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REVIEW ARTICLE

The Pain of Tendinopathy: Physiological or Pathophysiological?

Ebonie Rio · Lorimer Moseley · Craig Purdam · Tom Samiric · Dawson Kidgell · Alan J. Pearce · Shapour Jaberzadeh · Jill Cook

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Abstract Tendon pain remains an enigma. Many clinical features are consistent with tissue disruption—the pain is localised, persistent and specifically associated with tendon loading, whereas others are not—investigations do not always match symptoms and painless tendons can be catastrophically degenerated. As such, the question 'what causes a tendon to be painful?' remains unanswered. Without a proper understanding of the mechanism behind tendon pain, it is no surprise that treatments are often ineffective. Tendon pain certainly serves to protect the area—this is a defining characteristic of pain—and there is often a plausible nociceptive contributor. However, the problem of tendon pain is that the relation between pain and evidence of tissue disruption is variable. The investigation into mechanisms for tendon pain should extend beyond local tissue changes and include peripheral and central mechanisms of nociception modulation. This review integrates recent discoveries in diverse fields such as histology, physiology and neuroscience with clinical insight to present a current state of the art in tendon pain. New hypotheses for this condition are proposed, which focus on the potential role of tenocytes, mechanosensitive and chemosensitive receptors, the role of ion channels in nociception and pain and central mechanisms associated with load and threat monitoring.

E. Rio (✉) · S. Jaberzadeh · J. Cook
Department of Physiotherapy, Faculty of Medicine, Nursing and Health Sciences, School of Primary Health Care, Monash University, Peninsula Campus, PO Box 527, Frankston, VIC 3199, Australia
e-mail: ebonie.scase@monash.edu

L. Moseley
Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia

C. Purdam
Department of Physical Therapies, Australian Institute of Sports, Bruce, ACT, Australia

T. Samiric
School of Public Health and Human Biosciences, La Trobe University, Melbourne, VIC, Australia

D. Kidgell
School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC, Australia

A. J. Pearce
Faculty of Health, School of Psychology, Deakin University, Burwood, VIC, Australia

1 Introduction

Tendon pain is baffling for clinicians and scientists alike. It is difficult to understand why it is so persistent and why it comes and goes with little reason. Scientifically this translates to the absence of a clear mechanism that can explain the clinical features of tendon pain. It is therefore no surprise that treatments for tendon pain are often ineffective [1–4].

Tendinopathy, the clinical syndrome of pain and dysfunction in a tendon, is often a chronic condition. Like other chronic pain conditions, in tendinopathy there is disconnect between tissue damage seen on clinical imaging and clinical presentation, which creates confusion for both patients and clinicians. However, key features of tendon pain are different from other chronic pain conditions. The purpose of this review is to (i) explore the clinical questions surrounding tendon pain; (ii) summarise what is known about tendon pain; and (iii) examine evidence from relevant fields to provide direction for future research.

1.1 Clinical Features of Tendon Pain

The clinical presentation of tendinopathy includes localised tendon pain with loading [5–7], tenderness to palpation [8] and impaired function [9–11]. Pain defines the clinical presentation [10], regardless of the degree of tendon pathology. Tendinopathy, despite being an umbrella term, is usually limited to intra-tendinous presentations, with more specific terminology being applied to pathology in surrounding tissue with different disease processes, such as paratendinitis [10]. Microscopic examination of tissue biopsies from painful tendon reveals variable features of tendon pathology, including collagen disorientation, disorganisation and fibre separation, increased proteoglycans (PG) and water, increased prominence of cells, and areas with or without neovascularisation, which collectively are termed tendinosis [12]. Many imaging studies (i.e. ultrasound, magnetic resonance imaging) indicate that these changes can exist in the tendon without pain, and people without symptoms rarely present clinically. Therefore, tendinosis may be an incidental examination finding and does not in itself constitute the diagnosis of tendinopathy, which requires clinical symptoms [10].

Tendon pain has a transient on/off nature closely linked to loading, and excessive energy storage and release in the tendon most commonly precedes symptoms [13–16]. Pain is rarely experienced at rest or during low-load tendon activities; for example, a person with patellar tendinopathy will describe jumping as exquisitely painful yet not experience pain with cycling because of the different demands on the musculotendinous unit. A further characteristic pain pattern is that the tendon 'warms up', becoming less painful over the course of an activity, only to become very painful at variable times after exercise [7].

1.2 Defining Pain Concepts

Clinicians and researchers distinguish between physiological and pathophysiological pain. Physiological or 'nociceptive' pain is considered to reflect activation of primary nociceptors following actual or impending tissue damage or in association with inflammation. This type of pain is a helpful warning sign and is considered to be of evolutionary importance. Pathophysiological pain is associated with functional changes within the nervous system, such as ectopic generation of action potentials, facilitation of synaptic transmission, loss of synaptic connectivity, formation of new synaptic circuits, and neuroimmune interactions as well as cortical topographical changes [17], making it resistant to tissue-based treatments and it appears to provide no evolutionary advantage or helpful warning.

