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Review article

New finding on fascia-traditional target of acupuncture

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Abstract

Acupuncture has often been applied for pain relief, improving motor functions, and manipulating the autonomic nervous system. Depending on the disease, the condition of the patient, or the purpose of the treatment, the target tissue is different. The stimuli by acupuncture and moxibustion may be mechanical, chemical, and/or thermal in the periphery, so that the afferent fibers innervating the tissue can respond to the stimuli and the signals can be transmitted to the central nervous system. This peripheral acceptance may be the first step to elicit the acupuncture effect. It is well known that thin afferents innervating the skin and muscles accept and respond to the mechanical, chemical, and/or thermal stimuli. These thin afferents consist of A**δ** and C fibers. In addition to the skin and muscles, there is another tissue, the fascia, which is a connective tissue wrapping the muscle. Although it appears that the fascia can perceive a noxious stimulus, limited information is available about its function in nociception. In this article, we review recent reports about fascial nociception in both animal and human subjects. The recent basic research results clearly indicate the existence of nociceptive Aδ and C fibers in the fascia. First, we introduce the basic structure of fascia and knowledge regarding nociceptive nerve fibers. Second, we review a recent anatomical and physiological study about fascial nociception in rats. Next, we summarize the results from a psychophysiological study with human subjects. Finally, we discuss the possibility of the fascia as the third tissue for acupuncture following the skin and muscles.

Key words: *myofascia, polymodal receptor, afferent, nociception, pain, thin fiber, myofascial pain syndrome, trigger point*

I. Introduction

Muscle fascia (myofascia) is a type of connective tissue that is present throughout the body[1)]. The word "myofascia" anatomically indicates some type of fascia. The outermost layer is the superficial fascia, while the deep fascia is underneath this. Furthermore, endomysium, perimysium, and epimysium wrap the muscles, muscle bundles, and muscle fibers, respectively. In this review, myofascia is used in the sense of a thickening of deep fascia, which consists of dense connective tissue layers covering the muscles and connecting the skeletal muscle each other, thereby creating continuous myofascial linkages throughout the body. Fascia is referred to as the second skeletal structure because of its three-dimensional distribution. The functional roles of fascia had been classically considered to be maintenance of posture and control of body position, as well as production of smooth and coordinated movement. Other classical roles include protection by covering the organs and making the passageway for nerve, blood, and lymphatic vessels[2, 3)].

An acupuncture needle sometimes stimulates the connective tissue, including fascia. Langevin et al. have reported that the needle rotation produced changes in connective tissue structure[4)] and referred to the sensory innervation of the connective tissues[5)]. In fact, acupuncture therapists know that the fascia may have a function as a nociceptive sensor because the acupuncture needle sometimes causes a pain sensation when it is at this depth. It has been reported that the electrical pain threshold around the fascia is remarkably low in the deep tissue in human subjects[6)]. A well-known pathological condition originating from the fascia, myofascial pain syndrome (MPS), is characterized by a localized tender region with a palpable band (a so-called trigger point). Ito et al. have shown a localized sensitive region that was generated at the palpable band of the fascia using experimental muscle contraction in animals[7)]. These results suggest the possibility that the sensory receptor exists on the fascia and it may sensitize following muscle contraction or damage to generate a

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trigger point on the fascia. From this point of view, the acupuncture manipulation of the fascia may be effective for disorders originating from there, such as MPS. As has already been reviewed, the effect of acupuncture may be mediated by the activation of afferent nerve fibers including Aδ and C fibers innervating the skin and muscles[8], and thus the existence of these nociceptive fibers in the fascia may make it a nociceptive tissue that responds to acupuncture stimulation.

In last decade, some basic research reports have shown the existence of nociceptive Aδ and C fibers not only in the skin and muscles but also in the fascia. In medical experiments with animals, thoracolumbar or crural fascia (CF) has often been examined by immunohistochemical and functional studies using an electrophysiological approach. In addition, results from a psychophysiological study with human subjects have also been reported. The present review focuses on the fascia as a nociceptive tissue, introduces the recent knowledge gained from basic research, and addresses the importance that fascia can be a pain generator, and furthermore, a functional target for acupuncture therapy.

