Topical Review

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Tendon pain – what are the mechanisms behind it?

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Abstract

Objectives: Management of chronic tendon pain is difficult and controversial. This is due to poor knowledge of the underlying pathophysiology of chronic tendon pain, priorly known as tendinitis but now termed tendinopathy. The objective of this topical review was to synthesize evolving information of mechanisms in tendon pain, using a comprehensive search of the available literature on this topic.

Content: This review found no correlations between tendon degeneration, collagen separation or neovascularization and chronic tendon pain. The synthesis demonstrated that chronic tendon pain, however, is characterized by excessive nerve sprouting with ingrowth in the tendon proper, which corresponds to alterations observed also in other connective tissues of chronic pain conditions. Healthy, painfree tendons are devoid of nerve fibers in the tendon proper, while innervation is confined to tendon surrounding structures, such as sheaths. Chronic painful tendons exhibit elevated amounts of pain neuromediators, such as glutamate and substance p as well as up-regulated expression and excitability of pain receptors, such as the glutamate receptor NMDAR1 and the SP receptor NK1, found on ingrown nerves and immune cells. Increasing evidence indicates that mast cells serve as an important link between the peripheral nervous system and the immune systems resulting in so called neurogenic inflammation.

Summary: Chronic painful tendons exhibit (1) protracted ingrowth of sensory nerves (2) elevated pain mediator levels and (3) up-regulated expression and excitability of pain receptors, participating in (4) neuro-immune pathways involved in pain regulation. Current treatments that entail the highest scientific evidence to mitigate chronic tendon pain include eccentric exercises and extracorporeal shockwave, which both target peripheral neoinnervation aiming at nerve regeneration.

Outlook: Potential mechanism-based pharmacological treatment approaches could be developed by blocking promotors of nerve ingrowth, such as NGF, and promoting inhibitors of nerve ingrowth, like semaphorins, as well as blocking glutamate-NMDA-receptor pathways, which are prominent in chronic tendon pain.

Keywords: mast cells; nerve tissue proteins; neuronal plasticity; pain; receptors; tendon.

Introduction

Chronic tendon pain is a common disabling condition that affects the quality of life for millions of people, leading particularly to impaired limb function and reduced physical activity [1], thus impacting the general health condition of patients [1–4]. Still today, we do not have any effective pharmacological treatments, the main reason being that the underlying pathophysiology of chronic tendon pain has been largely unclear.

Chronic tendon pain is included in the terminology of tendinopathy [1, 5]. Tendinopathy was formerly known as “tendinitis” [6, 7]. However, the etiological origin of inflammation has been questioned over the years and therefore in 1998 the confusing terminology of “tendinitis”
was changed to tendinopathy [8]. Tendinopathy depicts the clinical syndrome of swelling, pain and impaired performance, with chronic pain being the predominant symptom [1].

There are more than 1,000 tendons in our body that potentially can present with chronic tendon pain. Common localizations of tendinopathy include the upper extremities, which are more often affected in work-related situations, whereas tendinopathy of the lower extremities more frequently is related to sports activities (Table 1). Interestingly, chronic tendon pain may evolve also without repetitive loading and therefore a deeper causal understanding is warranted.

The diagnosis of tendinopathy is mostly based on a careful medical history and detailed clinical examination with the aim to determine whether the tendon is the source of pain. Pain induced by loading and stretching of the tendon is pathognomonic for tendinopathy [9].

Diagnostic imaging is mostly used for differential diagnosis, and will not tell whether the tendon is causing pain or not [10]. MRI and ultrasound may depict pathological tissue alterations commonly seen in tendinopathy such as swelling, thickening and increased vascularity. However, tendon pathology displayed on imaging may in individual cases have no correlation to the patient’s symptoms [10].

Establishing the diagnosis of tendinopathy also includes assessments of intrinsic and extrinsic risk factors [2]. Intrinsic factors include biomechanical abnormalities, e.g., limited joint mobility, and systemic, metabolically related disorders such as diabetes, obesity, hypercholesterolemia, inflammatory disorders, and genetic variants [2]. Extrinsic factors include excessive and uneven mechanical loading due to training or work [5, 11]. Moreover, certain drugs, such as corticosteroids, aromatase inhibitors, quinolone antibiotics and statins [12], are known to increase the risk of developing tendinopathy. Therefore, it is essential to be aware and if possible to avoid these drugs and especially combinations of e.g., corticosteroids and quinolones. Accordingly, in- and extrinsic factors must be excluded or handled as part of diagnostics and treatment of tendinopathy [2].

Several hundreds of different treatments have been suggested for chronic tendon pain [1, 13]. However, most treatments are lacking in efficacy for pain relief, the reason being that most treatments are not addressing the underlying pathophysiological mechanisms of tendon pain. Thus, in order to cope with this disappointing situation and improve efficacy for pain relief, treatments must target the actual pain mechanisms in tendons.

The aim of this current topical review was to document and present the pathophysiological mechanisms of action, pain receptors and mediators underlying the development of chronic tendon pain that have recently been identified. This new understanding may allow us to develop new targeted treatments for managing tendon pain.

