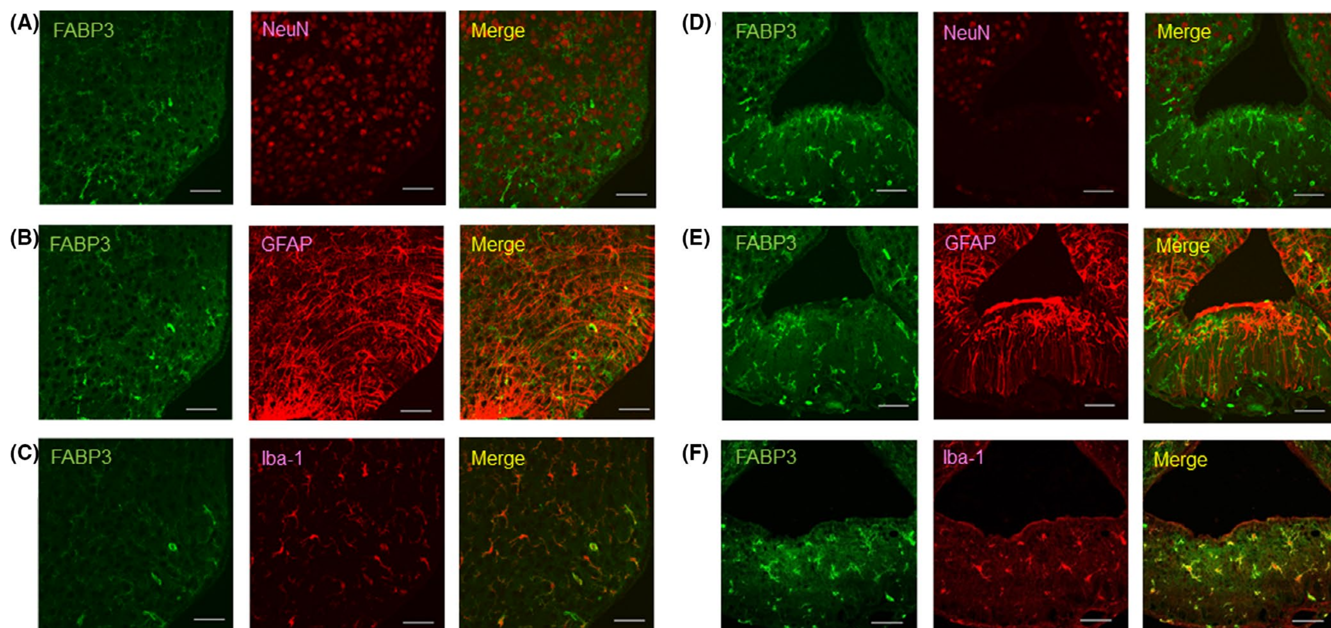

FIGURE 3 Double labeling for FABP3 with NeuN (neuron marker), GFAP (astrocyte marker), or Iba-1 (microglia marker) in the arcuate nucleus and median eminence from the naive mouse. Colocalization of FABP3 (green) with NeuN (red), GFAP (red), or Iba-1 (red) was shown by using confocal laser scanning microscope. Arcuate nucleus (A-C), Median eminence (D-F), Scale bars: 50 μm (magnification 40×)

which were diluted in 3% BSA containing PBS and Triton X-100 for 24 hours at 4°C. Sections were then washed three times with PBST for 5 minutes each and incubated with secondary antibodies that were conjugated with Alexa Fluor® 594 and 488 (Alexa Fluor 488 goat polyclonal anti-mouse IgG antibody, 1:200, A11029, Alexa Fluor 594 goat polyclonal anti-rabbit IgG antibody, 1:200, A11037, Thermo Fisher Scientific Inc.), and diluted in reaction buffer at RT for 2 hours. Finally, the sections were washed three times with PBST for 5 minutes each and mounted on cover slips with PermaFluor (Thermo Fisher Scientific Inc.). Immunoreactivity was examined with a confocal fluorescence microscope (FV3000, Olympus Corporation). In control sections, no staining was detected when the corresponding primary or secondary antibody was omitted. The immunoreactivity of FABP3-positive cells was quantified with the ImageJ (Image Processing Software, National Institutes of Health) in defined area of immunoreactivity on the arcuate nucleus and the median eminence.

2.6 | Statistical analysis

GraphPad Prism, version 7.0 (GraphPad Software, Inc.), was used for the analysis of all data. Student's unpaired *t* tests were applied (real-time PCR and double immunofluorescence analysis) for comparisons between the two groups. Two-way analysis of variance was used, which was followed by Bonferroni's *post hoc* test to determine the individual group differences (behavioral test) for multiple comparisons. The data are presented as the mean ±standard error of the mean. *P* values less than.05 were considered statistically significant.