Ⅱ. Studies with rat fascia

1. Basic structures of the fascia

Thoracolumbar fascia (TLF) covering the elector spinae and multifidi muscle in the low back is very thick and easily separable from the adjacent tissues (i.e. the skin and muscles). TLF has often been studied for basic research with animals (mainly rats). It has been suggested that the TLF plays a role in non-specific low back pain[9, 10]. However, there is little data regarding the TLF as a potential source of pain, even though low back pain has become a major problem in our health care system. The rat TLF has three layers that are visible medially close to the spinous processes[11] (Fig. 1A). The outer (superficial), middle, and inner (deep) layers are composed of transversely oriented densely packed collagen fibers, massive collagen fiber bundles, and loose connective tissue, respectively. The outer layer of the TLF includes dermal adipose tissue that supports dermis. The innermost layer, deep fascia, links with the epimysium surrounding the muscles. In contrast, CF, which is another thick fascia covering the tibialis anterior muscle, does not have any critical separated layers.

2. Basic knowledge about the nociceptive fibers

Nociceptive input such as noxious heat, mechanical, or chemical stimuli on terminal tissue is generally conducted by thin fibers (Aδ and C). Several peptides, such as calcitonin gene-related peptide (CGRP) and substance P (SP), have been identified in the peripheral terminal of nociceptive neurons. In general, almost half of all thin fibers are peptidergic, containing the peptides such as CGRP or SP. They are released from sensory nerve endings to induce many of the signs of acute inflammation including vasodilatation and plasma extravasation, and to play roles such as the principal mediators of neurogenic inflammation and axon reflex flare[12]. Without going into detail, both peptidergic and

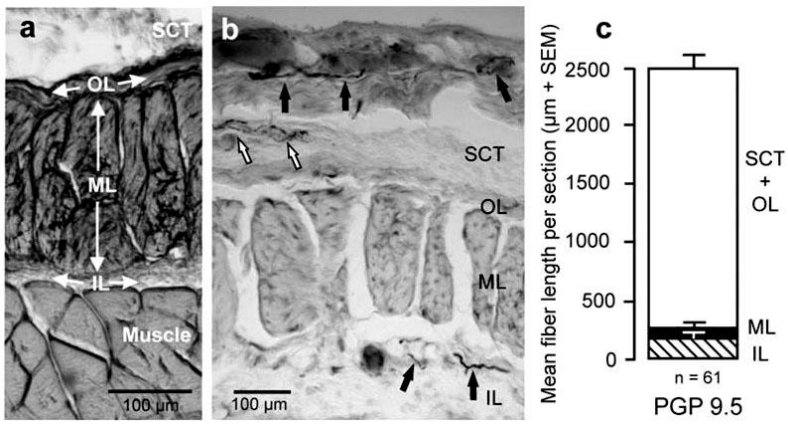

Fig. 1. Structure of the rat thoracolumbar fascia (TLF) close to the spinous processes L4/L5. (A) Transversal section the three layers of the TLF: OL, outer layer with transversely oriented collagen fibers; ML, middle layer composed of collagen fiber bundles oriented diagonally to the long axis of the body; IL, inner layer of loose connective tissue covering the multifidus muscle (muscle). SCT, subcutaneous tissue. (B) PGP9.5-ir nerve fibers in the layers of the TLF. Black arrows, fibers on passage; open arrows, nerve endings. (C) Mean fiber length of PGP9.5-ir fibers in the TLF. The majority of the fibers were located in the OL of the fascia and in the SCT. White part of the bar: SCT plus OL of the TLF; black: ML; hatched: IL. n, number of sections evaluated. Republished with permission of ELSEVIER BV from "Sensory innervation of the thoracolumbar fascia in rats and humans" in Neuroscience, J. Tesarz, U. Hoheisel, B. Wiedenhofer and S. Mense, 194, 2011 of copyright; permission conveyed through Copyright Clearance Center, Inc.

non-peptidergic neurons are involved in nociceptive signal transduction.