Methods

The aim of this topical review was to examine the five etiological theories for tendon pain that have been postulated: degeneration, collagen separation, neovascularization, neurogenic source, neuro-immune connection. This was performed by posing the following questions: (1). Do histologic or radiographic findings correlate to tendon pain? (2). Does neovascularization correlate to tendon pain? (3). Does tendon neuroanatomy correlate to tendon pain? (4). Is there a neuro-inflammatory immuno connection in tendon pain? Only original articles about chronic tendon pain and tendinopathy were included. The Web of Science, Scopus and PubMed/MEDLINE databases were searched up to May 26, 2021 using combined terms related to tendon, injury and pain. The following MESH-terms were used: tendon; tendinopathy; rupture; pain; pain mechanism; degeneration; collagen separation; neovascularization; neurogenic; nerve; immune, and a search string was constructed. We additionally used review articles to check that relevant articles were included. Articles in other languages than English were excluded. Identified records were screened by AA and PA according to the eligibility of the aim. Articles were first screened for eligibility based on their title, and then, if needed, based on full text. We then performed a narrative synthesis of this extracted data. The extracted articles were grouped into the five postulated etiological theories for chronic tendon pain. The aquired material was synthesized into relevant underlying mechanism related to chronic tendon pain.

Results

Do histologic or radiographic findings correlate to tendon pain?

Histologically, tendinopathy may display degenerative changes such as disorganization of collagen fibers, increase of collagen type III, increase of extracellular matrix and blood vessel ingrowth into the tendon proper (Figure 1). However, these aforementioned tissue pathologies may also be exhibited in asymptomatic persons [10, 14, 15]. In addition, patients can recover from chronic tendon pain without reversal of imaging-identified tendon pathology [10].

Collagen separation is neither correlated with tendon pain since large asymptomatic ultrasonographic hypoechoic regions (i.e., abnormal collagen) can be found in tendons without a history of pain [16, 17]. Thus, tendon degeneration and separation are not directly
Table 1: Twenty-five of the most common tendons with chronic pain.

| Pain in Upper Extremities | Tendon Diagnosis | Risk Factors |
|---------------------------|------------------|-------------|
| **Shoulder**              |                  |             |
| Lateral                   | Supraspinatus (SP) | SP pain with resistive adduction | Overhead sports and laborers |
| Lateral                   | Deltoid (D)       | D pain with resistive abduction | Winged scapula and head in forward posture |
| Ventral                   | Long head of the biceps (LB) | LB pain with 10 degrees of resistive internal rotation | Worse if sleeping on the shoulder |
| Medial                    | Subscapularis (SS) | SS pain on resistive internal rotation | Overhead throwers |
| Lateral                   | Extensor carpi radialis brevis (ECRB) | ECRB pain on activities that require resisted wrist extension | Tennis or repetitive wrist extension |
| Ventral                   | Biceps (B)       | B Pain on elbow flexion and supination | Men with tobacco and anabolic steroid use |
| Medial                    | Flexor carpi radialis (FCR) | FCR pain on resisted pronation and/or wrist flexion | Golf or repetitive wrist flexion |
| **Elbow**                 |                  |             |
| Radial                    | EPL and APL (de quervain) | Pain on resisted radial deviation/extension of dig. 1 | Hammering, cross country skiing, pregnancy |
| Palmar                    | Finger flexor tendons (trigger finger) | Pain/nodule on the A1 pulley and triggering/locking of finger | Women with diabetes or RA |
| Ulnar                     | Extensor carpi ulnaris (ECU) | ECU pain with gripping activities | More often in nonathletes |

| Pain in Lower Extremities | Tendon Diagnosis | Risk Factors |
|--------------------------|------------------|-------------|
| **Hip**                  |                  |             |
| Lateral                  | Glutes medius (GM,trochanteric bursitis) | GM pain standing on one leg or sleeping on the side | Excessive hip adduction. |
| Ventral                  | Iliopsoas (I)    | I Pain and or clicking/snapping with hip flexion | Women >40 years |
| Medial                   | Adductors (A)    | Pain of a on resistive abduction | Repetitive hip flexion |
| Dorsal                   | Hamstring (H)    | H Pain on terminal hip flexion or prolonged sitting | Sports as soccer, lumbar hyperlordosis |
| **Knee**                 |                  |             |
| Lateral                  | Iliotibial band (ITB) | ITB pain on leg horizontal and adducted. ITB popping. | Runners, friction of ITB on femoral condyle |
| Ventral-distal           | Patellar (PT)    | Pain on proximal insertion of PT on the patella | Young athletes with jumping sports |
| Ventral-proximal         | Quadriceps (Q)   | Pain on distal insertion of Q on the patella | Soccer, volleyball or running |
| Medial-distal            | Pes anserinus (PA) | Pain on PA 5–8 cm below knee joint on e.g., Climbing stairs | Runners, outer-rotation of lower leg |
| Dorsal-lateral           | Popliteus (PO)   | PO pain on resisted knee flexion (15–30°) or internal rotation | Athletes with other knee ligament injuries |
| **Ankle**                |                  |             |
| Lateral                  | Peroneus (P)     | P Pain on eversion and dorsiflexion | Feeling of ankle instability |
| Ventral                  | Tibialis anterior (TA) | TA weakness with dorsiflexion | Runners >45 years |
| Medial                   | Flexor hallucis longus (FHL) | FHL pain with resistive flexion of the great toe | Ballet dancers |
| Medial                   | Tibialis posterior (TP) | TP pain with inversion and planter flexion | Women >40 years |
| Dorsal                   | Achilles tendon (AT) | Mid-portion AT pain with planter flexion | Running |
| Plantar                  | Plantar fascia (PF) | Pain in the proximal PF by passive ankle/first toe dorsiflexion | Obesity |

The table depicts the upper- and lower extremity joints associated with the pain locations, risk factors and diagnostic tests that will render suspicion on one of the twenty-five most common tendons that are the origin of chronic pain.
correlated with tendon pain similarly as joint degeneration not is correlated with pain in osteoarthritis [18, 19].

