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MINI-REVIEW

Delayed onset muscle soreness: Involvement of neurotrophic factors

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Abstract Delayed-onset muscle soreness (DOMS) is quite a common consequence of unaccustomed strenuous exercise, especially exercise containing eccentric contraction (lengthening contraction, LC). Its typical sign is mechanical hyperalgesia (tenderness and movement related pain). Its cause has been commonly believed to be micro-damage of the muscle and subsequent inflammation. Here we present a brief historical overview of the damage-inflammation theory followed by a discussion of our new findings. Different from previous observations, we have observed mechanical hyperalgesia in rats 1–3 days after LC without any apparent microscopic damage of the muscle or signs of inflammation. With our model we have found that two pathways are involved in inducing mechanical hyperalgesia after LC: activation of the B2 bradykinin receptor–nerve growth factor (NGF) pathway and activation of the COX-2-glial cell line-derived neurotrophic factor (GDNF) pathway. These neurotrophic factors were produced by muscle fibers and/or satellite cells. This means that muscle fiber damage is not essential, although it is sufficient, for induction of DOMS, instead, NGF and GDNF produced by muscle fibers/satellite cells play crucial roles in DOMS.

Keywords Delayed-onset muscle soreness · Exercise · Mechanical hyperalgesia · Nerve growth factor · Glial cell line-derived neurotrophic factor

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Introduction

It is likely almost everyone has had more than one experience of delayed-onset muscle soreness (DOMS) after, e.g., mountain climbing for the first time for a long while, an occasional baseball game, or running in a once-a-year school sports meeting. It is quite a common consequence of unaccustomed strenuous exercise, especially exercise containing eccentric contraction (lengthening contraction, LC), in which muscle is being stretched while it is contracted [1]. Even athletes who exercise every day experience DOMS when they perform a different type of sport or practice new skills. DOMS is different from the acute pain experienced during and shortly after exercise; it usually appears after a pain-free period (12–24 h), peaks at 24–72 h, and disappears within 7 days of the exercise [2–4]. The existence of this pain-free period has made DOMS somewhat mysterious. The most characteristic symptoms of DOMS are tenderness and movement-induced pain in the exercised muscle; both are types of mechanical hyperalgesia, and there is usually no pain at rest [4]. DOMS is usually subclinical, because people recover from the soreness without medical treatment. However, DOMS may interfere with the motor performance of athletes, and there is a possibility that DOMS will lead to more debilitating and chronic injury [5] and result in chronic pain and/or hyperalgesia, with plastic changes in the central nervous system [6]. Decreases in the maximum power of the muscle and in the range of motion accompany DOMS [7–9]. These decreases are believed to be related to micro damage of the subcellular structure of the muscle fibers [10], but a discussion of the mechanism is beyond the scope of this review.

Many possible causes of DOMS have been proposed [9]; the most popularly accepted is damage of muscle fibers and

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subsequent inflammation [11]. Our recent research has revealed that muscle fiber damage and inflammation are sufficient but not essential for DOMS. In this review we give a brief overview of these factors; we then describe our recent findings obtained from experimental DOMS in rats and mice. Finally, we briefly introduce methods for prevention and treatment of DOMS.

Historical overview

The first report on soreness (DOMS) that appears 12 or 24 h after exercise was made by Hough [12], who proposed a hypothesis of "rupture of the muscle fiber (or connective tissue between muscle fibers)" as the cause of DOMS because soreness was observed after quick and strong contraction.

That lengthening (eccentric) but not shortening (concentric) contraction (abbreviated LC and SC, respectively) is associated with DOMS was first proposed by Asmussen [1], and later confirmed by other researchers [13, 14]. As suggested by Hough [12], muscle damage was observed after exercise, especially after LC [15–17]. In mice, slow muscle (e.g. soleus muscle) was shown to be less susceptible to LC than fast muscle (e.g. the extensor digitorum longus, EDL, muscle) [18]. With a biopsy of human muscle, type II muscle fibers (fast twitch fibers) were reported to be more susceptible to damage following exercise [19, 20]. After LC, damage including ballooning of the fiber, marked streaming, broadening, and sometimes total disruption, of the Z-band, focal disruption of the striated band pattern, and disorganized sarcomeres [15, 17] were found in the muscle of both humans and animals. Accumulation of inflammatory cells (neutrophils and then macrophages) is found in or around damaged muscle fibers after LC [3, 21], but was also observed after stretching and SC [22]. Increase of IL-6 was found in human plasma [21], and that of mRNAs for IL-6, IL-8, and COX-2 was observed in exercised muscle of humans [23]. In these studies no comparisons were made between exercise patterns (LC or SC).