3. Anatomical analysis with intact fascia

One of the methods frequently used for anatomical study is immunohistochemical analysis with a specific antibody for peptides/proteins. Some universal peptide/ protein markers to visualize primary afferent fibers are well established, such as protein gene product 9.5 (PGP 9.5), peripherin, and CGRP (or SP). These are neuronal markers for general, non-peptidergic and peptidergic fibers, respectively. Tesarz et al. have reported that the immuno-reactive (IR) fibers for these markers were observed not only in rats but also in the human TLF[11]. In a more detailed analysis, they analyzed the nerve ending distribution in each of the three layers (i.e. outer, middle and inner layer) in the rat TLF. The distribution of nerve endings were dense in the outmost layer and decreased at the innermost layer (Fig. 1B, C). Moreover, they showed that both rat and human fascia had a rich innervation with sympathetic fibers using tyrosine hydroxylase as a marker for postganglionic sympathetic nerve fibers. These results suggest both sensory and sympathetic nerve fibers containing neuronal peptides innervate to the TLF the same as skin, muscle or other tissue. The existence of CGRP-, peripherin-, and PGP 9.5-IR nerve fibers was also evident in the CF (Fig. 2)[13]. CGRP- and peripherin-IR fibers were more dense on the superficial side (skin side) rather than on the deeper side facing the muscle. Few nerve fibers ran among and/or across the collagen fiber bundles in the CF.

4. Physiological analysis with intact fascia

Several reports of neuronal activity recordings from both the primary and secondary afferent fibers innervating the fascia have been published. The result using a single-fiber recording technique from the common peroneal nerve in a rat has shown the existence of functionally active C- and Aδ-fibers innervating the CF[13]. The fascial neuronal activities were recorded under three types of stimuli (mechanical, chemical, and thermal) and the identified fibers were categorized by their sensitivities (Fig. 3). First, they roughly searched a mechanically sensitive receptive field (RF) by manual pinching of CF with blunt forceps. The CF alone could be stimulated separately from the muscle underneath because it has sufficient thickness and is connected to the muscle with a loose connective tissue. Fibers with conduction velocity (CV) of <2.0 m/s were classified as C-fibers, whereas those with CV of 2.0 to 20 m/s were classified as Aδ-fibers. After nerve detection, pinching with sharpened forceps, quantitative ramp mechanical (392 mN/40 sec), chemical (bradykinin), thermal (cold (32°C to 8°C), and heat (32°C to 50°C)) stimuli were applied to the identified RF (Fig. 3B-F). Finally, 43% of C-fibers were concluded to be polymodal receptors,