Does neovascularization correlate to tendon pain?

In the healthy tendon proper there are no visible blood vessels, but in tendinopathy blood vessels grow into the tendon proper (Figures 1, 2). Several studies, however, demonstrate no correlation between blood vessel ingrowth and increased flow detected with power Doppler sonography and pain or changes in function [14, 20–23]. To further confirm these data, contrast-enhanced ultrasound has been used, which found more abundant neovascularization in tendinopathy compared to non-contrast ultrasound. However, there was no correlation to symptoms of pain [14].

Does tendon neuroanatomy correlate to tendon pain?

The nerve supply of intact healthy tendons is localized in the tendon sheath, whereas the tendon proper, i.e., intrafascicular matrix, is devoid of innervation (Figures 2, 3) [24]. This anatomical finding implicates that the tendon sheath is regulating acute episodes of tendon pain.
After tendon injury and during repair, extensive nerve ingrowth into the tendon proper has been found [24]. This nerve ingrowth was followed by a time-dependent expression of different neuronal mediators, which regulated healing pathways and nociceptive behaviour as demonstrated in a rat tendon healing model [25]. After tendon healing was completed, the nerve fibers retracted to the tendon envelope and nociception subsided [25].

In chronic painful tendons, excessive and protracted nerve sprouting with ingrowth into the tendon proper has been discovered (Figure 2) [24, 26–33]. This protracted nerve ingrowth exhibits a dysregulated expression of different mediators involved in pro-inflammatory, hypertrophic and nociceptive tissue responses (Table 2) (Figure 3) [34]. Among the sensory neuropeptides found upregulated in painful tendons, substance P (SP), has demonstrated effects on cell proliferation related to degenerative changes associated with tendinopathy, in addition to pro-inflammatory and pain-triggering mechanisms (Figures 2, 4) [35–37].

Tendons also exhibit autonomic- and glutamate signaling that may be involved in several persistent pain conditions. Accordingly, elevated levels of glutamate have been detected in patients with tendinopathy [38, 39] occurring in sprouting nerve fibers, which may represent glutamate involvement in nerve ingrowth and nociception [39–41].

Furthermore, painful tendons also exhibit upregulated expression of receptors for sensory, autonomic and excitatory mediators [24] (Table 2). The SP-receptor (neurokinin 1, NK1) was found up-regulated in painful tendons [42], and involved in up-regulation [40] and activation [43] of the excitatory glutamate receptor N-methyl-D-aspartate receptor 1 (NMDAR1), implicated in various pain disorders (Figure 4). Thus, in painful tendinopathy, a significant up-regulation of NMDA1 (9-fold) and of the activated receptor, Phospho-NMDAR (5-fold), has been found [39, 40].
Is there a neuro-inflammatory immuno connection in tendon pain?

One key effector cell in inflammation is the mast cell, which serves as an important link between the peripheral nervous system and the immune system [44–46]. These immune cells can be found in close proximity to peripheral nerve endings and are one of the first to respond to sensory nerve activation [47, 48]. In support for a nerve-mast cell axis, the SP-receptor NK1 has been identified on mast cells [49].

Recently it was demonstrated that glutamate also exhibits a signaling pathway to mast cells, when the expression of glutamate receptor on mast cells was

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Table 2: Neuromediator: receptor pathways in painful tendons.

| Type                      | SUB-TYPE                  | Mediator         | Receptor                          | Actions on nerve fibers  | Actions on immune system |
|---------------------------|---------------------------|------------------|-----------------------------------|--------------------------|--------------------------|
| Sensory                   | Sensory                   | SP↑              | NK1↑                              | Sensitizing              | Pro-inflammatory          |
|                           |                           | CGRP↑            | CRLR, RAMP-1                      |                          |                          |
| Opioid and opioid like    | Enkephalins               | Enkephalins      | δ-opioid receptor                 | Desensitizing            | Anti-inflammatory         |
|                           | Cannabinoids              | Cannabinoids     | CB1↑                              |                          |                          |
|                           | Opioid like: GAL, SOM    | GalR1-3α, SSTR1-5α |                          |                          |                          |
| Autonomic                 | Sympathetic              | Noradrenaline↓   | α-,β- adrenoceptors↑              |                          |                          |
|                           |                           | Acetylcholine↑   | Y1↑                              |                          |                          |
|                           |                           | VIP↑             | Nicotinic↑                        |                          |                          |
|                           |                           | VPAC1-2α, PAC1α  | VPAC1-2α, PAC1α                   |                          |                          |
| Excitatory                | Glutamatergic amino acid | Glutamate↑       | NMDA1↑                            | Sensitizing              | Pro-inflammatory          |
|                           |                           |                  | Phosfo-NMDA1↑                     |                          |                          |
|                           |                           |                  | mGluR1↑                           |                          |                          |

The table describes the type and sub-type of mediators and receptors, which have been identified dysregulated in chronic painful tendons, and their actions on peripheral nerve fibers and immune cells. ↑, mediators/receptors that are upregulated in painful tendons; ↓, mediators/receptors that are downregulated in painful tendons; →, mediators/receptors that are equal amount in painful and non-painful tendons; SP, substance P; NK1, neurokinin 1; CGRP, calcitonin gene-related peptide; CRLR, calcitonin receptor-like receptor; RAMP-1, receptor activity-modifying protein 1; CB1, Cannabinoid receptor type 1; GAL, Galanin; SOM, Somatostatin; GALR1-3, Galanin receptor 1–3; SSTR1-5, Somatostatin receptor 1–5; NPY, Neuropeptide Y; VIP, Vasoactive intestinal peptide; VPAC1-2, Vasoactive intestinal peptide receptor 1–2; PAC1, Pituitary adenylate cyclase-activating peptidergic receptor; NMDA, N-methyl-D-aspartate receptor; mGluR, Metabotropic glutamate receptor.

aNot yet assessed in tendon. bC-fibers and A-fibers. The immune system includes a variety of cells, e.g., Mast cells. This figure was modified and adapted with permission from Ackermann et al. 2016 [24].

