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Review Article

Pain and the pathogenesis of biceps tendinopathy

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Abstract: Biceps tendinopathy is a relatively common ailment that typically presents as pain, tenderness, and weakness in the tendon of the long head of the biceps brachii. Though it is often associated with degenerative processes of the rotator cuff and the joint, this is not always the case, thus, the etiology remains considerably unknown. There has been recent interest in elucidating the pathogenesis of tendinopathy, since it can be an agent of chronic pain, and is difficult to manage. The purpose of this article is to critically evaluate relevant published research that reflects the current understanding of pain and how it relates to biceps tendinopathy. A review of the literature was conducted to create an organized picture of how pain arises and manifests itself, and how the mechanism behind biceps tendinopathy possibly results in pain. Chronic pain is thought to arise from neurogenic inflammation, central pain sensitization, excitatory nerve augmentation, inhibitory nerve loss, and/or dysregulation of supraspinal structures; thus, the connections of these theories to the ones regarding the generation of biceps tendinopathy, particularly the neural theory, are discussed. Pain mediators such as tachykinins, CGRP, and alarmins, in addition to nervous system ion channels, are highlighted as possible avenues for research in tendinopathy pain. Recognition of the nociceptive mechanisms and molecular of biceps tendinopathy might aid in the development of novel treatment strategies for managing anterior shoulder pain due to a symptomatic biceps tendon.

Keywords: Biceps, tendinopathy, pain, pathogenesis, tachykinins, ion channels

Introduction

Pain is a multifactorial experience that incorporates various facets of sensation. It is initiated by a noxious stimulus that then activates the sensory component, which, in turn, is shaped by an emotional aspect. This, while modulated by social and environment factors, subsequently influences the reaction, or behavior, of the individual, thus integrating several systems within the human body.

For millennia, it has been a main concern of the medical field, yet much is still unknown about its components and mechanisms. Particularly of interest is the development of chronic pain, with a recent focus on as to why tendinopathy is so often accompanied by it. Tendinopathy is a term that generally addresses pathology of the tendon; classically, the pathology encountered is a loss of the typical parallel, longitudinal collagenous architecture and its subsequent replacement with an amorphous, mucinous material that lacks the orderly structure of normal tendon [1]. Tendinopathy is correlated with overuse and often presents in the affected tendon as pain with activity as well as focal sensitivity to palpation. Furthermore, the pain and degeneration of tissue lead to decreased ability to tolerate tension on the tendon, and consequently decreased functional strength [2].

A tendon of clinical interest is that of the long head of the biceps. The biceps are closely associated with the rotator cuff; thus, tendinopathy arises due to repetitive traction, friction, and rotation of the shoulder joint, and often occurs with rotator cuff degeneration. This article presents a critical review of what constitutes pain, and how it pertains to tendinopathy, particularly of the long head of the biceps. The goal was to elucidate the pathogenesis of pain associated with biceps tendinopathy to develop more effective treatment strategies to manage this debilitating disease.

Categorization of pain and management

There is no direct pathway that describes pain sufficiently; pain can embody multiple manifestations, and is often categorized by the stimuli that generate the pain. The two main groups that the stimuli fall into are nociceptive and neuropathic. Nociceptive pain refers to the unpleasant feeling that results from direct activation of pain nerve fibers via a noxious stimulus; mediators can be inflammatory, thermal, chemical, and mechanical in nature. This kind of pain is usually resolved upon removal of the noxious stimulus. Neuropathic pain results from damage to the neural processes that convey nociceptive information to the brain, thus the pain is generated and/or sustained by the nervous system. Examples of this are diabetic neuropathy and spinal cord injuries.

Nociceptive pain

Nociceptive pain is the most common presentation of pain, and is the dominating symptom of any kind of injury or localized inflammatory process. Extreme mechanical forces and various chemical mediators, whether from tissue damage, nerve endings or inflammatory processes, promote activation of this system. Initially, highly ramified nerve endings known as nociceptors are stimulated, and propagate the signal down the corresponding nerve fibers. The nociceptive nerve fibers subsequently activated fall into two basic types: Aδ fibers and C fibers. Aδ fibers are myelinated, thus are referred to as “fast pain fibers” (12-30 m/s) [3]. They relay sharp, stinging sensations to a specific area in the margin of the dorsal horn, and function primarily in alerting the central nervous system to the presence of pain. This specific pain is referred to as physiological pain, and serves a protective purpose, as the nervous system of an organism can localize this pain swiftly and precisely, allowing the organism to withdraw from the painful stimulus to prevent further damage [4].

In contrast, C fibers are smaller in diameter, and are unmyelinated. The type of pain that is relayed by these fibers is poorly localized; rather, it is conducted to higher centers via the dorsal horn. Burning, aching pain is transmitted via C fibers in a slow manner (0.5-2 m/s), and it is believed that they are integral in determining intensity of pain [3]. It is thought that they do so by modulating dorsal root ganglion sensitivity through altering intracellular calcium concentration, therefore affecting N-methyl-d-aspartate receptor configuration and sensitivity [5]. This pain is alternatively called pathophysiological pain, and it is associated with the delayed pain sensation that often occurs after tissue disruption, such as surgery, trauma, or inflammation, and is what is believed to encourage tissue healing. This is accomplished through eliciting certain behaviors that protect the injured tissue.

It should be noted that activation of a nociceptive nerve fiber does not necessarily result in pain; in fact, throughout the nervous system, there are several mechanisms in place to allow only certain signals through, most notably in the dorsal horn and the thalamus. If the signal does overcome the barriers in place, then treatment of this type of pain necessitates elimination of the stimuli producing this pain, such as removal of the painful stimulus or reducing a local inflammatory reaction [6].

Neuropathic pain

Neuropathic pain is significantly different from nociceptive pain, and is produced or sustained by the nervous system. This category of pain can impact both the peripheral and central systems separately, thus it manifests in diverse ways. In the peripheral nervous system, the fibers’ sensitivities and responses can be modified, and this can be attributed to numerous causes. Reorganization of the pathways in the central nervous system that transmit, filter, or suppress the pain signals may alter the sensitivity or response of the system. Furthermore, central and peripheral nerve pain mechanisms can coincide to generate neuropathic pain syndromes.

