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Adiponectin receptor 1 gene is potentially associated with severity of postoperative pain but not cancer pain

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Abstract

Adiponectin is an adipose tissue-derived cytokine that exerts its antiinflammatory effects by binding to 2 adiponectin receptors, adiponectin receptor 1 (ADIPOR1) and adiponectin receptor 2 (ADIPOR2). However, the role of these adiponectin receptors on inflammatory pain remains unclear. We investigated the association between single nucleotide polymorphisms (SNPs) of these genes and inflammatory pain, such as postoperative pain and cancer pain.

We analyzed 17 SNPs of the ADIPOR1 gene and 27 SNPs of the ADIPOR2 gene in 56 adult patients with postlaparotomy pain. We compared these genotypes with pain intensity and opioid consumption, adjusting for multiple testing. We analyzed the genotypes of 88 patients with cancer pain and examined the association of the relevant SNP(s) with pain intensity and opioid consumption.

One variant of the ADIPOR1 gene (rs12045862) showed significant association with postoperative pain intensity; patients with minor allele homozygote (n = 7) demonstrated significantly worse pain intensity than that of combined patient group exhibiting major allele homozygote or the heterozygote (n = 49; Mann-Whitney test, $P < .00002$), although their opioid consumptions were comparable. Cancer pain intensity between minor allele homozygote patients (n = 7) and other 2 genotype patients (n = 81) were comparable.

The rs12045862 SNP of the ADIPOR1 gene was associated with postoperative pain but not cancer pain. This might result from functional alteration of the ADIPOR1 signalling pathways, which influence the inflammatory process. ADIPOR1 may be a novel potential target for developing analgesics of postoperative pain.

Abbreviations: ADIPOR1 = adiponectin receptor 1, ADIPOR2 = adiponectin receptor 2, AMD = age-related macular degeneration, AMPK = adenosine monophosphate protein kinase, IL-6 = interleukin-6, K-W test = Kruskal-Wallis test, MAPK = mitogen-activated protein kinase, M-H test = Mann-Whitney test, NRS = numerical rating scale, PPAR-α = peroxisome proliferator activated receptor α, QC = quality control, SNPs = single nucleotide polymorphisms, TNFα = tumor necrosis factor α.

Keywords: adiponectin, ADIPOR1 gene, cancer pain, postoperative pain

1. Introduction

Obesity is a known predictor of severity and chronicity of various types of pain.[1] Its mechanism is yet to be fully understood but it is considered that not only excessive mechanical load of body weight on the musculoskeletal system but also the systemic inflammatory status due to obesity is associated with pain.[2]

Under obesity, the adipose tissue becomes hypertrophic and hyperplastic. Such altered adipose tissue, in addition to functioning as a fat storage, causes systemic inflammatory responses that are self-generating and enhance the expression of pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin-6 (IL6), and monocyte chemoattractant protein-1.[3] Adiponectin is one of the major adipose tissue-related cytokines (also called as adipokine). Adiponectin is secreted from adipocytes of 'lean' white adipose tissue, and has the potential of an antiinflammatory cytokine, which suppresses the inflammatory processes.[4] Considering this, adiponectin is known to have beneficial effects, whose examples include improvement in insulin sensitivity by activating adenosine monophosphate protein kinase (AMPK) in the liver and skeletal muscles, vasodilation by stimulating nitric oxide production in endothelial cells, and attenuation of the inflammatory response of endothelial cells by inhibiting TNFα-induced nuclear factor-κB activation.[5,6] On the contrary, adipocyte hypertrophy and hyperplasia leads to reduction of adiponectin secretion from

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adipocytes, and then, leads to insulin resistance and atherosclerosis by restoring the inflammatory processes.[3] Focusing on the antiinflammatory effect of adiponectin, we hypothesized that adiponectin is associated with inflammatory pain. We investigated the relationships between postoperative pain intensity and genetic polymorphisms and serum concentrations of adiponectin. However, we could not reveal if adiponectin reduces postoperative pain intensity.[7]