Figure 4: Pain receptor/mediator up-regulation (A-C). Micrographs of tendon biopsies from a patient with a painful patellar tendinopathy (A-C). Immunostaining demonstrates expression of the pain receptor (A), N-methyl-D-aspartate receptor type 1 (NMDAR1), on the pathological ingrowth of sensory, substance P (SP) positive, nerves (B) seen in the intra-fascicular matrix. The yellow immunoreactivity shows co-existence of SP and NMDAR1 (C) displayed on the nerve fibers sprouting within the tendon proper. SP was shown to up-regulate NMDAR1 [40] and also to activate NMDAR1 by removing the magnesium block and thereby increasing the excitability of NMDAR1 [43]. Micrographs of longitudinal sections through patellar tendinopathy biopsies stained for NMDAR1 (Cy2 green; A) and SP (Cy3 red; B) as well as double-stained NMDAR1-SP; NMDAR1-PGP 9.5 co-existence (yellow, merged) respectively. Bar, 50 μm (These figures are previously unpublished).
established by both in-vivo and in-vitro studies (Figure 5) [50, 51]. Exposure of mouse mast cells to glutamate activates a transient expression of a range of glutamate receptors [51], and also resulted in an increased level of pro-inflammatory cytokines/chemokines, introducing the concept of a glutamate-glutamate receptor axis in mast cells, which can contribute to neurogenic inflammation and pain regulation in the tendon. Glutamate stimulation of mast cells resulted in upregulated expression of a number of transcription factors, in particular FosB (Figure 5) [51], which is implicated in pain regulation. Altogether, glutamate signaling and its various receptor involvement may evolve as a potential pathogenic mechanism operative in tendon pain [52].

Discussion

This topical review found no correlations between radiological and histological tissue alterations including neo-vascularization and chronic tendon pain. Substantial evidence, however, was found suggesting that chronic painful tendons exhibit (1) protracted ingrowth of sensory nerves (2) elevated pain mediator levels and (3) up-regulated expression and excitability of pain receptors, which participate in a (4) neuro-immune pathways involved in pain regulation.

Sensory nerve sprouting, regulated by NGF [53], with ingrowth into pathologic tendons seem to represent an important pain mechanism. Interestingly, this pain

Figure 5: Neuro-immuno connection with transcriptional factor in the control and injured tendinopathy tendon (A-G). Immunofluorescence image showing increased colocalization of FosB and MC tryptase (Mcp16) in the painful injured Achilles tendon (B) compared to the control tendon (A). Immunofluorescence images showing colocalization of FosB and glutamate in the control (C) and painful injured tendon (D). Note the abundance of cells double positive for FosB and glutamate in the injured tendinopathy, but not in the control tendon. In the right panel (E-G), MC tryptase (E, green) and glutamate receptor NMDAR1 (F, red) are colocalized (G, yellow) in the injured tendinopathy tissue. Scale bars: 100 μm. Reproduced with permission from Alim et al. 2017, 2020 [50, 86].
mechanism seem generalized since other painful dense connective tissue disorders exhibit similar pathophysiology, with nerve ingrowth into normally aneuronal tissue. Thus, in chronic low back pain, sensory nerve ingrowth into the normally non-innervated intervertebral disc has likewise been identified as a pain-generating mechanism [54]. Also in unspecific muscular low back pain conditions as well as pain conditions of the fascia, nerve ingrowth has been observed in normally aneuronal rat fascia tissue [55].

Other tissues that lack sensory innervation during normal conditions include healthy articular cartilage, subchondral bone marrow and meniscus. Accordingly, ingrowth of nerve fibers into these tissues has been established, and such nerve ingrowth has been suggested as a potential origin of pain in osteoarthritis [56–58]. Nerve ingrowth into synovial tissue joint tissue was furthermore regulated by NGF and it was shown that anti-NGF treatment decreased both nerve ingrowth and pain-related behavior in a mouse model [58].

Sensory nerve ingrowth into normally aneuronal tendon tissue has the potential to generate nociception in response to mechanical, thermal or chemical stimuli. Thus, many patients experience pain only on mechanical activation, i.e., exercise, of their tendons. In the progression of the disease, patients may additionally feel a lingering pain after the exercise is finished, indicating a sensitization of nociceptors. The patients’ differential experience of pain may thus be explained by alterations of both the amount of nociceptive mediators and nociceptors as well as sensitization of the peripheral and central nervous system [9, 59].

Current treatments of chronic tendon pain, which entail the highest scientific evidence, include eccentric exercises, i.e., muscle lengthening exercises under load, and extracorporeal shockwave therapy (ESWT), i.e., non-invasive acoustic shock waves leading to re-injury/regeneration of bone or soft tissue [1, 60]. Intriguingly, these treatments are both locally applied and target the peripheral nervous system, which seems to strengthen the conception of protracted neoinnervation as a driver of tendon pain.