Different forms of exercise have been used to induce DOMS, including downhill running, lengthening of the muscle by use of a machine while the muscle was contracted voluntarily, or by electrical stimulation by use of a surface electrode. It has been shown that lengthening exercise with voluntary contraction induces less muscle damage than contraction induced by electrical stimulation by use of a surface electrode, although the level of soreness was approximately the same [24]. Quantitative studies on the relationship between the extent of muscle damage or mechanical hyperalgesia and exercise conditions (angular velocity and range of motion) have been performed. Angular velocity dependent severe damage was observed in a study in which the muscle contraction was induced by a surface electrode [8] whereas almost no damage was observed with electrical stimulation of the nerve [25]. Even isometric contraction induced by electrical stimulation with a surface electrode resulted in more muscle damage [26, 27]. The authors of the latter experiment suggested that one possible reason is a high mechanical stress on the muscle fibers activated in a nonselective, synchronous, and spatially fixed manner. This may be also true for LC induced by electrical stimulation by use of surface electrodes.

Biochemical studies have revealed leakage of such enzymes as creatine kinase and lactic dehydrogenase from exercised muscle [17]. Both histological changes and leakage of enzymes from exercised muscle have led to the idea that muscle damage is the cause of DOMS. The presence of invading inflammatory cells (macrophages) in the muscle suggests that inflammation is a cause of DOMS (reviewed elsewhere [11]). A recent intensive, comprehensive study [28] of humans found no difference between markers of inflammation for subjects who underwent LC and those who underwent SC. The involvement of inflammation was also examined by using anti-inflammatory drugs. However, the effects of the drugs differed among laboratories, and there were more reports of effective results when a drug was administered prophylactically (before exercise) than when it was given therapeutically (after exercise) (reviewed elsewhere [9]). A very recent investigation with a placebo control showed that application of topical diclofenac sodium gel 1 % over the exercised leg every 3 h for 24 h helped to reduce DOMS [29].

Lactic acid, found at increased levels in muscles and plasma shortly after exercise [30], was once believed to be a cause of DOMS. However, this hypothesis has been strongly discredited by the discovery that concentric (shortening) exercise, which involves greater metabolism, fails to produce DOMS [30]. In addition, lactic acid levels return to pre-exercise levels within an hour after exercise. Therefore, although lactic acid may contribute to the acute pain associated with fatigue after intense exercise, or initiate DOMS, it cannot be a crucial molecule when DOMS is at its peak.

Increases in resting muscle activity (EMG activity) [31] and connective tissue damage [32] have also been proposed as the cause of DOMS.

New mechanism

Because mechanical hyperalgesia without damage is observed for muscle undergoing LC by electrical stimulation of the nerve [25], the mechanism of DOMS must

involve other than damage and/or inflammation. We propose here a new mechanism in which nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) produced by muscle fibers and/or satellite cells are themselves responsible for DOMS.

As mentioned in the previous section, muscle damage and the subsequent inflammation after exercise has been reported after many studies, and is thus the most commonly accepted cause of DOMS. However, several reports have suggested this may not be the real cause of DOMS. The time course of the damage and degenerative changes does not fit well with the time course of DOMS, and similar changes, for example disrupted sarcolemma, degenerating fibers, Z-line streaming, and central nuclei are observed among pain-free individuals and regularly exercising athletes [3, 33, 34]. Second, DOMS can be observed in cases without damage of the muscle [24, 25]. Third, anti-inflammatory drugs (NSAID) rarely help to reduce DOMS that has developed mechanical hyperalgesia (reviewed elsewhere [9]).

For better insight into the mechanism of DOMS, animal models are needed for evaluation of the mechanical hyperalgesia of exercised muscle. We contracted the hindpaw extensors of rats, mainly the EDL muscle, by electrically stimulating the common peroneal nerve while synchronously stretching the muscles [35]. The gastrocnemius muscle of rabbits [36], rats [5, 37] and mice [38] has also been used for this purpose.

To evaluate the mechanical withdrawal threshold a parallel of the human mechanical (pressure) pain threshold) of the muscle through the skin, we used a Randall–Selitto apparatus equipped with a larger tip than that supplied by the distributor. The same has been done for humans, using probes with a diameter of 1 cm or with surface area of 1 cm^2 [39, 40]. Use of larger probes is based on evidence obtained experimentally [41] and by computer simulation [42–44]. The measured mechanical threshold with these larger probes was not affected by surface anesthesia of the skin over the muscle [38, 41, 45], ensuring the value is indicative of the withdrawal threshold of the deep tissues, including muscles.