Endocrinological studies have revealed that the biological effects of adiponectin are affected by both pharmacodynamics (ie, serum concentration) and pharmacokinetics (ie, intracellular signaling through its receptor).[8] Adiponectin binds to 2 kinds of adiponectin receptors, adiponectin receptor 1 (ADIPOR1) and adiponectin receptor 2 (ADIPOR2).[9] ADIPOR1 is involved in activation of the AMPK pathway, whereas ADIPOR2 is involved in activation of the peroxisome proliferator activated receptor α (PPAR-α) pathway, both of which could inhibit the inflammation and stimulate energy combustion. By means of these biological mechanisms, respective receptors are associated with the insulin resistance, and the genetic polymorphisms of the adiponectin gene as well as these receptors genes could be associated with the insulin resistance and type 2 diabetes.[10]

Several factors have been found to contribute to individual differences in pain perception, including genetic factors. To date, various associations between genetic polymorphisms and inflammatory pain sensitivity and severity have been reported.[11,12] In the present study, we hypothesized that genetic polymorphisms in the adiponectin receptor genes influence interindividual variability of inflammatory pain severity via different mechanisms based on their anti-inflammatory effects and validated this hypothesis in Japanese patients with postoperative pain and cancer pain.

2. Methods

2.1. Experiment 1

The study protocol was approved by the institutional review board at each hospital (representative, the Ethics Committee, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo), and written informed consent was obtained from all participants. We examined the relationship among genetic polymorphisms of ADIPOR1 and ADIPOR2, postoperative pain intensity, and opioid requirements in patients after open laparotomy. The subjects were 56 adult patients who underwent open laparotomy for colorectal cancer under combined general and epidural anesthesia (Table 1). Their postoperative pain was managed with continuous epidural anesthesia using administration of 2 mL/h of 0.25% bupivacaine with fentanyl, through a catheter preoperatively placed in the lower thoracic or upper lumbar epidural space. When patients occasionally complained of pain worsening, rescue analgesics including opioids (fentanyl, morphine, buprenorphine, pentazocine and pethidine) and/or nonsteroidal anti-inflammatory drugs (diclofenac and flurbiprofen) were administered systemically according to the discretion of the attending physicians. The total intraoperative and postoperative opioid dosages (calculated by conversion into intravenous fentanyl equivalents when other opioids were administered) were recorded and normalized to the patients' body weight. The participants were asked to score the postoperative pain intensity 24 hours after surgery with a 5-point Likert scale (0 = no pain, 1 = mild, 2 = moderate, 3 = severe, and 4 = extremely severe) by their attending surgeon or the ward nurse who does not have specialized experiences to assess and manage pain.

Table 1

Characteristics of the patients and pain intensity of experiments 1 and 2.

	Experiment 1	Experiment 2
Age, yr	63.0 ± 12.3	58.3 ± 13.4
Weight, kg	54.5 ± 10.2	55.1 ± 10.5
Postoperative pain intensity	1.3 ± 1.1 (5-point NRS)	5.8 ± 1.9 (11-point NRS)
Fentanyl usage doses (μg/kg/d)	10.6 ± 3.6	7.3 ± 29.9

Data are shown as the mean ± standard deviation.
NRS = numerical rating scale.

Venous blood samples were collected from the participants. Genomic deoxyribonucleic acid (DNA) was isolated from peripheral blood lymphocytes using a standard salting-out procedure. The whole-genomic DNA was amplified, subsequently fragmented, and denatured DNA was hybridized to a prepared Omni-Quad BeadChip (Illumina, San Diego, CA), which contained 1,140,419 markers. Genotyping was performed for all 56 subjects using an Omni1-Quad BeadChip. PLINK version 1.07[13] was used for initial genotyping quality control (QC), including identify-by-descent (IBD) analysis to ensure individuals were unrelated, and heterozygosity testing and multidimensional scaling to identify population outliers compared to HapMap populations. For single nucleotide polymorphisms (SNP) filtering, we used sample and SNP call rates >95%. We used a MAF of 0.1% and a Hardy-Weinberg equilibrium threshold set at 1×10^{-3}. Normalized bead intensity data obtained for each sample was loaded into Genome Studio software (Genotyping module ver. 1.8.4; Illumina, San Diego, CA), which converted fluorescence intensities into SNP genotypes. Because the call rate for all of participants was more than 0.99 and their estimated IBD value was less than 0.8, none of participants was excluded from further analyses. The call rate for SNPs less than 0.95 was excluded, and further the MAF for SNPs less than 0.1% was excluded. Using genotype data obtained through whole genome genotyping, we analyzed 17 SNPs within the ADIPOR1 gene and 27 SNPs within the ADIPOR2 gene.