3 | RESULTS

3.1 | Pain behavior in the postoperative pain mouse model

One day after the surgery, the plantar incision-treated mice exhibited significantly increased responses to the mechanical stimuli of the ipsilateral hind paw. The pain was maintained for at least 3 days, and the paw withdrawal threshold was reversed to control responsivity within 7 days after the surgery. Control mice without incision had no effect on the paw withdrawal threshold in the ipsilateral hind paw (Figure 1A,B).

3.2 | Changes in FABP3, FABP5, and FABP7 mRNA expression in the hypothalamus of the postoperative pain mouse model

Two days after paw incision, FABP3 and FABP7 mRNA expression significantly increased and decreased, respectively, in Ope mice compared to that in control mice (Figure 2A,E). These changes in FABP3 and FABP7 mRNA levels were reversed to the control levels on Day 4 after paw incision (Figure 2B,F). On the other hand, FABP5 mRNA expression did not differ between the groups (Figure 2C,D).

3.3 | The cellular localization of FABP3 in the arcuate nucleus and the median eminence

FABP3-positive cells colocalized with the Iba-1-positive cells in the arcuate nucleus and median eminence (Figure 3C,F). However, these

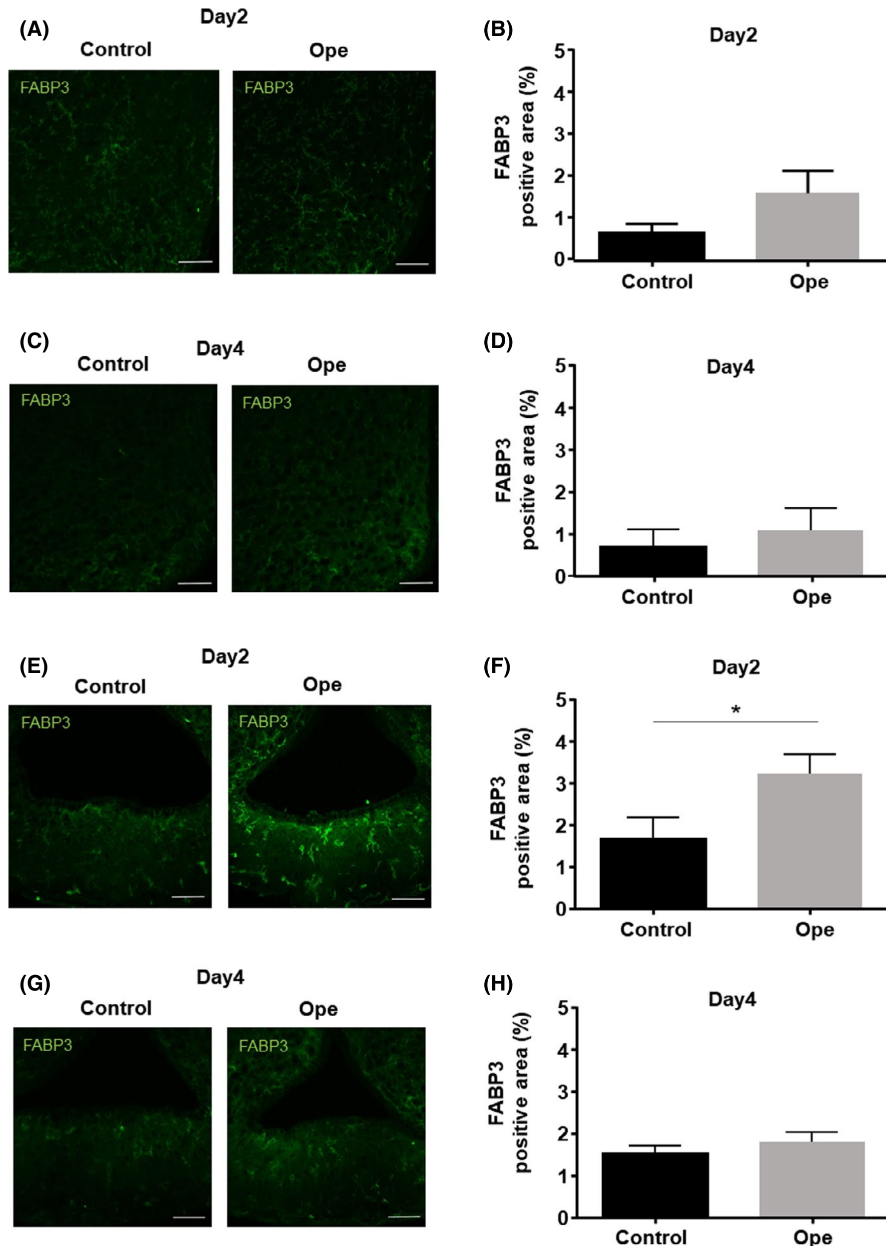

FIGURE 4 Analysis of FABP3 in the arcuate nucleus and the median eminence from the postoperative pain mouse model. Immunofluorescence images of FABP3 (green) were shown using confocal laser scanning microscope. Change of the FABP3 in the arcuate nucleus and the median eminence on days 2 and 4 after paw incision is shown in (A)-(H). Arcuate nucleus (A-D), Median eminence (E-H), Scale bars: 50 μm (magnification 40×). Data are presented as the mean ±standard error of the mean (SEM). (B) Control (n = 5), Ope (n = 6), (D) Control (n = 4), Ope (n = 4), (F) Control (n = 6), Ope (n = 7), (H) Control (n = 4), Ope (n = 4) *$P < .05$ vs. Control (Student's *t*-test), *$P < .05$ vs. Control (Student's *t*-test)

positive cells did not co-express with NeuN and GFAP marker in these regions (Figure 3A-F).

3.4 | Changes of FABP3 protein expression in the arcuate nucleus and the median eminence of the postoperative pain mouse model

FABP3-positive cells were expressed in the arcuate nucleus (Figure 4A,C) and the median eminence of the hypothalamus (Figure 4E,G). In the arcuate nucleus, the protein expression of FABP3 did not any change between Control and Ope group (Figure 4A-D). On the other hand, in the median eminence of Ope mice, FABP3 levels were significantly increased on Day 2 after the paw incision compared with Control group, and returned to the control level on Day 4 after paw incision (Figure 4E-H).

4 | DISCUSSION

In this study, we found that the mRNA expression of hypothalamic FABP3 increased in the early phase of postoperative pain, and the changes in FABP3 mRNA expression improved with the recovery of pain, suggesting that hypothalamic FABP3 may change by pain stimuli. Next, to characterize the cellular localization and site specificity of FABP3 in the hypothalamus, we performed double immunofluorescence stain for FABP3. We observed that FABP3 protein highly expressed in the median eminence and also slightly expressed in the arcuate nucleus. The median eminence and the arcuate nucleus are located around the third cerebroventricular, and it is known as a brain circumventricular organ.[26] In particular, the median eminence is an important site to incorporate nutrients including fatty acids into the brain from peripheral.[27] These sites primarily sense nutrient signals from the periphery via the systemic circulation.[18,19,28]