Some aspects of tendinopathy fit more clearly into pathophysiological pain. Painful tendons can have little pathology [18, 19] and pain can persist for years [20]. Furthermore, pain during tendon rehabilitation exercises has been encouraged [21–24] and may not be deleterious [25], providing evidence that tendon pain does not necessarily equate with tissue damage. Overuse tendon injury does not involve an inflammatory process with a clear endpoint that underpins most physiological pain (see Sect. 2.3 for more detail). However, other aspects of tendinopathy fit more clearly into physiological pain—pain remains confined to the tendon [8] and is closely linked temporally to tissue loading [26]. A clinical presentation that fails to be explained by either pain state classification is the rupture of a pathological yet pain-free tendon, where nociceptive input would have been advantageous.

In order to explore the cause of tendon pain, it is helpful to briefly review newer concepts of pain. Modern understanding of pain suggests that nociception is neither sufficient nor necessary for pain [27]. Nociception refers to activity in primary afferent nociceptors—unmyelinated C fibres and thinly myelinated Aδ fibres—and their projections to the cortex via the lateral spinothalamic tract (Fig. 1). The projections terminate in multiple regions but predominantly the thalamus, which transmits impulses to the somatosensory cortex. Primary nociceptors respond to thermal, mechanical or chemical stimuli. In contrast, neuralgia describes pain in association with demonstrable nerve damage and is often felt, along with other sensory symptoms, along the length of the nerve or its peripheral distribution.

Pain, on the other hand, is an emergent property of the brain of the person in pain [28]. A useful conceptualisation is that pain emerges into consciousness in association with an individually specific pattern of activity across cortical and subcortical brain cells [29]. Innumerable experiments and common everyday experiences show that pain is most often triggered by nociceptive input. However, carefully designed experiments in healthy volunteers show that pain can be evoked without activating nociceptors [30] and that pain is readily modulated by a range of contextual and cognitive factors [31].

The relationship between nociception and pain becomes more tenuous as pain persists, and research has uncovered profound changes in the response profile of neurons within the nociceptive neuraxis. The mechanisms that underlie these changes have been extensively reviewed [32–34]. The clinical manifestations of these changes—sensitisation and disinhibition (or 'imprecision')—are important because they can be compared and contrasted with the clinical presentation of tendinopathy. Sensitisation refers to an upregulation of the relationship between stimulus and response where pain is evoked by stimuli that do not normally evoke pain—allodynia—and stimuli that normally evoke pain evoke more pain than normal—hyperalgesia.

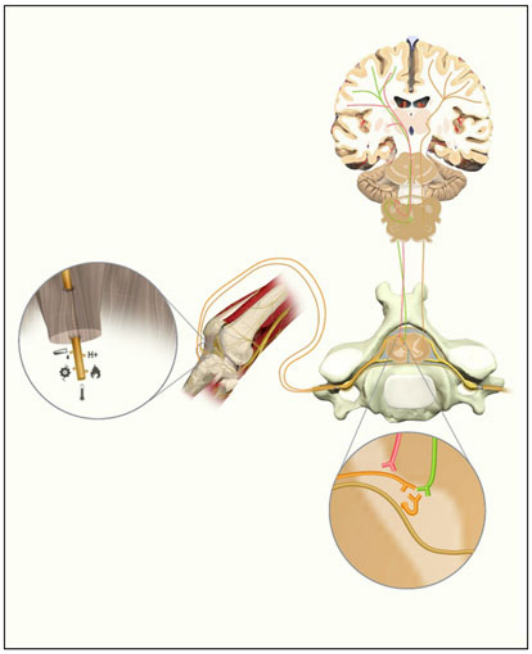

Fig. 1 Schematic representation of the basic physiology of tendon pain. The peripheral end of nociceptors, or free nerve endings, on thin unmyelinated (type C fibres) or thinly myelinated (type A delta fibres) situated in the peritendon and the peripheral portions of tendon tissue contain thermal, heat and mechanically activated ion channels. Changes in the chemical thermal or mechanical environment are transformed here to elicit signals or action potentials in the nociceptor. The signal travels to the dorsal horn of the spinal cord (in the superficial laminae I and II), where the nociceptor synapses with second order or spinal nociceptor. The spinal nociceptor sends a signal to the thalamus via the lateral spinothalamic tract and thence the brain. The medial aspect of the spinothalamic tract and the spinoparabrachial tract project to medial thalamus and limbic structures and are believed to mediate the emotional component of pain. A complex evaluative process occurs across multiple brain areas and protective outputs are activated. One such output is pain. Others include motor output, autonomic, endocrine and immune activation. In addition, descending projections (shown here in *red* and *green*) modulate nuclei in the brainstem, which in turn send signals down the spinal cord to modulate the same synapse in the dorsal horn. These neurons are activated to either facilitate or inhibit the spinal synapse, thereby either turning nociception up or turning it down. The manner of modulation here depends on the brain's evaluation of the need for pain and protection. As such, the spinal cord represents the first stage of integration and processing of the nociceptive signal

Allodynia and primary hyperalgesia are attributed to sensitisation of the primary nociceptor and relate to the area of usual pain. In tendinopathy, if normally pain-free movements, for example jumping, evoke tendon pain, this can be termed allodynia. If palpation of the Achilles tendon evokes more pain than usual, this can be termed primary hyperalgesia. In both scenarios, the tendon pain mechanism is over-sensitive. Notably, tendon palpation is only a moderately sensitive clinical test [35] and tenderness, or primary hyperalgesia does not correlate with tendon function.