Regardless of where the pain originates, neuropathic pain often responds inadequately to typical pain treatments, and could even be complicated by them. By definition, neuropathic pain is chronic, and it can intensify over time. It does not decrease with time and healing, as seen with nociceptive pain. This pain can be difficult to treat, though some studies suggest use of non-steroidal anti-inflammatory drugs, or opioids for more severe pain. Anticonvulsant and antidepressant drugs have been found to work in some cases [7].

Most situations that cause nociceptive pain can result in neuropathic pain, but there are also certain medical conditions that commonly lead to nerve-related pain. These include diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, deafferentation, and trigeminal neuralgia. Although the mechanisms underlying these states of neuropathic pain are progressively deduced, the mechanisms of chronic pain following trauma and other orthopedic issues have yet to be elucidated [8].

Peripheral neuropathic pain: Injury of nociceptive nerve fibers can result in an increase in the number of ion channels, as well as lead to an upregulation of receptors in the neuronal membrane. The result of this can be sensitization of the nerve to both mechanical and chemical mediators. This type of sensitization is documented in several known conditions, such as trigeminal neuralgia, radiculopathy, plexopathies, and certain compression injuries. Patients with these conditions often have projected pain, in which pain is felt along the periphery nerve fibers [9]. Treatment of this pain should commence with a targeting of the chemical and mechanical mediators at the site of injury. However, some of the changes that occur at the site can be chronic and resistant to alleviation.

Other cases of peripheral nerve pain involve ectopic foci of firing along the damaged nerve, with fibers often firing asynchronously. This is called small fiber neuropathy (SFN), as the small diameter (Aδ and C) pain fibers are preferentially affected in this malady, while the large diameter fibers are relatively unaffected [10]. As a result, there can be magnification of pain due to spontaneous firing of persistent small fibers. This pain is described as shooting, burning, or prickling in nature. Allodynia, pain caused by typically non-noxious stimuli, can be concurrent with this condition [11]. This type of pain can be controlled with stabilizing the oversensitive neuronal membranes, often through anesthetics and anticonvulsants [12].

In contrast to SFN, deafferentation results from the interruption of neuronal membranes of large diameter sensory neurons (ones that mediate touch and pressure sensory input). There is interruption of sensory conduction, and this process can increase sensitivity of neurons further along the sensory pathway. The transmission and perception of pain, which will be discussed further later, can be magnified due to loss of the large diameter fibers, which typically modulate the pain response. Furthermore, it is thought that persistent lack of normal stimulation of the nerve can lead to a decrease in inhibitory neurons that act on second and third order neurons, which can result in the firing of these nerves. This can result in what is known as “central pain”.

A final categorization of peripheral pain is complex regional pain syndrome, in which there are abnormalities in autonomic nervous system function, and this includes changes in circulation, temperature, and sweating patterns [13]. Additionally, there can be neurogenic inflammation, as sympathetic nerve fibers can secrete inflammatory mediators, including prostaglandins and nerve growth factors, which can also sensitize fibers. Neurotransmitters can also participate in the inflammatory reaction, as they can sensitize other pain fibers and activate vasodilation, edema, white blood cell infiltration, and other inflammatory cells. Thus, the nervous system can magnify and maintain inflammation.

Central neuropathic pain: The central nervous system also plays a significant role in neuropathic pain. The nervous system can construct a “memory” of pain, and a theory draws upon the fact that many of the neural factors associated with memory centers in the cerebral cortex are also found in sensory nuclei [14]. Glutamate channels play a large part; high-frequency, high-intensity stimulation facilitates formation of this kind of memory through “long-term potentiation”. This effect is intensified with co-activation of pain neuropeptides such as Substance P and calcitonin gene-related peptide, to name a few. The neurons become sensitized, thus can be activated more readily, or can even become spontaneously active, which has been posited as another mechanism through which chronic pain develops. These changes in the pathway also explain hyperalgesia, which is an abnormally heightened sensitivity to pain, as the neurons are so sensitized that even the lightest touch activates the pain pathway. Further studies point to glial cells having a critical role in this activation, as they produce growth factors and cytokines that lead to painful pathologies [15]. The pain transmission and modulation is depicted in **Figure 1**.

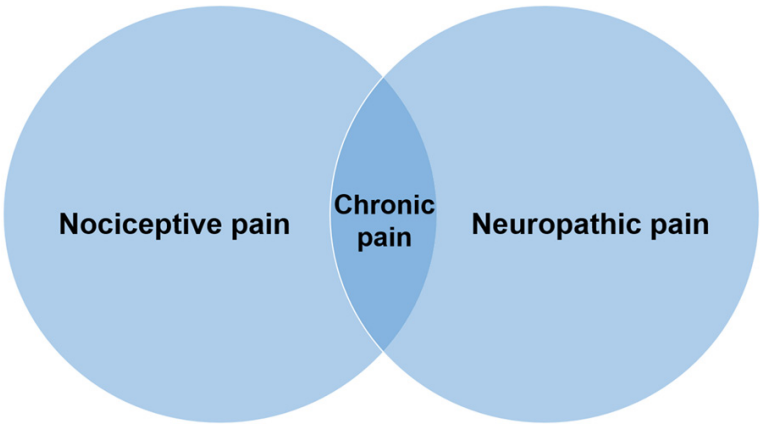

Figure 1. Classifications of pain based on stimuli. Nociceptive pain is caused a noxious stimulus which can be inflammatory, thermal, chemical, and mechanical in nature. Neuropathic pain results from damage to the neurons that convey nociceptive information to the brain, therefore the pain is generated and/or sustained by the nervous system. Chronic pain is thought to combine elements of both nociceptive and neuropathic pain.

Chronic pain

Chronic pain, unlike acute pain, serves no practical function, and the elucidation of its underlying mechanisms is even more elusive than that of the latter. Currently, four types of chronic pain are recognized: pain persisting beyond the normal healing time for an injury or disease, pain related to a chronic degenerative disease process or a persistent neurologic condition, pain that is produced and sustained though with no identifiable cause, and cancer pain.

Neurogenic inflammation, a peripheral pain process previously discussed, may be central to many chronic pain problems. The range of chronic pain issues clinicians see may be dependent on the differences in the tissues that neurogenic inflammation is acting upon [16]. Another theory is that after injury, there can be sprouting of A-category neurons to Rexedlaminae I and II of the grey matter of the spinal cord, possibly contributing to allodynia in addition to chronic pain, as both of these areas are significant checkpoints in the pain pathway [17]. Other theories for the development of chronic pain will be discussed throughout the article.