Mechanical hyperalgesia after exercise (DOMS) in animal models

In measurements with a Randall–Selitto apparatus (probe diameter 2.6 mm), the mechanical withdrawal threshold decreased significantly 1 day after LC in rats. It reached its lowest point on the second day, and remained low until the third day after exercise [35]. On day four the threshold completely returned to the baseline level [46]. For animals with DOMS produced by the same method, no apparent damage (light microscopic level) of the muscle fibers was observed [37, 47].

That the reduced mechanical withdrawal threshold reflects mechanical hyperalgesia in the exercised muscles was confirmed by an increase in c-Fos expression in the dorsal horn. Expression of this protein in the superficial dorsal horn of the spinal cord has been used as a neural marker of pain since Hunt et al. [48] reported that different kinds of noxious stimuli induce its expression in the superficial dorsal horn, which contains secondary neurons receiving nociceptive C-fiber inputs from the skin [49] and muscle [50]. The number of c-Fos-immunoreactive neurons in the dorsal horn was increased only in the animal group that received muscle compression 2 days after LC, especially in the superficial dorsal horn corresponding to laminae I and II at the L4 level of the spinal cord [35]. Compression alone, LC only, and stretching only did not increase c-Fos expression. Thus, neither the compression nor the LC used in this experiment activated the nociceptive pathway 2 days later, the latter corresponds to that spontaneous pain is absent in DOMS [4]. Increased expression of c-Fos in the superficial dorsal horn after compression 2 days after LC was completely suppressed with morphine (10 mg/kg i.p., given 20 min before compression) [35]. These observations provide further evidence that the muscle was hyperalgesic 2 days after LC.

Mechanical hyperalgesia is also observed for mice after LC, but the time course is much shorter than for rats or humans [38].

Facilitated response of muscle thin-fiber afferents in DOMS

What kind afferents are responsible for DOMS? Muscle nociception is believed to be transmitted by thin muscle afferent fibers (Aδ and C-fibers) [51]. To examine whether the activity of muscle thin-fiber afferents is sensitized in DOMS, we recorded single-fiber activity from rat EDL muscle–common peroneal nerve preparations in vitro [52]. We recorded activity from 25 muscle fibers 2 days after LC and from 33 fibers from control animals. The only difference we found was the mechanical sensitivity: the mechanical threshold was lower by half and the magnitude of the response (number of induced discharges) to ramped mechanical stimulation (0–196 mN in 10 s) was twice as large in the exercised group as in the unexercised controls. Spontaneous activity and the responses to other stimuli (ratio of responding fibers and the magnitude of the response to algesic substances, for example bradykinin and ATP [52], and to heat stimulation [53]) were no different between groups. The observed augmented sensitivity to mechanical stimulation is the neural basis for mechanical hyperalgesia after exercise, i.e. DOMS.

Different from our observations are reports suggesting that DOMS is transmitted by thick A-fiber afferents including muscle spindles. This hypothesis is based on observations that pain induced by hypertonic saline did not change after exercise, that A-fiber block increased the pain threshold, and that vibration of the muscle exacerbated muscle pain [54, 55]. The absence of increased sensitivity to hypertonic saline cannot be the reason C-fibers do not contribute to DOMS, because it has been shown that muscle C-fiber sensitivity to hypertonic saline does not change in DOMS [56]. The vibration might have induced reflex muscle contraction and this contraction might have resulted in more pain. Another possibility is that some of the sensitized C-fibers after exercise might be also be sensitive to vibration of the size used in these papers. The same authors also showed that differential block of A-fibers by compression of the nerve increased the pressure pain threshold in the exercised leg [55]. In this case, pain induced at the site of compression might have masked the pain in the exercised leg.

To examine the possible contribution of A-fibers to DOMS, we investigated whether DOMS could be induced in rats treated neonatally with capsaicin, which is known to destroy a large proportion of unmyelinated afferent fibers [57]. Among these animals, LC failed to induce muscular mechanical hyperalgesia [58]. mRNA of NGF in the muscle, which is crucial in maintaining mechanical hyperalgesia (described later in this review), was upregulated similarly in the capsaicin-treated and vehicle-treated animals. These results indicate that C-fiber afferents are essential in transmitting the nociceptive information from exercised muscle in DOMS, and that thick A-fibers are not crucially involved in DOMS.