Secondary hyperalgesia and allodynia are attributed to sensitisation of nociceptive neurons within the central nervous system (CNS), collectively called central sensitisation, and relate clinically to areas away from the primary 'zone'. Tenderness and evoked pain that spread, in a non-dermatomal, non-peripheral nerve distribution is best explained by central sensitisation [36].

The astute clinician will observe that, in the clinical presentation of tendinopathy, there is clear evidence of allodynia and primary, but not secondary, hyperalgesia [37]. This observation strongly implies the tendon tissue or the primary nociceptors that innervate it, are the nociceptive driver of tendon pain. We must look then more closely for potential local sources of nociception. However, tendinopathy is a chronic and persistent pain state and thus a scientist will ponder whether tendinopathy exhibits subclinical signs of central sensitisation and disinhibition identified in other chronic painful conditions [38–40]. We must then also look for potential central contributions to tendinopathy that may promote chronicity but not manifest in secondary hyperalgesia. To do this it is important to understand normal and pathological tendon structure.

2 Tendon Histology and Pathology

2.1 Normal Tendon

Normal tendons are mainly composed of fibroblastic tendon cells, called tenocytes, surrounded by extensive extracellular matrix (ECM). The ECM is predominantly made up of tightly packed collagen fibres (mainly Type I) that are orientated along the primary loading direction [41]. Also present are several PG (mainly small molecular weight decorin) and other non-collagenous proteins. Connective tissue both surrounds the tendon (peritendon) and infiltrates the tendon (endotendon).

Tenocytes manufacture all of the components of the ECM. Tenocytes lie end-to-end in channels between collagen fibres, with cell processes linking the cells within and between rows allowing communication [42]. Gap junctions that link cell processes are capable of being remodelled in hours [43], and appear to couple cells metabolically, chemically and electrically [42–44]. They allow rapid exchange of ions and small metabolites between cells, and different types have shown to be stimulatory and inhibitory in response to load [45]. Gap junction channels are gated open more often than closed, therefore it is the selectivity of the channel that dictates what passes from cell to cell [46]. The probability of gap junction channels being open or closed is influenced by pH, calcium concentration, the voltage across the gap junction and mechanical load [43, 47].

Whilst tenocytes have important roles in manufacturing ECM and load sensing, there are other cell types in tendon whose role is currently unclear, including a multi-potent population capable of differentiation [48, 49]. Mast cells, associated with immune function and found near blood vessels in tendon [50] are bone marrow derived and capable of phagocytosis, cytokine production, vasoactive substance release and immune receptor expression. Glial cells, not yet investigated in tendon but evident in other connective tissues [51], share a bone marrow lineage [52] and an immune role. Glial cells, which are capable of neurotransmission in chronic injury [53], communicate information between the peripheral nervous system (PNS) and CNS [54, 55] and when activated are implicated in ongoing pain [56] and may be another cell type potentially involved in tendon pain. Classic inflammatory cell types have been associated with rupture [57, 58] but have been infrequently shown in chronic tendinopathy [59].

2.1.1 *What is the Neural Supply to the Tendon?*

Tendon pain is well localised (implying small receptive fields) [60], occurs instantly with loading (implicating the involvement of myelinated/fast fibres) yet 'warms up' (implying a gating mechanism or exercise-induced inhibition); however, few studies have investigated these neural pathways.

Innervation studies in human tendon show scant innervation in the tendon proper; however, tendon connective tissue and blood vessels are well innervated [61, 62] with three neuronal signalling pathways: autonomic, sensory and glutamatergic [62–64]. Autonomic nerves, particularly sympathetic nerve endings in blood vessel walls [65], have been reported in the tendon, peritendon and endotendon of the patellar tendon [66, 67]. Sensory and sympathetic perivascular innervation of the walls of large and small blood vessels occur in peritendinous loose connective tissue, and there are some sensory nerve endings in the superficial endotendon [61]. Sparse sensory nerves have been identified in the body of the patellar tendon [64, 65]; in contrast, surrounding structures such as retinaculum and fat pad are richly innervated [68–70]. Mechanoreceptors are concentrated at myotendinous junctions and tendon insertions.

2.2 Tendon Pathology

Tendon pathology results in cell activation and proliferation, matrix change (collagen disorganisation and increased large PG) and neovascularisation, in various combinations and severity [18, 71, 72]. Tendon pathology is not always painful [73] but clinical presentation of tendinopathy is almost always associated with pain (tendon rupture may have been previously pain free). Change in collagen structure is the most obvious candidate for nociception because it is the load-bearing structure in tendon, but loss of collagen integrity does not correlate with tendon pain [18]. In fact, pain-free tendons can have sufficient structural disorganisation that they rupture [74].

