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INNERVATION CHANGES INDUCED BY INFLAMMATION OF THE RAT THORACOLUMBAR FASCIA

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Abstract—Recently, the fascia innervation has become an important issue, particularly the existence of nociceptive fibers. Fascia can be a source of pain in several disorders such as fasciitis and non-specific low back pain. However, nothing is known about possible changes of the fascia innervation under pathological circumstances. This question is important, because theoretically pain from the fascia cannot only be due to increased nociceptor discharges, but also to a denser innervation of the fascia by nociceptive endings. In this histological study, an inflammation was induced in the thoracolumbar fascia (TLF) of rats and the innervation by various fiber types compared between the inflamed and intact TLF. Although the TLF is generally considered to have proprioceptive functions, no corpuscular proprioceptors (Pacini and Ruffini corpuscles) were found. To obtain quantitative data, the length of fibers and free nerve endings were determined in the three layers of the rat TLF: inner layer (IL, adjacent to the multifidus muscle), middle layer (ML) and outer layer (OL). The main results were that the overall innervation density showed little change; however, there were significant changes in some of the layers. The innervation density was significantly decreased in the OL, but this change was partly compensated for by an increase in the IL. The density of substance P (SP)-positive – presumably nociceptive – fibers was significantly increased. In contrast, the postganglionic sympathetic fibers were significantly decreased. In conclusion, the inflamed TLF showed an increase of presumably nociceptive fibers, which may explain the pain from a pathologically altered fascia. The meaning of the decreased innervation by sympathetic fibers is obscure at present. The lack of proprioceptive corpuscular receptors within the TLF does not preclude its role as a proprioceptive structure, because some of the free nerve endings may function as proprioceptors.

Key words: fascia innervation, sympathetic fibers, inflammation, fasciitis, non-specific low back pain.

INTRODUCTION

The mechanical properties of fascia tissue have been and still are studied by many scientific groups (Macintosh et al., 1987; Vleeming et al., 1995; Benetazzo et al., 2011; Langevin et al., 2011; Corey et al., 2012; Schleip et al., 2012). Recently, the fascia innervation has become an important issue, particularly the existence of nociceptive fibers (Corey et al., 2011; Tesarz et al., 2011; Taguchi et al., 2013). Fascia can be a source of pain in fasciitis, non-specific low back pain, and also in cases of adhesions between the fascia and adjacent tissues (muscle, nerve; Rowe et al., 2013). Experiments on human volunteers showed that noxious stimulation of fascia tissue – including the thoracolumbar fascia (TLF) – evokes pain (Gibson et al., 2009; Deising et al., 2012; Schilder et al., 2014). There is also experimental evidence showing that injections of algesic agents into the fascia are more painful than the same injections into the skin or muscle (Gibson et al., 2009; Deising et al., 2012; Schilder et al., 2014).

An anatomical structure functions as a pain source only if it is equipped with nociceptors. Recently, several publications have described a dense innervation of the TLF including putative nociceptors in rats and humans (Corey et al., 2011; Tesarz et al., 2011). Also other fasciae are known to possess nociceptors (Taguchi et al., 2013). The nociceptive nature of the nerve endings was mainly identified with immunohistochemical techniques (e.g. immunoreactivity (IR) for substance P (SP) and calcitonin gene-related peptide (CGRP; Corey et al., 2011; Tesarz et al., 2011), but also in electrophysiological experiments (Taguchi et al., 2013).

In this article, the term fascia is used in the sense of a thickening of the epimysium, i.e. as a layer of dense connective tissue covering a muscle. The studied structure was the posterior lamina of the TLF, and the covered muscles are the genuine back muscles (erector spinae muscle). Additionally, the posterior lamina serves as an aponeurosis for the internal oblique, the latissimus

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Abbreviations: CGRP, calcitonin gene-related peptide; CFA, Complete Freund's Adjuvant; IL, inner layer; ir, immunoreactive; IR, immunoreactivity; ML, middle layer; OL, outer layer; PBS, phosphate-buffered saline; PGP 9.5, protein gene product 9.5; SP, substance P; TH, tyrosine hydroxylase; TLF, thoracolumbar fascia.

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dorsi, and (indirectly) for the transverse abdominal muscles (Gray's Anatomy et al., 2005). Other groups use the term fascia in a more general way including e.g. perimysium and endomysium (Langevin and Huijing, 2009).

It is well known that fascia tissue is plastic (Langevin and Sherman, 2007) and adapts to changing requirements, for instance mechanical loads. Repeated mechanical strain has been found to lead to microlesions in connective tissue that are repaired by a sterile inflammatory process (Solomonow, 2012). However, nothing is known about another aspect of fascia plasticity, namely possible changes in the innervation due to inflammation. Such changes may occur in clinical cases of pain where fascia tissue is involved.