What causes DOMS?: the B2 receptor-NGF pathway

Bradykinin (later shown to be Arg-bradykinin in rats [59, 60]), abbreviated in this review as BK, an agonist of the B2 bradykinin receptor) is released during exercise via activation of vascular endothelial adenosine receptors [59]. Bradykinin is known to sensitize thin fiber afferents in a variety of tissues to mechanical stimulation via the B2 bradykinin receptor [61–63]. However, BK is not present 2 days after exercise, and hence cannot be responsible for sensitization of muscle thin-fibers to mechanical stimulation in muscle that is hyperalgesic after LC. Its contribution to initiation of DOMS, however, has not been examined. B2 bradykinin receptor antagonist HOE 140 completely suppressed generation of muscular mechanical hyperalgesia when injected before LC, but when injected 2 days after LC failed to reverse the mechanical hyperalgesia that had already developed [64]. To determine the exact time

window in which BK acts, we injected B2 antagonist shortly after exercise. DOMS then developed normally, demonstrating that BK acts during exercise and possibly shortly after exercise (up to 1 h). B1 antagonist was ineffective, irrespective of the timing of its injection. These observations indicate that BK, via the B2 bradykinin receptor, is crucially involved in initiating the processes that lead to mechanical hyperalgesia, but it is not a substance that sensitizes nociceptors to induce mechanical hyperalgesia.

What, then, is the agent that sensitizes nociceptors when muscle is sore? NGF is known to be produced in the muscle after ischemia [65] or nerve injury [66], and is also known to induce mechanical hyperalgesia without inducing apparent pain when injected into muscle [67]. Therefore we examined the change in NGF after LC. Upregulation of NGF mRNA and protein occurred in exercised muscle over a time course (12 h to 2 days after LC) comparable with that for muscle mechanical hyperalgesia (Fig. 1a, b). Antibodies to NGF injected intramuscularly 2 days after exercise reversed the muscle mechanical hyperalgesia in 3 h (Fig. 1c). HOE 140 inhibited upregulation of NGF. In contrast, SC or stretching induced neither mechanical hyperalgesia nor NGF upregulation. Upregulation of IL-6 after LC has been reported for humans [21] and mice [68], and the possibility of a contribution by other cytokines has also been examined in this model [64]. All of IL-1, IL-6, and TNF-α mRNAs were upregulated immediately after LC (0 h) and 6 or 12 h after LC. However, they were also upregulated after SC and/or stretching, and, except for IL-6, were not affected by HOE140. However, a contribution of IL-6 to DOMS is not supported because anti-IL-6 antibody failed to reverse the established mechanical hyperalgesia after LC [64].

Murase et al. [64] also showed that rat NGF sensitized C-fiber afferents to mechanical stimulation in the periphery after 10–20 min in excised muscle-nerve preparation (Fig. 2). This latency is too short if it is caused after transport of NGF to the afferent cell body and changes the expression of ion channels or transducers, or neuropeptides, after which these molecules are transported back to the afferent terminals [69]. In addition, because this preparation was detached from the cell body, sensitization should have occurred at the periphery. Several mechanisms have been proposed [70–74] and the sensitizing mechanism of muscular C-fibers is now being studied. Thus, NGF upregulation by activation of B2 bradykinin receptors is essential to mechanical hyperalgesia after exercise.