2.2.1 *Does the Innervation Pattern Change with Pathology?*

There are few afferent nerves within tendon, and innervation patterns do not change with pathology [61, 75]. New vessels primarily bring autonomic vasomotor nerves (and some sensory nerves) but neovascularisation is not present in every painful tendon. Tendon pain may be associated with nerve-ending sprouting, or changes to nerve function rather than type; for example, Aβ fibre activation can cause pain when there is production of nociceptive substances and/or central sensitisation [34, 36, 76].

Innervation may not be uniform throughout a pathological tendon. The area dorsal to the proximal patellar tendon, which is targeted in some injectable and surgical interventions because of the neovascularity in this area, has mainly sympathetic nerves and few sensory nerves [67]. The vessels displayed marked perivascular innervations and adrenoreceptor immunoreactions [67].

These changes to innervation do not appear to explain the clinical features of tendon pain. To reflect all the clinical features, the local nociceptor must have a threshold for activation, be responsive to mechanical stimuli and exhibit saturation. Tendon pain may result from non-nociceptive pathways playing nociceptive roles.

2.3 Potential Contributors to Pain

If local nociception drives tendon pain then the nociceptive signal needs to be relayed to the CNS. One way to interrogate the nociceptive capability of tissue is via experimentally induced pain. Hypertonic saline activates nociceptors via chemically-driven ion channels. Hypertonic saline injected into healthy tendon induces pain and mechanical sensitivity but no pain referral—a pain pattern similar to that of load-induced tendinopathy [77]. In contrast, hypertonic saline injected intramuscularly evokes referred pain [78], which clearly implicates convergence within the CNS. However, chemically induced experimental pain studies do not mimic the characteristic load-dependent nature of tendinopathy pain [79]. A complementary approach is to look more closely at the tendon itself. As classical (i.e. cell-mediated/prostaglandin-driven) inflammation has not been associated with tendinopathy and as the innervation pattern does not differ greatly for normal and pathological tendon, potential sources of

nociception in tendon include changes in the matrix, vascular supply, cell function, bioactive substance production, ion channel expression, cytokine and neurotransmitter expression, metabolism and mechanotransduction, or a combination of these.

2.3.1 Matrix Changes

The increased production of large PGs seen with tendon pathology, most notably aggrecan, may compromise cell adhesion, migration and proliferation and interfere with cell–matrix interaction [80]. Large PGs, particularly aggrecan, attract and bind water causing the tendon to swell, which will stimulate local C fibres [81] and increase interstitial potassium (K+) and hydrogen (H+) concentrations. This in turn can stimulate nociceptors and influence ion channel expression and/or activation. Kubo et al. [82] reported that nociceptive neurons were sensitised by low pH through augmenting the mechanical response of thin fibre afferents, and that this sensitisation was attenuated by versican, but not by blocking intracellular signalling pathways.

Larger PGs may also disrupt mechanotransduction, reducing communication between cells and between the cells and the ECM [45]. This may result in a loss of gap junctions between parallel rows of tenocytes (mediated by connexin 43) and even between longitudinal cells. It is feasible that disruption of gap junctions alters tendon homeostasis sufficiently to activate nociceptors. Cell and consequent matrix changes may also compromise gap junction permeability and ion channels that regulate neuronal excitability [83]. Conversely, the disruption of communication in a disordered matrix may protect the tendon by isolating the cell and preventing toxic communication of substances to healthy neighbours.

2.3.2 Vascular Change

Increased vascularity has been reported to be a source of nociception in tendinopathy [84, 85]. Nerves, and receptors such as adrenoreceptors, are found in vessel walls in tendinosis and are likely to be associated with angiogenesis and blood flow rather than having any role in nociception. As the tenocyte is responsible for producing the components of the ECM, stimulation of tenocyte receptors may drive structural change rather than be involved in nociception [86].

Neovascularisation has been associated with degenerative tendinopathy but is not a feature of early pathology [18]. Not all painful tendons have increased vascularity [18, 87] and vice versa [18], therefore the vessels or the nerves and receptors on vessel walls fail to explain tendon pain across all pathological presentations. Sclerosing treatment of neovascularity has resulted in variable improvements in pain and vascularity [88–91]. Sclerosants may work by changing the biochemical environment or disrupting neural pathways. If local nociceptors are critical to tendon pain, then they must be present across all stages of pathological change, in which case the tenocyte may be the key.

2.3.3 Tenocyte Changes in Structure and Function

Tenocytes respond to changes in their mechanical, ionic and osmotic environment [92–94]. In tendinopathy, tenocytes proliferate, become more rounded, and contain a higher proportion of protein-producing organelles [18]. These changes appear to increase production of substances and receptors involved in nociception (Sect. 2.3.4). Cell changes may also alter gap junction function and affect cell communication, nociception transmission or mechanotransduction, affecting tendon homeostasis and possibly nociceptive communication [45]. In addition to changes in cell structure and communication, the biochemical environment in tendinopathy has a myriad of substances that may be involved in nociception and further alter cell function.

2.3.4 Biochemical Changes: Cytokines, Neuropeptides and Neurotransmitters

There are many biochemical changes in tendinopathy, none of which can fully explain tendon pain. Bioactive substances and their receptors may be important in pain behaviour. Neuropeptides and neurotransmitters, formerly attributed only to neurons, are now known to also be produced by tenocytes.