Pain pathway

The nociceptive pathway ultimately can be divided into four components: transduction, transmission, perception, and modulation. Briefly, nociceptive transduction is defined as the process that converts painful external stimuli into electrical signals that the nervous system can propagate and process. Transmission is the link between the peripheral and the central nervous systems; perception is defined as how the brain interprets and grades the pain. Finally, modulation encompasses how the nervous system controls what signals get through to the brain, as well as the descending pain inhibition pathway.

Transduction

Nociceptive transduction is the process by which the body transforms thermal, mechanical, or chemical stimuli into a transmittable signal. The free nerve endings of C and Aδ fibers spread between epidermal cells receive the painful stimulus, and as a response to it, somatosensory processes are activated and promote the opening of ion-gated channels. This leads to changes in membrane potential and the opening of further channels, resulting in depolarization of the afferent nerve. This propagates and generates a nociceptive electrochemical signal that can then reach and be analyzed by higher centers of the nervous system [18].

Common ion channels found in this process include acid-sensing channels (ASICs), transient receptor potential (TRP) channels, and voltage-gated sodium channels (Nav) (**Table 1**). ASICs are voltage-insensitive-proton-activated sodium channels located throughout the body [19]. They detect changes in extracellular acidity, and have been associated with various disease processes in which pain is the overarching symptom, including migraines and neuropathic pain. Recent studies have demonstrated that there is expression of ASICs on free nerve endings and on somatosensory organs, and that two channels, particularly ASIC3 and ASIC1b, function in acidic nociceptive processes (e.g. inflammation, ischemia) [20, 21]. Though recent research indicates that these channels are of increasing importance in nociception, the exact mechanisms, physiology and purpose of ASICs have yet to be fully understood.

Table 1. Ion channels and their pertinent subtypes, as well as what purposes they serve in the pain pathway

Family	Channels	Function
ASIC	ASIC1b	Na+ channels that detect changes in extracellular acidity; are particularly active in inflammatory and ischemic processes
	ASIC3	
TRP	TRPV1	Equi-permeable to Na+ and K+; also act as Ca2+ channels; activated by heat, acidity, and capsaicin
	TRPV3	Equi-permeable to Na+ and K+; also act as Ca2+ channels; activated by heat
	TRPA1	Equi-permeable to Na+ and K+; sensitive to thermal, mechanical, and chemical stimuli
	TRPM8	Equi-permeable to Na+ and K+; also act as Ca2+ channels; activated by cold and menthol
Nav	Nav1.7	Na+ voltage-gated channels; affiliated with Aδ and C fibers; aid in generation of action potentials
	Nav1.8	Na+ voltage-gated channels; affiliated with Aδ and C fibers; aid in generation of action potentials
	Nav1.9	Na+ voltage-gated channels; affiliated with C fibers; aid in generation of action potentials

Abbreviations: ASIC, acid-sensing ion channel; TRP, transient receptor potential channel; TRPV, vanilloid TRP; TRPA, ankrin TRP; TRPM, melastatin TRP; Nav, voltage-gated sodium channel.

TRP channels are a group of channels that are involved in myriad physiological processes, and have been found to be of importance in nociceptive transduction. Channels of particular importance in nociception include TRPV1, TRPA1, TRPV3, and TRPM8 [22]. TRPV1 channels are activated by heat, acidity, and compounds such as capsaicin [23]. TRPA1 channels are sensitive to thermal, mechanical, and chemical stimuli, and are expressed on neurons and non-neuronal cells alike. A gain-of-function mutation in TRPA1 channels results in a five-fold increase of inward current at resting potential, and this has been shown to result in the pathogenesis of Familial Episodic Pain Syndrome, from which patients suffer severe episodes of pain, typically localized to the upper body [24]. TRPV3 channels, like TRPV1 channels, are thought to play a significant role in the transduction of warmth and heat pain; however, their activity is potentiated by lower temperatures than that of the TRPV1 channels, nor do they respond to capsaicin [25]. TRPM8 channels are cutaneous in nature, and are involved in cold sensation and pain transduction [23].

Nav channels, though not conventionally involved in transduction, are voltage-gated sodium channels that serve a role in the transition from transduction to transmission, and thus in the generation of action potentials. Nociceptive transduction is mediated by the transducer potential generated by channels such as ASICs and TRP channels, and this in turn depolarizes Nav channels, forming an action potential [22]. The soma of dorsal root ganglion neurons expresses these channels, thus facilitating transmission to the spinal cord.

Transmission

Pain transmission is the integral step of the pain pathway in which nociceptive information is then passed to the spinal cord. The distal ends of pseudounipolar first-order neurons (C and Aδ fibers) bring the transduced signals from the receptor to the cell bodies located in the dorsal root ganglia (DRG). As discussed before, these C and Aδ fibers modulate slow and fast transmission, respectively. Each DRG is composed of thousands of distinct sensory neuron cell bodies that are capable of encoding and then transmitting the specific information gathered from the receptors [26]. Cells in the DRG are subdivided into peptidergic neurons and nonpeptidergic neurons. Peptidergic neurons synthesize peptides such as Substance P, calcitonin gene-related peptide (CGRP), and somatostatin, which all play a role in transmission [27]. Additionally, the cell bodies of DRG neurons manufacture and transport the substances necessary for neuron survival and function to the distant axon terminals, including receptors, ion channels, in addition to molecules essential for synaptic transmission [5]. Glutamate is the most common neurotransmitter synthesized in the DRG; however, many DRG cells also express Substance P, which, as noted above, is an important neuropeptide that facilitates pain transmission. There are no direct synaptic connections between DRG neurons but their activity is indirectly mediated by chemicals [28]. The central branch of the axon then projects from the DRG through the dorsal root and into the dorsal root entry zone (DREZ) of the spinal cord [5, 29].