In the present investigation, changes in the TLF innervation were studied in a rat model of fasciitis. As in a previous article on dorsal horn neurons (Hoheisel and Mense, 2015), the fasciitis was mimicked by an experimental inflammation induced by Freund's complete adjuvant. Inflammatory pain from fascia can be not only due to higher discharges in fascia nociceptors but also to an increase in the innervation by nociceptive endings. To our knowledge, the latter possibility has never been studied. Therefore, the aim of the present study was to obtain first data on changes in the innervation density of an inflamed fascia. For the determination of the overall innervation density, protein gene product 9.5 (PGP 9.5)-IR was used as a universal marker for all nervous structures (Lundberg et al., 1988). Tyrosine hydroxylase (TH-)-IR served as a marker for postganglionic sympathetic nerve fibers (Burgi et al., 2011), CGRP-IR and SP-IR as markers for sensory peptidergic nerve fibers (Danielson et al., 2006).

EXPERIMENTAL PROCEDURES

The experiments were performed on 10 adult male Sprague–Dawley rats (350–480 g). The experimental procedure was approved by the local ethics authority responsible for animal experimentation. The experiments were carried out in accordance with the German law on the protection of animals and with the ethical proposals of the International Association for the Study of Pain (Zimmermann, 1983).

The rats were divided into two groups:

1. Five animals received an intrafascial injection of Complete Freund's Adjuvant (CFA group).
2. Five naïve rats served as a control (control group).

The animals were housed in groups of 2–3 animals in standard plastic cages and maintained on a 12-h light/dark cycle. The experimenter was blinded to the experimental groups.

Intrafascial injection of CFA

To induce a chronic inflammation, 50-μl CFA (Difco Lab., USA) was injected into the TLF. In deeply anesthetized animals (Ketamine 100 mg/kg i.p. and Xylazine 7.5 mg/kg i.p.; Essex Pharma, Germany and Alverat, Germany, respectively) a small longitudinal skin incision (1–1.5 cm) was made about 2 cm caudal to the projected injection site. Because of the loose structure of the subcutaneous tissue in rats, the incised skin area could be pushed about 2 cm cranially to make the intrafascial injection at vertebral level L4–L5. Therefore, the skin incision did not overly the injection site, and the healing of the skin wound did not influence the course of the fascia inflammation. The intrafascial injection was made 3 mm lateral to the spinous processes L4 and L5 using a 27-gauge cannula. The cannula was inserted horizontally in the longitudinal direction (4–5 mm, Fig. 1A) into the TLF under control of a dissecting microscope. After injection the cannula was kept in place for 1 min. The immunohistochemical evaluation was carried out 12 days after the CFA injection.

In histological sections the inflamed fascia showed marked leukocyte infiltrations that were largely restricted to the fascia (middle (ML) and inner layer (IL), see 2.3). Only minor infiltrations were seen in the multifidus (MF) muscle underlying the fascia (Fig. 1C).

Immunohistochemistry

The histological staining techniques visualized fibers of passage and nerve endings alike. The nerve endings had the appearance of free nerve endings. According to the data of Stacey (1969) for muscle tissue, a free nerve ending consists of several unmyelinated terminal axons that are relatively straight and often course parallel to each other. For reasons of brevity, fibers of passage and terminal axons together were designated ''fibers'', except in places where the terminal axons were addressed specifically. The term terminal axon is preferred over free nerve ending because in our material it was sometimes hard to tell if a structure really formed the final ending or was a piece of the terminal axon. The decisive criterion for a terminal axon was the presence of several (more than 3) axonal expansions, so-called axonal varicosities.

Twelve days after induction of the inflammation, the animals were euthanized with an overdose of thiopental sodium i.p. (Trapanal®, Altana Pharma, Germany) and transcardially perfused with 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS) followed by PBS containing 10% sucrose. The TLF at vertebral level L4–L5 (containing the injection site) together with the surrounding tissue was removed close to the spinous processes, passed through PBS containing 30% sucrose for cryoprotection and snap frozen. Serial cryostat cross sections were made at a thickness of 40 μm and processed for the immunohistochemistry of intra-axonal substances as follows:

PGP 9.5: Primary antiserum: rabbit anti-PGP 9.5 (Biotrend), dilution 1:1000 in PBS, incubation for 24 h. Secondary antiserum: biotinylated anti-rabbit IgG (Vector), 1:200, 60 min.

TH: Primary antiserum: sheep anti-TH (Chemicon), 1:200 in PBS, incubation for 24 h. Secondary antiserum: biotinylated anti-sheep IgG (Vector), 1:200, 60 min.