Autocrine signalling occurs when a signalling molecule binds to a receptor on the same cell type. Paracrine cell signalling functions by signalling to another cell type. Signalling agents can have very short half-lives [for example nitric oxide (NO) is less than 0.1 s] and be influenced by the presence of concurrent substances such as glutamate and calcium ions (Ca^{2+}) [95]. It is not clear whether autocrine or paracrine signalling has a role in tendon pain.

Tendon pain is likely mediated by substances that have pro- and anti-inflammatory effects, for example cytokines [tumour necrosis factor-alpha (TNFα) and interleukin (IL)-1β], signalling molecules [Ca^{2+}, adenosine triphosphate (ATP)], neuropeptides [substance P (SP), neuropeptide Y] and neurotransmitters such as glutamate. These substances have been studied in other chronic pain conditions [96] and may be important contributors to tendinopathy (both pain and pathology). Cytokines are involved in intercellular communication and modulation of gene expression. The TNFα system, implicated in tendinopathy and possibly

activated by mechanotransduction, seems to be involved in matrix structure change and is capable of inducing apoptosis [97–101]. TNFα also causes a dose-dependent increase in afferent Aδ and C firing and may have a role in tendinopathy nociception [102]. IL-1β, upregulated in a human tendon cell culture model, is capable of causing cell proliferation and apoptosis [103]. These cytokines do not show rapid on/off response profiles, but that does not exclude them from being important in tendinopathy. Substances such as TNFα and IL-6 are among those that have thus far been studied in tendinopathy, yet there are many other cytokines that might play a role. Glial cells, a primary expressor of such cytokines, are critical for synaptic transmission [104] in spinal or supraspinal communication [105], and may be a feasible mechanism by which nociception could be upregulated at the level of the CNS.

Neuropeptides such as SP and calcitonin gene-related peptide (CGRP) transmit signals across a synapse. Both SP and CGRP are released by the terminals of nociceptors and SP has been shown to be released by tenocytes. SP afferent immunoreactivity has been demonstrated at the enthesis [106] and in tendon tissue [61, 64], which indicates thin fibre sensory innervation, most likely serving a nociceptive function. SP [and its receptor, neurokinin-1 receptor (NK-1 R)] and CGRP have also been identified in nerve fascicles in large and small blood vessels in tendinopathy [107]. Binding of SP to its receptor has been associated with the transmission of nociception [108].

SP can cause vasodilation and protein extravasation in surrounding tissue—a process termed neurogenic or peptidergic inflammation. SP increases cell metabolism, cell viability and cell proliferation in tenocytes [109]. The peptidergic inflammatory mechanism of nociceptors is initiated by nociceptor activation. However, antidromic mechanisms driven within the CNS can lead to peptidergic inflammation and this raises the possibility that central mechanisms influence tendon pain.

Acetylcholine (ACh), a neurotransmitter in the CNS and PNS that is also produced by activated tenocytes [94], is capable of modulating nociceptive input, influencing collagen production, inducing cell proliferation and regulating vessel tone [94, 110]. Muscarinic ACh receptors of subtype M2 (M2Rs) have been found on tenocytes (in tendons with hypercellularity), nerve fascicles and the local blood vessel walls [94]. Upregulation in the cholinergic patterning also correlated with recalcitrance to treatment [94].

Immunoreactions for adrenergic receptors have been found in blood vessel walls, tenocytes and in some of the nerve fascicles in the patellar tendon [66]. Increases in nerve fibres showing neuropeptide Y immunoreactions as well as those involved in synthesis pathway of norepinephrine and epinephrine and their receptors have been observed in vessels in pathological tendon [66, 67].

ATP can be released by neurons and has been implicated in both central and peripheral pain mechanisms as it functions as a signalling molecule [111]. ATP facilitates nociceptive behaviour and electrolyte transmission, elicits glutamate release [112, 113], acts directly on dorsal horn, regulates cell death and vascular tone, degranulates mast cells and induces prostaglandin synthesis. ATP is released from damaged cells [114] and could activate primary afferent nociceptors.

High intratendinous levels of glutamate and its receptor, the N-methyl-D-aspartic acid or *N*-methyl-D-aspartate (NMDA) receptor, have been demonstrated in tendinopathy [115, 116]. Glutamate, also produced by the tenocyte, is involved in nociceptive modulation in other persistent pain states, is involved in vasomodulation, is capable of inducing oxidative stress, has a role in ECM metabolism and is associated with tenocyte proliferation and apoptosis [117, 118]. Glutamate receptors can be activated by SP and it is the major neurotransmitter mediating fast excitatory transmission in the CNS. These factors seem to implicate glutamate in tendinopathy; however, resolution of tendon pain with rehabilitation did not change glutamate levels [119]. However, NMDA receptors require glutamate and glycine (also a neurotransmitter) interaction [120] so perhaps it is glycine levels that change (or another substance not examined). Notably, prolonged firing of C fibres is thought to increase glutamate release, which seems inconsistent with the on/off non-spreading nature of tendinopathy pain.