2.2. Statistical analysis

We analyzed associations among genotypes, postoperative pain intensity and opioid dosage using the Kruskal-Wallis (K-W) test and the posthoc Scheffe test. A P value < 0.05 was considered to indicate a statistically significant difference. In addition, among SNPs of ADIPOR1 and ADIPOR2 genes, rs12045862 was most investigated and it was significantly associated with insulin sensitivity. Previous studies showed that the minor allele homozygote of rs12045862 SNP showed extremely lower insulin levels than other 2 genotypes, and the insulin levels of the major allele homozygote and the heterozygote of rs12045862 SNP were comparable.[14] Considering such previous findings, the genotype related to the 17 ADIPOR1 SNPs and 27 ADIPOR2 SNPs was dichotomized into the combination of the major allele homozygote and the heterozygote (major + hetero) and minor allele homozygote (minor). To identify associations among genetic polymorphisms of these adiponectin receptors genes, pain intensity, and opioid dosage, we performed the Mann-Whitney test (M-H test), followed by Bonferroni post hoc test for 44 SNPs of the 2 adiponectin receptors genes. A P value $< .00113$ (0.05

before Bonferroni correction) was considered to indicate a statistically significant difference.

2.3. Experiment 2

Next, we sought to examine the relationship between cancer pain and the SNPs, which were significantly associated with postoperative pain in experiment 1. The study protocol was approved by the institutional review board at each hospital (representative, the Ethics Committee, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo), and written informed consent was obtained from all participants. The inclusion criteria were defined as follows:

(1) Patients were diagnosed as having cancer pain, irrespective of the original organ and pathology of malignant lesions;
(2) Age >20 years;
(3) Mean pain intensity in the past one week more than 3 on a numerical rating scale (NRS) of 0 to 10, with 0 as no pain and 10 as worst possible pain; and
(4) Pain duration longer than 1 week (recorded during recruitment). Instead of more simple pain assessments such as 5-point Likert scale used in experiment 1, participants were asked to rate an 11-point NRS by their attending experienced palliative physician, who routinely assesses pain and manages pain, in experiment 2.

The exclusion criteria included patients:

(1) Who exhibited mild or more severe cognitive function impairment;
(2) With relevant brain metastasis; and
(3) With pain suspected to be due to other causes than cancer.

Eighty-eight patients were enrolled in experiment 2 (Table 1). All participants gave their written informed consent. Pain intensity NRS and daily opioid dosages (converted into intravenous fentanyl equivalents, which is normalized to the patients' body weight) on the day of pain evaluation were recorded. The methodology of genotyping in these participants was same as that used in experiment 1.

2.4. Statistical analysis

Genotyping and the initial QC was performed. Again, the genotype of the relevant SNP (rs12045862) was tricotomized, and also dichotomized into the combination of the major allele homozygote and the heterozygote (major + hetero) and minor allele homozygote (minor). To identify associations among genotypes of rs12045862 SNP, pain intensity, and opioid dosage, we performed the Kruskal-Wallis test (K-W test) and the post-hoc Scheffe test for 3 genotype groups. Although we tested only one SNP in experiment 2, we should minimize the possibility of a false positive result and we again set a P value $< .00113$ (= 0.05/44) as significant.