Eccentric exercise has been called “probably the greatest single advance in the management of tendinopathy in the past 20 years” and many rehabilitation programs have been developed for different tendons [61, 62]. An interesting notion regarding eccentric exercise is that it has been demonstrated to stimulate synthesis of different neurotrophic substances such as NGF and BDNF both in muscles and tendons [42, 63–65]. Activation of neurotrophic pathways is related to survival and neuroregeneration of peripheral neurons [63, 64]. Whether eccentric exercise specifically can modulate nerve ingrowth, release of nociceptive mediators and up-regulation of peripheral nociceptors is mostly unknown. Eccentric exercise has, however, been demonstrated to activate the peripheral nervous system with release of neuropeptides [66], to modulate nerve plasticity, retraction and regeneration during healing [67] after injury [63, 64].

ESWT has recently been demonstrated to be efficient both as single therapy as well as in combination with eccentric exercise in chronic tendon pain [60, 68–70]. Interestingly, the most important effect of ESWT has been demonstrated to affect the peripheral nervous system by selective denervation of sensory, unmyelinated nerve fibers [71]. These data suggest a specific mechanism to target the pain mechanism in tendon, namely nerve ingrowth.

Given the identification of protracted nerve ingrowth as a predominant mechanism underlying chronic tendon pain, the question arises if drug therapies could be developed by targeting promotors and inhibitors of nerve ingrowth? Promotors of nerve ingrowth that have been identified include e.g., NGF and BDNF, while inhibitors of nerve ingrowth include semaphorins [72] and neuropilins [73].

NGF inhibitors in the form of anti-NGF monoclonal antibodies, are already present as hot drug candidates used in clinical trials and are projected to become the emerging treatment option for chronic pain conditions. Importantly, blockade of NGF will target all pain mechanisms shown in tendons by inhibition of NGF-stimulated: (1) nerve ingrowth, (2) synthesis of nociceptive mediators, (3) nociceptor transport and (4) mast cell degranulation. However, such NGF inhibitors have been on hold by the FDA in US due to development of osteoarthritis [74–77]. The mechanisms for developing osteoarthritis with anti-NGF are not fully explored, but may include excessive wear and tear in the absence of joint pain or/and that anti-NGF blocks pathways involved in neuronal regulation of tissue homeostasis [75, 77]. Thus, anti-NGF therapy has not yet been tested for chronic tendon pain.

Since anti-NGF therapy seems associated with certain side-effects, perhaps a more targeted blocking of nociceptive mediator-receptor pathways could have an ameliorating impact on pain without pronounced side-effects? One of the most prominent pathways in chronic tendon pain is that of the SP:NK1 axis, where both the mediator and receptor are up-regulated. The concept that NK1 receptor blockers would represent a novel class of analgesic drugs, as suggested by the preclinical studies, has however not been confirmed by the clinical trials that have been reported thus far [78].
Glutamate signaling arises as the second pathway with a potential pathogenic mechanism operative in chronic tendinopathy. Strategies to target both glutamate and its receptor, which both are upregulated in tendinopathy, could thereby represent potential therapeutic options in tendon pain disorders. NMDAR is the glutamate receptor that has been highlighted in a multitude of chronic pain conditions [79, 80]. There are several potent NMDA-receptor antagonists available, e.g., Ketamine, however most are associated with side effects in the central nervous system. Ways to overcome these side-effects could include more specific drug-targets for the peripheral nervous system, which could be locally administered. Ketamine has positive local effects when applied peripherally in low doses and should be further studied when it comes to tendinopathy.

Targeting the NMDA receptor with specific antagonists could, in addition to having direct effects on nociceptive transmission in nerves, affect the NMDA receptor on mast cells and thereby hinder the degranulation-dependent release of sensitizing substances [50, 51]. However, further studies are required to fully understand how the inhibition of glutamate signaling and/or mast cells can affect tendon pain.

The mechanisms presented in this article provides a basis for a mechanism-based treatment approach where pharmacological treatments could be developed by targeting promoters of nerve ingrowth such as NGF and BDNF as well as inhibitors of nerve ingrowth like semaphorins and neuropilins. Possible pharmacological treatment targets are also the SP:NK1 or the glutamate-NMDA-receptor pathways, both of which are prominent in chronic tendon pain.