The contribution of transient receptor potential vanilloid 1 (TRPV1) to DOMS and NGF-induced mechanical hyperalgesia has been shown by use of TRPV1-deficient mice and by use of a capsaicin antagonist, capsazepine [37, 38].
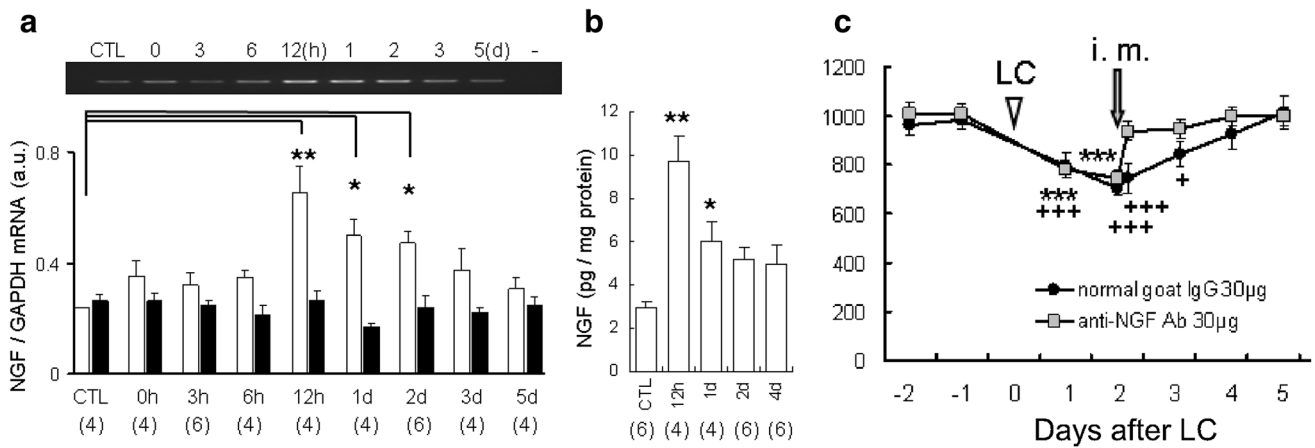
Fig. 1 NGF involvement in DOMS. a NGF mRNA of the EDL was upregulated first 12 h after LC, and continued to be upregulated up to 2 days after LC. b NGF protein was also upregulated in a time course similar to that for mRNA. c Intramuscular injection of anti-NGF antibody reversed already established mechanical hyperalgesia in 3 h. *Black filled circles*, normal goat IgG injection group; *grey filled squares*, anti-NGF antibody injection group. Modified from Murase et al. [64]
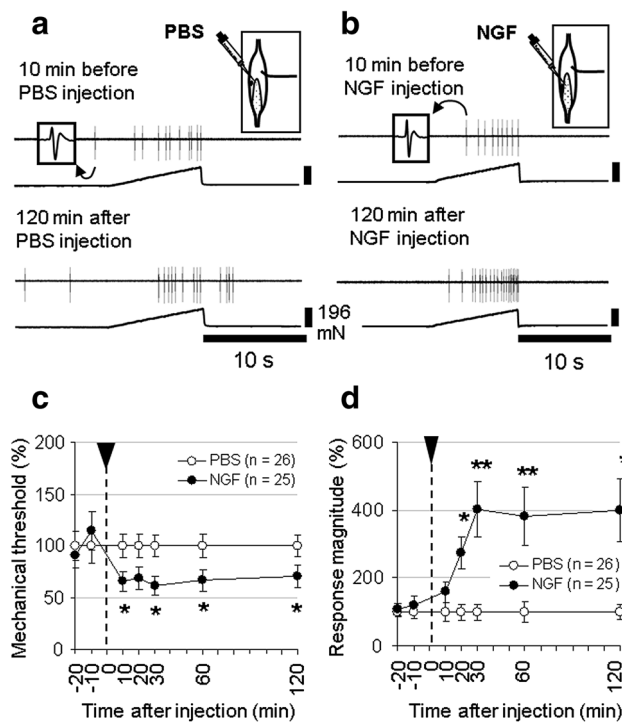

Fig. 2 NGF sensitized muscle C-fiber afferents to mechanical stimulation. **a, b** Sample recording of muscle C-fibers with intramuscular injection of phosphate-buffered saline (PBS) (**a**) and NGF (**b**). *Upper right insets* in **a, b** show the location of the receptive field of the fiber. The 1st and 3rd traces are raw recordings of the fiber, and the 2nd and 4th traces show readouts of the mechanical force applied to the receptive field. **c** Summary of the change in the mechanical threshold. The threshold of the PBS group at each time point was set as 100 %. *White circles*, PBS group; *filled black circles*, NGF group. **d** Summary of the change in the magnitude of the response (number of discharges induced by mechanical stimulation). The magnitude of the response of the PBS group at each time point was set as 100 %. NGF was injected at time 0. *$p < 0.05$, **$p < 0.01$ compared with the PBS group at each time point in both **c, d**. From Murase et al. [64]

Because our model showed no apparent inflammatory signs, inflammatory cells are unlikely to be responsible for the production of NGF. Instead, by use of in-situ hybridization, we found upregulation of mRNA signals around the nuclei of muscle fibers and/or satellite cells 12 h after exercise [75]. When inflammation is produced after severe LC or LC induced by surface electrical stimulation [8], or after LC for 2 weeks [5], NGF is produced in inflammatory cells and regenerating muscle fibers.