2.3.5 Biochemical Changes: Metabolites

All cells and tissues require the maintenance of intracellular and tissue pH, as many processes and proteins only function within specific pH ranges [44]. Cell membrane potential, which is the difference in voltage between the inside and outside of the cell, determines the excitability of the cell and is influenced by tissue pH. Lactate can decrease pH, and microdialysis of tendinopathic tissue showed lactate levels at rest were double that shown in healthy control tendon [121]. Increased lactate, due to a predominant anaerobic metabolism, occurs in tendons of older people as well as tendinopathy [122, 123], and is compounded by the high metabolic rate in tendon pathology (25 times that of normal tendon) [124].

At physiological pH, lactic acid almost completely dissociates to lactate and hydrogen ions; the latter are known to modulate nociceptor activity and alter ion channel expression. Lactate is not just a waste product—it is an active metabolite, capable of moving between cells, tissues and organs. Lactate can stimulate collagen production and deposition, activate tenocytes [125] and increase vascular endothelial growth factor (VEGF) and neovascularisation

[126]. Lactate also closes the inhibitory gap junctions between rows of tenocytes, which may exaggerate response to loading [127].

Accumulated lactate has been associated with pain in other tissues such as cardiac and skeletal muscle and the intervertebral disc (IVD), but it has not been fully investigated for tendons. It is notable that tendon pain has some features that are consistent with accumulated lactate: rapid easing in symptoms after a change of posture (sustained positions are painful in tendinopathy), poor response to anti-inflammatory medication (true in tendons for most anti-inflammatory medications, those that alter pain and function appear to do so by tenocyte down-regulation and PG inhibition [128, 129] and sometimes no evidence of clear pathology [76]. However, other features require further explanation—transient load-dependent pain (requires gating) and decreasing pain with ongoing activity (implies saturation).

2.3.6 Cell Changes: Ion Channels

Ion channels, present in cell membranes, alter the flow of ions in and out of a cell and respond to voltage, movement or chemicals. Ion channels in tenocytes may perform a number of roles, including mediation of calcium signalling, osmoregulation and cell volume control, control of resting membrane potential levels and the detection of mechanical stimuli [130]. Ion channels are important in tendon pain; they may be involved in sensing the nociceptive stimuli, communicating with the afferent nerves and neuronal transmission to and within the cortex.

Ion channels are often linked to the cytoskeleton and to an extracellular structure, allowing them to be directly gated by mechanical deformation and almost certainly altered with a change to tenocyte shape with tendinopathy. On nerve cells they enable neuronal communication (in both the PNS and CNS), communication between different tissue types and the conversion of a force or load into an action potential in a nerve.

2.3.6.1 Ion Channels: Sensing the Stimulus Ion channel expression is likely to change in tendinopathy because of a more acidic environment due to excess lactate. A decrease of the extracellular pH influences the expression of acid-sensing ion channels (ASICs) [131]. The magnitude of currents in ASICs is sufficient to initiate action potentials in neurons [131]; ASICs are activated quickly by hydrogen ions and inactivate rapidly despite continued presence of low pH, exhibiting features of saturation.

ASICs have been associated with painful conditions that have accompanying tissue acidosis and ischaemia, and they were therefore originally thought to only be expressed by neurons. However, connective tissue cells of the IVD [132, 133] bone cells [134], chondrocytes and synoviocytes [135–138] have been shown to express ASICs. These connective tissues share similarities with tendon; low blood supply, few nerves, subject to compression and tension and pain that is not always correlated with tissue damage [139]. In IVDs and articular cartilage, cell metabolism is almost entirely anaerobic [140, 141] and the tissues have high lactate levels and low pH, similar to tendinopathy. In bone, an acidic environment directly impedes osteocyte activity [142], thus ASICs have a role not only in nociception but also cell activity.

Other ion channels in tendons may be important in nociception. The transient receptor potential cation channel subfamily V member 1 ion channel (TrpV1) is believed to function as a molecular integrator of noxious stimuli, including heat, acid and endogenous pro-inflammatory substances [143]. Stretch-activated ion channels (SAC), voltage-operated ion channels [144, 145] or other mechanically gated channels may be implicated in nociception sensing and transmission [146]. Activation of SACs would fit the load based on/off nature of tendon pain and the clinical observation that pain gets stronger with increased loading (which would correlate with increased channel activation) and the 'warming up' phenomenon as ion channels become saturated. Mechanosensitivity (membrane stretch, fluid flow, etc.) is phenotypic [146] and therefore SACs are likely to be selective to other stimuli such as voltage or acid. SACs have been shown to be blocked by gadolinium and, more specifically, by mechanotoxin 4 (GsMTx4); a peptide that modulates ionic currents across calcium, sodium or potassium ion channels and blocks capsaicin receptor channels. Investigation of these blockers may lead to identification of potential treatment options for tendinopathy that may address both pain and the pathological process.

Voltage operated calcium channels (VOCC) have been demonstrated in human tenocytes, as well as the mechanosensitive tandem pore domain potassium channel [2PK (+)] TREK-1, which is sensitive to membrane stretch, intracellular pH and temperature [130]. Importantly, these channels are known to be associated with electrically excitable cells [147] so tenocytes may be capable of conducting an electrical potential as they open and close in response to voltage across the membrane.