Perception

The DREZ serves as a conduit for first-order neurons to develop contact with the cell bodies of second-order neurons that reside in the dorsal horn. Prior to synapsing, the first-order neurons travel vertically through Lissauer's tract for several spinal segments before terminating on the second-order neurons [5]. Aδ fibers may ascend 3 to 4 segments in Lissauer's tract before finally terminating in Rexedlaminae I, II_o, or V. C fibers usually ascend one segment before terminating, most often in Rexed lamina II, and somewhat in V [30]. Rexed lamina I consist of two main types of cells: nociceptive-specific neurons and wide dynamic range neurons. Nociceptive-specific neurons respond to noxious stimuli and express neuropeptides such as Substance P, CGRP, enkephalin, and serotonin. Wide dynamic range neurons transmit both noxious and non-noxious information [5]. The axons of these neurons then cross to the contralateral side of the spinal cord, and proceed cranially via the lateral spinothalamic tract, which ultimately terminates in the thalamus. After ascension to the medulla, some collateral fibers enter the brainstem reticular formation in the medulla and pons. Most the projections to the reticular formation arise from Aδ fibers, although C fiber innervation has also been chronicled. It has also been noted that reticular formation response is proportional to noxiousness of the stimulus [31]. Other fibers synapse on the hypothalamus and periaqueductal gray. Once in the midbrain, this tract is consolidated in the posterolateral aspect of the medial lemniscus, and ascends further to the thalamus, with some fibers arborizing to the reticular activating system [29].

The ventro-posterior (VP) nucleus thalamic nuclei are the most direct subcortical relay site for the spinothalamic tract; glutaminergic projections of the second-order neurons synapse here to relay pain signals to the primary somatosensory cortex and other cortical regions [5]. The VP is somatotopically organized so that the cell bodies excited by face stimulation are found medially (VPM), and those excited by arm and leg stimulation are found laterally (VPL). Projections from the VPM and VPL nuclei synapse directly in the primary somatosensory cortex. The neurons in this part of the cortex show a graded response depending on the intensity of a painful stimulus, suggesting that the primary somatosensory cortex plays a key role in discriminating quality of pain [32].

Modulation

Pain modulation is synchronous with perception, and incorporates the descending inhibition pathway that originates in the brain post-perception. It has been suggested that upon first-order neurons' entrance through the dorsal horn, Rexed lamina II, or the substantia gelatinosa, may play a role modulating the spinothalamic and spinobulbar (the second-order neurons that go to the hypothalamus and amygdala) projection neurons via numerous inhibitory interneurons that primarily release GABA (gamma amino butyric acid) [5]. Lamina II inhibitory neurons can synapse locally to other laminae, including I, II, III, and IV [17]. It has been hypothesized that chronic neuropathic pain is facilitated by disinhibition related to the functional loss of lamina II inhibitory neurons.

The "gate control" theory of pain proposed by Melzack and Wall in 1965 suggested that there were three spinal cord systems involved in pain transmission: the substantia gelatinosa, dorsal column fibers, and central transmission cells in the dorsal horn [33]. The substantia gelatinosa, as previously discussed, serves as a gate that modulates signals prior to reaching the brain. Large diameter (i.e. proprioceptive) fibers that have inhibitory properties "shut the gate" whereas small diameter fibers carrying painful signals "open" the gate to pain transmission. In a reduced view of this theory, massaging of the injured area promotes proprioceptive (i.e, large diameter) fiber input and reduces pain perception [33]. Despite advancing the medical cognizance of pain and its perception at the time, this model has been criticized and revisited by the authors, as it provides an outmoded and substantially incomplete view of the nervous system.

The anterior cingulate cortex (ACC) and middle cingulate cortex of the brain receive projections from the medial and intralaminar thalamic nuclei and the ventralis posterior inferior (VPI) nucleus of the thalamus. These areas are activated by noxious stimuli, eliciting an emotional, or motivational, response to pain. Thus, lesion of the cingulate cortex weakens these motivational-affective characteristics of pain, particularly in patients with chronic cancer pain. To

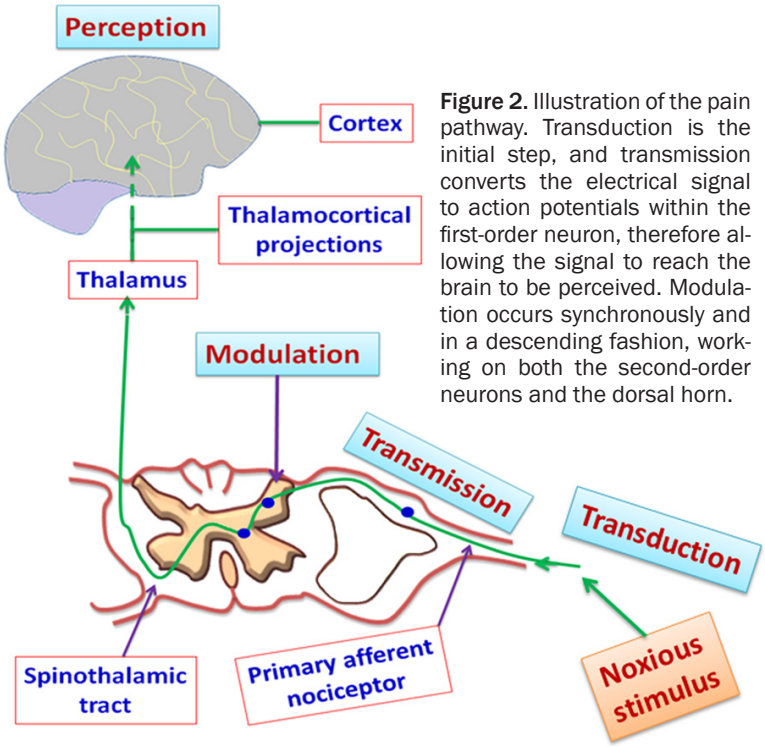

Figure 2. Illustration of the pain pathway. Transduction is the initial step, and transmission converts the electrical signal to action potentials within the first-order neuron, therefore allowing the signal to reach the brain to be perceived. Modulation occurs synchronously and in a descending fashion, working on both the second-order neurons and the dorsal horn.

further expound upon this, increased ACC activity may be seen in those with chronic pain [5]. In 1999, Melzack returned to the original gate control theory and proposed the neuromatrix theory [34]. In doing so, he amended his model to include higher cortical functions as key players in pain transmission and interpretation, and postulated that individuals possess a predetermined neural matrix that is shaped and modified by sensory input. The neuromatrix contains synchronous and interacting thalamocortical and limbic loops. Nodes in the sensory signaling circuitry are genetically determined pattern generators and contribute to aberrant nociception [5]. The structure and output of the neuromatrix is also controlled by cognitive and emotional regulation. Therefore, the final pain experience is born of sensory input in addition to behavioral and cognitive interpretation of pain, which includes prior experiences and cultural background.