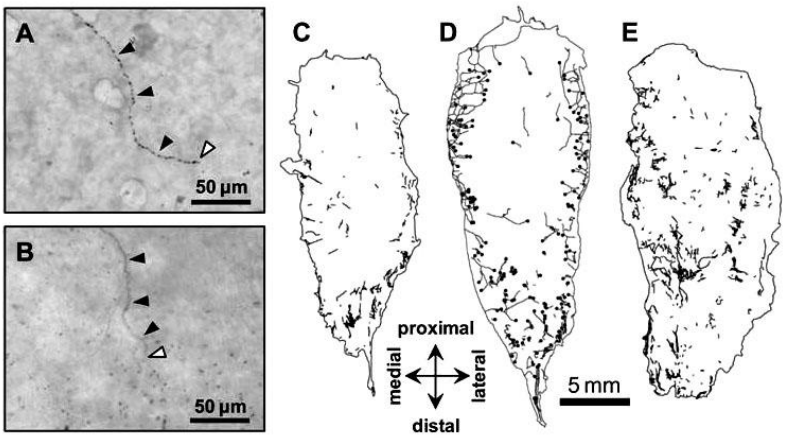

Fig. 2. CGRP- and peripherin-ir nerve fibers in the crural fascia (CF). Whole-mount fascia preparations. (A) A CGRP-ir terminal axon with a long chain of varicosities and its nerve terminal. (B) A peripherin-ir receptor terminal axon and its nerve terminal. Filled arrowheads: axon of immunoreactive nerve. Open arrowheads: peripheral nerve terminal. (C-E) Distribution of nerve fibers with CGRP- (C), peripherin- (D), and PGP 9.5-ir (E) in whole-mount preparations of the CF. They were traced under a light microscope and drawn on a plane. In the peripherin staining, peripheral nerve terminals are indicated by dots. Note that presumptive nociceptive nerve fibers (and their terminals) labeled with CGRP- and peripherin-ir were located in the distal third of the CF, and that there was some tendency for the labeling to be dense along the medial and lateral edge and relatively sparse in the center of the CF. On the other hand, PGP 9.5-ir (general marker for nerve fibers) was distributed all over the CF. Republished with permission of Wolters Kluwer Health, Inc. from "Nociception originating from the crural fascia in rats" in PAIN, T. Taguchi, M. Yasui, A. Kubo, M. Abe, H. Kiyama, A. Yamanaka and K. Mizumura, 154, 2013 of copyright; permission conveyed through Copyright Clearance Center, Inc.

which responded to all types of noxious stimuli (i.e. mechanical, thermal, and chemical), whereas almost all Aδ-fibers behave similar to mechanical nociceptors, responding only to mechanical stimuli. Moreover, 52% of C-fibers innervating CF responded to both mechanical and heat stimuli. Based on the previous single-fiber recording results, the proportion of the fiber responding to both mechanical and heat stimuli in the skin and muscle was about 80-90% and 40%, respectively[14, 15], therefore the result from fascial afferents seems to be appropriate.

The activities of the secondary afferent fiber (i.e. dorsal horn neurons) innervating the TLF have also been reported[16]. Hoheisel et al. performed the systematic extracellular recording of dorsal horn neurons that were examined in the lumbar spinal cord at segmental levels L1-L5, and in the thoracic spinal segment Th13 (rats usually have 13 thoracic and 6 lumbar spinal cord segments). In addition, the dorsal horn neurons having RF in the TLF were searched. The recording was made from a total of 211 neurons and 8 of them received input from the TLF (3.8%), while input from the multifidus (MF) muscle underneath the TLF was 9.5% and that from the skin was 51.7%. All of the TLF neurons were located in spinal segments between Th13 and L2. There were no neurons with TLF input found in the spinal segments L3-L5. They also indicated that most dorsal horn neurons with input from the TLF had convergent input from the MF muscle (87%), or from both the MF muscle and the skin (50%).

5. Anatomical and physiological changes under chronic inflammation of rat fascia

Even in a normal (i.e. intact) state, the functional afferents are innervating the fascia, which could sense the same kind of stimuli as the skin and muscles as described above. Moreover, it has been reported that inflammation induces both anatomical and physiological changes in the fascia[17, 18]. Complete Freund's Adjuvant (CFA), which is generally used as a reagent in animal experiments, was applied to the fascia to cause chronic inflammation. After inflammation occurred by CFA injection into the TLF, the density of SP-positive (presumably nociceptive) fibers significantly increased in all layers of the TLF. The CGRP-positive fibers were also significantly increased in the inner layer of the TLF[17].

The fascial inflammation also induced physiological changes[18]. Hoheisel et al. performed an electrophysiological recording from dorsal horn neurons in the lumbar segment L3. As described in the section II-4, the TLF neurons did not exist in the L3 segment in the