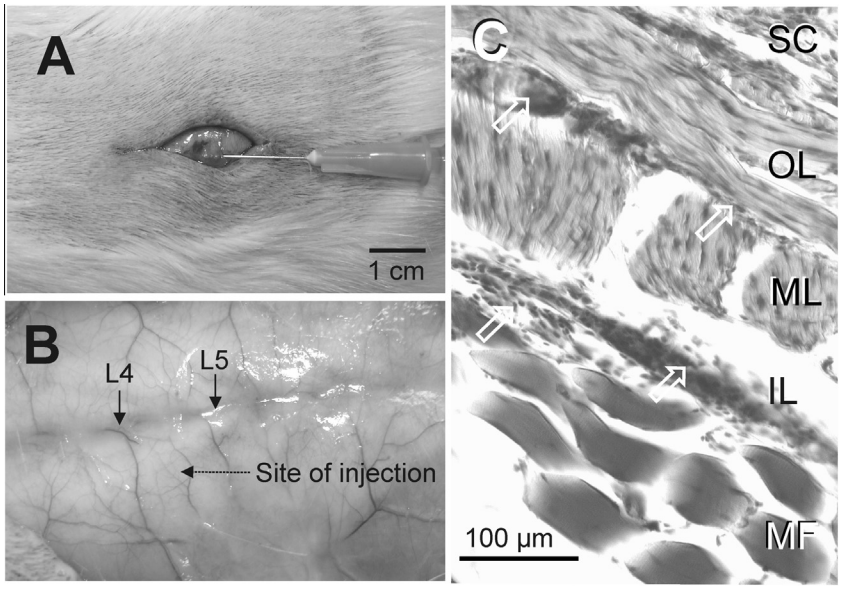

Fig. 1. Induction of the inflammation by injection of Complete Freund's Adjuvant (CFA). (A) Intrafascial CFA-injection through a small longitudinal skin incision. (B) Macroscopically, twelve days after injection no signs of inflammation such as reddening or edema were visible on the surface of the fascia (skin removed). Arrows indicate the spinous processes L4 and L5. (C) Histology showing the three layers of the inflamed fascia (12 days). OL: outer layer with transversely orientated collagen fibers; ML: middle layer composed of collagen fiber bundles orientated to the long axis of the body; IL: inner layer of loose connective tissue covering the multifidus muscle (MF); SC: subcutaneous tissue. Marked leukocyte infiltrations (open white arrows) were found mainly in the middle and inner layer, minor infiltrations in the muscle (MF) close to the fascia (Giemsa staining, 40 µm).

CGRP: Primary antiserum: rabbit anti-CGRP (Bachem), 1:4000 in PBS, 48 h. Secondary antiserum: biotinylated anti-rabbit IgG (Vector), 1:200, 60 min.

SP: Primary antiserum: rabbit anti-SP (Chemicon) 1:1000 in PBS, 24 h. Secondary antiserum: biotinylated anti-rabbit IgG (Vector) 1:200, 60 min.

All incubations were made at room temperature. To exclude unspecific staining, control experiments were performed by omitting the primary or secondary antibody. No staining could be seen under these conditions.

The quantitative evaluation of immunoreactive nerve fibers required a stable, non-fading staining. Therefore, the avidin–biotin complex method with 3,3-diaminobenzidine tetrahydrochloride as chromogen was preferred over fluorescent techniques.

Quantitative evaluation of immunoreactive nerve fibers

At least three random sections per animal and marker were used. All in all, 175 sections were evaluated in the present study. In all sections, the length of the stained fibers and/or terminal axons was determined. The distance between the sections was at least 10 sections so that a given fiber was unlikely to appear twice in the sections. However, since the length of the fibers was not known, this possibility cannot be completely excluded.

The evaluation was performed for each layer of the TLF separately in transverse sections of the TLF. The innervation density for each layer and fiber type was calculated by summing up the length of all fibers in all sections. In each section, a fascia area of 5-mm length measured from the spinous processes in the lateral direction was evaluated. In this medial part of the fascia, three layers can be distinguished (more laterally, the layers often merge). The three layers were (Tesarz et al., 2011): (1) A thin outer layer (OL) of transversely oriented collagen fibers directly underneath the subcutaneous tissue, (2) a thick middle layer (ML) composed of massive collagen fiber bundles orientated obliquely to the axis of the spine, and (3) a thin inner layer (IL) of connective tissue between the TLF and the underlying multifidus muscle. In each of these three layers, the length of all immunoreactive fibers was measured using an imaging software (analySIS B, Soft imaging System, Olympus Company), and for each layer the fiber length per 1000 μm^2 area was calculated. The fibers were identified at 400 times magnification under light microscope.

Data analysis

Comparisons between the groups were made using the U-test of Mann and Whitney. A probability level of less than 5% (two-tailed) was regarded significant. In the figures, the data are shown in a box-and-whisker plot with median, first and third quartiles (box) and range (whiskers).