Interestingly, we found that FABP3 colocalized with microglial cell in the median eminence. A more recent studies showed that FABP3 is expressed in primary mouse microglia and mouse BV-2 cells[29] although the physiological function of microglial FABP3 remains unknown. Generally, it is well known that FABP3 is predominantly expressed in neurons.[30-32] However, in the median eminence, we could not observe NeuN-positive cells, which is a marker of mature neuron. The reason why we could not observe neuronal cell body in the median eminence is because the median eminence is located in ventricular zone and it is rich site in some neuron terminal, other glial cells, tanycytes, and capillaries.[33-35] Therefore, these results indicate that the cellular localization of FABP3 may different between sites of the brain.

Furthermore, we demonstrated that FABP3 protein increased in the median eminence at early phase of pain. These results correlated with the changes of its mRNA expression, speculating that microglial FABP3 in the median eminence may involve in pain process.

On the other hand, there are some previous reports regarding relationship between pain and FABP5 or FABP7.[36-39] For instance, pharmacological deletion and inhibition of FABP5 and FABP7 suppress the formalin-, carrageenan-, and acetic acid–induced visceral, thermal pain, and inflammatory pain through the peripheral antinociceptive system.[36-38] However, in this study, hypothalamic FABP5 was not affected by pain stimuli, indicating that hypothalamic FABP5 might be ineffective in the early phase after pain stimuli in the postoperative pain mouse model. Furthermore, we are not able to explain why the levels of hypothalamic FABP7 mRNA decreased in the early phase after paw incision although these differences might depend on the types and nature of pain.

In summary, we demonstrated that FABP3 mRNA and protein expression were significantly increased in the hypothalamus of pain model mice. In particular, FABP3 protein was highly expressed and colocalized with microglial cell in the median eminence. Our findings suggest that hypothalamic FABP3 may, at least in part, involve in the molecular mechanism for the early phase after pain stimulation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

DT, KN, and ST designed and considered the study. DT conducted and analyzed experiments. DT, KN, and ST drafted the manuscript.

ANIMAL STUDIES

This study was conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals adopted by the Japanese Pharmacological Society. All experiments were approved by the Ethical Committee for Animal Experimentation at Kobe Gakuin University (approval number A19-06; Kobe, Japan).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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