Descending pathways originating in the brain modulate incoming signals from painful stimuli primarily through synapses on dorsal horn neurons. This pathway serves two important functions: first, it can amplify the noxious stimulus' signal, as observed in sensitization; second, it can suppress ascending pain signals during extremely stressful situations, particularly life-threatening events. Three important supraspinal structures in this pathway are: the rostral ventromedial medulla (RVM), the dorsolateral pontomesencephalic tegmentum, and the periaqueductal gray region [35]. These systems primarily mediate laminae I and II in the dorsal horn through the release of serotonin, norepinephrine, and dopamine. Either an anti-nociceptive effect or a pro-nociceptive effect is observed depending on which monoamine is released [36]. Dysregulation of this system is implicated in chronic pain states.

Descending systems from the brainstem to the dorsal horn of the spinal cord have been implicated in the induction of analgesia following stimulation of periacqueductal gray matter (PAG) [29]. Stimulation of the PAG blocks the response of lamina V interneurons to noxious stimuli. This overall analgesic effect of PAG stimulation depends somewhat on the release of serotonin from neurons activated in the RVM. Additionally, descending noradrenergic systems originating from the pontine subcoeruleus and locus coeruleus also show bidirectional pain control [5].

Another descending system, the endogenous opioid pain modulation system, also alters pain processing. Activation of opioid receptors in the brain, specifically the mu receptor, blocks pain transmission centrally in the brain but also activates descending systems [5]. The major events in pain pathway are shown in **Figure 2**.

Cells/molecules involved in pain pathway

While there are numerous molecules that are integral to the pain pathway, there are a few of great significance, with myriad studies dedicated to their roles in the pain pathway. Tachykinins, which include neurokinin A and substance P, have been largely studied, as have alarmins and CGRP, thus these are the ones that are highlighted in this review.

Tachykinins and their receptors

Tachykinins are structurally related peptides that are expressed throughout the nervous and immune systems. They and their receptors, neurokinin receptors (NKRs), regulate an incredibly diverse range of physiological processes; thus, it should come as no surprise that they have also been implicated in numerous significant pathological conditions.

Tachykinins exert influence on intestinal contractility and blood pressure, and are present in brain neurons, thus they have also been referred to as "brain-gut neuropeptides" [37]. They have been specifically localized to the primary sensory neurons of the dorsal root, trigeminal, and vagal ganglia. It has been proposed that they serve a major role in pain transmission at the first synapse in the nociceptive pathway, as they are released after a series of steps that are initiated by noxious stimulus acting on a nociceptor. The release of these neuropeptides from peripheral endings has been implicated in generating "neurogenic inflammation", in which arteriolar dilatation, plasma extravasation, and granulocyte infiltration from post-capillary venules occur.

The tachykinins substance P (SP) and neurokinin A (NKA) are produced from a solitary precursor, the preprotachykinin A (ppt-A) gene, and, following a noxious stimulus, act on neurons in the dorsal horn to induce pain responses. Neurokinin A often acts on the neurokinin 2 receptor (NK2R), whose existence in the spinal cord is controversial. However, studies have found low levels of NK2R mRNA and have visualized NK2R on astroglial cells in rat spinal cord, indicating that the receptor does serve a purpose in pain transmission [38].

Substance P

Substance P is a significant member of the tachykinin family, as it is involved in numerous systems. A large body of evidence supports the view that SP and its receptor, neurokinin 1 receptor (NK1R), contribute to nociception and hyperalgesia. In painful and inflammatory processes, activated nociceptors release this neuropeptide into peripheral tissues, where it acts on NK1R, which is embedded in the dorsal horn of the spinal cord [37]. Furthermore, they can activate mast cells, neutrophils, and Langerhans cells to amplify the inflammatory response.

Typically, Aδ and C fibers transmit pain while Aβ fibers transmit touch. However, after a nerve injury, Aβ fibers transform to signal pain. In models of inflammatory and neuropathic pain, SP is then upregulated in these large-diameter neurons. Furthermore, in a chronic constriction model of nerve injury, NK1R is upregulated in spinal neurons, which could also amplify pain [37].

Studies have shown that deletion of its gene, *Tac1*, attenuates moderate to intense pain in addition to almost completely eliminating neurogenic inflammation [39]. Furthermore, deletion of its receptor, NK1R, has been found to suppress stress-induced pain [40]. However, NK1R antagonists have failed to effectively work as analgesics in clinical trials, and it is now thought that CGRP is a more likely contributor to pain typical of migraine headaches [41]. Nonetheless, numerous studies support the theory that SP and NKRs play significant roles in pain modulation, though possibly in a more understated way than previously thought.

CGRP

Calcitonin gene related peptide plays an important role in neurogenic inflammation, and is also released by peripheral nerves in the pain pathway, in addition to other functions such as exerting chronotropic and inotropic actions in the heart or relaxing urinary smooth muscle [41]. Most importantly, it is a potent vasodilator, and it is thought that CGRP plays a hand in migraines this way. Historically, it is believed that the pulsing and throbbing pain associated with migraines is due to the vasodilation of intracranial and extracranial arteries. Intravenous infusion of CGRP has been found to cause a migraine-like headache in a significant proportion of migraine-sufferers [42].

CGRP also plays an important role in peripheral and central sensitization, and is a key molecule in the spino-parabrachial-amygdaloid pain pathway. High levels of CGRP binding sites and proteins required to construct CGRP1 receptors have been found in the dorsal horn and in the central nucleus of the amygdala, where CGRP-releasing fibers also terminate [43].