RESULTS

General features

In sections of both intact and inflamed fascia, the nerve structures appeared either as densely stained fibers of passage without recognizable nerve endings (Fig. 2A), or as terminal axons that looked like strings of beads with numerous varicosities (Figs. 2B and 3A). The latter are assumed to be sensory terminal axons (if stained

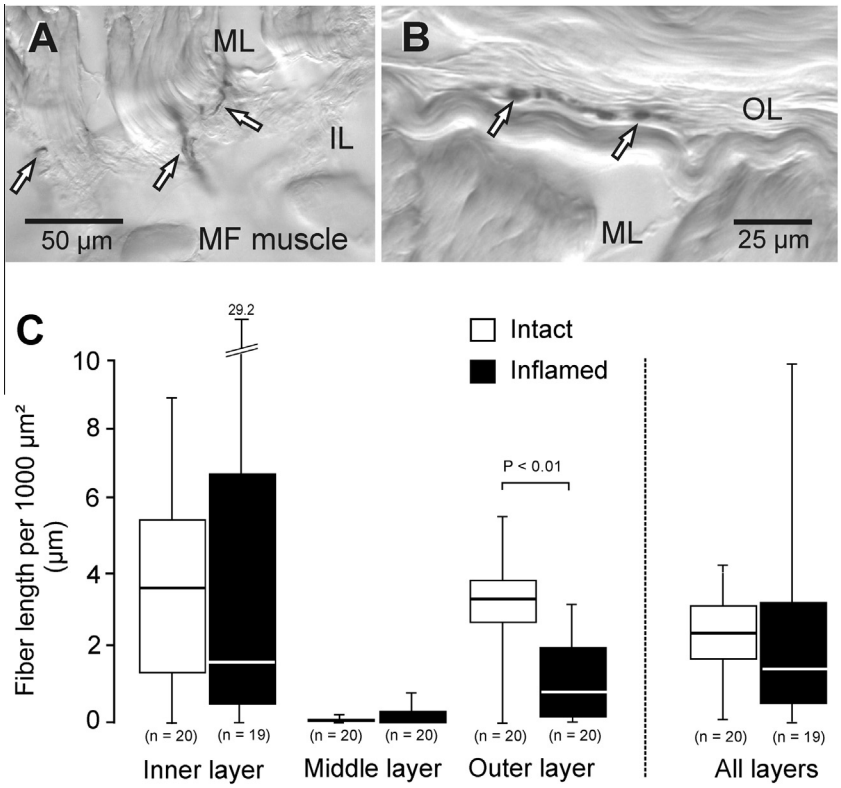

Fig. 2. Fibers immunoreactive to protein gene product 9.5. (A) Fibers of passage (arrows) in the inner layer (IL) coursing close to the collagen fiber bundles of the middle layer (ML), fascia intact. (B) Terminal axon showing a chain of varicosities (arrows; fascia intact). (C) Quantitative evaluation of the fiber length in the three layers of the fascia (see Fig. 1). Shown are median, first and third quartile (box) and range (whiskers). Open bars (intact), data from intact fascia; black bars (inflamed); inflamed fascia 12 days after injection of Complete Freund's Adjuvant; *n*, number of tissue sections; *P* value indicates a statistically significant difference between intact and inflamed.

with antibodies to CGRP or SP) or efferent sympathetic endings (if stained with antibodies to TH). Since many of the endings seen in the fascia sections looked similar to such terminal axons, we adopted this term. In order to be accepted as a terminal axon, the axon had to possess at least three varicosities. In the figures, "fiber length" includes both fibers of passage and terminal axons. In the ML of the fascia, the fiber density was the lowest independent of the fiber type studied.

A surprising finding was that we did not find any encapsulated receptors (e.g. Ruffini or Pacini corpuscles) in our material. We deliberately looked for these receptors not only with PGP 9.5, but also with hematoxylin–eosin staining. Since we had no problems finding thin terminal axons with these techniques, it is improbable that we overlooked the relatively large encapsulated receptors. Apparently, in the TLF area close to the midline – where the TLF originates from the tips of the spinous processes-, large mechanoreceptors do not exist (see discussion).

PGP 9.5-IR: The data obtained with PGP 9.5 staining showed that in the intact TLF the fiber length per 1000 µm^2 was greatest in the OL, i.e. this layer had the highest innervation density (Fig. 2C). Only a few nerve fibers were found in the ML. In the inflamed fascia, there was a trend toward an increase in the IL, whereas in the OL the innervation density was significantly decreased ($P < 0.01$; Fig. 2C).

Sensory fibers

CGRP-IR: CGRP-immunoreactive (-ir) fibers were the greatest single fiber population found. They were particularly numerous in the IL. In the inflamed TLF, the fiber length increased significantly in the IL ($P < 0.02$; Fig. 3B) while no significant changes occurred in the ML and OL.

SP-IR: In intact TLF, SP-containing nerve fibers were present exclusively in the OL (Fig. 4C), but the length of these structures was very short. In the IL and ML not a single SP fiber was present. After induction of the inflammation, SP-ir structures were also found in the IL. The ML remained free from SP-IR also in the inflamed TLF. In contrast to all other fiber types evaluated – which showed a decreased innervation density in the OL in the inflamed fascia, or at least a trend in that direction – SP-ir fibers were increased in this layer ($P = 0.054$; Fig. 4C). When the length of the SP-positive structures in all layers was added up, the resulting increase was statistically significant (Fig. 4C, right panel).