3. Results

3.1. Experiment 1

Among the 44 SNPs, only one SNP of ADIPOR1, namely rs12045862, showed a significant association with postoperative pain (K-W test, $P = .0023$; Fig. 1). The patients with the minor allele homozygosity (n = 7; female, 4; age 62.7 ± 14.1 years; 5-point Likert pain scale, 2.7 ± 1.3) demonstrated significantly worse pain intensity compared with the patients with the major allele homozygosity (n = 30; female, 16, age 63.2 ± 12.5 years; 5-point Likert pain scale, 1.2 ± 1.0, Scheffe test: $P = .0006$) and those with heterozygosity (n = 19; female, 10, age 62.7 ± 12.1 years; 5-point Likert pain scale, 0.8 ± 0.6, Scheffe test: $P < .0001$). The total daily dosages of opioid analgesics normalized to the patients' weight were comparable among the 3 groups (major, 10.4 ± 3.3 μ/kg/day; hetero, 10.6 ± 4.0 μ/kg/d; minor, 11.4 ± 3.9 μ/kg/d; K-W test, $P = .84$). Age and body weight were also comparable (K-W test, $P = .95$ and $P = .69$, respectively). Also, the patients with "minor" group demonstrated significantly worse pain intensity compared with the patients with "major + hetero" group (n = 49; female, 26; age, 63.0 ± 12.2 years; 5-point Likert pain scale, 1.0 ± 0.9; M-H test: $P = .00002$, Fig. 2). Age and

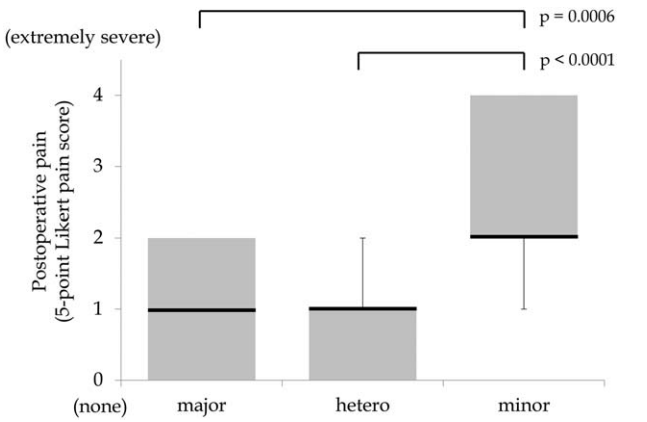

Figure 1. Association between postoperative pain intensity and the rs12045862 variant of the ADIPOR1 gene. The boxes extend from the 25th to 75th percentiles, with the extended bars indicating the 10th to 90th percentiles. The horizontal thick black lines indicate the median postoperative pain intensity value. Postoperative pain intensity was evaluated with a 5-point Likert scale (0 = no pain to 4 = extremely severe pain). The Kruskal-Wallis test was applied to compare 3 genotype groups. Patients with minor allele homozygote demonstrated significantly worse postoperative pain intensity compared with those with the major allele homozygosity ($P = .0006$) and those with heterozygosity ($P < .0001$). P values were determined by the Scheffe post hoc tests. ADIPOR1 = adiponectin receptor 1.

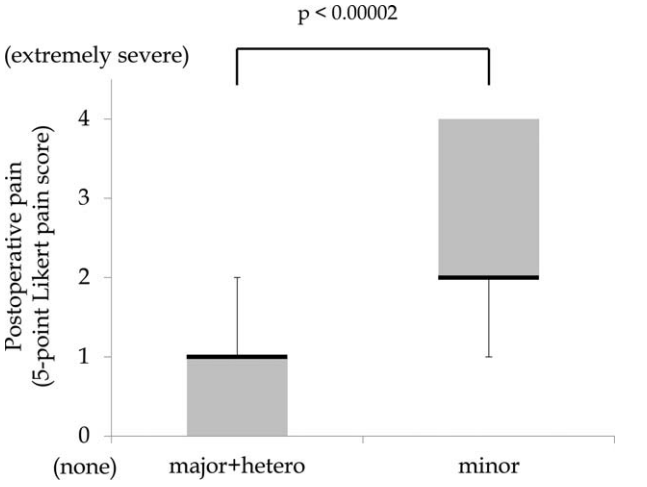

Figure 2. Association between postoperative pain intensity and the dichotomous groups of the rs12045862 variant of the ADIPOR1 gene. The Mann-Whitney test was applied to compare dichotomous groups. Patients with minor allele homozygote demonstrated significantly worse postoperative pain intensity compared with the combination of major allele homozygote and heterozygote ($P = .00002$). P values were determined by the Bonferroni post hoc tests. ADIPOR1 = adiponectin receptor 1.