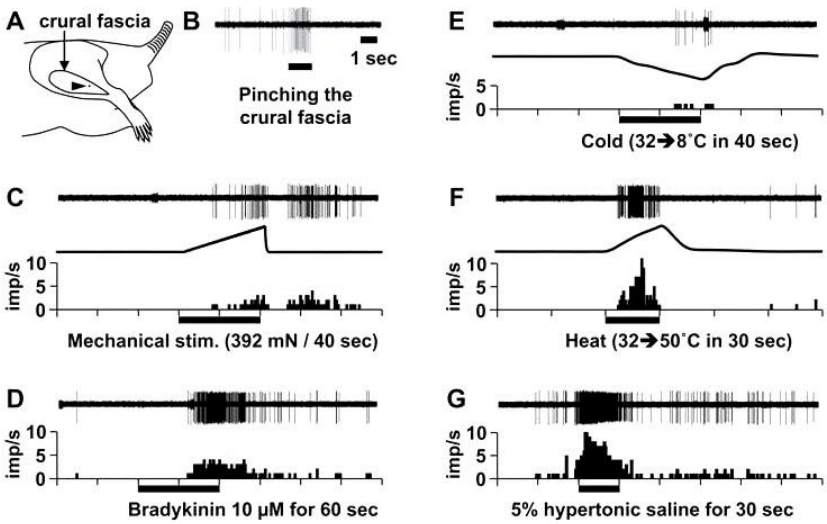

Fig. 3. Responses to various noxious stimuli of a C-afferent fiber having a receptive field in the crural fascia. (A) Receptive field of the fiber (arrowhead), (B) Responses to pinching of the CF with sharpened watchmaker's forceps, (C) quantitative ramp mechanical stimulus (392 mN in 40 seconds), (D) bradykinin 10 μM for 60 seconds, (E) cold (from 32° to 8℃ in 40 seconds), (F) heat (from 32° to 50℃ in 30 seconds), (G) 5% hypertonic saline for 30 seconds. Bradykinin and 5% hypertonic saline were applied with a small cotton ball soaked in the solution. Filled bars under the abscissas of the histograms indicate the time point and the duration of each stimulus. CV = 0.50 m/s. Republished with permission of Wolters Kluwer Health, Inc. from "Nociception originating from the crural fascia in rats" in PAIN, T. Taguchi, M. Yasui, A. Kubo, M. Abe, H. Kiyama, A. Yamanaka and K. Mizumura, 154, 2013 of copyright; permission conveyed through Copyright Clearance Center, Inc.

normal state. However, the proportion of dorsal horn neurons innervating deep tissues (i.e. muscles and fascia) significantly increased and there was a tendency to increase neuron proportion with TLF input following fascia inflammation. The new fascial RFs acquired by L3 neurons in an inflamed fascia were located exclusively at the level of the inflammation ipsilateral to the recording site (Fig. 4A). The locations of the RFs in other deep tissues were found outside the low back region, namely in the hip and in the entire hindlimb regions (Fig. 4B). The number of neurons having deep RFs in the hip and hindlimb was significantly greater in animals with an inflamed TLF.

Muscle inflammation has also exerted a physiological change in the fascia over the muscle[16]. Compared with intact animals, the proportion of neurons with RFs in the TLF following the MF muscle inflammation rose significantly. Specifically, 4 of 33 neurons in spinal segment L3 were found to respond to input from the TLF with an inflamed muscle, while none of 38 TLF neurons in L3 showed a response in an intact one (Fig. 5A). They also showed that the size of the RF in the TLF became wider under muscle inflammation than those in an intact muscle (Fig. 5B).

Ⅲ. Studies with human fascia

1. Human study focused on fascial nociception

Tesarz et al. have shown the preliminary immunohistochemical results of human TLF[11]. Similar to in rats, PGP 9.5-, TH-, SP- and CGRP-IR nerve fibers (or free nerve endings) also innervated in the human TLF. More clinically, the psychophysiological study with human subjects has been reported[19]. Schilder et al. performed bolus injections (400μL) of hypertonic saline into the posterior layer of the TLF, erector spinae muscle, or the overlying subcutis at L3/L4 level, approximately 4 cm lateral to the spinous processes using ultrasound images. They evaluated spontaneous pain intensity, pain quality, and pain distribution in response to isotonic or hypertonic saline. Overall, the injection of hypertonic saline induced higher and longer-lasting pain ratings in all tissues than stimulation by isotonic saline. The injection of hypertonic saline into the fascia evoked longer pain duration within 25 minutes post injection and higher pain intensities compared to subcutis and muscle injections. Moreover, the hypertonic saline injection led to a more widespread pain radiation after fascia than with the other tissue stimulation.