Sympathetic fibers

TH-IR: Apart from their TH-IR, the efferent terminal axons of sympathetic fibers were indistinguishable from those of sensory endings. The efferent endings exhibited axonal expansions (varicosities) which looked identical to those

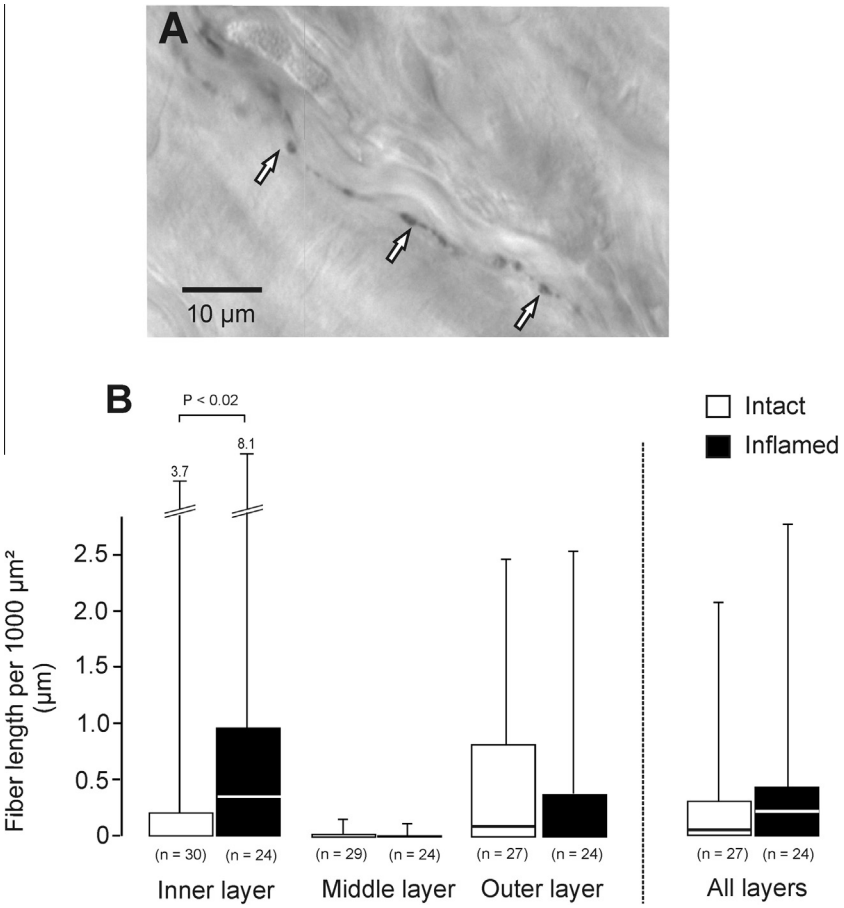

Fig. 3. Calcitonin gene related peptide-immunoreactive fibers. (A) Terminal axon in the outer layer (fascia inflamed). Arrows mark varicosities. (B) Quantitative evaluation of fiber length. Experimental groups, fascia layers, and numbers in parentheses as in Fig. 2.

of the SP- and CGRP-ir terminal axons. Two types of TH-positive terminal axons were found: one type surrounded blood vessels (Fig. 5A), the other one ended freely in the tissue without any relationship to vessels.

In the intact TLF, the majority of TH-ir structures were found in the OL and IL (Fig. 5B). In the OL, there was a significant decrease in fiber length in the inflamed TLF ($P < 0.03$). Also when the fiber lengths in all layers were added up, the decrease remained significant.

Fascia swelling

Since the fascia was locally swollen close to the CFA injection, the possibility had to be excluded that a measured lower innervation density was due to the swelling and not to a true decrease in fiber number. Therefore, a comparison of the evaluated section area (5 mm long measured from the spinous process toward lateral) was made between intact and inflamed fascia. As can be seen from Fig. 6, the areas of all layers were not significantly changed by inflammation. Apparently, the inflammation caused just a local swelling around the CFA injection without increasing the evaluated area as a whole.

DISCUSSION

The animal model of a long-lasting experimental fascia inflammation was chosen for our study, because it mimics several painful conditions in which the TLF becomes a source of, or contributes to, pain: (1) Fasciitis, which occurs in several forms such as necrotizing fasciitis (Malghem et al., 2013) or eosinophilic fasciitis (Lebeaux and Sène, 2012). A fasciitis can also occur in connection with the compartment syndrome, when the latter is complicated by an infection (Shore et al., 2013). (2) Mechanical overload leading to microlesions which are repaired by an inflammatory process (Solomonow, 2012). (3) Adhesions between fascia and muscle, or fascia and skin, resemble in some aspects an inflammation in that they cause tissue swelling and pain during movement (Ahn et al., 2008; Rowe et al., 2013). The mechanism by which adhesions cause pain is obscure; one possibility is that nerve branches are trapped in the adhesions, and the shear forces during movements excite nociceptors.