2.3.7 Ion Channels: Communicating with Nerves

To activate neuronal pathways, receptors and ion channels are required. Ion channel expression in tenocytes may change, but ion channel expression in the afferent nerve may also change in response to repeated activation [36]. This sensitises the primary neuron to the very stimulus that evoked the adjustment. Ion channels transduce noxious

stimuli into neuron membrane depolarisations that trigger and conduct action potentials from the peripheral site to the synapse in the CNS [148]. As there is a limited relationship between pain and the presence of neural ingrowth in humans [18], additional mechanisms may be performing a nociceptive function. Intercellular signalling via non-synaptic mechanisms are important in the nervous system and between tissues and the nervous system but are not as clearly understood as synaptic communication[149]. In fact, cells may communicate with glial cells [150] via neurotransmitters through neurotransmitter-gated ion channels [151, 152] and voltage-gated ion channels [152]; glial cells may also communicate among themselves. Cell–cell communication within a tendon and with the nearest sensory nerve may well occur via this form of signalling. Alternatively, perhaps load-sensing mechanisms within, or separate from, the tendon play a nociceptive function. If so, they would utilise complex threat-evaluation systems within the CNS.

2.4 How Might These Changes Relate to Tendon Pain?

The presence of stretch and ion-activated channels in either neurons or tenocytes would fit many features of tendon pain. Ion channels are normally closed in the absence of a stimulus, but open for a few milliseconds to allow equalisation along an electrical gradient [153]. With prolonged (chemical or electrical) stimulation, many of these channels close and desensitise, leaving them refractory to further opening unless the stimulus is removed.

Although ASICs have not been studied in normal, pathological or painful tendons, the tendon environment can become acidic [121] to levels that would open ASIC channels if they were expressed by tenocytes or neurons. Desensitisation occurs with persistent stimulation of ASICs after approximately 3 min [154], which may explain the clinical feature of tendons being initially painful during activity then warming up. Recovery from desensitisation occurs slowly, over many hours, which may fit with later pain and stiffness. ASICs are rapidly activating and inactivating (<5 ms to activate, 400 ms to deactivate) [155] which may also fit with the on/off nature of tendon pain. Further investigation of the presence and role of ion channels in tendon pain is warranted.

To be a practical theory, tendon pain must be explained across the range of clinical presentations. These presentations may be a combined result of changes in structure, biochemical levels and cell function that interact to cause pain. Theoretically, in reactive tendinopathy (as described by Cook and Purdam [156]) there may be increased expression of nociceptive substances because of cell activation and proliferation, but no change in innervation. In degenerative tendinopathy there may be little expression of nociceptive substances due to cell inactivation or death but greater innervation. At both ends of the spectrum pain is possible. The pain-free tendon may have substantial matrix disorganisation and cell compromise, but insufficient production of nociceptive substances and/or the neural network to reach a threshold to cause pain. An example is tendon rupture in asymptomatic people, where tissue threatening loads are not communicated to the CNS as pain prior to tendon rupture.

3 Central Mechanisms: the Spinal Cord and Brain

Primary nociceptors have their proximal synapse in the dorsal horn of the spinal cord where they communicate with spinal nociceptors, using glutamate or SP. The spinal nociceptor projects to the thalamus and then onward to access the network of cortical and subcortical areas associated with pain [157]. Experimental pain studies reveal that the contralateral insular cortex, the anterior cingulate cortex, cerebellum, the contralateral thalamus, the putamen, primary and secondary somatosensory cortex, prefrontal cortex and premotor cortex are involved in the pain experience, although much variability exists [158–162].

There is no theoretical or clinical reason to conclude that tendon pain serves an alternative purpose to other types of pain—to protect the painful part. This rather pragmatic view requires acceptance that the entire evaluation of whether or not a tendon is in danger occurs outside of consciousness, and that the spinal nociceptor is just one contributor to this evaluation. Theoretical models that attempt to integrate the research on pain all emphasise the multifactorial nature of pain and the complex and bidirectional interactions that occur between the state of the body and pain. This brings challenges because it raises the possibility that higher centres can target local tissues, if the brain concludes that they are in danger.

The tendon, attached bone and muscle, and overlying skin are all represented within the brain. All bodily representation (including motor, sensory, visual and auditory) is plastic and is influenced by use, injury, pain and disease [163–168]. Although motor and sensory representations, cortical excitability (or descending inhibition) and cognitive modulation of pain have all been well studied in other pain states, little research has been undertaken on tendon pain.

3.1 Does Tendon Pain Centralise?

The PNS and CNS neural networks that mediate nociception demonstrate plasticity in pathological states [169]. The regions that are most likely upregulated are the tendon itself, the nociceptor, the dorsal horn or in the brain.

Sustained peripheral nociceptive activity may lead to the development of central sensitisation [76]. Although central sensitisation accounts for widespread pain and hyperalgesia/allodynia in chronic pain patients, excessive pain response is not a clinical feature of tendon pain regardless of symptom chronicity. This may be explained by the on/off nature of tendon pain, reducing the likelihood of long-term potentiation or depression, or local saturation of the receptor that would then fail to stimulate the afferent nerve.

