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Research Paper Review

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Why Does My Shoulder Hurt? A Review of the Neuroanatomical and Biochemical Basis of Shoulder Pain

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ABSTRACT

If a patient asks 'why does my shoulder hurt?' the conversation will quickly turn to scientific theory and sometimes unsubstantiated conjecture. Frequently, the clinician becomes aware of the limits of the scientific basis of their explanation, demonstrating the incompleteness of our understanding of the nature of shoulder pain. This review takes a systematic approach to help answer fundamental questions relating to shoulder pain, with a view to providing insights into future research and novel methods for treating shoulder pain. We shall explore the roles of (1) the peripheral receptors, (2) peripheral pain processing or 'nociception', (3) the spinal cord, (4) the brain, (5) the location of receptors in the shoulder and (6) the neural anatomy of the shoulder. We also consider how these factors might contribute to the variability in the clinical presentation, the diagnosis and the treatment of shoulder pain. In this way we aim to provide an overview of the component parts of the peripheral pain detection system and central pain processing mechanisms in shoulder pain that interact to produce clinical pain.

ANALYSIS

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Background Information

Many theories regarding the nature and perception of pain have been developed and tested throughout history. In the 17th century, Descartes postulated that the intensity of pain was directly related to the amount injury to the soft tissue, and that pain was processed in one pathway – this is known as the Specificity Theory. This theory was then discredited in the mid 1960's, when The Gait Theory of Pain was proposed by Wall and Melzack. This theory describes pain as a perception that can be modulated by sensory feedback and the central nervous system (CNS). This particular theory took the clinical and research worlds by storm, replacing the Cartesian model proposed in the 17th century.

Shoulder pain is a common clinical problem, which requires a clinically applicable understanding of the way pain is processed by the body – a key factor in the diagnosis of this (and any) body region or injury. Understanding the mismatch between peripheral pathology and the patient's perception of pain may help practitioners understand why some patients fail to respond to certain treatments.

This narrative literature review aimed to discuss current neuroanatomical and biochemical theories as they pertain to shoulder pain and its clinical management. This review will summarize this paper in a lecture-type format.

REVIEW

Peripheral Sensory Receptors

Numerous peripheral sensory receptors are found in the human musculoskeletal system, and can be classified in 2 broad ways:

- *Function:* mechanoreceptor, thermoreceptor, nociceptor, etc.
- *Morphology:* free nerve endings, encapsulated receptors, etc.

Sensory receptors can be further divided into 3 main groups based on size, degrees of myelination and conduction velocities:

1. Thick diameter, myelinated group II or Aβ fibers (> 20 m/s conduction velocity).
2. Small diameter myelinated, group III or Aδ fibers (2.5-20 m/s).
3. Unmyelinated group IV or C fibers (< 2.5 m/s) (1).

The receptors that respond preferentially to noxious stimuli in addition to having a high threshold to an adequate stimulus are called nociceptors. These receptors can respond to multiple energy forms, such as thermal, mechanical and chemical stimuli. Nociceptors themselves can be subclassified by their molecular nature as either peptidergic or non-peptidergic, based on whether peptides are expressed in their dorsal root ganglion cells. Relevant peptides include:

- *Substance P (SP)*
- *Calcitonin gene-related peptide (CGRP)*
- *Somatostati*n

In spite of these various sub-classifications, nociceptors remain a complex animal, and have a remarkable amount of functional and chemical plasticity, ensuring their responsiveness, and their ability to efficiently manage their synaptic contacts to reflect changes produced by activity, inflammation and

axonal injury.

Another sensory receptor that needs to be defined is the mechanoreceptor, which conveys information about mechanical stimuli to the CNS. Generally, they can be classified as low-threshold mechanoreceptors (LTM) or high-threshold mechanoreceptors, depending on the level of mechanical force required to generate a response (via vibration, stretch, etc.)

The primary mechanoreceptors conveying information about innocuous touch are:

- Meissner corpuscles (dynamic deformation)
- Merkel cell-neurite complexes (indentation depth)
- Pacinian/lamellar corpuscles (vibration)
- Ruffini receptors/endings/corpuscles (stretch)
- Free nerve endings (touch)

A specialized type of mechanoreceptor termed proprioceptors, are designed to respond to mechanical variables associated with muscles and joints. These include muscle spindles, Golgi tendon organs and Ruffini-type receptors.

Generally, mechanoreceptors that are supplied by Aβ nerve endings are activated by innocuous stimuli, and are thus termed low threshold mechanoreceptors (LTMs). On the contrary, receptors supplied by Aδ endings can be either high or low threshold; typically, HTMs supplied by Aδ endings and C fibers can broadly be categorized as nociceptors. A high percentage of Aδ and C fiber nerve endings are insensitive to innocuous stimuli, and are therefore classified as HTMs.