The lack of Ruffini and Pacini corpuscles in our material is surprising. Also in a previous study, in which specimen from the human TLF were included (Tesarz et al., 2011), no such receptors were present. It is a clear

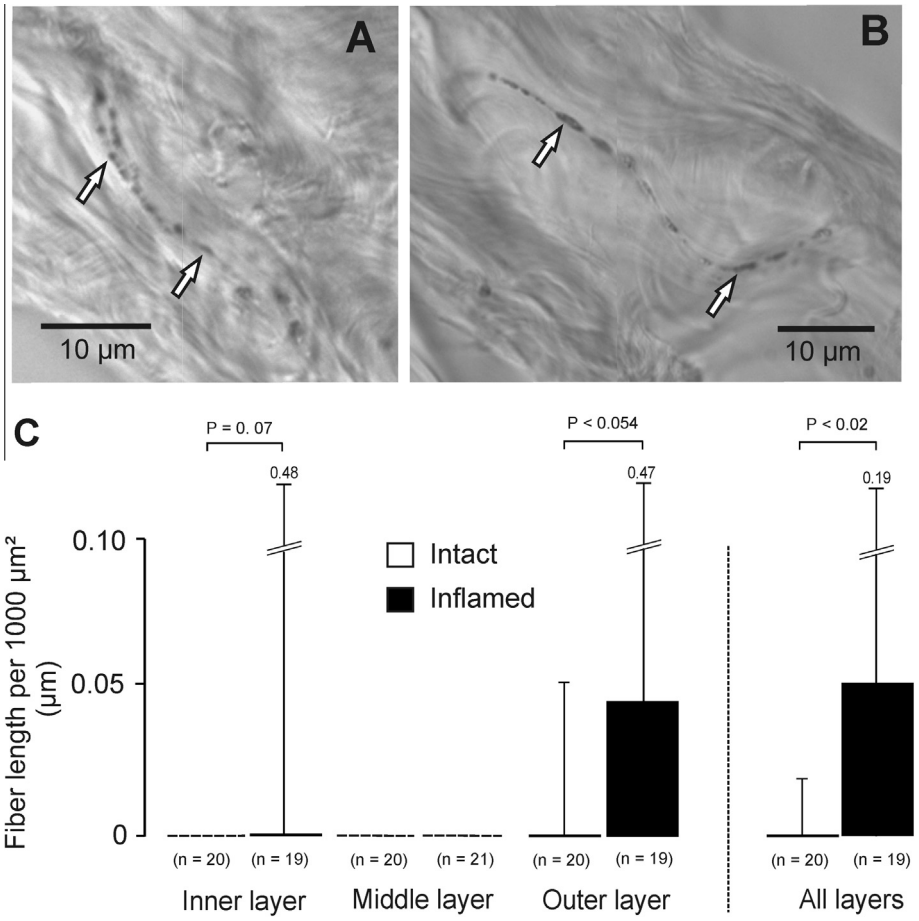

Fig. 4. Substance P-immunoreactive fibers. (A, B) Terminal axons with chains of varicosities (arrows) located in the inner (A) and outer layer (B) of an inflamed fascia. (C) Quantitative evaluation of the fiber length. Experimental groups, fascial layers, and numbers in parentheses as in Fig. 2.

difference to the work of other groups who found encapsulated mechanoreceptors in the human TLF (Yahia et al., 1992 using antibodies to S-100) and in the supraspinal and intraspinal ligaments (Jiang et al., 1995 using methylene-blue staining).

One possible explanation for this discrepancy is that in the cited studies the TLF specimen were taken from fascia regions other than used in our investigation. We evaluated the lumbar fascia close to the midline, where the TLF originates from the tips of the spinous processes. Probably, encapsulated proprioceptors and mechanoreceptors do not exist in all types of fascia and are not equally distributed over all parts of a given fascia. Differences in the density of these receptors in various types of fascia have been described, and as one possible reason for these differences the mechanical forces transmitted by the fasciae have been discussed (Stecco et al., 2007).

This is not supposed to mean that the rat TLF does not possess proprioceptive endings. As has been shown in an electrophysiological study on unmyelinated afferents from the gastrocnemius–soleus muscle – which all terminate in free nerve endings-, a considerable portion of the endings had a low threshold and could serve as proprioceptors (Hoheisel et al., 2005).