body weight were also comparable between the 2 groups ($P = .99$ and 0.61, respectively). The total daily dosages of opioid analgesics normalized to the patients' weight were comparable between the 2 groups (major + hetero, 10.5 ± 3.6 μ/kg/d; minor, 11.4 ± 3.9 μ/kg/d; $P = .59$). None of the SNPs of the other ADIPOR1 and ADIPOR2 genes demonstrated a significant association with postoperative pain or opioid dosages in comparisons of either tricotomized groups or dichotomized groups.

3.2. Experiment 2

The rs12045862 SNP of ADIPOR1, which was found to be associated with postoperative pain in experiment 1, did not demonstrate a significant association with cancer pain intensity (K-W test $P = .0017$, Fig. 3). Pain intensity of the patients with the minor allele homozygosity (n = 7; female, 3; age, 54.9 ± 13.3 years; 11-point pain NRS, 7.0 ± 1.2) was comparable to that of patients with the major allele homozygosity (n = 43; female, 24; age, 56.9 ± 13.9 years; 11-point pain NRS, 5.1 ± 1.8; Scheffe test: $P = .032$). Pain intensity of patients with heterozygosity (n = 38; female, 23; age, 60.6 ± 12.8 years; 11-point pain NRS, 6.3 ± 1.8) was comparable to those of the minor allele homozygosity (Scheffe test, $P = .62$) and the major allele homozygosity (Scheffe test, $P = .01$). The total daily opioid dosages among 3 groups were comparable (major, 4.6 ± 14.8 μ/kg/d; hetero, 10.8 ± 42.7 μ/kg/d; minor, 4.2 ± 7.1 μ/kg/d; K-W test, $P = .63$). Age and body weight were also comparable (K-W test, $P = .38$ and $P = .30$, respectively). Pain intensity of the patients with "minor" group was not significantly different from that of the patients with "major + hetero" group (n = 81; female, 47; age, 58.6 ± 13.4 years; 11-point pain NRS, 5.6 ± 1.9; M-H test: $P = .037$, Fig. 4). The total daily opioid dosages of the 2 groups were also comparable (major + hetero, 7.5 ± 31.1 μ/kg/d; minor, 4.2 ± 7.1 μ/kg/d; $P = .66$). Age and body weight were comparable between the 2 groups ($P = .43$, .60, respectively).

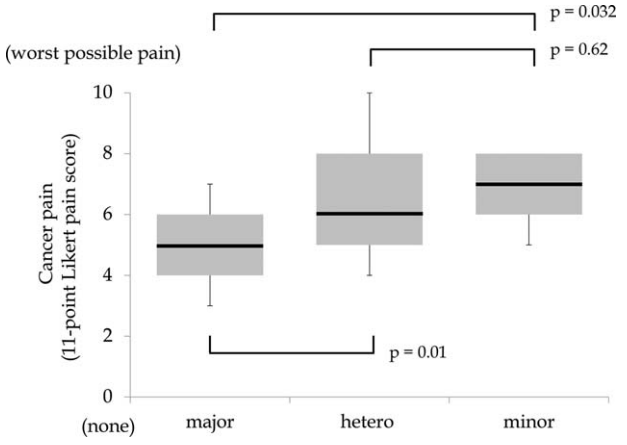

Figure 3. Association between cancer pain intensity and the rs12045862 variant of the ADIPOR1 gene. Postoperative pain intensity was evaluated with an 11-point numerical rating scale (0 = no pain to 10 = worst possible pain). The Kruskal-Wallis test was applied to compare 3 genotype groups. Patients with minor allele homozygote demonstrated significantly worse cancer pain intensity compared with the major allele homozygosity ($P = .032$). Pain intensity of those with heterozygosity was comparable to that of the minor allele homozygosity ($P = .62$) but worse than that of the major allele homozygosity ($P = .01$). *P* values were determined by the Scheffe post hoc tests. ADIPOR1 = adiponectin receptor 1.