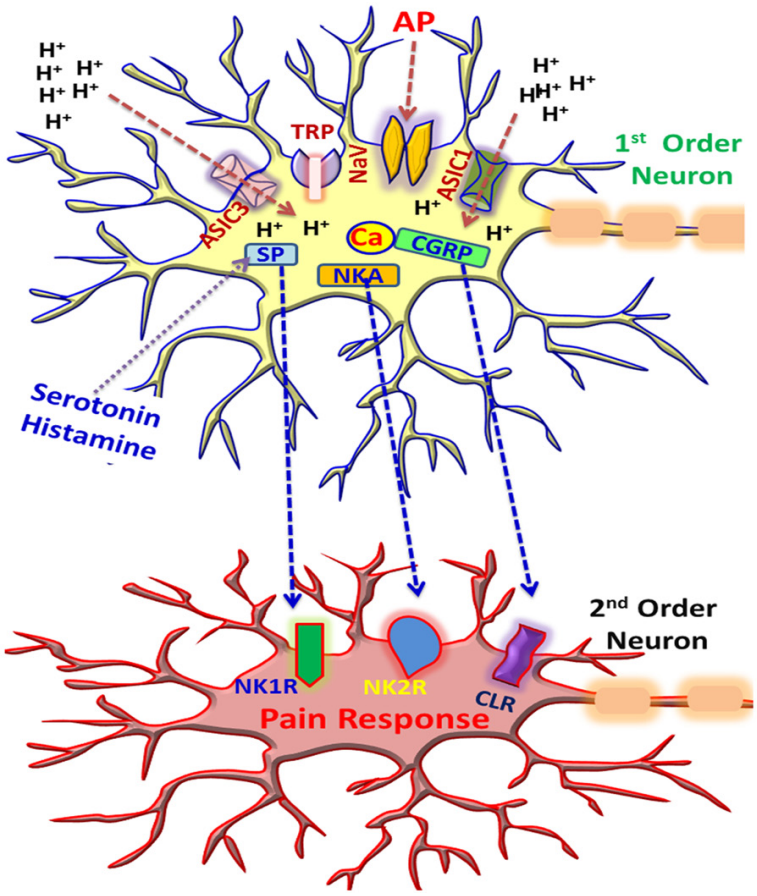

Figure 3. Contributions of tachykinins, CGRP, and alarmins to pain. Thermal, mechanical, and chemical mediators activate TRPs, Navs, and ASICs, which stimulate the release of tachykinins and CGRP into the synapse between the peripheral nerve and the dorsal horn. ASIC3 and ASIC1 stimulate the production of Substance P and CGRP, respectively.

Alarmins

Alarmins are endogenous molecules that work to maintain cellular homeostasis. They are found in the nucleus as transcription factors (e.g. high-mobility group box-1), in the cytoplasm as calcium regulators (e.g. S100s), in exosomes as chaperones (e.g. heat shock proteins) or as components of the cell matrix (e.g. hyaluronan) [44]. They are a diverse group implicated in nearly all inflammatory states.

Several members of the S100 calcium-regulator family (S100A1, S100A2, S100A4, S1008, S100A9, S100A11 and S100B) have been identified in human articular cartilage, and their expression is upregulated in diseased tissue, particularly in the inflammatory condition of arthritis. Both high-mobility group box-1 (HMGB1) and IL-33, another alarmin, have also been implicated in mechanisms of neuropathic pain [45, 46]. The integration of the pain signaling due to various mediators is given in **Figure 3**.

Pain and biceps tendinopathy: what causes the tendon to be painful?

Tendinopathy is relatively modern term used to address the broad spectrum of chronic tendon pain and insertion problems. It refers to the clinical presentation of a symptomatic tendon with no implication or assumption of underlying pathology. It is typically used as a nonspecific descriptor of the pathologic clinical conditions of the tendon and its surrounding tissues. The term therefore encompasses tendinitis, tendinosis, paratenonitis, and tendon ruptures [47]. Tendinitis denotes an inflammatory pathology, which differentiates it from tendinosis, a degenerative tendon condition without necessarily accompanying inflammation; paratenonitis is inflammation of the areolar tissue surrounding the tendon. Tendinopathy is delineated by diminished function, localized swelling, gradual onset of morning stiffness in the tendon, and sometimes neovascularization [48]. Palpable crepitation can result from fibrin precipitating from the fibrinogen-rich fluid around the tendon [49]. As a result, tendinopathy is a term of generality and is often used as a diagnosis of exclusion, since there is no implication of etiology associated with it. The diagnosis can be made clinically, based mainly on patient complaints (sensation of pain within the tendon) and palpation of the tendon, its surrounding tissue, and its insertion, though this can be difficult and can be wrought with inaccuracy. The condition is verifiable by ultra sound (US) or MRI, with US being particularly useful in determining neovascularization [48].

Presently, there are four etiological theories for tendinopathy in the literature: a mechanical

Table 2. Different manifestations of tendinopathy and the role of failed healing

Cause	Healing response	Failed healing	Histopathological changes	Clinical findings
Overuse	Inflammation	→	Continuous release of Proinflammatory cytokines	Pain
Intracellular stress	Innervation	→	Increased nerve growth and release of neuropeptides	Mechanical weakness
Microtrauma	Apoptosis/matrix remodeling	→	Hypercellularity, increased apoptosis, collagenolysis	Degeneration
Hypovascularity	Neovascularization	→	Hypervascularity	

Footnote: Although this table separates the four possible healing responses that constitute the different theories of tendinopathy pathogenesis, it is very likely that combinations of the four result in tendinopathy.