A general finding of the present study was that the inflammation-induced changes in innervation density did not occur in all layers to the same extent. For instance, CGRP-positive fibers showed a highly significant increase in the IL, but no increase in the other layers (Fig. 3). In the present study only cross sections have been evaluated. Therefore, we have no information on the rostro-caudal course and horizontal distribution of the nerve endings. In a future study on horizontal whole mount preparations, we will investigate whether the nerve fibers have different lengths in the rostro-caudal and medio-lateral direction. Moreover, we plan to study to what extent the inflammation-induced changes in innervation density are accompanied by changes in the branching pattern of single nociceptive and sympathetic nerve endings.

The IR to CGRP and SP was used as general stain for sensory fibers (Carr and Lipkowski, 1990). CGRP-ir fibers were more common than SP-ir afferents, and often SP coexists with CGRP in the same fiber (Merighi et al., 1988). CGRP-positive fibers contain both mechanoreceptive and nociceptive afferents; in inflamed fascia they showed a significant increase only in the IL at the border to the multifidus muscle (Fig. 3). This increase in fiber density may lead to a higher sensitivity to mechanical forces, when the multifidus muscle contracts and the muscle moves against the IL.

SP-ir fibers were special in that they were completely lacking in the ML and showed a marked – albeit not

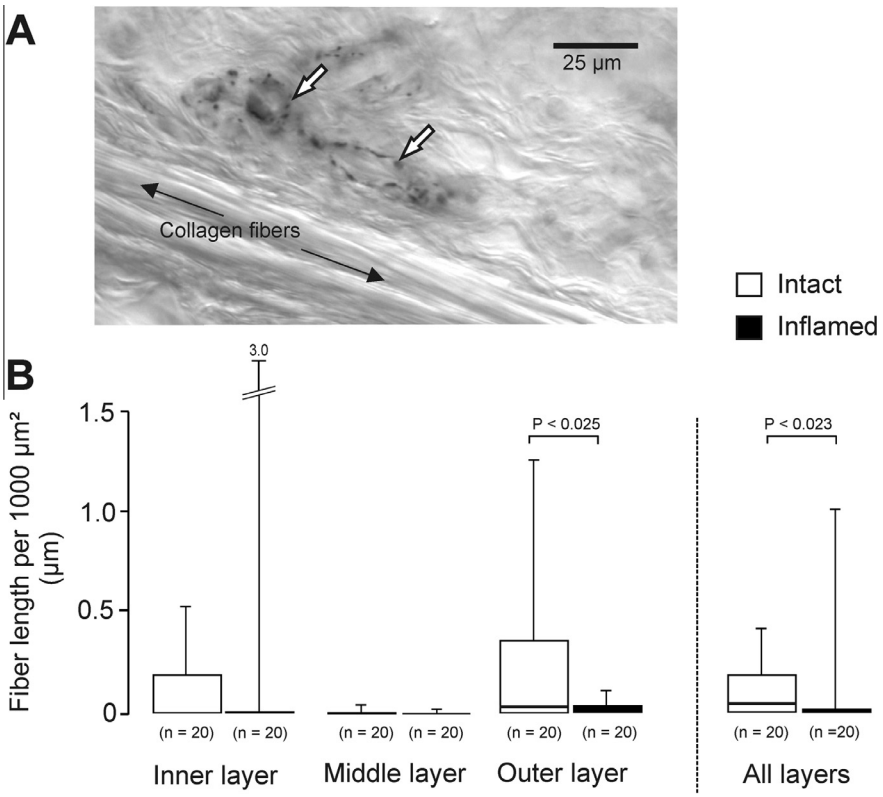

Fig. 5. Tyrosine hydroxylase-immunoreactive nerve fibers. (A) Tyrosin-hydroxylase-immunoreactive terminal axons in the outer layer of an intact fascia. (B) Quantitative evaluation of the fiber length of fibers and terminal axons. Experimental groups, fascial layers, and numbers in parentheses as in Fig. 2.

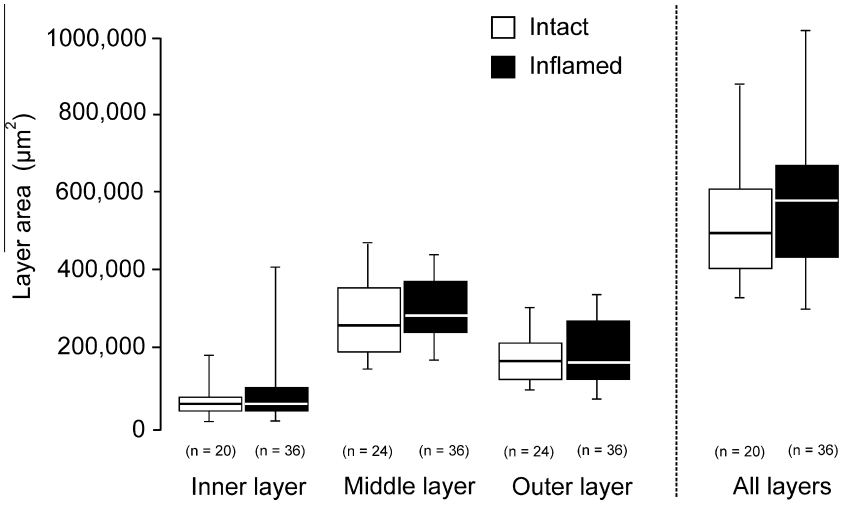

Fig. 6. Effect of inflammation on evaluated fascia area. To exclude a possible inflammation-induced swelling of the fascia as a reason for a reduction in fiber length, the evaluated fascia area (5 mm lateral from spinous process, whole fascia thickness) was determined. Meaning of terms and numbers as in Fig. 2.