What causes DOMS? The COX2-GDNF pathway

In addition to the B2 bradykinin receptor and NGF pathway, we showed that cyclooxygenase (COX)-2 and glial cell line-derived neurotrophic factor (GDNF) were also involved in DOMS [47]. COX-2 inhibitors, but not COX-1 inhibitors, given orally before LC completely blocked the development of DOMS, but when given 2 days after LC they failed to reverse the mechanical hyperalgesia. COX-2 mRNA and protein in exercised muscle increased 0–12 h after LC. This time course is a good fit for a trigger of NGF upregulation. However, COX-2 inhibitors did not suppress NGF upregulation after LC. Instead, we found that GDNF mRNA was upregulated in the exercised muscle 12 h– 1 day after LC (Fig. 3a) and that this upregulation was blocked by pretreatment with COX-2 inhibitors. mRNAs of other members of the GDNF family, namely, artemin, persephin, and neurturin, were not upregulated [47]. In-situ hybridization studies revealed that COX-2 and GDNF mRNA signals increased at the periphery of skeletal muscle cells and/or satellite cells (around nuclei) 0 and 12 h after LC, respectively (Fig. 3b–d for GDNF). Accumulation of COX-2 mRNA signals was also observed in small
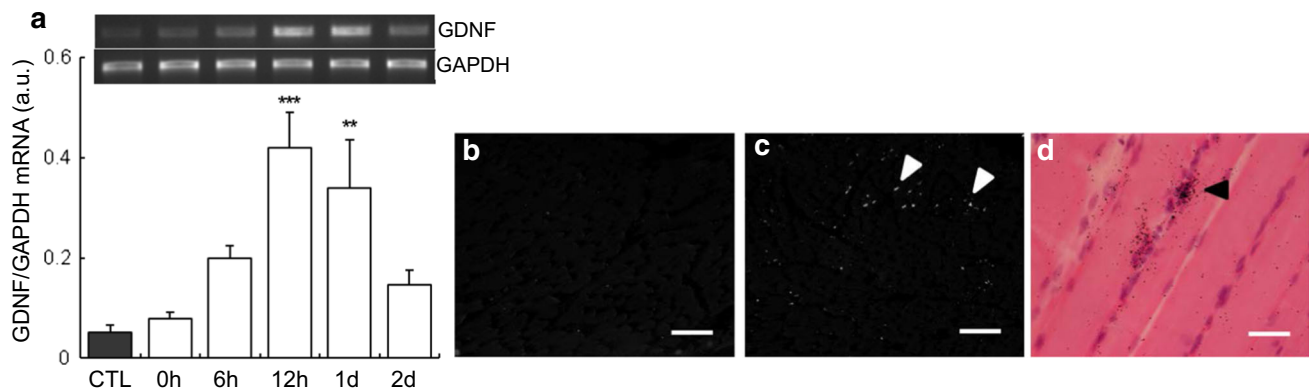
Fig. 3 GDNF upregulation in the muscle after LC. **a** GDNF mRNA of the EDL was upregulated 12 h–1 day after LC. **b, c** Expression of GDNF mRNA (*white arrowheads*) in EDL muscle 12 h after LC, shown by use of dark-field photomicrographs of in-situ hybridization histochemistry (oblique sections), was increased on the ipsilateral side (**c**) compared with the contralateral side (**b**). *Scale bar* 100 μm.

d Bright-field photomicrograph (longitudinal section) at greater magnification shows in-situ hybridization signals for GDNF mRNA (*black arrowhead*) in the ipsilateral muscle. *Scale bar* 10 μm. Note that GDNF mRNA signals are observed around the nuclei of muscle cells and/or satellite cells. Modified from Murase et al. [47]

blood vessels and epimysium. Intramuscular injection of anti-GDNF antibody 2 days after LC partly reversed DOMS. On the basis of these findings we conclude that GDNF upregulation via COX-2 activation is essential to mechanical hyperalgesia after exercise.

GDNF also sensitized muscle afferents but, in contrast with NGF, it sensitized Aδ fibers. C-fibers were not sensitized by GDNF (Fig. 4) [76]. This is unexpected because DOMS is a vague sensation and it is generally believed that Aδ-fiber activation in the skin induces sharp pain. Nobody knows what kind of sensation is induced when only muscular Aδ-fibers are activated.

Involvement of acid-sensing ion channels (ASIC) in DOMS mechanical hyperalgesia has been demonstrated pharmacologically by use of an antagonist, amiloride [37].

GDNF-induced muscular mechanical hyperalgesia was reversed by amiloride [76]. Fujii et al. [37] also showed that ASIC were expressed in muscle afferent neurons larger than those expressing TRPV1. These observations together are a good fit with our observation that GDNF sensitized Aδ-fibers.