From a morphological standpoint, articular Aβ fibers terminate as Ruffini, Golgi and Pacinian corpuscular endings located in the fibrous capsule, joint ligaments, menisci and adjacent periosteum. The articular Aδ and C fibers terminate as free nerve endings in the fibrous capsule, adipose tissue, muscle, ligaments, menisci, periosteum and synovium in different proportions. Muscles are supplied by thick, myelinated afferents, terminating as muscle spindles, GTOs. Cartilage is generally not innervated.

These receptors can still be further sub-classified in various ways; the substantial overlap between different functional classes of receptor can create significant confusion. Due to this, it is imperative for the reader to understand that there is no universally accepted receptor classification system, and that it is best to imagine these receptors operating on a continuum.

PAIN PROCESSING

Peripheral Pain Processing-Nociception

- Tissue injury involves many inflammatory mediators that are released by damaged cells at the site of injury (i.e. Bradykinin, histamine, K+ and H+ to name a few).
- Activation of the arachidonic acid pathway leads to production of prostaglandins, thromboxanes and leukotrienes.
- Also heavily involved in the inflammatory process are cytokines, (i.e. interleukins, tumor necrosis factor α [TNFα]) and neurotrophins (i.e. nerve growth factor [NGF]).

- Excitatory amino acids (i.e. Glutamate) and opioids (i.e. Indothelin-1) have also been implicated in the inflammatory process.
- Some of these cells activate nociceptors, while others recruit cells which release more agents to facilitate the pain process.
- This process occurring locally at the site of injury functions to increase the responsiveness of the nociceptive neurons to normal input (i.e. peripheral sensitization).
- A number of inflammatory/chemical mediators have been implicated in shoulder pain and rotator cuff disease. While some of these chemicals directly activate nociceptors, most others facilitate changes in the sensory neuron itself, rather than directly activating it.

Primary Hyperalgesia and Peripheral Sensitization

- Primary hyperalgesia is defined as hypersensitivity at the site of pain (the primary zone).
- The nervous system's reaction to both heat and mechanical stimuli are often increased.
- Increased sensitivity at the site of injury is thought to be due to sensitization of the primary afferent nociceptors – this is peripheral sensitization.
- Hyperalgesia to innocuous mechanical stimuli at the site of injury is likely a result of both peripheral sensitization and central sensitization.
- The clinical term for this neurological process is 'allodynia,' which is often defined specifically as 'pain provocation to stimuli, which typically do not provoke a painful response (i.e. pain to light touch)'.
- Primary hyperalgesia is a normal response. Think of sunburnt skin, whereby the acute injury to the skin leads to substantial lowered threshold to innocuous stimuli.

Secondary Hyperalgesia and Central Sensitization

- Defined as hyperalgesia outside the original zone of injury, related to the sensory system's response to mechanical stimulation.
- The localized increased sensitivity of nociceptors leads to a 'flare response' outside the zone of initial injury, through spreading of the chemical activation to adjacent nociceptors. However, the flare response does not account for the entire demonstrable quality of secondary hyperalgesia.
- It is thus important to understand that peripheral sensitization cannot, by itself, adequately account for secondary hyperalgesia – the CNS must have a role to play in this phenomenon.
- Primary hyperalgesia can be explained only by peripheral sensitization.
- Central sensitization is defined as: the ability of central pain signaling neurons to become hypersensitive to the input of LTMs. This process can also occur with an amplification of neural signaling within the CNS that leads to pain hypersensitivity. It is seen in many cases, including an acutely inflamed joint, arthritic knees and shoulder pain.
- The exact higher mechanisms of these central changes have yet to be defined. In spite of this, many theories have been developed.

Involvement of the Spinal Cord (SC)

- The SC receives information from primary afferents, such as nociceptors and mechanoreceptors, which synapse at the dorsal horn of the spinal cord.
- These synapse in two broad ways: 1) with projection cells which travel to the rostral parts of the

SC and higher cortical centers; 2) spinal interneurons, which are either inhibitory (use GABA/glycine) or excitatory (glutaminergic).
- Administration of drugs which antagonize GABA/glycine receptors can cause allodynia. This suggests that inhibitory interneurons function to suppress tactile afferents so that they do not elicit pain.
- The SC also receives neurons from higher cortical centers which produce analgesia when stimulated.