significant – increase in both IL and OL. Only when all layers were evaluated together was the increase in fiber density significant (Fig. 4). In a previous investigation of our group on peptidergic fibers in the gastrocnemius–soleus muscle, a significant increase in CGRP- and SP-fiber number was found in inflamed muscle (Reinert et al., 1998).

The mechanism behind the increase in fiber length is not clear. One possibility is sprouting or increased branching of the fibers. In the above study on afferents from inflamed muscle, also NGF-and GAP-43-positive fibers were increased in number, which speaks for sprouting. Whether this mechanism also applies to the TLF is unknown. Another mechanism would be that the

fibers contained more neuropeptides in inflamed fascia so that more fibers became visible.

Considering the general assumption that SP-positive fibers are nociceptive (Raja et al., 1988; Lawson et al., 1997), the increased density of these fibers in the inflamed TLF may indicate a greater pain sensitivity. However, results from behavioral experiments on rats in which the TLF had been inflamed by exactly the same technique (Hoheisel and Mense, 2015) did not yield a lowering in pressure-pain threshold. On the other hand, the dorsal horn neurons in these animals were sensitized by the fascia inflammation and showed increased responsiveness. Apparently, a weak sensitization of dorsal horn neurons may occur without being reflected in the behavior of the rats.

A conspicuous finding was the reduction in fiber length of TH-ir fibers in the OL of the fascia (Fig. 5). The mechanism behind this reduction is likewise obscure. Again, a decreased TH content in the fibers could make them invisible in our staining technique. On the other hand, the entire fiber length measured in PGP 9.5 sections, was likewise reduced in the inflamed fascia. Therefore, the decreased fiber length seems to be due to a real disappearance of some of the TH-positive (and CGRP-positive) fibers in the OL, even though the TH- fibers are just a small fraction of all stained fibers. A general swelling of the TLF as the reason for a (false) decrease in fiber length can be excluded, because there was just a local edema at the injection site of CFA (Figs. 1 and 6). A loss of sympathetic fibers has also been described in synovial tissue of patients with rheumatoid arthritis (Miller et al., 2000). One possible explanation is an inflammation-induced up regulation of certain nerve repellent factors. Semaphorin IV, for instance is known to have specific interactions with the autonomic nervous system (Varela-Echavarria and Guthrie, 1997). Bolden and colleagues (1997) described an antagonistic interaction between the sensory and sympathetic system, they showed that following sympathectomy the CGRP-expression in sensory neurons increased.

Many of the TH-ir fibers, e.g. that shown in Fig. 5, outlined blood vessels and therefore were probably vasoconstrictors. A reduction of these fibers could lead to an increase in local blood flow and thus contribute to the edema of the ML and IL of the inflamed fascia. In the ML, we never found an inflammation-induced change in innervation density, and for all fiber types the density in this layer was zero or close to zero. The latter finding may be due to the fact that the ML consists of thick collagen bundles that probably have to pick up the mechanical forces during trunk movements and move against each other. Therefore, if a receptive ending existed between the bundles it was likely to be squeezed and excited even during normal movements.

Limitations: 1.The course of single fibers was not reconstructed. Therefore no data on possible inflammation-induced changes in branching patterns have been obtained. Evaluations of this kind are planned for the future. 2. The non-peptidergic isolectin B4 (IB4)-ir fibers were not labeled in the present study. Therefore, our data do not show all components of the fascia innervation. However, the results obtained with PGP 9.5 staining give an overview of the entire innervation. 3. PGP9.5 labeling might be less pronounced in functional nerve endings which could be the reason that larger increases in innervation density of PGP9.5-ir nerve endings were not observed. 4. TH is not exclusively a marker for sympathetic nerve fibers. At least in the mouse, cutaneous C-fibers with a low mechanical threshold are also TH-immunoreactive (Li et al., 2011).

CONCLUSION

The inflamed TLF showed an increase of presumably nociceptive fibers, which may explain the pain from a pathologically altered fascia. The meaning of the decreased innervation by sympathetic fibers is obscure at present. Because some free nerve endings may function as proprioceptors, the lack of proprioceptive corpuscular receptors within the TLF does not preclude its role as a proprioceptive structure,

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