Involvement of TRPV1 and TRPV4 in GDNF-induced mechanical hyperalgesia has been shown in mice deficient in these receptors [38]. Upregulation of GDNF after LC was normal in TRPV1 knockout mice but decreased in TRPV4-deficient mice. Application of TRPV4 antagonist (HC-067047) reversed the mechanical hyperalgesia after LC, but did not affect upregulation of GDNF [38]; thus, the site of action of GDNF is, similar to NGF, in the periphery of the afferents.
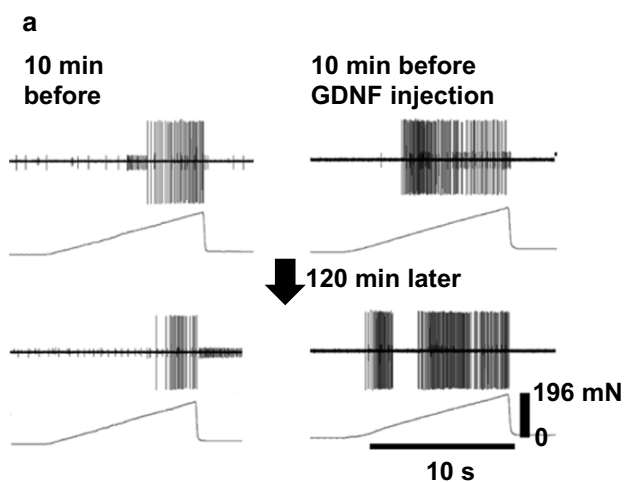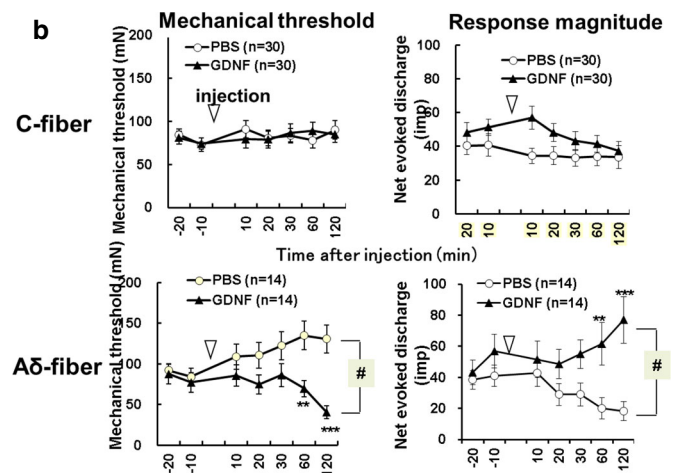

Fig. 4 a GDNF sensitized muscle Aδ-fiber afferents to mechanical stimulation. The method of presentation is similar to Fig. 2. The *black triangles* in **b** represent the GDNF injection group. $^{#}p < 0.05$, two-

way ANOVA, $^{**}p < 0.01$, $^{***}p < 0.001$, two-way ANOVA followed by Bonferroni's multiple comparison test. Modified from Murase et al. [76]

The receptor subtype for prostaglandin-E2 [77] that is involved in GDNF production after LC was sought by use of a pharmacological method and EP2 deficient mice, and was demonstrated to be the EP2 subtype [78].

A schematic diagram of the new mechanism for DOMS proposed on the basis of our observations is shown in Fig. 5.

When B2 bradykinin receptor antagonist HOE140 was administered before LC, upregulation after LC of not only NGF but also GDNF and COX-2 was blocked [47], i.e., there is an interaction between these two pathways at the COX-2 level. In contrast, NGF upregulation after LC remained unchanged after application of COX-2 inhibitors yet development of DOMS was blocked [47]. This observation might suggest that NGF produced after LC is not present in amounts large enough to sensitize muscle thin fiber afferents and induce mechanical hyperalgesia. The concentrations of NGF and GDNF used in the experiments that showed sensitization of muscle thin-fiber afferents to mechanical stimulation would have been much higher than those produced after LC. There may be collaboration between NGF and GDNF, although this is not supported by the current understanding that sensory neurons sensitive to NGF and those sensitive to GDNF belong to different neuron groups [80]. Further experiments are needed to clarify this point.
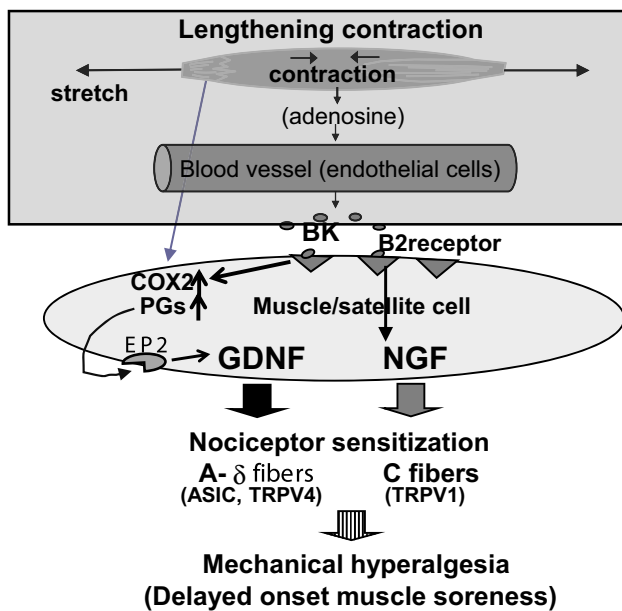

Fig. 5 Schematic diagram of the mechanism proposed for DOMS. The *upper part* of the figure in the *shaded area* was based on Boix et al. [59]. *BK*, bradykinin-like substance (Arg-bradykinin in rats); *COX2*, cyclooxygenase-2; *PGs*, prostaglandins; *EP2*, prostaglandin EP2 receptor; *GDNF*, glial cell line-derived neurotrophic factor; *NGF*, nerve growth factor; *ASIC*, acid sensing ion channel; *TRPV1 and TRPV4* transient receptor potential vanilloids 1 and 4. Modified from Mizumura et al. [79]