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References

1. Millar NL, Silbernagel KG, Thorborg K, Kirwan PD, Galatz LM, Abrams GD, et al. Tendinopathy. Nat Rev Dis Prim 2021;7:1.
2. Ackermann PW, Hart DA. General overview and summary of concepts regarding tendon disease topics addressed related to metabolic disorders. Adv Exp Med Biol 2016;920:293–8.
3. Vicenzino B, de Vos RJ, Alfredson H, Bahr R, Cook JL, Coombes BK, et al. ICON 2019 international Scientific tendinopathy symposium consensus: there are nine core health-related domains for tendinopathy (CORE DOMAINS): delphi study of healthcare professionals and patients. Br J Sports Med 2020;54:444–51.
4. Hopkins C, Fu SC, Chua E, Hu X, Rolf C, Mattila VM, et al. Critical review on the socio-economic impact of tendinopathy. Asia Pac J 2016;4:9–20.
5. Riley G. Tendinopathy—from basic science to treatment. Nat Clin Pract Rheumatol 2008;4:82–9.
6. Khan KM, Cook JL, Kannus P, Maffulli N, Bonar SF. Time to abandon the “tendinitis” myth. BMJ 2002;324:626–7.
7. Scott A, Squier K, Alfredson H, Bahr R, Cook JL, Coombes B, et al. ICON 2019: international scientific tendinopathy symposium consensus: clinical terminology. Br J Sports Med 2020;54:260–2.
8. Maffulli N. Overuse tendon conditions: time to change a confusing terminology. Arthrosc J Arthrosc Relat Surg 1998;14:840–3.
9. Rio E, Moseley L, Purdam C, Samiric T, Kidgell D, Pearce AJ, et al. The pain of tendinopathy: physiological or pathophysiological? Sports Med 2014;44:9–23.
10. Docking SI, Ooi CC, Connell D. Tendinopathy: is imaging telling us the entire story? J Orthop Sports Phys Ther 2015;45:842–52.
11. Magnussen SP, Langberg H, Kjaer M. The pathogenesis of tendinopathy: balancing the response to loading. Nat Rev Rheumatol 2010;6:262–8.
12. Knobloch K. Drug-induced tendon disorders. Adv Exp Med Biol 2016;920:229–38.
13. Acicale R, Bisaccia RD, Oliviero A, Oliva F, Maffulli N. Current pharmacological approaches to the treatment of tendinopathy. Expert Opin Pharmacother 2020;21:1467–77.
14. De Marchi A, Pozza S, Cenna E, Cavallo F, Gays G, Simbula L, et al. Achilles tendinopathy, the neovascularization, detected by contrast-enhanced ultrasound (CEUS), is abundant but not related to symptoms. Knee Surg Sports Traumatol Arthrosc 2018;26:2051–8.
15. de Jonge S, van den Berg C, de Vos RJ, van der Heide HJ, Weir A, Verhaar JA, et al. Incidence of midportion Achilles tendinopathy in the general population. Br J Sports Med 2011;45:1026–8.
16. Cook JL, Khan KM, Harcourt PR, Kiss ZS, Fehmann MW, Griffiths L, et al. Patellar tendon ultrasonography in asymptomatic active athletes reveals hypoechoic regions: a study of 320 tendons. Victorian institute of sport tendon study group. Clin J Med Sci Sports 1996;6:291–6.
17. Lian Ø, Holen KJ, Engebretsen L, Bahr R. Relationship between symptoms of jumper’s knee and the ultrasound characteristics of the patellar tendon among high level male volleyball players. Scand J Med Sci Sports 1996;6:291–6.
18. de Vos RJ, van Osch GJ, Bierna-Zeinhaagan S, Verhaar JA. Tendinopathy and osteoarthritis: a chance to kill two birds with one stone. Br J Sports Med 2016;50:1164–5.
19. Vincent TL. Peripheral pain mechanisms in osteoarthritis. Pain 2020;161(1 Suppl):S138–46.
20. de Vos RJ, Weir A, Tol JL, Verhaar JA, Weinans H, van Schie HT. No effects of PRP on ultrasonographic tendon structure and neovascularisation in chronic midportion Achilles tendinopathy. Br J Sports Med 2011;45:387–92.
21. Sengkerij PM, de Vos RJ, Weir A, van Weelde BJ, Tol JL. Interobserver reliability of neovascularization score using power Doppler ultrasonography in midportion achilles tendinopathy. Am J Sports Med 2009;37:1627–31.
22. van Snellenberg W, Wiley JP, Brunet G. Achilles tendon pain intensity and level of neovascularization in athletes as determined by color Doppler ultrasound. Scand J Med Sci Sports 2007;17:930–4.

23. Tol JL, Spiezia F, Maffulli N. Neovascularization in Achilles tendinopathy: have we been chasing a red herring? Knee Surg Sports Traumatol Arthrosc 2012;20:1891–4.

24. Ackermann PW, Salo P, Hart DA. Tendon innervation. Adv Exp Med Biol 2016;920:35–51.

25. Ackermann PW, Li J, Lundeborg T, Kreicbergs A. Neuronal plasticity in relation to nociception and healing of rat Achilles tendon. J Orthop Res 2003;21:432–41.

26. Schubert TE, Weidler C, Lerch K, Hofstädter F, Straub RH. Achilles tendinosis is associated with sprouting of substance P positive nerve fibres. Ann Rheum Dis 2005;64:1083–6.

27. Alfredson H, Ohberg L, Forsgren S. Is vascular-neural ingrowth the cause of pain in chronic Achilles tendinosis? An investigation using ultrasonography and colour Doppler, immunohistochemistry, and diagnostic injections. Knee Surg Sports Traumatol Arthrosc 2003;11:334–8.

28. Xu Y, Bonar F, Murrell GA. Neoinnervation in rotator cuff tendinopathy. Am J Sports Med 2006;34:1801–8.

29. Xu Y, Bonar F, Murrell GA. Neoinnervation in rotator cuff tendinopathy. Sports Med Arthrosc Rev 2011;19:354–9.

30. Ljung BO, Forsgren S, Fridén J. Sympathetic and sensory innervations are heterogeneously distributed in relation to the blood vessels at the extensor carpi radialis brevis muscle origin of man. Cells Tissues Organs 1999;165:45–54.

31. Spang C, Alfredson H. Richly innervated soft tissues covering the superficial aspect of the extensor origin in patients with chronic painful tennis elbow - implication for treatment? J Musculoskelet Neuronal Interact 2017;17:97–103.