Few studies have examined if central pain processes are involved in tendon pain states [77, 170]. Tendinopathy pain would seem a unique chronic pain because pain generally occurs during loading, and although there is more pain with increasing load, it disappears once the load is removed. Spreading of pain (for example secondary hyperalgesia) is not a common clinical feature of tendinopathy, especially in the lower limb. However, developing symptoms on the other side is common [171] and this mirroring is often attributed to bilateral loading patterns, although CNS neuroimmune mechanisms offer an equally feasible explanation [104]. The odds ratio of rupturing the other Achilles tendon after a unilateral rupture is 176, when compared with the general population (6 % of the participants ruptured the contralateral tendon) [172]. This may be due to high bilateral loads, but may also indicate central drivers to pathology and/or pain or systemic or genetic factors. Bilateral tendinopathy in both the loaded and unloaded limb of baseball pitchers would support this [173]. This view is further strengthened by data from an animal model where bilateral cell changes were observed in unilaterally loaded rabbits [174] and a unilateral chemically induced model of tendinopathy in horses [175].

There are several features of tendon pain that suggest cortical changes. High frequency train of input (e.g. repetitive high tendon load) strengthens synaptic transmission, and makes the next cell within the CNS more excitable for several days. In tendinopathy, substantial time between high loads is important to control pain [7]. It is possible that this may be not only related to local tendon adaptation such as collagen production and local cellular responses [176], but also to the sensitivity of the pathway.

Tendon pain has been associated with local sensory change such as increased mechanical sensitivity (pain with activity and tendon pressure) [177, 178]. Individuals with unilateral lateral epicondylalgia (LE) demonstrated hyperalgesia and bilateral changes to pressure pain thresholds [179]. The affected side was worse than the unaffected side, and both sides were worse than controls. Individuals also showed bilateral changes to thermal sensitivity [180]. These differences in mechanical and thermal hyperalgesia may indicate central sensitisation. However, another study in tendons demonstrated no differences in cold and heat pain, cold and warm detection thresholds [170].

van Wilgen et al. [170] completed quantitative sensory testing in people with and without patellar tendinopathy to assess central sensitisation. The pressure pain thresholds of asymptomatic athletes differed significantly from athletes with a diagnosis of patellar tendinopathy [181]. Mechanical pain threshold and vibration threshold were found to be significantly lower in people with patellar tendinopathy. Reduced mechanical pain thresholds or pinprick allodynia may reflect the involvement of central sensitization (myelinated Aδ-fibres).

If there are minimal cortical changes in tendinopathy, it is important to know if a tendon transmits pain in a way that protects the brain from central change. First, long-term cortical plasticity changes involve long-term potentiation (repetitive increase in the strength of synaptic transmission that lasts for more than a few mins) [76] or long-term depression (involving GABAergic pathways). The nature of tendon pain, being on/off may prevent long-term potentiation or long-term depression. Second, local inflammation, which is not a feature of tendinopathy, is an important event in the onset of many chronic pain states [182–187]. During inflammatory processes, pro-inflammatory mediators (e.g. prostaglandins, etc.) that are released from damaged tissues activate receptors, stimulate mast cells to release further pro-inflammatory cytokines, which lowers nociceptive threshold firing and increases the rate of firing. Third, the activation of intracellular second messengers is required and subsequent alterations to gene and ion channel expression may be a more transient change with expression changing with the removal of the painful load.

3.2 Central Mechanisms: Future Directions

There may be non-nociceptive mechanisms that play a nociceptive role in tendon pain. One such mechanism may be related to an internal calculation of tendon load. This idea is consistent with the modern idea of pain being about protection and not dependent on nociception, and shares characteristics with the central governor theory of fatigue [188]. Alternatively, tendon pain may reflect an error in the internal calculation of tendon load. Several of the local dysregulations discussed here could contribute to erroneous load information. These ideas are speculative but not outrageous—that central evaluation of danger to body tissue modulates pain is well accepted (see Butler and Moseley [27] for review), and that internal comparators evaluate predicted and actual motor responses has been established for some time [189].

4 Conclusions

The molecular biology of tendon in pathological and healthy states highlights many potential contributors to

pain and the search for these needs to extend beyond the tendon. Nociception could occur from cell–cell signalling via ion channels that communicate with an afferent neuron that could transmit, suppress or amplify the nociceptive signal. Nociception may be modulated spinally or above and descending mechanisms may exert nociceptive pressure that manifest locally. Finally, pain could be evoked via non-nociceptive mechanisms through a load detection system, which itself could be disrupted via local or central dysfunction. The question of the pain of tendinopathy, physiological or pathophysiological, remains unanswered; however, there is evidence for both—tendon based nociceptive contributions and extensive mechanisms within the periphery and the CNS. Importantly for clinicians, tendon pain is complex and requires thorough assessment of both musculoskeletal and neural contributors as well as excellent clinical reasoning to account for nociceptive input from local tendon pathology as well as potential central mechanisms.

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