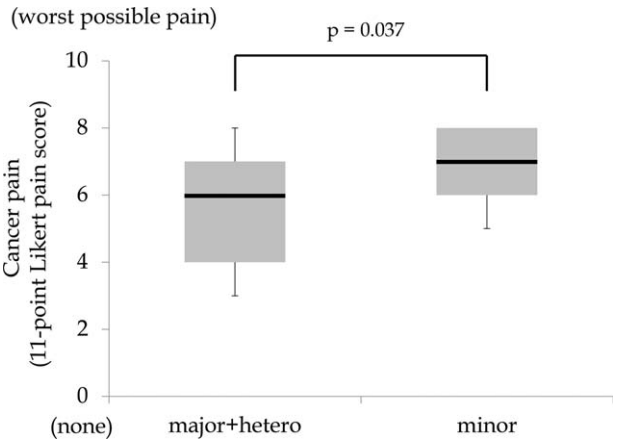

Figure 4. Association between cancer pain intensity and the dichotomous groups of the rs12045862 variant of the ADIPOR1 gene. The Mann-Whitney test was applied to compare dichotomous groups. Patients with minor allele homozygote demonstrated significantly worse cancer pain intensity compared with the combination of major allele homozygote and heterozygote ($P = .037$). ADIPOR1 = adiponectin receptor 1.

4. Discussion

Our present findings revealed 1 SNP of ADIPOR1 (rs12045862) was associated with postoperative pain severity. Patients exhibiting homozygosity for the minor allele with the rs12045862 demonstrated higher pain intensity, compared to those not carrying this minor allele. No SNPs of the ADIPOR2 gene showed any significant association with postoperative pain intensity. However, the relevant SNP was not associated with cancer pain intensity. Opioid consumption per body weight was not related with both postoperative and caner pain intensities. Some of previous studies on genetic polymorphisms clearly demonstrated that pain intensity and opioid consumption are not necessarily linked.[15,16] Our findings could suggest that the rs12045862 SNP of ADIPOR1 is associated with the aggravation of postoperative pain, but not cancer pain.

Adiponectin is an adipose tissue-derived cytokine, and exerts various effects by binding to 2 adiponectin receptors, ADIPOR1 and ADIPOR2, both of which are ubiquitously expressed in most tissues. Functional properties of ADIPOR1 and ADIPOR2 are associated with the activation of AMPK pathways and PPAR-α pathways, respectively, and these exhibit different impacts on glucose utilization, energy dissipation, and so on.[9,15] On the other hand, either cellular signaling mechanism of ADIPOR1 or ADIPOR2 can exert an anti-inflammatory effect by suppressing production of proinflammatory cytokines, such as TNF-α and IL-6.[17,18]

Previous studies have shown that genetic polymorphisms contribute to individual differences in the function of these cellular signaling mechanisms of ADIPOR1 and ADIPOR2. The rs12045862 SNP of the ADIPOR1 gene, which we identified to be associated with both postoperative pain and cancer pain in this study, was reported to affect serum insulin levels.[14] Other studies have also shown that some SNPs of the ADIPOR1 gene are associated with chronic systemic inflammatory conditions known as the metabolic syndromes, including obesity, lower insulin sensitivity, and type 2 diabetes.[10,14,19] In addition, lower serum adiponectin levels are associated with such chronic inflammatory conditions, and there has been no association between serum adiponectin levels and genetic polymorphisms of

the ADIPOR1 gene.[20,21] The strong association between genetic polymorphisms of the ADIPOR1 gene and the chronic systemic conditions can be attributed to reduced antiinflammatory responses, which could be caused by functional alteration in cellular signaling pathways of ADIPOR1.

Considering our present findings in conjunction with the previous notions, following explanation might be derived. The patients carrying the minor allele homozygote of the rs12045862 SNP of the ADIPOR1 gene, comparing patients not carrying this minor allele, might exhibit diminished anti-inflammatory property through the ADIPOR1 signaling, and possibly demonstrate higher levels of proinflammatory cytokines, such as TNF-α and IL-6. Such pro-inflammatory cytokines have the potential to sensitize nociceptive neurons, and consequently, the patients might demonstrate the lower threshold of postoperative pain. In contrast, our previous report indicated that serum adiponectin levels are not directly associated with postoperative pain intensity.[7] This seems to be incongruous with the present finding; however, these findings indicated that functional alteration of the adiponectin signaling pathways through ADIPOR1, and not serum adiponectin levels themselves, affects postoperative pain intensity.