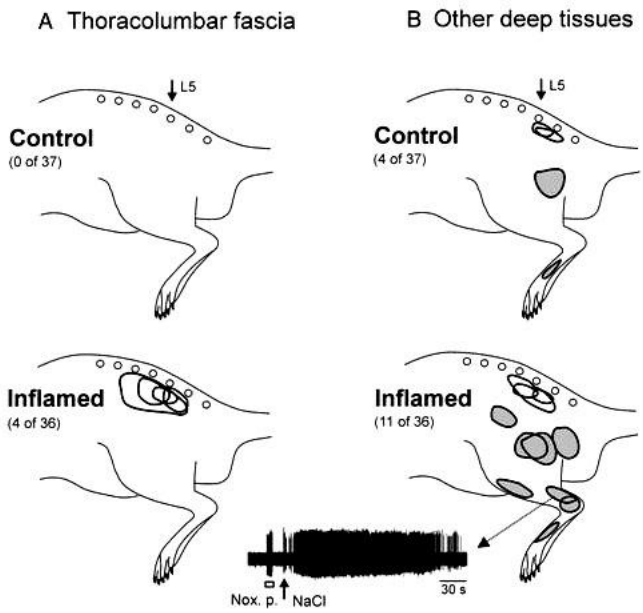

Fig. 4. Location and size of the deep receptive fields (RFs). (A) RFs in the thoracolumbar fascia. (B) RFs in deep tissues other than the thoracolumbar fascia. The numbers in parentheses are the number of neurons relative to the dorsal horn neurons recorded. Arrows in the upper panels indicate the spinous process L5. Open outlines: RFs in the fascia (A) or other deep tissues of the low back (B), Filled grey areas in (B): RFs in deep tissues outside the low back in the hip and hindlimb. The inset in (B) shows the responses of a neuron to noxious stimuli applied to the gastrocnemius-soleus muscle. Nox. P., noxious pressure; NaCl, injection of hypertonic saline (5%, 50 μL). Republished with permission of W.B. SAUNDERS CO. LTD. from "Inflammation of the thoracolumbar fascia excites sensitizes rat dorsal horn neurons" in European Journal of Pain, U. Hoheisel, S. Mense, 19, 2015 of copyright; permission conveyed through Copyright Clearance Center, Inc.

Ⅳ. Discussion

1. Can acupuncture and moxibustion manipulate fascia?

As we have briefly outlined in this review, there seems to be no doubt that fascia can accept a painful input. It has nociceptive fibers like the skin, muscles and viscera, and its anatomical distribution and physiological function changes in the pathological situation. After inflammation, density of nociceptive fibers increased, and the RF of nerve fiber innervating the fascia became wider and to innervate other tissue (i.e. skin or muscles).

As also mentioned at the beginning, it has been discussed which type of afferent can accept the input by acupuncture. As manual acupuncture can induce diffuse noxious inhibitory controls (DNIC)-like response and the activation of thin afferent fibers (Aδ and C fibers) is required by DNIC, the most plausible hypothesis is that acupuncture stimulation could excite these thin fibers[20]. It is well known that Aδ and C fibers are mainly nociceptors activated by a noxious mechanical, heat, and chemical stimuli. The nociceptors, especially polymodal receptors (nociceptors responding to multiple stimulus modalities), may be the best potential candidate as a peripheral receptor for acupuncture and moxibustion, as they would be mechanical, chemical or heat stimuli. The polymodal fibers are widely distributed in the skin, muscles, and viscera. The studies discussed in the present review have given new aspects on the fascia as a functionally active nociceptive tissue innervated by both Aδ and C fibers. These results suggest fascia can accept an input from acupuncture stimulation and be directly manipulated by acupuncture therapy. The fascia can also respond to moxibustion stimulation, as the polymodal fibers innervating it are also able to receive heat stimuli. Presently, it is unclear which receptor is activated by moxibustion, although transient receptor potential vanilloid receptor, such as TRPV1 and TRPV2, expressing on polymodal receptor terminals and activated by heat stimuli, are promising candidates. These findings may support that de qi sensation originates from the activation of these fibers innervating fascia during the acupuncture needle penetration. In some cases, local twitch response is also observed synchronously with de qi sensation. This phenomenon