The Brain's Involvement

- Several ascending pathways deliver nociceptive information from the SC to the brain.
- The thalamus is a key anatomical structure in pain processing, as it projects to several areas in the primary and secondary somatosensory cortices, the anterior insular cortex and the cingulate cortex.
- Subjective interpretations and experience of pain involves other regions such as the amygdala, prefrontal cortex, cerebellum, periaqueductal grey, rostocentromedial medulla, and basal ganglia; in other words, it's very complex!
- Emotion can also play a part in the pain experience, because the amygdala, anterior cingulate cortex and anterior insula play a part in the whole process.

RELATION TO SHOULDER PAIN

Peripheral Receptors and their Location in the Shoulder

Rotator Cuff (RC) Muscles and Tendons:

- A high number of nociceptors are present around the RC's humeral muscle insertions.
- Overall, the supraspinatus is most densely innervated with both mechanoreceptors and nociceptors.
- Golgi tendon organs (GTOs) have been described in tendons where they merge into muscle and in their tendinous insertions near the joint capsule.
- Muscle spindles tend to accumulate close to the musculotendinous junction.
- Few lamellated (otherwise known as Pacinian) corpuscles are found in the connective tissue of muscle septa and tendons.

Glenohumeral Joint:

- The superior, middle and inferior GH ligaments all contain mechanorecetors (GTOs, Ruffini endings and Pacinian Corpuscles) as well as free nerve endings.
- Free nerve endings have also been found in biceps tendons and glenoid labral tissue.
- A small number of free nerve endings have been found in the innermost layers of the joint capsule.
- Large diameter nerve fibers have been found in the anteroinferior and posterior superior portions of the outermost part of the capsule.
- Ruffini fibers have been exclusively found in the ventral part of the joint capsule, while lamellated/Pacinian corpuscles have been found in the axillary portion of the capsule.
- The greatest density of neural elements has been reported in the inferior capsule, particularly

with Ruffini-like endings.
- A high density of small, presumably nociceptive fibers, were found in the posterior half of the capsule.
- An increased density of mechanoreceptors in certain areas of the joint coincides with zones where sensory control is most important, due to increased biomechanical stress. The high density of mechanoreceptors in the capsule and labrum shows that they are important in providing a protective reflex while performing extreme or abnormal movement.

Subacromial Bursa:

- Generally richly innervated; more so than many of the other structures found in the shoulder.
- Chiefly innervated with large numbers of free nerve endings and mechanoreceptors (encapsulated corpuscles).
- A correlation exists between density of neural elements found in the bursa and shoulder pain at rest, indicating that those with higher densities of neural elements in this area may be more likely to experience pain at rest.

Long Head of Biceps Tendon (LHBT):

- An extensive neural network has been described along the length of the tendon, with densest innervation being present proximally.
- Thinly myelinated and unmylelinated free sensory nerve endings have been found.
- It is presumed that post-ganglionic sympathetic fibers are present, due to positive staining of tyrosine hydroxylase.
- The authors opine that neither the tendon itself, nor its sheath can be the sole cause of shoulder pain, as many of the studies performing immunohistochemical staining of the tendon are inconsistent in their results. Its role in shoulder pain remains controversial and incompletely understood.

Coracoacomial Ligament (CAL):

- This structure itself is aneural, but the adjacent connective tissue and fat are richly innervated.
- The superficial periligamentous bursal tissue over the CAL is richly innervated with nociceptive fibers in patients with rotator cuff disease, and not in controls. This may be the origin of painful symptoms in this group of patients.

Neural Innervation of the Shoulder:

- The nerves which contribute to the innervation of the anterior shoulder are the subscapular (C5/6), axillary (C5/6) and lateral pectoral nerve (C5/6).
- The nerves that contribute to the shoulder's posterior innervation are the suprascapular nerve and axillary nerve (C5/6).

General Principles in the Management of Shoulder Pain

- A combination of history, examination and imaging should be used to guide management.
- It is also important to focus on historical and physical markers that suggest central sensitization has occurred (i.e. history of pain radiating down the arm, or presence of 'light touch'

hyperalgesia/allodynia around the shoulder).

- Surgical treatment of assumed peripheral pathology in the presence of central sensitization may be disastrous for these patients, as it may facilitate sensitization.
- Nociceptive specific neurons often show a reduction in their mechanical threshold, and can become excited by otherwise innocuous stimulation, causing an irritable shoulder joint. This makes it difficult to clearly discriminate between different pathologies. This explains why many diagnostic tests have varying sensitivity or specificity.
- Nociceptive neurons can feature increased excitability at the spinal cord level, as well.

The Placebo Effect:

- A number of factors, including patient expectation, emotions (ex. anxiety) and mood all have significant effects on placebo analgesia.
- The placebo effect of sham surgery has been demonstrated as particularly strong.
- Clinicians must take advantage of the placebo effect by ensuring the patient has confidence in the treatment plan and decrease the patient's anxiety.