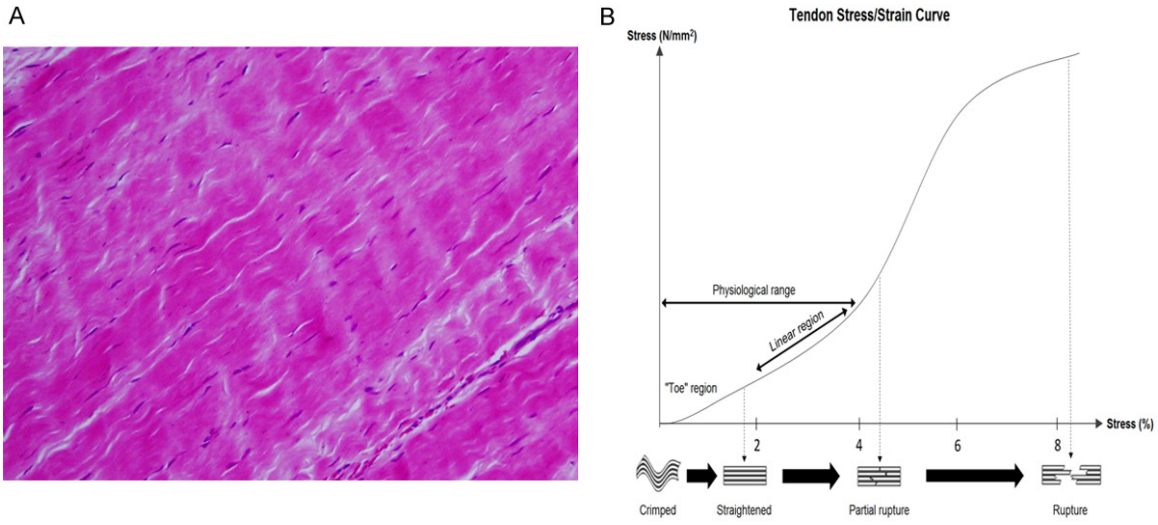

Figure 4. A. Hematoxylin and eosin stained section of normal biceps tendon. This illustrates the wave-like structure of the collagen fibers within the tendon. B. Graph depicting the conformations of collagen fibers within a tendon when strain is applied. Initially, the tendon is crimped or wavy, then as strain is increased, the fibers strain out, resulting in the toe region. Strain within the physiological limits results in elastic deformation. Any further strain progresses to partial and complete tears. This is a simplified diagram; tendons differ by individual.

theory, a vascular theory, an apoptosis theory, and a neural theory (**Table 2**). Briefly, the mechanical theory explores the notion that repetitive loading of the tendon causes microscopic degeneration. Fibroplasia is activated in the tendon, resulting in scar tissue. The vascular theory describes tendon degeneration with secondary areas of focal vascular disruption. The apoptosis theory alludes to a mechanism that causes increased programmed cell death, leading to degeneration of the tissue. Finally, the neural theory proposes that tendinopathy is born of neurally-mediated mechanisms, such as mast cell degranulation and release of substance P [50, 51].

The mechanical theory

The mechanical theory ascribes tendon fatigue and subsequent tendon failure to repeated loading that remains in the normal physiological stress range of a tendon. When at rest, the tendon is wavelike in appearance, and has folds of tissue that maintain its compact form (**Figure 4A**). Once loaded, the tendon can undergo two stretching modalities, or regions. The first, known as a toe stretch region, results from stretching out the crimped structure, which only requires a minimal amount of force [52]. If stretching is continued past the toe stretch region, then a linear relationship between load and strain is seen within the tendon (**Figure 4B**). The collagen fibrils take up the load; therefore stress-strain values typically used to describe tendon stretch are dependent on the physiological properties of the collagen fibrils. From this, tendons are divided into two categories: those that undergo low strains and those that undergo high strains. Those that undergo high strains are commonly loaded during locomotion, and can function as elastic energy stores. It is believed that physiological loads cause less than a 4% increase in strain (stretch) of the tendon. However, recent studies

have suggested that strain values of 6%, and even up to 8%, may be physiological in nature [53-55]. Within this physiological range, particularly towards the higher end, the tendon may start to experience microscopic degeneration; this is especially a concern in repeated and/or prolonged stress. Thus, it is hypothesized that a symptomatic tendon occurs because of this repeated microtrauma, as the mechanical properties of the tendon have been altered [52, 56].

This theory explains tendinopathy as a degenerative process rather than an inflammatory one, and denotes how chronic repetitive microscopic damages could accumulate over time. Furthermore, it effectively explains why older and more active individuals have a higher incidence of tendinopathy. However, the theory does not explain why only certain areas of the tendon are more susceptible to degeneration, nor does this theory explain the pain associated with the condition.

The vascular theory

Tendons, as part of skeletal muscle, necessitate a vascular supply for their metabolic needs. Any impairment to this supply may cause deterioration of the tissue. It has been proposed that some tendons, and certain areas of tendons, are more prone to vascular disruption than others. Those focused on thus far include the tibialis posterior, the Achilles, and the supraspinatus tendons [51]. The Achilles tendon in particular has been found to have an innately hypovascular swath of tissue in the mid-tendon area, throughout its length [57]. Therefore, this area is the most prone to degenerative change, in addition to neovascularization; furthermore, exercise can compromise the vascular supply to this region significantly.

However, this theory is controversial. Astrom and Westlin found that there was uniform blood flow in the Achilles tendon, with no evidence of pockets of hypovascularity [58]. Additionally, it seems contradictory that a young, athletic population often experiences tendinopathy, as exercise can lead to beneficial neovascularization of oft-used tissues [59]. Furthermore, it has been suggested that exercise-induced hypothermia may have more of degenerative impact than hypovascularity [60].

The apoptosis theory

Programmed cell death is increased as a result of intracellular stress, which could lead to the deterioration seen in tendinopathy [61]. Studies have shown that augmentation of amount and duration of strain induces a stress-activated protein kinase, known as c-Jun N-terminal kinase (JNK), in canine tendon cells, particularly when strain is presented in a cyclic manner [62]. This is significant, in that persistent JNK activation has been linked to apoptosis [63]. Increased cell death results in the breakdown of the collagen, since the collagen then has a propensity to break down due to increased friction between the fibers, making the tendon susceptible to tearing. One strength of this theory is that it sufficiently relates oxidative stress, acquisition of fibrocartilage, and activation of metalloproteinases (all findings in tendinopathy) to the development of degeneration by high quantities of cyclic strain [50]. However, this theory neglects the fact that increased proliferation and focal hypercellularity are common findings in tendinopathy, as well as fails to explain why pain often occurs with the condition.

The neural theory

Also, referred to as the neurogenic theory, this proposes that nerve endings and mast cells play a significant role in the development of tendinopathy. They both function as modulators of tendon homeostasis as well as mediators of adaptive responses to mechanical load [64]. Alteration of neural homeostasis due to excessive stimulation of these nerve endings and mast cells may then potentially result in pathological changes in the tendon matrix. Substance P, a neuropeptide, has been shown to mediate the expression of several tendon matrix enzymes and genes in rabbits. One protein it has been shown to modulate is MMP-1, an interstitial and fibroblast collagenase, although its impact may be dependent on sex and hormonal status [65].