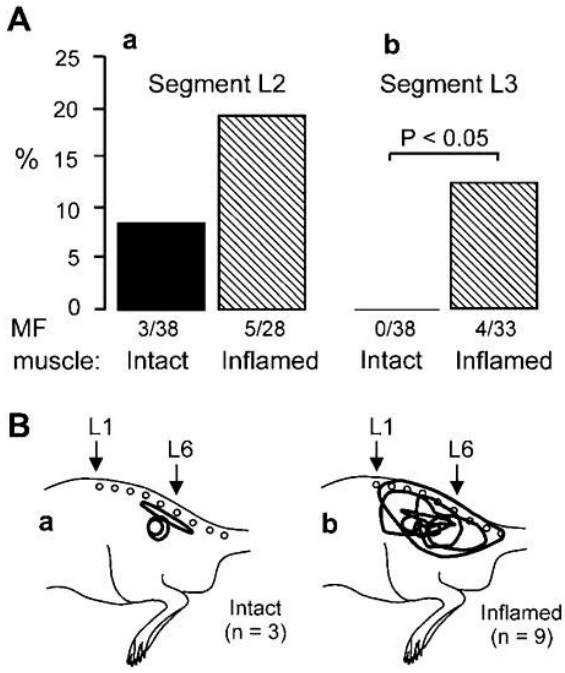

Fig. 5. Proportion of dorsal horn neurons with input from TLF after CFA injection into the MF muscle. (A) Proportion of dorsal horn neurons with TLF input in spinal segment L2: (a) and spinal segment L3 (b), black bars (intact), data from animals with an intact MF muscle. The numbers underneath the bars are those of the neurons from which the bars were constructed. (B) Location and size of the receptive fields in the TLF: (a) intact animals, (b) inflamed animals; n: number of neurons. Arrows indicate the lumbar spinous processes L1 and L6. Republished with permission of W.B. SAUNDERS CO. LTD. from "Nociceptive input from the rat thoracolumbar fascia to lumbar dorsal horn neurons" in European Journal of Pain, U. Hoheisel, T. Taguchi, R.D. Treede, S. Mense, 15, 2011 of copyright; permission conveyed through Copyright Clearance Center, Inc.

may be supported by the presence of contractile fibroblasts containing α-smooth muscle actin (α-SMA) in the fascia[10]. In fact, the gene expression of α-SMA has been reported, but it is currently unclear whether the myofascia has contractility similar to muscle or not. Further studies are necessary to clarify such possibilities.

2. Does fascia cause low back pain?

As mentioned in the introduction, it is believed that the TLF is potentially involved in non-specific low back pain[9,10]. The TLF is innervated by nociceptive free nerve endings and lumbar dorsal horn neurons. These fibers could respond to fascial noxious inputs and conduct the information to the spinal cord and brain. Interestingly, as most of the dorsal horn neurons innervating TLF had convergent inputs from the muscle and/or skin especially with an inflamed fascia, the referred pain between the muscle and fascia may be caused in a way similar to visceral pain. The input from the fascia not only at the original levels but also at lower levels of the spinal cord was observed following inflammation. Moreover, both rat and human TLF has a rich innervation with sympathetic nerve fibers. This finding may explain why patients with low back pain report increased intensities of pain when they are under psychological stress. In general, acupuncture therapy can also manipulate the autonomic nerve system by central mechanism. In terms of this effect, low back pain generated not only from muscle but also the TLF could be treated by acupuncture through both a peripheral and central mechanism.

Ⅴ. Conclusion

Recent studies presented us new aspect about the fascia as a nociceptive generator and the possibility that the fascia could respond to acupuncture stimuli has been raised. An acupuncture needle is a good device for directly stimulating the deep tissue (i.e. fascia, muscle, etc.) with less (or no) injury to the skin. This unique ability of acupuncture may lead to a distinctive effect by acupuncture therapy.

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