Adaptation (repeated bout effect)

It is well known that DOMS is reduced when the same exercise is repeated after a specific interval. This adaptation, called the "repeated bout effect", has been attributed to adaptations of neural or connective tissue or cellular mechanisms. In addition, adaptation in excitation–contraction coupling or adaptation in the inflammatory response have also been proposed as mechanisms (reviewed elsewhere [81, 82]; also see Ref. [22]). Hoping to shed light on this effect, on the basis of our findings described above, we found that mechanical hyperalgesia and NGF upregulation were reduced after the 2nd bout of exercise in rats [83]. In addition, these adaptation phenomena were observed even when downstream pathways of the B2 bradykinin receptor were unaffected by its antagonist HOE140. This observation suggests adaptation occurs in the process of BK release, or at a level upstream of adenosine release.

Muscle or fascia?

Some reports indicate fascia is important in DOMS. Itoh et al. [84] examined the electrical sensitivity of tissue at different depths from the skin to the muscle inside after LC in humans, and found the largest decrease in the current threshold of pain at the depth of fascia. Gibson et al. also found that injection of hypertonic saline [56] into the exercised muscle did not change the pain intensity (VAS) after LC in humans, but that injection into the fascia clearly increased it. This observation may indicate that the fascial afferents are important in DOMS. However, the response to hypertonic saline of muscle afferent fibers was not sensitized after LC [56], only mechanical sensitivity was increased [52, 53]. A recent report showed that the electrical pain threshold decrease after LC was greater for fascia than for muscle [85]. To understand the relative contribution of both structures to DOMS, we must differentially measure the mechanical pain threshold of both tissues, or record afferent activity after LC. Innervation of the fascia and its afferent characteristics were only recently reported [86, 87]. Whether fascial thin-fiber afferents are more strongly sensitized in DOMS than muscle afferents remains to be analyzed.

Prevention and treatment of DOMS

Because DOMS may interfere with everyday life and the performance of athletes, and because it may make it difficult for those who are not familiar with exercise to continue exercise for fitness, effective methods for preventing from DOMS are needed. As shown in the previous section,

B2 receptor antagonist, COX-2 inhibitor, anti-NGF antibody, and anti-GDNF antibody can, theoretically, be helpful. For the moment, the only drugs applicable for humans are COX-2 inhibitors. As described in the introduction, the effectiveness of non-steroidal anti-inflammatory drugs (NSAID) against DOMS is variable, depending on the time of administration and dosage [9]. A recent systematic review [29] of a large number of reports on the effects of NSAID found that many did not follow an appropriate experimental design. Therefore, they performed a randomized, double-blind, placebo-controlled within-subject experiment. Topical diclofenac (moderately selective to COX-2) sodium gel 1 % was applied over the exercised leg every 3 h for 24 h and was found to help reduce DOMS [29]. It would be interesting to study how this works in the context of the mechanism we have proposed (Fig. 5).

Exercise consisting of a small number of maximal isometric contractions [88] or weak LC [89, 90] beforehand (up to 2 weeks before) is reported to be effective in preventing DOMS. Massage after exercise has been proved to be effective in reducing DOMS in rats [91]. Reduction of DOMS by massage has also been reported for humans by Farr et al. [92], although they did not find any beneficial effect on reduced muscular strength or other functional decline.

Perspective

Several aspects of DOMS must still be studied. When one of the pathways described above (B2 bradykinin receptor-NGF pathway and COX-2-GDNF pathway) is blocked by a B2 bradykinin receptor antagonist or a COX-2 inhibitor, DOMS does not occur. This might suggest an interaction between the two pathways. In addition, the very early event that induces adenosine (possibly ATP) release from the muscle or activates muscle COX-2 during LC, and which might be related to the adaptation mechanism, is also unknown. This must be intimately related to why only LC, and not SC, induces DOMS, and must be studied.

The DOMS model has been used for study of myofascial pain syndrome, because it shows taut band-like muscle hardening, and localized decreased nociceptive threshold in it (trigger point), which are of diagnostic importance for myofascial pain symptoms. When LC was repeated every day, instead of adaptation there were longer-lasting mechanical hyperalgesia and muscle signs of degeneration and regeneration [5]. This observation suggests that this repetitive model is clinically relevant for study of myofascial pain syndrome. Further study of the DOMS mechanism might reveal the mechanism of myofascial pain syndrome and may suggest possibilities for treatment.

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