Additionally, it has been found that there is an increased incidence of tendon disorders in those with radiculopathy. One study found an association between Achilles tendon ruptures and sciatica in amongst peer-nominated controls [66]. Glutamate, a neurotransmitter found in the pain pathway, has been found in degen-

erated tendons, as well, providing further support for the neural theory [67].

Nevertheless, this theory has yet to be fully explored. Thus far, it is only a collection of observations, rather than a true theory. The presence of substance P, as well as other neuropeptides, does lend credence to this theory. Their involvement also explains the pain associated with some tendinopathy; however, not all tendinopathy is painful. More evidence is needed to develop a more complete theory regarding neural involvement in tendon degeneration.

These theories are not mutually exclusive, and in fact these pathological processes likely work in conjunction to produce the clinical signs of tendinopathy. It is reasonable to follow suit with Fu et al. and merge these ideas as different manifestations of "failed healing" [50].

Biceps tendinopathy

The long head of the biceps (LHB) brachii originates at the supraglenoid tubercle and superior glenoid labrum. It courses along a restricted path within the bicipital groove before inserting distally, in conjunction with the short head of the biceps, onto the radial tuberosity; the bicipital aponeurosis is a conduit for it to also insert upon the fascia of the medial forearm. The exact function of the long head of the biceps is controversial, as it has been described as a humeral head depressor, a glenohumeral anterior stabilizer, and a vestigial structure in humans, among others.

Biceps tendinopathy may arise due to repetitive traction, friction, and glenohumeral rotation, which lead to pressure and shear forces acting on the tendon. The bicipital groove is a constrained environment, so inflammatory processes often impact the biceps tendon as it travels through. Additionally, the LHB tendon has a synovial sheath, making the LHB subject to tenosynovitis [68]. Isolated or primary LHB tendinopathy is relatively uncommon; however, it can occur secondary to direct or indirect trauma, as well as to underlying inflammatory disease or in concurrence with tendon instability [69]. However, the pathophysiologic mechanism of what exactly causes a biceps tendon to progress to tendinopathy is largely unknown and controversial, which is the impetus for our review.

Tendinopathy of the LHB more often occurs in conjunction with other shoulder pathology. The rotator cuff is particularly prone to degeneration, and it is often the case the biceps tendon is impacted, as well [51]. Neviaser et al. found that there was a correlation between inflammatory changes in the LHB and rotator cuff tendinopathy, and that the relationship was stronger with increasing rotator cuff degeneration, while conducting a prospective arthroscopic evaluation of 89 patients [70]. The sheath of LHB is continuous with the synovial lining of the glenohumeral joint; thus, the sheath can become inflamed secondary to the inflammatory processes affecting the rotator cuff [69]. The presence of a 'critical zones', or watershed areas of vascularity close to the insertion points of the infraspinatus and the supraspinatus, has been suggested as a cause of rotator cuff disease, but this theory has been largely criticized [51]. Alternatively, Neer proposed that impingement of the rotator cuff, particularly the supraspinatus, plays a significant role in degeneration [71]. Impingement can occur in flexion of the arm when the acromion presses on the supraspinatus tendon, and the severity of impingement may be related to the shape of the acromion. These two theories may work in tandem, such that impingement could occur at critical zones of vascular supply, leading to the rotator cuff pathology that disseminates into biceps tendinopathy. Consequently, if the tendinopathy progresses enough, it can eventually cause the tendon to rupture.

Evaluation and management

Tendinopathy of the long head of the biceps is generally a clinical diagnosis. Patient history and physical examination are paramount in diagnosis [72]. Patients often report pain in the region of the bicipital groove; this pain can be aggravated by certain activities, especially those that incorporate shoulder flexion and forearm supination. Several patients find that their shoulders are easily fatigued. Imaging studies may be used to diagnose and ascertain the degree of degeneration of the tendon. Plain radiography, ultrasonography, and magnetic resonance imaging are all useful in determining tendon dysfunction [69].

The management of biceps tendinopathy incorporates pain relief and efforts to repair the tendon and restore strength. It is initially managed

conservatively in most cases. Patients are instructed to rest and modify their activities, and are prescribed physical therapy and drugs for pain control. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications after a diagnosis of tendinopathy. NSAIDs inhibit cyclooxygenase-2 (COX2), preventing the catalysis of arachidonic acid into prostaglandins and thromboxane, which are common mediators of inflammation [73]. Should NSAIDs prove to be unsuccessful in managing pain and inflammation, corticosteroid injections may be the next step, either in the subacromial space, the glenohumeral joint, or directly into the bicipital groove to reduce the extent of inflammation that occurs in this condition. Precise injections allow the steroids to penetrate the area in and around the groove without injecting the tendon itself [69].

If these strategies fail to provide relief for the patient, then surgery can be performed. Common indications for surgical management include partial-thickness tear of 25-50% of the LHB, medial LHB subluxation, LHB subluxation that coincides with a tear of the subscapularis tendon or biceps pulley/sling, and primary biceps tendinopathy [74, 75]. The two most commonly performed procedures are biceps tenotomy and tenodesis. In a tenotomy, the tendon is released from its attachment in the shoulder, removing the damaged, inflamed tissue from the joint. A tenodesis is more complex, as it involves detaching the LHB from the superior labrum and reattaching it to the humerus bone just below the shoulder [69]. However, optimal surgical management of LHB tendinopathy remains controversial, and continued study and exploration of methods to preserve the tendon and its attachment are necessary. In addition, understanding the precise causes of pain associated with the long head of the biceps will aid physicians in treating patients with this debilitating disease, and may lead to more effective treatment strategies.

Conclusion

Biceps tendinopathy can be a painful and debilitating condition. Previous research has investigated how pain develops and is maintained to the point that it is chronic, and how tendinopathy arises and is managed. There has been published work investigating why tendinopathy can be painful, as its manifestation is still unknown. Furthermore, there is still some debate as to the exact definition of tendinopathy. A standardized definition by those in the medical profession would improve documentation and augment awareness, allowing physicians to better address the problem. Prospects of research include investigating the roles of Substance P, CGRP, S100, other neuropeptides, and ion channels in tendinopathy, which could lead to more precise and effective treatments for this pain.

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Disclosure of conflict of interest

None.

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