32. Hackett L, Millar NL, Lam P, Murrell GA. Are the symptoms of calcific tendinitis due to neoinnervation and/or neovascularization? J Bone Jt Surg Am Vol 2016;98:186–92.

33. Xu Y, Bonar F, Murrell GA. Enhanced expression of neuronal proteins in idiopathic frozen shoulder. J Shoulder Elbow Surg 2012;21:1391–7.

34. Ackermann PW, Phisitkul P, Pearce CJ. Achilles tendinopathy – pathophysiology: state of the art. Orthop J Sports Med 2018;3:304–13.

35. Nilsson J, von Euler AM, Dalsgaard CJ. Stimulation of connective tissue cell growth by substance P and substance K. Nature 1985;315:61–3.

36. Tran PHT, Malmgard-Clausen NM, Puggaard RS, Svensson RB, Nybing JD, Hansen P, et al. Early development of tendinopathy in humans: sequence of pathological changes in structure and tissue turnover signaling. Faseb J 2020;34:776–88.

37. Oh SY, Kim DK, Han SH, Lee HJ, Jeong Y, Baek M, et al. Sustained exposure of substance P causes tendinopathy. Int J Mol Sci 2020;21:8633.

38. Alfredson H, Forsgren S, Thorsen K, Lorentzon R. In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper’s knee. J Orthop Res 2001;19:881–6.

39. Schizas N, Lian Ø, Frihagen F, Engebretsen L, Bahr R, Ackermann PW. Coexistence of up-regulated NMDA receptor 1 and glutamate on nerves, vessels and transformed tenocytes in tendinopathy. Scand J Med Sci Sports 2010;20:208–15.

40. Schizas N, Weiss R, Lian Ø, Frihagen F, Bahr R, Ackermann PW. Glutamate receptors in tendinopathic patients. J Orthop Res 2012;30:1447–52.

41. Scott A, Alfredson H, Forsgren S. VGlut2 expression in painful Achilles and patellar tendinosis: evidence of local glutamate release by tenocytes. J Orthop Res 2008;26:685–92.

42. Bring D, Reno C, Renstrom P, Salo P, Hart D, Ackermann P. Prolonged immobilization compromises up-regulation of repair genes after tendon rupture in a rat model. Scand J Med Sci Sports 2010;20:411–7.

43. Madden DR. The structure and function of glutamate receptor ion channels. Nat Rev Neurosci 2002;3:91–101.

44. Chen CC, Grimalde-Boston MA, Tsai M, Weissman IL, Galli SJ. Identification of mast cell progenitors in adult mice. P Natl Acad Sci USA 2005;102:11408–13.

45. Dahlín JS, Hallgren J. Mast cell progenitors: origin, development and migration to tissues. Mol Immunol 2015;63:9–17.

46. Kitamura Y, Shimada M, Hatanaka K, Miyano Y. Development of mast-cells from grafted bone-marrow cells in irradiated mice. Nature 1977;268:442–3.

47. Green DP, Limjunixawong N, Gour N, Pandir P, Dong X. A mast-cell-specific receptor mediates neurogenic inflammation and pain. Neuron 2019;101:412–20.e3.

48. Dothel G, Barbaro MR, Boudin H, Vasina V, Cremon C, Gargano L, et al. Nerve fiber outgrowth is increased in the intestinal mucosa of patients with irritable bowel syndrome. Gastroenterology 2015;148:1002–11.e4.

49. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J Pain 2013;14:1289–303.

50. Alim MA, Ackermann PW, Eliasson P, Blomgran P, Kristansson P, Peijler G, et al. Increased mast cell degranulation and co-localization of mast cells with the NMDA receptor-1 during healing after Achilles tendon rupture. Cell Tissue Res 2017;370:451–60.

51. Alim MA, Grujic M, Ackermann PW, Kristansson P, Blomgran P, Eliasson P, et al. Correction to: glutamate triggers the expression of functional ionotropic and metabotropic glutamate receptors in mast cells. Cell Mol Immunol 2020;17:1117.

52. Crupi R, Impellizzeri D, Cuzzocrea S. Role of metabotropic glutamate receptors in neurological disorders. Front Mol Neurosci 2019;12:20.

53. Barker PA, Mantyh P, Arendt-Nielsen L, Viktrup L, Tive L. Nerve growth factor signaling and its contribution to pain. J Pain Res 2020;13:e412–e419.

54. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O’Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet 1997;350:178–81.

55. Hoheisel U, Rosner J, Mense S. Innervation changes induced by inflammation of the rat thoracolumbar fascia. Neuroscience 2015;300:351–9.

56. Eitner A, Hofmann GO, Schaible HG. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. Front Mol Neurosci 2017;10:349.

57. Suri S, Gill SE, Massena de Camín S, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis 2007;66:1423–8.
58. Ghilardi JR, Freeman KT, Jimenez-Andrade JM, Coughlin KA, Kaczmarska MJ, Castaneda-Corral G, et al. Neuroplasticity of sensory and sympathetic nerve fibers in a mouse model of a painful arthritic joint. Arthritis Rheum 2012;64:2223–32.

59. Plaza-Manzano G, Rios-Leon M, Martin-Casas P, Arendt-Nielsen L, Fernandez-de-Las-Penas C, Ortega-Santiago R. Widespread pressure pain hypersensitivity in musculoskeletal and nerve trunk areas as a sign of altered nociceptive processing in unilateral plantar heel pain. J Pain 2019;20:6–7.