Pharmacotherapy:

- NSAIDs and Paracetamol are generally first line interventions for most musculoskeletal injuries, including painful shoulder conditions. Paracetamol and diclofenac have an effect peripherally by inhibiting the prostaglandin-induced nociceptor sensitization. They also have an effect centrally by inhibiting the prostaglandin-mediated glycinergic neurotransmission.
- Weak (ex. codeine phosphate and tramadol) and strong (ex. oral morphine solutions) opiates can be added in a step-wise fashion, if necessary. Coupling of these receptors to potassium and sodium channels is thought to be the primary mechanism by which endogenous and exogenous opioids produce analgesia. At the SC level, the opioids act as an antagonist to the presynaptic opioid receptor, leading to a decrease in nociceptive afferent transmitter release. The SC outputs are managed post-synaptically, through agonism of the interneuron opioid receptors. Supraspinally, opioids help manage the PAG and RVM centers.
- Neuropathic pain can often be helped through the use of antidepressants (i.e. TCAs and SSRIs), and anticonvulsants such as Gabapentin and pregabalin.
- The nature and chronicity of pain help dictate which medications physicians and other medical professionals might prescribe.

Injections and Nerve Blocks:

- Peripheral injections can be diagnostic, prognostic or therapeutic. Injections can be comprised of local anesthetics, which create a sodium channel blockade, thus decreasing nerve conduction. The injections can include steroids, which have an incredibly complex action, as they have anti-inflammatory effects, in addition to reducing nociceptor sensitivity and central sensitization.
- Steroid injections have been shown to be beneficial in the management of adhesive capsulitis and cuff tendinopathy (2, 3). However, systematic reviews have concluded that the effects might be small and not well maintained (4).

Nerve Blocks:

- Blocks, particularly to the suprascapular nerve, have been shown to be quite efficacious, particularly in cases of frozen shoulder and generalized chronic shoulder pain of multiple etiologies.

Acupuncture:

- It is theorized that acupuncture relieves pain by activating Aδ and possibly C-fibers via mechanical stimulation of the needles.
- A few studies have shown a benefit in treating shoulder pain over placebo, but this could be attributed to the greater placebo effect of actual acupuncture over sham acupuncture.

Physiotherapy and Activity Modification:

- It is proposed that physiotherapy produces analgesia through strengthening, augmenting scapulothoracic movement, increasing proprioceptive feedback and stretching tight structures.
- The exact mechanism of action and physiotherapy protocols vary widely in the literature.
- A Cochrane review (5) concluded that due to small sample sizes, variable methodological quality and heterogeneity results in little overall evidence to guide treatments.
- There exists evidence to support the use of some interventions in specific cases. An example of this is stretching of the posterior/inferior shoulder capsule. Research has shown this intervention to be effective in the treatment of glenohunmeral internal rotation deficit in overhead athletes (Writer's note: be cognizant of the fact that many of these studies are done on overhead athletes, who might have internal rotation deficit or a reduction in total glenohumeral rotation arc. Think about why you are stretching the capsule: could the athlete have 180° total external-internal rotation, with external rotation increase and internal rotation decrease? This could be a change in the anatomy of the patient, and not tissue hypertrophy or contraction. Also, think about non-athletes: would a change in total arc occur in that population?).

Surgery

- Many surgical procedures attempt to fix/repair causal pathological processes.
- Clinically, it is often difficult to ascertain an exact pathological process. This makes sense, when one takes into account primary and secondary hyperalgesia.
- There is a lack of high-quality evidence showing that surgery is effective in the management of rotator cuff disease.
- More large, high-quality randomized controlled trials are needed.

CONCLUSION

The effective diagnosis and treatment of a painful shoulder necessitates a detailed knowledge of both tissue-specific peripheral pathologies and an understanding of how pain may be generated, propagated and modified in the body. With this in mind, the location of receptors and types of receptors present in the shoulder are important to understand.

Additionally, understanding the plastic nature of pain signaling in the body, and how this dynamic

system changes in the presence of persistent pain are of key importance in explaining the interaction between peripheral pathology, pain generation and response to clinical interventions.

STUDY METHODS

No formal methods section included – this paper was a narrative literature review.

STUDY STRENGTHS & WEAKNESSES

Strengths

- The authors presented a balanced article, detailing both the known and unknown factors in the science of pain as it pertains to the shoulder.
- This article was well referenced, despite the lack of description of the authors' search strategy (see below).

Weaknesses

- The authors described neither their article search summary, nor did they perform a statistical analysis of the literature. This essentially means this article was written based on the consensus and opinion of a these researchers. Therefore there is a possibility of study selection and information bias.

Additional References

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