Alternatively, adiponectin might modulate functions of the neural substrates more directly. Adiponectin is confirmed to be present in the cerebrospinal fluids,[22] and adiponectin receptors are located in the neurons and glial cells. Especially, ADIPOR1 is highly expressed in spinal microglia.[23] The activation of ADIPOR1 involves p38 mitogen-activated protein kinase (MAPK) pathway,[9] which is known to activate microglia in the inflammatory pain state, and leads to hyperalgesic behaviors.[24] Thus, the genetic polymorphism of the ADIPOR1 gene might exacerbate postoperative pain by activating p38 MAPK pathway in the neural substrates.

In our study, it could not be demonstrated whether the functional properties via the adiponectin receptor signaling pathways are promoted or inhibited according to the genetic polymorphism of the relevant SNP of the ADIPOR1 gene. Notwithstanding, our findings supported the possibility that the ADIPOR1 genetic polymorphism aggravates postoperative pain via the ADIPOR1 signaling pathways.

With regard to SNPs of ADIPOR2, previous studies have revealed some associations with type 2 diabetes, lower insulin sensitivity, coronary artery disease, and atherosclerosis.[10,25] However, we found no association of the genetic polymorphisms of the ADIPOR2 gene with postoperative pain intensity in this study. ADIPOR2 was reportedly enriched in spinal dorsal horn neurons, while ADIPOR1 was mainly expressed in spinal microglia.[23] Such difference in distributions in the neural substrates between ADIPOR1 and ADIPOR2 might account for their contributions to inflammatory pain intensity. Focusing on neural substrates, an anecdotal evidence comes from age-related macular degeneration (AMD). AMD exhibits features of retinal inflammation, in which activated retinal microglia are critically involved,[26] and the genetic polymorphism of ADIPOR1, but not ADIPOR2, was reportedly associated with AMD.[27] Since activated microglia are linked to more severe inflammatory pain,[28] the genetic polymorphism of ADIPOR1, which is preferentially expressed in microglia, would more potently affect the inflammatory processes, and consequently, aggravate postoperative pain via ADIPOR1 signaling pathways, compared with ADIPOR2 that is preferentially expressed in neurons.

To our best knowledge, this is the first study possibly showing an association between the genetic polymorphism of the ADIPOR1 gene and severity of postoperative pain but not cancer pain. Our findings should be considered in the context of some limitations. First, the serum levels of adiponectin were not measured in this study. The analysis of serum adiponectin levels, in conjunction with the examination of the SNPs of ADIPOR1 associated with postoperative pain intensity, would reveal more precise mechanisms by which adiponectin and adiponectin receptors influence postoperative pain. This might help to explain the difference between postoperative pain and cancer pain, both of which are bundled in the inflammatory pain condition, aggravated by the ADIPOR1 gene polymorphism. Second, our study was an exploratory trial and the number of participants, particularly those exhibiting homozygosity for the minor allele of the rs12045862 SNP, was very small in both experiments. This could have led to false positive result and phenotypes of respective genotypes of the relevant SNP were not necessarily consistent between postoperative pain and cancer pain. Therefore, further large-scale study with a larger sample size should be necessary to validate our results although we carefully considered the multiplicity. Third, we did not conduct the linkage disequilibrium mapping because the rs12045862 SNP was known to be in very strong linkage disequilibrium with the functional mutation some distance away from it in a previous study[14] and the HapMap database. The genetic correlation between rs19045862 SNP and other SNPs should be explored in future studies.

Although our results were preliminary and there is a need for further researches to test our findings concerning the influence of adiponectin and adiponectin receptors on postoperative pain, our present findings suggested that ADIPOR1 is a novel potential target for developing analgesics.

Author contributions

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Writing – original draft: Jun Ninagawa, Masahiko Sumitani.

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