60. Fan Y, Feng Z, Cao J, Fu W. Efficacy of extracorporeal shock wave therapy for achilles tendinopathy: a meta-analysis. Orthop J Sports Med 2020;8:2325967120903430.

61. Rees J, Maffulli N, Cook J. Management of tendinopathy. Am J Sports Med 2009;37:1855–67.

62. Woodley BL, Newsham-West RJ, Baxter GD. Chronic tendinopathy: effectiveness of eccentric exercise. Br J Sports Med 2007;41:188–99.

63. Martins DF, Martins TC, Batisti AP, Dos Santos Leonel L, Bobinski F, Belmonte LAO, et al. Long-term regular eccentric exercise decreases neuropathic pain-like behavior and improves motor functional recovery in an axonotmesis mouse model: the role of insulin-like growth factor-1. Mol Neurobiol 2018;55:6155–68.

64. Kami K, Tajima F, Senba E. Exercise-induced hypoalgesia: potential mechanisms in animal models of neuropathic pain. Anat Sci Int 2017;92:79–90.

65. Hyldahl RD, Hubal MJ. Lengthening our perspective: morphological, cellular, and molecular responses to eccentric exercise. Muscle Nerve 2014;49:155–70.

66. Jonhagen S, Ackermann P, Saartok T, Renstrom PA. Calcitonin gene related peptide and neuropeptide Y in skeletal muscle after eccentric exercise: a microdialysis study. Br J Sports Med 2006;40:264–7.

67. Bring DK, Kreicbergs A, Renstrom PA, Ackermann PW. Physical activity modulates nerve plasticity and stimulates repair after Achilles tendon rupture. J Orthop Res 2007;25:164–72.

68. Liao CD, Xie GM, Tsauo JY, Chen HC, Liou TH. Efficacy of extracorporeal shock wave therapy for knee tendinopathies and other soft tissue disorders: a meta-analysis of randomized controlled trials. BMC Musculoskel Disord 2018;19:278.

69. Gerdesmeyer L, Mittermayr R, Fuerst M, Al Muderis M, Thiele R, Saxena A, et al. Current evidence of extracorporeal shock wave therapy in chronic Achilles tendinopathy. Int J Surg 2015;24:154–9.

70. Wilson M, Stacy J. Shock wave therapy for Achilles tendinopathy. Curr Rev Musculoskelet Med 2010;4:6–10.

71. Hausdorf J, Lemmens MA, Kaplan S, Marangoz C, Milz S, Odaci E, et al. Extracorporeal shockwave application to the distal femur of rabbits diminishes the number of neurons immunoreactive for substance P in dorsal root ganglia L5. Brain Res 2008;1207:96–101.

72. Kanemaru H, Yamada Y, Ohazama A, Maeda T, Seo K. Semaphorin 3A inhibits nerve regeneration during early stage after inferior alveolar nerve transection. Sci Rep 2019;9:4245.

73. Bear MF, Connors BW, Paradiso MA. Neuroscience: exploring the brain, 3rd ed. Philadelphia, Baltimore, New York, London: LWW Lippincott, Williams & Wilkins; 2016:699 p.

74. Wood JN. Nerve growth factor and pain. N Engl J Med 2010;363:1572–3.

75. Ackermann PW. Katz et al., Efficacy and safety of tanezumab in the treatment of chronic low back pain [Pain 2011;152:2248–2258] and Hill, blocking the effects of NGF as a route to safe and effective pain relief - fact or fancy? [Pain 2011;152:2200–2201]. Pain 2012;153:1128–9.

76. Katz N, Borenstein DG, Birbara C, Bramson C, Nemeth MA, Smith MD, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. Pain 2011;152:2248–58.

77. Hill R. Blocking the effects of NGF as a route to safe and effective pain relief - fact or fancy? Pain 2011;152:2200–1.

78. Alvaro G, Di Fabio R. Neurokinin 1 receptor antagonists—current prospects. Curr Opin Drug Discov Dev 2007;10:613–21.

79. Chang DS, Raghavan R, Christiansen S, Cohen SP. Emerging targets in treating pain. Curr Opin Anaesthesiol 2015;28:379–97.

80. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of inflammatory mechanisms in inflammatory effects of relevance to the pathophysiology of tendinopathy. Arthritis Res Ther 2013;15:R184.

81. Ahmed AS, Li J, Abdul AM, Ahmed M, Östenson CG, Salo PT, et al. Compromised neurotrophic and angiogenic regenerative capability during tendon healing in a rat model of type-II diabetes. PLoS One 2017;12:e0170748.

82. Millar NL, Murrell GA, McInnes IB. Inflammatory mechanisms in tendinopathy - towards translation. Nat Rev Rheumatol 2017;13:110–22.

83. Behzad H, Sharma A, Mousavizadeh R, Lu A, Scott A. Mast cells exert pro-inflammatory effects of relevance to the pathophysiology of tendinopathy. Arthritis Res Ther 2013;15:R184.

84. Ahmed AS, Li J, Abdul AM, Ahmed M, Östenson CG, Salo PT, et al. Compromised neurotrophic and angiogenic regenerative capability during tendon healing in a rat model of type-II diabetes. PLoS One 2017;12:e0170748.

85. Nagura N, Kenmoku T, Uchida K, Nakawaki M, Inoue G, Takaso M. The role of sensory and sympathetic nerve fibers in a mouse model of axonotmesis. Cells 2020;9:1134.